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With Brooke Fox, Archivist and Michele Lyons, Curator
Office of NIH History and Stetten Museum

Dr. Robert L. Berger of the Laboratory of Technical Development (LTD) at the National Heart, Lung, and Blood Institute (NHLBI) met with Brooke Fox and Michele Lyons to discuss the notebooks and papers that he had donated to the Office of NIH History and Stetten Museum. They began by discussing the early use of normal volunteers who were available to work in the laboratory between medical assignments.

Berger: There was, and is, Bridgewater College over in Bridgewater, VA, near Harrisonville in the Shenandoah Valley. This was the time when Vietnam was starting up and everything, and so these people could come and serve their military time being normal volunteers. I think it was a Brethren college. The girls over there decided that they should do something as well so they came over and volunteered too. During their stay, living in the Clinical Center or nearby in a rented room, they had also volunteered to work in one of the labs. I got one of them and I had brought two students from Utah State, we really didn't have IRTA's [Intramural Research Training Awards] at that time. This was my staff those first two or three years.

Fox: Well, when I first started going through these boxes, I was trying to look up some of these terms like "deconvolution." I didn't know what it is exactly, because you have some notebooks labeled "deconvolution." I'm trying figure out what some of this stuff is.

Berger: I wonder if we should stop and take an overall view of what I tried to do in marking this thing up [his list of publications]. The idea was to set the stage for the categories of work that we were doing. Mainly we were interested in developing instruments to study enzyme reactions and in particular the reaction of hemoglobin and its ligands, i.e. oxygen, carbon monoxide, carbon dioxide, etc. We wanted to develop instruments using calorimetry or heat flow or optical detection as ways of studying the reaction. These reactions were mostly pretty fast and so the device that you're using to measure them is sometimes slower, particularly with heat, than what they can really follow. So when you say you're going to deconvolute the true signal from the measured signal by various deconvolution mathematical techniques that we have, and that NASA developed for a number of their things, what it really means is that you've got a convoluted signal—it's convoluted from [electrical] noise, response time, slowness, and so forth, and so now you're going to take those out of that the true signal. It has to be deconvoluted.

Fox: So basically in your work you created instruments, you developed instruments?

Berger: Yes. I started out in graduate school working on hemoglobin and building a special instrument to measure the reactions with oxygen and carbon monoxide in very viscous solutions to see if there was any possibility that the reaction may be diffusion limited, which would have very interesting results for any number of aspects in physiology. And I went to Cambridge [University in England] for two years, working with Francis John Worsley Roughton. In that time another

colleague was coming back to the National Institutes of Health (NIH), Joseph Hoffman, and got me interested in measuring the powerhouse of the red cell, that is, the glycolytic energy source in the red cell that breaks glucose down to lactic acid. In doing that it generates two ATPs [Adenosine triphosphate]. Well, those ATPs are used by another enzyme in the membrane of the red cell called ATPase –they have very imaginative names you see–which is what pumps sodium out of the red cell and potassium in. So it's called the "sodium-potassium ATPase pump." And there's another pump for calcium and so on, you know. So we wanted to measure the energetics of that.

Fox: So how much energy is there?

Berger: The thermodynamic of this system turns out to be very complicated. We know experimentally that hydrolyzing ATP to ADP releases 7.5 kilocalories/mole as Gibbs Free Energy. Of that amount, about 5.5 kcal comes from heat and the rest is entropy. If we measure the heat released when glucose goes to lactate, we get 65 kilocalories/mole. If we stop this break down and just measure the heat of pumping, we get one thousand kilocalories per mole. We really still do not understand what this very high value means, but we think it is really is from a change in entropy of the system. That is, there is a large rearrangement of the membrane at the pores as sodium and potassium are exchanged.

Berger: I left Cambridge to take an assistant professorship in the Physics Department at Utah State University in Logan, Utah to try and get over a very severe sinus infection which, after two years, I did Roughton, at Cambridge, starting in 1920, had started looking at hemoglobin reactions in continuous flow, both optically and thermally. He had Archibald V. Hill's mechanic build thermocouples and a special high speed galvanometer to make these observations. This took four liters of solution for each curve, so he used mainly either horse or cow or sheep hemoglobin. I wanted to adapt it to human hemoglobin. We have spent the last 45 years doing that. Thus one line of research was to make an instrument that would measure the reaction rates of hemoglobin and its ligands, oxygen, carbon monoxide, carbon dioxide, etc., using no more than 250 micro liters of each reagent with a time resolution of .2 milliseconds and a sensitivity of .2 millidegrees. Hoffman had at gotten me interested in the red cell pumps and energy source and that required a different type of heat measurement. Small amounts of solution, 150 micro liters of each reagent and very high sensitivity, .2 micro degrees, was needed. I pursued both of these lines of research at Utah State and later over my career at NIH.

The fast reaction work on hemoglobin was an entirely new line of instrument research, while for the red cell work we had what we call, more or less, static calorimeters, which are literally calorie meters, which we adapted from an invention of the 1900s by a man by the name of [Albert] Tian. This calorimeter is really novel in that it measures the heat produced by how much leaks out through the sensors. As you may remember from high school physics, if you had a body of fluid in a beaker and you put in an ice cube and watched it melt and you wanted to measure how much energy was transferred, you did that with a little shield, in this case a Styrofoam cup, around the beaker. You might have used a thermometer to measure the change in temperature of the water as it melted. Knowing the volume and heat capacity of the water you

could calculate the heat of melting of the ice. Since no heat leaked to the outside, we call that an adiabatic measurement. That is, you made the measurement before any heat got lost. Or in these days, you can have a unit underneath the thermopile, called a Peltier unit, which can generate heat or take it away–either one. It's really just a big thermopile but it's a semi-conductor one. You may remember that a thermocouple is simply two dissimilar metals soldiered together, say copper and constantan. If you have copper attached to each end of the constantan and you put one end in the cup and the other outside with a voltmeter across the two copper wires you will get a voltage, and in fact it will be 40 microvolts per degree C. If instead you connect a battery where the meter was, you will find that one end heats and the other end cools. The semi-conductor materials simply does this much more efficiently, producing 200 micro degrees per degree C. and it has a very high coefficient of doing heating and cooling as well. And so when you do that, you keep the solution of whatever you're measuring at a constant temperature, so now that's called an "isothermal calorimeter."

Both of those are generally impractical, so Tian developed what he called a "heat conduction calorimeter." Or, for reasons I've never been able to ascertain, it's called an "isoperibol calorimeter." One can stretch one's imagination and come up with some reason why they chose that name, but anyway, what you do is you build up a unit with these thermopiles and, as the reaction goes on, all the heat generated by the reaction flows out through the thermopiles and so you get a curve that looks like a sort of parabola with the right side stretched out. You now integrate under that–you know what I mean by integration?

Fox: Yes.

Berger: You integrate under that curve and get the total heat that was yielded, okay? And you do calibrations with electrical heating or chemical reactions.

Now, in all of these instruments one wants to optimize the design of the instruments. One wants to be able to deconvolute the signals because this integration gives you the total heat, but you'd like the heat per unit time as well so that you can measure kinetics. Being rather lazy one says, "Whoa, there are computers! We don't need to do all this integration and playing around and so forth; we can say if Mr. Newton had a computer, he wouldn't have bothered with integral calculus." So we developed what is called the "finite element method." It's very simple. You start with the definition of calculus: the limit dx/dy as y approaches infinity, right? What it means is that it goes to smaller and smaller little units and when it gets to the limit that it can go to, that you can define mathematically the limit as a function called a derivative which is dx/dy. And then you go from there and define the integral calculus. Well, we don't do that, we stop back there at dx over dy, but we can chose to get as small as we want because we don't have to take a hundred years to integrate. And that's what we've done. And so there are a whole raft of papers adapting this method to various geometries and various problems and I've just called them "analysis" in the CV there.

Fox: So when I was looking through the papers, you seem to be working with or trying to get some computer company to create a database or software to use? There was stuff called "data

translation personal computer series." You had these books here.

Berger: All right. Now, this is where I've been a little bit concerned about how best to do this because, again, let's start out thinking about either the flow instruments or just straight micro calorimeters. In all of those instruments, what one needs to be able to do is take that electrical signal that comes out, which we call an "analog" signal, and you need to digitize it. Now the first commercially available digitizing boards were made by Data Translation, so what we did here was to be really one of the first groups to make use of the computer using these boards, which were built for a series of personal computers which were then just coming out. This was about 1968 or so. So this board went into the computer, you hooked on your electrical signal, and it produced every step along the way the correct number of zeros and ones to do this. So now what we then did was to fit that into the computer programs that we developed to translate the data into our analytical models and things of that nature.

You have three concepts here. You have the biological problem, and we used three or four problems as sort of classic examples that represented a whole field of problems. Hemoglobin being one for protein, lactate dehydrogenase one for enzyme, ATPase being a one for a transporter. And then you had to develop the instruments to make the measurements you wanted to make on these biological reactions.

Lyons: Excuse me, Bob, could you say those three biological problems again?

Berger: I had divided up–you got the problems, you got the instruments, you got the analysis. And we chose a series of models. One of the models was hemoglobin, as a model of enzyme reactions or a carrier reaction and we used other enzymes as well. We used lactate dehydrogenase, peroxidase, catalase, and ATPase over the years. I mean things changed as we went along, other investigators got interested and so on.

So then, having looked at the problem, and of course other people were developing instruments and doing experiments on a wide variety of problems, there were difficulties in the field. Nobody else was doing thermal detection methods. Nobody was doing the flow apparatus for use in electron spin resonance or nuclear magnetic resonance machines. So when people came and asked us about doing this, we adapted the instruments that we built for optical-thermal work to operate in these instruments too. Then when Dr. J. P. Froehlich in the National Institute on Aging wanted to study the reactions of Calcium ATPase in sarcoplasmic reticulum, we had to develop a special apparatus, which was the quench flow apparatus, for him. In all of these instruments one of the biggest problems is mixing the solutions rapidly with a minimum amount of heat, so we spent a lot of time developing mixers until we finally came out with the ball mixer. And so now in the industry all these instruments come out with that mixer. I just read one thing that came to me yesterday—it's now called the "classic Berger ball mixer." But it does this in a very gentle way and therefore you can put cells through it, whereas with these other mixers, what we call jet-type mixers, break up the cells.

Now there are different time domains in looking at chemical reactions. We were looking at what

we call “pre-steady state kinetics” which looks at A+B going to C, for instance. And not worrying about the quantum mechanical details of that but just observing the disappearance of A or the appearance of C or whatever, and those reactions for enzymes are pretty fast. You would like to have time resolution of one millisecond or less. But you want to preserve the solution—solutions are very expensive to prepare—so we had been developing (Roughton had been developing) flow methods that rapidly accelerated the solutions, then rapidly stopped the solutions. This is called “stopped flow.” And then you watch the reaction.

Now there’s always a little bit lost in there and there’s always pressure problems and so forth, so you know again in the CV I’ve marked which papers have to do with the flow apparatus and which papers with analysis, which papers have to do just with calorimetry, with titration or pH measurements, and in doing this we developed—well, we changed an industry actually. When we started with this, we had thermocouples. And so the first few papers that you’ll see on stopped flow calorimetry, number eight for example, was using thermocouples and a special galvanometer system that Professor A.V. Hill had [used for] his Nobel Prize looking at muscle energies and so forth. It was his machinist who developed that. And I’d gotten his machinist, after buying a number of rounds of beer on half a dozen occasions going down to London from Cambridge, got him to make me one of these galvanometers that had a millisecond response and millidegree sensitivity.

Lyons: That’s the one that’s in your tool box.

Berger: What’s left of it. We had lots and lots of mechanical troubles with the flow being as fast as it was; it would wipe off all of the coatings we would put on. You can’t put too thick a coating or you slow the whole thing down. Yet you have to be thick enough so that no metal is exposed, otherwise you get what’s called streaming potentials which are larger by three orders of magnitude than the thermal measurements that you want to make. You have to realize a single thermocouple puts out forty micro-volts per degree. We were looking at sub-milli degrees, so you see that it had to be very sensitive and very well protected.

We wanted to use thermistors so that we could use a modified Wheatstone bridge and electronic amplifiers instead of a galvanometer. A thermistor is a semi-conductor device which changes its resistance with temperature. Now, normal metal if you heat it, the resistance goes up; but for a thermistor it goes down. And these thermistors almost all have about 4% change in resistance per degree of temperature change. So we spent quite a bit of time developing, with the help of the excellent engineering department over at BEIB [Biomedical Engineering and Instrumentation Branch], amplifiers that would allow us to amplify these signals at the levels we wanted. We were aiming at about ten micro degrees in roughly a milli-second. So when we got the thermistors and measured things, the resistance of that thermistor was a thousand times higher than it would be if it were just a simple resister. One could calculate that from what is called the Boltzmann equation.

I went to the manufacturer, who at that time was Victory Engineering, up in New Jersey, and the chief engineer there was a man by the name of Meyer Sapoff. He was very knowledgeable—he

had an electrical engineering degree from MIT. This material had been developed and whipped up by the West Electric Company during WWII and was open to anybody who wanted to use it. He didn't know why resistance was so high. But thermistors are made up of oxides of metals—magnesium, iron, so forth—well, it turned out there was an oxide of copper in there and when that was taken out, the resistance became exactly what it ought to be for thermistors. Then they had stability problems and he didn't know why that was there. I said, "Why don't you try platinum wires?" So he did and the next step was that they still aged a bit, and I said, "So age them." So they aged them for a year. And now they are so stable that they are secondary thermometer standards. We developed that for the clinical labs and for hospitals and so forth. I have a commercial version of that unit, all digital and everything, that measures directly to a tenth of a millidegree.

Now, what that did was allow the thermal dilution catheters that physicians were taught how to use then by—well, this company had morphed into a new company that Meyer set up called Thermometrics. It still operates in New Jersey, but has been bought up by a big conglomerate. Meyer retired. We had a meeting there, and I have it noted, we had a big clinical round table and I brought in a person I met out at UCSD [University of San Diego] who was an expert on and developed this technique called thermal dilution. But the thermistors that he was using were very noisy. So he and Sapoff got together at that meeting and out of that came the thermal dilution catheter that's used for measuring cardiac output. That's one of the very few methods with which they really have a good measure of cardiac output. Now, from the manufacturer's standpoint it was great because it was a throw-away [disposal] device.

So out of this has come a lot of different things. We developed testing measurements for when the thermistors were properly insulated, and developed a routine for testing their response time and things like this. Now all this is written up in seven various reports that Norman Davids, Bohdan Balko, and I made over the years, but, as you probably know, NIH doesn't publish technical reports. But having started doing a lot of research for the Army, back in undergraduate [days], it became clear to me that the easiest way to write a paper was to do a technical report first and then extract it. So there were seven of these technical reports. I think you have them, don't you?

Lyons: I think I have most of them. I'm not sure I have them all.

Fox: I have a few in here.

Berger: Well, I have them all.

Fox: But did you work...I have a number of records and notebooks with the name Davids, like Davids/Berger kinetics and this person wasn't at NIH so that's why I ask.

Berger: Professor Norman Davids was a professor of Engineering Science and Mechanics at the Department of Engineering at Pennsylvania State University. I had him for a math course my last year in graduate school. I ought to have had him the first year but he didn't teach it then.

When I came back from a five year stint in academia, I started working on these simulation sorts of things. I went up to him and I said, "There's got to be an easier way to do this than the way we're doing it; can't we use computers?" And we fussed around and I went through my Newton scheme. He was a very, very smart man, and he came up with the finite element method of solving these. He and his students have expanded that to aeronautics—all of the hydrodynamic problems they're solving in air flow at the Boeing Company are now done in this manner. Davids spent a summer out there lecturing to them.

He then had grants at the request of the Heart Institute [NHLBI] for nine years developing the mathematics to look at the bifurcation flow in the aorta and the sludging effects that occurs. You've seen this ad they've had on: if you don't take this medicine, you get clogged. Well, this sludging is what he was looking at but particularly at the bifurcation point and which led eventually to the need to know the elastic constant of the vessel. Larry Thibault, who was an engineer over at BEIB, actually made that measurement with Dr. Donald Fry in the Laboratory of Experimental Arteriosclerosis in the Heart Institute. And that has developed into ... well, at the last symposium they had nearly 200 different people working on those problems.

So as I say, Davids and I wrote, I guess, about five or six of the seven reports. He came down three different summers on an IPA [Intergovernmental Personnel Act] which turned out to be very nice for him—it raised his retirement by $10,000 a year. He didn't realize this, nor did I, until he started to get his money when he retired.

Then Dr. Balko was a technician for me here in the 1960s. He went to graduate school—he had a Master's—he went to get his Ph.D. at Boston University and actually developed this Mossbauer technique that he used. He was Ukrainian and spoke and read Russian as well as Ukrainian. He saw this paper in the Russian literature, a theoretical paper, and he built the apparatus. And we spent about five years trying to do this problem which we never really solved in the end because of purely technical problems; we needed a much stronger [power] source than we had and we needed much higher sensitivity detectors. That was Balko.

Lyons: What was his first name?

Berger: Bohdan. He's over at the Institute of Defense Analysis now. But he was a very good theoretical and experimental physicist. After he got his Ph.D., he came back to me for about five years all told, I guess. It was actually a very interesting turning point because I had a long talk with Jack Orloff about him [Balko] becoming a permanent staff member. Jack thought he didn't know enough biology to carry on when I retired. Basically, it came through that they weren't planning on going on with the Laboratory [of Technical Development] after Robert Bowman retired. The utilization of the kinds of instruments that we had made before was going to die out because of molecular biology. And that's exactly what happened of course.

Fox: Is this pretty much your whole career here in these boxes? I'm kind of trying to figure out the space. We have stuff from 1995, and this goes back to 1952-53.

Berger: Yeah, my first publication was a signal corps report which I still have a copy of actually, from 1949, I think.

Lyons: Except for the papers of his I have downstairs.

Fox: Okay.

Berger: Now I have a lot more—you don't want to hear this—I have a lot more correspondence at home yet that I am still using. And I have a thing that might be of interest, Michele. When we were developing the high speed accelerated flow—we call it the "PAF," pulsed-accelerated flow apparatus. It uses a thermistor and a dual optical path. It's a differential instrument which nobody's ever built before. You can use it in accelerated as well as stopped flow. We're just now beginning to really take data on this after twenty years. And I've got three folders of reports that the engineer that I worked with at Commonwealth [Technology] produced on basically a weekly basis, as we went in and did this and did that and that didn't work. I don't know if you're interested in that or not but it shows various mechanical barriers and things we tried, a whole bunch of interesting things.

Lyons: Well, yes, that's the stuff we're interested in.

Berger: Well, what both of you could do is just come to our house and park. Vicky will make pecan pralines, and we'll go over to the institute at Walter Reed—it will just be ten or fifteen minutes—and then we can go over to Baltimore. This time I got things organized a little better now. There's no point in you having the other reprints from all over the world that I used. They're all referred to.

Lyons: No, I have a collection of your reprints.

Berger: I just now have about four or five papers to write and so I'm beginning to get everything organized.

Fox: I thought I'd get you to look at what some of these notebooks are. I couldn't tell, there's just some lab notes.

Berger: The older notes...let me introduce you to the hard, cold facts of the laboratory scientist. The technicians do a far better job, because we make them, in keeping fairly good notes. An awful lot of my friends are just like I am, they have a notebook but they're working on half a dozen different things at once and so it becomes very difficult sometimes to follow through. Now, at some place along the line, I started where if it was going to be a major project that was going to go on, then I made a notebook at called it "Thermal Stopped Flow" or something like that. And that I've strived to follow through. But again a problem is as a project expands and lots more things are involved in it, you tend to get away from the notebook and depend more on reports of contractors or students or whatever. So just keep in mind.

Fox: Because there were some notebooks that seemed to be by technicians.

Berger: Yeah, now see this is one by Gary Liesegang. Gary was a post-doc, and then these are some later high school students, and he kept a daily log for a while. This is all of his stuff, this was what he was doing. See, that was another aspect that came along about 1975 or '76, when he joined me to do pico-second spectroscopy. Do you know what that is?

Well, you have milli-seconds, you know that is thousands of a second, and you have micro-seconds, that's a millionth of a second, and you have nano-seconds, that's 10^{-9} seconds. Well a pico-second is 10^{-12}. Real fast. But we're now into fento-seconds. But there was work being done at the Bell Telephone Laboratories on hemoglobin in this range. There was a question about how fast the interchange is, so we still don't understand how oxygen is bound by hemo. It isn't bound in a chemical reaction, it comes on and off just by changing the pressure. Well, at the same time there was a lot work going on both in Russia and the United States on looking at the initial steps in bacteria rhodopsin. You know what rhodopsin is, it's the stuff that allows you to see in your eye. And there's bacterial rhodopsin and there's human rhodopsin too.

It was known that these were very, very fast reactions; you know light hits your eye and reactions start to occur—but the Russians and the Americans had a great discrepancy in the time domain. The Russians had it at about twenty pico-seconds and the Americans had it at about forty pico-seconds. Well, I didn't pay a lot of attention to that but I was worried about what was happening with this great pulse of energy they were putting into hemoglobin. So we decided that that's an area we ought to take a look at.

Liesegang was a postdoc up with a Nobel Prize winner at Harvard, and I got a note from the Office of the Director down through my command, "Do we have a place for this guy?" I don't know how, I still don't know how, that came about, but it did and it just happened that we were looking for just that sort of person. So anyway he came down and we set this all up. The interface between that instrument and the computers that we wanted to use was called "an optical multiplier analyzer" because it had to look at the whole spectrum. A really interesting device. It had been built first in the laboratories in Russia and was built and used by astronomers in the United States. Princeton Applied Research Corp. made a commercial model of it. That's what the Americans looking at bacterial rhodopsin were using and that's what the people at Bell Tel were using. And I said, "Well, we'll get an OMA, but we've got to put our own computer interface to go about it the way we want it." Which made Liesegang very angry, actually, because he didn't want to be bothered with it. I made him go off to tech school and learn how to program. In the end, he decided he really loved it and he went to work for Perkin Elmer as a programmer! Anyway, the point is that when we did that [put our own computer program in], we discovered that the instructions that Princeton Applied Physics had given as to how to use this instrument were totally wrong. And then we corrected it, and the people who were doing the bacterial rhodopsin corrected theirs and they got the same answers the Russians did.

So this was a simple example of technical development, as it were, and what I learned about the thing is, first of all, you can't use a giant laser pulse to initiate a biological reaction because you

blow up the biological sample. And secondly, there really isn't all that much to be learned in the way they were going about it. Bill [William A.] Eaton, now chief of Chemical Physics in NIDDK [National Institute of Diabetes and Digestive and Kidney Disease] and [James] Hofrichter, his associate, spent an enormous amount of money building up machines to look at hemoglobin reactions in great detail. And you know it's one of those, sort of those semi-negative things that does come out of research. It elucidated where the time ranges of interest really are, and they aren't down in the pico-second region really, they're more up in the actual micro-second region and some things of interest in the nano-second. But these are all fairly large molecules that you're dealing with.

So that was the area that Liesegang worked in; we have notebooks with his name on them. Here's one in which he's collected a certain amount of data here and then somebody else came along and he hadn't used this notebook up so they used it. Things like that. There are [computer] programs that he wrote to do data collection and analysis. You must remember that when we started doing all this work there weren't any programs, they all had to be written. So an enormous amount of effort was spent in just doing things like that. Paul Smith had joined me as a laser physicist about this time and he and Liesegang did a lot of work together. He and Liesegang finished up the Calcium-EGTA experiments for Dr. [Richard] Podolsky, the chief of Physical Biology in Arthritis [National Institute of Arthritis and Musculoskeletal and Skin Diseases]. I had met him [Podolsky] while at Cambridge when he was with A.V. Hill working on muscle. This was one of these experiments. We did it roughly in 1968 to help him correct some muscle response data which turned out to be fairly important theoretically. We were rebuilding the optical apparatus to get to much faster response times and to include fluorescence as well as absorption spectra. We published this paper in 1984.

At the same time all of this was going on, we had been working on calorimeters with Ed [Edward] Prosan and Bob [Robert] Goldberg out at NIST. This was also being pursued by a new post-doc I had in about 1972 or 3, after I got back from a two year sabbatical at UCSD with Nate [Nathan] Kaplan and Jo [Johannes] Everse learning to purify proteins, both hemoglobin and lactate dehydrogenase, in very large amounts. Mario Marini at Northwestern [University] Medical School started working with me on building a titration apparatus while I was out there, and we were also working on various instruments with the Milan [Italy] group. I had spent five weeks in Rome in 1968, with [Eraldo] Atonini at the University of Rome, and results we obtained indicated we should prove the instrument with a similar reaction, which is what we did with the Ca-EGTA reaction. We had worked on the batch calorimeter doing possible clinical chemistry problems that Don [Donald] Young, chief of Clinical Chemistry in the Clinical Center, was interested in. This worked but was so slow that we decided to build a decent flow calorimeter based on stopped-flow and a very small sample. This is how we got to Ed Prosan. He helped us build a much better batch calorimeter, but even that was too slow, so by 1980, we were working on the stopped flow version with Harry Hopkins, a visiting scientist from Georgia State. We worked on the high-speed flow thermistor system and the slower reaction flow system. After Harry went back to teaching, Dr. Courtney Mudd of BEIB got interested. We built up an all-tantalum differential batch calorimeter and then a differential flow calorimeter. Both of these were done with the technical help of Commonwealth Technology over in Alexandria, VA.

This collaboration resulted in several commercial instruments being built and sold. We had gotten to know CTI back in the mid 70's when Dr. Froehlich in Aging had wanted a quench flow apparatus for studying ATPase. The first two instruments were built with the help of BEIB, particularly Jim [James] Sullivan, the head of the instrument machine shop. When others wanted versions of it, we went to CTI. They built and sold about 15 of these instruments around the world. In 1975, Bob [Robert] Winslow jointed [William] French Andersen in our Hematology branch to work on sickle cell hemoglobin and take care of the patients we were seeing come into the Heart Institute. He needed a much better oxygen equilibrium curve apparatus, so we began building one of these for him, again using BEIB, our own little machine shop in LTD and CTI. To assist him in data analysis, I introduced him to Richard Shrager of DCRT [Division of Computer Research and Technology]. This developed into programs that were used and published over the next ten years.

Mudd and I decided that the flow calorimeter we had been working on with Balko and Hopkins needed a complete redesign which should also include optical paths, thus allowing us to see the hemoglobin reactions optically as well as thermally. This work is just now coming to completion. Its development was largely done at CTI as directed by Mudd and myself. To improve the coating and response time of the thermistors, we started doing [coating] argon ion deposition of diamond on the thermistors. This worked very well and was taken up by CTI for us.

In 1988, we started work on near-infra red studies of the nucleotides ATP, ADP, AMP, and phosphate. We think this is working but will pass it on to a group at NIST [National Institute of Standards and Technology] who have also been doing NIR [near infrared] standards for industrial uses. LTD was closed in 1988, and my section joined the Laboratory of Chemistry, which was renamed the Laboratory of Biophysical Chemistry. We were physically moved to Building 3. Winslow had gone to the CDC [Centers for Disease Control and Prevention] and then the Army, and in 1985, became the Commander of the Blood Research Detachment out at the Letterman Army Institute of Research. I was asked to consult for him and did so until it was closed in 1992. He had left in 1990 to become a Professor at UCSD. John Hess had taken over and the unit was moved to Rockville where they built a pilot plant to make kilograms of hemoglobin. Dr. [Mark] Chavez, a post-doc who joined me in 1989, and I were asked to come join them to help set up the plant. I went in 1994 as an IPA until my retirement in 1996, and he went as a contractor.

I mentioned to you that the coatings on these thermistors were a real problem because you wanted them to be very thin, and yet you wanted them to be inert to everything. This turned out to be a typical technical development by what was really serendipity. So about that time, this so-called diamond-like carbon coating by argon ion deposition came along. I had been looking at this technology and Commonwealth Scientific in Alexandria had started building the instrumentation to do it. Dr. [Robert] Bowman came down to my office late in August and said...see the Heart Institute [National Heart, Lung, and Blood Institute) did a lot of surgical operations in their Surgery Branch, and they had to set aside a certain amount of money for emergencies—somebody split open and so forth, you know. Well then, come July they stopped

doing operations and they had a bag of money left that they didn't want to give back to Treasury, so we'd get it. Everybody in the Heart Institute always had a list of wants, and you know, the office would say, "We need it by tomorrow." So he [Bowman] came down and he said, "Didn't you say you wanted one of these deposition apparatuses?" Sometimes you have to be careful about what you want. So we got this thing and I learned how to use it, a big vacuum thing, a lot of work. I spent a lot of work on that and I had a lady, and she was really good. She had her Ph.D. and her husband didn't want her to work—she had a little girl about two or three years old—so in the end he didn't let her take the job. So then I gave the apparatus to the NIST, and they went ahead and produced some very nice stuff for, actually, lithography. We had done our coatings and proved it would work. In the meantime, CSI and developed the process and we got them to do the coatings for us after that.

But we did produce the coatings and we did publish on the coatings and they were great. I mean they really did everything I had hoped they would do. The vacuum required had to be less than .01 millionth of a millimeter of mercury and we had untold problems making everything work.

Lyons: Now the DEC computer boards that are in the collection, are they from you?

Berger: Some of them are. Not all of them.

Lyons: What are they from? Are they from this?

Berger: Well, I don't know which ones you have. The ones that I had were the interface boards that were used for data collection in the old PDP-8 [computer]. I don't know if that's what you have or not because the other group on campus was over in Neurology and they had a roomful of PDP-8s. I think they had seven or eight of them when I had one.

So that's where we've come up to, and I think that covers most of it. I haven't published much in the last ten years. But when you look at a notebook, think of it in terms of when there's a name on the notebook, it will either be the name of the person working on that particular project or it will be the name of a project. The way I've outlined the people, you can pretty well tell what those people were working on. Again, we weren't just building an instrument; we were trying to solve a lot of physical problems that were associated with either making the instrument or using the instrument.

End of interview