NIDCR Oral History Project

Interview with Dr. Bruce Baum

Conducted on August 29, 2023, by Kenneth Durr

KD: This is an interview with Dr. Bruce Baum for the NIDCR Oral History Project. Today is August 29, 2023, and I'm Kenneth Durr. Bruce, good to talk to you, despite all of our technical difficulties on both sides.

I'm intrigued. And you know I always start with a little background and I'm intrigued with your undergrad degree in history. It's something rare in a scientist, so let's start there and talk about how you got to train in dentistry and beyond.

BB: I was always interested in history as a kid. I don't know if you're old enough to remember the Landmark series of books that Random House or somebody like that published. They were about famous American historical figures. My mom was a librarian, so we had tons of books in the house, and I had this massive collection of Landmark history books. And I liked science but I always enjoyed history and I liked to read.

So probably, what in my mind, got me interested in science and medicine was the Salk vaccine. I knew kids that had polio and I'd seen kids with braces and whatever and that discovery certainly made a huge difference in every kid's life at that time and had a big impact on me. My folks were—I'm Jewish—my parents were very happy that I was interested in medicine, that was a good thing. I always did well through high school—I was National Honor Society junior year. I did well in all the sciences. But I liked to read, and I liked history.

When I got to UVA, it was kind of a no-brainer for me that I was going to major in history. I was premed, but I was going to take the minimum required science: I took biology, inorganic chemistry, organic chemistry and physics. So I took the minimum that was required for medical school or dental school or vet school. I had fully intended to go to medical school, and I was, in fact, elected in my junior year to the national premedical honor society, Alpha Epsilon Delta. I also graduated UVA with distinction. I had good grades.

The summer before my junior year, I had just gotten engaged to my wife and instead of going back home to Boston, I stayed in the D.C. area, where she lived. In the mornings I worked at Washington Adventist Hospital in Takoma Park as a volunteer in a combined clinical lab/pathology department. In the afternoon, I worked construction. I was a hod carrier, bricks. The father of one of my friends, who also worked with me, said to us, "Anyone who said hard work was good for you never did hard work in their life." But the hard work was good for us.

Anyway, at Washington Adventist I helped with everything ranging from bone marrow aspirates to drawing blood to autopsies. But I was kind of a mush melon. I was very sensitive. I felt badly for sick people. I identified with very sick people. When I went back home to Massachusetts at the end of the summer, I was talking to my dad (who worked in real estate) and I said, "I don't know what I'm going to do. I have a low draft number, 17. And I don't know if I'm right for medicine or if medicine is right for me."

He had a good friend, actually a guy who was a member of our synagogue, who was an endodontist, a guy named Harold Levin, who went to Tufts Dental School and who was later a professor at Boston University's Dental School. I spoke to Harold, and we spoke for a long time. I told him what my concerns were, and he said, "You know the best thing about dentistry? You

can have relationships with people and you very rarely have to tell them that they have a fatal disease."

And that just resonated with me. So I think I had already applied to a couple of medical schools, but from then on I just applied to several dental schools. I had really good grades—I don't know what my score was, but I guess I did fine on the Dental Aptitude Test—and got in everywhere I applied.

I had intended all along to go into private practice. In fact, my mother had picked out an office for me. I grew up on North Shore of Massachusetts, a little north of Boston, in Lynn. My mother thought it would be nice to have an office overlooking the ocean. Anyway, as soon as I got into Tufts I accepted that. I didn't even apply to Harvard. I had no interest in research or a more medical slant.

KD: When did the research come in?

BB: I'll tell you, but it's a bit of a story. The summer before I went to dental school I cut grass in the municipal cemetery in my hometown. My father knew a lot of people, and I got a job with the city's Public Works department. I became very good at evading gravedigging, but it was not a very stimulating job. In September I started at Tufts, and the very first day at Tufts, the dean gave a welcoming speech to the new students. He said something in that speech that changed my life. The dean was a guy named Lou Calisti. We later became friends and I quoted him in a "Lancet" article once about his words to us that day. What he said was, "the goal of the health profession is to eliminate itself". Beautiful statement, something I had never thought of.

I was 21, I have a Y chromosome, and basically I'm immature. My wife hadn't worked the XX chromosome magic on me and matured me somewhat. And when I heard him say that, I said to

myself, “I can never open a business that’s health care. I just can’t.” So I was very lucky. My folks paid my tuition to college, they paid my tuition to dental school.

And while I was in dental school, I began to think, “what am I going to do, and they are paying all this money for me to become a dentist?” I had already taken a physical for the Army, and I knew with number 17 I’m going to be drafted and the Vietnam War is raging. Someone had suggested to me to enlist in the Naval Reserve, while I was in dental school. I did, as it meant that at least I would have a choice in where I would serve, i.e., a ship was safer than being in Vietnam. The “Tufts Naval Reserve” unit met once a month at the dental school. There was a little Navy stuff, but mostly it was oral medicine and it was led, funnily enough, by a professor and an associate professor of oral medicine, which is what I later practiced. The only obligation I had, other than going to those meetings, was what my wife called summer camp at Newport after my junior year in dental school for three weeks. That program, called officer indoctrination school, was to make sure you knew the difference between a boat and a ship. This is a destroyer and this is a battleship. This is how you shine your shoes, etc.

So I’m in dental school and I don’t want to cut grass and avoid gravedigging the next summer, and I notice that the school—no email or anything— had a poster, “summer jobs in research, apply.” I really had no background in doing research, and the first summer I got a job in what was then called the Department of Social Dentistry. It would be called Community Dentistry now.

I worked with a guy named Norman Gerrie, who was a very nice man. He was a public health service retiree, a dentist MPH, and he helped me design a questionnaire, which I sent to 300 or so dentists in Massachusetts. The goal was to determine the effects of Medicaid on practicing dentists. I got a pretty good response to the survey. Dr. Gerrie helped me write a paper, and it

was published in the *Journal of the Massachusetts Dental Society* with just my name. He didn't add his name on it - very impressive on his part.

That publication was a major high for me. Any time dental school would get me down, I'll tell you in a minute how it got me down sometimes, I would walk into the Tufts library and pick up the *Journal of the Massachusetts Dental Society* and see my name in it.

What used to get me down about dentistry was the pre-clinical training, like doing cavity preparations on plastic teeth. I appreciated that it was important—and by the way, I graduated dental school with honors, Omicron Kappa Epsilon. I had done well everyplace. I was very lucky, I picked up a good set of genes.

KD: But you gravitated towards research.

BB: I knew I couldn't just be worrying about millimeters and cavities. I understood that it was important if you're going to be a restorative dentist or prosthodontist or something like that, but that wasn't me. Clinically I gravitated to periodontics, which, as you probably know, at the time (and I think still is) the specialty that is most aligned with research and science in dentistry. And at Tufts we had a really excellent periodontics department. The Chair was a guy named Irving Glickman, who had written a major textbook and was a big kahuna. I was pretty good at it and during my senior year I was allowed to treat post-graduate (usually assigned to residents) perio patients. I did fine with restorative too. As it happens, I couldn't stand endo, much to Harold Levin's chagrin, though I did everything I was supposed to, but I gravitated clinically towards perio.

Anyway, in an oral pathology lecture during my second year, a man named M. Michael Cohen gave a lecture. He was a pediatric dentist—and if you have a copy of my CV, you'll notice there

are a lot of papers during the years I was in dental school with Michael Cohen. As a pediatric dentist, he was interested in oral-facial anomalies, so we worked on conditions like Down syndrome. However, most of my work with him on was agenesis of teeth. Some people, my wife, my daughter, one of my granddaughters, have agenesis of certain teeth. Most commonly it's maxillary lateral incisor, but it can be premolar, whatever. For example, my wife is missing six permanent teeth, which is all due to genetics. Michael Cohen had this idea that agenesis was one end of a spectrum that started with smaller tooth size, i.e., that people who had agenesis had smaller teeth. It's not going to get you a trip to Stockholm. What I ended up doing when I worked with him, actually that summer after my second year and part of my third year of dental school, was going out to orthodontists' offices in greater Boston. I used models they had of people's teeth, who had come in for orthodontics, and compared people who had agenesis with people who didn't.

KD: So this is research that you were doing in dental school.

BB: In dental school. And, yes, I had a couple of papers published from this research in the *American Journal of Physical Anthropology*.

KD: OK. Did you have to go into the Navy after dental school or did you go right to your biochem PhD?

BB: The Navy was absolutely wonderful. I guess they had enough clinical dentists. They knew that I was academic in my slant, I had good grades. I applied to four PhD graduate programs and got into all of them. I decided to go to Boston University. BU is a good school. They have a really good biochem department. I was afraid to apply to a place like Harvard or MIT because I'd been

in dental school, i.e., I'd been out of real basic science. BU at that time was probably rated third in biochemistry in Boston.

I'd never had a course biochemistry until the first year in dental school. I was probably the only kid in my class who liked biochemistry because everything made sense. I don't know if you ever took a biochemistry class. There's a thing called the Krebs cycle, and everything adds up. I mean, it was brilliant. In addition to my work with Michael Cohen, I worked in a lab also during my third year, and the summer following, with a guy named Len Corman. So Michael Cohen and Len Corman were big influences for me.

Len was a dentist PhD who was then an assistant professor of biochemistry. He was an enzymologist, really well trained at Brandeis. After he realized my interest in biochemistry, he gave me a paper on something called tooth-lid factor. I'm sure you've never heard of it. A Nobel Prize came from it. It's now known as epidermal growth factor. It originally came from ground-up salivary glands injected into neonate mice—Stanley Cohen of Vanderbilt, who was at Washington U at that time, did the work and wrote the paper. This factor caused premature dental eruption and eyelid opening, and over the years it evolved to be known as epidermal growth factor.

KD: I want to get you through the biochemistry program and move toward your career here. So you took biochemistry at BU, and then was the next step into the Navy and the Naval Medical Center?

BB: Yes. But let me mention, because you had asked, I was trained as a protein chemist. I worked with collagen and hemoglobin. I did my PhD with a guy named Carl Franzblau, who was also a

wonderful mentor. I was really lucky that I had such terrific mentors. And Carl was really well known, and that fact comes into play later.

So I finished my PhD in the summer of 1974 and I had to go into the Navy. And the Navy detailer, who made duty assignments for dentists was a guy named Gordon Rovelstadt, who also had done a lot of research during his career in the Navy. He, blessedly, decided to assign me to the Naval Medical Research Institute at Bethesda Naval Hospital. So I did my two years of active duty, full uniform, all that, there. However, I was in a research lab, and it was right across the street from NIH. The guy who was my department head was a man named Bob Longton, who also was a really nice guy. He was a captain, career naval officer, dentist, PhD. He had done his PhD at Northwestern, also working on collagen. He was very well trained. He was interested in a very strange group of highly cationic salivary proteins. Unlike being in graduate school, where you can pick your project, I was given an assignment. Because I was trained as a protein chemist, literally my assignment was to isolate these proteins and characterize them. And I did that, and I called them histidine-rich proteins, because they had high percentages of histidine and, thus, were highly cationic.

KD: Histidine?

BB: Later, a former lab mate of mine in graduate school, Frank Oppenheim, coined the term "histatins" for them and they are now known as the histatins. But when I worked on them, I called them the histidine-rich proteins and developed ways to purify them, to study them electrophoretically, etc. Because they had really high isoelectric points, they didn't behave normally on gel electrophoresis or typical column chromatography.

There were things I liked about protein chemistry, but it also took a long time. For example, in the case of saliva, I'd collect 100 milliliters of saliva from individual people and then treat it in a certain way, run columns, etc., and after a year or two, I would get to write a paper. However, for part of my graduate work I did some work with rabbit reticulocytes. Those studies were done with a friend of my advisor, a guy named Bob Troxler, also a really nice guy. Bob taught me how to make and obtain reticulocytes. Typically, we would do experiments in the morning, and at the end of the day we'd know the result. We'd go home, think about the experiments, come back the next day to do a different experiment. These were still sort of protein chemistry experiments because we were putting modified amino acids into hemoglobin to see if it affected its structure. The key thing was that you got new results daily and could design new experiments based on those results. It was very dynamic.

While in the Navy, I decided that I liked saliva, but I wanted to work with salivary glands and learn how they functioned, what controlled secretion and what controlled problems of secretion. That meant working with salivary cells, in a manner like I had worked with reticulocytes during grad school.

I continued to be blessed with a lot of good fortune. Every once in a while, I would go across the street to NIH. I knew people at NIDR. One was the late Karl Piez, and one was George Martin, whose name you may have come across. George is a scientist emeritus and a longtime friend. And I would talk to George. I don't know if you've talked to him, but he was an excellent scientist and always very blunt. And he gave me lots of really good advice. One time he said to me, "Biochemists are a dime a dozen. Put your dental degree together with biochemistry."

Anyway, George was a runner, and he used to run at lunchtime, almost every day, with another guy at NIH who was interested in collagen named Ron Crystal, from the Heart Institute. He was

head of the pulmonary branch. Apparently one day they were running. and this is my take on what happened. Ron must have told George that he was looking for a new postdoc, and asked did George know of anybody. And George must have said, "One of Carl Franzblau's PhD students is at the Navy now and is looking for a position." Ron Crystal hired me on George's recommendation.

KD: At NHLBI.

BB: At NHLBI. And it was terrific because, with the notable exception of gas exchange, salivary gland biology is very similar to lung biology. Even more so than my PhD working with Carl, having a postdoc at NHLBI was probably the best calling card I could have because it's obvious you're not there as a dentist. While I was there, what I worked on was intracellular collagen degradation and how it was controlled by cyclic AMP, and by receptors on lung fibroblasts that stimulated cyclic AMP production.

This experience was perfect for me in so many ways. We worked on a disease, idiopathic pulmonary fibrosis. We studied possible mechanisms, and then they treated people. I didn't treat people of course, but there were many pulmonary fellows to do that. While at NHLBI I was second author on a paper in *Nature*, I had a couple of first-author *Journal of Biological Chemistry* papers, a coauthored paper in the *Journal of Clinical Investigation*, a ton of papers.

Okay, so I knew there was no future for me in the heart institute. I started looking for "real" jobs toward the end of my first year and I wrote letters to the deans of many dental schools; My wife and I had decided where we would be willing to live. Without getting political, there were many places that we wouldn't live, but I wrote to, I think, 40 dental schools and sent my CV. I got one response, from Harald Löe, who was a future director of NIDR, who was then Dean at the

University of Connecticut. He said in his letter to me something like, "You have a terrific background; we just don't have any positions. I wish we could hire you."

Now I'm starting to sweat a bit, because I've got two kids and a wife, and so I started doing some moonlighting for a dentist in Chevy Chase. I would work one night a week to be sure I still could do dentistry as a fallback. I even did a crown for my mother-in-law. I mean, that's high pressure to say the least. I was really worried, but then somebody from Tufts told me, "You can always come back to Tufts. Don't worry about it." Then one day, out of the clear blue sky, I get a call in my NHLBI lab from a guy named Dick Greulich, who was the then scientific director of the aging institute (NIA), but also a former scientific director of the dental institute, and very good friends with Marie Nylen, then the scientific director of NIDR.

Little did I know it, because I didn't know Marie, but she had been watching me while I was in the heart institute. She also didn't have a position, and she spoke to Dick Greulich about a possible position for me. Dick was interested in having a dentist come to NIA, because he had been dean, founding dean, actually, of the dental school at UCLA. He wanted to include an oral study in the aging institute's big clinical program - the Baltimore Longitudinal Study of Aging (BLSA). People volunteered to join this study and the NIA followed them for the rest of their lives. All participants started off healthy, taking no significant prescription drugs, having no major medical disorders, and then they were followed for their whole life regardless of how their medical status changed.

KD: Were you involved with that?

BB: Yes. Dick Greulich wanted to include an oral physiology component, and I started that. I was a Senior Investigator in the Public Health Service, so no tenure track. As long as I didn't commit

some moral turpitude or whatever, after a year I was in the Public Health Service forever. But I had to be assigned to a lab or branch, and they assigned me to the Laboratory of Molecular Aging, which was again a terrific fit. Because what that lab worked on was kidney function. And remember kidney function involves water movement and electrolyte fluxes in epithelial cells. And what is it that salivary glands do?

I was a little on the outside, but I learned from all these people. And the guy who was the lab chief was the late Bert Sacktor, who was a really well-known renal physiologist, again an absolute luck out for me. I kept picking up good credentials by association. So I started the oral physiology component and had my own lab. The aging institute had colonies of aging rats. Each month you'd write an application stating, "I need so many 3-month-old, 6-month-old, 12-month-old, 24-month-old (the latter were very valuable). And you had to have good reasons for whatever you requested. Thus, I began studying cell preparations from parotid glands of different aged rats.

At the time, there was a stereotype that as humans got older, salivary gland function decreased. So if you're an old person, you're going to make less saliva just because you're older. And I think what we showed there is that isn't the case from our BLSA studies. Rather it was due to medications or illness. People who are healthy can make as much spit when they are old as when they were younger. We showed this in both cross-sectional as well as longitudinal studies. There was no question, if you made a lot of spit when you were young, you made a lot of spit when you were older. So, the clinical study went really well. In my lab research I collaborated with an endocrine physiologist named George Roth, and a post-doctoral fellow that worked with him, Hideki Ito, a young geriatrician from Japan. Both of them became dear friends for life. They worked with different cell preparations, but they were asking the same sort of questions that I

was asking with salivary cells. We published a bunch of papers in the *Journal of Biological Chemistry*, *American Journal of Physiology*, etc., and really did well.

And then one day in the summer of 1981, I got a call from Marie Nylen, and she had an opening to become NIDR's Clinical Director and Chief of the Clinical Investigations and Patient Care Branch. I don't know if you know this, but Pam Robey and I just published a paper about Marie in "Oral Diseases," and you might want to look it up. If you have trouble finding it, let me know. I really loved Marie. She was wonderful, like a wise old aunt. She was patient with me. She gave me advice when I screwed up. She knew me before I got there. She knew what I needed to succeed and made sure I had it. She nurtured, absolutely nurtured, me. She was a great mentor and, in her own right, a terrific scientist, and probably had to go through hell as a woman at that time to achieve what she achieved.

I was fat, dumb and happy at NIA, and I said to her, "Please let me think over the weekend." And I'll tell you this: When I was in the heart institute, I certainly looked into the dental institute, but historically what I found was that the dental institute hadn't been too friendly towards dentists. They were treated as second-class citizens. This may not have been true, but it certainly was my impression. NIDR had terrific science when I was coming up in science. Folks like Karl Piez, George Martin, Steve Mergenhagen, etc. They had some really terrific science, but very few dentists succeeded there. Marie was one of the few.

And I was a little leery. When I was in the heart institute, the people I worked with knew I was a dentist, but I was as good as them scientifically and it didn't matter. I had a very good self-image as a scientist from NHLBI, and as a clinical scientist from my time at NIA. Anyway, my wife and I talked a lot and, long and short, I joined NIDR.

The position was interesting because the NIDR Clinical Director is like chief of a hospital dental service. I had to sit on the Clinical Center's medical board, as I represented the dental service if you will. Thus, on the Medical Board there was somebody from NEI, there was somebody from NHLBI—from each institute—who was a clinician that was relevant to that institute, and you dealt with hospital policy. That's not the way it's run now, but that's the way it was run then.

I always felt good as a dentist from my days working with Michael Cohen. The mantra in dental school was "the mouth is connected to the rest of the body." However, ninety-five percent of the faculty didn't pay attention to it, but he did. And I bought that, and I was very comfortable as a dentist sitting at the medical board and never let anybody shortchange dentistry or the dental institute. I always spoke up.

And when Marie hired me, again, she knew me. She knew I was interested in oral medicine, and I was not so interested in endodontics or restorative dentistry. And when she hired me, she said, "I'm going to hire a Deputy for you." And that's an interesting statement because usually the person you hire would hire their own Deputy. And she hired as a deputy a guy named Mike Roberts, who again became a dear friend. He was a hospital dentist, a career Public Health Service officer, and a pediatric dentist. Mike could stand on his head and do a restoration on a kid who was screaming and, importantly, he previously had run a hospital dental service. For Marie, it was like, "Bruce, you do not have to worry about the dental service part. We've got this terrific guy, who's also a good human being, and who will let you do the bench to the clinic research part."

She also assigned to me three dentists that were then doing research in Building 30. One was Phil Fox, one was Martha Somerman, who later became a Director of the Institute, and another was Terry Hoffeld, who left the lab after a couple of years and went to work in extramural. All

excellent people, all good scientists. Phil and I became very close. Phil had worked in—Do you know the name Reuben Siraganian?

KD: No.

BB: Reuben Siraganian was an MD immunologist, MD-PhD who worked in Building 30 initially and then later in the Clinical Center, near our labs. Reuben was an excellent immunologist and had Phil as a postdoc. Phil was an oral and maxillofacial surgeon who also decided to go into research. He was interested in immunology, and in particular about Sjogren's syndrome. I worked closely with Phil and the lab evolved thematically, just like Crystal's lab, with a focus on salivary glands and their disorders.

KD: I'm sorry to interrupt, but this was a new branch at this point, Clinical Investigation and Patient Care, right?

BB: Yes. Technically there was a previous branch, but I don't know what it was called.

KD: I'm trying to get a sense of if something new was going to happen here.

BB: The previous clinical director, Karl-Åke Omnel. had a small lab. He left NIDR, and the opening came up. He became dean at the University of Washington's dental school in Seattle. He had a small research program. It was, let's say, 10-15 percent research, 85-90 percent clinic. And when I took over, I don't know whether Marie gave it that name or that was the previous name, but when I came, the department had something, I don't know the exact number, but let's say 40 people in the clinic, and seven or eight of us in the lab. We took over space in Building 10 on the 1A corridor that previously had been office space. While I was finishing up my last six months at NIA, NIDR renovated the space. Thereafter, Terry, Martha, and my group moved into the lab. Phil had a small lab in the clinic.

I told you I had a lot of respect for dentistry. I'm very proud of the fact that no one in the clinic was fired by me or driven out by me. People knew I appreciated what they did, but they saw the direction the branch was going. Some people who were career officers in the Public Health Service, and senior, after a couple of years just retired. People who were more junior in the Public Health Service wanted to move around anyway, and those positions became available. Almost always I would recruit someone who would either be in the lab or be straddling the clinic and the lab like I was and like Phil was.

Also, we started a training program. Going back to pulmonary branch in NHLBI, they trained people in pulmonary medicine. People who had done an internal medicine residency came, they got trained in pulmonary medicine, they did research, they went out and became pulmonologists or assistant professors of pulmonology. We wanted to do the same sort of thing. We started an oral medicine program. The Institute stopped it, which I think was a terrible idea, after I left being Clinical Director. We trained some unbelievably good people who continued to contribute much to dentistry and science. For example, we trained Jane Atkinson, who was, a really good clinical researcher, then a professor at U Maryland, and then became a very big kahuna in extramural at NIDR and then at NCATS. Jon Ship, who was just wonderful and was a professor at U Michigan and NYU, Ava Wu, who is a professor at UCSF,. Ingrid Valdez, who was for many years at the Denver VA hospital. Mike Brennan, who became head of oral medicine at Carolinas Medical Center, Vidya Sankar who was at UT-San Antonio and now is head of oral medicine at Tufts. Lorena Baccaglini, who's at the Institute now in extramural, after being an epidemiology professor at U Nebraska. We trained a whole host of people who did really well and who are still having an impact on oral medicine. Many, many good people.

KD: This training program, was that within the intramural program, or was it a fellowship kind of thing?

BB: It was within the intramural program, but it was a fellowship, an oral medicine fellowship. It came from the slots when we had turnover in the clinic. So these people did hospital dentistry. They went on rounds in the hospital, and by going on rounds, they advertised to the hospital what we in the dental clinic were capable of doing for patients/research subjects of other institutes. We sent them to special courses. I tutored them in biology. It was just a terrific program.

I also recruited postdocs that could come help us in the lab. For example, I recruited Indu Ambudkar to work on intracellular calcium mobilization. Indu took over as branch chief after I retired and is the new Acting Scientific Director. We began in my lab working with parotid cells and submandibular gland cells from rats just as I had done at NIA. We also took a different approach, based on something I learned from Bert Sacktor. I recruited a wonderful fellow, Taishin Takuma from Japan, who later became a professor of biochemistry there. The different approach was that if you want to study electrolyte fluxes which drive water movement, you also should study them in membrane vesicles, little circular membrane from the epithelial cells. It's too complicated to study electrolyte fluxes in whole cells.

Thus, from my connections in NHLBI, where the major NIH renal group was situated, I asked a friend of mine, Mark Knepper, who was a nephrologist, if one of my fellows, i.e., Taishin, could come up and learn how to make vesicles. He said that was ok and Taishin did just that. He then came back to our lab and now we knew how to make vesicles. Then I had another position available, a more senior one. I called Mark Knepper again and I said, "Do you know anybody who might be looking for a permanent position at NIH or a tenure-track position at NIH who is

really good at electrolyte fluxes like you guys do?" He said, yes, a guy named Jim Turner. Jim Turner was then associate professor at University of Toronto. He had done a postdoc in the kidney lab in NHLBI, met his then girlfriend, now wife, and wanted to come back to Bethesda. You know sometimes the gods are shining down. I had a position. Jim was a really first-class biophysicist—it was a perfect match.

All of a sudden, we had an incredible lab, with Jim doing world class electrolyte fluxes with sodium, potassium and chloride, and Indu doing world class work on calcium fluxes, i.e., we suddenly had a lab better than anybody in the world in studying ion fluxes in salivary glands.

In the meantime, Phil and I had decided that we were going to follow the classic NIH model of conducting bench-to-clinic research. You need a disease, in our case a symptom (dry mouth). You need to understand the physiology. I had my lab, Jim had his lab, Indu had her lab. We knew a lot about the salivary physiology. We also knew a lot about the inverse, the pathology, especially radiation damage and Sjogren's syndrome. We had all of the ingredients to develop meaningful salivary gland treatments.

Clinically, it was nice, as I was interested in radiation, while Phil was interested in Sjogren's. Since both conditions had as a sequelae dry mouth, but for different reasons. We decided to establish a dry mouth clinic. We didn't want to see people that were taking medications that blocked salivary flow; we just wanted to see these two types of patients, radiation and Sjogren's. It took us a few months to get the word out, but I think we ended up with 3,000 patients or so. We would see them and evaluate them. All of them weren't necessarily appropriate for our studies, but this was classic NIH. This was a big pool of patients. And as everything evolved, Phil had the idea to test pilocarpine for treating a dry mouth. It's an old drug that we used all the

time in the lab to stimulate salivary flow in animals. Phil held the IND for it. Do you know what an IND is?

KD: Yes.

BB: Investigational New Drug, i.e., permission from the FDA. Phil got that for pilocarpine, and we did the initial two studies together, and it worked. Later, for the Phase III studies, Phil and Ingrid Valdez, who was then an oral medicine fellow, represented our group with the multisite study of pilocarpine that ended up as a *New England Journal of Medicine* paper. Pilocarpine for clinical use in dry mouth became, Salagen, and was the first dry mouth medication approved by the FDA.

KD: So you're looking at neurotransmitters and pilocarpine as an antagonist? Is that how it works?

BB: No, actually pilocarpine is a cholinergic agonist, so it stimulates secretion.

KD: OK.

BB: The idea for Phil and me was that both radiation-damaged and Sjogren's-damaged salivary glands are sort of mucked up. they've got damaged tissue, with inflammatory cells, fibrosis, etc. Maybe the neurotransmitters can't get to the receptors and signal the cells to secrete, so let's try increasing the secretory stimulus. Already pilocarpine drops were being used in the eye for dry eye complaints. We had used it tons of times in animals, all different kinds of animals, and Phil had no trouble getting the IND. It worked very well. However, it comes with some side effects like an urge to urinate, sweating, so some people are uncomfortable with it, but it was the first drug ever approved for salivary dysfunction.

Phil, as an oral surgeon, was very well versed in practical medicine. I became reasonably well versed in practical medicine because I had friends in the hospital. For example, I was interested in swallowing. I had a friend who was a neurologist, and he taught me to do a good head and neck neurological exam. The kinds of patients we dealt with always had medical problems. The Clinical Center, at the time, was like a dream. Our role as the dental service was to help anybody who had oral problems that was in a protocol someplace else. If I didn't understand something, I could ask somebody in NHLBI or NIDDK or NIAID or whatever. People didn't blow me/us off; it was just really good.

Also, Phil suggested, and I agreed, that we needed an internist for the Sjogren's clinic, and that's how Stan Pillemer came to us. Stan was a friend of Phil's, and became a friend of mine, and still is. Stan is a rheumatologist, and rheumatologists are really good clinical immunologists. I don't know how Phil convinced him to come, but it was great, and Stan was a terrific guy and that worked out well. And when he retired, I did the same thing; I recruited a rheumatologist, Gabor Illei, who was also terrific and played a big role in our gene therapy study. Also, I got more involved with radiation damage and radiation biology, collaborating with a wonderful guy in the NCI, Jim Mitchell, who was Chief of Radiation Biology there.

I always read widely in science and in medicine. I read an article in, I don't know whether it was *Nature Biotechnology* or *Nature Medicine* or *Nature Genetics* or something, but whatever the journal was, the cover story showed a picture of a blue lung. The picture and the paper within were from Ron Crystal's lab, where I had been a postdoc. They had used an adenovirus to transfer a gene encoding a protein call beta-galactosidase, which is like lactase. If you're lactose intolerant, the pills that you take are an enzyme that breaks down lactose. There's a very nice, simple assay where you incubate cells or tissue, if you want to see if beta-galactosidase is

expressed. You incubate the tissue or the cells or whatever with a substrate called X-Gal, and if the enzyme is there, it reacts with the X-gal and turns everything blue, i.e., blue lung.

I saw that and I said, If Ron can do it in lung, I can do it in the salivary gland. They did essentially a bronchoscopy, where they stick a tube into the lung, squirt in the adenovirus containing the gene. After x number of days, they kill the animal, take out the lung, incubate it in X-Gal, and the lung turned blue.

KD: We're heading down the gene therapy path here, and I just want to wrap up with NIDR in the 1980s. Did Harald Löe come in at some point there?

BB: Harald Löe was Director. When I came, he was already the Director. And he was very supportive. I mean, he was over at Building 31, but he got what we wanted to do. In his day, the kind of research he did had, and still has, a huge impact on clinical periodontal research. And he was really overwhelmingly supportive. Marie was my boss day to day. Directors have to deal with extramural, they have to go to NIH-wide policy meetings, they've got a whole set of other things to address, so most of my contact was with Marie. I certainly knew Harald, and told him about how I appreciated his letter when he was the dean at Connecticut, and unfortunately couldn't hire me. Harald, Marie and the 80s were really good and supportive. We established a lab that did all the things Marie hoped for and I wanted; we did cells and vesicles, had radiation studies, had Sjogren's studies, and were developing clinical treatments.

KD: There was a restructuring in the late 80s where you went from two sections to four sections.

BB: There was always a section for the clinic, i.e., Mike Roberts' section. I had my section, which probably started off being called Secretory Physiology or something, whatever Indu's is called now. And we eventually added three sections. One for Phil, which was Clinical Investigations;

one for Jim, Membrane Transport, and then when I drifted off into gene therapy, Indu took over Secretory Physiology.

The way intramural NIDCR used to work, the Scientific Director gave the lab chief the budget. So whatever our budget was, x million dollars, the SD gave it to me. I could do whatever I wanted with it. What I did with it was as follows; I sat down with Mike, Phil, Jim and, Indu in a room and said, "What do you need?" Every year, that's what we did. They knew what I got from the budget and I knew what they got. I didn't take most of the money for me and they got screwed. None of that. It was just, these people were my friends and still friends, and we just helped each other. And it was just terrific. The clinic budget was pretty well set, but as soon as Phil's lab was established and he was doing well, certainly with Jim and then when Indu became tenured, interesting story, they had to have money, so we just sat down together.

KD: Why was that an interesting story?

BB: Unfortunately, when Marie left being Scientific Director (her husband died tragically and she left to head extramural), the person who took over was a guy named Abner Notkins. I won't speak ill of the dead other than to say in our house he was known as Darth Vader. He was not a nice man. I was sort of protected, he couldn't hurt me because I had too many positive accomplishments with good people under me. But he could hurt people who worked with me. It happened that while I was on a sabbatical in NHLBI (I will discuss later), Abner wouldn't approve Indu's tenure. I took the tenure papers to the then-director of the intramural program of the NIH, Carl Kupfer, who was also director of the eye institute. I knew Carl because he was formerly a clinical director, and we were friendly and we had respect for one another. And I said, "Carl, can I please have a meeting?" "He immediately said yes." He and I sat in his office and I said, "This person

was refused tenure by Abner. Please look at her credentials and letters. Before I left the office, he signed the tenure papers for Indu.

KD: Yes, we'll talk about that in a little bit. That's great. I just wanted to get a sense of how things were, how the lab developed during the 1980s. So we started talking about gene therapy. This was the early 90s.

BB: I got the idea in ... I don't know when the Crystal paper was published. Let's say in '91. In early '91 I began thinking about it. And I spoke with Ron. Ron and I are still friends and he's continued to help me, and I think I've reciprocated as best I could. Ron's a professor of genetic medicine now at Cornell, but we're still friendly.

Ron was a tough cookie in the sense that, like George, very blunt. And if you said something that was ridiculous, he would just say, "That's stupid" or something like that. I went up to see him and I said, "I saw this paper of yours, and I was thinking that we could do the same sort of thing with salivary glands." And I described what my idea was.

I knew two things: If he could use an adenovirus in a lung, I would bet my paycheck on the fact that I could use it in a salivary gland. And if he could do a bronchoscopy and infuse a virus into the lung, we could do a similar thing in a salivary gland. We were doing sialograms, cannulating the ducts of parotid glands, and doing contrast x-rays, in the clinic, so we could certainly cannulate glands and infuse a suspension of a virus—what gene I didn't know. You're not going to cure Sjogren's or radiation damage with a blue gland. But we needed to prove it could be done. It was the early days of gene therapy, and we needed to prove we could transfer genes into salivary glands.

Ron said, "Not bad. That's reasonable. Here's the deal. You get a postdoc to work with one of my postdocs. My postdoc's first author of the resulting paper, your postdoc's second author. I'm last author, you're next-to-last author. We'll give you everything you need. We're here to help."

So there were still a couple of problems. I knew no molecular biology and no virology. So I did two things to address that. First thing I did was—you're in Rockville, right?

KD: Germantown.

BB: Right, but you're here. So you know in downtown Bethesda there is a Hyatt Hotel? I took a week-long course in the basement of the Hyatt building from I think it was—I don't know what the name of the group was, maybe American Association of Pathologists or whatever—on molecular biology for newbies. I learned how to run gels, PCR, etc., do whatever, and learned vocabulary. It was crazy. I didn't know any of it.

And then I had another friend. NHLBI was very, very good to me. I had a very good friend there, the late Vince Manganiello, who was a Section Chief. He was a pediatrician/biochemist. We were really good friends—good friends for a lot of reasons, even socially—and Vince worked on fat cell metabolism. It was also controlled by receptors, and it involved cyclic nucleotides. The physiology was different but sort of the same. Vince had started a couple of years before doing molecular biology, just changed his lab from more protein, classic biochemistry to molecular ways to answer questions.

So for six months beginning in '92, I put on a pair of jeans and t-shirt and functioned like a postdoc in Vince's lab. Whatever he told me to do, I did. I learned how to sequence DNA, learned how to do all kinds of gels, make plasmids, whatever. And so I worked like a postdoc. I came in on the weekends, etc.

And I was very good friends, from the time this guy was in dental school, with someone named Lawrence Tabak. You know the name. So Larry, when he was in dental school at Columbia, worked with Irwin Mandel. Although I never worked directly with Irwin, Irwin was a mentor in many ways and helped me enormously when I started looking at salivary glands at the aging institute, e.g., how to do clinical studies on salivary glands. He was always there to answer questions and advise. And he was also an avid reader. We would often talk about books, and we just talked about so many things, science, literature, and, by the way, he was also Phil Fox's mentor in dental school.

Anyway, at an IADR meeting in Los Angeles, I gave a talk. It was while I was at the aging institute. Irwin introduced Larry to me and said something to Larry about, "I want you to listen to this guy. This is what you've got to do."

And Larry and I just became good friends. Larry's done a different career path than me, but he got a PhD, and he did, and still does, really high-quality research. Larry and I, once he became faculty at Buffalo, used to talk a lot. And so maybe it's appropriate to tell you about writing down on a napkin the idea for gene therapy.

KD: Yes.

BB: I told people in the lab what I was going to do. I couldn't really tell Abner Notkins, because he was not nurturing, whatever the inverse of nurturing is, that's what he was. And to take a sabbatical, at NIH you don't really have sabbaticals. If there's a reason, like I say I want to learn molecular biology, okay. As long as you sign the paperwork that you have to sign in your office, you're going to be in the same building, you don't have to make a big deal out of it.

So there was a salivary gland meeting in a hotel in Buffalo in November ’91, and Larry and I were sitting in the back of the room. It was in a big hotel ballroom with chairs. In the back there were some chairs next to tables, and Larry and I had gone to this lecture, and we were kind of bored, so we sat at this table way in the back. I took a cocktail napkin, which unfortunately, I didn't save, and wrote down with a pen the idea of using an adenovirus to transfer a gene to salivary glands—he was the first person outside the branch that I told. Well, that’s not true, I told Vince and Ron. I told Vince before my sabbatical.

But I told Larry and sketched out doing the sialogram, using the adenovirus. I told him I’d spoken to Ron Crystal. And I said I didn't really have a gene but I thought if we could do it, then the gene will come along. And Larry said, “Great idea. Just terrific idea.”

So I went back home the next day on a plane, an early morning plane, with Jim Turner, who also had said terrific idea. I specifically told him, and I also told Larry, how I thought I could get it to work, i.e., how to make ducts secrete fluid. About two or three weeks later, I get a call from Larry, who is by now at the University of Rochester; he left Buffalo to become a professor at U Rochester. And we often did this sort of thing, i.e., called one another, and he said, “Did you see this paper in PNAS by a guy named Peter Agre about a water channel protein called CHIP 28 (later known as aquaporin-1)”? I said I hadn’t read the issue yet. Our lab subscribed to PNAS, so I just hadn't gotten around to it. I said, “I’ll look at it.” I called Larry back, “Looks good. I’m going to contact Agre” So I contacted Peter Agre, asked him for the cDNA and if he would be willing to collaborate. I also told him my crazy idea and he said he would be willing to collaborate.

KD: This is where you found out about aquaporin.

BB: Yes, Larry told me about the paper and within a week I contacted Peter. To send somebody a cDNA is no big deal, and so it was no problem to get it. And we were now able to use it. Also thanks to Larry, I recruited a guy named Brian O'Connell. And I don't know if you know Brian's name. He's certainly on a lot of papers with us. Brian is also the immediate past-president of the IADR, so he's certainly done very well for himself. He's a professor at Trinity in Dublin.

Brian got his PhD with Larry and was well versed in molecular biology and I recruited him to be the postdoc to work with Crystal. Brian's first year here at NIH was entirely in Ron's lab and he basically finished everything that we needed to show that we could get blue salivary glands and came back for his second year to our lab and just tidied that work up a bit, i.e., finished that paper up with Ron's fellow. That research was published in an *American Journal of Physiology* paper in 1994. Basically Brian published a picture of a blue parotid gland, another picture of blue submandibular gland, and another picture of blue sublingual gland to show you could do it. It now was a fait accompli. So before Abner had a chance to complain, before the Board of Scientific Counselors said, "You have no business doing this," we did it.

And when Brian came back to the lab, he wanted to start his own work, so he worked on the histatins, and on using gene therapy with histatins as a type of anticandidal treatment to block or prevent oral candidiasis.

And I also recruited another wonderful post-doc, Christine Delporte , from the Free University of Brussels. She had done her PhD working a little bit with salivary glands, knowing epithelial cells very well, and knowing receptors and transport physiology, but also knowing molecular biology. I recruited her specifically to make the adenovirus vector encoding aquaporin-1 and do the studies that would show if it worked. And she was terrific.

And at the same time, we recruited two other people who were very important. Both individuals worked with Brian as postdocs. One, Changyu Zheng, who is still in the lab and became my staff scientist. He's a wonderful guy, a good friend, and you'll see his name on tons of papers related to the gene therapy from our group. We also recruited a guy named David Lillibridge, who was also a wonderful guy. David married Christine, so we also were the matchmakers. He moved to Brussels with her and went into industry. He still works with Pfizer and runs clinical trials related to vaccines for Pfizer.

Anyway, so Christine made the vector, which we called AdhAQP1. We tested it in irradiated rats. It worked well and we published the results in PNAS. Then we started doing initial safety studies, working also with Brian's wife, Anne, who worked as a visiting fellow both in the clinic and in the lab with Indu— Anne is a pediatric dentist and now also a professor at Trinity. With Anne we did our first big animal study with macaques, *macaca mulatta*. Unfortunately, we didn't have enough, but we did a study with six animals. It wasn't enough to show efficacy but it was enough to suggest safety.

KD: Are we still in the 1990s?

BB: We're still in the 1990s. And in order to do really first-class safety studies to satisfy the FDA, we needed to do studies with a large number of animals. Somehow I got hooked up with Drs Molly Vallant and Rick Irwin at NIEHS', the National Toxicology program. They had realized that genes were going to be a new type of medicine, and they were willing to work with us and do the toxicology studies if we supplied and delivered the vector. They had a big contract with some company in Rockville. You know where all the universities are in Rockville now?

KD: Yes.

BB: There are biotech places all over that area. There was a place doing animal studies for NIEHS. Changyu used to go out there, cannulate parotid glands or submandibular glands and deliver the AdhAQP1 vector. Then, at different times, they would sacrifice the rats, take out the glands and other tissues, and do the toxicology studies. Changyu would do all molecular biological determinations of vector, in different tissues and fluids. They'd give pieces of tissue to us, and Changyu used QPCR to measure if vector was in the liver, spleen, kidney, whatever. Our lab would do all the molecular stuff and they would do strict, classic tox studies. We published a paper on the toxicology in 2006 in *Molecular Therapy*, but before that we presented all of the toxicology results to the FDA. They were truly superb tox studies. The other thing we needed to go to the FDA for approval was to have large animal studies. And although it was the NIH and money compared to a university was a little better, we couldn't get enough monkeys. We decided to collaborate with another former fellow of mine, Songlin Wang, who was then and still is a professor at Capital Medical University in Beijing. Songlin is an oral maxillofacial surgeon/PhD, whose research was focused on radiation damage; he was very well trained in radiation biology. He had a model for salivary gland radiation damage that he developed using parotid glands in miniature pigs. Basically, they were cheap, he had a lot of them, and he and I worked together to get his animal facility approved by the NIH so that we could do safety studies there.

We would ship vector to China, by FedEx, on dry ice. Songlin knew how to cannulate because he'd done a lot of that here and they would do the same kind of studies Christine did in rats, but adapted to work with pigs +/- radiation and then look to see if the vector was effective. It also nicely worked, and once we knew it worked I called up Larry, who by then was the NIDCR Director, and I said, "I think it's a go. Are you guys going to be able to support going to the FDA

and all that entails if the study's approved?" "Yep," said Bob Angerer, who was then Scientific Director, and "Yep," said Larry. Everybody's on board. NIDCR was very supportive.

In late 2005, I submitted the clinical protocol to use AdhAQP1 in humans to the NIH Recombinant DNA Advisory Committee and to the FDA. The FDA has both a scientific review and a biosafety review. The FDA was going to let the Recombinant DNA Advisory Committee be the scientific review and they would do the safety review, in house, in their Cellular and Gene Therapy Branch.

In early December of 2005, I had to go before the Recombinant DNA Advisory Committee, which then met at the Marriott Hotel over here in Pooks Hill. It was like testifying at a House or Senate committee. A U-shaped table. I'm sitting at the front by myself with a microphone, very intimidated, but actually it was no problem. The proposed therapy was not for a cancer, not for heart failure, not for muscular dystrophy; this was for a dry mouth, for a symptom.

And it was the first oral gene therapy study, and one of the first quality of life studies to use gene therapy; the earlier ones were related to blindness. Thus, there were protocols approved before they would use vectors delivered to the eye, but this was a little different from that. The RAC didn't question any of the science. They questioned me a lot on how we were going to judge quality of life improvement, i.e., subjective responses. Interestingly, one or two people questioned me on why we didn't use AAV as a vector because we'd already had made an AAV2hAQP1 vector and AAV vectors were considered safer than adenoviral vectors (and still are).

Jay Chiorini, who I recruited to the branch, was previously a postdoc with Rob Kotin in the heart institute. Notice I had a lot of heart institute collaborations. He collaborated with one of my

postdocs, Ginger Braddon, to make that vector, AAV2hAQP1 that we published while he was still at the heart institute. Jay is now using that vector in his own clinical studies.

And so my answer to the RAC was funny in retrospect, because it was wrong, but they accepted it. I said I chose to use an adenovirus because we know from our mouse, rat, monkey and miniature pig studies that after two weeks, the adenoviral vector is all gone, i.e., it no longer works. And they said, "Good reason." I wanted to make sure it was safe. I didn't want to cause anybody to grow teeth out of their salivary glands or some sort of strange thing. And they accepted that.

So got approval in, I think, January of 2006 from the FDA and in February we started recruiting patients. Recruiting was hard. That was a problem. We didn't have a CRO to work with. You know what a CRO is, a Clinical Research Organization? So when you do a clinical study, you have to dot every "I" and cross every "T", and particularly if it's something as invasive as gene therapy. A CRO has people watch over you and make sure you follow every rule. They also develop case report forms, make sure you fill them out right, and make sure they're done in a timely way. They also make sure that you report adverse events correctly and promptly. Somebody is absolutely looking over your shoulder to make sure you don't screw up.

Since NIDCR didn't have a CRO under contract, Bob Angerer arranged for us to use a CRO that the eye institute used. I'm sure money changed hands at scientific director levels. NIDCR, after a year or year and a half got their own CRO contract. But working with the NEI CRO helped us get started in a big way.

KD: So you're starting this up in 2006?

BB: We started recruiting in 2006 and we had problems recruiting. You might remember in 1999 that a death occurred following use of an adenoviral vector in a liver study in Philadelphia. And without going into that at all, a lot of people were leery. And I had at that time only one research nurse working with me, Linda McCullough, and she and I were doing everything we could to recruit patients—contacting oral maxillofacial surgeons, contacting otolaryngologists, using friends who were otolaryngologists to contact their friends, it was on clinicaltrials.gov, etc. We also put notices in different places. Anyway, finally we got the recruiting ball rolling, but it took probably well into 2007 to really start having cohorts coming in.

KD: So you're recruiting people who had had radiation therapy and Sjogren's?

BB: Only radiation therapy. So you know the Marine mantra, KISS—Keep It Simple Stupid— we focused on just one problem. Like when you go to the FDA. One problem, simple, and a certain type of radiation damage. You couldn't have glands that were completely whacked out. Also, some people recover from radiation damage. We had to select people that had some evidence of gland function, but not enough to make them comfortable. They complained of a dry mouth swallowing problems, whatever.

And we were very lucky. Actually, the first person recruited was a federal prosecutor, so if we had screwed up, we'd have been in big trouble. He was a great guy, but unfortunately, it didn't work for him. However, it worked on the second person. So we had three people per cohort (that was typical of the early gene therapy studies) and did a vector dose response study. The third person, it turned out, had a latent adenovirus infection in the parotid gland. This is very unusual. When we put the vector in, the latent adenovirus was reactivated, recombined with our vector, and he started spewing adenovirus into his saliva, both wild type adenovirus, as well as the vector. His glands were a little machine. But importantly, he never released adenovirus into the

bloodstream. This was a big deal. Not into the bloodstream, so no systemic release. That eventually pooped out, i.e., the cells that were infected were, for the most part, cleared by his immune system, leukocytes or macrophages, etc.

But that was a serious adverse event, and due to the vector. We had to put a hold on the study. We had to do all kinds of tests. We actually published a paper on him in the *Journal of Gene Medicine*. Not by name, but on what happened and how it resolved. The data safety monitoring board for the study reviewed every single thing that we did, and then finally they gave us approval to continue the study.

It was really unusual, but I think we handled it in a really good way. And again, the CRO, which I think at the time was still one from the eye institute, people were just great. The DSMB was really good and helpful and doing just what a DSMB should do. They asked us good questions, made sure we did all the right things.

Thereafter, we continued with the study and, as it turned out, we saw a very good dose response. You expect with almost any drug that with an increasing dose you get more of an effect, and then you reach some point where if you give too much, the drug effect either plateaus or diminishes. We reached that point by the time we had to stop in early 2011. The FDA made us, like all medicines, put a use-by date and that was in 2011.

I didn't tell you earlier, but the vector was made in Ron Crystal's department at Cornell. They had a lab that could make clinical-grade vector. George Martin's run with Ron blessed me in so many ways. I called up the guy who was in charge of making the vector and said, "The FDA wants some "use by date" on the vector. He simply said, "put five years on it." So that was 2006, and now it's 2011, so that's it; the study is over. The vector was still good, because we used it in

the lab for other studies in cells and animals for many years, but we couldn't use it for people. We had to stop. We only saw 11 subjects. However, we would have stopped after the twelfth subject, because it was clear that the last couple subjects had gotten too much vector and they were having immune responses to it.

We published our first clinical gene therapy paper in PNAS showing the efficacy and safety of AdhAQP1. It was a classic NIH clinical study, a Phase I/Phase II. It showed safety and a little bit of efficacy. We decided to put in another protocol to follow the responders in the study for a much longer time. Originally, the FDA required us to follow everybody for one year, but we wanted to follow the people who responded (we had five responders, people who made more saliva and had less of a dry mouth) for up to three or four years.

I retired at the end of 2011, and Ilias Alevizos, who was a co-Investigator, took over as PI. But I was still working in the Clinical Center on the Medical Research Scholars Program, so I was still here and I was very much involved. For me the interesting thing was that all five people who responded kept responding. The adenovirus was mostly cleared, but it wasn't fully cleared, and we could take biopsies from the gland and show that parotid epithelial cells were still making aquaporin-1. These responder subjects were still making high levels of saliva and they were still happy campers in terms of their alleviated dry mouth. We only followed them up to their third and I think one up to the fourth year, but they were essentially happy campers. We published another paper in *Gene Therapy* about the long term follow up phase.

I retired because I did what I wanted to do. I wasn't Jonas Salk, but I took something from an idea and, knock wood and whatever else, I was blessed to be able to do something that could help people, so there was no need for me to hang around.

At the time I was retiring, the NIH had this program called the Clinical Research Training Program, and I had been on the board of tutors of that program. The board of tutors advised people who were selected to come. They were medical or dental students who could come to the NIH to do clinically-related research and work under the auspices of a senior investigator as a research mentor. They would have one of the tutors as an outside advisor to make sure they weren't getting the short end of the stick, that they were doing okay, and that they were happy. If they had problems, we were there to help them with the problems.

I had been a tutor for many years, and about the same time as I retired, the Howard Hughes Medical Institute decided to stop their NIH program. They had a research scholars program and they decided to stop it. In response, the NIH decided to put the CRTP together with something like the Howard Hughes program, i.e., expand the Clinical Research Training Program to include people who wanted to do basic research. So it was a pool of medical, dental, and now veterinary students who could come to the NIH.

The guy who ran the Clinical Research Training Program, CRTP, was named Fred Ognibene, who is still a good friend. He is a critical care medicine doc. At the time I was retiring, he had moved to be Director of all clinical training programs in the Clinical Center, so he oversaw all the fellowship programs, everything related to training in the hospital. He was given responsibility to oversee the new Medical Research Scholars Program (MRSP) and he hired me to run it.

He just called me up and said, "I hear you're retiring. Any interest in the MRSP?" I said, "Hmm, right up my alley." It was half time, i.e., supposedly half time. I got paid for 20 hours a week. It was really kind of a labor of love because I could start it from almost nothing and develop a program that became highly successful. I told Fred I would stay three years. I really wanted to

retire in the sense that I had other things in my life. I'm lucky, I'm blessed with a wonderful wife, two wonderful kids and three terrific grandkids. I have outside activities I wanted to do.

But I said to Fred, I'd give him three years, until 2014, and that gave him plenty of time to look for somebody after we set up the program and worked out the kinks. And it was terrific. It remains a wonderful program. I was always interested in education, and so it was a nice way to sort of finish off my NIH career.

KD: Specifically regarding dentistry, a few years earlier, you had written a commentary in the *Journal of the American Dental Association* about an impending crisis in dentistry. What was that about?

BB: Well, I don't know if you know the history of dentistry. Dentistry was originally part of medicine. And the first dental school was in Baltimore, now University of Maryland Dental School, Baltimore College of Dentistry. It basically was thrown out of the medical school there. I chose to go into dentistry for the reasons I mentioned to you. They were excellent reasons for me, and dentistry has been very, very good for and to me. I've tried to give back. But dentistry has moved further away from medicine. I'll tell you a funny story. I once was recruited for a job at the University of Kentucky, and I went for an interview. I was talking to people, and I met someone who was, I think, a restorative dentist who worked part-time at the school. He said the way he deals with medical problems, was that his office is a second-floor walkup. If they can make the stairs, he can treat them. I mean, at least that was thoughtful.

But there are a lot of people that forget what they were exposed to the first year and a half of dental school. I worked in hospitals as a dentist for around 40 years. When I was at NIA in Baltimore, the longitudinal study was carried out at what was Baltimore City Hospital. It's now part of the Francis Scott Key Medical Center of Johns Hopkins. Then I worked in the Clinical

Center. So if I didn't know anything that affected my patients/subjects that involved the heart or the lungs or whatever, I asked somebody. Or if I didn't know the medication or whatever, I did the same. I was never ashamed to ask. I bought the dental school mantra that the mouth is connected to the rest of the body and that you can see things in the mouth that reflect the body. Maybe you don't have to be a physician like European stomatologists of the old school, but I think dentists should know some general medicine. Almost like an ophthalmologist. Working in the Clinical Center, I never had a big clinical problem because I could ask. I would literally say, "Can you excuse me for a minute?" and go down the hall of the clinic and get to a phone and say to somebody, "What does this mean? Should I do this or that?"

Also, dentistry was moving away from biology, cutting back hours in biological science teaching just as biology is going through this gigantic, exponential boom. I thought then, and still think now, it was bad. I thought it was bad for a health care professional. And while I remember the words of my dean at dental school, "The goal of a health profession should be to eliminate itself," I didn't want dentistry to become unimportant. I thought and still think oral health is integral to general health.

There was a then Institute of Medicine, now National Academy of Medicine, study on Dentistry at the Crossroads. Do you know about it?

KD: No.

BB: It's a report, book length, published in 1995, titled, "Dentistry at the Crossroads." It basically said dentistry has to firm up its biological and medical base and use auxiliaries more. It was essentially completely ignored by organized dentistry. The profession blew it off. In 2007, I was elected to the National Academy of Medicine (NAM), then Institute of Medicine. Since then, my

impression is that dentistry is an afterthought at the NAM. However, like when I was on the medical board at the Clinical Center, I still speak up.

For example, the NAM has programs on education in the health professions and often they don't have a representative of dentistry included. For one major panel discussion, a plenary session at the annual meeting, I wrote the president of the National Academy to complain. I asked a couple of my friends that are dentists in the National Academy to cosign it with me and they did. We complained, "How can you not have a dentist? There are X million dentists in the United States, all these patients, etc." Thankfully, they put a dentist on the program.

I guess I am like a splinter to them. However, dentistry truly seems to me almost an afterthought to the NAM. It's terrible. And I think the organized profession has caused it. Dentistry is an honorable profession, but the profession needs to work more closely with other health providers to offer optimal patient care. Dentistry needs to work more with nursing, more with nutrition, etc. Dentists can be isolated; you can still hang up your shingle and practice in your house.

KD: Right. So NIDCR, certainly in recent decades, has emphasized this idea that it doesn't stop at the mouth. The mouth and the body are connected. And that's a big cultural change. It underpins the Institute. That wasn't always the case. I'd love it if you could sort of talk about the way that the culture of NIDCR has changed over the years since you first came in. Has the emphasis changed? Has the message coming from the top changed over those years?

BB: This is just my personal perspective. It represents nobody but Bruce Baum.

KD: That's why we're here.

BB: And so as I mentioned to you, the Institute was the third institute on campus. Do you know the reason why? Because so many recruits in World War II were rejected. They didn't have 12

opposing teeth or whatever. The dental institute always had done excellent science. Trendley Dean's picture is on the walls in the Clinical Center as having won a Lasker Award for fluoride. It has always done great science. And when I came, they had some really terrific people. Steve Mergenhagen, Karl Piez, George Martin, terrific science, but much of it never really linked the two, dentistry with the science. That is fine, because people in the extramural community could pick up on the great science and apply it more directly to dental problems.

However, if you look around at the NIH institutes, essentially all have excellent bench to clinic research programs. I think because of the way our branch was structured, we provided that for NIDR/NIDCR. For example, if you look at the gene therapy papers published by us, you'll see on some of them Indu Ambudkar's name, on some Jim Turner's name, on some Phil Fox's name, on some Gabor Illei's name, as well as my name and a whole bunch of other people. It was truly integrated. I think there is not much of that now in the Institute.

The late Ron Dubner, who was a Lab Chief when I first came, did that. He set up the first real model in the Institute, that I know about, of a problem, pain, and studied key mechanisms, developed treatments, etc. My impression is that there isn't a lot of that now. There is certainly some of it. As part of the anniversary celebration, the Institute is going to have a big symposium, coming up in October, on McCune-Albright's disease. Absolutely terrific work has been done for this condition. However, what does that have to do with dentistry? I'm not saying it shouldn't be done, but I think NIDCR needs other similar programs of more relevance to oral health care. Salivary glands have to do with dentistry, pain has to do with dentistry.

I certainly don't think the dental institute should do just tooth and gum and salivary gland stuff. For example, NHLBI does superb research on kidney and electrolyte problems. You don't know where an idea is going to come in and make a difference. Remember tooth-lid factor and how

important it now is, as epidermal growth factor, in cancer. You have no idea. If Stanley Cohen tried to get a grant now, he would probably be in the 99th percentile or something.

But I don't see a lot relevant bench to clinic research relevant to dentistry now in NIDCR. I'm not there, so maybe I'm totally misinformed. The good science is certainly there. I know a couple—like Niki Moutsopoulos, who's a tenured Senior Investigator. Excellent periodontist PhD. Also, Blake Warner who took over the salivary gland program in building 10. He is tenure track and an excellent oral pathologist PhD. I wish they had kept the oral medicine program. Not just because I was involved in its starting, but because it attracted and brought into research many high-quality young people. They do have a public health training program, but that's in an office outside. It's not in the Clinical Center or Building 30.

People in the oral medicine program worked in Building 10 with us as well as other labs in Building 30. They didn't just work with us. They could work in anybody. So I'd like to see more young dentist trainees. I don't know. I'm an old guy.

KD: All right. I just wanted to get a sense of how things had changed during your years there.

BB: I was there in prime time—both my prime time and NIH/NIDCR's prime time. The institute was extraordinarily supportive of me—absolutely the gene therapy stuff couldn't have been done. Who's going to fund a dentist at a university to do that? At that time we began, there were companies that were funding people or people started companies. Where were you going to find a company for supporting salivary gland gene therapy in the 1990s? But now Jay and Blake's studies are supported by a well-established gene therapy company.

KD: This has been great. Is there anything that we haven't talked about that you think we need to touch on?

BB: I don't think so. I think you got most of my professional life. I'm a very lucky guy, both to have had all these funny things come together, as well as the having the Institute be very good to me.

KD: Perfect. That's a great place to leave it. Thank you so much.

BB: You're welcome. Take care.