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HENRI TERMEER

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Transcript of an Interview
Conducted by

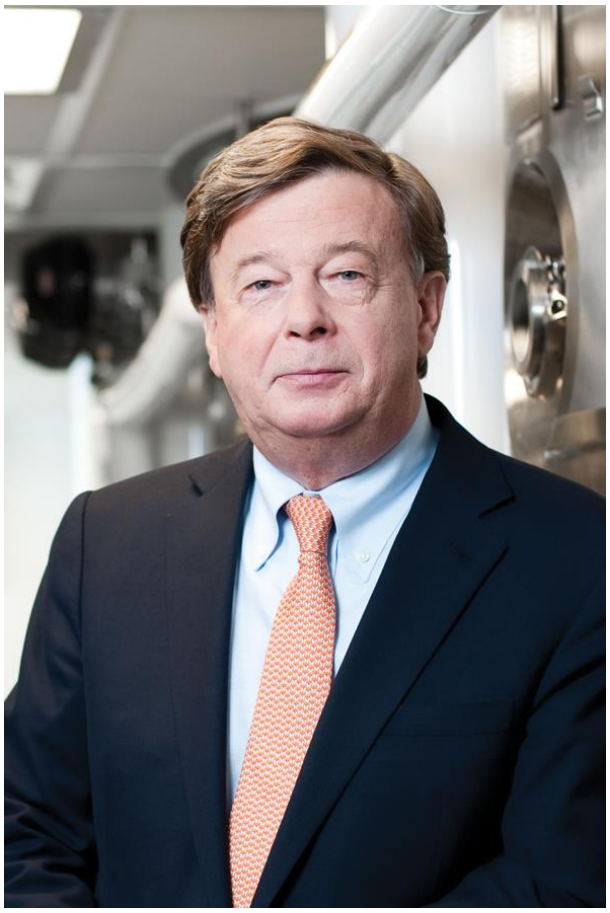
Ted Everson and Arnold Thackray

Cambridge, Massachusetts

on

23 May 2006, 7 December 2006, 2 August 2007, 18 December 2008, and 30 September 2011

(With Subsequent Corrections and Additions)



Henri Termeer

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HENRI TERMEER

1946	Born in Tilburg, Netherlands, on 28 February

Education

1973	MBA, Darden School, University of Virginia

Professional Experience

	Norvic
1969-71	Manager, Management Services
	Travenol Laboratories
1973-75	Manager, International Product Planning
	Baxter International
1975-76	International Marketing Manager
1976-79	General Manager, Travenol GMBH
1979-81	Executive Vice President, Hyland Therapeutics Division
1981-82	International Marketing Manager, Artificial Organs Division
	Genzyme Corporation
1983-84	President and Director
1985-87	Chief Executive Officer
1988	Chairman

Honors

1990-1992	Wall Street Transcript Gold Award
1991, 1994	Laguna Niguel Best of Biotech Award (for Genzyme)
1992	Merrill Lynch and Ernst & Young, Inc., "Entrepreneur of the Year"
1995	Success Magazine, "Renegade of the Year"
1995	Anti-Defamation League's New England Region's Torch of Liberty Award for leadership in human rights and for promoting understanding among people of diverse religious, ethnic, and racial backgrounds
1997	Cardinal Cushing School for Exceptional Children, "Humanitarian of the Year"
1997	Hall of Fame Award (for Genzyme). Special Recognition for an Individual Award, Biotech Meeting at Laguna Niguel, Tenth Anniversary Celebration

1997	Governor's New American Appreciation Award for his success as a foreign-born entrepreneur in America
1999	Fellow in the American Academy of Arts and Sciences
1999	Genetic Disease Foundation Humanitarian Award
1999	Honoree of the Biomedical Science Careers Project's Evening of Hope.
1999	Golden Door Award, International Institute of Boston
2001	Boston History Collaborative's 2001 "History Makers' Award in Biotechnology (accepted on behalf of Genzyme)
2003	Cor Vitae Award from the American Heart Association
2003	Franklin Delano Roosevelt Humanitarian Award, March of Dimes
2005	United States National Medal of Technology and Innovation (accepted on behalf of Genzyme)
2005	Honorary Fellowship at the British Royal College of Physicians
2007	Ernst & Young's "Master Entrepreneur" Award
2008	Chemical Heritage Foundation (CHF) and Biotechnology Industry Organization (BIO) Biotechnology Heritage Award
2012	RARE Lifetime Achievement Award.

ABSTRACT

Henri Termeer begins his interview by discussing his parents' histories, the influence of family, and his entrance into the business world. He describes how, as a boy, he began to develop leadership skills as early as his Boy Scout years and built upon them in military service after high school. He also showed a strong interest in the business process and describes how he studied economics in university. While writing his master's thesis, he acquired his first job in systems engineering. He recounts how he developed, implemented, and then managed the computerization of Norvic, a now defunct European shoe company. From shoes, Termeer describes his move into the medical and healthcare product business, holding various management positions at Baxter Travenol Laboratories Inc. (now Baxter International) in the United States and Europe, including executive vice president of Baxter's Hyland Therapeutic Division and General Manager of Travenol GmbH in Germany. Through his work for Baxter, Termeer gained the experience necessary to head Genzyme in 1983, a then two-year-old start-up biotechnology company, located in Cambridge, Massachusetts. Under his leadership, Genzyme pioneered treatments for patients with rare genetic diseases. Termeer recounts Genzyme's experience with Gaucher disease and the developments of Ceredase and then Cerezyme, and how Genzyme developed and distributed other innovative treatments to patients. Under his leadership, Genzyme became a global biotech business, diversifying through acquisitions across areas including LSDs (lysosomal storage disorders), orthopedics, cancer, transplant and immune diseases, and diagnostic testing. Termeer found time to be involved in many bio-related organizations, including BIO and PhrMA, and to be involved in policy issues regarding drug development and healthcare as well as in a number of local community organizations in Boston. He concludes his interview with comments on Boston biotech, the future of biotech more generally, and personalized genomic medicine.

INTERVIEWER

Ted Everson the director of clinical communications at Vital Issues in Medicine (VIM), a medical education company, earned a PhD in history and philosophy of science and technology from the University of Toronto and an MS in medical genetics from the University of British Columbia. During his tenure at CHF he founded the biotechnology program, which included focused scholarship on industry development. He is the author of *The Gene: A Historical Perspective* (2007), "Genetic Engineering Methods" in *The Encyclopedia of Twentieth Century Technology* (2004), and "Genetics and Molecular Biology" in *History of the Exact Sciences and Mathematics* (2002).

Arnold Thackray founded the Chemical Heritage Foundation and served the organization as president for 25 years. He is currently CHF's chancellor. Thackray received MA and PhD degrees in history of science from Cambridge University. He has held appointments at Cambridge, Oxford University, and Harvard University, the Institute for Advanced Study, the Center for Advanced Study in the Behavioral Sciences, and the Hebrew University of Jerusalem. In 1983 Thackray received the Dexter Award from the American Chemical Society for outstanding contributions to the history of chemistry. He served for more than a quarter

century on the faculty of the University of Pennsylvania, where he was the founding chairman of the Department of History and Sociology of Science and is currently the Joseph Priestley Professor Emeritus.

ABOUT THIS TRANSCRIPT

This interview was part of the Life Sciences Foundation's collection of oral history and research interviews with individuals who played significant roles in the birth and growth of the biotechnology industry. In December 2017, the Chemical Heritage Foundation and the Life Sciences Foundation merged to become the Science History Institute.

The Center for Oral History, Science History Institute, is committed both to preserving the recording of each oral history interview in our collection and to enhancing research use of the interviews by preparing carefully edited transcripts of those recordings. The preparation of interview transcripts begins with the creation of a verbatim typescript of the recording and proceeds through review and editing by staff of the Center; interviewees also review the typescript and can request additions, deletions, or that sections be sealed for specified periods of time. We have established guidelines to help us maintain fidelity to the language and meaning of each recorded interview while making minor editorial adjustments for clarity and readability. Wherever possible, we supply the full names of people, organizations, or geographical locations mentioned during the interview. We add footnotes to the transcript to provide full citations for any publications that are discussed, to point to extant oral history interviews, and to clear up misstatements or provide context for ambiguous references in the transcript. We use brackets to indicate the addition of material that was not in the audio, and bracketed ellipses to indicate the deletion of recorded material. The transcript also includes time stamps at five-minute intervals. We omit without noting most instances of verbal crutches and all instances of nonlexical utterances. We also make small grammatical corrections where necessary to communicate interview participants' meaning. Finally, staff of the Center create the abstract, chronology, table of contents and index.

This interview was transcribed, edited and published by the Life Sciences Foundation. With its accession into the collection of the Science History Institute, the transcript has been reformatted to include our front matter and index, but the text of the transcript itself has not been re-edited. Thus, it does not include our standard timestamps and editorial indications, and it may diverge significantly from the audio recording of the interview. Original audio files of the interview are in the collection.

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INTERVIEWEE: **Henri Termeer**

INTERVIEWER: **Ted Everson**

LOCATION: **Genzyme Corporation**
Cambridge, Massachusetts

DATE: **23 May 2006**

EVERSON: Mr. Termeer, let's start with your early years.

TERMEER: I was born in 1946, in a town in the Netherlands, called Tilburg. I lived there through the age of nineteen or twenty. Tilburg is a medium-sized town—it had a population of 140,000 when I lived there. It was the eighth largest town in a very small country.

EVERSON: Is Tilburg the main town in the region?

TERMEER: No. A better-known town is Eindhoven, where Royal Phillips Electronics has its headquarters. The other towns are Breda and Den Bosch. All are about the same size. Tilburg is in the south of the Netherlands, close to the Belgian border, between Amsterdam and Brussels. There is a university [Katholieke Universiteit Brabant] that focused primarily on social sciences like economics. Now it has many different faculties.

EVERSON: Tell me about your parents.

TERMEER: My mother is still alive. She's ninety-two. My father passed away eight years ago. My mother was born to Dutch immigrants in Strathmore, Alberta, Canada, a small town outside of Calgary, on the prairie. It is lovely. The space is amazing, with big horizons. My grandmother was a great adventurer. She did not want to sit still, and it was this urge that convinced her husband, my grandfather whom I never met, to go on this immigration adventure and start a new life. They were very happy. My mother still recalls meeting Indians. The family had a ranch, and lived in Strathmore until my grandmother began having difficulties with her eyes. The doctors felt that the very sharp air in the Rocky Mountains was not good for her. She needed the Dutch clouds. So, the family went back to the Netherlands when my mother was about six or seven years of age. It was sad in a way, because her father had given up an interest in the family business when he left the Netherlands. When he returned from this adventure, he had to start from scratch. My mother's brother actually went back to Canada many years later. He had been born in Strathmore. When he was in his thirties, he left the Netherlands with his

family and went back to Calgary. He died there not long ago. My mother's family was always very connected to Canada.

My father was born in the Netherlands, in Tilburg. His father had a small shoe manufacturing operation, and he became active in it. The family has a book tracing the Termeers back five hundred years. It's not a prominent family. It's just a normal family, but they wanted a way to reconstruct the family roots. My mother and father met in Tilburg and eventually produced six children. I was number four. The first two were girls, then four boys. I was the second boy. The first four were each one year apart, and then there was a five-year gap before the last two. In good Catholic fashion, my mother had two miscarriages. That's why there was a hole. My siblings are mostly still in the Netherlands. My eldest sister has lived in different places around the world, but settled long ago in Rouen, France. Most of my brothers and sisters are connected to France. They have second homes there. The French connection grew over time, for no particular reason other than that it is a pretty country. Now we're divided up between France and the Netherlands. I'm the only one over here.

EVERSON: Do you go back?

TERMEER: Often. We're close. We have all done well professionally and are very independent, but we like to get together. We get together for big reunions and for smaller reunions, just brothers, sisters, spouses and my mother. We also get together with all the grandchildren—a big crowd. We meet quite regularly, and I sometimes fly them over here.

EVERSON: Was your mother employed?

TERMEER: No, she was a housewife.

EVERSON: What was family life like? What roles did things like music or religion play in your family?

TERMEER: My mother was a good pianist. All the kids were asked to play the piano too. It was not successful, but making music was always great fun for the whole group. I played the trumpet for a little while, not very well. I tried the violin because my father had played it. That was too hard on everyone's ears. I never became a music person. But my parents really liked the performing arts. We regularly went to concerts, ballets, and the theater as a family. We were quite Catholic. Our family would sit in the front row of the Catholic Church, every Sunday morning, and we went to a Catholic school as well.

EVERSON: Was that a private or a public school?

TERMEER: I don't remember whether there was a distinction. It was clearly run by priests and people in black outfits. The Catholic Church probably had a great deal to do with how it was run. Whether it was financed publicly, I don't know. There was a very strong Catholic influence on our schools. They were very good, highly disciplined. I actually have good memories of my time in primary school. I went to St. Thomas and then St. Christopher. There was also the Montessori school that each of us attended before primary school. I don't remember much of that. My high school was St. Odulphus, also Catholic. When I came out of high school, I went into the Air Force. National military service was mandatory at that time in Holland. I was fortunate to be selected to go to officer's school. If you were a regular soldier, you had to go for twelve months, or if you became an "under officer"—a sergeant—you stayed for eighteen months. If you became an officer, you had to stay for two years, but you got real training and were put in charge of a number of different things. I stayed two years and became an officer. It was a very important experience for my future. After two years of service, I went to university to do economics.

EVERSON: Did you have to travel away from home for your military service?

TERMEER: I went to Breda, which was pretty close to home, for basic training and boot camp, and then to a nearby airbase, but I spent about a year and a half in the Hague, again on an airbase. I wasn't a pilot. I was in charge of logistics, materials inventories, and the warehouses at this base where a lot of plane repairs were done. When you're young, being asked to take responsibility for managing people or operations is a magnificent experience. I learned a lot. Thousands of things needed to be managed and controlled in order to keep the planes in the air. We had a large group of people that did this work, many of them professionals. I was in charge, and I was a kid, nineteen or twenty years old. Fifty-year-old sergeants had to acknowledge me as an officer. They resisted a little bit, and tried to challenge me, to see whether I was really worthy of being the boss. It helped me build a high level of confidence at an early age. Even though I was young, I could manage and get along with people. I was able to be friendly with subordinates while maintaining good discipline. Designing and implementing data management systems was another great experience, because computers were not well developed at that time. There were no national systems in place.

EVERSON: Do you mean inventory controls?

TERMEER: Inventory controls, replenishment processes, implementation of SOPs [standard operating procedures], and all those kinds of things. For an impressionable young man, the management experience was great. You can't learn these things in school, and nobody in business would take the risk of putting somebody so young in there. The military training was a

great experience, too. There was continuous training in terms of basic health, survival, and military operations. I had two great years in the military. They were formative to me in terms of my self-confidence. I realized then that I wanted to run something. I wanted to be in charge.

EVERSON: Was this the first time you had played a leadership role?

TERMEER: No. I had taken a leadership role before, at a much younger age, in the Boy Scouts. I also decided at that time that I liked business, or the processes of business. I started to read *Wall Street Journal*-like newspapers and familiarize myself with the world of business, even though there was a lot, of course, that I didn't understand. I read about what was happening in industry.

EVERSON: When you were in the Boy Scouts?

TERMEER: Yes, even before I finished high school. I also played a lot of chess in high school. I played it fanatically for three years—so fanatically that I stopped doing my schoolwork. I failed for a few years because I was going to chess tournaments. When you're young, you're very impressionable. You become successful at something, and people give you compliments, and you think, "This is more important than studying." I bought books about chess and spent a lot of time learning about the game, reading about openings, closings, and all of the different plays. There was a fellow at the local university—which was then a leading economics institution—a professor by the name of Max Eeuwe, who became a world champion. He was well known because he was the first and only Dutch world champion in chess. He was a theoretician. It made an impression on me. I felt that chess was really where it was at. Of course, it wasn't. It got so bad that I would play chess in my head, and didn't really need the board. I would sit quietly in class, so the teachers had no idea. They thought I was paying attention, but I didn't hear a word they said. One day, my mother said, "Enough is enough." She is a magnificent woman, very decisive. I woke up one day, and my chess pieces were gone, all the books on the shelf were gone. She said, "It's over now. No more chess." She thought I would react terribly, and was prepared to manage that reaction. She told the school I would no longer participate and would no longer represent the school or the city. I must have realized that this was not a good way to go on, because I was fine about it. I don't remember it as traumatic. I've never played chess since. I read the chess column in the newspaper, but I don't miss it.

EVERSON: That's a very decisive change.

TERMEER: That period was important for me, and the sudden stop.

EVERSON: These were your high school years?

TERMEER: Yes—twelve, thirteen, fourteen. My parents were an enormous influence on all of us, my brothers and sisters and me, at that time. They were talented in dealing with kids, in giving them disciplined input while being warm at the same time. We were very fortunate.

EVERSON: You earned a BA in economics at the University of Rotterdam.

TERMEER: No. I never got a BA. There's no such thing in the Netherlands. You go straight to the equivalent of a master's degree. I studied economics, and had to write a thesis. Midway through the program, I went to England, to a shoe company like my family's. They had many retail stores around the UK and throughout Canada, Australia, and South Africa—the Commonwealth countries. The company was called Norvic. It doesn't exist anymore. They had a retail headquarters in London. I went there to write about the early computerization of retail stores and the economic effects.

EVERSON: This was your thesis?

TERMEER: Yes. I never returned to school in the Netherlands. I wrote the report, which I submitted as a thesis, and then the company asked me to implement what I had proposed. It was very interesting. It was a relatively big firm. They had hundreds of stores. They invited three companies to help them computerize their operations because they couldn't keep track of their entire inventory – they had trouble monitoring, replenishing, and changing it. They invited IBM, ICL [International Computers, Ltd.], and Cambridge Computer Services (CCS) to develop plans. They put teams from each in a corner of a big conference room. I had the fourth corner. We were competing, but it was a very friendly situation. Over a period of a few weeks, each team had to develop a proposal for computerizing operations. I gleaned what I considered the best of the best and wrote a proposal. When I handed it to management, they liked it best, and asked me to implement it.

EVERSON: That's very impressive. Was the proposal your thesis or was it separate?

TERMEER: It was separate. The thesis was mundane. I can't remember much about it. I remember the proposal because it became the first step that this company took to computerize itself. I was in charge of it. This was my first real job, my first real salary. They allowed me to choose one of the three firms to select the hardware, do the programming, and all of that. In the military, I had been paid a little money, but not much. This was the first time I got money that allowed me to live in a normal way. I stayed with Norvic for two and a half years. They had

manufacturing plants in East Anglia. I moved there and computerized the factories. We became one of the first computer service companies in that part of the UK. We started doing payrolls for competing shoe companies, and production planning. The department broke even. We were able to service the company and other companies, as well. Norvic provided a very good service for free. This was 1968. I was at Norvic until 1971. When the company accepted my proposal, I chose Cambridge Computer Services to assist with the implementation. I traveled to Cambridge regularly to work with them. We connected to a large computer in Cambridge through telephone lines. I learned about computers as I went. My experience in the Netherlands had given me some insight into automation. My background in economics gave me some knowledge of systems input. Back then, it was pretty straight forward. I wasn't a programmer. I was really a systems engineer and a manager. I brought in programmers from CCS to do the highly technical work.

EVERSON: Was systems engineering something that you learned in your economics courses?

TERMEER: Yes. I learned it in the military as well. Shoe manufacturing was similar. There were inventories that had to be replenished, and twenty-five steps in the factory production of shoes, in which all kinds of different materials are used. There were no spreadsheets then, but we invented a system for ordering and keeping an inventory of materials.

EVERSON: Did you move to East Anglia as a full-time employee?

TERMEER: Yes.

EVERSON: Did you eventually set up your own computer consulting service?

TERMEER: No. Norvic had departments that sold computer services to other companies, many of them competitors. We had to set up walls to make sure that information didn't leak. That kind of stuff was very new. An East Anglia newspaper wrote an article on the service company that grew within Norvic, and I was interviewed for the first time. They were quite curious and I was excited, particularly about being able to say, "We can service the company, but also generate revenues and actually break even as a department." It was a valuable learning experience for running a business. The kinds of people I had to attract were not those typically found in shoe factories. They were mostly young people. We had lots of data entry work, so we trained unschooled people for that. That was a good experience. Our system replaced a complex card system. At the London location, there was a large hall full of card racks. Every card represented a pair of shoes—one of a hundred different styles and a particular size—distributed among hundreds of retail stores. The cards had holes in them. Indian and Pakistani ladies would

work with them to sort out what was happening. It was very charming to see, very colorful, but it was never timely, and always hopelessly inaccurate.

EVERSON: IBM was one of the three firms you mentioned.

TERMEER: IBM and ICL. I don't know what became of ICL. They were taken over by a larger firm. IBM was there. We worked with the 370 processor, which was fast for the time.

EVERSON: Were you setting up these systems from scratch?

TERMEER: Yes. My title was Group Systems Manager. In the process, I met my first wife. I also met English people who had gone to business schools in the United States, and were asked by their business school to recruit potential students. Those were the early days of international students attending American MBA programs. That's how I ended up going to the United States.

EVERSON: Did you meet your wife in London?

TERMEER: No, I met my first wife in Norwich. We later divorced. Her name was Maggie. She grew up there. We were there for a short time, and then she joined me when I came to the United States. We left in September 1971.

EVERSON: Were there people who influenced your decision to move?

TERMEER: Yes, particularly ex-MBA students who had become recruiters for American business schools. I met people from Cornell [University], Harvard [University], and the University of Virginia. The University of Virginia [UVA] person I got to know best because he also lived in Norwich. He convinced me to go to UVA, which was then a new school. I wrote to all three schools, and completed very long applications. In the end, I decided to go to UVA because they expressed a real interest in me. There were only five foreign students in our class of one hundred and five, and I was one. They wanted to remedy the shortage of foreign students, so they offered me a marvelous place to live. It was very nice. I didn't know much about the University of Virginia. I didn't know much about Harvard either, for that matter, other than the name, and I knew nothing at all about Cornell. Going to UVA was by far the best financial decision in the absence of real knowledge. The former students were very helpful in the recruiting process.

EVERSON: Were these people hired recruiters?

TERMEER: No. They were alumni who had been asked or maybe volunteered to look around for students that could come to their school. They were competitive. They really did their best to convince you that their place was the best. Financially, UVA was much more attractive than the others. They gave me a home. They gave me a scholarship for the first year and I had to pay something very marginal for the home. I had always been self-sufficient growing up. I always paid my own way. I was never satisfied to go to a school to sit and then go to my family for money.

EVERSON: Did you work in high school?

TERMEER: Yes. I worked for my family's business. I worked Saturdays and earned as much as I could. When I was studying economics, I worked days and studied in the evening. I learned a lot about economic systems at my day job. At Norvic, I had earned good money. I had a nice car and a good life. I saved up, and then sold everything in order to support myself at UVA and buy a little car, but I couldn't have done it without support from the school.

EVERSON: Do you remember the name of the recruiter from UVA?

TERMEER: John Baker, if I remember correctly. He was a well-known tennis player and lived in Greenwich, Connecticut. He moved there after completing his MBA. I met him in the UK. I had never been to the US. It was a great adventure. I arrived at JFK with my girlfriend, Maggie. We had five cases—four were hers, one was mine. We sat innocently in the terminal waiting for a bus to Greenwich, Connecticut. We were meeting our host there. He was to take us to the city, and make sure we got to Charlottesville, which was a long way. When the bus arrived, we realized that my girlfriend's suitcases had been stolen. I had my case and she had nothing. It was very sad. We were running around in a panic for a few hours, and eventually took a later bus. That was a good lesson. We had no money, so we said, "OK, let's regroup." We stayed in Greenwich for two days, and then took a Greyhound from 42nd Street. It was September, still very warm. The bus to Charlottesville was filled with all kinds of colorful people. Those first moments in a completely new country really made an impression on me. And that bus trip took forever. In the Netherlands, you can get anywhere in half an hour. Living in Charlottesville was a great experience. We had two good years there. They gave me a place behind the William Faulkner house, an old slave cottage. It had two floors. We lived upstairs. The room downstairs wasn't used. We quickly discovered a cultural difference. This was the South. They gave me the house, but not to live in sin. There was frowning as soon as we arrived.

At orientation, they mentioned that I would have to work day and night because the program involved three cases a day and an examination every seventh day. They said I wouldn't

be able to look after my girlfriend, and that she could only stay six months because she didn't have a student visa. If she married me, all of that would change. So, two days after our arrival, we decided to get married. We notified the school and our "big brother," a second-year student whose family was looking after us. The family organized the wedding behind our backs. They said, "Don't worry about a thing." They organized a wedding on Jefferson's old grounds. It was probably one of very few weddings to take place there. It was quite lovely. They asked us what we liked. I said, "I like classical music." My wife said, "I like candlelight." They put candles around a beautiful, classic garden, and invited all of the students and faculty. Our parents weren't there, but they made it magnificent. Somebody gave us a car, and we got a room at the Holiday Inn in the Shenandoah Mountains for one night. We had new suitcases, of course. The wedding was a tremendously powerful statement of welcome. Nobody knew us, and we had only been in the country a month. Giving us that great embrace was, I thought, very impressive. That was my first impression of the United States.

EVERSON: How did you find the MBA program over the next two years? Was it lots of work?

TERMEER: Yes, and lots of fun. I did a lot of things on the side. They had a consulting group, and I got some credits for doing that. I did some work at the World Bank and wrote my thesis there. I audited a course on international law. I made great friends, learned a lot, and I loved the case method. All of it convinced me that this was the right direction for me.

EVERSON: What about Maggie?

TERMEER: She did a little bit of babysitting and helped in some antique stores. It was tough on her because I was extremely engaged. We had many friends, but she found it lonesome. Our parents came to visit, which was nice. I worked hard because I had to earn a renewal of my scholarship for the second year. The second year was like the first with a few more electives. Between the first and second year I went back to Europe to look for a job. I went to Unilever, the consulting unit of *The Economist* magazine, and Royal Dutch Shell. They were very unsatisfactory. They didn't have a good understanding of what an American MBA meant. That experience made me want to work in the United States. UVA had an on-campus recruiting program. Eventually I ended up at Baxter Travenol.

EVERSON: Were you recruited straight out of your MBA?

TERMEER: Yes. I interviewed with all kinds of banks and consulting firms. I didn't really know what I wanted to do other than get experience. I had a work visa for only two years. It was a special kind of visa. I intended to go back to Europe with American school and work

experience, and to see what would come of it. My last interview on campus was with Baxter. They were looking for people who spoke European languages and understood European cultures, to become general managers in Europe. It was an attractive opportunity. We moved to Chicago late in the summer of 1973. I started as an Assistant to the International Marketing Vice President. It was a rapidly growing company at the time. It seems very small compared to where Genzyme is today, but they had about two hundred seventy million [dollars] in revenues and were active globally. They made interesting products: artificial organs, kidneys, blood bags, stuff like that.

EVERSON: Was this your first exposure to biological products?

TERMEER: It was my first exposure to healthcare and medical products. Baxter was recruiting in five or six schools. Fortunately, UVA was one of them. Harvard was another, as well as the University of Chicago, and Stanford [University]. They brought in students and made them assistants, creating a natural mentorship program. Within six months to a year, the trainees would move on to more permanent positions. The program was managed by the CEO, Bill [William B.] Graham. There was a book written on it by Monica Higgins, a professor at the Harvard Business School. It came out last year. She called us the "Baxter Boys" because a disproportionate number of ex-Baxter people started biotechnology companies. There is a big piece on me in the book.

EVERSON: The book was focused on careers?

TERMEER: On career imprints. You go through a career in one company—I did it for ten years—and then you start and shape another in a similar mold. The idea is that early career impressions become reproduced. Anyway, I joined Baxter as an "assistant to," but I didn't like being an assistant, so I asked them for a real job. After three months, I became the International Product Planning Manager—a big title for a young man. The job specifically focused on Hyland Therapeutics, an Orange County, California, subsidiary. Hyland made plasma products—proteins isolated from plasma—and diagnostic products. They were one of four Baxter divisions, and the only one not in Chicago. They were in conom Mesa, near Irvine. This was the beginning of biotechnology. You took plasma and pulled it apart, fractionated it. Hyland sold Factor VIII, Factor IX, immunoglobulins, and albumin. The plasma was collected through plasmapheresis performed at collection centers all around the country. They paid people for plasma. They returned the red cells and paid for the plasma.

EVERSON: Were these independent centers?

TERMEER: We owned the centers. That's another very big issue—the plasma industry.

EVERSON: I suppose the practice started during World War II.

TERMEER: Yes. There were ethical concerns about the payments. Very vulnerable people were being paid. Companies are permitted to bleed people just twice a year for plasma, but some donors would come back more often. Some blood came out of South Africa, Belize, and Nicaragua, countries virtually owned by political figures. I was in charge of certain aspects of this business, later on. I learned a great deal. At the time, I was primarily trying to figure out how to make diagnostic and therapeutic products that we could sell internationally. I would go to our subsidiaries, which were very small, and tell them about our products, how to market them, how to run the sales force, and how to prepare. I didn't know that much either, because I wasn't a specialist on these products. I learned as much as I could.

EVERSON: Your goal was to understand both how to develop and market them internationally?

TERMEER: Mostly how to market them. There was one product that was thought to be very important, for Chagas disease, a parasitic disease, sometimes called "sleeping disease." It's very prevalent in Latin America. We developed tests for Chagas disease based on feedback indicating that it would be a big market. Baxter asked me to head up this project. They said, "Figure out a way to set up the connections." That was a very Baxter thing to do.

I traveled to Venezuela and to Brazil, and approached the CDC [US Centers for Disease Control] and the military. The military was very concerned about exposure to Chagas. I learned a great deal, including that we had no business trying to do this. There was no real commercial market, and other companies were very focused on doing it. It was an extremely interesting experience to go to very foreign places, and to meet people who were powerfully motivated by the science and the healthcare concerns related to this particular disease. That was the early part of my career at Baxter. Not long after was the year of the great oil shortage. Baxter didn't have high international sales. It was decided that we needed to squeeze assets, inventories, and accounts receivable to make operations as efficient as possible. A team of five people was pulled together. One was heading it up, reporting directly to the CEO, and for each of the four divisions there was one person pulled out of the general corporation to focus on completely reengineering how business was done: minimizing inventories, minimizing the sales force, minimizing assets, working capital, and investments. They asked me to do the Hyland piece. The others were young, but they had been with the company for three, four, or five years. I had been there for less than a year. I had just bought a house in Evanston, Illinois but was transferred to Brussels for this project. They had given me an apartment in Costa Mesa, California when I moved there, because I was going back and forth all the time. Now I was given an apartment in Brussels. I thought, "Wow. American business." My wife and I moved to Brussels for three months. I traveled around to all the subsidiaries to set up new systems. It was

an incredible amount of fun. It was such a strange time, and such a focused project. Reporting directly to the CEO, you could get a lot done. It was a very good experience, but it only lasted three months.

Afterwards, they asked me to come back to Chicago for a new position. I stopped working on the Hyland stuff and became the International Marketing Manager for the Artificial Organs Division—artificial kidneys, dialysis equipment, heart/lung machines, stuff like that. That lasted for several years. It was very interesting. Great pioneering work was being done in dialysis at that time, and in the development of heart and lung machines for open heart surgeries. It was not dissimilar from the job I had been doing before, except that it was on a larger scale, and in a more senior role.

EVERSON: Was this position also marketing focused?

TERMEER: Yes. I was faced with questions like: "How do you do business?" And, "How do you get regulatory approvals?" It was amateur hour at that time in terms of regulatory approval since everything was so new. Europe was doing well in this space. We competed with the Swedes in particular.

EVERSON: Did you lose your apartment in Costa Mesa?

TERMEER: I lost my apartments in Costa Mesa, Balboa Island, and Brussels. I became the general manager for Baxter in Germany in 1976. The process started mid-1975, when I was asked whether I wanted to become the general manager at a joint venture in South Africa. I spent three weeks there but I didn't like it. Their political circumstances were very complex. Plus, there's a long history with the Dutch in South Africa, so I decided against it. Baxter also offered me an opportunity to go to Brazil. They were preparing me for a general manager position, and I was looking forward to it. In early 1976, they took me by surprise and asked me to become the general manager in Germany. It was their largest sales and marketing subsidiary, and the largest market outside the United States. That was very exciting. I had arrived back from a business trip in Europe on a Saturday and by Monday morning, the president of the division called from Deerfield asking, "How was your trip?" I had visited one country a day, and when he asked about Germany, I said, "Well, they have a lot to learn, but they're getting there." Then he asked, "How would you like to be the general manager, the *geschaftsfuhrer*?" I was shocked.

The general manager had gotten himself into trouble with the unions and there was a strike. Baxter was very anti-union. They were concerned. They made a decision to change the management. I called my wife and asked, "What do you think?" That night, I took a red-eye back to Europe. I went to Brussels and picked up my new boss. We flew to Munich late that night. He met with the incumbent general manager in the airport, while I stood behind a pillar so he wouldn't see that I was there. They had dinner, and he resigned. The next morning I took

over at seven o'clock. By ten o'clock, all of the employees except for the management went on strike. Big signs appeared and women came in wearing black as if in mourning. The ex-general manager was a good friend of mine. He was an Australian with a Czech background who had gone through Harvard Business School. He was a really smart, nice guy—probably too nice. He got himself into problems with some of the employees, and that got him moved out of his office. Although it was painful, we were friendly, so it was okay. The strike started as soon as I moved into his office.

EVERSON: Backing up for a moment—you called your wife, and that night you moved permanently?

TERMEER: Well, permanent is too big a word. It was a quick decision, but I was twenty-nine. We didn't sell the house. We rented it out and became expatriates in Munich. I spoke German which helped greatly. I spent the first day just meeting people. My new boss stayed for a few hours, then I turned around and asked, "Where's Gabe?" He was gone. He wanted me to be independent. By the time I got to dinner that night, most places were closed. I stopped in a wine cellar and "ate" a bottle of wine. I got nicely drunk. I staggered to my hotel. I was tremendously excited by the opportunity. I felt very sorry for George, the ex-general manager, but we became good friends afterwards, so things worked out very well. My wife joined me a few months later. I had three very good years there. Germany had strong local healthcare companies that were competing hard with Baxter. Baxter was trying to make its way in the market, and the Germans were resisting. The dynamics of competition was in our favor. We sold all the products that Baxter sold throughout the world, and had divisions for each of them. Our infrastructure was compact. We had a regulatory infrastructure and a clinical infrastructure. We had warehouses and everything else required to run the operation. Everyone was German except for me. It was a very good experience. The company grew tremendously over those years. I learned a lot about management, and gained a lot of confidence.

EVERSON: You mentioned that the German subsidiary didn't have a manufacturing facility.

TERMEER: It didn't, but it had everything else. It had very little research capability, except for a particular technology in artificial organs for kidney dialysis. It was mostly marketing and sales, distribution, regulatory, and clinical development for Baxter's products: artificial organ products, the Hyland products, Factor VIII and Factor IX, and hospital products like IV solutions and the blood bags. In addition to diagnostics, those were the four or five main areas, with managers in charge of each. We had a sales force, in-house marketing people, and financial specialists. I think I may have had a hundred people at the beginning and around three hundred people when I left. As a subsidiary, we built all of the markets, but the largest single market we had—it may have been larger than the US—was Factor VIII. There were strong clinical leaders in Germany who upgraded the treatment of patients to, by far, the best in the world. It was prophylactic for children in many cases. That market developed quite well. I benefited from

that, coordinating much of the clinical work in terms of proving that early treatment was a good thing to do. The Germans were very important participants at international hemophilia meetings.

EVERSON: Was this prominence specific to hemophilia, or was this the general pattern of German healthcare leadership?

TERMEER: This may be naïve in hindsight, but I attributed it to a law in Germany at the time that said something like, "No citizen, if it can be avoided, should be disabled." If you can manage the health of a citizen in order to avoid an ailment, then that individual has an absolute right to treatment. In hemophilia, that means stopping bleeding that might otherwise occur. Germany was very decisive in the way they looked at the treatment of hemophilia. Of course, there was a global shortage of product which drove the price up. The German prices were higher than elsewhere, but their consumption was also higher than elsewhere. Other countries would complain that the Germans were cornering the market. Economically, Germany was doing extremely well. The ethics of the business were very interesting.

EVERSON: Who were you selling to?

TERMEER: Mostly to specialized hematology centers where patients are still treated today. I learned a lot about the history of rare diseases in Germany, and how they were viewed ethically. In the Second World War, citizens with genetic diseases were in a very difficult position. They were ostracized, not supported at all. Many families went into hiding, so to speak, for generations. I learned a lot about the international politics of genetic diseases. These were life lessons that are still valuable to me today.

EVERSON: Am I right that Factor VIII development occurred at the Hyland Division as well?

TERMEER: Yes.

EVERSON: Is there anything more we should talk about regarding your German history? Are we ready to move to LA?

TERMEER: Yes. We still had the house in Chicago, and all that time, I knew that we would eventually return to the United States. Due to my success with Hyland products in Germany, I was asked to come to California, to Hyland again, this time as vice president in charge of the research, development, global marketing, and regulatory divisions. It was the first time that Baxter set up a global division. Usually it was a domestic component, with the International

Division taking care of the international piece. This time Hyland became organized on a global basis. I became Executive Vice President, and a bit later I also took on manufacturing, and all other functions except human resources. My hope was to become the President of the division, but I left before that happened.

EVERSON: So you were very connected to the United States?

TERMEER: Yes. It was an extremely challenging environment, but very nice. I was in my early thirties by then. American industry was moving rapidly. I couldn't see these stale European firms making the same kind of progress. I was enthralled by American entrepreneurship. This new development at Baxter was very entrepreneurial. There was tremendous camaraderie in the company. People got to do things they had never imagined. It was a great culture shock from Munich to California, and again in Boston, but it was a lot of fun.

EVERSON: So you had the personal goal of becoming President upon that move?

TERMEER: I knew I could eventually run the business, and they were very open to that. That's why they let me run a good-sized division. I had even more responsibility two years later, but Genzyme intervened.

EVERSON: What sorts of activities were related to biotechnology at Hyland?

TERMEER: I ran research and development, and that was the intersection. We were acutely aware of the limitations of plasma. We had exposure to non-A, non-B hepatitis. Hepatitis C wasn't yet identified, but we knew people got non-A and non-B hepatitis, and we couldn't test the plasma for it because there was no test. A few years later in 1981, the whole HIV crisis began. Genentech was started in 1976, and went public, and was a great success story. Genetics Institute [GI] had been started, Hybritech had been started, Genex had been started, Biogen had been started, and they looked at known proteins early on. They looked at a lot of stuff, including Drain-O, indigo, whatever. It's kind of funny to think that people were trying to develop biotechnology companies on the basis of industrial products. They also looked at blood products. There was an established market, and it was clearly crazy to collect millions of units of blood, or plasma the way we were doing it, so it made sense to investigate alternatives. If you could produce albumin or Factor VIII by recombinant means, that would be good. Many of these companies started to produce known proteins. Genentech started with insulin and human growth hormone. The whole thing with cadavers entered there. The challenges with plasma proteins turned out to be big. We had no recombinant technology at Baxter.

EVERSON: Did you know about recombinant therapy in 1979?

TERMEER: Yes. We were a well-known company in the protein business, and biotech companies needed money, so they would come to try to sell their services. I went to all the well-known biotechnology companies, and did contracts with a number of them. We started a contract with Genetics Institute for Factor VIII and Factor IX, and albumin. We worked with Hybritech on some highly specific immunoglobulins—hybridomas for septic shock. In the process of setting up these contracts, you visit people, you negotiate, and you make choices. You learn a lot.

EVERSON: You meet people.

TERMEER: Right. And they get to know you. We were a powerful company because we had money and a very obvious need. Biotech companies wanted to work with us. Baxter was in the blood business, in terms of purifying it through dialysis machines, collecting it in Fenwal bags, and then breaking it apart through fractionation, and adding IV solutions to it. Hyland and Baxter knew a lot about blood and blood ingredients.

EVERSON: And these were skills that molecular biologists in these small companies didn't possess.

TERMEER: That's right. We knew all about red cells, damaging red cells, blood machines, and so on. We knew about EPO [erythropoietin] and t-PA [tissue plasminogen activator]. Anyway, it was this interaction with biotech companies that led me to leave. There was a change in CEO at Baxter, from Bill Graham to Vern [Vernon R.] Loucks. The company became much more oriented to the "low-tech" side of the healthcare field. They were not about to go into biotechnology. I was not allowed to develop biotechnology capabilities within Hyland, although we were continuously exposed to it. A well-known consulting firm told Baxter that it was too late because the experience curve that had been accumulated in the biotechnology industry was so large in established companies like Biogen, GI, Genentech, and Amgen that it was too late to catch up. This was the early 1980s. It was a well-known consulting firm—bad advice. We were at the very beginning of the technology then and Baxter was led to believe that it was already mature. We had lots of discussions in the company about this. I decided I had to look elsewhere because the company was losing its courage to do new things. Science gets squeezed as companies mature. Operating realities overwhelm companies' abilities to go into the unknown. Organizations can tolerate only so much uncertainty, and the number of people employed on the "known side" becomes so large that it overwhelms the few who want to go to the "pioneering side."

EVERSON: Okay. Should we stop here and pick up on those new opportunities in our next interview?

TERMEER: Sure.

[END OF AUDIO, FILE 1.1]

[END OF INTERVIEW]

INTERVIEWEE: **Henri Termeer**

INTERVIEWER: **Ted Everson**

ALSO PRESENT: **Jennifer Dionisio**

LOCATION: **Genzyme Corporation**
Cambridge, Massachusetts

DATE: **7 December 2006**

EVERSON: Mr. Termeer, when we last spoke you described how you had moved to LA in 1979 to head up R&D at the Hyland Division of Baxter, and how, in that position, you were often in contact with biotech companies. How did you then become interested in moving into biotech yourself?

TERMEER: From 1979 through 1983, I was at Hyland. Those years were difficult for Baxter. They had been growing for a long time, but management changed and the direction changed. Loucks took over from Graham and the company became much more device-oriented and less science-oriented. Biotech was just beginning, but Baxter wasn't interested in it. Young biotechnology companies were looking for management, and venture capitalists wanted people in more mature companies, particularly Baxter, to engage in entrepreneurial activities with these companies. I got many calls, as did other Baxter executives. People that I worked with and respected left, either to start their own biotechnology companies or to take over existing ones. That was a very intriguing prospect for me. I always felt that at some point in my career I would become involved in building my own company. I was very happy at Baxter, but I noticed that it was going through a change. I became more receptive to taking calls. I went to see venture capitalists and companies, and became acquainted with the possibility of stepping out of Baxter and engaging the uncertainties of a completely new situation. I seriously considered a few offers, but didn't find the right connection until I got a call from the venture capitalists that were supporting Genzyme.

The company had been formed a year and a half earlier, in 1981, and had seventeen employees in Massachusetts. It also had a small diagnostics operation in England, and had recently developed close ties with a group of professors from MIT. One was at Harvard. They were well-known, full professors who had a lot of multidisciplinary postdocs. They formed a consulting company called BIA, Bio Information Associates, and received shares in Genzyme as part of building that early connection. Genzyme was just starting out and they were trying to figure out what to do with it. During the interview process, I met the management, primarily Henry Blair and Sheridan Snyder. I met venture capitalists Ed Glassmeyer from Oak Ventures, John Littlechild, and David Cooksey from Advent. I also met the head of Montgomery Securities' Bridge Fund, Tom Weisel. Montgomery was a boutique merchant bank with an arm

that invested in companies like Genzyme. These funds were looking for someone like me to become CEO. The professors, the venture capitalists, and I all decided to join within four months of each other. I was last because I was waiting for the money to go in. Snyder was Chairman and CEO, and the largest shareholder, but the venture capitalists wanted to get someone with a proven track record in the healthcare field. Snyder had been in the packaging field and was a very successful serial entrepreneur. He wasn't happy about yielding to the venture capitalists' demands to bring in someone like myself, but he was tolerating the process.

The company had recently acquired a small diagnostic enzyme business in the UK that had been found by Henry Blair. Blair was a scientist at Tufts [University], engaged in enzyme research. He's really the founding scientist at Genzyme, the person who brought in the enzymology, the enzyme production techniques. Blair's company was called Whatman Biochemicals. It was a subsidiary of Whatman Reeve Angel, Ltd., which provided enzymes to the clinical chemistry industry. Genzyme bought Whatman Biochemicals with money from Oak Ventures, the earliest venture capital investors. An important element of Genzyme's success was acquiring an NIH [National Institutes of Health] contract. It involved the supply of an enzyme that was later used for Gaucher disease.

EVERSON: Glucocerebrosidase.

TERMEER: Yes. The NIH was experimenting with the enzyme as a potential treatment for Gaucher disease. Genzyme supplied it. In the early days, we collected placentas and extracted the enzyme. We purified it and sent it to the NIH for their experiments. In that same time frame, 1983-1984, they started to understand that the enzyme alone was not enough for the treatment of these patients. They needed to target the enzyme, and for that they needed to modify the glycosylation. That eventually became Genzyme's Ceredase. Dr. Roscoe Brady, the godfather of the whole field, had been experimenting with very large doses of the unmodified enzyme but couldn't achieve clinically relevant results. In 1984, the first patient, Brian Berman, was injected with a modified enzyme, and we started to see remarkable results. However, there were eight patients in the group after Brian with no results. The failure was dose-related. They used the same units of enzymes on much heavier patients, but it was discovered later that you needed to change doses depending on body weight in order to see an effect. Brian is a well-known patient. He's now a young married man. As a kid, he was very sick. When he was three years old he had a belly that looked like he swallowed a basketball. He was supposed to get his spleen removed at one point, but his mom, Dr. Robin Berman, worked at the NIH. She pleaded with Dr. Brady, "Give my child one last chance before we do this operation and remove the spleen." It worked dramatically. It was remarkable. Brian, who previously was very anemic and didn't behave at all like a three-year-old, suddenly started to run through the corridors of the NIH. It was a beautiful story. We kept running out of enzyme—because we needed massive amounts of placentas—and he would get sick again. His own control was pretty illustrative. But the NIH rushed to the next group of patients, had the wrong dose, and the effect couldn't be measured. That was a major setback.

EVERSON: Did the NIH do any more trials?

TERMEER: That trial was completed and published. It was announced that enzyme replacement therapy for Gaucher disease didn't work. But some of us didn't give up. Dr. Brady didn't give up. Dr. Berman didn't give up. Before we made the plunge into the scientific work needed to understand the dosing issues. I pulled eight scientists together from MIT. These were big names like Harvey Lodish and George Whitesides. We met for a whole day and asked ourselves, "Should we push this forward or should we move on to something else?" This was in 1985. They decided that it was not right to go on because they thought that gene therapy was just around the corner, and, in any case, we couldn't get enough placentas. They said, "You need recombinant technology, and if you get that, you may as well go right on to gene therapy, because that's the next proper step." I didn't take their advice. I respectfully continued to push forward, based on my observations of the patient. There was such a clear effect. When we stopped, he got worse. When we gave him product, he did well. It was not a little effect; it was a miraculous recovery in a kid who couldn't fool you. It was very convincing to everyone, especially Dr. Brady, who knew the scientific underpinnings of why it should work. We started to engage in the scientific work to allow the treatment to be proven properly. By 1991, many years later, it was successful and the product got approved.

EVERSON: You mentioned these eight scientists from MIT. Can you list their names?

TERMEER: Absolutely. Chris Walsh and George Whitesides, who are now at Harvard, Harvey Lodish, who's now at the Whitehead Institute, Charlie Cooney, Cho Kyun Rha, Tony [Anthony J.] Sinskey, Graham Walker, and Bill [William] Roche, who is now at Indiana University.[1] They were multidisciplinary. Some were chemists, some were biologists, some were biochemical engineers, and so on. They had a company that did public and private advising, and they partnered with Genzyme. Harvey Lodish now teaches this case to his class at MIT. When scientific advisory boards composed of noted people recommend not doing something, they're not always right.

EVERSON: How did you move forward once you got their input?

TERMEER: We had to raise money because the company had several other goals, like developing diagnostic enzymes. We didn't follow the early biotechnology model of doing research, being supported by larger companies, and then raising a lot of equity. Instead, we funded the company independently, with small, incremental steps. During that period we were

[1] Charles Cooney, interviewed by Brian Dick, 14 August 2012 (Philadelphia: Science History Institute, RI0154, in process).

privately held. We would meet every Saturday and Sunday to discuss what everyone else was doing in biotechnology and to figure out what we could do that was unique. We decided to invest only in what we could afford. We didn't want to support the company through research contracts with major corporations. We wanted to own our technology. We eventually built a hundred-million-dollar business out of diagnostic enzymes. I always felt a great sense of pride when customers asked for repeat deliveries of a product. I felt that was confirmation. Each year we learned more, used more advanced technologies, increased efficiency, and found ways to compete. Today, we control a good piece of the global market. We did the same with research reagents. We went to other companies and said, "We'll take your reagents and we'll make them available to the research community around the world."

EVERSON: So you obtained these reagents from other companies and sold them?

TERMEER: Yes, and to academic institutions. We would often characterize the products ourselves or we would use their characterization. The NIH was our largest customer. We later sold that part of the company. Prior to my joining, Genzyme was involved with a small chemistry operation in England called Koch-Light [Research Laboratories, Ltd]. It was a research reagent company that focused mainly on chemistry. It had seventeen thousand products that were sold primarily in UK research markets, and, to a lesser extent, in the rest of Europe. The company was bought out of bankruptcy. We tried to make a go with it, but it was stupid. We weren't a chemistry-based company. However, we did pick up a beautiful piece of land outside of Cambridge in the United Kingdom, in Haverhill. While selling that business, we learned how to engineer and build a pharmaceutical plant to produce a product called clindamycin phosphate, used for nosocomial infections. It was an Upjohn product that was very tough to produce. There were many, many steps. It had come off patent. We were able in an efficient way to do it with the help of the MIT scientists. We entered the generic market in a sense, although there were no other available entries, so we didn't gain from it financially. We did get some funding from the Department of Trade and Industry in the United Kingdom, and became FDA-approved, which gave us experience in the FDA approval process. It also gave us experience with quality control and quality assurance. At this time we were shipping to AstraZeneca and other major corporations, which gave us a lot of experience in meeting the quality requirements of sophisticated pharmaceutical companies.

EVERSON: You scaled up products that you acquired elsewhere, and you got a lot of experience prior to your major product launch?

TERMEER: Yes, and it allowed us to attract people who were quite different from those you normally attract to a biotechnology firm. Aside from scientists, we brought in business people, manufacturing people, and regulatory people on two continents. It was very significant that we had an early UK starting point because Europe became a natural part of our business. My

background, of course, helped. The fact that we were a player in the emerging biotechnology scene in the United Kingdom was very helpful as well.

EVERSON: Charlie Cooney told me to ask you about the importance of manufacturing in biotech companies.

TERMEER: As I would tell Charlie, it's very important. We are vertically integrated, and manufacturing is an extremely important component of our competitive positioning and of our asset base. We think of manufacturing as a fundamental skill and asset on the regulatory side, the continuity side in terms of quality, and forever-improving margins. Each year we learn to do things better.

EVERSON: With incremental improvements to your manufacturing capabilities?

TERMEER: Yes. It pays. The returns on our capital costs are extremely good compared to taking equity capital and putting it into research where you have a very low probability of success. I'm very much an opponent of just being R&D-focused, particularly for companies like Genzyme. In companies where you have an enormous critical mass, you can outsource pieces of it. If you've got nothing, you need something to rely on, and manufacturing capability is very reliable.

EVERSON: What kinds of enzymes were in the early diagnostic tests?

TERMEER: Cholesterol esterase, cholesterol oxidase, amylase, and the like. These are enzymes used in clinical chemistry. They're very important commodities and the amount of enzyme used today is relatively small. They were produced using fermentation or extraction—sometimes from plants or beans, but mostly from animal tissues. Charlie Cooney and others were able to do this using recombinant DNA, so we were able to bring the price down and compete effectively. We're still about 50 or 60 percent of the global market for those kinds of enzymes. They were sold to Abbott Laboratories, Roche, and others to make enzyme clinical chemistry kits, and they were sold en masse in the diagnostics market. In the meantime, we were progressing with biological products, particularly with glucocerebrosidase for Gaucher disease. That time period was very interesting for the biotechnology industry. Companies like Amgen, Genentech, Genzyme, and Genex were all searching for what to do. There was a major push to figure out what we could do with industrial enzymes. They were needed for the production of wine, ink, or indigo for blue jeans, to curl your hair, or for Drain-O. Today these things look like odd, funny approaches, but in those days companies didn't know quite what to do. They didn't know much about mammalian cells or the requirements to get a product approved. The logical targets were plasma proteins—extracted proteins that you could produce through recombinant

technologies. We spent a lot of time pursuing options, particularly because we had a diverse technology platform due to the broad-based representation in our science advisory group. For instance, we even worked on oil recovery, which again feels like a totally silly activity in retrospect.

Other biotech companies have interesting stories of trial and error experiences when they explored the possibilities of biological production beyond plasma proteins, which were the obvious first targets. In 1983, when I first came here from California, I thought, "What can we do that's interesting?" I looked at scientists' resumes—many of them twenty or fifty pages long—and found that Professor Cho Rha had supervised a post-doc in the field of hyaluronic acid, which is a polysaccharide. I knew something about it because, as part of my earlier investigations of entrepreneurial opportunities, I had spoken with one of the early pioneers in the field, Dr. Endre Balazs. He created a company called Biomatrix, and wanted me to become the CEO. When I sat down with him, I found that the world was too small for both of us in the same empire. He was a marvelous man, but he really needed to be in charge and didn't need me. I knew a lot about hyaluronic acid as a result of that and another visit. It had many different indications, so I met Cho. I asked about her hyaluronic acid project. I subsequently hired Cho's postdoc, Dr. Betsy Robertson, a fabulous person, and we introduced hyaluronic acid into the company in early 1984. Today, we have a very large and interesting program in that field. Many of the things that we set out to do then still carry on today. Being able to execute those things ourselves provided a significant sense of independence. In the midst of this, we went public in 1986. The prospectus described a company that was good at a number of different things. We had diagnostic enzymes, research reagents, hyaluronic acid, and projects with the NIH to treat an awful genetic disease. As we discussed earlier, for that to work, we needed to change the glycosylation of the enzyme and target it to macrophage cells.

EVERSON: The enzyme had been remodeled by 1984, right?

TERMEER: Right, we made that an aspect of our new technology. Attempts to remodel t-PA [tissue plasminogen activator], a well-known protein that Genentech and Genetics Institute were going after, showed that if you remodeled a protein sequence you could get effects like a longer half-life and better targeting. That was why we believed glucocerebrosidase worked. I hired some people out of Cornell and MIT who were experimenting with it. Dr. James Rasmussen, a carbohydrate chemist who studied at MIT before going to Cornell, introduced us to the field. The Genzyme IPO describes our platform technology for remodeling proteins, but we framed it in the context of a company that sold things to diagnostic companies, that had a plant, and had other things going on. We had about nine million dollars in sales by 1985. We were just breaking even, but we had very big-name support. Nineteen eighty-six was a good year for IPOs in biotechnology. We went public and were oversubscribed in June of 1986, raising twenty-six million net. For the first time we could breathe. Prior to that, we had been living hand to mouth. We were able to do more with that money, but I insisted that we wouldn't spend all of it on research, and end up like everyone else. We needed to finance the future, so we started using

R&D limited partnerships. We weren't the first company to use limited partnerships. I think Centocor and Genentech may have been the first.

EVERSON: Stephen Evans-Freke in particular was instrumental in pioneering R&D limited partnerships. Did you work with him?

TERMEER: We did later on, but the first one wasn't with him. Stephen was at Paine Webber. We only needed ten million dollars to do the glucocerebrosidase experiment. That was too small for Paine Webber to get involved. They didn't like the idea of Gaucher disease, either. They called around to check it out, but nobody they talked to knew what it was. I went to the bankers who had taken us public and they were very happy because we had traded up, but they had no experience in R&D limited partnerships. Stephen had cornered that market to some extent. There was a firm called Cowen & Company that did very good basic research, and entered investment banking through our offering. The chairman, Joseph Cohen, was so intrigued by developments in biotechnology that he said, "I'm going to give you guys a chance." He was a marvelous man. We learned how to do a limited partnership, and made a deal for ten million [dollars] starting in 1987. We needed to sell two hundred units at fifty thousand dollars each, so we offered warrants, the normal R&D partnership structure. This was May or June 1987. We only had about four months to get it done. I went around the country to the usual places, but there was no interest in Gaucher disease. You could talk about heart attacks, t-PA, sepsis, but not Gaucher disease. Cowen & Company had no constituents and no track record, not even as a bank. We had a very hard time. Mr. Cohen bought some units, and somebody else bought some, but we couldn't sell ten million [dollars'] worth. I became frantic. I met with oil companies in Houston and couldn't sell to them either. They said, "You're going to buy this back, and when I finally get the oil going you're going to take it from me? It's a good thing to help these kids, but . . . ." By mid-September, we were still doing poorly. By the end of the month, we would have to give up. We still had a few weeks left, but not enough of a book to close the transaction. We were selling this unit by unit to individuals. It was very painful.

We ended up in Albany, New York. We flew up the Hudson River from LaGuardia with Dr. Robin Berman—the mother of the first patient, and Dr. F. Scott Furbish, whom I had hired into Genzyme from the NIH. We went to a meeting with thirty or so brokers and wealthy individuals. It was a secondary city—Albany, New York. What do you sell there? Nothing. Dr. Berman was eight and a half months pregnant. She was this tall [gestures] with a big belly, but she's feisty and can explain things beautifully. She was talking about her unborn child who could also have Gaucher disease, and there's nothing more convincing than a mother talking about her child. Suddenly, she grabbed my arm and said, "Henri, I think I'm in labor." I took her outside and told Scott, "Keep talking." Then I told her, "I'm a derailed economist. You're a doctor. I can't help you." She said, "It's OK. It's probably a false sign." It was, from flying on the little plane. We put her on a train to go back, but at that moment these people in the room got it. It was an absolutely amazing moment. They saw it, and they reacted magnificently. The broker started taking orders, and the buyers called their colleagues. Others bought in, and we

finished the ten million [dollar] transaction by the end of the month. Suddenly there was great momentum.

Two weeks later, was October 17, Black Monday. The marketplace fell apart. Had we not been able to do that transaction, you and I would both be sitting somewhere else. We would have given up. The R&D partnership allowed us to move forward with off-balance-sheet financing, which was the trick. It protected the P&L [profit and loss] statement, and allowed us to negotiate to reacquire the technology. We started with the biopsy-based trial to determine the dose, then the final trial. We didn't have a lot of money or placentas. We needed twenty-two thousand placentas to treat one patient in a year. We knew that once we started treatment, we could never stop, so we needed to secure approval if we wanted to continue. Parexel told us that we would need 144 patients for the trial to be reliable. I said, "We just can't do that." We went to the FDA and told them we could only do twelve patients, so we did. It worked very well twelve times. We followed twelve other patients who were untreated, and the difference was powerful. We published the results in the *New England Journal of Medicine*, and that became the underpinning for regulatory approval. We even got permission to double the dose for two patients who were doing very badly. They were dying and they recovered. They're now young women with families. There was another patient who flew over from Germany. The German government paid for this patient to fly from Bonn and back for their infusion every two weeks. One family moved here from South Africa and went back after successful treatment. It was an extremely successful trial.

EVERSON: At what point did the FDA say your numbers were sufficient?

TERMEER: We never agreed on a number. We had one shot at it, and I took a gamble. The FDA then was not the FDA that we know today. I don't know if it was a massive difference, but it feels different now. Once we knew that we had a dose response, I simply refused to consider that it might not work, so long as the patients were diagnosed correctly. That's the advantage of not being burdened by knowledge. When you're an economist you can make that assumption. A biologist could think of five million reasons why it might not work. I tend to be right by pure luck. There were a lot of people who told me this was crazy and tried to direct us differently. The great advantage of doing the R&D limited partnership was there was nowhere else we could spend the money. We were forced to try what we had described in the partnership prospectus. At the same time, the HIV crisis was unfolding, and the FDA realized that we had to pool 22,000 placentas per patient. If you suspected that HIV could cross-contaminate, then pooling this many placentas was 100 percent likely to result in contamination. Gaucher is chronic, so every two weeks you could expose people to HIV. The plasma industry got into deep trouble as a result of this situation. Eventually they were forced to use newer technologies to inactivate viruses like HIV and hepatitis C. Prior to this, many hemophiliacs died of HIV. Some people in Japan, France, and other places who made decisions to let these products continue to be sold were put in prison. There was an enormous sensitivity to HIV at that time, particularly related to human, blood-based products. Ours was a tissue-based product, not plasma-based, but we employed powerful technologies nonetheless to decrease the viral load. We never had a

problem. Later, we processed the enzyme for a thousand patients, which required millions of placentas.

EVERSON: The plasma crisis did not affect this clinical trial or your research?

TERMEER: It had no effect. Many people wanted to stay on the sidelines, but we were able eventually to get them on board. When we tried to get approval in Japan, they flatly said, "No. We will not approve a human product. We'll wait for the recombinant product." They had put a number of well-known physicians and officials in prison because of the HIV crisis. It was in the early 1990s. Japanese patients had a very serious mutation. They were very sick, and needed treatment. We couldn't import the product, even to save the lives of these patients, because we didn't have regulatory approval. I went to Walter Mondale, the US ambassador to Japan, and showed him pictures of the patients. I told him that this product was now available in Europe and approved in the United States. The Europeans hadn't fully approved it—they allowed availability on a case-by-case basis, and paid for it. Mondale was a real humanist. He was so upset that he said, "Let's move these families to Hawaii and treat them. How many patients are there?" I said, "Maybe twenty-five." He said, "At least we'll give these kids a chance." The Japanese got wind of this, and it forced them to approve the product.

To get all the placentas for the clinical trial, we were going to hospitals in New England. A little car would arrive and collect the placentas. They were lugged up to the fifteenth floor in Chinatown where we purified them. In order to make the product available to more patients than the twelve in the trial, we needed access to more placentas. It turned out that the French never allowed plasmapheresis as a way to collect plasma for the production of albumin and immunoglobulins. Here in the United States we used plasmapheresis, but in France they used placentas. They put placentas through beautiful wine presses to extract the liquid, which went to a plant for fractionation. The tissue was discarded. We needed what they were throwing away. The extraction work in France was done at the Pasteur Merieux Institute in Lyon. They collected placentas from all around the world, particularly Western Europe, but also the United States. I went to Pasteur Merieux and said, "We want the tissue that you discard. We'll give you money to build a plant." Five million dollars was tough money for us, but I said, "We'll tell you what we need and build the plant next to yours, so we can process the tissue." We would then send the enzyme to Cambridge for purification, modify the glycosylation, and then send it to Albuquerque, New Mexico where it was put into vials by an Italian company. The French thought we were crazy, but they didn't want the tissue, and they knew it was for treating kids. We said, "We'll take all the risk and give you some royalties."

We didn't need this forever because we were working on recombinant methods. We built the plant and it became a great success. We processed almost 70 percent of placentas from all births in Western Europe, and 30 percent of placentas from all births in the United States. They found their way, through mechanisms that are a long, long story to explain, to our plant in this little town in France outside of Lyon. Then, after the vials were filled in New Mexico, the product would go around the world. We saved the lives of a thousand kids. The HIV concerns

were all resolved because of the new technologies that we had put into place. We developed our own, because we had a starting point that was completely independent. The plasma industry had to come out of the past and adapt to new a technology. They came at it quite differently than we did. The facility in France was operational by 1990.

EVERSON: Before FDA approval?

TERMEER: Yes. In fact, having the plant helped in obtaining approval. There was a big discussion during the advisory committee meeting at the FDA about whether the French knew enough about HIV to be trusted. Remember, this was many years ago. There were a lot of people pointing fingers. Ours was the only placenta-derived product allowed by the FDA. The difficulty with placentas is you can't test unit by unit. With plasma, you can test unit by unit and so you can minimize cross-contamination. With placentas it was not practical, although we had technologies for decreasing viral load.

EVERSON: Was the research around the recombinant product underway by 1990?

TERMEER: We started to work on it in 1986, but we were amateurs with recombinant DNA technology. Despite the fact that we had a good scientific base, we didn't have a critical mass in that area. We were looking for either a way to continue developing it ourselves, buy access to the technology, or merge with a company that had the technology. We looked at a company called ZymoGenetics, which is a recombinant, protein-based company in Seattle. We negotiated to acquire them, but we lost to Novo Nordisk, who already owned a significant share. ZymoGenetics became 100 percent Novo and then was spun out; now it is an independent company.

After we lost that deal, we looked at Integrated Genetics, which was a very successful company in the Boston area. It came out of MIT and had an ex-Baxter executive running it, Bob Carpenter. He's still on our board. They were 90 percent focused on mammalian cell technology and they were competing for t-PA. They were in the clinic for t-PA in Japan and Europe, with Factor VIII for hemophiliacs. They also worked on albumin and protein C, which was later developed by Eli Lilly. They were working with erythropoietin as well, and were number two or three in all of these products, although the patents were held by other companies. They knew a lot about mammalian proteins, and CHO [Chinese hamster ovary] cell production, and glycosylation. All of these things had come together at their pilot plant. They had all of that, but were having a hard time. They were late to the party. Everybody was working on the same things in those days, but Integrated Genetics was doing well among the latecomers.

We talked with them for about a year and a half before consummating the merger. It was an interesting financial equation. They had only research contracts with large companies like BASF and others for the development of big proteins. They were losing a million dollars a

month and we were breaking even, even though we had no contracts or fancy recombinant technology. The merger was very high risk. People knew us to be very sound in the field, with one solid goal. They knew that Integrated Genetics was a tremendous technology player, but behind on patents. We were afraid that if we merged, we'd have shareholders who didn't understand each other, who owned shares for different reasons. We overcame all of our fears and said, "It's better to do this than for us to reproduce years of experience."

We merged the two companies and it was a fantastic success. The combined valuation was close to a one hundred million [dollars] and stock went from nine dollars to sixty dollars in a three-year time frame. I forget the precise numbers, but it was a fantastic success. Generally, the marketplace said, "Here's a good business model coming together with a good science model, and they're local." They were absolutely right, because it worked. Today, there are twenty-five hundred people employed at Integrated Genetics in Framingham. Integrated Genetics' chief scientific officer became Genzyme's chief scientific officer. The recombinant replacement for Ceredase became Genzyme's first approved recombinant product. We were able to get rid of the placenta technology by the mid-1990s. The recombinant process and the first recombinant product were approved in 1994. Our big Allston plant, next door to the Harvard Business School, was built around the recombinant technology. That facility was approved in 1996. We haven't used placentas for years. Many of the more traditional biological science components at Genzyme were acquired through the merger, which was enormously important from a value-creation point of view. We did the transaction in 1989. We agreed to it in April and closed it in August. The stock price was positive. By September, I felt confident enough to do an R&D limited partnership, this time through Evans-Freke, to finance our hyaluronic acid program in biosurgery, an anti-adhesion product, which today is a very successful program. In October, I decided to make an offer to buy back the first R&D partnership, which had financed the Gaucher program, and we did a secondary public offering in late November. That injected a significant amount of money into the company. It was an enabling merger, with tremendous leverage, and the stock price kept rising. It built the corporation up materially and changed many aspects of what we did. By 1991, the first product for Gaucher disease gave us tremendous credibility. By that time, we became convinced that you could do almost anything if you had something that worked. It provided a tremendous boost to the culture. We embraced the value of persistence, not giving up on things that are worthwhile, and taking big steps even if success is a long shot.

EVERSON: Was the location of the manufacturing plant near the Harvard Business School accidental or intentional?

TERMEER: In 1991, just before we decided to put it there, we had an annual meeting, the first after the merger. We had decided to start building the plant ahead of having the technology ready. At the meeting, we said, "We will need to build a recombinant plant and we've got to build it in North Carolina." We thought about Berlin, Belgium, and Scotland. We never gave any thought to Massachusetts. The next day, the governor of Massachusetts, Bill Weld, called me. He said he'd read in the *Boston Globe*, "Genzyme will build in North Carolina, not in

Massachusetts.' The journalists were upset about it, but we felt that the culture in Massachusetts was not right for that kind of manufacturing. Weld showed up in my office the same morning, and said, "What's the matter?" I said, "You don't build this kind of a plant in Massachusetts." "Why not?' he asked. I said, "It's Taxachusetts"—taxes, unpredictability, instability, abusive legislature, permitting, and all that kind of stuff. You can't predict when you're going to get permitting. Every city makes its own rules. You spend enormous capital with manufacturing. You'd like to do it next-door when you're young and new, and you have few scientists, but unfortunately we couldn't do that. North Carolina was the next best place, because they had experience in manufacturing. Bill said, "Henri, I want to convince you that you can do it here. Why don't you advise me on what to do differently?" I pulled together a group of about fourteen CEOs and advisors to CEOs—lawyers, auditing firms, accounting firms and so on. We met, made a list, and provided a report to the governor, saying, "If you do something about all of these things then you may create an environment where we can consider manufacturing." He said he would, and I took him on his word. The following year, all of the changes were implemented. Genzyme was given special treatment in terms of getting permits. The city came up with the site along the river. The neighborhood had rejected the John F. Kennedy Presidential Library and Fenway Park. They didn't want those things, but they embraced biotechnology, and we received permits within four months. Becoming operational was fast, but the engineering presented great risks. A young company that hasn't done this before depends on advice. We had no one in-house who knew how to do this, but Charlie Cooney, and Tony Sinskey, from MIT, and United Engineers from Philadelphia knew how. We took some big gambles on perfusion technologies that weren't used by Genentech or anyone else.

EVERSON: Can you describe perfusion technology?

TERMEER: Perfusion technology is a fermentation process, similar to continuous technology using micro carriers. We didn't use deep tanks. We used relatively small 2,000-liter tanks that were continuously harvested. It was very high risk and it happened fast. Much of the process was developed while the work was going on. We knew that the plasma product worked, but we didn't know whether the recombinant product did. The suspicion was that we would have a difference in immunogenicity between the two products. It turned out that the recombinant product worked very well. It was an improvement. The visibility of the effort was enormous. Twenty-two million people drive along that road each year. They saw the work going on and the papers were filled with news about it. Weld thought this was the best thing that ever happened to him.

EVERSON: Putting a manufacturing plant in the spotlight seems unusual.

TERMEER: It was a very unusual location, but the city's promises and its willingness to expedite permits were very convincing. In addition, it was a very visible statement. I liked that it was a manufacturing statement. It was Genzyme saying, "Yes, we are here." I didn't like many

of the sites that were offered in other states on beautiful hills where you had to move loads of trees. You got a nice view, but sent the cows home. It didn't feel appropriate for an industrial site. The plant became an opportunity to put the company on the map in Boston in a significant way.

EVERSON: Was the building designed to showcase manufacturing?

TERMEER: It was built for transparency, so you can see the reactors and how it all works. It's all a matter of taste whether you like the design. The architectural critic of the *Globe* didn't like it. He felt it looked too much like a cathedral and not enough like a plant. That was his view. We won numerous awards and people still comment that it's a great building. I have to admit, it does look a bit like a cathedral. Looking at it with the architect was a lot of fun. We worked on Saturdays. When you're on Memorial Drive, you can look to the Boston side and see the Harvard Business School with all the red brick. Then you see the parking lot, and it had to fit this picture. It did in the end, and it's now a very well-known unique landmark. Harvard's going to build a very large science complex in Allston, which is what [Harvard President] Larry Summers wanted as a great legacy, but couldn't execute. When I went to Washington—which I did many times because Genzyme's orphan drugs became a lightning rod for cost of treatment debates—people knew the building. [President William] Clinton said, "Oh, you're from Genzyme—with that building. That's where your office is?" I said, "No. That's the plant. My office is in some place you couldn't find." Genzyme, like many others, was a young, unknown company and that was part of getting on the map. It's the best economic decision we ever made. Today, there are three products manufactured there. The plant operates day and night with fantastic output.

EVERSON: I'm curious about the general lessons that you might have learned from producing Ceredase and then Cerezyme, particularly involving patients and their families.

TERMEER: There were numerous lessons. The first one we learned is that, even if it seems impossible, you have to try. That's a big lesson, and we've applied it a number of times since. If it is worthwhile, then you can get people onboard, even the greatest cynics if you work hard enough and long enough. The power of effectively treating a chronic disease, particularly when it involves children, is massive. We know that, in cases of chronic disease, not finding a product is devastating for patients. Once you start and you have a positive effect, you can never stop, which is a very big lesson that we've discussed at the board level. We've done many of these products now, and we know we can't stop once we see results, because the patient relies on it. We also cannot say, "I'll treat you, but not you, because you can pay and you can't pay." It's like saying "We treat people with HIV in the United States, but not people in Africa." In healthcare, you get very strong support from the public, but you have to be fair. That was another very big lesson. You need to make these things available to all patients, whether they

are in Africa, Sri Lanka, or Vietnam. There are healthcare system limitations around the world, but you can't rest until you get there.

We've made good progress. Treatment of Gaucher disease is more broadly distributed today than for hemophilia or any other similar disease. We treat people in countries where we will never get paid for it, and at the same level of therapeutic efficacy in terms of following the patients in registries and training physicians. It's quite interesting that when you do this long enough, you see that society will say, "OK you did your bit. We want to make a contribution. We want to take responsibility." The Vietnamese health minister came here recently. He heard that we were treating two siblings. It was very difficult to import biological products to Vietnam, but we figured out a way to do it. Those kids are doing very well. It had an effect on the hospital, everyone's curiosity, and so on. He said, "This is fantastic. Why are you doing this?" He went to Washington and raved about what we were doing and how grateful he was. It had a motivating effect on our employees and on the community of Gaucher patients, who today can be in contact online. It's also motivating for physicians, who can now talk about treating these patients. It affects politicians, the people who make rules on pricing and payment. For example, Canada doesn't like to pay for anything, but it likes this product. They say, "OK, we have to do our bit." Creating an orphan drug policy that's sustainable and that's not discriminatory is key. We don't discriminate, we sell on one price or it's for free.

Another lesson is that the world is as flat as you can imagine. That attitude carried us to Japan in 1987. Today we have a very good company there. We're in most European markets, Israel and many Latin American markets: Brazil, Colombia, Chile, Argentina, Mexico. We have free drug programs in many countries, and recently made big breakthroughs in Russia, where they've started to pay for the drug. In some places there's no infrastructure and nobody but maybe a patient or a physician who may have heard about it. The internet makes it easier for people to be in touch with us. Now we have four products in the same category. The last one, approved this year, is Myozyme for Pompe disease, which is another beautiful story for another time.

EVERSON: Fabrazyme wasn't approved until 2003 in the US, but work on it began in the 1980s at the Mount Sinai Medical Center, correct?

TERMEER: No, Mount Sinai produced a mouse model of the disease in 1995, but the NIH did the early work on the enzyme, agalsidase beta. We were working with the NIH in the early 1980s, extracting the enzyme from placentas, supplying Roscoe Brady and his group at the same time we were working on glucocerebrosidase. It wasn't until Mount Sinai established the knockout mouse model that we felt we had something therapeutically useful. That accelerated the project and product approval.

EVERSON: Was Brady's group doing clinical experiments?

TERMEER: They may have done some clinical experiments, but there was no confidence that anything really worked. Nobody understood where it needed to go. We knew that Gaucher disease affected the spleen, but we didn't have the same kind of understanding for Fabry disease. It was much more in the vascular system.

EVERSON: Was the enzyme shown to be effective in the knockout mouse?

TERMEER: The recombinant enzyme showed efficacy in the mouse model. That's when the project really accelerated. In the early 1990s we shifted from using the placental enzyme to the recombinant enzyme. At that point, the NIH was no longer involved. They felt a little bit left behind in this process. Several of the highly specialized labs had become fairly competitive. Mount Sinai had done a lot of the early pioneering work. They licensed some patents to Genzyme, so our work continued with Mount Sinai. Robert Desnick was the lead investigator behind the program, which generated quite a few inventions, including this one.

EVERSON: Let's talk a bit about BIO [Biotechnology Industry Organization]. What was your early role and what involvement did you have in the merger between IBA [Industrial Biotechnology Association] and ABC [Association of Biotechnology Companies]?

TERMEER: I was on the IBA board for a number of years. It became obvious that having two trade associations was very silly and inefficient. People began asking, "How can we do this better? How can we merge?" There was resistance until the chairman at IBA, a guy named Steve Duzan, who was the CEO of Immunex, made things happen. Constructive discussions started, both boards approved consolidation, and we merged to form BIO. Kirk Raab, the CEO of Genentech, became the first chairman of the new group. Carl Feldbaum became the executive director. The previous directors of both organizations left. I became vice chair, and then the second chairman two years later.

This was a busy time in Washington for biotech and pharma. Hillary Clinton was building support for healthcare reform. The biotechnology industry was still very vulnerable and decisions made in Washington had an impact on its financial health. There was a lot of fighting about orphan drugs. There was a lot of in-fighting among companies about patents, especially between Amgen and the Genetics Institute, and XOMA and Centocor. We weren't fighting with anybody, which helped me become the chairman. Nobody else was focused on Gaucher disease. Hillary Clinton thought that the price of Cerezyme was too high. People in Washington began to call for a price control system for breakthrough drugs. One very famous politician asked, "What if one of you guys comes up with a treatment for HIV? You can charge any kind of price." I gave many speeches about this. I said, "The problem is not that we have a treatment for HIV. The problem is that we don't have a treatment for HIV." The virus was killing millions of

people all over the world. Trying to control the pricing of a non-existent cure was a little premature. I advocated that it was important to create incentives to look for a cure.

That was the back and forth of those days. It was an interesting time. It was very dangerous for the industry when Hillary Clinton was trying to create a breakthrough pricing control system. Fortney Hillman "Pete" Stark, Jr., a US representative from California, was aggressively against the pharmaceutical industry. His mantra was "price controls, price controls, price controls." It was a difficult time. Wall Street dried up, the industry dried up, and many companies had to let people go, slow programs down, and halt licensing activities. Then, in 1994, it became clear that the Republicans would take over the House and that healthcare reform would not progress.

EVERSON: Were the IBA and the ABC generating mixed messages?

TERMEER: Yes, because they represented different sectors of the industry. One represented mainly early stage, small companies while the other advocated for the needs of large companies that were close to commercialization. Both groups agreed on fundamental issues like supporting technological advancement through education and NIH funding, but they differed on issues such as intellectual property protection and orphan drug status. They also had different agendas in terms of FDA regulation. When you have products awaiting approval at the FDA, you have one set of concerns. When you don't know whether you'll ever get a product to the FDA, you have another set of concerns. Small differences of opinion became big differences. Was it a disaster? No, but it was inefficient. It was not one voice. Merging was a great success because the two groups were meant to be together.

EVERSON: Who initiated the merger?

TERMEER: Informally, people on both boards talked to each other about it. Steve Duzan of the IBA and Thomas G. Wiggans of the ABC started the discussions. The IBA board in particular told Steve and the executive director, "Get on with it and try to accomplish this." Thinking back, I don't think there were great uncertainties. It was a young industry, and even the larger companies were still young companies. Eventually, they merged and renamed the organization.

EVERSON: What role did G. Steven Burrill play?

TERMEER: Steve played a role at Ernst & Young. At the time, he was writing a book. Steve was on the accounting and research side of the equation. He set up the annual meeting in Laguna Beach [California] that has become very important over the past twenty years. That was

a tremendous contribution. He wasn't very involved in BIO and or Washington; he wasn't very involved in policy formation, then or now. He serviced the industry as a banker, but he didn't lobby for the industry. He was trying to understand the industry and he explained the industry. He gave frequent speeches. People could learn a lot about the industry by seeing it through his eyes. He wasn't involved in passing the orphan drug law, getting PDUFA [the Prescription Drug User Fee Act] implemented, or thinking through issues related to CMS [Centers for Medicare and Medicaid Services], but he deserves a lot of credit for bringing people together through meetings.

EVERSON: I'm interested in his Laguna Niguel conference.

TERMEER: I've been to all twenty meetings. It's a great place to observe the evolution of the industry. Brook Byers and Fred Frank have also been at every meeting, but it's very much Steve's meeting.[2] It's his baby and we all acknowledge that. He's been a great friend to the industry.

EVERSON: You became chair of BIO in 1995, and were chair for two years. The FDA Modernization Act [FDAMA] was passed in 1997.[3] What role did BIO play and what role did you play?

TERMEER: BIO played a big role. Senator Edward Kennedy played a very big role. He was very powerful force.

EVERSON: Could you explain PDUFA?

TERMEER: PDUFA was about user fees. That marked the beginning of a campaign to get better support for FDA review, which meant implementing benchmarks, establishing responsibilities, and organizing the review process. Kennedy effectively forced David A. Kessler, the FDA Commissioner, to speed things up. Kessler had been a very tumultuous commissioner, and is remembered for seizing 24,000 gallons of orange juice that was made from concentrate but labeled as "fresh." In later years, he tried to create a legacy; FDAMA became that legacy. At BIO, we developed a team of CEOs supported by staff. I was supported by a fantastic person, Lisa Raines, whose name you may have heard. She was at BIO before me, in charge of legal and government affairs. She became my assistant in Washington. She was

[2] Frederick Frank, interviewed by Mark Jones at Peter J. Solomon Company and via telephone, 25 May 2011, 14 September 2011, and 16 August 2013 (Philadelphia: Science History Institute, Oral History #1005, in process).
[3] The United States FDA Modernization Act of 1997 amended the Federal Food, Drug, and Cosmetic Act, passed in 1938, to reflect changes in the way FDA operates in the 21st century. The main focus is the acknowledgment in the advancement of technological, trade, and public health complexities.

brilliant. Everybody agreed that she was extremely talented at getting legislation defined, stating how to do things, and writing them out. Tragically, she was killed in 9/11. She had been very active. Kessler was trying to support the indications he got from the Senate, and particularly, from Senator Kennedy. Kessler would meet with me—in fact, he had my home phone number and my cell phone number—and we would talk. Eventually, FDAMA became a reality. The fast track provision was created which was hugely important. The fast track attitude was, "We can do things differently and more efficiently without giving up on the standard of care and the gold standard of approvals." Industry wants a strong FDA, but an FDA that has the courage to make decisions and to move forward, and is able to say, "Do this, but not that.' The industry doesn't want an agency that equivocates, or says, "We don't dare." With FDAMA, the FDA had a much better understanding of how it could serve society by being more streamlined. BIO played a large role and I was lucky to be a part of it. It was exciting.

EVERSON: Did you and BIO work with PhRMA [Pharmaceutical Research and Manufacturers of America] on FDAMA?

TERMEER: Very little. Those were not the best days for PhRMA. We recognized each other and had a high degree of cross membership, but we didn't really work together as much as we do today.

[END OF AUDIO, FILE 2.1]

[END OF INTERVIEW]

INTERVIEWEE: **Henri Termeer**

INTERVIEWER: **Ted Everson**

LOCATION: **Genzyme Corporation**
Cambridge, Massachusetts

DATE: **2 August 2007**

EVERSON: Last time we spoke, we ended by discussing your involvement with BIO. I thought I'd pick up by talking about the Genzyme products launched in the mid-1990s, like Seprafilm, Renagel, Thymoglobulin, and Myozyme.

TERMEER: So, now we're into the 1990s. I'll talk about the Genzyme products launched in the mid-1990s, including Seprafilm, Renagel, Thymoglobulin, and Myozyme. I'll start with Seprafilm, which is a product for the surgical field. It's hyaluronic acid, a biopolymer. When I joined the company in 1983, we had, as I said, the eight scientists from MIT. Shortly after I got to know them, I asked for their resumes and publications. Each had about two hundred publications. I found that one of them, Professor Cho Rha, was working on hyaluronic acid and supervising a postdoc in the field. I was familiar with hyaluronic acids from a company called Biomatrix. The owner of Biomatrix, Dr. Endre Balazs, is the grandfather of hyaluronic acid indications. He had tried to recruit me to be the CEO of Biomatrix. I declined because he had a very strong personality. I saw there little space for anybody else. That was probably a wise decision, but in the process, I got to know a lot about hyaluronic acid. Biomatrix developed the first product for ophthalmic surgery, called Healon, which was marketed by Pharmacia, and is still very successful in the marketplace today. In any case, I was intrigued by Cho Rha's work. I asked Cho to tell me about hyaluronic acid and she was very energetic about it, and, in particular, a microbial method of producing it. We talked about all of the different clinical indications the material could have, including surgical indications. Then I said, "Tell me about your postdoc," and she told me a very energetic story. I said, "Let me meet this person."

In 1983, we were a tiny company, but when I met Rha's postdoc, she impressed me as a very entrepreneurial young lady, and she had great ideas about hyaluronic acid, so I hired her. We brought her in and started to work on hyaluronic acid. We didn't copy what Biomatrix had done, but created a different way of manufacturing it, and brought it to the marketplace for different purposes. We were involved with hyaluronic acid research since the beginning of 1984. We first worked on an indication using fermented HA [sodium hyaluronate] as a viscoelastic surgical aid. That became a successful product called Provisc. Alcon marketed it. They're still selling it, and we still produce it. It's the leading product in the ophthalmic surgical space. Then we started to work on other indications. We found a way to produce anti-adhesions post-surgically, and got the Seprafilm program. We raised money for it, and, in 1989, did an R&D partnership specifically to develop hyaluronic acid for post-surgery anti-adhesion

purposes. We took it through clinical trials and received FDA approval. Today, it's the leading anti-adhesion product in the United States, Japan, and France. It has many applications, particularly in abdominal and gynecological surgery. We haven't developed other markets, but we're still working on it. It's growing very rapidly in the US as a product used in abdominal surgeries. A lot of adhesions occur during C-sections. If a woman wants to have a second child after a C-section, Seprafilm reduces post-surgical adhesions and significantly decreases the difficulty of delivering a second child. It is very broad-based and I'm very proud of it. We ended up buying Biomatrix. They had the leading treatment for osteoarthritis pain in the world—a modified form of hyaluronic acid injected into the knee joint. Today it's a very large product for us with profits in the hundreds of millions of dollars.

EVERSON: Synvisc, the drug for osteoarthritis pain, is quite a change of pace from Cerezyme. Was that the first step you took in terms of diversification? Was diversifying a conscious decision?

TERMEER: It was very conscious. The decision to work on rare orphan drugs, and the broad-based hyaluronic acid program, was made very early on. It was based on the hedging effect that we could create, due to the availability of an early market, and the uniqueness that we could bring in terms of going from rooster combs to microbial fermentation via the MIT connection. In the case of Provisc we had a market within reach. That went very well. I'm pleasantly surprised by Provisc's longevity. In 1991, enzyme replacement therapy was introduced for Gaucher disease. Today, in 2007, the product is still growing each year. The first product for hyaluronic acid was also approved in the early 1990s. We started work on that in 1984, and it's still growing every year. Now we're the lead program, from a market share point of view, in ophthalmic surgery through Alcon, and in anti-adhesions and arthritis knee pain, through our own sales and marketing organization. When we present our company to investors, we say, "Look at the facts—we're spending to improve these programs." The longevity of our innovative products has been fantastic. I credit our success to fortunate choices. Vertical integration was the key, along with manufacturing expertise that enabled us to by cost-competitive, and to improve each year. We made several fortunate choices, to tell you the truth. We chose good materials, and good advisors.

EVERSON: It seems to me that vertical integration, and good communication across R&D, manufacturing, and marketing must help once you find new indications.

TERMEER: Absolutely, we need to stay ahead of the curve. We've been able to stay ahead of the curve because we understood the importance of the big biotech innovations and breakthroughs of the past twenty years and took action on them. Many companies are too narrowly involved in one area. It's tough to see that through. Genzyme has been lucky. For us, broad involvement has always worked well. We recognized, for example, when the opportunity

presented itself, that polymers were a promising technological field. When Renagel became a possibility, we jumped on it.

EVERSON: Let's talk about Renagel.

TERMEER: Renagel is a polymer-based drug that was created in the mid-1990s around technology that came out of George Whitesides' lab at Harvard. George was one of our advisors, so we had a close relationship. We tried to bring the technology to Genzyme, but we couldn't find the right connection. Then I became a board member of a new company called GelTex. Bob Carpenter was also a board member at GelTex and Genzyme. Whitesides became a board member, and we hired a good friend of ours, Mark Skaletsky, as well. He had been the chief operating officer of Biogen, and then moved to Enzytech. He sold that company to Alkermes, and became CEO of GelTex. Henry Blair was also on the Genzyme and GelTex boards. The company developed non-absorbed polymers—polymers designed to bind things: iron, phosphate, or cholesterol, for example—and transport them through the gut to be discarded naturally. It was a non-systemic approach.

Early on, GelTex developed a method to lower LDL [low-density lipoprotein] cholesterol, and a method of phosphate management. The phosphate management approach generated great interest at Genzyme because it had great clinical potential. The cholesterol-lowering statins were doing well, so we made an arrangement in the late 1990s, at arm's length. I excused myself from the board, and Genzyme made a fifty-fifty arrangement with GelTex—they were the developer, and we became the marketing arm. We successfully introduced products in the United States. At first, we had to explain why our treatment was ten times the cost of the current treatment, which was calcium. But Renagel had great potential that has now been proven in clinical trials—it lowers the LDL, doesn't involve calcium, is non-systemic, and effectively manages phosphate. We worked continually on clinical trials to improve our clinical knowledge. Once the product started to take hold, I felt we should own it and the technology. I went to the GelTex board and said, "We'd like to integrate these technologies into Genzyme and take full possession." We did it. During the first step, we were the distributor and the marketer, and the deal cost about twenty-five million dollars. We built our sales force, and split the profits evenly.

The second part of the deal cost well over a billion [dollars]. We created tremendous value for GelTex by making Renagel look like a real commercial product. It was a great success for GelTex's investors, and for Genzyme, as well. The product is still very important for us. It's very successful around the world, and generates close to six hundred million [dollars] in annual revenues. GelTex was a more or less virtual operation. They didn't have manufacturing. We bought the factories and brought costs down, which helped them create a successful enterprise. Every year, the margin improves because we develop better manufacturing practices. We now have a second-generation form of the product in front of the FDA. We're hoping it will be approved for dialysis patients and CKD [chronic kidney disease] patients. The product brought the non-systemic approach to Genzyme, and it's got a great future because it's much safer. It led

to the cholesterol-lowering program that we're now introducing in Europe. The program is directed toward patients who don't benefit from statins or Zetia. They're relatively small in number, but large enough by our terms. We're second in the marketplace with patients who are very sick and need help.

EVERSON: Is it marketed to those patients as Renagel?

TERMEER: No, the brand name is Cholestagel. In the US, it's marketed by Sankyo. GelTex has made arrangements in which it's called WelChol. It generates about two hundred million in annual revenues for Sankyo in the US—we started much lower in Europe. We're completely vertically integrated. We do our own R&D, and all the manufacturing, clinical development, and marketing, except when GelTex has already made other arrangements in the US.

EVERSON: Clearly, Genzyme still looks externally for promising research. Once you make those agreements, is there a fairly conscious effort to become vertically integrated around that technology?

TERMEER: Yes. For almost all the transactions we've done, we've integrated the company. GelTex was located in Waltham, Massachusetts. They had about one hundred and fifty people. We've doubled the size of the facility—they now employ between three hundred and four hundred people, so that's a positive experience. The same is true of Biomatrix and ILEX Oncology, the company that got us into cancer. We always hope to acquire talent and enthusiastic employees, and to create an infrastructure that works. Only in the case of one product did we close the doors because there was no critical mass. But in most cases we've persevered.

EVERSON: Do these companies remain independent entities within Genzyme?

TERMEER: GelTex is no longer called GelTex—the name disappears over time. But the entities exist as divisions. It takes a particular attitude and tolerance, and that skill to permit and ensure it has developed within the company over many years. Now, before we do a transaction, we can say, "Talk to this group or that group. They became part of Genzyme." You don't persist in these things unless it works consistently.

EVERSON: Johnson & Johnson employs a similar strategy. Do you see it as similar?

TERMEER: J&J has as a very similar model, but it's more mature. They benefit greatly.

EVERSON: You mentioned that the technology involved non-absorptive drugs. Have other new drugs been developed on the platform?

TERMEER: Yes. There was one drug that unfortunately didn't work in Phase III called Tolevamer. It was developed to treat patients with *C. [Clostridium] difficile* colitis. It absorbed the toxins A and B, which cause diarrhea. It's a nosocomial infection. We took it to Phase II, and then did the largest Phase III we've ever done. We spent a lot of money. When we opened up the first Phase III trial, we were short. This happened very recently. We had other things succeed in this timeframe, but not this one. We measured Tolevamer against vancomycin and metronidazole. It was a non-inferiority trial and a superiority trial in terms of recurrence, but we couldn't prove non-inferiority in terms of resolution. We were superior in terms of recurrence, but that doesn't matter. You first have to solve the problem. It didn't solve the problem very well. It simply wasn't good enough. That's a hard lesson. We've had very few experiences where we've made deep, long-term investments and things didn't pan out. This was one of the very few.

EVERSON: What about Thymoglobulin?

TERMEER: Thymoglobulin is a typical Genzyme product used for the induction of tolerance or to prevent acute rejection of solid organ transplantation. It was a product marketed by a company called SangStat. They were headquartered in California, but had a very large manufacturing operation in Lyon, France. Many years earlier, we had built a factory on this same site to extract glucocerebrosidase. The SangStat product has done well. It's the leader in its field for saving people's lives. The indication is very narrow, but it's very important. It's difficult to produce. The process is the product, actually. The opportunity appealed to us for many reasons. Many other indications become possible when you influence the immune system in the way that this particular product does. We're looking at a number of them, including type 1 diabetes. In the meantime, the product is doing quite well in the area of transplantation. We went to France and took over the manufacturing. We're building a new factory in Lyon. We're working on new indications, and we've taken over the sales force. We're adopting a global pricing approach. Previously, there had been a big disconnect between prices in country A and country B. Lining these things up can be a painful process, but we're going through it in a systematic way. Last year, we acquired a company called AnorMED, which is working on a stem cell mobilization technique. We recently announced two Phase III trials. In one, we announced—just yesterday—a successful result in increasing stem cell mobilization and harvesting for transplantations.

EVERSON: Was SangStat marketing the product for a while?

TERMEER: They were marketing in the US. They were marketing overseas through a few different outfits, but it was very thin.

EVERSON: What about Synvisc?

TERMEER: Synvisc came out of Biomatrix. That's a hyaluronic acid product for osteoarthritis. We haven't discussed Campath and Clolar. A few years ago, we acquired a company called ILEX, in San Antonio, Texas. We had been working on R&D in oncology for a long time because we were naturally primed to appreciate the narrowness of oncology markets. We were excited about what biotechnology could do for them. We spent a lot on R&D in the area over five or six years, but still didn't get to a product. Eventually, we took the plunge and acquired ILEX, which had Campath, and was in the process of getting FDA approval for Clolar. Both had very narrow indications, but they were important for pediatric leukemia and CLL [chronic lymphocytic leukemia]. ILEX had also started a clinical trial of Campath for the treatment of multiple sclerosis. A year and a half ago, we got the results from the first year of the trial, and then last year we got the results from the second year. This year we'll get the third-year results. So far it's highly successful. It has a 75 percent treatment effect against Rebif, both in progression and relapse. This result led us to enter into the Phase III clinical program. It will take a long time and hundreds of millions of dollars, but we're confident that it will completely change the way in which we think about the treatment of MS. With Campath, you treat the patient once a year, twice at most, since we don't know how long you can avoid relapse. It completely changes the way you treat this disease. It's not insignificant, because by the time we get to the endpoint of the trial, probably sometime in 2011, the market will have grown from five billion to seven or eight billion dollars.

EVERSON: What's the technology?

TERMEER: It's difficult for me to explain. It's a monoclonal antibody that attacks and kills T-cells. It can also be used for induction in the case of transplantation. In that realm, it competes with Thymoglobulin. It does pretty much the same thing as Thymoglobulin. It's a miracle antibody, but it's quite toxic. You have to be careful. There's a risk management program that comes with it because it can cause ITP [idiopathic thrombocytopenic purpura]. The risk management program ensures the identification of platelet effects. Campath came originally from ILEX, a company that has a thriving facility in San Antonio. The acquisition was truly additive. We're now in late stage oncology trials. If we can show that Campath can be used safely, it will have the most transforming effect that we've seen. It will become the largest single multiple sclerosis product.

EVERSON: Should we move on to Myozyme?

TERMEER: Yes. Myozyme is a very interesting story. It treats Pompe disease, a rare genetic condition, a lysosomal storage disorder. Glycogen accumulates in muscle cells causing them to clog up. Patients with severe cases die within twelve months after birth. Sometimes the heart gives in, and they die very quickly. In cases where patients have some residual enzyme, there is a much slower progression of the disease. Patients are affected as adults, and may end up in wheelchairs with respirators. Eventually they become totally dependent on others. You need to start treatment within the first six months, but the disease is progressive and most patients do not live long. Myozyme is the missing enzyme. When we delivered it to patients, we saw an effect, but it followed an incredibly convoluted route in the body. Two excellent biomedical researchers were working on this—Arnold Reuser, in Rotterdam, and Y.T. Chen, at Duke University. The Rotterdam team developed a relationship with a company called Pharming and started to produce the enzyme transgenically in rabbits. Chen worked with a Chinese company called Synpac. They produced it in CHO cells. We prefer to use CHO cells, but when we looked at both programs, we chose to work with Pharming because they were about to go into the clinic and had access to a very large clinical practice in Rotterdam.

A critical mass of people interested in Pompe disease had formed in the Netherlands. Patients came from all over the world to be infused with the enzyme. They had some success but they needed massive amounts of enzyme to treat patients, and couldn't get enough rabbits. They went so far as to plan a factory in Belgium that would breed tens of thousands of rabbits, but it would have been impossible. Eventually, the company couldn't uphold its part of the bargain with us, which stipulated that it would pay half. We were paying half. They asked for loans, but we said no. We bought the program from them. They still exist today, but they've moved on to different things. They couldn't afford this program. It was very interesting. Holland is a small country and nine patients were being treated. The company was going bankrupt, and the Dutch Parliament was discussing how to save the company so that the patients could continue to receive treatments. We were accused of being bad Americans who were not giving them the money to survive. We were on the news and in the papers. My mom asked, "Why are you not treating these patients?" I said, "Ma, it's OK that they complain. We'll treat these patients. Trust me. We won't let them down."

We made arrangements to treat the patients for two years. It was very costly. We reserved seventy million [dollars] to support the patients. In the meantime, we negotiated with Synpac. I went to Taiwan and made a deal because CHO cells were a more predictable method of manufacturing the enzyme, and we knew a lot about it. They were treating three patients at Duke, and at least two of them were benefiting significantly, but they couldn't reliably produce the enzyme. The cell line was unstable. We couldn't start a clinical program serious enough to prove that the replacement therapy worked. In the meantime, we started work on a different cell line. Another candidate line came out of a company called Novazyme. They had developed a way to target the enzyme so that, hypothetically, it could be one hundred times more effective. We bought the company. The story is actually in a book written by Geeta Anand from the *Wall*

Street Journal. It's called *The Cure*.[4] We also tried our own enzyme, the transgenic enzyme, and Synpac's enzyme. We put them all through the "mother of all experiments" and tested their effects. We said, "Whichever wins, we'll use that one." It turned out that the Genzyme enzyme was the most effective, and eventually it became an approved product.

We ran a clinical trial for eighteen babies at five centers around the world, including Duke, Tel Aviv [Israel], Lyon [France], and Manchester [United Kingdom]. We flew patients and their families to these locations for nine months. As soon as we found a patient and the parents were prepared to go, we would fly them to one of these centers. Without treatment seventeen of these eighteen patients would have died within twelve months. Those were the odds. All of them survived. That was a great success, and it became part of the filing package in Europe and in the United States. The treatment was approved last year in Europe and the United States, and last month in Japan. The critical part is that for this enzyme to work you need a very large dose—twenty times the replacement dose for Fabry disease, and something like thirty times the dose for Gaucher disease. You need large amounts of protein, and to make that work commercially you need a really effective and high-yield process. We had learned how to do it over the years because we had set up and operated protein manufacturing factories. That skill figured into the way we thought about our future. Today [August 2007], we're able to support Pompe patients. We have seven or eight hundred worldwide undergoing the treatment. The Allston plant has been approved by twenty-eight countries, but not the FDA. They want to have proof that the cell lines work on a large scale. That's a problem. We're currently running out of product for the US market. It's interesting from a bio-generics perspective. How will the FDA look at bio-generics? This is product that's being made by the same manufacturer with the same assays, and they're not prepared to give approval without clinical proof that the product has the same clinical effect as the product at a lower scale. It's extremely costly. What they do allow is for us to make the product available for compassionate use. It's not a safety question—it's a process question, a bureaucracy question. Even without FDA approval, we generated forty-seven million dollars in sales last quarter. It could grow to a billion dollars over time.

EVERSON: Where do you see it going with the FDA? Are there any indications?

TERMEER: We have a trial going on now for adult patients that will finish up in September [2007]. We will have the data in November. We know we're going to get there. When we got approval in April of last year, we announced that we had spent six hundred million [dollars] on this program through 2005. That is a massive amount.

[END OF AUDIO, FILE 3.1]

[END OF INTERVIEW]

[4] Geeta Anand, The Cure: How a Father Raised $100 Million-and Bucked the Medical Establishment-in a Quest to Save His Children, (William Morrow Paperbacks, 2009).

INTERVIEWEE: **Henri Termeer**

INTERVIEWER: **Arnold Thackray**

ALSO PRESENT: **Pei Koay**

LOCATION: **Genzyme Corporation**
Cambridge, Massachusetts

DATE: **18 December 2008**

THACKRAY: Henri, let's talk about Fabrazyme.

TERMEER: Fabrazyme, like Cerezyme, Aldurazyme, and Myozyme, is important for a lysosomal storage disease. It's a product that we're very proud of—it's the first treatment for a disease that had no treatment. It's important because patients develop severe medical problems such as kidney failure. They have shortened life spans. Fabrazyme is the missing enzyme like Cerezyme is for Gaucher disease and Myozyme does for Pompe disease. We are now treating these patients. It's very much a part of our orphan drug program.

THACKRAY: Where are the natural limits of this strategy?

TERMEER: That's a great question, Arnold. I think we'll see many more orphan or ultra-orphan treatments. We found that it's sometimes very difficult to find treatments that work across diseases. Diseases are highly specific. Personalized medicine, of course, will guide us to figure out what therapy is appropriate for individual patients. I think in the future we'll see a lot more of that. I would say we are at the very beginning of recognizing the potential of personalized medicine.

THACKRAY: I have a daughter who is the vice president of clinical trials at a biotech startup. I'm very aware of lab and clinical difficulties around any new drug. What is it that Genzyme in particular brings to the table?

TERMEER: We started our life with a highly specific therapy for Gaucher disease. It took ten years to establish this program. Essentially, we developed a personalized medicine. All of the products we currently have on the market or in development have similar characteristics. These programs are highly specific. The treatments are almost guaranteed to work, provided that the patient is correctly diagnosed. We bring effective therapies to the table. In terms of finding these

therapies, I don't think we can claim insights greater than anyone else's, other than to say that this is what we focus on. We try to get beyond trial elements in a very deliberate way. We keep looking until we find something that will benefit patients. We developed a broad-based diagnostic division in the company called Genetics/Diagnostics. We're currently the second largest laboratory in the country, and the largest in oncology and prenatal genetic testing. We've developed a genetic counseling capability. In fact, we're the largest employer of genetic counselors in the country. We employ about 10 percent of all genetic counselors nationwide. They are dispersed around the country to advise patients and parents on the outcome of genetic testing. They also sometimes advise physicians on how to communicate with patients. These operations are partially aligned with treatments that we offer, but go far beyond. We have only a handful of treatments. The counselors deal with straightforward chromosomal abnormalities seen in Down syndrome babies and amniocentesis, and more advanced derivatives of that kind of testing, like highly specific testing for breast cancer. We do about a third of all breast cancer testing in the United States. We run all of our operations as self-sustaining businesses. They're connected to each other, but they are run as businesses. We want to be as good as possible at running them. In this case, it means having very extensive IT and other capabilities because the work is extremely labor intensive. It involves hundreds of thousands of tests.

KOAY: What year did you start doing the genetic counseling?

TERMEER: We started in 1989, when we acquired Integrated Genetics, a company that had a small genetic testing business. They were in the race to figure out the gene for cystic fibrosis. They didn't win, but they participated. From that, we developed broader capabilities, but our focus is still esoteric in comparison to Quest or LabCorp, which are both multi-billion-dollar corporations. Genzyme's annual genetic testing revenues are maybe three hundred and fifty million dollars.

THACKRAY: Is Genetics/Diagnostics strongly or weakly connected to Genzyme's personalized therapies?

TERMEER: It's strongly connected, but that's not the only connection. All the work we do in terms of personalized medicine goes through that operation. For instance, we are more advanced now in introducing routine newborn screening for the lysosomal storage diseases for which we now have therapies. That operation, from a technology standpoint, helped to develop the tests. We qualified what we had on a global basis. We're involved with the CDC because we don't want to distribute reagents when we're the only suppliers of the therapeutics. We want to have an arm's length distance. In that world, the CDC has a lot of credibility. Screening is public policy, not medicine. For the most part, we screen healthy people. We supply the technology and we supply the reagent, free of charge. The CDC then distributes them to countries and states. This is a work in progress. In Taiwan, for instance, we test 100 percent of the newborn babies. Taiwan is the first country to test for Pompe disease. Austria is well ahead, as are Illinois

and New York. It's happening a little bit more each year. Our task, our mission, is to do the best we can for these ultra-orphan diseases. Because they are ultra-orphan, there is no critical mass of esoteric activities on the outside. We take a very comprehensive approach. Because the diseases are chronic, we've become a lifeline for these patients and their families. Because of the morbidity associated with these diseases we try to do this early. Newborn screening allows you to make decisions before it's too late. It's not a product on a shelf, it's a therapy. We provide the service of carrier testing through our genetic testing operation. You need two carriers in order to have this single gene disorder in some percentage of the offspring.

KOAY: Is it a co-development of the diagnostic test and a therapy?

TERMEER: It's not a co-development. We develop these diagnostics in a very deliberate way, and we involve many other people in the outside world.

THACKRAY: But the therapy came first?

TERMEER: Yes. Each of the therapies was very specific to a particular genetic disorder and was highly efficacious. The products work every time, so long as the patient is appropriately diagnosed.

THACKRAY: If I'm the Taiwanese Minister of Health, the good news is that you're helping me to identify problems in my population. The bad news is that you're helping to define a treatment expense that I might not have otherwise even known about.

TERMEER: The good news is overwhelmingly more important. Knowing something that allows you to avoid morbidity and other problems is similar to prenatal testing for chromosomal abnormalities. Parents have a choice.

THACKRAY: Is there a sense that ultimately all diseases will be orphan diseases because they'll be so specifically defined?

TERMEER: Many will be. Once you have a disease, it's likely to be highly specific. Regarding wellness, if you have high cholesterol, you don't have a disease, but you can get a disease. More philosophically, the world is likely to go two different directions. There will be programs that deal with defined and acute chronic problems and others that deal with managing wellness and staying healthy. They belong to completely different worlds. Education will play a large part in wellness. Wellness is about avoiding problems. The statins fall into that category

because they prevent problems. In a healthcare sense, that's almost un-financeable because every single human being is involved in managing wellness and health. I think we should take personal responsibility for our health. If you develop a chronic problem, like heart disease or cancer, we should, as a society, do our best to help you.

THACKRAY: At the BIO [Biotechnology Industry Organization] conference a couple of years ago [2010], former President Bill Clinton said, "We spend 15 percent on healthcare. We're the only country that does that. It's too high." Steve Burrill said, "We spend 15 percent on healthcare and it's going to 25 percent." Do you agree with Steve?

TERMEER: I don't necessarily agree with Steve, although as an economist, I cannot say that he's wrong. There is nothing more valuable than health. The frustration is that we spend a great deal and still have a lot of health problems. We still have Alzheimer's and heart disease. It's an employment problem. In Massachusetts, we employ four hundred sixty thousand people in the healthcare field, which is by far our largest area of employment. We have good healthcare in this state, but it is an expensive proposition. When it was published that healthcare employment in Massachusetts was being surpassed by Pennsylvania, people started saying, "We're losing our position." We should instead be saying, "How much health can we produce with three hundred fifty thousand people, rather than four hundred sixty thousand?" Of course, in order to improve efficiency, we need technological breakthroughs. But people have jobs and they have unions. It's just as difficult as making a change in undergraduate education. It's tough to do. People have jobs. That's why in India and China we ought to do it differently. They're in an earlier stage of development. We can build it up there in a much more critical way. We can look after the wellness part, but as part of a different equation.

THACKRAY: Are they receptive to that message in India and China? If you look at Genzyme's business globally and compare the percentage here and the percentage there, what's the trend?

TERMEER: The international market is larger than the US market. They're poised to develop over time. India and China are still very much at the beginning, but Genzyme is seriously developing its activities in those countries. In China, we're building a big research center outside of Beijing. We have offices in Shanghai and Beijing. The research center will do many interesting things, some of it uniquely important. I spent a week in India just around the time of the explosions in Mumbai. I was in Bangalore, and met with many people there. Among other things, we talked about what we can do to leapfrog treatments, technologically. In India, you have a capacity shortage: you have more than a billion people, and twenty-five million births a year versus four million here. It's an incredible number of people, and a very young population compared to the aging population in the United States. Of course, there's an enormous disparity in terms of efforts, but the capacity problem is particularly problematic. It's a democracy—

you're not free to help one person and not another. People notice. You have to be fair. You have to be ethical, otherwise it's not sustainable.

We talked to some high-level people in the government, some academics, and a number of companies. We asked what we have that suits India's market. In the United States and Europe you work with a saturated wealth, but then in India you work with a lot of capacity, poorly utilized capacity, and you work with well-compensated capacity. We came up with a number of very interesting things. We are currently doing some safety work here on gene therapy trials. We want to have control over the safety side. But in terms of development they say, "If you do that we'd be very interested because it allows us to leapfrog and we will learn from it, too, and we will be first maybe." They said, "We're going to do that." We will guarantee that we treat all patients. For those who can't afford it, it will be free of charge. For those who can afford it, we will charge. You pay one-third, the Indian government pays one-third, and we pay one-third. We do the clinical trials in India, and the whole deal is bracketed just for India. We are at the beginning in India. They get something that they otherwise would only have twenty-five years from now, and we get access to another environment that is not so saturated. The Indian companies don't have to try to develop a product that competes in this very saturated world. Everybody looked at the terms and said, "It's just too good to be true." It's very encouraging. But India and China are particularly interested, more so than Brazil. We have large businesses in Brazil and Russia that actually sustain themselves in a very good way.

THACKRAY: Are they equivalent to the American business?

TERMEER: Yes, very similar. The model in Brazil is quite different from what we would need in India and China. Taking a twenty-five-year view, India and China will become larger economies than the United States. We hope to be real participants in that.

THACKRAY: Henri, your own career has had three parts: shoes, Baxter, Genzyme.

TERMEER: Shoes first, assuredly.

THACKRAY: How many times has the mission and identity changed at Genzyme? You wouldn't use the same words today that you used on day one.

TERMEER: That's a very interesting question. Early on, we met with eight professors from MIT every Saturday and Sunday of late-1983 to figure out what we could do that would be new. We didn't want to just replicate what Genentech or Biogen had already done. We decided to do original things, and if we couldn't afford to do original things, we wouldn't do them. We do things that we can call ours. We work in a way that makes a real difference. We could never

have predicted our success with our Gaucher disease treatment. As we grew over time and our experiments yielded successful results, we felt a responsibility to continue our work. We try to pursue interesting opportunities and promising therapies. Our ability to see and seize those opportunities developed over time.

THACKRAY: Crucially between when and when? Was it clear in 1990?

TERMEER: In 1990, our best opportunity was the treatment for Gaucher disease, which was approved in 1991. We saw an opportunity, but everybody else said, "You're crazy." In the end, we were able to get it done. Eventually, our treatment went global. That experience taught us many lessons, including the responsibility to carry things through. It is not just an opportunity, or something of value – it is a responsibility to go to the next stage. We went to the recombinant form to manufacture more product, and make sure we reached all patients. We give free treatment in areas where support isn't available. I spent two hours today [18 December 2009] discussing a very complex set of dynamics in China. China is now opening up for us. We've established a path into the country, and people like what we do. However, we don't yet have an infrastructure there, so it will take some time.

Our responsibility is to get the treatment to patients as soon as possible. They're sick today. They need to get help today. China is so large that we need to make sure everything we do there is sustainable. It's a very complex equation in terms of time and money investments. We learned during the development of Ceredase and Cerezyme that it is our responsibility to recruit whatever kind of help we need. One interesting example is when Japan didn't allow us to introduce Ceredase because it was a tissue-derived product released at the height of the HIV crisis. As I told you before, we knew about thirty-six kids in Japan who were very sick so I went to the US ambassador, Walter Mondale, and he said, "Let's move these patients to Hawaii. We'll treat them there." Of course, when the Japanese heard about that they decided to approve the product. The lesson from that experience was that we were responsible. We had looked these patients in the eye and knew we had to do something about their treatment. That sense of responsibility is the backbone of everything we do at Genzyme. If you interviewed eleven thousand people employed at Genzyme, that's what gets repeated, because that is our purpose. It is bigger than any one of us individually. It is the current that drives us and it's stronger than stock prices, stronger than this, that, and the other.

THACKRAY: Genzyme has been positioned in these territories of orphan drugs and personalized medicine in a very broad way. Have you seen a shift in that sense of understanding?

TERMEER: Yes, although it has sometimes posed some challenges. Our therapies are expensive. In the UK, there's a group called NICE [National Institute for Clinical Excellence] that studied our orphan drugs with our collaboration and cooperation. They said, "Wow, this is

very expensive and we can't afford to do this. It's unfair. We leave too many things untreated if we invest so much in one patient." We have had many philosophical discussions on this and I've given a number of speeches in the UK on this point. I sometimes use the example of animals, because animals are very popular in the UK. At one point, I was speaking when a highly publicized story was circulating through the media. A circus was visiting York. A [giraffe] slipped in the streets and its legs went in four different directions. People tried to lift it with a crane, but they couldn't because it was too heavy and the crane would break its chest. It took two days to save this giraffe. Traffic was diverted and they dug a hole and saved him. It's the same as whales when they get caught in the ice. We send boats to save them. It's part of civilization. We don't say to a child, "You have this genetic disorder, but we have to build that road. We can't help you." When we can help, it is our obligation to do so.

THACKRAY: I'm interested in the UK example. Have you prevailed?

TERMEER: We do very well in the UK. We do very well in Holland and we even do well in Canada despite their big bureaucracy. Our most successful market on a per person basis is in France. The French love these kinds of treatments. They actually approved them well ahead of the EMEA [European Medicines Evaluation Agency] approval through special mechanisms. Holland is the second most successful market —and not because I came from there! Dutch people are very careful spenders. They like the drugs' efficacy, but we explained to them that we treat people free of charge in Africa and Sri Lanka—and even Russia for a long time. The Russians started to pay once they started to have oil income, and it's now a very important market for us. Many of the old Soviet countries are also important markets. In China, we still treat patients free of charge. We are in the process of changing that now.

THACKRAY: If you go back in time and think of Biogen or Genentech, they were both very science-driven companies. You came from a very different place. Were other people coming from the same place?

TERMEER: Not so much at the time, but now there are other companies that are using orphan drugs or personalized medicine as a starting point. Increasingly, big pharma is moving in that direction. It's such a fragmented field.

THACKRAY: Who is your direct competition today?

TERMEER: There's not one company that we think of as our direct competitor because everyone diversifies. We are however, competing with Shire Pharmaceuticals. Shire had some products in the attention deficit disorder field. Then they purchased a company called TKT [Transkaryotic Therapies] here in Boston which moved them into the genetics disease and renal

arena, and we do compete with some of their products. But it's a big world and it's not like pitting Zocor against Lipitor, for example. It's still early.

THACKRAY: How does the model connect to the business of the generics as opposed to patent expiration?

TERMEER: Patent expirations, small molecules for research, and eventually biosimilars, are very well established and do influence the market. They encourage continuous innovation and have created a pretty remarkable market situation. In 2002, 50 percent of all prescriptions in this country were generic. In 2007, 67 percent of all prescriptions were generic. In the second quarter of this year, over 70 percent of prescriptions were generic. By 2012, that number will be 85 percent. But generic drugs only support manufacturing and distribution. Proprietary drugs support R&D and education. The generic drugs better be good, because they need to be very high-priced and for them to be high-priced, they need to be very valuable in the eyes of the purchasers. The rise of generics is forcing us to create much higher-value pioneering drugs. At the moment, innovation investment is in danger because of bad capital markets. In the biotechnology industry, 95 percent of companies are unprofitable. A while ago, Europe faced a similar situation where the number of biotechnology companies shrunk massively. It's happening here now and soon we will see many companies go under or be put on the shelf. Luckily, President [Barack H.] Obama is attuned to the importance of innovation and R&D. He will not deal with the cost of medicine, but instead with how we can encourage innovation. This new cycle of generics will cause the average cost of medicine in this country to decline in the coming years. There will also be some pioneering drugs that are very expensive. The problem is that we don't have enough new drugs.

THACKRAY: At Genzyme, you just had some drugs go off-patent.

TERMEER: Yes, that happened just recently. Cerezyme is off-patent. Two are still on-patent. You can produce the patent that is specific to the cell line, CHO cells. Our markets are a little cumbersome for generic competitors because there are so few patients. That gives us some level of protection.

THACKRAY: Is it true that Genzyme is more likely to be the pharma of the future than, say, Pfizer? Is the industry going to be driven towards the models you use because of these pressures?

TERMEER: Yes. It's happening right now. Regulators will figure out a way to approve more OTC [over the counter] products, because they're cheaper. You don't have to insure them. If we had an FDA that had some courage, we would get there faster. We can't afford to regulate every

single thing. This risk-benefit equation will move towards putting things on the shelf and creating a big industry. The big companies like Pfizer have a choice—where will they go? I have a sense that they will choose to be in this other part, because it's easier to manage for a large company. There are companies that will go the other way, and they will become part of the world that Genentech, Genzyme, and Biogen inhabit.

THACKRAY: Are Genentech and Biogen similar to Genzyme, or are they still radically different?

TERMEER: Clearly, they are radically different. Genentech is a subsidiary of Roche. They've done a fantastic job in oncology, and that's their niche. Biogen was formerly Biogen and Idec. They are involved in oncology through Rituxan, which also belongs partly to Genentech. They also work with multiple sclerosis. Biogen was basically a single disease company. They had the MS drugs Tysabri, Zenapax, and Avonex. When somebody gets PML [progressive multifocal leukoencephalopathy], the stock moves. Biogen does a fantastic job with MS. Can they move away from it? They weren't successful when Idec did that. That's still a question.

THACKRAY: Do companies like Biogen wish they could become Genzyme or does Genzyme wish it could become Biogen?

TERMEER: No. With all humility, we are happy where we are. Being diversified is very important because it opens more opportunities. You get a very different orientation, and it's much more sustainable than being singly focused. Pfizer's Lipitor and Biogen's Avonex have proven very difficult.

THACKRAY: Can you talk about developing your management team over time?

TERMEER: It is a process and you grow into it. Turnover in our senior management groups is very small—it doesn't happen very often. There are many people who have been here for a long time and have kept up with the changing requirements of running a small operation. There are some operations like manufacturing that started out small and then grew. The person who now runs manufacturing has spent seventeen or eighteen years with the company. I didn't put him in charge, but he proved himself after a number of years and was the right person for the job. We do run quite horizontally. I like running the company. I like to know everything. I don't sit in an ivory tower—that would drive me crazy. I am a part of things. Fortunately, I have no need for control, but people think of me as having a lot of control. I've learned to delegate because if I didn't, I would drown in work. We have a great team, and we like and respect each other.

THACKRAY: Have you started managing parts of the business from places other than Cambridge?

TERMEER: Yes. We now have a very large infrastructure in Europe. The people who run that feel comfortable in Cambridge and in Europe. They are nationals for the most part who have been given a lot of authority and a lot of power to run their manufacturing, marketing, sales, or clinical operations. Sometimes there is a movement to centralize. We try to resist that. There is enormous need to know, so the underlying systems for safety, for instance, have to benefit every single system and be instantaneous everywhere. Finance has to be instantaneous everywhere. We spend a lot of money on IT because we need good underlying systems. It drives me crazy sometimes. I can never keep up with it. There's a booklet we published for our twentieth anniversary called "Vision." It's actually quite nice and it talks about who we are. We are our acquisitions, and our acquisitions are us.

THACKRAY: If you look back to the very first acquisitions, why did you acquire them?

TERMEER: Our first really significant acquisition was Integrated Genetics [IG] in 1989. It took two years to accomplish and IG went public before us. They were very successful. They were competing with Genentech and Genetics Institute and Biogen, but they were late on a few things. They were in the clinic with all the well-known proteins, but they were late on the patent side. They had great skills on the mammalian side, but they struggled financially. We acquired them to expand our skillset and our ability to produce mammalian proteins. In the late 1980s, that was still an art. IG was located in Framingham, here in Boston. There were one hundred fifty people in the company when we merged. Today there are over two thousand people in Framingham in a different building. Our chief scientific officer was from Integrated Genetics, and is still with the company today. Our head of corporate development was with Integrated Genetics, and held the same position at IG and Genzyme. Through our acquisitions, we've become more sustainable in terms of technology, space, and people. Acquiring high-quality elements is a great way to build a company.

We've had the good fortune of growth, and our current programs continue to grow. In 2011, we will be about seven billion [dollars] in top line, and about seven dollars a share, bottom line. We're factoring in all the staff that will cost us money through 2011, so we have to earn these financial shares while building the company for the next five to ten years. We worked very hard from that point internally and externally and tried to execute deals that we could afford, and that were late-stage enough for us to benefit from. This year we did three such deals. One was for mipomersen [Kynamro], which is in Phase III trials. Another was acquiring PTC Therapeutics, which developed a way to read through nonsense mutations to get highly specific treatments for a subset of Duchenne dystrophy patients. That innovation is in late-stage Phase II B trials. We also did a transaction with Osiris Therapeutics this last quarter. We liked their approach to stem cell research. We've been investigating stem-cell therapies for a long time, and Osiris has a highly specific therapy. It's supposed to work every time. We bring all of these

things in knowing that not all are going to succeed. We are also developing things internally that we hope will produce results like the Campath MS program. The growth rate is relevant in a shareholder support sense.

THACKRAY: Do you have an internal group that's scanning for potential acquisitions?

TERMEER: Yes, a very competent group. The group has existed for at least a decade, and has really grown. It's a great place to develop people, because they get to look at the outside world while being quite critical to the inside world.

THACKRAY: Do you remember the moment when this endeavor moved beyond just a hope and prayer?

TERMEER: The critical moment must have been when Ceredase became a success. In 1989, two years before we got approval, we saw the results of the little clinical trial that we could afford, and the treatment worked magnificently. That gave me and everyone in the company a boost of confidence. We can actually do it. It can be successful.

THACKRAY: Suddenly, it's twenty years later.

TERMEER: Right, but there's nothing more exciting than working hard on something and having it succeed. It changes a person's life. That's a rare moment.

THACKRAY: Could you talk a bit about Boston and Cambridge as a place for biotech? In 1989, this industry was still a curious diversion, what about now?

TERMEER: It was a defense and computer town at the time. Boston's environment is heavily influenced by academic institutions, particularly MIT and Harvard. They're working on base-level discovery. I'm on MIT's board, so I am exposed to their extraordinary research. Very smart young people are willing to work for years off the adrenaline that comes from trying to figure something out. There are quite a few competing technology groups here besides MIT and Harvard. Our academic hospitals are capturing a disproportionate amount of NIH funding. They're closer to patients, so they're very efficient at discovering diagnostic tools. Boston also has some great venture capital firms. They funded tech companies before becoming interested in biotechnology in the 1980s. Students graduate from these institutions, and sometimes they want to stay. We know these students. They're here for years. They are summer workers and then they become postdocs. They're the best. We try to convince them to stay. When we were a very

tiny company, we had almost no employees. We employed quite a few postdocs at MIT. We had them work on the weekends or overnight because we didn't have enough labs. They would work in three-hour shifts, three times a day, in order to do the early discovery work that led to our patents. MIT loves us, especially the entrepreneurial craziness that we brought to Boston. The area has a "you-can-actually-do-this" attitude.

Boston is extraordinary; it's different from San Francisco and San Diego. It's so set up for this market there's a special intensity within this cluster. We've changed forever how patients are treated. Boston is very friendly. All of its large research institutions interact, but they also compete. I've been back two weeks from Holland, and four scientists have introduced me to fundamental discoveries in areas in which they've been working for ten to fifteen years. All of these large well-funded institutions helped feed people to Genzyme and other companies.

The future of biotech lies in knowing patients. Highly personalized genomic therapies are the future. Advances in diagnostics will lead to more and better therapies, and that will lead to changes in Washington. The US has a pioneering role to play in the future of biotech and healthcare.

THACKRAY: Is this the youth or middle age of the whole venture?

TERMEER: This has to be its youth. We are in new era of prosperity, with complex dynamics. And it's not just the United States anymore. We'll change energy by moving away from fossil fuels, and developing technologies and products for capturing, storing, and transporting solar energy. Our planet is being killed by over-development. If we had continued using the early manufacturing operations of the Industrial Revolution we would not exist today. Similarly in China, India, and all the other parts of the world, they need to find a way to develop what is best for their populations. We are beginning to make these developments available for millions and billions of people who don't have access to them. We feel guilty about our prosperous existence in comparison to less fortunate places. Today, we strive to change that status quo.

THACKRAY: What about the other side of that coin? Is Genzyme's most serious competition going to come from China or India or even Japan?

TERMEER: Absolutely, there will be global competition. We started a company in Japan in 1987 and it's highly profitable today. We will also be in China and India. You can't sit and wait for them to come here.

THACKRAY: It seems that biotech from 1968 to 2008 belonged to the United States. How far in the future do you think we're going to be able to say that?

TERMEER: Not very far. Technology and science are now universal. However, some of these biotech clusters are unique. It would be difficult, but not impossible, to reproduce the Boston cluster somewhere else. The discoveries made in this country belong to the global community, and to the markets in India and China. Our task will be to continue to support innovation. Europe has had a very hard time with that and they're paying the price. That doesn't mean that Europe will go out of business. It means that Europe is not as exacting. We want to say biotechnology is an American development, but it is becoming much more global, which isn't so bad.

THACKRAY: Within Genzyme, how have you maintained that orientation towards innovation?

TERMEER: We preach it continually and we also remind ourselves of our purpose, which is to get innovative treatments to patients. We don't forget our purpose. We speak about it at board meetings and when we see subsidiaries offsite. We've had some very interesting, very expensive failures and if you don't have the ability to foresee and avoid similar problems in the future, then it's a waste. Every failure is a fantastic lesson. We failed twice on Parkinson's disease. Parkinson's might be the ugliest disease. You're a prisoner in your own body. It couldn't be worse. We did two clinical trials, one with porcine fetal cells and another with gene therapy all the way through Phase II. Neither succeeded. In both cases, the placebo worked very well. We injected the cells into the brain surgically and apparently the surgery itself creates a reaction that we don't know how to measure. We had internal discussions and said, "How are we going to show that something is active, if we don't know how to deal with the placebo?" When something showed promise in animal trials, then we became interested. We had to make sure we didn't become too risk-averse.

[END OF AUDIO, FILE 4.1]

[END OF INTERVIEW]

INTERVIEWEE: **Henri Termeer**

INTERVIEWER: **Arnold Thackray**

LOCATION: **Genzyme Corporation**
Cambridge, Massachusetts

DATE: **30 September 2011**

THACKRAY: How did the recent economic crises affect Genzyme?

TERMEER: Initially, in 2008, when the financial crisis began and the world started coming apart, Genzyme was well-positioned. The company was doing well. We had worked through a number of integration issues. We had combined several units and were operating as one entity. The company was strong and diverse. There was strong cash flow. The only problem was pressure on the manufacturing side—it wasn't clear that we had enough manufacturing capacity for the products in the pipeline.

In late 2008, we encountered our first activist shareholder, Carl Icahn. He appealed to other investors who saw the high cash flow. In 2009, we took advice from one of our investors, Ralph Whitworth, to guide us through the cash flow issue. Looking back, perhaps it was hubris; we were overconfident that we could manage the activist investors. They're short termers with no real interest in the business.

We might have been okay without the manufacturing issues. That situation really weakened our ability to manage. The company was growing at about 20 percent per year. We weren't able to generate new manufacturing capacity at an adequate rate. Equipment and staff were strained, especially at Allston, and that created compliance issues. Our backup inventory was insufficient. We ordinarily kept nine months of inventory, but during this growth phase, some of it was absorbed.

In June of 2009, a virus appeared at Allston, the virus that had previously been a problem at our Belgian plant. It was one of those incredible moments. The scientists didn't believe it could be happening again. They said there was no way the two incidences could be connected. I made the decision to close the plant. It was one of the most excruciating and sensitive decisions I've ever had to make. It was very tough. It involved a finished product that was in distribution, but too much was unknown about the virus. In the end the whole plant had to be taken apart—ceilings, pipes, reactors, all of it. It was an incredible effort. We received magnificent assistance from our vendors too.

THACKRAY: How did it feel to be the person in charge?

TERMEER: The whole episode was highly visible, globally, and it often felt like the FDA was in charge. I made the difficult decision to write off all the work in progress. In all, the impact was over one billion [dollars]. Even more important was the impact on patients—the interruption in their treatments. Three diseases were involved. It affected about ten thousand patients. Most impacted were the fifty-six hundred Gaucher patients. We set up town hall meetings to open up discussion with those affected around the world. We were all learning. I wouldn't say the reputation of the company was destroyed, but it was a significant shock to the patient community.

The government agencies became very competitive. The European Medicines Agency (EMEA) didn't necessarily trust the FDA. Interaction with regulators is always intense, but this was especially so. And all the while, the financial community and shareholders were wondering how long it would take to sort it out. They're focused narrowly on financial returns. I remember saying somewhere that closing the plant may have saved a thousand babies. Someone on the financial side told me that I'd made a mistake: "Babies die," he said. With hindsight, of course, we should have had extra capacity earlier.

THACKRAY: How did the problems with manufacturing affect the patients with Gaucher disease?

TERMEER: The nature of the disease is such that without treatment you get a re-accumulation of lipids. There is a range of severities. Some people have none of the enzyme; others have a little. The most severely impacted were children. If their spleens no longer function, the build-up can affect the bone marrow. If the bone marrow stops growing, permanent damage can result. The psychology of managing patients through this time was tough. It wasn't easy, but everyone was still receiving treatment.

THACKRAY: How did the episode change Genzyme?

TERMEER: Surviving an episode like that makes an organization stronger. It builds backbone. We said to ourselves, "We will be strong." We had allowed compliance issues to hijack us. We didn't pay sufficient attention. As an organization, we were more focused on output. The FDA had already pointed out some compliance issues in 2008.

We decided that we needed greater concentration on quality control. We hired new people, let some go, and set up an enterprise risk management unit. These kinds of issues are not resolved by simply saying "Do this better." You have to put in new skills—it's always people related. We hired people with experience in dealing with these issues. Scott Canute came from Eli Lilly. He had experience solving a similar problem at one of their insulin plants.

The financial problems were caused by the lack of inventory when the bug hit, and because we also had to write-off the work in progress. We survived the challenge by Icahn because we had prior credit with investors. We didn't need a new board. Icahn couldn't get the votes he needed. Even so, the stock was still depressed, so we had to dig ourselves out. We made a deal with Icahn a couple of weeks prior to the proxy vote and accepted two of his nominations to the board. Before that, in May, I had already had a call from Chris [Christopher A.] Viehbacher at Sanofi, offering help. We had a very comfortable conversation but I still had to report it to the board.

THACKRAY: Is that when the prospect of a takeover arose?

TERMEER: We were always concerned that outside interests might step in. Takeover is always in the air—we had made plenty of acquisitions ourselves. Many similar biopharmaceutical companies had already been acquired by larger corporations. The number of companies was dwindling and fewer new companies were being set up, so we realized we would be attractive—even though some analysts did not believe it would happen because we were so specialized in the rare diseases field. They thought we would not be attractive to large companies.

After the annual meeting, Sanofi called again. I reported that to the expanded board in June. The board decided it was an inappropriate time to be discussing anything. That's recorded in all the filings. However, the strategic fit of the two companies was obvious. Once it was clear that Viehbacher wasn't going away, it was really a matter of price. The discussions took over nine months.

As with the manufacturing problems, everything was conducted in the open, in broad daylight. Restarting the plant was not easy. None of it was easy—interacting with the patient communities, meeting regulatory demands, hiring new people—all of it was hard. There was a lot of scrutiny from all sides, and we were in the middle, being evaluated. We did roadshows. Analysts were trying to work out the right valuation for the company. We had new product in the pipeline. We decided to simplify the company, and to divest the diagnostic services unit. I found that I had to do a fair amount of internal handholding, as it were. I told people they should stay with the company because the Sanofi deal was far from certain.

The difficulties were considerable. Even so, I wouldn't call it a nightmare experience. I wouldn't call it a perfect storm either. It was a challenging moment, but not all negative by any means. In many ways, the whole thing came about for positive reasons. A massive corporation was prepared to pay more than twenty billion dollars for us. That's a huge compliment to the value that we created in Genzyme. I don't feel hurt in any way, and I have no regrets. A lot of good things came out of it. At least ten new biotech CEOs came out of Genzyme, and there will be more. Shire also did well because of our difficulties. To their credit, they were able to step up.

THACKRAY: How did you cope?

TERMEER: My coping mechanism is to confront things head on. Also, I was surrounded by really fine people at Genzyme and had great external advisors. I could call Carl Icahn personally. I called Chris Viehbacher, even though Goldman Sachs advised against it. I called him later on. He came to my home in Maine. We walked on the beach and shared a bottle of wine. It felt right. We shook hands on the deal at the Davos economic forum. We cemented it with a glass of whisky. At 6,000 feet up that hits you right away! It was emotional. We talked about the patients. I think he understood me very well. He accepted that responsibility. The context was different with their company, of course, but different is okay.

THACKRAY: Where are the compliance and patient issues at now?

TERMEER: The compliance issues will stay around for a few years. The availability of product for patients is still an issue, but I think it should be resolved very soon. We've built a new plant in Framingham, which is close to being approved. That will resolve any outstanding issues. We should look again in six months.

THACKRAY: Where have Genzyme alumni gone in the industry?

TERMEER: Mark Enyedy, who ran our oncology efforts, has just accepted a CEO position. The person who ran the Cerezyme program is being courted by two companies. We should really make that list. I think Genzyme may have more CEOs coming out of it than any other company.

THACKRAY: When was your last day?

TERMEER: The last day of June, 2011.

THACKRAY: Having lived through the sequence from 2008 to 2011, what do you know as a result that you didn't know at the start?

TERMEER: On the positive side, I know that a patient-centric approach is not unique to Genzyme. It's central to the future innovation of health care, it will have many consequences.

Something I stress on boards I'm involved is the importance of more sophisticated internal controls in the manufacturing and inventory side of the business. I wish I had learned the manufacturing lesson less painfully. Of all the lessons I have learned, that experience will stay with me most vividly. Overall, I've been very impressed with how strong people are, how they can manage many conflicts and rise to the challenges.

THACKRAY: What do you think you brought to your career at Genzyme?

TERMEER: I do think that in the first ten years I had the insight to focus on one disease and not get distracted. I was fortunate. I had enough confidence to trust my gut feeling and to stick with it. I learned there was power in looking after patients rather than simply the internal rate of return. I learned to allow people in the company to be individuals.

THACKRAY: Who else would you say is in your class?

TERMEER: A person who comes close is Josh [Joshua S.] Boger, who built Vertex [Pharmaceuticals]. Perhaps John Martin at Gilead [Sciences, Inc.], and Sol Barer at Celgene [Corporation]. There are maybe four or five of us.

THACKRAY: Henri, how do you maintain your own sanity?

TERMEER: Fortunately, I am married to a very, very nice person. I have a son from an earlier marriage, a very nice young boy who is in his twenties and lives in England. I have a young daughter from my second marriage. We're a happy family. We get along very well and travel together. We all like to be together. That is the most important break. In terms of my daily life, I work long hours. I start very early, and then come home to see my daughter before she goes to bed. I spend time by myself with a good glass of wine. I go to bed sometimes with a big smile on my face, thinking, "Wow, that was a great few hours." In the summer, I sail in Maine. Years ago, we bought our first house there and have upgraded it a few times over the years. We go up regardless of the weather, to escape. It's on the ocean. We go there for Christmas, too. We ski first and then head to the house. My son often visits, as do a lot of other people.

THACKRAY: Are you serious about the sailing?

TERMEER: I'm not overly serious, but I like to sail. I have an old thirty-five-foot Hinckley Pilot that I've kept in good condition. For the most part I sail by myself, which I enjoy, or sometimes with my son who lives in England.

THACKRAY: Do you compete?

TERMEER: Not very often. Sometimes I compete with myself. You need to be careful. The winds and the rocks around here can surprise you. You need to make sure you don't take any unnecessary risks.

THACKRAY: What does your son do in England?

TERMEER: He's learning to be a photographer. He lives in Norwich. His mom is British, so all of his schooling was in the UK. He wants to be a photographer. He doesn't want to do what I do. He has said, "There's nothing wrong with it, but I'm going to make pictures."

THACKRAY: Do you have any specific plans for the future?

TERMEER: No. For a while, I thought I would do something very different. I became a board member and chair of the Federal Reserve of Boston. That work keeps me busy both here and in Washington, DC. I'm on the board of Partners, which is the umbrella organization for Massachusetts General Hospital, the Brigham and Women's Hospital, the Dana Farber Cancer Institute, and others. I founded an organization locally in Boston called the New England Healthcare Institute [NEHI], which works to break silos in healthcare. It's been involved in healthcare reform issues. I get involved in that maybe a little more than I should. There are lots of organizations to contribute to, and it doesn't take that much effort. My wife is very active with the Boston Ballet. She has been on the board forever. Ballet is a fantastic and beautiful art form. It has its own fanatic supporters, though most of society does not know ballet except for *The Nutcracker*. I'm trying to help them become a sustainable organization.

THACKRAY: To return to BIO and PhRMA for a moment, are those going to remain two separate organizations, in your opinion?

TERMEER: Yes. PhRMA has a large budget and a membership of only fifty companies. They deal with the commercial aspect of the pharmaceutical industry. For a time, the industry grew every year, and they were prepared to spend more money to defend themselves. I think that will change over time. BIO is a technology-based group that represents many different industries. The two groups have IP (intellectual property), in common. They're both dependent on IP. Without investment, they will dry up. BIO and PhRMA need each other, but they're probably better off separate. I think it's tough to manage BIO because it's very broad.

THACKRAY: Is Boston your long-term home?

TERMEER: We like Boston a lot. We have a lot of connections here, but I will always be rooted in Holland. All of my brothers and sisters are in Europe. My mother, who is ninety-six, is still alive so we travel back and forth. Boston is really convenient for that. It's a non-stop flight to Amsterdam. I like it here. Boston has great sports teams and museums. However, it is small compared to some cities.

THACKRAY: Any thoughts about future roles for you?

TERMEER: I'm not disappearing. I'm going to be looking for places where I can really make an impact. Large companies have limitations. I hope to share my advice, instincts, and experience with younger companies. I'll be doing my best to continue to make things happen without trying to take control. I see myself in informal kinds of roles that are more about the long term than short-term financial gains. The New England Healthcare Institute is becoming a very credible source of advanced thinking about healthcare reform. I'd like to do some things better in my personal life too, like spending time with my eleven-year-old daughter, and having a relationship that grows. That requires my availability and time. And, of course, I look forward to spending time with my wife.

THACKRAY: Henri, you've done a fantastic job. You're clearly not about to sail away! We should come back in ten years and check-in with you again.

TERMEER: Maybe ten years is too long, I have a sense the next five years will be very interesting. I'll be laying the foundation for a new future.

THACKRAY: Henri, thank you.

TERMEER: Thank you.

[END OF AUDIO, FILE 5.1]

[END OF INTERVIEW]

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