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Voices of Experience

Those Who Have Played Pioneering Roles in Biomedical Engineering Come from Many Fields. In These Excerpts from the Oral-History Project, Some of the Pioneers Tell of Their Involvement in Shaping the Discipline.

The oral-history project, initially funded as part of the EMBS anniversary project, was substantially expanded through a grant from the United Engineering Foundation, which made possible the interviewing of an additional dozen pioneers of biomedical engineering from other engineering fields, mainly chemical and mechanical engineering. This article includes a large collection of excerpts from all of the oral histories, hence providing some indication of the full range of biomedical engineering.

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Robert Arzbaecher
Director, Pritzker Institute of Medical Engineering Illinois Institute of Technology
(*interview by Frederik Nebeker on 14 October 1999*)

Nebeker: *Your work was on control systems.*

Arzbaecher: Yes, I focused my graduate work on that. When I finished my degree in 1960 and left [the University of Illinois at] Urbana I took a teaching position at the Christian Brothers College in Memphis, Tennessee. Christian Brothers College had a good undergraduate engineering school, particularly in the electrical area. … It was not a small school, but not much was going in on the area of control. Certainly not much in my area of reactor control was going on in Memphis. I taught electrical engineering but was not able to continue my research. It was in that context that my conversion from electrical to biomedical engineering began.

For a year I looked for a challenging research opportunity in Memphis to go with my teaching. Then I met Daniel Brody at a cocktail party. He was a cardiologist from the University of Tennessee College of Medicine in Memphis. Unknown to me at the time, he was a very well-known cardiac theoretician. Brody's undergraduate training was in physics. … When I found out more about his background, it was the beginning of a wonderful relationship. I spent the next seven years working with Brody in his laboratory every chance I could get, on Saturday, Tuesday, and Thursday afternoons to the extent I could arrange my teaching schedule. We worked in what is now called theoretical electrocardiography, which is the physical and mathematical basis for interpretation of the human electrocardiogram in health and disease. Brody and I wrote a lot of papers together. That's how I became a biomedical engineer.

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Arzbaecher: After six years of theoretical mathematical modeling work I had an urge to get closer to clinical electrocardiography. I had an opportunity to go to Europe for a year on a National Science Foundation fellowship, and Dan Brody set up an opportunity for me to work in the laboratory of Dirk Durrer at the University of Amsterdam. That experience was of major significance in my career. Durrer had a concept for removing the human heart soon after clinical death and keeping the heart alive long enough to map its electrical activation. This had been done with the hearts of animals, and Durrer was poised to do the same thing with the human heart. The instrumentation requirements of that task were significant. With the isolated heart on a perfusion stand, needle electrodes were placed all over the heart to record on a multichannel basis. This was in the mid-60s, when that was not an easy thing to do. My time in Amsterdam was fortuitous for him and for me. I became involved at the highest level of experimental cardiology, and he found a trained electrical engineer to help him with instrumentation problems. During that year we did the first isolated human heart mapping experiment and published in *Circulation*.

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Nebeker: *What was the impact of the minicomputer on electrocardiography and similar areas?*

Arzbaecher: There were two impacts. First, it made it possible for many laboratories without major computer resources to acquire significant computing resources. Secondly, it led to digital signal processing, which is now standard, and also to on-line real-time signal processing. Without the smaller computer and its capabilities for on-line acquisition, analog-to-digital conversion, and processing in the digital domain, that wouldn't have happened so quickly. My experience before then had been with punch card machines, batch processing, and number crunching.

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Nebeker: *Was delivering the drug automatically your objective?*

Arzbaecher: Yes. That was my dream. It has been a long time in bearing fruit.

Nebeker: *It sounds very ambitious for the 1970s.*

Arzbaecher: Yes, it was. Support came from the pharmaceutical company G.D. Searle. They were particularly interested in finding out whether their drug Norpace was effective in treating atrial arrhythmias. Necessity being the mother of invention, I invented the esophageal electrode for recording the electrocardiogram from the esophagus.

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Arzbaecher: It is interesting how I discovered the pill electrode. … In the lab, I had a graduate student of mine push a catheter electrode down my nose and into my throat and esophagus. I was able to measure a beautiful p-wave, which was an atrial recording in the electrocardiogram.

Nebeker: *Did you get a much clearer signal that way?*

Arzbaecher: The p-wave obtained is three to four times bigger than QRS. Compared to routine electrocardiography on the body surface, the esophagus gives a beautiful p-wave from the atrium. The recording we made was clear, but it hurt. That night I could still feel the

irritation in my throat that had been caused by the catheter.

Nebeker: *You're in the class of people who experiment on themselves.*

Arzbaecher: That was in the days before we were so careful about human investigation. My throat and sinuses hurt, I realized that the problem was that big old stiff catheter. All I really wanted were the two rings at the end of the catheter. The next morning I went into the lab, took a pair of diagonal cutters, and stripped away the polyethylene coating until I was left with the tip of the catheter and the pair of wires. Then I buried the catheter tip in a spoonful of ice cream and swallowed it. My students laugh about this. One doesn't chew ice cream, so the bipolar pair of electrodes caused no problem. I just swallowed it, and down went the pill. That was the first pill electrode. That was the business end of a catheter electrode with a bipolar pair and a pair of wires holding it up. Within a week or two I discovered a source of very thin and flexible stranded stainless steel wire with Teflon insulation.

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Arzbaecher: The esophageal electrode gave us the signal with which atrial arrhythmias could be instantly recognized. Atrial arrhythmias are not easy to recognize on the body's surface.

Nebeker: *Is this a recognition that comes through visual analysis by a cardiologist?*

Arzbaecher: It's computer recognition. The algorithm looks at the esophageal signal, analyzes it, and comes up with a rhythm diagnosis in real time. The whole spectrum of cardiac arrhythmia can be detected, including atrial fibrillation, atrial flutter, atrial tachycardia, premature atrial beats, and ventricular arrhythmias.

Our interest was in treating atrial arrhythmias with a Searle drug. I had the first half of that problem solved, which was how to automatically recognize the onset of an atrial arrhythmia in a coronary care patient.

Nebeker: *Did you write programs to analyze the p-wave?*

Arzbaecher: Yes, my students and I wrote them. A student who helped with that was Janice Jenkins. She is now a professor at the University of Michigan and on leave from Michigan serving as the program director of bioengineering at NSF. She took the esophageal signal and wrote the program to analyze the arrhythmia. It was the first dual chamber arrhythmia analysis program ever written.

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Arzbaecher: One day in my laboratory in Iowa City I disconnected the pill electrode from the electrocardiograph, connected it to an external stimulator, and discovered I could pace my heart.

Nebeker: *More experiments on yourself.*

Arzbaecher: By connecting the electrode located immediately behind the left atrium to an external pacemaker I was able to capture the heart and run it at any rate I wanted.

We proved that esophageal pacing was both safe and effective and received premarket approval. No longer a substantial equivalence thing, this required the full FDA premarket route. It was necessary to perform experiments and prove there would be no damage to the esophagus. It also had to be proved that this device was effective in pacing the heart. Following all those studies we appeared before the FDA Cardiology Advisory Board at the end of 1986 and got the PMA approved. I developed a small battery-operated electronic external pacemaker to which the pill electrode could be connected. That was it. It could pace the heart.

This created an opportunity to do a number of things that couldn't be done before. For example, a lot of patients can't exercise due to age, infirmity, obesity, and other reasons. Cardiac stress testing can be done by pacing the heart rather than by exercising the patient. That was an important development. Imaging studies such as echocardiograms could also be done. Temporary esophageal pacing could be used to convert arrhythmias. Atrial flutter, especially in children, is easily converted by over-drive pacing. A short ten-second burst of temporary pacing from the esophagus could convert the arrhythmia to normal rhythm.

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Arzbaecher: The dream of the drug pump people is the treatment of diabetes. A drug pump with insulin to automatically treat the diabetic patient would be a marvelous technology. Bil-

Dr. Robert Arzbaecher swallowing the Pill Electrode, which he invented, for recording the electrocardiogram from the esophagus.

lions of dollars have been spent to develop that technology, and several companies are involved. They have been stymied largely by the absence of a good glucose sensor. The pump can deliver insulin, but no way has been found to close the loop. Insulin is not an easy drug to store and deliver in an implanted pump, but the biggest problem is the measuring of glucose levels to trigger the pump. That technology is still being developed. I believe implantable pumps will become more commonplace, and maybe with time the particular notion of an implantable pump for the treatment of atrial fibrillation will become more attractive.

Nebeker: *Is the control system developed?*

Arzbaecher: Yes. For my own lab I have published protocols for running a pump. The implantable pumps that are available do not have motors in them. They have valves. There is a pressurized reservoir of drug with a valve. When you open the valve, drug squirts into a catheter and then moves into a central vein. That device is pretty reliable. There are not many moving parts, and it is easy to control. All that has to be controlled is the rate at which the valve is operating.

Nebeker: *Are these valves controlled electromagnetically?*

Arzbaecher: Yes. I have a concept I have tested on animals in which I programmed an implantable drug pump with a valve to deliver pharmacokinetically designed exponentially tapered infusions, which are known to give and maintain a good therapeutic response. Control of the pump is not difficult, and the problem of recognition of atrial fibrillation is well in hand in my laboratory as well as in other places.

Babb: [Babb, in charge of the nuclear engineering program at University of Washington, had just begun using a teaching reactor for neutron activated spectroscopy] … a secretary … said, "My daughter has cystic fibrosis, and one of the manifestations of it is the abundance of sodium chloride in the sweat, fingernails, and toenails. Maybe you should get together with the people at Children's Hospital and see if you may have a way of screening newborns for the presence of cystic fibrosis so that they can get into early treatment." Dr. Stanley Stamm came down, and we talked about it. The result was that we set up a protocol whereby he advertised around the country and overseas that we were accepting toenails which would be irradiated with neutrons.

We accepted maybe a thousand samples from all over the world to irradiate. Here is a picture of a resident clipping the toenails of a baby at the University Hospital. There was a writer for *Life* magazine who lived in Belleview, just across Lake Washington, who did a story on this novel use of a nuclear reactor. That's what got me associated with some clinical people.

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Babb: Early in 1963 Dr. Moulton called me into his office and said, "I just had a telephone call from Belding Scribner, M.D. He wanted to know if there's a young faculty member here that could work with him in reducing the cost of hemodialysis." I had never heard of this procedure. The reason Scribner called him was because he took care of Moulton when he was sick the year before I came. Suddenly Moulton said to me, "You've always been interested in medicine. Why don't you go and see him?" Thus we made an arrangement. I went down to the University Hospital to a little room off the cafeteria. It was a daunting situation. There were about six physicians in white coats sitting there. They explained to me how they had just developed a way of permanently implanting plastic tubes in the artery and vein of patients, bringing them out through the skin and connecting them with a U-tube so that when they were not on dialysis the blood flowed at a high enough velocity to prevent clotting. Then they were clamped off and connected to the dialyzer with the artery going to the inlet port and the vein to the outlet port to start a dialysis episode.

Nebeker: *How long had that kind of extracorporeal dialysis been possible?*

Babb: It was first used during World War II. A physician named Willem Kolff treated patients in Kampen in the south of Holland. … but they could not treat patients whose kidneys would never return to normal function. They were only able to keep the patency of the blood access to the cardiovascular system for a few weeks or a month at the most. If their function were not restored they would die. After the war everyone was trying to develop permanent access.

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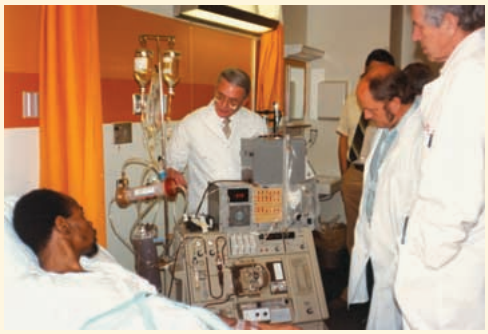
Babb: I assimilated all this information, looked at the tanks in use, made some mental notes, and came back to my office in the nuclear

Albert "Les" Babb
Professor Emeritus of Chemical and Nuclear Engineering, University of Washington
(interview by Frederik Nebeker on 6 December 2000)



Albert "Les" Babb describes an extracorporeal system for the continuous treatment of patients with sickle cell anemia in 1981. The design of the machine was based on the pioneering prototype designed and built by Babb and his team at the University of Washington for overnight-unattended home dialysis.

reactor building. I had barely arrived when there was a phone call from Dr. Scribner, who had told me it cost about $20,000 per patient per year for two 12-hour dialysis sessions per week.

I said to Scribner, "I take it your are interested in reducing the cost," he said, "Yes, we'd like to get the cost down. Do you think you can help us?" And I said, "I need more information. I need to be walked through the whole procedure."

From this idea we said to ourselves, "Why don't we premix those chemicals in a concentrate and dilute it in the right proportion continuously. In this way we'll remove the tank from each bedside and pipe the dialysate around the walls to maybe five stations where they can be connected to the dialyzers. The dialysate would flow through and then come back into a waste line." … it was dubbed "the monster!" Then all hell broke loose because manufacturers of commercial machinery besieged us, each wanting to be a supplier.

[The Milton Roy Company of St. Petersburg, Florida] flew me down as a consultant. I was there at the startup at the old VA Hospital in Coral Gables, Florida. From that beginning these central systems appeared all over the world.

Nebeker: *Were these multipatient dialysis systems?*

Babb: Yes. Here we could handle five patients at once. … it was working and at half the cost; i.e., the annual patient cost was now about $10,000. A lot of the work we did after that was mathematical, and we tried to model this process to see if it could be optimized. We suggested three 8-hour treatments per week rather than two 12-hour treatments were more optimal and convinced the medical staff to switch to this practice.

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Babb: Then I received a call early one Saturday morning [in 1964]. [Dr. Scribner] explained to me that a 15-year-old girl he'd seen many times had been turned down for treatment by the deciding committee I mentioned earlier. He told me she was going to die if she didn't get treatment within four months, and the university had prohibited him from taking any more patients. He said, "Could you take this monster and miniaturize it?" … He said, "It would be the same principle, diluting concentrate, but for one patient and portable so it could be taken to a patient's home." I said, "I don't know. I'll have to talk to my engineers and technicians." I called them together and put the problem before them. And I said, "We'd have to make most of the stuff ourselves." We couldn't buy heat exchangers, for instance, that were this small, and the instruments weren't readily available and we'd have to modify them. I said, "It really has to be almost automatic." The patient could not be expected to do too much. We went for an automated system wherein at the push of a button the machine would pasteurize itself using hot water then. Then it needed to produce dialysate at the right temperature and composition and give an indication when one could hook up the blood lines. My staff said they'd like to do it, and I told Scribner we'd take a shot at it.

Nebeker: *This was a bootleg development.*

Babb: Yes. And I couldn't have done it if I hadn't had control of it. I could not do that here now. And at that time we happened to have probably the best cadre of electronics technicians on campus, and they were all under my supervision. We had a lot of ex-Navy people who had been in the nuclear propulsion program. We couldn't have done it without them. If I had gone to this current chairman and said I wanted to do this, there would be no way. It was just the right time.

Nebeker: *How many people did you have working on this project?*

Babb: I would say about eight at the peak of it. [The machine was a success.] People came from literally all over the world—Sweden, Denmark and so on—to photograph the machine and take away drawings.

Nebeker: *What was Norman Jeff Holter's motivation for using this ambulatory ECG?*

Bailey: His idea was that taking a single resting ECG was too narrow a slice in time. The idea was to capture a much larger block of cardiac activity—throughout the day and night—to get a better picture of what was happening with the patient during his normal daily routine.

"Every ten years someone comes up with the idea of applying harmonic analysis to the ECGs. The problem is that harmonic analysis doesn't tell whether the T-wave is before or after the QRS. That is critically important loss of information."

Nebeker: *Whereas a stress-test ECG could be connected and done in a single location?*

Bailey: Right.

Dunn: There was a classic study, from the 1960s perhaps, monitoring workmen—I can't recall the industry involved, perhaps stevedores or electricians—who were wearing these Holters for at least one day, if not more. These strapping, healthy men were throwing spurious arrhythmias like PVCs and PACs. This may have been the first study documenting significant "normal" variation. What did this mean prognostically? They didn't know.

Nebeker: *Was this the first time somebody had done ambulatory ECGs?*

Bailey: Holter's was the first, yes. And it was all analog when he started. Avionics was still analog even in the late sixties.

Dunn: This capability for monitoring would not have been available from the average cardiologist, but it was used in some hospitals.

Bailey: Yes. Where I did my residency, the cardiology department used one. That was in 1966-1969.

Nebeker: *Was the Holter Monitor something that was manufactured?*

Bailey: Yes. Avionics was the company that made it. For patients that were having palpitations or seizures or fainting spells, it was appropriate when the cause was not otherwise clear. It also probably unmasked coronary disease for some patients.

Nebeker: *Has this kind of diagnosis continued to the present?*

Bailey: Oh yes. It's big business.

Nebeker: *I suppose these Holter Monitors have become transistorized and miniaturized.*

Dunn: Hardware has been miniaturized, including compressed software and more sophisticated analytic programs for diagnosis upon playback, or even better, immediately.

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Dunn: Hubert Pipberger was interested in determining the physiological phenomena behind the production of the ECG signals, developing the model that could accurately reproduce such signals, establishing the external electronic system, which could detect these signals, and, by use of a validated model, properly interpret them with a high level of sensitivity and specificity.

Nebeker: *His way of creating that model was going to be on a digital computer?*

Dunn: He saw the computer as his basic tool, capable of reading tracings with higher resolution, consistent accuracy, and greater speed.

Nebeker: *There were quite a number of people in various areas of science, with, for example, analog harmonic analyzers, looking for periodicities in data.*

Bailey: Every ten years someone comes up with the idea of applying harmonic analysis to the ECGs. The problem is that harmonic analysis doesn't tell whether the T-wave is before or after the QRS. That is critically important loss of information.

Nebeker: *Was the use of harmonic analysis ever fruitful with cardiographs?*

Bailey: I don't think it has been helpful, except for the fact that in the early sixties people believed that all the information was contained below 60 Hz.

Bailey: Later people found important information at the 100 Hz level. Some investigators have found important information at even higher levels than that.

Nebeker: *How did they learn that these higher frequencies were important?*

Bailey: They learned that by studying patients with cardiac pathology.

Nebeker: *Earlier they might have filtered out that part of the signal?*

Bailey: That's right. In the old PHS-D program of 1964 was based on the idea that the signal would have been passed under a 50 Hz filter. It really distorted the QRS.

Dunn: When I began to work in this field in the seventies, a large percentage of papers presented at conferences dealt with filtering and massaging the signal.

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Bailey: I am skeptical of cardiologists uncritically taking interpretation from a computer program.

Dunn: This became a serious issue. Pipberger himself always warned against "heart disease of computerized ECG origin."

James Bailey and Rosalie Dunn
Bailey: Center for Information Technology, NIH
Dunn: National Heart, Lung, and Blood Institute, NIH
(interview by Frederik Nebeker on 25 April 2000)

Nebeker: *"If the computer said it, it must right."*

Bailey: A lot of them had that kind of naiveté.

Dunn: Some preferred a system whereby everything that came out of the computer should be over-read—that some cardiologist should at least take a look at it and sign off on it.

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Bailey: What evolved in the seventies was simultaneous collection of multiple leads. In the beginning, in the late sixties and early seventies, there were carts that collected three channels of leads simultaneously. In the eighties there were carts that could collect 12 or 15 leads simultaneously; i.e., the standard 12 and the XYZ. Either analytic approach could be taken. Controversy between the 12-lead and the XYZ-lead adherents could be studied more effectively when data was collected by a 15-lead cart. The logical question was, why not use the highly powerful multivariate techniques that the XYZ-lead people were using on 12-lead data? I think that's where Jos Willems came into the picture.

Dunn: Jos Willems had been a fellow in Hubert's lab when I was there. He was the bridge between the two camps. And he showed that comparable results could be obtained, for the most part.

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Nebeker: *The way it was actually implemented was that a cardiologist would run this program, over-read it, and then feel free to disagree if his interpretation was different?*

Dunn: And the cardiologist would notate the tracing for differences. Computerized rhythm determination was probably the first aspect about which the cardiologist became comfortable.

Nebeker: *Maybe it was something the computer could do a more accurate job of measuring.*

Dunn: With proper wave recognition—the points of the QRST, the ST-T segment and the baseline—the computer could make better measurements than the cardiologists and save time. The computer could merely print out the ECG measurements, and the cardiologist was already provided some assistance.

Bailey: When I first had to read ECGs in my residency, we had little calipers where we had to manually make measurements on magnitudes and intervals and so forth. Then we had to record them before offering an interpretation. The measurements are what the computer produces automatically.

James Bassingthwaighte

Professor, Department of Bioengineering, University of Washington

(interview by Frederik Nebeker on 5 December 2000)

Bassingthwaighte: In 1950 I was in Air Force officer training at Crumlin Air Base, London, Ontario. This led to summer research the next two summers at the Institute of Aviation and Medicine. In 1951 I worked with A.W. Farmer, professor of surgery at the Hospital for Sick Children, and Prof. Wilbur Frank at the Banting Institute, both at the University of Toronto. I was asked to design and develop instrumentation to measure the spreading and disappearance of fluorescein injected along with hyaluronidase into the skin of the forearm. It involved having a source of ultraviolet light and a receiver that excluded the source light and looked at the fluorescence. In that way the fluorescence could be looked at as a function to time after injecting a tenth of a milliliter of fluorescein-containing material into the skin. I designed the instrument and the circuitry and contracted out to get the device built, a huge, heavy thing. We observed fluorescence intensity to determine whether the rate of disappearance of fluorescein was affected by the hormonal level of corticosteroids in the blood. At that time it was thought that this might become a useful clinical measure of the stress levels in children in the Burn Unit at the Hospital for Sick Children. The first summer was on the instrument development and the second, 1952, on using it in the Burn Unit.

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Bassingthwaighte: We began this [in about 1960] as an analog computer model [to determine the transfer function of a portion of the vascular tree, namely that of the artery in the leg going from the femoral artery in the groin to the dorsalis pedis artery on the top of the foot]. A convolution integration is essentially a digital process, unless you can write the transfer function as a differential operator, something that one cannot do for a lagged normal density function. If you ever saw something strange, it was doing a convolution integration on an analog computer. You had to have a perfect gain of one through a system and then do repeated recordings onto a tape in order to do the integration. It was crazy, and very tedious, but worked.

Nebeker: *The purpose of this work was to understand the circulatory system better?*

Bassingthwaighte: One reason is to want to understand its hemodynamic characteristics. Another is to characterize the changes that occur

when there are changes in flow through a limb. Third, potentially this same femoral-to-foot transfer function might be used diagnostically to assess limb flow in patients with ischemic arterial disease.

The actual mathematical technology that we developed is not used diagnostically but is used in research.

Nebeker: *That's quite a span of years from when you began working on it.*

Bassingthwaighte: Most of 40 years. And that kind of beginning expanded into other applications of mathematical modeling that we have used for image interpretation using positron emission tomography and MRI, particularly for the measurements of flows and metabolism within organs.

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"One of the intriguing things we discovered very early on was that the heart is very heterogeneous in its regional blood flows. In the sixties we had learned that different regions had different flows. In the early seventies we learned that the different flows stay that way when examined at several later times."

Bassingthwaighte: I chose to look at cardiac metabolism, which was not being explored much at that time, and to try to develop techniques for doing that. To start that off, I started doing multiple tracer indicator dilution experiments. I needed to use pairs or triples of substances simultaneously. The idea is to use reference tracers along with the tracer-labeled substrate of interest. The three tracers are injected together in a short bolus injection into the coronary arterial inflow, and a sequence of samples is taken from the outflow at 1 or 2 second intervals.

Nebeker: *What were the technological challenges in getting this to work?*

Bassingthwaighte: One was multiple tracer techniques. We were the first people to use triple label beta counting. All my advisors told me it was impossible. It took us a little while. The reviewers send these [grant proposals] back saying it's impossible. You have to do it before they'll give you the money to do it.

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Bassingthwaighte: Physiology is an integrative discipline, historically speaking, so one is expected to integrate diverse observations into a self-consistent scheme and to look at the time courses of events to understand relationships. These cannot be very well understood without having some modicum of control systems analysis.

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Bassingthwaighte: Bob Rushmer had founded the bioengineering program at the University of Washington in 1968, and I had come to UW twice as a site visitor on behalf of NIH to see whether his program should be funded. I liked his program. Dr. Rushmer got to know that I had been in the market for the position at McGill, and when he decided to retire I was recruited here.

The reason I came here was because UW had one of the Mayo Clinic's prime attributes, namely, an atmosphere in which people would collaborate across departmental lines freely and openly in a noncompetitive way. The University of Washington had another attribute similar to McGill: a medical school and engineering school on the same campus, right beside each other, and furthermore, the Center for Bioengineering was part of both schools.

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Bassingthwaighte: The central theme is still cardiac metabolism, unraveling it in the normal state and to a lesser extent in cardiac ischemia. Ischemia has been a secondary mission. In the process of getting at these nuances of metabolism, I started, in collaboration with Harvey Sparks at Michigan State University, a program to look at purine nucleoside transport and metabolism in cardiac capillary endothelial cells and myocytes. ATP is the prime energy source for cardiac contraction. Therefore looking at the ingredients that make up ATP and play a role in its regulation was important. Harvey Sparks was an expert in this; I had the technology for looking at the transport and metabolic rates. We applied tracer techniques to that. That was a step exactly in the direction I needed to take. Working with the group at Michigan State and with Ray Olsson at University of South Florida to develop some new tracer labeled compounds was a neat thing to do. That has evolved into more research in purine nucleosides, and I am still doing that. I also started looking at substrates for energy supply, glucose and fatty acids, characterizing their pathways from the blood through to the cell, an important part of cardiac metabolism.

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Bassingthwaighte: The heart is interesting from a structural as well as metabolic functional point of view. One of the intriguing things we discovered very early on was that the heart is very heterogeneous in its regional blood flows. In the sixties we had learned that different regions had different flows. In the early seventies we learned that the different flows stay that way when examined at several later times. There are two problems here that I struggled with for years. One was how to measure heterogeneity. The other was how to ascertain its cause. With respect to its measurement, if one uses different scales of measurement, one gets a different measure of heterogeneity.

Anyway, the blood flow distribution throughout the heart tissue is a fractal and so is its vascular system, so we are characterizing the network properties of the vascular system in terms of fractals. Fractal methods are good statistical tools.

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Bassingthwaighte: We have one system we developed over the years. Actually in 1967 I put together a simulation interface system called SIMCON, which was short for simulation control. It was the interface between man and machine that allowed one to use models to check data and thereby parse the transfer function of the black box. That turned into a very good modeling system with automated ways of fitting equations and models to data, evaluating the accuracy of the parameters that came out, and displaying the solutions in real time so that one could see that the right result was being obtained. It allowed people to get a feeling for the data analysis; to see it as they do it. Our whole philosophy of the resource is centered on that, "You should be able to do your analysis and see it happen before your eyes and understand what you are doing as you are doing it." The idea is for people to be able to look at the behavior of these models and understand the sensitivity of various parameters. This then enables the user to explore what the models can reveal about the system that wasn't previously known. A model is always a mind expander, and so the simulation tool is an augmentation to one's set of thinking tools.

Nebeker: *How has this been received*?

Bassingthwaighte: The grant has received funding for over 20 years. My original experimental grant, starting in 1964 and still running, supported the early SIMCON. The Simulation Resource Facility has supported the advanced efforts since 1978.

John Chato

Professor Emeritus, Mechanical Engineering Department, University of Illinois

(interview by Frederik Nebeker on 11 October 2000)

Chato: I've worked in heat transfer pretty much all my life— although it's what I'd call "oddball" heat transfer—such as biological heat transfer and electrohydrodynamics with heat transfer.

"Oddball" heat transfer is where you really have to work with another field, such as biology, physiology, or electrical engineering, as with electrohydrodynamics, so that another discipline must be combined with heat transfer in order to do the work well.

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Chato: I always tell my students that when I did my initial work I never had any problem with data acquisition. I had a potentiometer and wrote down the numbers by hand. However now we consistently have trouble with computerized systems. Occasionally a computer will screw up due to a glitch in the software or an electronic disturbance. We have to be very careful checking over our numbers to make sure that the numbers we get from the computer are correct.

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Chato: In 1960 I took a phone call that came in from a doctor at Massachusetts General Hospital who was looking for a heat transfer expert. He wanted to have a brain probe—used for surgery—insulated so that he could cool *only* the tip. The probes were typically about 20-30 cm long and 2 mm in diameter.

Nebeker: *Why did he want to cool the tip?*

Chato: He was working with cerebral palsy, which is somewhat similar to Parkinson's disease. The hypothalamus is deep in the brain, and it has been found that if a small part of it is destroyed, the uncontrollable shaking of the patient ceases. It doesn't cure the disease but stops the shaking typical of both cerebral palsy and Parkinson's disease. He was trying to get to that little spot in the brain. When the temperature of the nerves is reduced to below 27 °C, they essentially stop functioning—as when fingers exposed to cold get numb. He wanted to insert the probe, turn on the cooling, and see whether or not this would stop the shaking. If it did stop then he could apply rf (radio frequency) current to permanently destroy the tissue.

The doctor explained that he wanted to insulate a long tube, not to exceed 2 mm in diameter, so that only the tip would be cold. I didn't think it could be done. When he explained to me why he wanted this, I said, "I think what you really need is a new refrigeration system." I went on to develop for him what I call "the smallest refrigera-

"Bioheat transfer is still a relatively small arena. Even in bioengineering, the bioheat transfer area is relatively small compared to bio-fluid-dynamics for instance or biomechanics in general."

tor ever built," and it worked out very well. The cooling tip was 2 mm in diameter and 5 mm in length. That was the evaporator. That's how I got started in bioengineering.

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Chato: Probably the most commonly used cryosurgical protocol is in cancer surgery. For instance, the liver cannot be cut but can be frozen. Therefore when there is cancer in the liver, if it's in one area the tumor can be frozen with some rather clever techniques. The frozen volume is followed using an acoustic radar technique, on-line, and when the frozen ball is big enough one can be sure that the cancerous tissue inside has been destroyed.

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Chato: The next question the doctor asked me was, "If I make the tip 0 °C so that it is as cold as it can be without freezing the tissue"—because he wanted to use rf current to create the lesion, not freezing—"where is the 27 °C surface going to be?" My first reaction was to ask myself, "What is the thermal conductivity of brain?"—and of course there was no answer to that. That led me to measuring thermal properties of biological tissues.

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Chato: A good example of obtaining important information with simple but effective analysis occurred when I started looking at the heat transfer effectiveness of various blood vessels. The early bioheat transfer models assumed that the most significant heat transfer occurred in the capillaries. I applied well-known heat exchanger analysis to the various kinds of blood vessels in the human body and found that virtually all the heat transfer should occur in the small arterioles and venules; the capillaries should be essentially at the surrounding tissue temperature with no significant heat transfer. That was an important discovery.

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Chato: Then later, through one of the NASA faculty grants, I spent a couple of summers out at NASA Ames in California and got into the thermal regulation and thermal control of space suits for astronauts—the cooling of astronauts in the Apollo spacesuits. One thing led to another and I did more bioheat transfer work.

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Chato: Cancer treatment with heat—hyperthermia—was particularly a big stimulus of research efforts in bioheat transfer. Researchers were trying to estimate how much heat must be applied to the various parts of the tumor and worked on the associated problem of deciding how best to aim the heat source, such as an ultrasonic beam. For instance, in using an ultrasonic generator, the question was how to aim properly and how to move it so that it would heat the tissue properly.

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Chato: Another field I worked in that was "oddball," as I told you, was electrohydrodynamics.

Nebeker: *How did you get into that?*

Chato: The Electric Power Research Institute (EPRI) was formed while we worked with its predecessor the Edison Electric Institute. The project on which I worked had to do with underground electric cables using oil as a cooling medium. We were looking at the heat transfer and flow characteristics. I took some courses in electrical fields and magneto- and electro-hydrodynamics at MIT. I had some time for extra courses, and even then I was willing to go up to strangers like electrical engineers and ask questions. What happened was that I looked at that project and said, "Here is oil, which is a dielectric fluid. Pumping is not possible with magneto-hydrodynamics, but maybe we could pump with electro-hydrodynamics. Dielectric fluids would be ideal for that."

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Chato: Bioheat transfer is still a relatively small arena. Even in bioengineering, the bioheat transfer area is relatively small compared to bio-fluid-dynamics for instance or biomechanics in general. However, I think it is a very important field.

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Nebeker: *Have you been involved with the heat destruction of tissue for surgical purposes?*

Chato: Not as such. I was involved in burn damage, but mostly in terms of legal problems.

Nebeker: *What was that work?*

Chato: There were things like, for instance, someone worrying if a certain piece of equipment that has hot air going through it may actually cause a burn on a human body in the case of a patient who is exposed to it.

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Chato: I remember looking at an electrical engineering paper that had to do with a question of the electric field distribution around buried cables. It was the same problem as the temperature distribution around the buried pipe—same geometry, same controlling equation. For instance, in conjunction with this cooling of underground electric cables, I used the solutions from an electrical engineering paper that was from the twenties. As a matter of fact I modified the same solution to estimate the heat transfer from a blood vessel near the skin surface.

Shu Chien

Professor, Whitaker Institute of Biomedical Engineering, University of California San Diego

(interview by Frederik Nebeker on 11 December 2000)

Chien: [We published] a series of three back-to-back papers in *Science* on [the flow properties of blood] in 1967. … they triggered my 30 years of collaboration with Richard Skalak in the Department of Civil Engineering and Engineering Mechanics at the Columbia Engineering School. He expressed his great interest in them, especially the paper on the flow of red blood cells through narrow filter pores, which is very similar to capillary flow.

Dick had a student, Tio Chen, who was starting to work on a thesis computing the flow of small particles through a narrow tube, a situation analogous to blood cells flowing through a capillary. Dick put me on Tio's thesis committee, and through that we began to collaborate. We continued to collaborate for 30 years and published together many full-length papers. That's where I received a lot of my engineering training. So I was able to go from physiology to the biophysics of flow properties of blood and to engineering simulation and modeling. Then I began to appreciate the power of simulation and modeling. That really put my math interests into practice.

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Chien: Later on I realized that using the network theory and related areas one can begin to understand how the physiological systems work. There were several papers out during those years [the early 1970s] about how to simulate the physiological systems using the engineering control theory. Therefore, I took a course in control theory.

Nebeker: *Was this kind of engineering systems analysis something that a number of people were beginning to explore at that time?*

Chien: That's right. Dr. Arthur Guyton of the University of Mississippi was one of those people, but there were not too many.

I became interested in this and gave a course on "The Application of Control Theory in Physiological Systems" in the physiology department at Columbia.

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Chien: I am always interested in merging [engineering and biomedicine]. Hemorrhagic shock is a major medical problem in intensive-care surgery, which in turn is closely related to engineering. At the same time, we also moved from studies on the blood as a suspension to investigations on individual cells.

Nebeker: *Do you mean in the sense of modeling of the processes?*

Chien: Both in experiments and modeling. We isolated the individual cells, determined their viscoelastic properties, and modeled those properties. Dick Skalak, two of his students (Aydin Tözeren and Richard Zarda), and myself published a paper about the mechanical properties of the red blood cell (RBC) membrane.

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Chien: I think the problem with engineering modeling in the early days [the 1960s and 1970s] is that many of the modeling studies were not done in relation to the biological reality.

Nebeker: *More abstract mathematical models?*

Chien: More abstract and very elegant solutions to a problem, but not necessarily applicable to biological systems. Therefore, it is very important that biology and engineering be brought together.

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Chien: Shelly Weinbaum and Bob Pfeffer (Professor and chairman of chemical engineering at the City College at that time) each spent a sabbatical year with Colin Caro [at Imperial College] working on atherosclerosis problems in the early seventies, and they talked about continuing that work after Shelly returned to New York. Shelly told me that Colin said, "The person in New York you should collaborate with

is Shu Chien." I already knew Shelly and Bob from other contacts in New York. In 1969, Dr. Y.C. Fung traveled from San Diego to give a number of special lectures at CCNY, and he made sure that Shelly met Dick Skalak and me during his visit.

Nebeker: *Can you describe their interests?*

Chien: By training Weinbaum was a mechanical engineer and Pfeffer was a chemical engineer, so they were primarily interested in engineering modeling. Both of them were interested in transport phenomena; how molecules move.

They had not had much contact with biology until they took the summer physiology course at Columbia and then went to work in Caro's lab. As mentioned above, they wanted to continue in this line of research after returning to New York, so they came to me and said they wanted me to collaborate on this project. At that time I was working very heavily with Dick Skalak, so I got Skalak involved in it too. This is a problem related to my interests because of the blood vessels and fluid mechanics. I was focusing more on the blood cells for quite a while, and here was an opportunity to look at the blood vessels and the cell-vessel interface as well. I was interested in initiating new approaches, and we began to work together.

Nebeker: *When was this?*

Chien: This was in 1974. We later submitted a proposal titled "Studies on Endothelium in Atherogenesis" to the NIH, and this grant application was funded in 1976; it is still active now after 24 years.

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Chien: Rheology is the study of flow and deformation of matter. There is a Society of Rheology, which is part of the American Institute of Physics.

Nebeker: *Do you know the history of the physiology interests of rheologists and when it developed as a field?*

Chien: Biorheology probably developed in the forties and fifties. The late Dr. Alfred Copley was a strong proponent of the field. He formed the International Society of Biorheology and organized many congresses. He also started the journal *Biorheology*, which has Dr. Harry Goldsmith of McGill University and Montreal General Hospital as the Editor-in-Chief. The Congresses were usually attended by several hundred people and they provided a forum for the exchange of scientific information on a lot of interesting work in the field.

Nebeker: *It strikes me as a bridging field.*

Chien: It's a bridging field. That's right. It overlaps a lot with bioengineering and physiology, but it's a very specialized area of bioengineering. However, when one talks about biomechanics and biorheologists, it is very hard to distinguish these two. For example, Dr. Fung's pioneering work in biomechanics is also pacesetting in the field of biorheology.

"I think the problem with engineering modeling in the early days [the 1960s and 1970s] is that many of the modeling studies were not done in relation to the biological reality."

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Chien: In the most recent edition of this excellent book *Molecular Biology of the Cell* by Alberts et al., there is a chapter on the mechanics of cells, which is a new chapter not present in previous editions. This is a clear indication that cell and molecular biologists are now seeing the importance of engineering in the study of biology. There is still not sufficient quantitative treatment in biological research, but I think the next generation of biologists will be educated with the quantitative capability. Quantitative treatments are already being used in some of the biological fields. For example, signal processing is being used in the study of ion channels in excitable cell membranes. The opening and closing of these channels in a particular pattern of frequency distribution modulate the function of cells such as the neurons. The analysis of such data requires the application of quantitative methodology. I believe such quantitative analysis and engineering modeling will be increasingly applied to biological research. In my current research, we study how cells modulate their signal transduction and gene expression in response to flow or deformation of the cell. The time course and the extent of the responses need to be analyzed by treating these molecules as a circuit or network, because of their interrelations and interactions.

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Chien: One of the emerging areas in biomechanics is molecular biomechanics. We have begun to have the instrumentation and capability to study the biomechanical properties and behaviors of individual molecules. For example, the cytoskeleton network is composed of

structural proteins including actin. What are the mechanical properties of the actin filaments and the network during cell movement and in other functional states? The answers to this are important in understanding the mechanisms controlling the motion, mechanical stability, and shape of the cell. How do the cytoskeletal elements change to deform the cell during adaptation to the environment? For instance, in the endothelial cells subjected to sustained flow, the cells and actin fibers become oriented and aligned with flow. What are the mechanics involved in such reorganization?

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Chien: For example, there are now several people working in my group on bioinformatics because we are doing DNA microarray studies to systematically assess gene expression in response to mechanical stimuli. With this novel technology, we can simultaneously search for the expression of 10,000 or more genes, whereas the previous techniques only allowed us to study one gene at a time. Bioinformatics is needed in order to sort out the meaning of the response pattern of a large number of genes. We need people from all of these different disciplines, and we also work with colleagues in our department and in other departments and institutions.

Clark Colton

Professor of Chemical Engineering, Massachusetts Institute of Technology

(interview by Michael Geselowitz on 20 February 2001)

Colton: [For my Ph.D. thesis] I chose to focus on understanding the process of hemodialysis. That involved a multiplicity of things: diffusion in blood, diffusion through dialysis membranes (particularly cellulosic membranes), convective transport in well-defined geometries (I picked the flat plate, which was the most common at that time), and overall analysis of performance. In the course of doing that I began measuring membrane properties in a batch dialysis device I designed. I did the drawings, the whole works. It was modeled after something Ed Leonard had published, and he was willing to sell me one of his devices, but Prof. Ed Merrill felt that I should design and build it myself, so I did.

Building something mechanical with pipe threads and screw threads was something new for me. In any event, I got into how the fluid mechanics and mass transfer worked in the device. That was a kind of side study. I wound up with publications on that. We did a numerical analysis finite difference solution of the convective transport equation. It's a very complicated system that had never been looked at intellectually. That turned out to be a lot of fun. Then I made measurements with it and had an undergraduate doing measurements of diffusion in blood. I then put it all together in a dialyzer in a very well-defined geometry.

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Colton: At that time MIT had a grant from the Ford Foundation. They hired a lot of their own students and made them assistant professors and Ford Foundation Fellows. I got that and I had it for one year, but when the program ended I was allowed to stay. Thing were very tense at that time, I've got to tell you, because the percentages were poor. When I joined the faculty I had a debate within myself. "Well what am I going to do? I want to do biomedical work, but is it really legit and will it be viewed as legit?" I knew that Professor Merrill was not universally viewed as doing solid work because of his work with blood. There seemed to be an attitude of "What kind of nonsense is this?" I wanted to continue in this direction but I also had to do good engineering. I wanted to pick problems where I could see an engineering component.

Geselowitz: *Did you want it to have an engineering component so that you could explain to other chemical engineers who had no interest in biomedical work the problem in terms they would understand and think of as relevant?*

Colton: Exactly. We would make use of the skills we learned as chemical engineers and apply them to a new system. That characterized some of my early work, although I rapidly became a lot more biological or physiological than I had anticipated in some ways. And at that time I was in touch with a small number of students around the country who had obtained their Ph.D.s working on biomedical problems. When I graduated I knew everybody in the country who was working on a biomedical problem. That was only about three or four people, although it started to grow rapidly. At meetings or talks we gravitated toward one another because we were not part of the mainstream.

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Colton: I continued to be interested in membrane processes. My interests bifurcated and trifurcated over the next couple years. Right after my thesis I had a summer job at Amacon Corporation. That was an incredibly stimulating environment. I was out there when fiber ultrafiltration membranes were first developed. They were looking for applications and trying to

understand how they worked, and I became involved in some basic work in an application that led to a new process called hemofiltration. That was really very exciting.

When I was a student, I was involved in work on membrane oxygenation through some consulting. I had sat next to a student, Richard Buckles, who had worked on oxygen transport in blood. There was a request for a consultant that came while I was a doctoral student working on a device to take oxygen *out* of blood to power a fuel cell for an artificial heart. I made use of the work in his thesis in my consulting. That got me interested in oxygen transport in blood.

"If you give students just a bit of engineering and get into the applications too early, you have stolen from them the opportunity to develop some competence. For that reason bioengineering is a really tough thing."

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Colton: Then there was yet another area in which I became involved, and that was through our department chairman at MIT, who was pushing enzyme engineering. It was part of a larger program aimed at using enzymes to carry out a chemical process to synthesize chemicals. We were looking at antibiotics with enzymes using ATP as an energy source to push the synthesis. That was very exciting, and I had a very big lab on that.

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Colton: Right now I am focused on diabetes and the area of artificial organs that I got started in about 1973. I've expanded that work. A lot is going on with islets of Langerhans per se. It might be called cell biology or biochemistry or biochemical engineering, but the obvious application is biomedical. It's for transplantation. It's really a blending of everything. It does have a transport flavor. A lot of what I'm doing deals with oxygen consumption and uptake. Someone in the lab introduced me to NMR, and now we're using NMR to study islet properties in vitro and possibly in vivo. I'm still getting into new things— that doesn't end—but it's all now more focused in the diabetes area.

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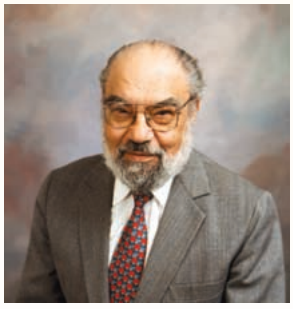
Colton: The point is, this stuff [engineering] is hard to learn. If you give students just a bit of engineering and get into the applications too early, you have stolen from them the opportunity to develop some competence. For that reason bioengineering is a really tough thing. I think that in most cases it's been a mistake to develop large numbers of engineering programs. Graduate programs? Yes. Those are appropriate. And there you focus in certain areas and develop confidence in certain areas. The students can choose when they decide where they want to go in what subareas a department should be active, because every subarea is a bit different. That's dangerous at the undergraduate level, because you run the risk—which I think has played out—of training people who are only modestly competent, if at all, in fundamental areas.

Murray Eden

Professor Emeritus of Electrical Engineering, Massachusetts Institute of Technology

(interview by Frederik Nebeker on 10 November 1999)



Eden: My uncle was not much older than 12 or 13 or 14 when he came to the U.S. He must have been a remarkable man because he was ultimately admitted to Harvard and received his undergraduate degree, and he then obtained a Harvard M.D. about 1924 or 1925. He was a very important influence on my life and the lives of some of my cousins. We used to pal around; he would take us with him and try to teach us something. He was a pediatric cardiologist and was director of a hospital for rheumatic fever kids in Roslyn, Long Island [New York]. He had one of the earliest of the electrocardiogram machines. He was interested in observing what happens if you put the old-fashioned three-position connections (electrodes) anywhere other than the two arms and the left leg. He and I designed a corset. It had buttons on the side so that you could open it and put it on, and it was full of buttonholes. There were buttonholes all over this corset, and we had little brass buttons to put through the buttonhole, then you could put it anywhere you wanted on the chest.

Nebeker: *Just to have controlled positions?*

Eden: That's right. I don't know whether he ever used it on patients or not.

Nebeker: *So that was biomedical engineering at an early age.*

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Eden: I worked on two important pieces of work at that time [the mid 1950s]. We developed a special-purpose analog computer to analyze the kinds of spectra that you might get in electrophoresis, or anywhere the curves of the experimental data had peaks, under circumstances where you know that these peaks and valleys represent concentrations of some entity, molecules or ions usually, but with a lot of overlap of

the peaks. This is the kind of problem that is amenable to mathematical description, usually, and it's surprising what you can do. We could take the circumstance where you had a peak and just a little teeny bit of shoulder on one side and you could estimate the concentrations of the two components that are overlapping with remarkable sensitivity, so long as you knew the distribution function that the peaks followed. So it could be used in a variety of applications, including optical spectra where there is pressure broadening. We built this device, and it worked fairly well. It was ultimately manufactured by Dupont for a period of ten or 15 or 20 years.

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Eden: Another instrumental development I worked on [in the mid 1950s] had to do with separating out groups of red blood cells based on their density. Human red blood cells reach a maximal age of about 60 days. The young are lighter in terms of density than the old ones, so you want to separate them out by tagging the newly formed cells with some radioactive material to identify a particular fraction. I also continued to work on what I had done at Princeton, basically a growth model. As far as I can tell … it is the first algorithmic, computer-worked-out model of two-dimensional growth. The original model is very easy to describe.

Nebeker: *Microbial growth, for example?*

Eden: That's precisely what I was trying to model. A cell divides in two. They remain sitting next to each other. Then one or another or both of them divide. There are all kinds of algorithms you can invent. My algorithm was very straightforward. I said, "One of these two cells shaped as squares will divide, and as they're still connected each has only three sides that are not covered. It can divide right, left, or down. You build more and more." The work on this model and, later, on others reflects the development of computers, because the first use of this model back in Princeton was on what was a computer called the Johnniac. There were three names: John von Neumann, Herman Goldstine, and Julian Bigelow associated with this computer. Bigelow was the engineer. We made pictures. The way we made pictures prevented us from adding many cells. The most we could do was on the order of 20 or 30 cells—the computer was too slow and the only output was a Hollerith punch card. We would produce a picture on a punch card. The holes on the punch card are rectangular, not square, in columns. But if you look imaginatively you can see a picture.

Nebeker: *An early graphical output*.

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Eden: By that time or shortly thereafter I left Rosenblith's group and set up a group with William Schreiber and Samuel Mason. Mason's claim to fame was that he invented flow graphs. He was an ingenious engineer with a wry sense of humor. His research was on sensory aids for the blind. One such, with Schreiber and Don Troxel, was a machine that read printed books. Bill Schreiber came to MIT from Technicolor. He has worked mostly on picture processing. In recent years he has been one of the leading experts on high-definition TV.

So we set up this lab. We had a number of graduate students who later became faculty including Troxel, Tom Huang, Oleh Tretiak, Jon Allen, Ted Young, and Barry Blesser. After a while we were joined by Paul Kolers, a psychologist who had been at Harvard. We couldn't get him an appointment at the MIT Psychology Department, but he stayed with us a while and he chose our name. We became the Cognitive Information Processing Group, and it was that from about the early 1960s until long after I left in 1976. We had hired some strange people. We had a psychiatrist for a while who tried to model the very different world perceived by very disturbed children.

Nebeker: *Can you give some examples of things you and the others in this group worked on in those years?*

Eden: Yes. Most of the things that I worked on had to do with biology. That's how I came back to biology; I had sort of drifted away. Most of the pattern recognition problems that we proposed for students to work on came from medical applications, diagnostic applications, and we really worked on a whole range of problems. We look at patterns.

Chromosome karyotyping is a very good example. When we started, it was very difficult. We knew very little other than each chromosome's size and shape. Then a biologist by the name of Caspersson, if I remember correctly, discovered that you could differentially stain the genes in the chromosome so you've got a bunch of transverse stripes of different widths and gray levels. Suddenly the problem changed because we now had additional information related to structure. We looked at debris in urine. We looked at cancer cells in Papanicolau stains. We looked at X rays to tell the difference between the presence of tubercular lesions or not.

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Eden: We independently invented computerized tomography. I think it's fair to say we did it independently, although Hounsfield at EMI may have begun a year or two earlier. We published the first section of a human tissue in the 1969 International Conference on Engineering in Medicine and Biology.

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Eden: We went over to the Brigham and talked to Herb Abrams, chief of radiology, and his staff. They were mostly interested in angiography. They wanted to look at skinny little blood vessels in the hand or the heart or maybe elsewhere. Our pictures were very crude. They looked like a patchwork of different colored squares. We could only digitize in a matrix of 32×32 or 16×16—very small numbers. We could have done better, but it would have required more computer power than we had readily available to us. They looked at our pictures, which were full of quantizing noise, and said, "Well, we have no interest."

Yuan-Cheng "Bert" Fung

Professor Emeritus of Bioengineering, University of California, San Diego

(interview by Frederik Nebeker on 12 December 2000)

Fung: Dr. Sechler, my mentor [at Cal Tech], asked, "What would you like to work on?" "Well," I said, "I would like to work on aeroelasticity." "Ah," he said, "just right. In 1942 the Tacoma Bridge on Puget Sound in Washington State was blown down by wind. Von Kármán said that the oscillation was caused by vortex shedding from induced aerodynamic forces. The State of Washington Public Works sponsored a research project here. When von Kármán retired, that job was given to Dr. Louis Dunn. When Dr. Dunn became the director of the Jet Propulsion Laboratory a few months later, he handed the job to Maurice Biot. Biot soon left. They left a filing cabinet here which you may take a look at."

I inherited a wind tunnel designed particularly for this project. I used it to study the bridge. I found bridge aerodynamics very difficult, very awkward. Airfoils are simpler and cleaner. So I began working on aeroelasticity of the wings. I formulated the general aeroelastic problem and then designed ways to systematically study it step by step.

Nebeker: *You were interested in a general theory of aeroelasticity rather than in how a particular structure responds?*

Fung: Yes. I wrote one of the first books on aeroelasticity.

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Nebeker: *Can you tell me how you first became interested in biomedical problems?*

Bert Fung working on tissue remodeling with Wei Huang, Ghasan Kassab, and a student at the University of California, San Diego.

Fung: I became interested in biomedical problems for a personal reason. In 1957 I took a sabbatical leave with a Guggenheim Fellowship and went to Germany. My mother had acute glaucoma, a very painful disease, and I could do nothing for her. In frustration, I read American literature on glaucoma and sent her a weekly translation or summary. I told her, "If you cannot use it, give it to your surgeon." Many years later, in 1973, I finally went back to China. My mother's operation was a success. Her surgeon thanked me.

In Germany, right across the street from the Aerodynamics Research Institute was the Physiology Institute of the University.

Nebeker: *This is in Göttingen?*

Fung: Yes. It was the Göttingen Physiology Institute. I enjoyed their library and their facilities. That's the beginning of my interest in that field. Gradually one thing became quite clear to me: the biologists do not think about what we engineers always think about—namely, the force, motion, and transport phenomena. Furthermore, biology is full of interesting nonlinear problems. The field seems to ignore the kind of things which you can do. I found the field very attractive.

After returning to Caltech I began to work on physiology. A few years later my feeling was that I wanted to work on it full time; I didn't want to dilute it with other work. That's how I ended up at UCSD.

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Fung: Now, the mechanical properties of biological tissues were virtually unknown in the 1940s. The question was how to describe the mechanical properties and what to measure. Today you would consider successively the hierarchies of organelles, cells, interstitial materials, tissues, organs, and the individual. Historically, the study was done in downward order of hierarchies.

Every step is difficult. For example, it was very difficult to quantify the mechanical property of tissues, but without that you cannot begin. With testing, theorizing, and hypothesizing, you hope that you'll eventually understand the materials that you are dealing with.

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Fung: Capillaries have a diameter of about ten microns (about one-third the thickness of our hair) and a wall thickness of one or two microns. Dr. Zweifach and his associates could not detect the change of the capillary diameter when the blood pressure was changed by as much as 100 millimeters of mercury. Since they used an optical microscope for the measurement, this means that the change of diameter is much less than one wavelength of light, or 0.5 micrometer.

Nebeker: *Isn't it surprising, because such a thin structure should respond to that change in pressure.*

Fung: Yes. Very surprising if we think of the capillaries as small cylindrical tubes. Collagen or steel tubes can do it, but not a single layer of endothelial cells with a thickness of one to two microns.

Where did this rigidity come from? I looked at the problem and my suggestion was that the rigidity came from the surrounding media. In other words, the capillary blood vessels we have are not a tube, but a tunnel lining.

To verify that the rigidity comes from the tunnel material outside, I measured the material properties of the stuff outside the capillary, then computed the expected deformation of the capillary. I found agreement. That kind of thing makes engineering thinking suddenly relevant.

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Fung: The next thing I wanted was to determine the elasticity of the capillaries of the lung. Then … work out the implications of the new understanding on the physiology, pathology, diseases, and injury of the lung. In this endeavor, I was fortunate to have the collaboration of a famous physiologist, Dr. Sidney Sobin, and my former student and colleague, Michael Yen, and many graduate students of ours.

This was where the payoff from an engineering point of view of physiology came in. If you look at the lung, you see that it is an organ of capillaries. These capillaries, however, are not single long tubes; they are organized into two-dimensional sheets. The geometry is unique. We had to measure the dispensability of the sheet, analyze the flow, and understand the physiology.

Nebeker: *Even the microanatomy wasn't fully known at that time?*

Fung: The Sobin-Fung sheet-flow model of pulmonary capillary was novel. It changed the language of pulmonary microanatomy. It showed that the classical Poiseuille formula of blood flow does not apply to the lung. It showed that it is simpler to think of a continuous sheet with a pattern of obstructions.

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Fung: [At UCSD] we had tremendous relationships with the surgeons.

Nebeker: *More so than with other doctors?*

Fung: I think so. Surgeons really see immediately that engineering is what they need. We had very good collaborations with the surgeons. The barrier was broken down almost without effort. I think we were extremely lucky on that.

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Fung: Microcirculation is a big field, but really the organs they study are not many: the mesentery, the cheek pouch, the skin flap, and a few others. Everybody is interested in muscle, but there aren't many muscles tested. First the frog.

Nebeker: *That goes way back.*

Fung: When A.V. Hill worked on muscle mechanics he used British frogs and got poor results. One day he visited Italy and got the Italian frog; then [his experiments] worked.

Nebeker: *So that was the advantage Galvani had.*

Fung: There are really not many models that people make observations on.

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Fung: I think biomechanics will be there always. No understanding can be reached if force and motion are ignored. I don't ever think that application can be minimized. Applications always have surprises of some real good important discovery.

Nebeker: *From the purely scientific viewpoint.*

Fung: Even from the scientific point of view. Biomechanics is the middle name between structure and function.

Geddes: My first paper described the RC AMC electromyograph. It was published in April 1945. I was working on it in 1944. It was quite an elegant device with a differential amplifier, a loudspeaker, and oscilloscope. There were a lot of soldiers returning home with nerve injuries. You could diagnose nerve injury with the electromyograph—just place some electrodes in a muscle and one could detect a characteristic electrical activity. That was what I was doing during the last year of the war at McGill.

I then joined the Montreal Neurological Institute in 1945 as a research assistant and stayed there until 1952. I was an instructor in the Electrical Engineering Department at McGill from 1945 to 1946. I was one of the early biomedical engineers. They didn't know what that was at the time. It was all medical physics at that time. I was responsible for the operating room equipment and for the electroencephalography laboratory.

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Geddes: At Baylor I built the physiograph. The teaching of physiology was in the dark ages then. Everybody used a smoked drum (the Ludwig kymograph) to record only mechanical events. So, I built the physiograph as a modular electronic system that permitted recording many different types of physiological events. This is where my Northern Electric experience and ham-radio experience paid off. The Bell Telephone System has a philosophy that any new device that is made must fit with the old system—it must be compatible. So a modular concept was the keynote for the physiograph, which had a transducer, an amplifier, and a display device. One could connect a variety of different compatible transducers to the amplifier, which energized the transducer and amplified its signal. One could then have the event written out on a graphic recorder, or displayed on an oscilloscope, or heard by a loud speaker. We displaced the smoke drum kymograph around 1954 or so.

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Geddes: This system created so much attention that the NIH funded us for a training program which originated in the following way.

My mentor (Hoff) and I were sitting in the Washington National airport about 1955 or so. We had three hours to kill. We sketched our ideas for a summer course on physiology on the restaurant menu.

On arriving home, we applied to NIH for support to teach modern physiology. The program was titled, Classical Physiology with Modern Instrumentation. The concept was like "Shakespeare in Modern Dress." We received the funds for a six-week summer course with stipends for tuition and expenses. We had people from all over the world as well as the United States. This National Heart Institute training program was the longest single managed training grant that NIH had ever funded up to that time. It ran from 1956 to 1974—18 years. We trained about 1,000 people.

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Geddes: Let me tell you something about the early days of ventricular defibrillation. The first human transchest defibrillation was in 1947. By about 1954 our students had all done ventricular defibrillation with a physiograph. We had several calls in 1957 and 1958 from the local hospitals where we had former students. They would call and say, "Send us over the physiograph defibrillator and the paddles. We have a patient in fibrillation. We're doing cardiac compression. Hurry up. Send us the defibrillator." So we sent the defibrillator over and they put the paddles on the heart and defibrillated.

Nebeker: *There were few companies out there producing any kind of defibrillator at that time.*

Geddes: As a matter of fact, it didn't really start until 1952 with transchest defibrillation with a 700-volt, 60-cycle alternating current defibrillator. Then Lown did it in 1962, ten years later, with a damped sine wave. And so, human defibrillation didn't start until the early 1960s.

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Nebeker: *What was the response of the medical community [to your publication of the defibrillation dose concept]?*

Geddes: You see, cardiologists only saw adults. They knew they had difficulty defibrillating 200-pound subjects. But they could defibrillate most of the subjects with the defibrillators they had. Turn it up to the top and we defibrillate all. So, who is interested in the dose concept? That fight went on from 1974 for about the next eight or so years. It was only when they decided to make defibrillation efficient because they had to implant them that they began to know that big hearts are difficult to defibrillate. Small hearts are easy to defibrillate.

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Geddes: I was a consultant for the VSAF at Brooks AFB in San Antonio, Texas, for many years. In the early 1960s, when I was at Baylor Medical College in Houston, NASA contacted me and invited me to be a consultant on physiological monitoring of astronauts before there was a suborbital flight. I, along with other scien-

Leslie Geddes
Showalter Distinguished Professor, Emeritus, Department of Biomedical Engineering, Purdue University
(interview by Frederik Nebeker on 13 October 2000)

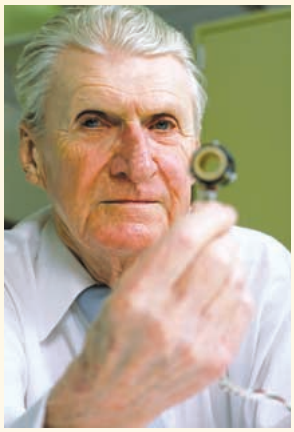

PHOTO BY VINCENT WALTER

tists (Pat Meehan and Col. Jim Henry), met with a few NASA people in a garage rented from Homco Oil Co. located at the intersection of Old Spansh Trail and Wayside streets in Houston. Then there was no Manned Spacecraft Center. We all discussed the important physiological events that we should measure and telemeter to earth from the astronauts.

From the outset it was obvious that it was desirable to telemeter the four vital signs: temperature, pulse rate, respiration rate, and blood pressure (T, P, R, and BP). It turned out that the chimps on the sleds at Holloman AFB would not tolerate a rectal thermometer; they unceremoniously ejected it. The heart rate could be detected from the ECG. Respiration was detected by the cooling of a heated thermistor on the microphone in the helmet when the astronaut exhaled. In the first flights, indirect blood pressure was not obtained due to the cramped space. Accordingly, only ECG heart rate and respiratory rate were telemetered to the earth-bound monitoring stations. But there was a problem because the respiration signal was lost when the astronaut turned his head away from the microphone. At this point NASA contacted me and asked if I could devise a more reliable method of detecting respiration. On a Saturday afternoon at Baylor, I went into the lab, placed two electrodes across my chest at the xiphoid level, and measured the 20-kHz impedance changes that occurred with respiration. The method was described later in *Aerospace Medicine* in 1962, and we used it in the medical student physiology laboratory; the method became known as impedance pneumography.

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Geddes: During my time at Baylor, I had always been interested in the measurement of direct and indirect blood pressure. I published two books on the direct and indirect measurement of blood pressure. We actually developed the oscillometric method, which is the standard method used now. We did the study that showed that when cuff pressure is decreased, the amplitude of cuff-pressure oscillations increased, reached a maximum, and then decreased. The maximum oscillation point signals mean pressure.

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Nebeker: *Was it in 1968 that the first edition of your book with L.E. Baker on medical instrumentation was published?*

Geddes: Here is the first edition, 1968.

Nebeker: *Would you tell me a little about how that book came to be?*

Geddes: That book came as a result of teaching medical students, residents, and interns, and the need to make devices for research. It also came as a result of the summer course "Classical Physiology with Modern Instrumentation." There was just no way you could buy devices to make the measurements. Lee Baker was my graduate student. We decided that we would put this all down so people could learn how to make their own devices from a book. It's really a measurement handbook.

Nebeker: *It's become a real classic with three editions.*

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Nebeker: *You were saying that it is very important as a teacher to provide historical background.*

Geddes: Yes. I think it is important because by knowing that, down the road the student will perhaps be able to make the next leap from the knowledge that he or she has now. It gives them the thought that discovery is an evolutionary process. For every discovery, there is a little background and there is going to be a future. We are not at the end of the discovery road now.

Nebeker: *Occasionally, an earlier approach that didn't result in anything useful might become feasible when new technology arrives.*

Geddes: That's exactly the point. New technology is around, and one can do things now that were very difficult to do previously. The knowledge was around, but the execution was very difficult.

So, I always start my lectures with the history and what was done and why it was done. To just say what was done is not enough. One has to get into the mind of the person who did it to find out why he did it.

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Geddes: I don't know that biological engineering it is getting fragmented. It has changed. The transactions on biomedical engineering are becoming a little more theoretical and more concerned with modeling than they used to be. The trouble is that doing experiments is expensive. It is easier to sit at the computer and put data in and model. It is expensive to take those data and subject them to the real-world animal or human test. So that is a change that I am not particularly happy to see because I like to see theory and practice joined.

Nebeker: *I understand that while you were at Cornell you started working with some instrumentation for animals for the Psychology Department.*

Greatbatch: Yes. At that time Cornell's Psychology Department was one of the country's foremost centers of Pavlovian psychology, which is a physiological psychology. I got a job building amplifiers for a hundred sheep and goats, measuring their heart rate and blood pressure and so on. I also participated in conditioned reflex experiments. My experience there turned out to be quite useful. Because I knew what conditioned reflex was, a few years later I had the opportunity to build all the amplifiers for one of the first monkeys shot up into space. That was what really got me into the field of medical electronics.

"One of the first pacemakers that ran on a lithium battery was implanted in a patient in Australia. That patient went out into the outback and became sort of lost from civilization. They finally caught up with him and discovered that his pacemaker had been running for 22 years."

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Nebeker: *I'd like to hear more about your instrumentation for these animals. Were you first building amplifiers for the EKG?*

Greatbatch: Yes. The heart generates a signal which is about a millivolt in amplitude, so this has to be amplified by a factor of something like a thousand before it can get up to the point where it will record. At that time we didn't have transistors yet, so all our work was done with vacuum tubes—which is not the right way to do this sort of thing.

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Greatbatch: A friend of mine in Minneapolis, Earl Bakken, was building battery-operated pacemakers that could be worn on a belt. They had wires going right through the skin. That was only marginally satisfactory, though some people lived a long time with them. We engineers have not to this day learned how to run a wire through the skin and have it seal. It's always an open wound. Therefore the people have to put antibiotic jelly around it every morning and every night. They can't bathe, go swimming or take showers. They can take a sponge bath, but that box is always there. They roll it over at night and they can never forget that it's there.

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Greatbatch: Five years later when transistors had been invented and had become readily available I thought, "Now I can make a pacemaker."

Nebeker: *Can you recall dates?*

Greatbatch: It was somewhere between 1949 and 1951 when I learned about the disease. We built our first pacemaker with transistors for implantation into an animal in 1958. Much to my wife's consternation, when I realized I could actually make pacemakers I quit all my jobs. I had two thousand dollars in cash, which was enough to keep my family going for two years [1958 to 1960]. I gave the family money to my wife and went up in the barn behind my house. In two years I made 50 pacemakers.

Nebeker: *You made them by yourself?*

Greatbatch: Yes.

Nebeker: *Did you make any attempts to interest a medical equipment manufacturer? I would think a young engineer might go that route with a good idea like that.*

Greatbatch: I considered that and I did talk to some people, but no one was really interested in it. Of course we hadn't implanted devices in our first patients yet. Once we had our first patients with the device successfully implanted, there was a great deal of interest. We worked fairly closely with Earl Bakken and his Medtronic Company at that time.

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Nebeker: *How did the connections with Doctors Chardack and Gage come about?*

Greatbatch: Our local chapter of the PGME [Professional Group on Medical Electronics of the Institute of Radio Engineers] in Buffalo had a meeting every month. Ours was the first chapter in the country. We tried very hard to get an equal number of doctors and engineers to attend the meetings, and sometimes we had as many as 50 people at a meeting. The engineers offered to send a team of engineers to help any doctor that had a research problem—for free. Quite a few doctors took advantage of that offer. In fact, about five different medical doctor-engineer teams that resulted from that stayed together for quite some time. I went up with one of those groups to see Dr. Chardack.

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Nebeker: *It sounds like you became very interested in battery design.*

Greatbatch: Yes. Once we realized that the

Wilson Greatbatch
President and CEO of Greatbach Enterprises
(interview by Frederik Nebeker on 4 April 2000)

battery was the limiting factor, we started looking at all sorts of power supplies. We even looked at rechargeable batteries. However, we found out that the life of a rechargeable battery with recharging was not as long as the life of our primary cells without recharging. That knocked out that idea.

Nebeker: *Would this have been a kind of recharging that could be done through the chest?*

Greatbatch: Yes, inductively through the skin. That would have been no problem.

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Greatbatch: We came up with the lithium battery in 1970. The lithium battery had a much longer life than mercury. And it didn't generate gas, so it could be hermetically sealed. The fact that it didn't have gas was a big deciding factor. The fact that it could be hermetically sealed was an even bigger factor, because that meant we were no longer running under water. One of the first pacemakers that ran on a lithium battery was implanted in a patient in Australia. That patient went out into the outback and became sort of lost from civilization. Last year they finally caught up with him and discovered that his pacemaker had been running for 22 years.

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Nebeker: *Did the paper published in* Surgery *and other publications create an immediate demand?*

Greatbatch: Yes. Of course we also went to all of the shows. Medtronic had a booth at every show. I published in the IEEE/PGME journal, and I published any new battery developments. Dr. William Chardack and I published jointly in the medical journals. I used to accompany a Medtronic salesman and visited a lot of hospitals, and I gave talks at their research seminars. We gave a very strong educational push in those first five years. It is interesting to me that it took only five years for the pacemaker to become universally "indicated"; that is, accepted as the way to treat complete heart block. That was almost unheard of in the industry.

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Nebeker: *Was Wilson Greatbatch Ltd. established in 1970?*

Greatbatch: Yes. It has expanded ever since with new battery models and more people until today. We either make or license over 90% of all the batteries in the world that go into pacemakers and implantable defibrillators.

Nebeker: *Was that always your market? Were you always exclusively aimed at these implantable devices?*

Greatbatch: We have diversified somewhat, but it took just about all of our abilities to satisfy this one market. We also make batteries for use in outer space. Any time that the astronauts go outside of their bird they carry with them a television camera, a life support system, and communication equipment—all of which run off of our batteries. We also make a battery that will run at 150 °C. They are taken down to the bottom of oil well holes to log up the results. We have specialty markets like that, but our biggest business is in implantable medical batteries, implantable power. Now we are into implantable power for artificial hearts.

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Nebeker: *What was the rationale for freely licensing rather than selling your own patents?*

Greatbatch: Building confidence in the field was our main objective. We didn't want to have an image like that of Microsoft. We wanted our customers to be good friends. We are very careful in quality control and look for and find the one bad battery in 10,000 before it gets out of the factory. People like that, and the FDA is agreeable to it too. We are very careful. If there is a problem, our customer finds out from us rather than from their customer. We've built a good relationship with our customers, and part of that goodwill is from freely licensing.

Dov Jaron

Calhoun Distinguished Professor of Engineering in Medicine, School of Biomedical Engineering, Drexel University (*interview by Frederik Nebeker on 6 October 1999*)

Jaron: While I was an undergraduate student I worked as an electronics technician at the Medical Center of the University of Colorado in Denver. I worked for a psychiatrist named Sidney Margolin, who actually was trained under Freud and did what was called psychophysiology. He lived in New York for many years and treated some of the most famous movie stars as a psychiatrist, then he decided he had enough of the city life and moved to Denver to be on the faculty. He was an electronics nut. He had the first electronics system to measure psychological responses. Dr. Offner built it for him.

Nebeker: *Do you know what sort of psychological responses?*

Jaron: Yes. ECG, EKG, galvanic response—any electrical response that is measured today, he had the first unit that did that. I maintained this unit for him. It was built with tubes and all done by hand.

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Jaron: If you have a current generator inside the body, it generates potentials on the surface. The electrical activity of the heart is the equivalent of such a generator. You can measure the potential distribution on the surface of the body because you have access to the surface. The question is, from the surface of the body, can you deduce what happens to this generator and in particular, when there is a problem with it. That is done to a certain extent with electrocardiography—that is what electrocardiography is all about. But electrocardiography has serious limitations. [David Geselowitz], one of my Ph.D. advisors, was trying to figure out whether there is a better way of getting more information about the generator. We realized that an implanted pacemaker can be used as a model to study the relationship between an internal generator and the potential distribution on the body surface that results from its action. With a pacemaker, we knew exactly its properties as a generator. We knew exactly what the current of the pacemaker is, what the voltage is, so we tried to measure surface potentials and relate those surface potentials to the current generated by the pacemaker.

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Jaron: I then [in 1967] went to work with a heart surgeon by the name of Adrian Kantrowitz at Maimonides Medical Center in Brooklyn, New York. He had just received a very large grant from the NIH to develop and test heart-assist devices. Together we developed the intraaortic balloon pump. The intraaortic balloon pump is a plastic balloon, maybe 20 centimeters long, mounted at the end of a hollow catheter. It is introduced through the femoral artery all the way into the descending thoracic aorta. The balloon is inflated and deflated in synchrony and out of phase with the heart's action. When the heart begins to eject blood (systole), the balloon is deflated, thereby creating a lower resistance in the circulation, making it easier for the heart to pump the blood. When the ejection period of the heart is finished and the aortic valve closes (beginning of diastole), the balloon is inflated. This displaces the blood to the periphery, but more importantly, also towards the heart. The coronary vessels get all their blood supply during diastole, when the heart is relaxed, which is the time when the balloon is inflated. As a result, you are increasing the blood supply to the heart and also to the periphery, and at the same time you are reducing the workload on the heart, making it easier for the heart to recover from a heart attack.

Nebeker: *You worked with Kantrowitz in actually building this device?*

Jaron: That is right. We actually produced the balloons. We made the drive units, tested the system on animals extensively, and then used it on patients.

Nebeker: *What year was this that you were first using the device?*

Jaron: It was 1968. We had done maybe five or six or seven patients, and the word began to spread around the country and people started calling us and asking for our team to come and treat a number of very famous individuals.

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Jaron: Ever since I was president of the EMBS I have pointed out that the EMBS focuses only on those professionals whose roots are in electrical engineering. Biomedical engineering has become much more than electrical-engineering oriented. As a matter of fact, many biomedical engineers now may not even know what an electrical circuit is. There are many more mechanical-, chemical-, information-, computer-, and materials-based biomedical engineers. I predicted it ever since I became president of the Society, and I have urged the Society to move more and more in that direction.

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Jaron: We are entering a new era. When we finish sequencing the genome, we will begin to understand how the genes relate to proteins and how they relate to cell function. How the cells behave, how tissues behave, and finally how whole organs and the organism function. I think the only people that will be able to put this picture together are biomedical engineers. The way scientists approach a problem is by the reductionist approach. They break the system down into its smallest components and concentrate on the very small elements on the system. Engineers try to integrate. Biomedical engineers who understand the living system should be able to integrate facts and knowledge about the system's components and begin to understand how the whole system functions.

Richard J. Johns
University Distinguished Service Professor, Johns Hopkins Medical School
(interview by Frederik Nebeker on 26 April 2000)

Johns: The action potentials [in neurons] that you evoke from this are in the millivolt region, so you had to have very good differential amplifiers. Otherwise, if you charged up the input capacitance of your amplifier, all you would be looking at is the exponential decay from the stimulus artifact. You had to have very good differential amplifiers with low input capacitance to be able to do that. Those were some of the technical parts of it.

Our research interest was in finding out the nature of the disorder of neuromuscular transmission in myasthenia gravis. There was a big controversy at that time as to whether the problem was in the nerve ending with not enough acetylcholine being released. Or, whether the disease was of the musclemotor end-plate and that a normal amount of acetylcholine was being released, but it was insensitive to it.

Nebeker: *Were you able to answer that question?*

Johns: Yes. The way that we were able to answer it was by comparing the effect of externally injected acetylcholine in normal subjects and in patients with myasthenia gravis, when you put the same amount in. Since acetylcholine is quickly destroyed in the blood, the trick was that you had to put it into the artery so that it would go directly to the muscle very quickly before it was destroyed. That showed very clearly that there was a diminished response to injected acetylcholine. So we knew that the problem was not in the nerve but in the motor end-plate, and that subsequently was shown by other methods as well.

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Johns: One of the great unexplained things was the nature of joint stiffness in rheumatoid arthritis. The thought was that because the joint cartilage was destroyed, it was friction that gave them the stiffness. Nobody could understand one of the real characteristics of rheumatoid arthritis, which is called morning stiffness. People would wake up and their hands would be very stiff, and then as the day wore on their stiffness would decrease. Well, there is no reason that the friction should change, and that did not make sense.

We developed a method of measuring joint stiffness with a hand-holder, which is something that mechanically moves the finger so as to have passive movement of the finger sinusoidally. We would impose a sinusoidal rotation, and it would sense the force that was required to do that.

Nebeker: *A device to move the finger and sense the force that is encountered?*

Johns: Yes. The other thing which is important is the axis of rotation. It was a cantilever bar with strain gauges on it that measured the force, and then there was a sinusoidal rotational drive. The bottom line was that the stiffness of rheumatoid arthritis is a visco-elastic stiffness and nonfrictional—there is no excess friction. It was this visco-elastic stiffness that increased in the morning. It was an actual swelling in the joint capsule that produced it.

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"One of the great unexplained things was the nature of joint stiffness in rheumatoid arthritis. The thought was that because the joint cartilage was destroyed, it was friction that gave them the stiffness."

Johns: I was the national president of the IEEE Group, too. It was then called the Group on Engineering in Medicine and Biology, and in 1973 and 1974 I was the chairman.

The IEEE Engineering in Medicine and Biology Society was primarily the electrical engineers in biomedical engineering. They were a fairly diverse group. They weren't all circuit design for biomedicine people, and there were many of the Dave Robinson types (the guy studying control of eye movement who was an electrical engineer). They didn't think much of chemical engineers and the kind of stuff that they did. I was okay, coming from medicine.

Nebeker: *So an M.D. had no trouble?*

Johns: Yes. But a chemical engineer, they didn't quite see what they were doing in that. Then the Biomedical Engineering Society was primarily people in the systems physiology business.

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Johns: [At Hopkins] we were talking about myocardial contractility and how to measure it. Some of the myocardial contractility people and the MRI people and the image processing people came together. What you can do now is, with magnetic resonance saturation, in essence, put a whole bunch of planes through the heart and then watch those lines, those planes, move as the heart beats. They said that we could see if there are some areas of the myocardium that are not contracting. Then the imaging folks figured out how to create a pseudo-color display, such that the less it contracts the bluer it is, and so forth. Then they get the cardiologist in on it doing thallium scans to see if that is where the thallium uptake is wrong. It does make a good environment for doing collaborative stuff.

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Johns: Then I was personally interested in the clinical information system business and was involved with those. In one piece of that, Don Simborg and I were interested in seeing about using information to save costs. It turns out that the biggest wastes of money in terms of laboratory and ancillary services are not the big-ticket items but often the very routine items. At that time, the most expensive thing was CT scans, and the cheapest was X ray. If you could reduce your chest X rays by 10% you would save more money than if you eliminated CT scans entirely because of the tremendous volume. We tested to see how hard would it be to save 10% in that. It turns out, I think, 3% of all the X rays were taken of the same person on the same day.

J. Lawrence Katz
Professor of Biomedical Engineering, Case Western Reserve University
(interview by Frederik Nebeker on 15 October 1999)

Katz: For instance, how did the motion of atoms or molecules relate to elastic properties, a field called lattice dynamics. We worked on zinc from liquid helium temperature all the way up to just below the melt, and measured the properties both in plane—how the zinc atoms vibrated—and perpendicular, and that gives you a relationship to the internal forces. That started me in good stead. The way I got into bioengineering is I saw this announcement to apply for a science faculty fellowship. I had only been at Rensselaer a couple of years. It was not so much research, but you went some place to learn what to do for teaching. The English system for teaching crystallography was very good. I wanted to go to University College, London, to work with Dame Kathleen Lonsdale, the first woman member of the Royal Society and a Dame of the British Empire.

While I was there we received an announcement of a minisymposium at the Cavendish Lab where Perutz and Kendrew were giving their talks on hemoglobin and myoglobin for which they won the first Nobel Prize for the structure of proteins.

I had kind of an epiphany attending that meeting with Perutz and Kendrew in England where I said, "Gee, fantastic, you can use these techniques and really work on living things."

Nebeker: *And you felt real breakthroughs were possible in biology.*

Katz: Yes, that is right. I think these other old-timers had the same kind of feeling. Suddenly they say, "Hey, with the kind of things that I am doing I can make a contribution to understand how it may be possible to improve the quality of life." I really think that has been the driving force, even with the young ones now who take it up as a career.

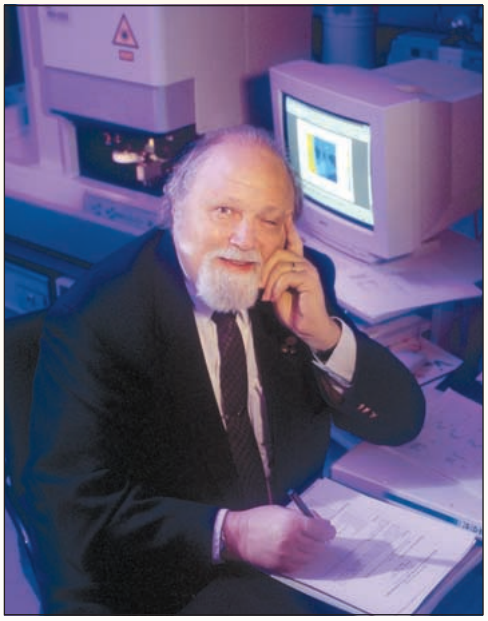

PHOTO BY JIM THOMAS

J. Lawrence Katz' major interest is studying how and why bone structure forms and how it relates to properties.

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Katz: I did have a state-of-the-art laboratory. I found out later I had one of the only labs in the world at that time which had a computer-controlled system to measure the crystal properties. This is 1963 and early 1964. I had one of the early DEC-PDP8s, and I had some brilliant freshman and sophomores because we had an honors program where undergraduates could pick a lab to work with. Since I had one of the best computers on the whole campus of Rensselaer at the time, my lab was a focus. The PDP8 was driving this device, and it was dumping the information into another early computer, an IBM 1620, with a tape drive. When we received the money from the Institute of Health I could upgrade it to a card-driven computer to speed up the way the Fourier calculations were done.

I started this working with very bright students. The beauty of it was that I did not have to write a research proposal. If I wanted to do something, I could take on a student as a trainee. The idea was to train them in how to do research. We began by trying to understand how bone and mineral form. Very early on that it became clear also that you had to understand something about how to measure these things nondestructively,

and that is how I got into the ultrasound work. RPI was a good place to be for that. Dr. Huntington during the war years worked at the MIT lab where they developed sonar for anti-submarine warfare, and he had used those techniques to measure the properties of single crystals. This is the way you measure the elastic properties, the relationship between the sound wave and elasticity. You learn about the wave equation in any kind of instrumentation electrical engineering course, then the diffraction work to look at structure. It turns out there was important work considering that there was probably an electrical driving force in the development of bone. So this thing began to integrate looking at mechanical properties, electrical properties, and ultrasound measurements.

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Katz: Our publications in the mid to late 1960s on some of these ultrasound properties were the first saying, "these are the properties, but this is how they relate to structure." Prior to that was, "here are the numbers, this is the value of the elastic modulus of a bone or the elastic modulus for a tooth," because they wanted this general information to see how it related to the amalgam. Coming from the solid state, crystal physics, my interest was very basic, as what is the relationship between structure and properties? I essentially first developed the conception that for bone you could not just simply consider it as a mixture of the inorganic apatite and the organic collagen. Because there were so many different levels of structures involved and each one contributed to it, you had to consider it as a hierarchy. That way you had to understand how the apatite crystallites and the collagen organize and how they form their joint structure.

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Katz: When I started I called my laboratory the Laboratory for Crystallographic Biophysics. When I began to go to some of these meetings like the ASME meetings and other engineering meetings, they said you are doing biomedical engineering, and I had to say, "What is that?" In the 1960s, being a physicist, I said I am working on "bio" things so it is biophysics. If you are interested in bone as a structure and its properties, then that is engineering. Then eventually the school changed my title from Professor of Physics to Professor of Biophysics and Biomedical Engineering. So early on I had a bioengineering title, probably even before there were any departments of biomedical engineering.

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Katz: Dentistry was the leading [area for implanted materials] because they already knew about amalgams and they already had the polymers to make impressions, and so they knew these things could be used inside of biological tissues. Already, some orthopedic implants were being made out of steel and cobalt chrome alloys, even produced commercially, because some of the post World War II people began to try implants when people had accidents and so on in order to replace damaged tissues. There was also the neat external orthotics materials and prosthetic materials for all of the war injuries which happened after World War I, but even more after World War II.

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Katz: That time period in the 1970s was when the space R&D went down, and they began to fire a lot of the solid-state and material scientists. The National Academy of Science (NAS) had a special meeting in Washington to see what could be done in applications and material science. I was invited to speak about biomaterials. They had a whole session on bone, and they had some other people there. Starting in the late 1960s, when all the societies had their annual meetings they had a symposium on biomaterials—chemistry, physics, and the old Institute of Materials and Mining Engineers. It was almost the same working group giving the talks at each symposium.

Nebeker: *The idea was that some of these materials people were no longer employed in the space race.*

Katz: So they wanted to find out where to go. Even before the National Academy of Engineering (NAE) existed they were concerned, because a lot of them were scientists, chemists, and physicists. Biomaterials at that time was beginning to blossom.

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Katz: For instance, I got into acoustic microscopy because an electrical engineering colleague at Rensselaer, who worked on surface acoustic waves, was developing a transmission system in the early days and he thought it might be useful for us in bone. I said, "You bet it is useful!" Before we were only measuring average properties. We would take transducers and put it across the material to get its property on the average. In that case the resolution went down to 100 micrometers as opposed to millimeters. This was very exciting, and that led us into acoustic microscopy full time.

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Katz: My major interest is still to understand how and why the bone structure forms, and how it relates to the properties. Any tool or device that will do that, I will either work with those people who use it or work with it myself. Each case is like a bug zapper that attracts bugs to it—because of my interest and of having a history of publication and being at the cutting edge in this, my colleagues who themselves are not biomedical engineers but who have something like this will say, "I have this thing and it looks like it should be related to your work." I say you bet it does, and we start working on it, then we merge our expertise.

Robert Mates

Professor of Engineering Emeritus, State University of New York Buffalo

(interview by Frederik Nebeker on 13 December 2000)

Mates: By then [in the early 1970s], the space program thing was starting to wind down a little bit, at least the basis research part of it, and so money was starting to dry up. I was kind of looking for new things to do, and, again fortuitously, I became very good friends with David Greene, a cardiologist at the university. We served together on the University Personnel Promotions Committee for three years. He was quite a bit older than I and was an intensely curious person, a very bright guy. But he had never studied anything about mathematics or physics. He would read articles in the cardiology journals that would have some equations. People were just starting to do some modeling and he would bring these to me and say, "Could you explain this to me?" I said, "Well, this is really kind of intriguing stuff." It was getting harder and harder to get funding in the space areas, so I thought, "Well, let's give it a try."

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Mates: I became more intrigued with the physiology of the heart, and what we could do with patients was very limited because you could only make measurements of the overall behavior. During the time I was in the Department of Medicine, I became good friends with another cardiologist who was about my age, Fran Klocke, who was more of an experimental cardiologist. His interest was in the fundamentals of cardiac contractility and using animal models, where you could make much more detailed measurements. So I started working with him, and got into sort of a more fundamental level, not only in the muscle mechanics, but at that point we also got into modeling the behavior of coronary arteries, particularly coronary arteries that were partly constricted.

Nebeker: *Modeling the flow behavior?*

Mates: Yes. We actually built a large coronary artery of plastic that we could instrument, and we had a pulsing pump that would simulate the flow as a function of pressure upstream. We did some very detailed measurements, and that turned out to be pretty interesting.

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Mates: I spent a year in the physiology department and I learned how to operate on dogs, and do surgery, implant flow meters around coronary arteries, and all those kinds of things. I became much more independent then. Using that background I was able to do a lot more detailed studies of coronary flow distributions. We would take dogs with flow meters on the coronary arteries and insert catheters to measure pressure, and we obtained much more detailed information on the way in which the coronary flow distributed, particularly in disease states.

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Mates: One of the practical problems with coronary artery disease is that most patients are asymptomatic until the artery is just about totally closed because the circulation compensates. As your artery starts to constrict, the downstream circulation starts to relax to reduce the resistance. So you can occlude, in most cases, over 90% of the area of an artery without reducing flow. All of a sudden though, you get to that critical point and then flow starts dropping off.

Nebeker: *Were you able to model that?*

Mates: Yes. We were able to do a lot of modeling of that.

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Mates: Very complex models can simulate anything you want, but the problem is how to select the parameters. My idea was that unless you had a simple enough model so that you could identify the parameters in a particular animal or in a particular patient, the model wasn't terribly useful from a practical point of view. Although we never quite made it, I thought that eventually we would come to the point where you could take measurements in the catheterization lab, model the behavior of the coronary circulation and say, "Okay, this patient has an 80% occlusion in this artery," just from the wave forms. Now we weren't there, but eventually somebody will be able to do that, for sure.

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Mates: One of the things that complicates the coronary circulation is the fact that the heart is beating. So every time the heart contracts, the pressure goes up. But simultaneously, those vessels downstream get squeezed by the heart muscle. They're going through the heart. So it's not like a simple hydraulic system, and that makes it much harder to understand the phasic relationships between pressure and flow because the resistance is varying as the pressure varies. We were able to uncouple those with this device we had because we could stop the heart from beating for a moment, and then still perfuse it with the same pressure and look at the difference in flow patterns.

So we were able to get some information about the relative importance of the squeezing effect and the pressure. That device, called the hydraulic servovalve, was a feedback control system where you would prescribe a waveform, and then it would follow electrically whatever waveform that you prescribed using electrical engineering principles. We could simulate all kinds of waveforms. We actually did a frequency response in the coronary circulation by applying sinusoidal input pressure of varying frequencies and measuring the amplitude of the flow response, and we could determine the frequency response of the circulation under different conditions, beating and nonbeating. So that's basic mechanics, but also with the electrical technology to make it work.

"The other thing that has happened in physiology, which is even more dramatic, is the shift in emphasis from the sort of systems physiology, like large scale stuff, down to cellular and molecular."

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Mates: A lot of physiologists worry that since there's so little systems physiology research being done, probably because they can't get funding for it any more, who's going to teach the medical students how the heart works? All the lectures will be about the cellular and molecular physiology of the heart, but nobody will actually ever study the intact organ.

Edward Merrill

Professor Emeritus of Chemical Engineering, Massachusetts Institute of Technology

(interview by Michael Geselowitz on 22 February 2001)

Merrill: Then in about 1959 or 1960, kind of by accident, two doctors at the Peter Bent Brigham Hospital in Boston by the names of Dr. Roe Wells and Dr. Robert Denton called up the Department of Chemical Engineering to find out who knew something about rheology, and they were put in touch with me. They came over and said, "Can you help us measure the viscosity of lung mucus?" It turned out to be an intractable job, a terrible job, because it's so widely variable and the mucus itself is so complex a mixture of thin and thick liquids.

As a result, they turned their interest and my interest to the flow properties of human blood. At first blush you might think that human blood is a straightforward fluid, but it isn't. We found out it's complex, and it has what we would call a "yield stress." That is to say, like yogurt or mayonnaise, as you slow down its stirring, suddenly it stops flowing so that you can get to the point where it won't flow at all, even though there is a residual pressure.

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Merrill: In conjunction with the Fulton-Berman film on the flow of blood through the hamster's cheek pouch and the transport properties going on, it then led me to think about what chemical engineers might be able to do in connection with medicine, since chemical engineering involves, as one of its major thrusts, transport of molecules back and forth across membranes between fluids, as well as chemical reactions.

It then became of interest to think about what we would do with machines through which blood would be circulating, and there are two principle machines. One would be the so-called artificial kidney, or the hemodialyzer, in which blood is purified by being taken from a patient, run

Edward Merrill looks at an experimental biomaterial made with polyethylene glycol and silicone with students (from left to right) Cynthia Sung, Jennifer Raeder and Rovena Sobarzo in the chemical engineering lab at MIT.

through the machine, and circulated back to the patient. This would be presumably on a chronic basis for patients who have lost kidney function. The other one, back around 1960, would have been the so-called bubble oxygenator, because at that point, blood oxygenation during open-heart surgery was brought about by making a trough and simply bubbling oxygen through the blood. As we recognized at the time, this doesn't do the blood any good. It denatures proteins in the blood and breaks up red cells.

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Merrill: So, what I am talking about is how [biomedical engineering] started, and so we go back again to the decade from 1960-1970. In 1963, I gave the first graduate course titled "Chemical Engineering in Medicine" and the MIT course titled 10.56, and I offered it in 1963, 1965, 1967, and 1969. Then it was taken over by one of my doctoral students who is presently a professor here, Professor Clark Colton, who did his doctoral thesis on the artificial kidney. Colton's contribution was to completely elucidate the mass transport aspects of this, so you could design the artificial kidney with the optimum membrane, the optimum flow rates of the dialyzing fluids, and of blood.

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Merrill: I guess it was natural that a major component of my research in biomedical engineering … somehow involved the issue of what kind of polymers can you use to achieve the results you want, especially that of preventing or mitigating clotting. A major part of my output over the years has been addressing that issue, which is an issue of polymer chemistry and polymer modification. I am credited … [with] the perception of polyethylene oxide or polyethylene glycol, one and the same thing, as being an almost magic biomaterial in that it is remarkably inert. In 1974 or 1975, I wrote a paper for the *Transactions of the America Society for Artificial Internal Organs* (TASIO) and the title of it was "Polyethylene Oxide as a Biomaterial." That turned out to be enormously important because now, as the fellow cited, all kinds of people are involved in proprietary secret research in putting polyethylene oxide and polyethylene glycol onto proteins and onto surfaces and so on.

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Merrill: Although on the one hand Dean Gordon Brown thought that getting into this blood research was not in my best interest, on the other hand Jerry Wiesner (then president of MIT) and Walter Rosenblith (then provost of MIT) were very much interested in the application of engineering to medicine and surgery. In fact, Wiesner called me into a meeting at the highest level with the head of NIH at the time, Jim Shannon, and the idea was that NIH was trying to get MIT to set up a medical school because the idea of bringing engineering into medicine was being widely promoted, and Jerry Wiesner and Walter Rosenblith were particularly interested in this.

I might also point out that by the same token my story would not be complete if I didn't mention my dear friend, John Trump of the Department of Electrical Engineering. John Trump was the one who was sitting on what we call the Rosenblith Committee and coined the phrase "Engineering and Living Systems," and that is what we worked on and what the title of it was.

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Merrill: Another part of my story has involved the use of electron irradiation to carry out polymer chemical reactions and make new and interesting polymers, thanks to the input from John Trump and from his enthusiastic collaboration with me through his [high-voltage research] laboratory. Many of my graduate students worked in the high-voltage research laboratory carrying out their work. Briefly what happens is that electron beams can cross link polymers, and they can also graft new materials onto old materials. So you can make, for example, a hydrophobic (water repelling) polyethylene sheet hydrophilic (water loving) by grafting a hydrophilic layer onto a hydrophobic support.

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Merrill: It now turns out that biomedical engineering is far more entrepreneurial than it used to be. People are moving away from the kind of basic research that I was doing in blood viscosity, the results of which are unpatentable, to producing fruits of research that are patentable, that are products.

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Merrill: The other thing that I observed back in the days when I was deeply involved with Boston hospitals, it turned out that in some cases some of the physicians and surgeons treated engineers as if they were light-bulb changers. In other words, there was a kind of pecking order in which the surgeon or the chief was the chief on top of everything else, and everybody else reported to him. There was a certain, how shall I say, arrogance that I think is now gone, because I think the medical profession realizes how much engineering has changed what they're doing.

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Merrill: If there are two areas where the chemical engineers are going to be highly involved or are already, one is tissue engineering and the other one is drug delivery, for sure.

Nicholas Peppas
Showalter Distinguished Professor of Chemical and Biomedical Engineering, School of Chemical Engineering, Purdue University
(interview by Frederik Nebeker on 12 October 2000)

Peppas: We find ourselves very well prepared right now to contribute to a major area of bioengineering called metabolic engineering, because chemical engineers have an exceptional background in computers and in understanding cells. The result is that the chemical engineers have "jumped" into the area of metabolic engineering trying to understand how metabolic processes can be optimized. This is only one of many areas that I could suggest where the chemical engineer has contributed because of his or her background—the mathematical background and the physicochemical background

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Peppas: We [that is, Peppas as a graduate student and his advisor Ed Merrill] worked at MIT in the very early days of biomedical engineering. We started developing a series of materials that could get in contact with blood and would not cause blood clotting. Therefore, they could be used for artificial organs. These materials are known as nonthrombogenic biomaterials.

Nebeker: *Surfaces?*

Peppas: Surfaces, but these surfaces are modified with the appropriate utilization of anti-clotting agents, which in this particular case were heparin. So we were really the originators of the earliest heparinized materials that were used in catheters, in artificial kidneys, and to some extent a little bit later in artificial hearts, although we were not directly contributing to this.

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Peppas: It's important to appreciate that the biomedical field is such an interdisciplinary and cross-disciplinary field that good training is very important. I'm delighted that I did postdoctoral work at that time [1974]. But it was only one year. It is not unusual to have biomedical engineers who spend two or three or four years, especially learning new cellular techniques or getting into genetics or into gene therapy. So postdoctoral work has become a "must" for the field. In classical electrical engineering or chemical engineering you can have students who become professors immediately after their Ph.D. degree. But in biomedical this additional work is needed.

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Peppas: In the very early days of our contributions to biomaterial science, one thing that became very obvious was that the biomaterial itself was not toxic. What created the toxicity was a series of unreactive monomers, adjuvants, stabilizers, and other compounds that were added to make the system more stable, as well as a variety of other chemical compounds that were needed in order to "solidify" the material. So in the very early days I became interested in coming up with alternate ways of preparing materials without using toxic compounds. That led to the very early studies of benign manufacturing of biomaterials.

By serendipity I discovered in 1974 that if I take a solution of a particular biomaterial and freeze it and thaw it several times, I can create a solid structure by a process of solidification that requires entanglement of the macromolecular chains and at the same time formation of crystals. It doesn't work for any material, but it does work for a rather wide range of biomedical materials. Some of the early studies were done in 1975, the year of the first paper, and the patents were filed. Over the last 25 years such materials have been used for a wide range of applications.

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Peppas: I think another major milestone in our development as a group here [Purdue] in biomedical engineering was in 1978. Steve Ash had just arrived in the town. He arrived from the University of Utah where he had studied with one of the fathers of biomedical engineering, Wilhelm Kolff, in the artificial kidney program. When he came here he established a kidney program. What was happening with artificial kidneys in the 1960s and 1970s is that a patient would have to go to a hospital, lie on a bed, be connected to a dialysis unit. This unit required all this water in order to take away the urea and uric acid. That process would take four hours every second day.

So, Steve's idea was, "Can we come up with a portable artificial kidney?" He received money from various sources including some companies, and for a period of about five years we had a tremendous development in that particular area. I was developing the biomaterials that were used in this artificial kidney.

At the same time I got much more into the artificial kidney as a biomedical engineer identifying flow behavior and transport phenomena. I can tell you the kidney worked very well and it was sold to a small company that was created. Now they are in the second generation of systems with artificial livers.

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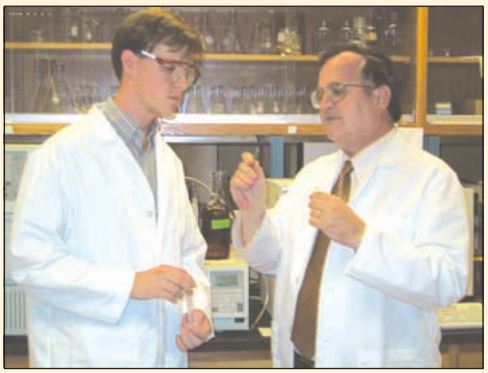
Peppas: In 1982-1983 we started working with smart gels and smart materials. There is nothing "smart" about them except that they have certain functional groups that interact with a surrounding environment in a particular way. For example, we know that if we have certain



Nicholas Peppas (right), the Showalter Distinguished Professor of Biomedical Engineering at Purdue University, and graduate student Aaron Foss discuss the latest oral delivery system for insulin developed last year at Purdue.

functional groups such as carboxyl groups, these groups in a low-pH environment will not be ionized while in a high-pH environment they would be ionized. What this means is that the gel in a low-pH environment would stay collapsed while in a high-pH environment the gel will expand. That can be used to our advantage to create switches—biomedical on-off devices to release drugs, to release proteins, to push valves, and to push molecular pistons. We started with these smart materials around 1982, which have become a major part of our work. It is interesting that smart materials were developed predominately in Japan. Since these early days we had significant interaction with Japan, so it was only natural to be involved in those developments.

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Peppas: There was no way for us to develop better drug delivery systems or improved therapeutic devices without a true molecular design. It was important to go back to the principles and try to understand the molecular structure that creates a particular property, and whether the material can release a particular protein very fast, or the ability of the material to adhere to a particular surface. We were able to come up with a series of papers in which we defined how molecular design could be used in these new biomaterials and drug delivery systems.

Nebeker: *This field is called molecular design?*

Peppas: Molecular design of biomaterials. There are several groups working in this area.

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Peppas: Recently, we have also embarked upon new areas of biomedical engineering. We are working on biochips and bionanotechnology.

Nebeker: *Are these chips silicon chips?*

Peppas: They could be silicon based. The ones we have are methacrylate based. In fact, we use the same type of micro-lithographic techniques that could be used for integrated circuits. The work is performed in electrical, biomedical, and chemical engineering. This shows how these areas merge together.

I think that in the next 20 years nanotechnology and bioengineering will merge. I really think we are leading towards more miniaturized devices. I tell my students that in 1950 an artificial kidney was a big hospital unit, to which one had to be connected for four hours. In 1980 or 1985 the kidney was a unit about 30 centimeters long and often portable. Don't you think there will be a progression and that perhaps by 2020 it will be replaced by a small box with a few "chips"?

Buddy Ratner
Director, University of Washington Engineered Biomaterials
(interview by Frederik Nebeker on 5 December 2000)

Nebeker: *What other applications were thought of at the time for hydrogels?*

Ratner: A lot of people were exploring them for medical implants, the kind they use on the surface of the eyes, a contact lens. But there were all sorts of medical-implant applications. In fact, what I was looking at was a membrane for an artificial kidney. That was the specific area that I was working. So, I was working in membrane transport and also on the physical chemistry side, the fundamental interactions of molecules.

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Ratner: I came up here [the University of Washington] and started doing the post-doc. One of Allan Hoffman's specialty areas at MIT was radiation grafting. It was using radiation, like gamma radiation, and the cobalt 60 reactor to graft or covalently attach one polymer to another. Allan had the idea of taking the hydrophobic engineering plastics (silicone rubbers and polyethylenes and such) and seeing if he could graft this hydrogel (the same material I worked on in my thesis) to the surface to make a hydrophilic water-like surface. The basic philosophical idea is, what could be more biocompatible than water? What would the body like better than water? The body would obviously tolerate water very well. This was an extremely stimulating idea, and it used a very interesting polymer technology.

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Ratner: This led us into an exploration of how blood clots interact with synthetic materials

and how we might design interfaces that look better. There were good engineering plastics out there. There's polyurethane, there are silicone rubbers that are strong elastomers, and people know how to manufacture them. We wondered if we could just alter the surface structure to make them more compatible with biology.

This led me into what has been one of the major focuses of my career, which is how we analyze surface structure and how we relate surface structure to biology. It turned out that although there were some things going on, the best work on surfaces was being done in those days on semiconductor surfaces. The microelectronics community and the petrochemical catalysis community were looking at the surfaces of semiconductors and catalysts. These two communities had very powerful tools, particularly the semiconductor people.

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Ratner: There were three components. One component was making the materials. One was learning how we could analyze and characterize them. This was very different from characterizing semiconductors, so we had a lot to learn there. The third area was the biological interactions of these. All these three things were going on pretty much simultaneously here.

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Ratner: At the same time I had applied to the National Institutes of Health. I had become known as one of the proponents of using modern surface tools for biology and biomaterials. A lot of people were gaining interest in this and I thought everybody could benefit from it. I made an application to the NIH to start a national center to make this type of technology available for biomaterial studies. This national center was funded and we gave it the name NESAC/BIO, which is National ESCA and Surface Analysis Center for Biomedical Problems.

We brought in new types of instrumentation, such as a machine called SIMS, which stands for Secondary Ion Mask Spectrometry. It allows you to do a mass spectrum of the surface zone. We had a few very powerful pieces of equipment. The scanning-tunneling or atomic-force microscope was one. This added another surface tool that the Center uses, and we started building on all these things. On one hand I was looking at surfaces and trying to relate them to biology. The other side of it was looking at biology. We were doing biological experiments. We still had grants from the NIH on making materials and biologically evaluating them for medicine.

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Ratner: I came to realize that although we're making better materials and we're getting very neat medical materials here, there's no way a living cell could ever recognize a piece of Teflon or one of these hydrogels or a piece of titanium or gold that is used in medicine. Evolution had never provided the recognition mechanisms or receptors for biology.

Nebeker: *Wasn't the idea that you just needed a benign substance that wouldn't cause a problem?*

Ratner: Yes, that was the original idea. We wondered how benign we could make it. It turns out that the body's response to these materials was to look at it and say that this is benign. There's nothing benign in the body. Consequently, it must be foreign, and the body's response to it was to put a wall around it.

We started asking whether biomaterials, instead of being inert, should be recognized by the body. Maybe we as the engineers should be able to control the healing reaction, the biological response. So we started looking at things like normal wound healing and the sorts of molecules, proteins, or signaling molecules that are involved there. Then, taking some of our surface knowledge and skills, we ask if we can take existing medical devices—they're basically manufactured in the right shapes, FDA approved, and the surgeons know how to handle them—we'll just take the surfaces of these things, use our surface skills to put on the right receptors, and instead of making them inert, we turn on and control specific biological processes to engineer biological reactions.

I had this idea to start another center, namely an engineering research center through the National Science Foundation, to see if we could take the field of biomaterials to another level or new paradigm, instead of inert, to bioactive and engineered surfaces. We called these engineered biomaterials. The center is UWEB, University of Washington Engineered Biomaterials. This center is now working in collaboration with some 22 investigators, including material scientists (the roots I came from), fundamental biologists that don't really know much about materials (it was never their area) but they know a

Buddy D. Ratner is using an electron spectroscopy for chemical analysis (ESCA) instrument in 1980 at the University of Utah.

lot about wound healing and proteins in biology, and physicians and people involved in healing.

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Ratner: For example, we did a very interesting study that was published in *Nature* last year [1999]. We took protein molecules and stamped them into a polymer surface and made pits or imprints in the shape of the proteins. Within those pits or imprints there were receptor chemical groups that kind of gave a "lock-and-key" interaction with the proteins. So, instead of trying to sell a medical device with proteins on it, we might sell a medical device with pits in it, and those pits would attract or interact with proteins in your own body to turn on the signals that we want at the surface.

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Ratner: But what has happened is the realization that there's a real profession here. There's a certain way we have to educate our students. There's a core knowledge base that gives us commonality. A person that does electrical engineering, a person that does the mechanics of a hip joint, the person that designs a pacemaker that goes into the body and designs the electrodes for the pacemaker, the biomaterials person, the person doing a chemical sensor or biosensor—there's a commonality within what all these people do. They borrow from other engineering disciplines, but there's a central core that is the biomedical engineer.

John M. Reid

Professor of Bioengineering Emeritus and Research Professor, Drexel University

(interview by Frederik Nebeker on 6 October 1999)

Nebeker: *Can you tell me about this first ultrasound system that you built in John Wild's basement? What was the design, and what equipment you were able to use?*

Reid: The biggest help in the design was the Radiation Laboratory series of books on radars, because the circuits were very close. I had already gone through the sonar classes and had kept my Navy notebooks and knew that was an entirely different kettle of fish. I had some guidance there. I bought a big power supply, figuring that I would have to power Lord-knows-what by the time we got it running. I had 300 volts at 1-2 amps, I think. I built a calibrated attenuator by using dc measurements in the electrical engineering building, filing the carbon resistors to value. The signal generator I already owned because of the radio repair business, so I brought that along, also my tube tester. I decided to see what I could use in surplus. I found a 60 megahertz IF strip complete, which looked like a good place to start. I would have to run an oscillator at 45 to beat the 15 up to 60, which was sort of backwards for most equipment in those days. They very seldom went to a higher frequency. I was a little unsure about designing an oscillator because we did not go into that, but I found the instruction books for the Hewlett Packard equipment that we had in the linear accelerator project. I copied down an oscillator using a triode, and that's what I built.

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Reid: One thing that impressed John [Wild] was when he brought in a cube of beef and said, "Let's see if we can get echoes." He sat it on the transducer and there were a few little echoes at the start, but not much. I looked at it and said, "All the muscle bundles are going this way [indicating longitudinally with his hands]." I turned it 90° so we were going crossways, and the screen was suddenly filled with echoes. It was wonderful. He thought that was a wonderful discovery, the anisotropy of reflections from skeletal muscles. He quickly ground it up, and we obtained an intermediate picture.

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Reid: Once I was back at the linear accelerator lab where I had a bunch of friends working, one of them said, "Why don't you make images? Why don't you scan the pictures?" I said, "We need some position data transmission system. We need sweep resolvers or sine/cosine potentiometers." My friend at the lab said, "No you don't. If you keep your angles small the sine is approximately the angle and the cosine is about one. You can use linear potentiometers and make an image." I thought about it and went back and told Wild, "Let's make images." We had the signals and the video coming out of the machine since I had detected the RF, and he said, "Oh Jack, that is getting so complicated. Things in medicine have to be as simple as a paperclip or a hairpin. If it gets more complicated than that, nobody will use it." I said, "John, it is already pretty complicated. I don't think it will take a lot more." He wanted to know what more it would take, and that is what hooked him. I said, "We need a motor to drive this thing back and forth—a variable speed." He said, "I have this wonderful variable-speed drive, based on overdriven clutches." It turns out he had been looking for a project to use this thing. The idea of hooking up a dc motor to it and running it really intrigued him. We had to make a mechanical linkage to run some dual potentiometers only for the sine, because the cosine was constant. The vertical coordinate was just the range sweep and the horizontal coordinate was the fraction of the

range sweep picked off by a potentiometer. I had to build a little 12-volt dc power supply for one of the surplus motors we had.

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Nebeker: *Was that 1952* Science *article much noticed?*

Reid: Yes. We had reprint requests from all over the world, and it is the basic reference that people use if they want to go back to the beginning.

Nebeker: *At the time there was considerable interest?*

Reid: Yes, up to a point. Radiologists considered that radiology was X rays. It was not until they lost all the business in nuclear medicine that they realized that maybe they should broaden the field. It was just in time for the CAT scanners and MRIs.

Nebeker: *In the medical profession there was not a great deal of interest immediately?*

Reid: [Nodding "yes"] Wild was an odd character. He tended to get people's complete support or complete animosity; there was very little middle ground. People used to say that "nobody else was imaging soft tissue, much less trying to differentiate cancer in the image from noncancer." It did not seem to be possible. "How were we doing it?" Using sound waves. Sound was something you used to talk with people on the telephone. "You guys are some kind of nuts. What kind of crazy idea is this?" After meeting Wild, they became firm in that conviction. One of the things that led me to leave was that people were starting to look at me a little funny, too. "How can you stand to work for that guy?"

John Reid (left) with Dr. John Wild using the view camera that was mounted for specimen and scope photography.

Murray Sachs

Massey Professor and Director, Whitaker Biomedical Engineering Institute, Johns Hopkins University

(interview by Frederik Nebeker on 25 April 2000)

Sachs: I became tired of doing radar kinds of things very early on—in my first semester of graduate school. I asked Moise Goldstein what I could do in bioengineering, though it wasn't called that at that time. The Communications Biophysics Laboratory at MIT had been started years before by Walter Rosenbluth and was doing what we would now call bioengineering. It focused largely on processes of hearing, applying engineering and communication theory and computers—such as existed at that time—to solving biological problems. Moise, who had worked on the first computer for averaging biological transients, wrote a paper with Larry Frishkoff and Bob Capranica, both of whom were at Bell Labs. Capranica was also a graduate student with me at MIT. I think their paper, published in the *Proceedings of the IEEE*, was titled "What the Frog's Ear Tells the Frog's Brain," something like that. It was a very influential paper because it was the first paper to demonstrate that some animals have communication systems—both receivers and transmitters—that are attuned to each other. The frog's auditory system is closely attuned to its vocal communication system. Bullfrogs from neighboring counties have different croaks and different inner ears that filter the croaks. I went to work with Moise studying that phenomenon in the frog and did that for my master's thesis. That is how I got into this business.

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Sachs: For my doctoral thesis I recorded from single auditory nerve fibers primary afferent neurons in the auditory nerve and studied a phenomenon we called two-tone inhibition. It is very much like center surround inhibition in the retina. I remember my very first experiment. I guess I was doomed—or privileged—to continue to find myself in situations where I had to be the first to do things. This was the first time the LINC computer was ever used in the Peabody Laboratory.

I remember my excitement when I recorded from my first single neuron. I called Nelson Kiang at 1:00 in the morning and told him, "It works, it works, it works."

Nebeker: *For what purpose were you using the LINC?*

Sachs: We used Schmitt triggers. We recorded spike trains and used a threshold device to trigger the computer to record the times of occurrences of the spikes, and we then used those to construct interval and poststimulus histograms. It was the signal processing frontier at the time. Everything was stored on LINC tapes. Those became DEC tapes when DEC took over the industry. I remember transferring the LINC tapes to IBM mag tapes and schlepping them across the river to the TX0 computer in Building 20. Then it took all night to process the data from one experi-

ment—which would take about 20 minutes today. We had to read in all the programs with paper tape and control the computer with toggle switches. And things would go wrong. It was like boot camp, and there was such a spirit of camaraderie that we were working on the edge of something that was going to really blossom.

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Sachs: Another major influence on my work came from Bill Peake who was my official thesis advisor. About three-fourths of the way through my thesis, I had done what could have qualified as a neurophysiological thesis. But Bill said, "This is not an electrical engineering thesis unless you do some modeling." That had a profound effect on my life. I did models that I have pursued ever since and still use today. In many ways it was Bill's push to modeling that turned me from neurophysiology to bioengineering.

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"The question was: How is the sound of the voice—which is very complicated—encoded in those patterns of those 30,000 neurons? We tried to record from as many as 300 or 400 neurons in the same animal, which is why the experiments took three or four days."

Sachs: At that time no one believed biology could be nonlinear. I went way out on a limb with this model because it tried to relate the auditory nerve data to nonlinear cochlear mechanics. It was the only time in my life that one of my papers was rejected by a journal. I fought back and finally had the paper published. It is the most important paper I ever published. Experiments and modeling have been done many times in the subsequent 24 years since 1976, and much more elegantly than I did them, but the answer is still the same.

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Sachs: The idea was to try to understand how speech is encoded in the auditory nerve. The auditory nerve consists of 30,000 neurons carrying electrical signals from the ear to the brain. Any information that the brain gets about the sound has to be carried in those electrical signals. The question was: How is the sound of the voice—which is very complicated—encoded in those patterns of those 30,000 neurons? We tried to record from as many as 300 or 400 neurons in the same animal, which is why the experiments took three or four days. By doing this we were able to build up a picture of the coding of the sound across this whole population of 30,000 neurons. We sampled 400 in one animal and extrapolated from that—reasonably, we think. We now know how sound is coded in those discharge patterns.

Nebeker: *Is it not coded in a simple-minded Fourier way?*

Sachs: Yes and no. It is clearly coded as a spectrum. When we started out there were a lot of questions about how that could possibly work. There were limitations on the systems—largely dynamic range and nonlinear properties—that made it questionable that the code could work. We discovered that by applying mathematical analysis of the discharge patterns, signals could be pulled out even with a highly limited dynamic range. You can hear and understand my voice if I whisper, and you can hear and understand my voice even if it hurts you when I shout at 120 decibels.

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Sachs: One thing is that the nonlinear phenomenon seems to disappear. In a hearing-impaired person, the ear gets linear. The nonlinearity that enables the bandwidth to remain fairly narrow is gone. It is as though the ear is trying to listen through filters that have a bandwidth too wide to filter individual frequency components. Therefore our current approach is to try to understand the coding in the pathological ear. We use cats that are deaf in some ways.

Nebeker: *Is this specifically with the intention of being able to design better hearing aids?*

Sachs: Ultimately, yes. The current goal is to develop a model precise enough to predict the patterns of discharges in the auditory nerve in pathological ears so we can use those models to test hearing-aid designs.

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Sachs: We do not have enough graduate students because of our limited space resources, but there are 500 students in our undergraduate program. Of the 1,100 or 1,200 students in the engineering school at Hopkins 500 are bioengineers. This is also happening in other places. If an undergraduate bioengineering program is begun, it rapidly becomes the largest and best in the university. That is because there are a lot of kids who want to be engineers and want to be technologically involved but also want to do things for humanity that involve medicine and biology.

Herman Schwan
A.F. Moore Professor of Biomedical Engineering Emeritus, University of Pennsylvania
(interview by Frederik Nebeker on 6 October 1999)

Schwan: [Shortly after coming to the University of Pennsylvania in 1950] I became a member of both groups [concerned with medical electronics, one in the Institute of Radio Engineers (IRE) and the other in the American Institute of Electrical Engineers (AIEE)]. At that time, I became aware of the Joint Executive Committee in Medicine and Biology (JECMB), which was a small group of about six people, two appointed from each of three societies: two from the medical electronics group committee of the IRE, two from the AIEE committee on electrical techniques in medicine and biology, and two from the Instrument Society of America. The Joint Executive Committee was primarily responsible for organizing the so-called annual meetings.

In 1952, here is the program of the fourth conference on electronic instrumentation and nucleonic medicine, reflecting how the field was conceived at that time. There was a strong interest in the atom bomb and all related topics, nucleonics and medicine and electronic instrumentation. At that meeting there was a total of just 18 papers.

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Schwan: There was a quantum jump. At the ninth conference there was the usual small number of papers. Attendance was declining. That meeting had only five papers each day, 15 papers in all. Then came a meeting that Otto Schmitt organized. He was not a member of the Joint Executive Committee. I had suggested to the Joint Executive Committee that we must broaden our perspective and had suggested that Schmitt be asked to organize the next meeting. Otto organized an annual conference [in 1958] dedicated to computers in medicine and biology. It was attended by about 400 people and was a huge success.

Nebeker: *It is still called "conference on electrical techniques."*

Schwan: Yes, but the heading changed slowly but steadily. We … moved away from the nucleonics image which had been used before without success. The annual meeting still used "electrical techniques" and was still sponsored by three societies, but this was now a big meeting. I organized the next meeting in Philadelphia, and that was an even larger meeting as you may see from this conference attendance record here. It was the 12th annual conference on electrical techniques in medicine and biology.

Nebeker: *Was part of that jump due to including computers in medicine?*

Schwan: No, it was not computers alone. The topics at our Philadelphia meeting had nothing to do with computers, but it had to do with radiation, but not with ionizing radiation. There was a cardiovascular session, an ultraviolet one; a more general one on microwave radiation biological and health effects, one on ultrasonic radiation; and one on infrared radiation. There were several general sessions, a cardiovascular session, and one on various types of nonionizing radiation. You see in the program that we have now a large number of papers. The attendance at that meeting was even larger than in Minneapolis. Otto Schmitt had attracted around 400 people. The previous conference had something like 50 people. In Philadelphia it was again significantly more; we had around 550 people attending.

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Nebeker: *When did IRE or AIEE start publishing in this area?*

Schwan: The first regular publication was from the IRE. It was first *Transactions for Medical Electronics*, but then they changed the name. Particularly, it reflected Otto Schmitt's and my constant hammering on what was important in the field, and that slowly but steadily changed the name of the *Transactions*. The earliest *Transactions* came out somewhere between 1952 and 1955. There was a special issue in 1955 on the biological and health effects of microwaves.

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Schwan: The Biophysical Society went its own way and became highly successful. It was not strongly engineering oriented at all. The bioengineering community split a bit. The ultrasonic group became primarily active outside the IRE and IEEE when the American Institute of Ultrasound in Medicine was formed. That was primarily due to the late W.J. Fry at the University of Illinois at Urbana.

There was a reason for the development. In the ultrasonic case there was strong participation by medical people. By definition they could not be counted part of the IEEE, because to be a member of IEEE you must have a certificate or a degree in engineering, which medical people of course do not have. That led to a severe crisis in 1968, which I have discussed in several of my publications. In 1968 I served two consecutive years as chairman of what was then called the Group of Engineering in Medicine and Biology. At that time I was striving to find ways to achieve recognition of medical doctors who had significantly contributed to this field as full members. That, of course, shook up the IEEE very badly since that would have meant a major change in its total policies. It was debated in many sessions over a period of two years of the IEEE, but it was to no avail. An associate membership was established, but the associate mem-

Dr. Herman Schwan adjusting a doll, filled with appropriately chosen saline solution to mimic a human body. It was exposed to a calibrated microwave beam in an unechoic chamber. This type of research helped to establish standards of safe microwave exposure during the 1960s.

bership never came off very well since it was perceived by the medical profession as a second-rate membership.

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Schwan: I had developed a training program already at Pennsylvania. We offered a number of specialty courses in the field. My early students received their degree in electrical engineering, not yet in bioengineering. With NIH help I established in 1961 our graduate bioengineering program, separate and independent from electrical engineering. As a result of our recommendations, an NIH committee, a study section was established, making funds available. A key role was played by another pioneer, Jack Brown, associate director of the National Institute of General Medical Sciences, one of the five major institutes which compose the National Institutes of Health. He pushed bioengineering. He obtained special funds allocated for training purposes. The first NIH supported training programs were set up at Rochester, Pennsylvania, and Johns Hopkins. I obtained significant NIH support for our training program for 25 years. It was a very substantial amount of money. This has helped us to attract so many excellent people in the field, of course.

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Schwan: The negative attitude of the molecular biologists for biomedical engineering has deep roots, in my opinion. In 1955 I worked during the summer at the famous Cold Spring Harbor laboratories. I moved up electronic equipment to measure the electrical properties of *E. coli,* together with the old and famous Hugo Fricke. At that meeting I usually had lunch in the cafeteria. I remember my conversations with a famous man whose name was Max Delbrück.

Nebeker: *Yes, I know of the physicist-turned-biologist.*

Schwan: Yes. Max Delbrück was curious, and he wanted to know what I was doing there with Fricke, so I told him. Then he challenged me in stating that there were all sorts of people such as Fricke and Cole, "What's all that stuff good for, what Cole did?" That was at a time when Cole's work had led to the Nobel Prize for [Alan] Hodgkin and [Andrew Fielding] Huxley. I was amazed at his negative comment. So there was already under the molecular biologists a preconceived negative attitude about electrical measurements of biological material and related things.

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Schwan: Clearly, the IEEE has played a dominant role in the creation of the new discipline of biomedical engineering. Its annual conferences have grown far above anything anticipated originally. I regretted the membership issue. Another basic regret that I have about the field is that it is split too much. We have many biomedical engineering organizations now, including the International Federation, the American Institute of Medical and Biological Engineering, the Biomedical Engineering Society, and the IEEE Engineering in Medicine and Biology Society. But the cooperation between the various societies is not quite clear.

Tirrell: I actually started in three main areas. One was an attempted outgrowth of my Ph.D. thesis, in which I tried to get an early start in bioengineering. I had a very significant colleague at Minnesota named Ken Keller who, at the time that I went there, was the department chair of chemical engineering and material science. Later on he became president of the University of Minnesota. He's a fellow of AIMBE (American Institute of Medical and Biological Engineers). The idea that we were pursuing was related to his own work. It was on shear flow damage to blood cells.

Nebeker: *That must happen in open-heart surgery when the heart-lung machines pump the blood.*

Tirrell: What are the mechanisms of cell breakdown? We did some things. We had a joint student together, Becky Bergman. In fact, she's very successful now. She's a vice president of Medtronic.

Matthew Tirrell
Professor and Dean, College of Engineering, University of California, Santa Barbara
(interview by Frederik Nebeker on 7 December 2000)

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Tirrell: In the course of this, I also became interested in two other areas of technology that ultimately come back to some implications for biology. One was adhesion. What is it that makes things stick? Why do polymers stick to surfaces and how can they augment and enhance the adhesion between surfaces? We started to tackle that problem to develop some methods to measure and actually predict adhesion a little better.

Nebeker: *Predicted on the basis of the actual molecular configurations?*

Tirrell: That's right. If you look at some of the publications early on my list we did some of these things that we called, "Calculations of the Healing Process." What we were talking about there is kind of a leap from what I was just saying, but it's another problem in this spirit. If you take two chunks of plastic and you stick them together and supply enough thermal energy, how long does it take them to weld just because the polymer molecules diffuse across the interface to the point where you can't tell where the interface was anymore?

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Tirrell: To keep the connection to our bio topic, I'll say that cells have a form of polymer layer like this on them, too. They're covered with polysaccharide molecules, and the purpose of the polysaccharide molecule is to create generic repulsion between the cells and a kind of a cushion into which the cells want to adhere to form a tissue. Specific receptors stick out and they form ligand receptor interactions. But before you can have specific binding, you have to block all the nonspecific binding, and to some extent, that's what we were doing with the colloidal particles: blocking the nonspecific binding.

Nebeker: *That's how nature works. It first blocks the nonspecific and then provides for the specific binding.*

Tirrell: Because if anything stuck to anything, we'd look a little different. We'd be kind of blobs of cells or something. So in the back of my mind, there was always a learning process and a fermentation of some of the things that we were learning and how to apply it to biology.

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Tirrell: As a parallel thing this has fed into my bioengineering interest in one way, and that is that we do new material synthesis in my lab. The ability to make your own materials is a tremendous asset in the biomaterials area. If you have to get stuff from other people and try it out, the time scale is slow, the creative cycling is slow. We have done a lot of things on studying, optimizing, and just performing polymerization reactions better that have led to an ability to make our own materials.

"I see the interface between biology and engineering as a lot broader than medicine. There's all this material science that might eventually have something to do with medicine, but there's agriculture and the environment."

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Tirrell: The other was that in 1987 or 1988 we were awarded an engineering research center from the National Science Foundation at the University of Minnesota. It was about a three-million-dollar-a-year grant that had several programs within it. I was the original director of the polymer program. That was very successful in the sense that we trained a lot of students and we attracted a lot of industrial support. For the first four years we had a polymer program, a coatings program, a surfactant program, and an inorganic thin films program.

As we went out to industry, we started to attract, somewhat to our surprise, a huge amount of interest from companies making biomedical devices. It shouldn't have been much of a surprise in Minneapolis, to tell you the truth. Medtronic, Saint Jude, 3M all have a huge number of interests in this area. After a couple of years, probably 1991 or 1992, within the Center for Interfacial Engineering we decided to start a bio-interfaces program. That was a key moment for me. I just basically volunteered to start it and to develop the relationships with companies, and I saw that as a way of rekindling my long dormant interests in this area.

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Tirrell: I started thinking about our surface forces apparatus, about our block co-polymer work, and how we could display peptides and organize a layer of peptides on the surface in a spontaneous way, and that's when we developed molecules like this. Now, this is a triad of molecules for a particular reason, but what we have done and are still doing is making synthetic molecules that we call peptide amphiphiles, where we take a small piece of protein and put a synthetic lipid tail on it. If you take a surface that's

hydrophobic, like a piece of polyethylene, and dip it in a solution of these molecules, these molecules spontaneously organize on the surface with the lipid tails packing like they would in a cell membrane, and the hydrophilic head groups going out. So these are like little block co-polymers. These are the stickers and these are the things that stick out, but now they're there for the purposes of mediating the interaction that the surfaces have with their surroundings in a different way, not just to keep everything off. However, this keeping everything off comes right back into this problem, too. Lots of things could stick to that. What you also want to do is mix this with inert molecules that kind of shield the surface from cells and other things that are sticking for the wrong reason, and you can then really try to highlight the specific interaction that you get.

Nebeker: *So, you're trying to do something like nature—having specific ligands there.*

Tirrell: Exactly, and spaced out and interspersed in a background of protective, nonadhesive stuff. That's what we're doing now.

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Tirrell: One of the types of cells that we have worked with is endothelial cells, cells on the inside of blood vessels. Through a collaboration we are, in fact, looking at whether one could, in synthetic materials for small diameter vascular grafts or stints that are used to hold open blood vessels, put our coatings on to help develop a viable layer of real cells—anchor a real endothelium on a synthetic surface. It's a challenge.

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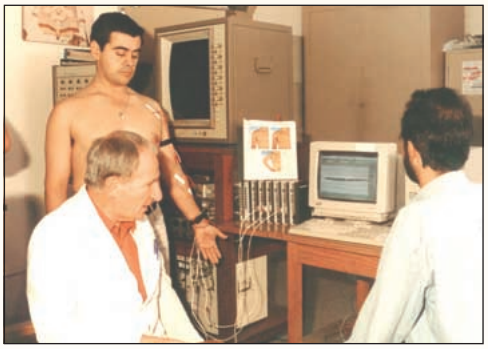
Tirrell: I see the interface between biology and engineering as a lot broader than medicine. There's all this material science that might eventually have something to do with medicine, but there's agriculture and the environment. It all involves having people with the analytical quantitative computational skills that one normally associates with engineers, but with a sophistication in biology that you don't normally associate with engineers. We're in the process of trying to design what I'll call "bio-nonmedical engineering" here at UCSB.

Max Valentinuzzi

Professor of Bioengineering, Universidad de Tucumán, Argentina

(interview by Frederik Nebeker on 13 October 1999)

Valentinuzzi: Another technological concept was measuring maximum and minimum systolic mean pressure. Due to friction and the blood column (inertia), the response time was slow. Actually, it was average pressure that [Stephen] Hales measured [in the early 18th century]. You can read the original version in his classic book, *Haemastatics*, a nice description, indeed. It is probably one of the first scientific papers ever written in English. In those days they still wrote scientific papers in Latin. He described also two oscillations, a slower one, respiration, and a quicker one, which corresponded to the heart beats.



Max Valentinuzzi in his lab in 1997 controlling movements and actions during an experiment with "subject" Julio C. Politti, a graduate student.

Nebeker: *You actually recreated those experiments!*

Valentinuzzi: Yes.

Nebeker: *Did they work? Were you able to do them?*

Valentinuzzi: Oh yes, it was beautiful.

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Valentinuzzi: Early in 1962, I received a little brochure about a symposium that was going to be held in Houston on information theory applied to neurophysiology. I thought, "Information theory is what I like. This is for me," and sent in my name. I didn't present anything, because I didn't have anything to present. I had a baby a few months old, and we drove all the way from Atlanta to Houston to attend the three-day symposium. It was there that I met Dr. Hoff and Dr. Geddes. That turned out to be a major turning point in my life. On a Friday night, I went to a cocktail party in the Doctors' Club at the Texas Medical Center. I told Dr. Hoff that I was an electronics engineer at Emory University in Atlanta and explained my unhappy situation to him. He was always very kind and happy. He said, "Why don't you postpone your leaving by another day and come to my lab tomorrow morning?" and I agreed to do that. He said, "Come at 9:00 tomorrow morning to the lab. I'm going to show you something, and I'll intro-

duce you to Dr. Geddes." When I went there, there was another person visiting the laboratory at the same time as me, Dr. Mary Brazier, a top neurophysiologist.

When I first visited the laboratory I had no idea that I would be spending many years there. After that Dr. Hoff said, "When you get back to Atlanta, send me your curriculum vita, and I might have something for you." Five minutes after getting back to Atlanta I sat down to write out my curriculum vita and sent it to him. A few days later I received a letter saying, "We have a spot for you here. We have a contract with NASA, and there are some respiratory physiology subjects on which we would like you to work." One month later, in March or April of 1962, I went to Houston. I was within that contract with NASA, and they were developing the first impedance pneumograph, which was used in the first suborbital flight with John Glenn.

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Valentinuzzi: [Baylor] had a biomedical engineering program with a Ph.D. in physiology. I took a major in physiology and a minor in biophysics. The program was based strongly on experimental aspects, and we did a lot of laboratory exercises. I will never regret that, because physiology is intrinsically an experimental science. This is a very important point in light of the new tendencies toward replacing experiments with computer models. I am not against the computer models and they are a complement, but please do not forget that in the end we want to understand our body. We want to understand the animal.

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Valentinuzzi: I have been rather successful in Argentina in spite of many, many difficulties. When I returned to Argentina, the country was in a very dark period. Some of the obstacles were really huge.

Nebeker: *Did that adversely affect you or people you knew personally?*

Valentinuzzi: Yes, it affected us. We lost many people and many opportunities. For several years I was torn with the question of whether to stay or leave. I feel fine in the [United] States. In the States I feel at home, have many friends, and there are no real problems. The years I spent in the United States were very productive. I produced a high concentration of papers during my years in the States. I recognize how much I received there and maintain strong contacts with the U.S. On the other hand, I felt I needed to do something for my country. So much needs to be done. Ten days ago we celebrated the 25th anniversary of our laboratory. I review everything for the laboratory, and it has been productive.

There was some activity in bioengineering in Argentina before, but it was a very small seed. Now we have a relatively solid laboratory with the first biomedical engineering master's degree and Ph.D. programs in Argentina.

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Valentinuzzi: In the Electrical Engineering Department—there were a number of details in between not worth going into here—almost immediately I became the head of the Laboratory of Bioengineering. It was a small laboratory, with only a couple of students and myself. It was really nothing. Essentially, we built everything up from zero to what we have now. I consider the birth of our laboratory to be in 1974, so we now have been in existence for 25 years.

Nebeker: *Did you change its name?*

Valentinuzzi: It went from Laboratory of Bioengineering to Institute of Bioengineering to what it is now, which is the Department of Bioengineering. This is because of the faculty organizations in the university. There is, for instance, the Faculty of Social Sciences, Faculty of Engineering, Faculty of Medicine. It is the European scheme. Within the Faculty of Engineering we now have the departmental organization, so we say Department of Electrical Engineering. We report directly to the Dean of the Faculty.

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Valentinuzzi: With electrical impedance you can detect the presence of microbes in different kinds of materials, especially liquid samples. It started what is now called "impedance microbiology," with its origins in a paper by Stewart back in 1899. For the next 50 to 60 years probably no more than five or six more papers were published on the idea.

One day, 20 years ago or so, a biochemist and colleague of mine, Dr. Richard (Ricardo) Farías, called me up and said, "There is a paper in the *Journal of Applied Microbiology.* Apparently, they are doing something with that thing that you mentioned so many times. I do not know what it is about." I told him to send it over. It was a short paper, two or three pages in length. I read it and said, "Easy, we can do this in two or three months." Never say that! Well, it has taken us 20 years to fully understand what it is, how it works, and how it should be developed. Now we are at the stage in which we can really do many things. It is full of possibilities, especially in the food industry ….

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Nebeker: *Are you developing instrumentation for this purpose [detecting contamination in dairy products]?*

Valentinuzzi: Yes. Other people have done it, but we think that ours is better. We have obtained two patents for that. In fact, we did some calibration with one of the big dairy plants in Argentina. It's a beauty, it works perfectly. In less than six hours you get the results. Not only that, you can detect which farm's milk was too contaminated. Probably, their milking techniques are not hygienic enough. Then you can say, "You have X number of days to correct it. Otherwise, we will no longer buy your milk." It has an important feedback effect.

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Nebeker: *You have been president of the Latin American Regional Council of Biomedical Engineering.*

Valentinuzzi: Yes. I was one of the organizers of the Council.

Nebeker: *Has there been good cooperation between Latin American countries in this field?*

Valentinuzzi: Yes. It has been ten years since we started with the project of the Regional Council.

Nebeker: *Do they have a meeting every year?*

Valentinuzzi: Yes. Right now there are nine or ten Latin American countries that are official members of the Regional Council. Those countries are Argentina, Brazil, Mexico, Cuba, Chile, Venezuela, Peru, Uruguay, and Colombia.

Nebeker: *What has the attendance been like at these meetings?*

Valentinuzzi: Good. Always they try to have it during a national conference. Its influence has been very positive. It has made it possible for us to stimulate the organization of laboratories, programs, and societies in each place, both the national societies and regional groups within the IEEE structure. It's been highly beneficial. For example, in Peru we started in 1994. They now have a laboratory of bioengineering, a master's degree program in biomedical engineering, and one of the newest societies.

Walter Welkowitz

Professor Emeritus, Department of Biomedical Engineering, Rutgers University

(interview by Frederik Nebeker on 18 October 1999)

Welkowitz: [At the University of Illinois] I had originally been a teaching assistant in machinery laboratories, but that was not a research activity, and I was interested in doing research. I was offered an assistantship with Bill Fry, head of the bioacoustics laboratory. The laboratory was in electrical engineering, but he clearly was oriented toward bioacoustics.

Nebeker: *That was not because of any previous work of yours in that kind of engineering, but because it was a research lab.*

Welkowitz: The work they were doing looked interesting. I spent the rest of my time at Illinois in that laboratory.

Nebeker: *What projects was Bill Fry's group doing?*

Welkowitz: The major ones were ultrasonic projects. The strongest area was probably in ultrasonic effects on nerves, and the group ultimately developed equipment for radiating various brain regions to correct disorders. While everyone was somewhat involved in that program, I did a Ph.D. thesis on ultrasonic effects on muscle.

Nebeker: *Like a diathermy treatment?*

Welkowitz: We were able to prove that our effect was not diathermy but was something else.

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Nebeker: *All this time, after the first year, you worked in Bill Fry's group and on your dissertation?*

Welkowitz: Yes. I also did some other things because I had a good friend who was working in the original computer laboratory at Illinois. Illinois was then building the ORDVAC and the ILLIAC I. I had a friend in that group, so I did two projects there. I designed an ultrasonic transducer using the ORDVAC. At that time there were only about a half a dozen electronic computers in the world. I did something more interesting on the ILLIAC I. On the bioacoustics laboratory nerve project, when they were destroying neuron sections, they had people count up how many cells were destroyed. To do this, one looks in a microscope and counts destroyed cells in a region. I became interested in whether one could do this automatically. At that time there were some experimental flying-spot scanner microscopes, where the image was projected onto a pickup tube and scanned. I did not get involved in counting and sizing scanning equipment, but I was interested in whether one could program the ILLIAC I computer for use with such equipment. I actually fed in simulated images from such a scanner, with a goal of being able to count and size cells for any shape of cell. If you had cells of different shapes, the program would tell you that there were five in this size range and 23 in that size range. I published this work in the *Review of Scientific Instruments* in 1954. As far as I know it was the first computer vision work published.

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Nebeker: *Was Bill Fry's group doing imaging also?*

Welkowitz: Not at that time. He did set up a series of meetings at Illinois where he invited all the people working in medical ultrasonics. People came in and presented what they were doing, so we were fairly current in the field. That is where I met Jack Reid, since he was doing ultrasonic imaging. He was working with Dr. Wild, a physician at the University of Minnesota. All the different people who were working in ultrasonics in medicine met together. Bill Fry was considered to be an outstanding scientist, and people came from many places to meet with the group. For example, while I was there, Herman Schwan came because he was interested in mechanisms of electronic and acoustic interaction with tissue. The group with McCullough and Pitts came out from MIT, because Bill Fry was doing brain irradiation and they were very interested in a more rigorous approach to studying the brain. McCullough and Pitts did the original work on neural networks.

Nebeker: *I remember Schwan telling me that he was looking more at electromagnetic fields and impedance of tissue, and that his main idea was to try and understand the physics of these biological materials. It sounds like at least your thesis was related to this.*

Welkowitz: Yes, but it was based more on the mechanical properties of the tissue, rather than the electromagnetic properties.

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Nebeker: *What did you work on initially [at Gulton Industries in the mid 1950s]?*

Welkowitz: I started by designing some medical instruments. I first worked on some catheter instruments.

Nebeker: Intracardiac catheter microphone?

Welkowitz: Yes, I designed some of those. One could insert them in a typical cardiac catheter, and they were good for locating holes in the heart wall. The sound was localized, and if you moved the microphone around and watched it under a fluoroscope you could see where the sounds were greatest. That led us into designing intracardiac pressure gauges. There was always a big interest in intracardiac pressure gauges. People had made some very complex ones using electrodynamic approaches; but that required winding hundreds of turns of tiny wires. They were very difficult to construct. We used piezoresistive silicon to make a unit. It was one of the very early ones using that approach. People are still using similar designs. This was the first one built by a company, and naturally the company patented it.

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Welkowitz: At Rutgers I was offered an electrical engineering professorship. It occurred at the same time that Rutgers started the medical school that is now the Robert Wood Johnson Medical School. At that time it was the Rutgers Medical School and was part of Rutgers University. I met with the Dean of Engineering and with the Dean of the Medical School, and they both felt that my interest in biomedical engineering would be desirable for them. (It was being called that at a number of schools.) I started a program in the electrical engineering department in biomedical engineering.

Nebeker: You were the first one in the EE department doing that sort of work?

Welkowitz: Yes. I actually started with a master's program here, which later developed into a Ph.D. program.

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Welkowitz: When I first came to Rutgers there were other such programs in the country, and there were programs that clearly preceded ours. Originally, there was a question of whether this was really an academic field, and how one could describe it. It was a strange field. Companies were not very receptive to hiring such graduates. I remember talking to the Hewlett-Packard people, because at that time they went into and are still in monitoring, and they did a lot of patient monitoring. They told me that they would not hire somebody with a degree in biomedical engineering—they concluded that such a person could not do electronic or mechanical design. They were very skeptical that this was really an academic field. In fact, they tended to discourage schools from starting it as a separate field. They said that they would rather hire an electrical engineer and have that person meet with physicians to pick up medicine and biology while working. It took a long time before people recognized biomedical engineering as an engineering discipline.

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Welkowitz: It turned out that some of the more accepted concepts in blood flow physiology were probably not correct—physiologists rarely analyzed the system as an engineering system. There have been other engineers who analyzed it that way and came to the same conclusions that we did. For example, the aorta tapers both geometrically and, interestingly, in its elasticity. The amount of elastin in the walls varies. It turns out most people said that many of the waveforms observed in the aorta are just due to reflections at the end of the aorta. We showed that you could get the same waveforms with no reflections. If you analyze the taper carefully, you find that tapered systems can give you the same waveforms without reflecting. Why is the sys-

tem tapered, and why isn't it a nice uniform tube? It isn't. I suspect the reason it tapers this way is to match varying terminal impedances, so you get the appropriate pulsatile flow most easily.

This is the sort of information you get only if you do an engineering analysis. If you were a traditional physiologist and you made waveform measurements (which they do, and make some very good ones) you might look at them and say, "Why does the input look one way and the output look different?" You might say, "Somebody told me that there is such a thing as wave reflection, so maybe that is what is causing the change." That is a typical traditional physiological approach to analyzing the problem, after doing very good pressure measurements. It is not an engineering analysis, and it will come up with an explanation that may or may not make sense.

We engineers try to approach the problem differently. Suppose we say that their approach is not what occurs. What would happen if this were a nicely matched system. Would this difference in waveforms occur? What I show in my book is that the input and output waveforms match up very well with this tapering concept, rather than with a concept that does not match the anatomy. A reflection approach might match well if these were uniform systems. One realizes that there are many systems in the body that are well designed, but much thought is not often given as to why they are designed the way they are.

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Nebeker: *Since you have written about medical instrumentation generally, could you comment on what developments over the last decades have really had major consequences?*

Welkowitz: There is no question that far above everything else was the development of imaging systems. Thirty years ago the only way of looking inside the body was with an X-ray system. That produced a crude picture because it was a summation of all the absorptions through the body. Bone is more absorbing than other tissue, so one mostly saw bone. Many tissues are not very absorbing and you do not see them at all.

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Welkowitz: I think medical people now fully accept modern imaging to provide them necessary information. Now they say, "Maybe engineering has something to offer."

Nebeker: *Do you think if there had not been this visual output, if we were talking about impedance measurements or something like that, it would be a harder sell?*

Welkowitz: A much harder sell. With imaging they get an internal picture that they recognize as something they have seen in surgery or in medical texts.