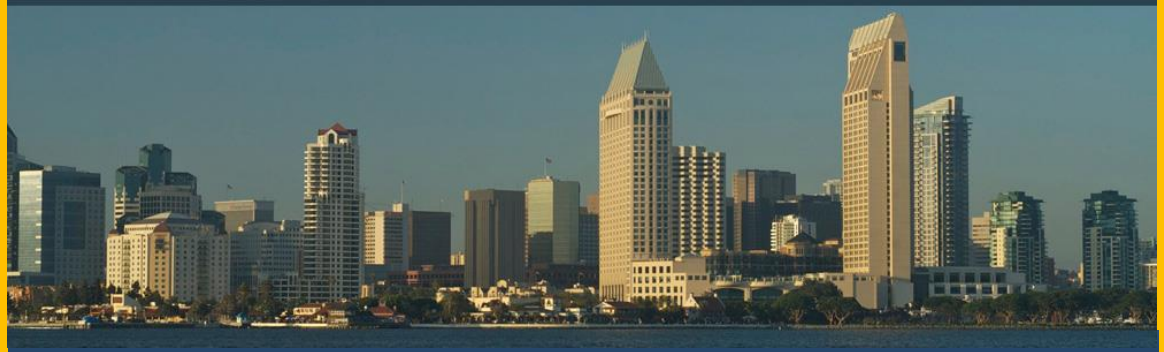
William Comer

Interview conducted by

Matthew Shindell, Historian

June 20, 2008

San Diego Technology Archive



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William Comer

Dr. William T. Comer Ph.D. co-founded NeuroGenetic Pharmaceuticals, Inc., in 2009 and serves as its Chief Executive Officer, President and Director. Dr. Comer co-founded Torreypines Therapeutics, Inc. (formerly, Neurogenetics Inc.) served as its Interim Chief Executive Officer from March 2000 to March 2002. Dr. Comer served as President and Chief Executive Officer of SIBIA Neurosciences Inc., from April 1991 to November 1999. Dr. Comer served as a Consultant to Merck from December 1999 to August 2000. Dr. Comer resigned served at Merck until December 31, 1999. He served as Director of Department of Chemistry and Biochemistry at UCSD since 1992. Prior to joining SIBIA, Dr. Comer worked for Bristol-Myers Squibb Company for nearly 30 years in various scientific and management positions. He served as Executive Vice President, Science & Technology, and President, Pharmaceutical Research & Licensing at Bristol-Myers Squibb from 1989 to 1990. Thereafter, he served as Senior Vice President, Strategic Management, Pharmaceuticals and Nutritionals at Bristol-Myers Squibb from 1990 to 1991. From 1961 to 1991, he was a Scientist at Mead Johnson & Co., including Vice President of Research. He served as Chairman of Torreypines Therapeutics, Inc. from May 2000 to 2005 and Director from October 2006 to May 23, 2007. He served as the Chairman Emeritus of TorreyPines Therapeutics, Inc. since May 23, 2007. He served as the Chairman of Prescient Neuropharma, Inc. from 2000 to December 17, 2002. He has been a Director of Tetragenex Pharmaceuticals, Inc. since February 2001. He serves as a Director of Innapharma Inc. He served as a Member of the Board of Directors of SIBIA Neurosciences Inc. from April 1991 to November 1999 and Epimmune Inc. (formerly, Cytel Corporation) from January 1994 to 2005. Dr. Comer served as a Director of Trega Biosciences (formerly, Houghton Pharmaceuticals) from 1993 to 1996. He served as a Member of the Board of Directors of TorreyPines from May 2000 to May 23, 2007. He served as a Director of TRACON Pharmaceuticals, Inc. since January 2007. He served as a Member of Special Committee of IDM Pharma, Inc. He has been a Director of the University of California, San Diego ("UCSD")

Cancer Center Foundation since 1992. He is a Director of The San Diego Chamber Orchestra. He has been Director of La Jolla Institute of Molecular Medicine since 2000. He serves on Dean's Advisory Board for UCSD Skaggs School of Pharmacy. He serves on the California Governor's Council on Biotechnology, California Breast Cancer Research Council and several national and divisional offices of the American Chemical Society. He is a Member of the Executive Committee of BIOCOM. Dr. Comer received a B.A. degree in chemistry (Alumni Achievement Award 1997) from Carleton College in 1957 and a Ph.D. in Organic Chemistry and Pharmacology from the University of Iowa in 1961.

Source: Bloomberg Businessweek

THE SAN DIEGO TECHNOLOGY ARCHIVE

INTERVIEWEE: **William Comer**

INTERVIEWER: **Matthew Shindell, Historian**

DATE: **June 20, 2008**

SHINDELL: June 20, 2008. Interview with William T. Comer. This is Matthew Shindell doing the interview. So, we can start as early as you like. How did you get interested in, or when did you realize you were interested in pharmaceutical sciences? How did you become involved in pharmaceutical development? Now, if you want to go back and talk about your childhood days, if there were any influential figures?

COMER: No. But, it would start in graduate school.

SHINDELL: In graduate school? Okay.

COMER: I think it was a somewhat interesting story that clearly influenced the rest of my life. I was in my last year of undergraduate study at Carleton College in Minnesota and I was finishing my bachelor's degree, majoring in chemistry, and really had not taken any biology courses but wished in my senior year that I had. In any case, I was accepted for a graduate program in organic chemistry at the University of Chicago. My parents had just moved to Iowa City, where my father was in business, and I visited them at spring vacation. Since they were both in the store working, I wandered around the U. of Iowa campus, and stumbled into the Department of Chemistry and the chairman's [Prof. Ralph Shriner] office. They said that I could talk to him in about ten or fifteen minutes, so I sat in his outer room, picked up a magazine, and it happened to be that week's issue of Science magazine. So, when he came out ten minutes later and had me come into his office, he immediately started writing all these things on the board, thinking that I had been accepted to the program there and was interviewing him as a possible PhD mentor. As I talked with him and he scribbled all these structures on the board and tried to explain his projects, he turned to me and he said, "Which of these programs would you like to work on?" [Laugh] I rather embarrassingly said, "None of the above, thank

you." "Well, what do you want to do then?" "I don't know. While I was waiting to talk to you I picked up this week's Science and there was an interesting article in there. I thought it was interesting." "Well, what's that?" This clearly dates me, but it was an article describing this new neurotransmitter in the human brain called serotonin.

SHINDELL: What year was this?

COMER: This would have been spring of '57. And, he said, "Well, I don't know much about that," but I pointed out that the chemical structure wasn't that far different from some of the things he had just described to me that he was working on, so I thought he might find the chemistry interesting. "Well, what would you do? I mean, okay, you read this article that summarized the last couple years of publications and the field seems to be taking off, but what would you do in this area?" "Well, I don't know. It described serotonin playing a role in the stomach, and in the brain, and all kinds of things in the body. I thought maybe you could modify the structure a little bit and get it to work specifically in one part of the body or the other." "Well, that's interesting. I don't know anything about that. Just a minute," he said, and he picked up the phone and he said, "I've got a new neighbor at my house. I think he's in pharmacology over in the med school." So, he called and he talked to this man who said, "Well, I was just reading that article when you called." And, he [Prof. J. P. Long] slammed the phone, got in his car, came across the river, about ten miles from the med school, and sat down, the two professors and me. And, I recognized this guy when he came in the room. He had just received the award for the Outstanding Pharmacologist of the Year, internationally. It was called the Abel Prize. But, he came in and sat down and started talking about serotonin and how you might modify it, what you might hope to achieve by modifying the structure. We started at one o'clock and we all broke up to go home for dinner at six. [Laugh] I told my folks at dinner that evening, "Gee, I thought it was a pretty exciting afternoon, but I may have to call and cancel my fellowship in Chicago, [Laugh] because these guys are trying to put together a program to get me to come to Iowa City," and, well, you have to understand I'd been away from home for three years of prep school, and four years of college, and my parents couldn't afford any of this. [Laugh] So, the thought that I might come home for a few years they thought was pretty exciting. [Laugh] And, the next day I got a call saying, yes, they offered a teaching assistantship in chemistry and a research fellowship in pharmacology. So, I worked on both sides of the campus, finished a PhD with double major in four years, and as I interviewed for jobs I was all set to go in the drug discovery business then. I mean that's exactly what I focused on,

but there was no formal program like that in any other university in the country at that time. And, they were just getting chemists and pharmacologists to talk to each other, for goodness sakes. I interviewed at a lot of companies, none of which excited me at all. And, the last place I interviewed, a little company in Indiana– when we finished, I kind of liked the people, and liked what they were talking about, and I said, "Gee, I don't want to be presumptuous but if you were to make me an offer here, where would my office or lab be? Who would I report to? And, what project would I be working on?" "Oh, no. No. No. You don't understand. We do want to hire you, and we're working out the offer terms right now, but we would like to hire you to come and tell us what we ought to be working on." [Laugh] Well, I was a rather cocky twenty-five-year-old kid, [Laugh] you know. I thought, "Yeah, I can do that." But that was because no one had bridged those two sciences academically. No one had thought about drug discovery with a strong background in the targets, as well as the molecules it takes to specifically get at that target. So, I was . . .

SHINDELL: You were a unique product on the market?

COMER: I was and hadn't realized it. But it absolutely engraved in my brain, "That's what I want to do." And, I took that job and in the first couple of months I was there we discovered the first beta blocker. And, we went on and then we got the first beta2 agonist, which was a whole new approach to bronchodilators. The leading product on the market is the one that beat us out after we finished. But, you know, from the beginning it was the choice of target, biologic target, that would be responsive to small molecules, as they're called now, drugs, and to get selectivity, to get safety, and to really be effective in treating these diseases. Moved into CNS and cardiovascular, and we approached them from several points of view, and then after Bristol-Myers had acquired it – this is called Mead Johnson Company, and Bristol-Myers acquired Mead Johnson, so all of my time was considered an employee of Bristol-Myers. They moved us to the East Coast and put me in charge of not only Discovery but Development, Clinical Development worldwide, and that was like January of '82. But, our first assignment was to find a piece of land and build a whole new research center to combine all of these different pieces that had been acquired around the country.

SHINDELL: That was your first job for Bristol-Myers, was to . . .

COMER: No.

SHINDELL: That was for the other company?

COMER: That was my first job after Bristol-Myers moved me to New York to consolidate the different labs– they had Bristol Labs, which were famous during the Second World War for developing the early antibiotics, penicillins, and then later cephalosporins. And, the Mead Johnson Company, at that point we had the first cancer drug. We also had an antidepressant, which had really opened up the whole field. It was just before Prozac. It opened up the whole field of antidepressants. We had the beta blocker as a cardiovascular, and the bronchodilator for asthma. So, we had a pretty broad group, had been incredibly successful, and yet a couple of the early targets that our labs worked on, we were successful at the discovery stage but the target was before its time, so the business people didn't know what to do with it. For example, we had really targeted going after lowering cholesterol. And, we had worked with the expert at the University of Chicago, a man by the name of Bob Wistler, who fed high cholesterol diets to rabbits and monkeys, and they got all these fatty aortas, and then you would sacrifice them and look at all the aortas full of plaque. Then you'd give them a drug and see if you could reduce the plaque in the aorta. Well, the drug worked really well and its mechanism was, pardon me, but frankly obvious, and we got the first compound that really lowered cholesterol by blocking its formation in the body. You know, there are two kinds of cholesterol. They're identical but one you eat and the other your body makes. Two-thirds of the cholesterol in the average body you make. One-third you eat, unless you eat too much fat. But, that which you make we could block the synthesis of that with this particular drug. Well, they didn't know what to do with that. The marketing people had no understanding so, they dropped the program rather than going into clinical trials, because they didn't know what to study, what endpoints they should measure in a clinical trial. And, they said, "Well, if someone else figures out how to do it, then we'll go back and pick up this project." That is a death knell because that said, "We don't want to be innovators. We want to be followers." And, it took about six years, and then three different groups simultaneously discovered what we now call the statins. And, all the statins that are being used came way after this. We had published it and everybody thought it was great science, but they didn't realize that you could reverse the plaque in the arteries of someone with vascular disease by giving this drug, because we were not allowed to study it in people. And, that has evolved. Then, the last seven or eight years I was at Bristol, we were really focusing on cancer and AIDS, HIV AIDS, and put a lot of really exciting drugs on the market, but the key to all of this is understanding the biologic target. Where you can intervene in that target and affect the course of the disease without too many side effects, or as we've learned in cancer, the immune system is an

incredible responder and you get so many compensatory mechanisms coming into play. You can knock it down here, cell growth, or blood supply to the tumor, you can knock that down but then it pops up somewhere else where your body compensates for what you just did. And, it's a much more complicated process. I made a comment to a group of biology undergraduates at a lecture I'd given here at the university about a month ago, and I said, "It was interesting in those early days in the '60s and in the '70s. We were trying to find these targets that seemed to relate to the disease, find a molecule or drug that was specific for intervening at that target, and then take that through animal studies, and the clinical trials. You try to develop animal models that would predict the clinical outcome. Many times they did not. And then you really weren't sure how to develop the clinical study to measure the right thing, to get the right kind of an outcome, and that has developed very slowly over several decades." But now, I view it a very different process. And, I've learned from some of our mistakes. We didn't realize they were mistakes at the time. Now we do. And, I think the far better approach today to discover new drugs is to look at the disease in people and then go backwards. Genomics. Genetics. And, now you can approach that with monoclonal antibodies or other biologics, even stem cells, because you understand the disease process at the molecular level in people. I think it will eventually evolve into using less animals in research and a lot of other things. We may well be able to go from in vitro experiments directly into people, as long as our target is a uniquely human target. So, these animal experiments may not be predictive. We know enough about genomic differences, and genetic differences. So, I think that's changing the direction of what I would call "target discovery," and you have to really have a good grip on the target for a disease before you can start discovering a drug that's going to intervene at the right place.

I make a distinction between discovery and development. Discovery is identifying a target that you think is involved in the disease process, screening a lot of molecules, big, small, any kind of molecule that you think might selectively affect that target. And, when you come up with one then you make a lot of modifications, so you optimize and pick the best molecule to selectively affect that target. A major concern is what the animal or person does to the drug; rats, dogs, and people process the same drug differently in terms of absorption, distribution, metabolism and excretion (ADME). Several drug candidates of good efficacy in animals should be screened for pharmacodynamics and ADME to optimize the discovery process. All of that is the discovery process, until you are able to pick an optimal compound or molecule which

really does what you want it to do at your chosen target. The development process starts about that time, when you start taking that molecule and you look at it a lot of other ways. Well, what else does it interact with? If you dose that molecule to an animal for weeks, are there any safety concerns? Again, you're looking for what's wrong with it, not just what's right with it. And, a lot of work goes into purifying the molecule so you have no impurity. So, you're looking at the stability of the molecule. And, all of that must be done before you can go to the FDA and propose doing clinical trials. There always should be and will be checks and balances so, especially with stem cells and larger molecules that prevent you from going into clinical trials prematurely. And yet, once you have shown that you have a well-characterized molecule, you believe it does exactly what you want it to do in the disease stage, they're even abbreviating Phase I studies in so-called “normal” prisoners, college students, male and female, etc. They're focusing more on using real patients right at the beginning, and looking for safety as well as efficacy from the beginning. So safety will always be a concern, especially if you're going to dose that drug long-term. But some of the really exciting new drugs will not require chronic dosing--take a pill orally every day for the rest of your life. You can take certain kinds of radiation and kill tumors. You can take certain kinds of drugs that will selectively stop the exact process that is causing the problem; e.g., some ant-infectives, gene therapies, stem cells. And, it may require dosing every day or every third day for a couple of weeks, and at the end of that time you stop. You have fixed what's broken. That's a whole new era that we couldn't conceive of in the '50s and '60s. But, we're there now and that's why I think it's much more important to understand the disease process. And, with the aid of genomics and genetics, what we're finding is that some people have a unique genetic profile that makes them more susceptible to certain kinds of diseases, like cancer. And not just the metabolic diseases at birth, but even things like rheumatoid arthritis, and immune system collapses that come at a later stage in life. And, what's really exciting is we not only can, through these genetic understandings, with specific mutations that seem to relate to a disease, not only can we go into those diseases and treat that mutation, but we can go in and identify that mutation before the disease gets too far along and that means an early diagnostic. We're moving now pretty aggressively from treatment to early diagnostics, which will ultimately lead you to prevention. It's a very slow and long pathway. I mean, a scientist working in this area has to be impatient as hell from day to day [Laugh], extremely patient from year to year, or decade to decade, because things just take that long. But, we're getting there and I find it so exciting to be able to look at a genetic profile, and now you can

do this almost with a blood sample, like a finger prick [Laugh] at a shopping mall, like they do for cholesterol testing, and find out whether you have particular genetic mutations that make you susceptible to a given disease before it gets too far along. Well, then you can treat that person at an early stage with a much better chance of really becoming effective. There's no question that the rapidly-increasing treatment rates, even – I hate the word – "cure" rates in cancer are a result of being able to diagnose people sooner. We not only have better drugs to some extent, but primarily we're identifying those people sooner. That will continue and it's going to make drugs work better because you're identifying the patient sooner. And, what's even more exciting now, one particular gene mutation that predisposes somebody for a disease, if you pick that up in genetic testing you can start to treat them before their disease is even apparent. Now, that's pretty exciting. Yeah.

When I came to San Diego, I took a retirement from Bristol-Myers after the merger with Squibb and they were going off in directions that I didn't agree with. So, I sat and asked myself, "What do I really want to do?" My mother had just passed away from Alzheimer's disease and I thought, "Okay, I've been lucky. But, if I had been able to discover some real breakthrough drugs for diseases that had no treatment before, I want to focus my attention on Alzheimer's." Nobody in the industry was doing that. Nobody understood what really caused it, or how to fix it. So, I said, "That's what I want to do." I looked around the country and I tried to find anybody that was working on it in an academic situation so I could start getting clues to it. There wasn't much. It was embarrassing how little work was really going on at the start of the '90s. George Glenner, at UCSD, was one of the real frontline mover and shakers in characterizing beta amyloid and the plaques of Alzheimer's disease, but this was going to be a curse. It was going to be a curse that people couldn't solve quickly. Because, unlike most diseases that are a result of an invading organism, a virus, a bacteria, whatever, certainly all infectious diseases are an adaptation of the immune system, and cancer and all these things, you can get to a particular mechanism. But, Alzheimer's requires two events and no one knew how to link the two. One is a pathology. You get this accumulation and aggregation of the forty-two amino acid beta amyloid in the brain, and it kills brain cells. It starts small and makes these little aggregates, so then they get to be bigger aggregates, and then they get to be plaques, and they're killing brain cells, and they're plugging the synapse that connect the cells. But Alzheimer's is recognized and diagnosed clinically as dementia. People, at that time, really didn't understand how the pathology related to the dementia, but at the

end of the 19th century, when Aloysius Alzheimer, an old German professor, first characterized this disease he did it both ways. He found people with dementia and when they died he did a brain autopsy and he found all these plaques and tangles in this brain and he related those, without knowing exactly how, he linked the pathology to the dementia. Ever since then we've been trying to find various ways to measure the dementia so we could tell whether it's Alzheimer's or just getting old, or something else. Scientists have had a very difficult time understanding the plaques and tangles, the pathology of the brain. But once it kills the brain cells, that we can understand as a cause of the dementia. But there are always these funny stories about the early '90s. True stories, [Laugh] unfortunately. The one professor at MIT that was in his late '80s and he was going to work at his lab every day, very bright guy, and he had a friend, a neurologist, and he confided to his friend one day, you know, "I'm forgetting things," he said. "I just started really forgetting some things and I don't understand that." Well, the neurologist said, "Okay. You're the smartest guy I've ever known. I don't think you're forgetting anything, but I'll give you a test, the test we use to detect Alzheimer's disease." And he gave him this test, the so-called ADAS Cog test, and the guy got a perfect score. He said, "All the years I've been giving this test I've never seen [Laugh] a perfect score. There's nothing wrong with you." A few days later, unfortunately, the man got hit by a bus and was killed. They did a brain autopsy and his brain was absolutely riddled with plaques and tangles. So, if he had those, why didn't he have dementia? There are other cases of people that had dementia and had no plaques and tangles. Or maybe they had one and not the other. So, linking the two has been very difficult over time. Probably seven years ago in paper, French workers had done autopsies on – well, they looked at 5,000 different plaques from brains of people that died with a diagnosis of Alzheimer's. Every one of 5,000 plaques, there were I think 1,200 or so patients, every one of those plaques had a single forty-two amino acid amyloid molecule at the center. The nidus that all of these plaques grew from was exactly the same molecule in all 5,000 plaques and it was so remarkable it stunned the world. But, at that point they knew, "Yeah, that one molecule does seem to be responsible." Right away that became a very convincing approach for new drugs. Stop the formation of forty-two amino acid beta amyloid. And, various companies took various approaches at trying to do that. And, as they started to evolve and they found molecules or drugs that seemed to stop that formation, albeit some in different mechanisms from others, they found it also stops a lot of other proteins and things that you need. So, gee, maybe it's not just a good idea to stop all beta amyloid formation. And, people were measuring this in the

blood. Well, that gave some wrong information. You want to decrease it in the brain. So, if you give something that decreases its formation in the brain, it may dump all of that into the blood so your blood level goes up, even though the brain level is down. If you only measure the blood you're getting the wrong endpoint– so the FDA's saying, "Wait a minute. I don't know how you're studying these patients to show that a drug is effective for Alzheimer's disease, but you're measuring the wrong things." So, as they looked at trying to detect AD, they weren't excited about the cognitive tests that were given, they were less excited about measuring pathology that didn't really make sense. So, they really shut down research for several years. Now, it's coming back and people are finding more selective ways to just inhibit the forty-two amino acid. Some recent work has even shown that if you traded off, if you block the formation of forty-two but you increase the formation of thirty-seven, and thirty-eight, those smaller amyloid fragments may be helpful in building the membranes of new brain cells. They're necessary even. So, you don't want to just shut off all beta amyloid. But, if you can decrease forty-two and increase thirty-seven, thirty-eight, that's a good thing. So, all of this is happening and yet – I have a bad analogy: it still takes nine months to have a baby. You know, you can't put more people on the project and make some things happen faster. If you have to do a six-month tox study it still takes six months [Laughter] to do the study, then longer to interpret the results. But, I think we're still bogged down. People thought we were going to be able to do a lot of things in vitro and get away from these animal tox studies and so forth. I don't think so. Not in my lifetime. And, it may be good that we're not able to do that. We need to see how some of these changes, the molecular changes in a biological system, take place over time, and there's an adaptation to these changes. So, safety is not a one-dose effect. Safety is something that has to be over many, many months before you put it in people. And, I think it should, whether it will or not, it should always require that kind of understanding that you're safe in giving that drug to somebody before you start to say, "Well, does it work?" And, so there are a lot of tricks to the development side.

Another comment I made to people here and elsewhere, personalities, I think, play a great role in this. There are some people that like to be different. They like to be at the cutting-edge. They want to do something for the first time. Maybe they want to get a Nobel Prize for it, but whatever the motivation they want to do, they want to really be innovators, and then they don't stick around to see whatever happens to it. They move on to something else. There are a lot of other people, equally bright and

capable, who like to follow things through to completion and get the entire package done, get all the Is dotted, the Ts crossed and when they're through they've got a perfect package. Those people are much better qualified for development. Both are necessary, it's just that there are different tasks and require different talents.

SHINDELL: And which, which camp would you put yourself in? Are you in discovery?

COMER: I understand both, but I would say I'm clearly in the innovator camp, rather than the development camp.

SHINDELL: And . . .

COMER: I enjoy getting everything right and the detail of it, but I don't have enough patience [Laugh] to enjoy the development phase.

SHINDELL: Well, let me ask you a question about being an innovator. As we said before, when you came out of your grad work you were pretty unique compared to other people on the job market at that point. Is it difficult to be unique? Is it difficult to be an innovator in terms of working . . .

COMER: At that time I thought it was fun. Well, not difficult at all because – as long as no one else thought it was difficult. I thought it was fun. Because, I could sit down with the chemist and the pharmacologist, in fact the chairman of each of those departments were responsible for hiring me. I could sit down and get a really heated discussion going among the three of us and when we finished it didn't matter who was right or wrong, we all three were smarter for having had the discussion. So, yeah, just bridging that gap. And now, it's between genetics and electrical engineering or some, you know, very different kinds of backgrounds. I really admire, I even push young people to get very broad backgrounds and to learn a lot about several different areas. You never know when it's really necessary to fuse some of those areas or the information that you glean from those areas into the project you're working on at that time.

Another comment I wanted to make for this discussion is, at the time that I came here in early '91, my first visit was right, the day after Christmas, I think, '90, but basically January of '91, and I had a couple of friends here. Rusty Gage was one of them. We had sponsored some of his work at Bristol-Myers and I was very fond of

what he was – at that time he was UCSD, later became Salk. But, I came out to talk to him about some things he was doing and met another fellow from Salk, Steve Heinemann, and they were talking about a new area of science at that time. I didn't see exactly how it was going to fit with Alzheimer's but I thought it was pretty intriguing. It was a next step. Because of the work that I had done in cardiovascular and CNF had been involved with a lot of the neurotransmitters, and we knew how to move serotonin all over the place, and norepinephrine, and dopamine, and acetylcholine, and all these neurotransmitters, but there were a whole lot more that we didn't understand very well, and what was most intriguing about them is as we'd gotten more molecular in our biology we're able to look at receptor subtypes. And, Steve Heinemann at Salk had put a lot of work in his lab into breaking down these receptor subtypes. And, you may have seven, eight, ten, twelve different subtypes for each class of receptor. And, he would break those down into building blocks, we'll call them, where they could express some of these different units and then they could co-express several of these units until they got lucky and could co-express different units so that they came together in such a way that they made a functioning receptor subtype. He did this in rats. It's almost like a Lego set, but you're really starting at the ground floor and you're cloning and expressing very small fragments of a biologic system, but you're able to express them at the same time so that they come together and in their natural way they make a functioning unit, an ion channel for example, or a receptor in the brain. I thought that was a fascinating way to build a smorgasbord of all of these units and get them to self-express so you could start building all of the receptor subtypes for each of these classes. I also wanted to see if that could work with Alzheimer's and get some biologic systems that were starting to come into Alzheimer's. And since George Glenner was here I had run into a fellow – they also had a good Alzheimer's program at UC Irvine, and one of the postdocs there was finishing and getting ready to strike out on his own and he wanted to chase Alzheimer's. So, I was visiting my in-laws at Christmas, he was visiting his parents at Christmas, and they were a hundred miles apart. His were in Louisville. My in-laws were in Evansville, Indiana. So, I drove over to Louisville in the middle of a snowstorm the day after Christmas. We got together, then I came out here to California, saw him, saw the Salk people, and agreed to come out here and start a company with Salk. Technology and no money. So we started with this technology and we called it SIBIA, Salk Institute of Biotechnology Industrial Associates. S-I-B-I-A. It was a bit of an unusual structure because we had a lot of people that, some of whom had worked with Salk and were split up in this company and they were trying

to do all the cloning and expressing of these systems for contracts to get companies to fund them. They had a small funding for doing some genetic tomatoes and making some proteins on a larger scale, but none of these neurotransmitter receptors or ion channels had any funding. So, when I first came we got funding from Eli Lilly first and then Novartis, and they would fund a particular area. We would not only clone and express all these receptor subtypes but then we would screen compounds and find compounds that were selective for each of the different systems, so that our goal was to co-express all of the different receptor subtypes that we could identify, and then find molecules selective for each one of those. And, we built the company not with venture capital. Venture capital simply said, "We're not going to put a penny into the company because Salk owns all the shares," and they didn't put a penny in it. So, we had to get a different model, and that was a model where we got the companies to sponsor the research in exchange for rights to what came out of it. But, we were able to build it. After about three or four years we had four different companies and projects, so that we had, at that point, about ninety-five to a hundred employees, and we had some Chinese walls between each of these projects, because each one was for a different company. But, we then went public. We did an IPO, did a public offering, and that got a lot of outside investors and then we really moved very quickly. So, that was in '95 that we did the IPO. And, by '99 we had five projects in clinical trials and like other biotechs our share price was down because when we started the IPO was at thirteen. We were trading at about five, because the whole market got cut in half. And when you're in the discovery business they don't like to wait too long for discoveries to happen. So we were trading around five but moving along pretty well with our clinical projects. One day we got a letter in the mail and Merck said, "We're going to buy you." We couldn't fight it. They had it legally set up so that we had to sell. But they gave us a good enough offer relative to our share price that we sold it to Merck, and they were excited about starting a new research lab in San Diego because of the type of innovative scientists who didn't want to be "me too." They came out and interviewed all the scientists in the company and got very excited. So, they bought the company, and then the next day they fired eleven out of the twelve officers, all the top scientists. I couldn't figure out what the hell they were doing. But, they brought their own people in and they only continued one of the projects that we had left over. But you see, what they really did was they killed their competition. Because, the Lilly's, Novartis', Bristol-Myers' each had one project. They were not going to continue to develop those compounds in clinical trials because the arrangement was they give a lot of milestone and royalty payments to SIBIA. They

weren't going to give all those payments to a competitor like Merck. So, the projects that were moving quickly died the day Merck bought SIBIA. That was fine for them, because they stopped their competition. We had technology that we were licensing. We were getting a million dollars a year from four companies for one assay, and some of those companies were paying their million dollars a year on top of the other project. Merck took over. We just won a big lawsuit. We beat Carl Icahn of all things in a lawsuit here in San Diego over the assay patent. Once Merck bought SIBIA, they dropped the lawsuit, which meant they dropped the patent, so there's no more income from that. They only continued one project and they shut that down after a couple of years. So, when they bought us we were 120 people and they said they would expand that to 300. They moved up on the Mesa, occupied two or three buildings, and they got it up to about 220, 230, but then they just started cutting it back and then they shut it down. Nearly everybody from Merck left San Diego. They brought in one guy to leave here for licensing, but basically Merck took their presence from zero to about 230 and back to zero again, all in a couple of years. And, that was a huge disappointment because all that we had worked for just disappeared, but that was their objective. They wanted to keep the competition from getting all those things. And, it's one of the tough lessons in the competition.

But, let me just go back to the time that I came here in '90, '91. Because, I think that was a critical time. Now, that's a few years after the Hybritech acquisition by Lilly. We're starting a lot of these new companies, and all the new companies they're starting were focused on some kind of innovation. They had no idea what kind of diseases or targets they've got to go for. They really didn't have many drug discovery or drug development people. They had people who were very good at working on monoclonal antibodies, and they had a lot of good molecular biologists, and those are the people that started a lot of new little companies. Well, there's a two-way situation in '90, '91. Big companies around the world, and especially in the United States, were starting to go from what I call big R, little D, to little R, big D. They were putting so much money into clinical trials and the development of projects, which was taking a lot longer than they had previously, because the FDA rules were getting a lot tighter. And, they had limited budgets, so they were cutting back on their research. And, they had better odds of getting products through clinical trials if someone else had already shown that the target related to a disease, and that disease had very high need for a new therapy. So, the marketing people started really driving the selection of projects that got funded in Big Pharma, which really cut back significantly on the number of

people doing discovery and the number of projects being discovered in Big Pharma. That became the raison d'etre for all the small biotech companies. It wasn't just biotech. Big Pharma was handing over the responsibility for drug discovery and maybe to some extent even target discovery to the small companies, because they had hired the innovators. A real innovator didn't want to stick around in Big Pharma and have their budgets cut back, and back, and back, and then be told, "We want you to discover a compound just like the one that this competitor got, but make it a little bit better." Wasn't exciting at all to them. So there, over the next couple of years, '90 through even '95, there was a great exodus of some of the top innovative scientists from Big Pharma and they all seemed to show up at small companies.

SHINDELL: And so had you – or . . .

COMER: A good number of them showed up in San Diego.

SHINDELL: You had experienced some of these budget cutbacks before you left?

COMER: Oh, yes, but on a smaller scale. At that time, the budget cutbacks, well at Bristol, but also at Merck, at Pfizer, all the big companies were not so well publicized in the financial pages of the Wall Street Journal. Now, a layoff of twenty people gets big news. But, it was a cycle during the calendar year. Come August all the companies had projections and Wall Street was reminding them, all the analysts reminded them, "You projected you were going to grow profits and sales so much this year," and about August, "Oh my god, we're running behind. We're not going to make it. We're, you know, we're below projections." Fear sets in so they have to cut back discretionary spend in August. Invariably they would go to R&D and say, "Cut back discretionary spend." Well, that usually meant cut back some of the clinical trials because that was more, you didn't want to cut people in those days so they would turn projects, unfortunately some of the more advanced projects, off and on, and off and on, like a spigot. And, that was the way they could control the flow of expenses during the year. Marketing expenses were largely the number of sales people. You're paying salaries. You couldn't cut all, so cutting down clinical trials, grants, and so forth, that was their leverage. Well, what do you know, suddenly in the fourth quarter they started selling all kinds of things. They started pushing things from the wholesalers into the retail shelves. So, on paper, man oh man, profits go up, sales go up, just in time for the end of the year. "Oh! Now we've got to hurry up and spend. Now we've got to spend a lot of things in the month of December," but you can't start a clinical trial and finish it,

but anything that, you know, consultants, or a lot of that kind of money would get spent in the month of December because they suddenly found they had not spent what they said they would during the budget, because they cut it off in August. So, there was this, this kind of activity of off and on, off and on, in the spend of R&D throughout the year. But, I think what you were referring to were more massive layoffs or cutbacks in R&D, and at the same time, in the early '90s they started buying technology. Not compounds or products yet, but technology. High throughput screening technology, and we started a lot of that at SIBIA. Aurora picked up a lot of that and they started manufacturing big pieces of equipment and selling the equipment and everything to Big Pharma. So, they would set up their own high throughput screening activities. And then they got into high throughput synthesis. People started doing chemistry, doing reactions in little tiny tubes. I mean, you're talking about making a thousand compounds, two milligrams each. We never thought of making compounds less than ten grams in the '60s and '70s. So, that got miniature, micronized, and then high throughput automatic, you know. The way we would test compounds was amazing. And, we would use dyes that would show whether a cell was increasing or decreasing calcium, whether it was doing various kinds of functions, and then you'd have these things happen in what were called the 96-well plates in those days. Now they're 384-well plates. [Laugh] But, you're running a different reaction between a molecule and a biological system in each one of those little tiny wells. And so, here are 384 reactions going on at the same time and you move that on a belt under a camera that's taking millions of pictures per second. And, then the computer is trying to digest all this. But, there's so much information coming out of taking pictures of these dyes, reflecting the biological process, 384 times on each plate, that with that mass of data you end up having more scientists trying to understand the data from the computer than you did making the molecules or setting up the biological systems. But, that was a whole new model and Big Pharma bought into that. So, they cut back their staff even more and got more automation, got more of these high throughput screening capabilities, and then they would buy new targets that were coming out of small companies. A lot of those targets started in universities. There were a lot of people here as well as Salk, and Scripps, later at Burnham, that would take a particular system and they'd start working on it and then they would move that into a corporate environment where they could get one of these teams of chemists, and biologists, and everybody working to get sort of a seamless translation of drug discovery through target discovery and even into clinical trials. So, at that time it was also popular for a lot of the top

professors in medical schools but also in biology and some of the other sciences to either become founders or principal scientists in these small companies. Not much movement back and forth but it was a one-way street from academia. But, they brought credentials and a very great academic reputation into the company. So, the company started to get funding by VCs by selling the reputation of their scientific founders. It made a great marriage and I don't take away from the Bay Area at all, no question that Berkeley and Stanford were at the top of the game, and not just because Genentech and other big biotechs started there, but because they had this tremendous give and take between the small companies and the professors in the universities. So, that got copied in San Diego and left Los Angeles and other big centers high and dry, because they moved quickly, and there was a lot of interaction between the academics and the corporate types. But also, at that time as the big companies were starting to reduce their staff and programs they started coming out here. We transferred a lot of people from a Big Pharma environment into the companies in San Diego during that period of time.

SHINDELL: After they moved into the startup companies out of the big companies would you say that discovery continued to occur in the same sort of way or in the same sort of culture of innovation that had existed in the bigger companies, or do you think that in the new smaller biotech startup companies there was a new type of culture of innovation? Or, you know, was it the same thing in a new place or was it a whole new ballgame?

COMER: It was a new ballgame, not a whole new ball game. I think there was such a strong scientific foundation built in the good Big Pharma companies that couldn't go away, couldn't be modified overnight. But people were willing to try a lot of new targets. They'd get, maybe through their graduate work they get married to a given biological system. They'd think that got really exciting so they would push it without breaks, without any regard for safety or other competing mechanisms and they would rush to get things into clinical trials. That's both good and bad. I think a lot of times they didn't see the train coming toward them when they were doing that. They were in too big a hurry to take their hypothesis forward without understanding the problems, but at the same time they weren't going to wait for everybody in Big Pharma to bless them. So, one of the excitements about the culture in the '90s, San Diego was very much a part of it. Because when these small companies would have a couple of highly-focused projects and they would take these projects and sell them to Big Pharma, I mean the way they described what they had done, they were using

techniques that had not been picked up at Big Pharma yet. They were using some slower and more cumbersome techniques, even animal models for human disease. Boy, some of those got developed very quickly in small companies willing to take chances, willing to solve problems more quickly than Big Pharma was willing to solve a problem. Because, Pharma already kept asking the question, "Well, what's wrong with it? What does it not do?" And, the small companies started out with the glass half full. They said, "Well, does it do what I want it to do? Well, forget about these other things for the time. We'll come back and check them later. If it does what we want it to do, let's see if it goes to the next step, and the next step, and the next step." And it's that kind of mentality that developed some of the really outstanding scientists who were bridging both academia and corporate. The whole idea of biological system, or systems biology, evolved at that time because somebody had a pet project of "Gee, if you knock out this kinase or this enzyme you're going to be able to stop the whole cancer." Well, it didn't work. I mean, it worked in vitro, it worked in a couple of animal systems, but when they got into people it just didn't – first of all, the tumor mass was too big to be able to take care of that little [tapping table] one molecule at a time change, but also there were so many compensatory mechanisms. The body is amazing [Laugh] at how it can fight what you're trying to do and make you look like a loser. So, when people got so married to their hypothesis that's all they were trying to do is show that it worked in people, and a lot of projects failed in a hurry. A lot of that was built around monoclonal antibodies that shut down one particular system but didn't stop the disease because of a lot of compensatory effects, not because it wasn't a selective monoclonal antibody, but because that one system was not the whole answer to the disease. I think biology moved far more quickly than any other science at any time in history. During the '80s, the latter part of the '80s specifically, and certainly the first part of the '90s, molecular biology and systems biology – they started seeing huge involvement of so many things simultaneously that it's not a single linear process, and fortunately, students coming in as freshmen at UCSD got it. They didn't wait until they were seniors. They got it as freshmen. So, by the time people are getting to be juniors and seniors in college, genetics is a second language, which fed into genomics, and so forth. But, man, molecular biology as it was taught in the late '60s and early '70s was so archaic and linear that it took a real push. And, the push was corporate if you wish, but I think the push was the personal satisfaction of saying that you discovered a drug that will [pounds table] fix what's broken. So, when cure rates started to go sky high with cancer and a lot of other diseases, we started understanding things better. And,

because molecules started really treating these diseases, we understood the disease a whole lot better. And now, we are catching a lot of, not just MIs, but life-limiting heart attacks before they happen. And, we – okay, you can say cardiovascular disease is still the number one killer, or heart attack is still the number one killer, but you look at the longevity of how many people are walking around that had heart attacks, a near-death experience, and twenty years later they're doing just fine, thank you. So feeding from treatments into early diagnostics, we're going to be able to, with a genetic profile, say, "Well, you're looking pretty good right now, today, but you've got a couple things here that may start to sneak up on you, and you can either do something about them now or keep an eye on them. But, these things and your genetic makeup you should keep an eye on. You're only thirty, but you should keep an eye on them and every ten years or so see whether they . . ." So, you may start taking a drug that treats something when you're forty, or fifty, not when you're sixty-five and just died. I think that is huge progress that has become possible through this interaction of molecular biology, genetics, the whole thing, and innovative scientists. People that are driven to get answers. They don't follow it all the way through. They don't get recognized, perhaps, for having put a product on the market, but boy they were out there saying, "Ah. Here's the problem. You've got to do . . . " And then they identify all the things that involve that problem.

One other quick story. I was fortunate to be in the situation where I was. At Bristol-Myers at that time the offices were right on Park Avenue in New York City, and this was the mid '80s, I was sitting in my office when I got a call from the chairman of the company, and he said, "There's a lot of ruckus downstairs, and a bunch of people beating a drum, blowing a horn, protesting, saying they want to boycott Bristol-Myers products worldwide." It turned out they were young and screaming about a compound that I was responsible for just licensing from the federal government for HIV/AIDS. They assumed we weren't going to do what they wanted us to do with that compound. Well, this was the first clue of any drug that might be able to affect HIV/AIDS. So, he asked me to take a policeman with me and go downstairs and talk to these people. Well, it turned out there were four people. They made enough noise for four hundred. They got a big demonstration started and they were threatening to boycott all the products worldwide and they were pretty strong. I quieted them down by agreeing to sit at the table and discuss it. A few weeks later and we were just pushing real hard to get this thing into the company, digested, set up the process, try to get clinical trials started and really get moving. At that point, virology was a dead

science. Nothing had changed in fifteen years. And now, you're coming and saying "retrovirus." What the hell is a retrovirus? How does that relate to a virus? Well, nobody really knew. So, we had a tough problem finding any scientist that understood how a retrovirus was different, how it was replicating itself, how you can intervene to stop the replication or to stop any other aspect of the disease process. And, these people, one in particular, but the four people turned out to be the four founders of a group called Act Up. They were four gay men whose disease was far enough progressed they lost their job. All of them were very bright people and they had little to do all day long but sit and read about it. And, they were protesting. What they really wanted, since we were going to be developing the first drug that had a chance to do something for AIDS, they wanted a seat at the table. We left after about three or four days of discussion with a table of five people that directed that project. And, one of the seats at the table was represented by the company. [Laugh] One out of five. One was NIH. One was NCI, the National Cancer Institute, which was also involved with doing some testing on this AIDS drug, and then the FDA, and then Act Up had a fifth seat at the table. Basically, the same power at that table as the company who was paying the money, designing the studies, trying to set timelines, and layout the project. They kept pushing. That was the first really effective patient advocacy. I've never seen anything as effective or as well directed as that was. I'll jump just a minute, and leave out a lot of the good stuff in the middle. [Laugh] One of the good things in the middle was that I had decided, having this R&D budget, that instead of spreading our money over about ten to twenty different projects that we were trying to push through clinical trials and get to the market, we would put all the money that we could behind one project, a number one priority project. And, it turned out it was the project for AIDS. And, it was taking us on average eight to ten years of clinical trials to go from IND to NDA and get approval from the FDA. We thought we might be able to reduce that to six, five or six. Five was really optimistic. We went from IND to submitting an NDA to the FDA in eighteen months, and we got approval from the FDA in nine months. At that time, the average was running about, well it was running twenty-eight months just for the FDA to make the approval. So, we cut twenty-eight down to nine months. And, it was urgent. I mean, the government recognized it. It was urgent to the whole country and the world, so it had to be urgent to the company. So, how you spend your money was a very key part of that. The other key part of it was, I had to change the attitude. Maybe it's bringing an innovative attitude to a bunch of development folks, but still getting it right, [Laugh] and that attitude was, "Assume the positive and then prove that it's not so."

So, instead of saying, "Well, we've got to do all these safety studies and tox studies to see what's wrong with the drug so we can kill it without spending unnecessary money on it." "No. You do everything that you need to do concurrently, rather than sequentially, and you do it not only at the same time but you do it in a way that you try to make it succeed." It is amazing how much that changed the attitude of people, scientists working on the project. "Gee, rather than looking for what's wrong with it, I'm supposed to show that it really does work. Well, I think I can do that," and they did it. They found a few things that you might like to change – but they found them. You know, if you notice what you're not looking for as well as what you are looking for you're a much better analyst. We had to look for what we were not looking for out of the side of our eye and really focus on getting it right the first time. When we presented results to the FDA for their approval, this is an open forum, public's invited. You have to sign up if you're going to speak ahead of time. The company made their presentation of all the clinical results. The FDA gave their interpretation. They were pretty similar. They had worked together all along. And so, they had a new Scientific Advisory Board. They never had an antiviral Scientific Advisory Board before. The first time these people ever met, well they didn't know what the hell was going on to speak of, all academics, but they sat there and listened to this presentation of data, what it meant, and so forth. Then they were going to cloister themselves and make a decision, just like a jury. But wait a minute. There was one person that had signed up to speak from the public. Ah, there he is. So, in the back row this guy walks up to the microphone. He's got on blue jeans and a t-shirt, and the guy walked up and he said, "Well," he says, "sorry for being so disorganized and late, but I just came from my lover's funeral. I have AIDS myself. This is a tough one. This is what happened to him. It's what's happening to me. And, difference is I took the drug, he did not. Here are my vital signs today. Here's what they were when I started taking the drug." I mean, when that guy finished speaking there wasn't a dry eye in the crowd. Thirty seconds and that Scientific Advisory Group said, "We recommend it. We recommend approval of this drug." [Laugh] Done. Nobody but me knew that was the same guy that had been protesting at the front door of Bristol-Myers a couple years before. He was the president of Act Up. Larry was his name. And, I mean this guy is famous today and still alive in 2008, nearly 20 years later. He's legion, but he was so involved. He made sure, as a patient advocate, he drove that thing from the day one all the way through to the FDA approval. So, I really gained a great appreciation for how patient advocates that really understand the disease, the drug discovery process, can participate. So, if you take that kind of understanding but also

innovation and ambition of a real good patient advocate and you put them into a discovery lab, see I'm looking for those kind of people that are freshmen in college, [Laugh] because they're going to be the ones that are going to make it happen in the future. And, it's surprising how many people combine both. They get excited about the science. They learn what science they need to know, but they also have ambition, maybe it's a personal or a family situation, but it's just grinding them, you know, like a dog with a rag, [Laugh] they're not going to let it go until they win. So, I think we've come a long way but in a hurry, and it's kind of exciting to see now, as genetics and genomics, and all these things really move you from not just target, end of the disease, but now we can start with the disease, understand it better, and move backward into drug development, drug discovery, early diagnosis of a patient, and even into prevention. So, we're not there yet, but I can see the concrete being laid for that road, all the way back. It wasn't even dreamed of twenty years ago.

SHINDELL: Now, I hate to stop you but I'm worried that you might miss your lunch if we, keep going. Would you be willing to do a second interview to talk more specifically about San Diego biotech or do you feel like you've already said everything?

COMER: Well, yeah. I don't know what more I can say specifically about it. There was a lot of interaction. In Big Pharma we would go to meetings, scientific meetings, but you were trying to learn what they were saying but you knew whatever they were saying was six months old. And, you weren't allowed to get social with people from competitive companies. I mean, they are competitors. In San Diego biotech, I think biotech in general, that's true for the Bay Area and Boston, totally different attitude. We're basically fighting the same game. There needs to be something unique about our company approach and we keep that to ourselves. How we're playing the game is a trade secret. But, just like academics we're out there trying to publish data. We're out there trying to patent information. We're trying to have a leading edge on everybody, but you do not know what the cutting edge is until you're talking to other people at the same cutting edge. I learned that the first day I was in town. I walked into my office, I pull up my screen and here's a calendar of events in La Jolla. There was a lecture being given that same day, my first day. That lecture was being given at Scripps, Timken auditorium. I got there and here are people from Scripps, and Salk, and all these different places, they're all sitting there listening to this Japanese scientist talk about a subject that was near and dear to my heart. So when the guy finished giving the lecture, I argued with him then and we talked about some things

after he gave his lecture. When I got up and walked out, there were four men standing right at the doorway to the back of the auditorium. Because I had challenged the speaker, they stopped me and got me involved in the conversation. One of these guys was the editor of Science Magazine, a very famous top neuroscientist from Scripps. One of them was Francis Crick. These are the people who are at the cutting edge. To be able to talk with them and know what they were thinking, I mean I went back to that office and I was charged up. I was ready to go for the next couple of months, based on that conversation, because I learned more from talking to them than had I sat in my office and tried to do my job. So, it's a need to communicate, and that has changed. You now see Big Pharma and small companies interacting more. You see discovery people from Big Pharma interacting with other Big Pharma. Unfortunately what that means in Big Pharma is trading people. They'll move from one company to another very easily now. That never used to happen. So, I think that's a very good aspect. And, San Diego biotech did start a decade after Boston and San Francisco. But, when it started they were already into that highly interactive mode, and BIOCOM and other organizations would get the CEOs together all the time. So yeah, I got to know Bill Rastetter. I got to know a lot of other people quite well, because we were all talking to each other. Definitely did not ever happen in Big Pharma. And, that's a cultural difference. You may say it was biotech in general, but it was very noticeable here in San Diego, the highest density of biotechs in the country. It's really La Jolla biotech. [Laugh] I mean, they used to have this Biotech Beach map.

SHINDELL: I've seen that.

COMER: And, when I was at SIBIA we were downtown La Jolla, right down on the coast by the Museum of Contemporary Art, and that was the furthest south of any biotech company in town at that point, or in the state, maybe the country. But, then you started seeing all the movement out to Sorrento Valley, a little bit Carmel Valley, now the so-called Golden Triangle is just exploding, even Carlsbad. They're leaving behind the Mesa where a lot of the companies started with academic roots, but it got too high priced to start new companies there. So you have three different La Jollas. You have the village, which all the tourists know about. You have the Mesa, all the academic institutions and everything, and some biotechs. And then you have the Golden Triangle spilling over into Sorrento Valley. But, that's contrasted with Boston and San Francisco, they don't give you numbers for Boston. They give you numbers for the state of Massachusetts, and that is much more widespread. The most

widespread is what they call San Mateo. It's not San Mateo. It's the Bay Area, South Bay, but the distance from the top companies, quite a few are Oakland, and Berkeley, and clear out into Walnut Creek, and then you go Palo Alto and south, and San Jose, and Foster City. I mean, there's really a large area. So, this is the tightest area, even though we're third largest it's the densest area in the country. So, the tighter it is the more interactions you have. That becomes a hallmark. I won't say unique to this area, but it clearly is a hallmark for the success. So, when they start another new company, the VCs come in and they'll pick people that they know have been very good CEOs, or CSOs, or whatever, at some other company. They may have been bought by Big Pharma or whatever, but success breeds success. So, these same people now are moving around a lot of different companies and that's, I mean it's good, it's exciting, and I think that will remain a major hallmark for this community. So, I think it's also exciting, Duane Roth and others have moved some of this culture into the high tech. I mean Qualcomm had its own commanding position over all the companies of its type, but I think that's going, now that you get a lot of e-business companies and so forth starting in the San Diego area. It's because of that same kind of culture between the high tech companies. So, you know, Bill Otterson received the national award for a good reason, as the Entrepreneur of the Year. When he started – and, catchy word – but when he started CONNECT, he was the epitome of what CONNECT is all about, should be all about, and people from CONNECT have been invited to Finland and all over the world to answer, "How'd you do it? How'd you do it?" It really is all about the people that you work with that they work together and share ideas. I would be remiss if I didn't say that Bill Otterson was – I don't like to pick any one single person most responsible for this culture of the San Diego biotech, but if I had to pick one it would be Bill Otterson, because he just kept everybody moving at ten times the pace that they would otherwise. And . . .

SHINDELL: Uhm-hmm. And he kept people talking to each other, right?

COMER: Always.

SHINDELL: Yeah.

COMER: Always.

SHINDELL: This is what Duane Roth pretty much told us as well.

COMER: Always. I was at Bill's house and saw him the evening before he passed away, and his wife told me to go back and talk to him in his bedroom. He was lying in bed. He was very sick. And, Bill looked at me and he said, "I was talking to somebody the other day. I've got something I want you to do for me." He wrote down a name, a phone number, and he said, "I want you to call that person because he . . ." he was making a connection right then on his last day. Now, you know, that's just [Laugh] who he was, it's how he worked, and it did work. It really did work. So, I think he infected a lot of other people with this increased communication rather than trying to keep things to yourself. So, yeah, I know many companies that have worked together, shared ideas, and even consolidated, merged as companies within San Diego. So, it's easier to do if the geography is a little tighter. It's also easier to do if everybody looks at their competitors as friends. So, it's very clear that those are the components that make what you call San Diego Biotech, I think, unique, but at least different from other parts of the country. So now, when you go to a bio meeting you have governors from about a dozen states coming to the meeting trying to tout the biotech in their state. They're all trying to find out what CONNECT is doing today. They can't do in a large state. I mean, if you think you can do in Texas what we do in La Jolla, you're crazy. But, it does work in La Jolla.

SHINDELL: All right.

COMER: Yeah. I think, in terms of interaction with other companies, description of the culture, you might get some additional thoughts out of Joe Panetta. David Hale was, well I think he and Ted Greene will give you a similar story, but a lot of interesting anecdotes. They are the ones that will give you the best. They'll tie down the roots of the sale of Hybritech. Or, even before the sale of Hybritech to Lilly. But, how Hybritech just started to explode and people went off in all kinds of different directions and started a lot of other new technologies, because they were excited about the possibilities of the technology. Not about the funding or anything else. They were not financial people, for the most part, and the excitement of the technology is why Hybri[tech] people started many companies. It's written down in some of these newspaper reports how many companies in the area started with roots going back to Hybritech.

SHINDELL: There are some pretty impressive family trees that have been brought up?

COMER: Yeah, there is.

SHINDELL: Yeah.

COMER: I don't like the word 'unique' but probably as impressive as any family tree in the country. I mean, you could see family trees coming from Genentech. You can see family trees from other places, you know, original biotech companies, late '70s, early '80s. But, I would say Hybritech – which is interesting because Hybritech was not that well known as a company in its time. It was still in its early years. But, they got hot early and with their monoclonal antibody work they really were at the cutting edge of the technology. There's a small, but not that small group out of Seattle that has moved the same way and they have looked inside and out at the San Diego model as they've tried to move Seattle. They're doing a pretty good job but there's still a lot of connections between companies here and companies in Seattle. And, that's because a couple of the people that were original biotech, George Rathman, the head scientist, and then the president and CEO of Amgen, when he retired from Amgen he went to Seattle and invested, started new companies and carried a couple of other companies forward in the Seattle area, and that was another one of the major seeds that got planted. But it wasn't any one person. Hybritech was a large part of it but it was at least half of those and maybe a dozen people out of Hybritech that all were starting several companies. So, it really was an explosion out of Hybritech, whereas the Genentech tree and the Amgen tree were pretty much one or two people.

SHINDELL: Uhm-hmm. Now, with that big explosion coming from Hybritech was that because venture capital was becoming more and more available in San Diego, or what do you attribute that explosion to?

COMER: Venture capital came to San Diego later.

SHINDELL: Oh.

COMER: Venture capital was focusing on the earlier companies. They were just getting successful and it took five, seven, eight years before they got enough success to attract venture capital. So, as the Amgens, Genentechs started becoming really successful on a global scene, the VCs moved to San Francisco. But, San Francisco and Boston were big banking towns anyway. So, it was the banks that started spinning off VC groups, not technology. And, the banks in San Francisco started sending all of their banker types down to Sand Hill Road in Palo Alto, where now it's just one VC

group after another. All of the major VC groups have offices there. You know, Bill Rastetter is now a partner in one of the original VC groups out of New York, but they set up Boston and San Francisco sites. He's the only one located here. It became important for them to have someone in San Diego, even though they continued to be Boston and Bay Area based. They picked someone that had background in Boston, but Bill does. The company's called Venrock, but like Venture for Venrock, and Rockefeller. [Laughter] So, it was New York founded, but clearly one of the best of the original biotech groups. Now, they're off on their own, they're independent from Rockefeller but, yeah, I think very late. BIOCOM organized a major effort like eight to ten years ago to increase the capitalization in La Jolla. Biotech companies here started with all the technology in the area but they were always going to the Bay Area, Boston, or someplace else to try to raise money. Their money was not here. San Diego's never been a banking town and it probably never will be. But, we now have VC groups here, even if they're second or third offices for groups that are located in the Bay Area or Boston. And, that's helping. It clearly is helping. I say that because now we're in a very low period, not much money available, VCs or otherwise. So, no companies are starting. Big pharma isn't buying anything that doesn't have clinical data on it. So, you know, to get in at the ground floor on a startup, VCs come around and shop a lot. You also have people that have been chief scientists or CEOs of bigger companies. They retire, maybe early, maybe late, but they retire. They like the style of living here, so they move to La Jolla and the first thing they do is they start a new fund. I could point out three or four this month that are just starting new funds in La Jolla, who have come from somewhere else. So, we're always going to be I hope not too little too late, but we're always going to be second cut on the capitalization of these companies. But, if you catch that American Airline flight, the only nonstop from New York City into San Diego, you get on that flight on a Friday, leaves 5:15 in New York, so with the three-hour time saving, the evening is young when you get to San Diego. [Laugh] Every night that plane is full, full, full. Every night. Everybody on that plane is from biotech. They may have to go from Boston to New York to catch it, or Philadelphia to New York, but – I saw some people come in last night, board meeting yesterday, saw some people leave yesterday afternoon. Yeah, the airlines are crowded around here. Not just by tourists [Laugh] but biotech.

SHINDELL: Interesting.

COMER: Yeah. Well. [Laugh] It will be even more interesting if we – and there is a lot of really good technology coming out of Arizona, coming out of Texas, coming out

of other places, call them south, call them whatever you want. Well, they're not close enough to the VCs. They're not close enough to this. They're not close – the founding technology may have come from someplace else. So, one year, two years into the new company they're struggling. They pick up and they relocate to San Diego. A lot of them are transplants that are coming in now. So, it's – and they are moving a little further east, because real estate's still pretty pricy right on the Mesa. [Laugh]

I think the other thing that has happened recently that I'm very, very pleased about, just absolutely excited about, is that the Salk Institute, who has struggled for many, many years, they had a man that was president of Salk called Fred De Hoffman. He died from HIV, contracted by blood infusion. He was a physicist but he really brought Salk to a great new level financially. Ever since then they turn over the president of the institute about every three or four years, because -- and then they've had several interim. They keep trying to hire a top scientist, but what they really need is a fundraiser. And, they can't get somebody who's both. So, they hire people who think they're top scientists but they never get along with the other scientists over there; and the Board, they bring in New York people to bring all that money into San Diego. It just hasn't worked as well as it should. Now, they have a new chairman, Irwin Jacobs, the founder of Qualcomm. Scripps has a new chairman of The Scripps Research Institute, John Moores. So, with Irwin and John Moores together, and then their good friend, Malin Burnham has gone back for the second time to be chairman of the Burnham Institute, these people are working together. Those three institutes are working together like I've never seen competitors in the same community work before, so it's not a surprise when the Stem Cell Initiative from California with its $3 billion are putting a new building to get all these research institutes under one roof, and it's by the glider port, but it's on a property donated by UCSD. But, all of these institutes are working together and now they work together on many fronts. The Mesa can become the Mecca. And, what it takes is it takes people that keep the good scientists, keep the good science working together, feeding off each other, keeping it located here. The money will come if the science is here, and I think that move of having these people who are based in La Jolla and whose success has been based in this area, they will take it to a new level and to a new generation, for sure. It's worked well in other communities. It has to work here. But, all these things evolve and I think they're going in a great direction.

SHINDELL: I probably really should let you go. [Laugh]

COMER: If you have any other questions or anything about it, or want to go a different direction I'd be happy to come back and do it again or something.

SHINDELL: All right. Great. Well, thank you very much. I'll stop the recording.

END INTERVIEW

Recommended Citation:

Comer, William. Interview conducted by Matthew Shindell, June 20, 2008.
The San Diego Technology Archive (SDTA), UC San Diego Library, La Jolla, CA.

The San Diego Technology Archive (SDTA), an initiative of the UC San Diego Library, documents the history, formation, and evolution of the companies that formed the San Diego region's high-tech cluster, beginning in 1965. The SDTA captures the vision, strategic thinking, and recollections of key technology and business founders, entrepreneurs, academics, venture capitalists, early employees, and service providers, many of whom figured prominently in the development of San Diego's dynamic technology cluster. As these individuals articulate and comment on their contributions, innovations, and entrepreneurial trajectories, a rich living history emerges about the extraordinarily synergistic academic and commercial collaborations that distinguish the San Diego technology community.