Dr. Edward Lakatta

June 14, 2024

Addy: Good morning. Today is June 14, 2024, My name is Grayson Addy, and I'm a volunteer at the NIH Office of History and Stetten Museum. Today, I have the honor of speaking with Dr Edward Lakatta, a senior investigator and a founder and director of the Laboratory of Cardiovascular Science [at the National Institute on Aging, NIA]. Dr. Lakatta has a multitude of accomplishments, including receiving the distinguished leader award from the International Society for Heart Research. Dr. Lakatta will be speaking today on his early life, education, career, and accomplishments. I'm excited for this opportunity to speak with you. To start us off, would you please talk a little about your family, early life, and education through high school, especially concerning any family members or teachers who nudged you towards medicine?

Lakatta: I was born in Scranton, Pennsylvania, and moved to Wilkes Barre, Pennsylvania, in northeastern Pennsylvania, an anthracite coal mining area. I attended St. Therese School in Wilkes Barre up until eighth grade, and then I transferred to the public school, Myers High School. I got to Myers High School in ninth grade, I had already accomplished most of the coursework because the nuns taught me in such a good way and pulled my cheek when I got the English grammar wrong, so I was off and running when I got to high school. I had a number of jobs when I was in high school, paper routes in the morning and evening, or sweeping factories in the evening. I was a fairly independent person. I had a little bit of my own money. I participated in sports, track and field, and I was in honor courses at Myers High School. I remember a teacher named Casimir Tyberski. She had a very big influence on me with respect to thinking about being in the pursuit of excellence, and that reading generates ideas. I went then to the University of Scranton which was a Jesuit school. I got a broad-based liberal education there; with a major in biology and pre-med and a minor in philosophy. I had a wonderful teacher there who prepared us well. His name was Professor Leonard Wolf. Almost all of the people who were in the pre-med course got into very good medical schools. Then I went to Georgetown School of Medicine. I graduated there in 1970 with a doctorate in medicine. You may wish to have other questions about filling in anything along the way that I skipped.

Addy: Sure, you said that you went to the University of Scranton, was there any big decision leading up to that choice?

Lakatta: It was financial because our family was not very wealthy. I was only the second person ever who went to college. I had to stay with my grandmother and grandfather in a suburb of Scranton about two miles away. The choice was made for me, but it was an excellent choice in retrospect.

Addy: After Scranton, you went to Georgetown University, and you graduated with your MD, Magna Cum Laude. What made you decide on Georgetown?

Lakatta: As you know, there [is] a hierarchy in the realm of prestige and whatnot, and I was accepted to a number of others, but I liked [it] a lot, everything about Georgetown. When I went there, I was a Prefect in the

freshman dormitory, there were no women in the dormitory at that time, so my job was to be sure that the young men were in [on] time and not doing anything outside the regulations in the dormitory, but for that, I got room and board. I was very fortunate in that regard. I got married when I was in the second year of medical school, and my wife, Loretta, was a nurse. She was trained in Wilkes Barre at the Mercy Hospital. She had an RN, and she worked during the rest of my medical school to support us while I was continuing on in school.

Addy: That's amazing. It's very sweet. Throughout your education, you alternated between clinical and research-based. You went on to a cardiovascular research fellowship at the NIH and as we said, you did Georgetown, you went for cardiology at Georgetown University Hospital. What drove this connection to both research and clinical work, and how do you think this aided your career?

Lakatta: Initially, Georgetown was not very well known [for] research, and I had one research experience there when I was in my third year of medical school. My mentor was Edward Freis; he won the Lasker Award for proving that hypertension was dangerous and needed to be treated, and he gave me a project as a technician during an elective there; he was at the Veteran's Hospital in Washington, DC, Georgetown faculty had a service there. I got so thrilled, that was the first time that I got some answers, and it was what's called the "thrill of discovery" in research. I was able as a junior in medical school to present at the National Annual Scientific Meeting of the American Heart Association, which was a big deal, and it was at that time held every year on the boardwalk in Atlantic City. I got to make an oral presentation, and that added more wood to the flame. Then I came as a senior [to] what was called a co-step appointment in the Public Health Service. It was a commissioned officers training program for the summer of 1968. I was at the Gerontology Research Center, which then was antedated the National Institute on Aging. It was part of the Gerontology Branch of the National Institute of Child Health and Development (NICHD), and I had a wonderful experience there. My mentor, who was a fellow then, his name was Myron Weisfeldt. He went on later to become the Chief of Cardiology at Johns Hopkins, the Chief of Medicine at Columbia, and then the Chief of Medicine at Hopkins until he retired at about the age [of] 75 or somewhere thereabouts.

I returned to Baltimore for a two-year fellowship [from] 1972 to 1974, that's what you mentioned as a Clinical Research Associate. Now, that's a very interesting story, because the people who went to NIH, doctors who went to NIH [for] a period of several years during the Vietnam War were referred to as the "yellow beret" because they were among the brightest doctors and opted to work in research at NIH rather than in an Army Field Hospital somewhere. Just at the time I was to start, I was accepted into the program, but they lifted the consignment, so it was no longer obligatory, but I wanted to do it anyway for the training. I stayed for two years from 1972 to 1974. The two years in between that we skipped, from 1970 to 1972, I was a medical intern and resident at Strong Memorial Hospital in Rochester, New York. Then, following my tour as a Clinical Research fellow at the National Institutes of Health, I became a cardiology Fellow at Georgetown, and I wanted to design my own program. I had been accepted in many other fellowship positions, but I knew the people there; an outstanding professor in addition to Edward Friese was W.D. Proctor Harvey. They were very good at finding out what's wrong with the heart before you took any tests. They used their ears and their hands, and they had a Thursday night conference where they would examine patients, and the doctors in the greater Washington area could tune in, or they could come there to Georgetown and sit live in the audience, and on the seats there was a stethoscope so they could hear exactly what the cardiologists who were examining the patient on the stage

could hear. There was a palpator on the arm of each chair, and they could feel the thrust of the heartbeat and decide its rhythm. Then they would show all additional tests, which at that time weren't very many—echocardiography was just coming onto the scene. The EKG was there, of course, and the chest X-ray, and then the special test, cardiac catheterization.

All of that led up to a clinical experience in the middle of my first year; it was a two-year program, Dr. Freis alerted me to an opportunity to go abroad to learn more basic research. It was under the auspices of the American Society for Clinical Investigation, or Internal Medicine. It was a $20,000 prize offered by the Eli Lilly [Company]. The purpose of it was to take someone who had done some basic research, which I did at the NIH, to go to another place abroad to learn new techniques and bring them back. Although the course I had set at Georgetown was to go into hemodynamics, which would have been cardiac catheterization and a very clinically oriented practice, Dr. Freis, who was a hemodynamicist himself, said, “There's not a big future in that. The stuff you were doing with cell calcium during your time at NIH, that's where the future is.” You had to have an invitation, and people wrote to Arnold Katz, who wrote to people in London for me, and so did Dr. Harvey. I didn't know there was only one such award, but it was coming to be springtime in 1975 and we hadn't heard, and I said to my wife, “You might call them.” She called me, I was in the hospital then, and she said, “Well, you know, there was only one award, and they gave it to some Slovak boy from Scranton named Edward Lakatta.” So, we realized we were going to London for a year.

We had a great time. I learned a lot of new techniques, and this solidified my desire to be in research with the thrill of discovery. I was supposed to have other jobs in Minnesota. [Many] people from Georgetown went to Minnesota. They had my name on a new building in a suite of laboratories, et cetera. But I stuck it out, and the National Institute on Aging was just created. Then, the Gray Panthers in 1974 began to put pressure on Congress. This was a new institute, and they were looking for people, and because of the track record I had when I was there for two years in Baltimore, they hired me, [and] appointed me as a Section Chief. It was just one other person and me, and that was in 1976, in Baltimore.

Addy: That's amazing.

Lakatta: Things happen.

Addy: Okay, you previously mentioned that as a fellow, you decided to drop from rounds in favor of studying in the library after you became inspired by the fact that there was only one commonly prescribed drug, I think it was, digitalis.

Lakatta: Yes, you remember that correctly. This was during the first year of my fellowship at Georgetown. Actually, [it was] before I came to Georgetown as a cardiology fellow, while I was a medical resident at Strong Memorial Hospital. A person there who was one of my mentors, his name was T. Franklin Williams, he became the head of the NIA after Robert Butler. I was on a very easy rotation because T. Frank Williams ran the rehab unit at the Monroe County Hospital, and they had an acute ward for people who were in that facility. When they became acutely ill, they would come down there. It was my job to take care of those patients, but there wasn't a whole lot of action. I began to stack up papers that I got that were talking about muscle mechanics and cardiac

muscle mechanics. I couldn't understand the words at first. I had to read the papers several times, but I had a stack and fortunately, I had the time. When I got to be an NIH Clinical Associate, the clinical part was taking care of doing histories and physicals for the Baltimore Longitudinal Study participants, but that only took about 5% of my time. The rest of the time was dedicated to basic research, and that's where I studied muscle mechanics and learned how the old heart changes with respect to the way it contracts and relaxes and how it responds to signals from the brain like neurotransmitters.

Jump ahead two years to [my] cardiology fellowship, I began to look for new things to do besides walk around with a white coat, prescribing the same old drug. Calcium was coming on the scene, and it was a big to do in all sorts of muscle physiology. I began to read about it, and that was what I focused on when I went to London during the next year, from 1975 to 1976.

Addy: When the Laboratory of Cardiovascular Science first started, it was just a two-person team. Could you possibly talk a little bit about how the branch came about and why it was so important?

Lakatta: Okay. Yes, they have a designation for branch versus laboratory, and my initial appointment was as section Chief in the Clinical Physiology Branch. Another person who was an inspiration to me in my career, his name was Ruben Andres. He was the head of that branch, and I was appointed as section chief. That was the two-man [team]. We recruited several people, fellows from Johns Hopkins and from elsewhere, and started to make some important discoveries. [At] that time, the peer-review system was put in place for the intramural program. We now have a Board of Scientific Counselors, and they review what each tenured investigator does every four years. When they came this time, around 1982 or 1983, they said, “Lakatta should have his own lab.” That's a step up from a section. I was given more resources, and that was the laboratory. I've named it the Laboratory of Cardiovascular Science. I didn't lobby for that. I was just happy [with] whatever I had to work with. I was very happy.

Addy: You and your team discovered and coined the Coupled-Clock System.

Lakatta: Yes. I could talk about that forever, but that came later. Initially, we were interested in [the] heart, excitation, calcium release, and contraction. When we first started, it was called excitation-contraction. No one could measure calcium, but they knew there was something going on after excitation. There were a lot of inferences and deductions made about how things were getting stronger or weaker because the calcium was going up or down over time. Later on, we had [the] calcium measurements we took. The way the system ran, we had the Baltimore Longitudinal Study on Aging, and that's about 65 or 65 plus years old now, and I guess I was around for the first 50 of those. But we did the cardiovascular testing, given my background in medicine and cardiology. We would have lots of data on humans, and at that point, we found out very new information about how the heart was changing as one aged in the absence of disease. Prior to that study most of the data on older persons were gathered from people in hospitals who had other illnesses. Nathan Shock, who founded the Baltimore Longitudinal Study on Aging, wanted to study what he called ‘normal aging,’ separate from disease. [He] did not believe that aging was a disease. He was initially studying people in the Chronic Disease Hospital at the Baltimore City Hospital. Some of his colleagues said, “You're not studying aging, Nathan. You're studying mostly disease. Why don't you let us volunteer?” There was a community of scientists, [who] lived in a

community called Scientist Cliffs, on the western shore of Maryland, and they volunteered and got their families to volunteer. It was initially, until maybe 1988 or something, all males. Initially, it was a skewed population, but since that time minorities and women were added. It's a full-scale, good epidemiologic study now but we had lots of data and showed how the old heart was unique. What we did was find animal models that showed the same characteristics with aging as humans so we could take out their hearts and tissues. We went from the intact human to the intact rat, at that time, to the isolated rat heart, to cells, to muscle isolated from the rat heart, and then finally to cells isolated from the muscle. Then we designed some novel instrumentation to simultaneously measure the membrane potential or ion currents of calcium using novel calcium indicators and contraction all in one cardiac myocyte. We studied how receptors that were on the cell surface—autonomic receptors, alpha, beta, cholinergic, opioid receptors, a whole lot of stuff—how they signaled once they were excited to go through calcium and the ion channels, et cetera. We spent a lot of time and did a lot of seminal work [with] lots of publications.

Then it dawned on me [that] as trained as a cardiologist, I should have realized most of the diseases of older persons in the cardiovascular system are vascular in origin: coronary artery disease, thrombosis, stroke, hypertension. Then we took on a new dimension in addition to [the] heart, we took on a vascular mission. Throughout my career, I must have had the equivalent of 12 PhDs without any certificates, because everything was connected, and we had to learn new things. In this case, it was learning about cell biology in the myocardium. The cells we were studying were post-mitotic cells. We were studying their biophysical properties, as I mentioned. Now we had to learn new words of proliferation, growth, migration, invasion, secretion, and how all of this fit together. But we did it, and we then found out a whole lot of other new stuff. We focused on central arteries and how they can impact the health of older persons. The bottom line is [that] they get stiffer, and that's what makes the blood pressure go up. You have an 80% plus chance of becoming hypertensive during your lifetime, we all do. As you get older, it's more likely to be predominantly systolic hypertension and it's because of this arterial stiffening, which we learned how to quantify using a pulse wave velocity.

Then after all of that, in the course of continuing our interest in biophysical mechanisms of how calcium was important in the cardiac muscle, we got away from things that were happening in the big world. When you excite a cardiac cell or a muscle, you see a big contraction or a big calcium signal, but if you then look in between beats, most of the researchers thought everything was quiet in the heart between beats, but we increased the sensitivity of our apparatuses to their limit, and we began to find calcium leaks. Calcium is a very important messenger. There's a 10,000-fold gradient between what's in your interstitial space and your blood and the level in between beats in the heart so it has to be kept low inside the cell, and there are hiding places for it. When the excitation comes, the calcium is spit out so that it can go to the contractile apparatus and make a contraction. But between beats, if it gets too high, we found it can talk to the cell membrane and create an inward current that shouldn't be there. The cardiac muscle in the ventricle protects itself from these things but we showed [that] when this occurs, you could get a spontaneous action potential and arrhythmias and that was the basis of what's called ‘abnormal automaticity.’ It was calcium starting something to happen and binding to proteins on the cell membrane to cause depolarization, and if that was severe enough, you would get an action potential.

Am I getting too technical? I'll just go to the next stage. Then we said, “Well, gee, if abnormal automaticity is this, what about normal automaticity? Let's start to study sinoatrial node cells.” It took us almost 10 years

before we were able to isolate them with sufficient quality. We then discovered the Coupled-Clock System. Prior to that time, there were pioneers who brought science from squid axons and from Hodgkin and Huxley to the quantitative biology of cell membranes; they brought those to the heart, to the pacemaker arts, pacemaker, but they were only focused on what was in the cell membrane, ion channels. I like to say that for 60 years or so the whole field was in an 'intellectual phase lock.' Everyone who was trained in electrophysiology [their goal] was, "Go find a new current [and] get famous, an ion current." We realized that stuff could happen with these calcium leaks from inside the cell; that could attach to the cell membrane. That's the coupled clock. In a nutshell, the calcium is initiating, and it ignites. [Then the] calcium leaks out and ignites the cell surface membrane. The cell surface molecules make an action potential and that's the excitation. That's followed by a bigger calcium release within the cell.

Addy: You mentioned that you collected the electrocardiograms of mice at different ages, with and without autonomic input, and then you set these beats to music, correct? Can you explain?

Lakatta: I guess, one day, when I learned how to sing out loud in the shower, I realized that I could sing. I never studied music and didn't understand. I can't read notes or read music. [I] don't play an instrument except my voice. We did this, a remarkable study because we measured the electrocardiogram and the echocardiogram. We were looking at the ventricular structure and function and the pacemaker function every three months from adulthood until the end of life, about 30 months. We began at six months of age. This is a longitudinal study design. This is like when I mentioned the Baltimore Longitudinal Study that doesn't compare young and old people only, that's a cross-sectional that compares different people at different ages. But now if you have repeated measures—we had a lot of repeated measures in a given mouse—we wanted to get into the issue of cardiac frailty. We called this paper, 'Heartbeat Frailty.' Normally when people study mice, rats, or rodents in that way they have a mortality curve, they have just one curve. We divided our data into those that achieved the median lifespan and those that did not, that was 24 months of age. We had a short-lived cohort or a long-lived [one]. We focused initially on the long-lived. We wanted to see what was happening in a given mouse. My very first project was taking muscles from the back wall of the heart and applying catecholamines to see how strong they contracted and whether muscles from the old heart contracted not as strongly when the catecholamine was applied, as it did in the younger one. For one reason or the next, we know a lot about the crosstalk between the brain and the heart. We thought that if the heart was getting weak, the brain [would] be sending [an] extra boost, more NET sympathetic input. We wanted to study those measurements in the presence and absence of what we call a double autonomic blockade. The two major neurotransmitters, there are a number of them, but the two major ones are sympathetic and parasympathetic. The sympathetic is norepinephrine or epinephrine, and the parasympathetic is acetylcholine. In a given mouse, the difference between studying the data in the absence and in the presence was the autonomic signature. That was how the input from the brain, from the autonomic nervous system, was modifying what we were measuring in the ambient state.

We also began to understand [that] even though when you look at an electrocardiogram and your doctor says, "You have a normal sinus rhythm, at a rate of 70," when you look close, no two intervals between heartbeats are the same. The heartbeat is generated in a stochastic way, and essentially, in the heart, the sinoatrial node dies and reawakens, and when it's going to make the next beat depends upon how much memory it has left. We began to look at that. Then we plotted the intervals. If you can imagine a graph with the y-axis saying: the

intervals between peaks of the QRS complex. [Gestures with left and right index finger together to indicate the intervals between peaks.] The R wave is this R interval. [Uses index fingers to show the R wave as the higher peak by bobbing the right finger and moving it away from the left.] It's the inverse of heart rate. We put those as a function of time. Let's say over just several seconds you could see a pattern. We numbered these intervals and then I got some people in the lab who had some training in music, but the frequency at which this music was could not be heard by humans. It was too low. We scaled everything up but kept the proportionality between the young and the old. We then put that on a musical staff. I learned what a staff is in the UK, they call it a stave. We began to display the R to R intervals. They looked like musical notes.

We were not finished with that yet because we had more granular data. Those were just from the peaks of every out interval. Now we have stuff from individual pacemaker cells as they go through their repertoire of, as I mentioned, falling apart and coming back together again. We look at all sorts of new ways of analysis that people have learned to use in neuroscience and when we look at the sinoatrial node, if we look at its calcium signals what you see is, see my fingers [movies fingers back and forth and hands around], there you see. These are like squirmy worms. These are local calcium releases that are propagating local calcium signals. [Moves hands back and forth while moving fingers.] Every once in a while there'd be a bright flash. [Moves hand up vertically extending fingers out to show a flash from the previous normal hand motions.] If you look at those calcium signals in the mouse brain, you can't tell the difference between the sinoatrial node, the heart's pacemaker, or the CNS brain. We found more about the cytoarchitecture of the sinoatrial node, that it looks a lot like the CNS and neural networks, and there are glial cells that secrete different types of products. It's a whole new world that requires a whole new paradigm.

I use some of the words about stochasticity combined with chaos and things of that sort. Those were not meant to offend anyone. The biologists are just learning how to use the words that physicists and mathematicians invented, and sometimes we don't use them correctly, but we can see [the] similarities. I think the two disciplines are converging now because if you're a mathematician and you have a nonlinear equation, you can follow it and change a lot of parameters and describe its behavior and you can make up words for that behavior and then we try to apply them for the behavior that we see. But we don't really need those words. They're just words. We have to have language ultimately, but for the imagination, a little bit of both, I think, helps. Sorry that was long-winded, I told you [that] if you got me on the coupled clock, I wouldn't stop.

Addy: It's understandable. It's very interesting, especially the project where you talked a little about the potential of using external sensory stimuli to affect the person's or a rat's, in this instance, heart rate.

Lakatta: That was the idea that came to mind. We heard the music when the mouse, the same mouse, [was] at six months of age and 30 months of age. At 30 months of age, the music was very low-pitched. They couldn't hit the high notes. You have to process information rapidly. [The] high notes were low, small intervals and high frequencies. You have to do the next thing fast. And we realize that throughout the body, high-frequency signals can't be processed. We lose hearing of the high frequencies when we get older. We began to think about the memory. I mentioned memory in passing earlier, a few minutes ago. We began to see that the heart near the end of life, in the absence of help from the CNS brain, sounded something akin to Mozart's Requiem in D minor. We said, "Well, what if we could take these mice and give them some sensory input before their heart gets this

way? Let's play their young music all the time to them." We realized [this] just recently. We're working on that but it's an uphill battle. We've come to realize that when mice get past 12 months [of age], they don't hear much. We're trying to get away from [the] soundproof living quarters to [instead] implanting vibrators. The parallel to this is that in an EEG, there is a whole range of frequencies, and the fastest ones are called gamma frequencies, and those fall off with age just like [how] you can't hear the high-frequency notes in your ears. People who [study] Alzheimer's disease found that the gamma frequency falls off much more rapidly, much more intense, [with] greater gamma deficit, and they started to put gamma sensory input into the ears and flashing into the eyes. There are some human studies in progress now, but they had initially done this in mice, so there is some precedent. We then began to say, "Well, the heart gets demented. It can't remember when it gets older. This part is [the] pacemaker, and it can't remember how to hit the high notes, so we want to keep reminding it throughout middle age, to have this happen [we need] to make them aware of some signals." We're not there yet, but the work is in the planning stages.

Addy: You've also talked before about the interactions of signaling of DNA and its multi-leveled environments, describing it as a mutually enslaved system. How did this idea develop, and what was the concept like to present to your colleagues?

Lakatta: Well, it's part of a part of a presentation that I make from time to time about, "So what's aging?" I mentioned Nathan Shock. He was very adamant in distinguishing aging from disease. He thought that a disease could be treated, and it could go away. He must have been thinking of antibiotics. Aging cannot be changed so much, and for a number of years, because I was taught that way, I believed it, but I don't believe it anymore. When it comes down to, "So, what's aging? Is it a disease?", there's no real answer to that. These are my perspectives. I draw from all sorts of scientific [and] philosophical whatnot, and I began to think, "Well, what's our reality? Aging is a shift in our reality. Then what's reality?" At the basics, it's the interactions between DNA and its environment. And then what's the environment? It just sounds so simple. It's not simple because you have the nuclear environment and cells right? The cytosol. Then you have tissues, organs, communications between organs, nerves, blood, and stuff in the blood.

Then you get to what's really exciting in reality; I call it "The Essence of Diversity." These are emergent characteristics like innate brain behavior [and] personality cognition. In addition, those are modified along the way by more parts of the environment, friends, relatives, bugs, [etc.] They're also modulated by other parts of the environment, [by] society, mandates, religion, [and] traditions. That is our reality, being modulated by the environment. Plus, we have the atmosphere, right? We have the Earth. We have cosmic connections. I like to say on my little diagram, [that] the Russians beat us there, and I have the word "Sputnik." Anyway, all of that is there, now there are arrows going across all those interfaces; from the cosmic connection down to DNA, and I realized, that there's continuous signaling across those interfaces, and we don't think about all that signaling and the impact of all of it. Some of it is fast and rapid and strong, and some of it is slow, and aging is a slow change. So, what's aging? It's a deterioration and it's enslaved. I call it mutually enslaved because the signals are going in both directions, from the universe to the DNA inside of a person, they go one at a time, and aging then essentially becomes a molecular disorder. I don't even give it the credentials of being a process. If you've ever seen an egg after it's fertilized and measured calcium signals, it's what I told you was happening before in the hearts—a pacemaker in the brain. Peter Hoffman wrote a wonderful book called Life's Ratchets, and he

described the process of molecular machines within cells extracting order from chaos. I turned it around to say, “Aging extracts chaos from order, so [that] there's progressive molecular disorder.” Your proteins don't stay healthy. They don't work together like they should. It's throughout our whole body, and you can measure things if you don't measure the reserve functions. If we have [say] 100 functions, aging first becomes evident as a reduction in our reserve functions. We can't run fast, so we know about that, and what we say, “Oh yeah, we're getting old.” That's aging. But all of the other processes, they all deteriorate at different rates; there's one net vector but it's always going down and some of the functions can be increased through endurance training, for a certain period of time [some] of them can go up, like wisdom or accumulation of money. But if you go farther in life, they all join that vector that's going down, and when these reserve functions deteriorate to a level below the resting level they call us frail because we cannot perform the activities of daily living. We don't feed ourselves, we can't go to the toilet, we can't walk, those sorts of things. That's the aging process if we don't get disease.

There are other diseases that medicine has named: coronary heart disease, hypertension, etc. What's happening with aging? Those are clinical diagnoses. I'm describing [the] loss of reserve functions, subclinical, and we could see how the subclinical changes as they progress. They have to [become] very deteriorated in the absence of any other helper disease. When you get a helper disease—this is the first time I’m using that [term], looking at you and thinking of this word, “helper disease,” as you're helping me with this interview. There are comorbidities. When a specific disease [or] pathophysiology becomes superimposed on the aging deterioration, you get a different clinical picture, and you get a different prognosis. They feed back and forth and they interact, the aging deterioration with the pathophysiology of what doctors have learned to call ‘diseases.’ I like to say, “You have to age, and that lifestyle is important. Lifestyle, at the moment, is the only chance we have to modulate our health span.” When you get past the age of 50 or so, you're living on borrowed time, [and] your natural selection life insurance policy has run out. [For] nature, there's no purpose, the pressure is to create offspring but because of medicine, public health, and everything, humans live a lot longer. If you look at other species, look at the relationship between how many heartbeats you have and your lifespan, there's a very straight line, and humans are way over to the right of that line because of medicine and public health. We're out there and we're at very big risk, that's why you see these age-associated diseases becoming so prominent: dementia, cardiovascular disease, etc., and then the frailty part. I like to think of us not [as] getting a disease but, over time, we become a disease. And that's what aging is. Nathan Shock, if he heard me say that he'd probably roll over in his grave, but that's the way I feel about it.

Addy: Interesting. To reorient, your career has been based, obviously, around aging and heart-related conditions. Why do you believe it's important to focus on heart conditions related specifically to aging?

Lakatta: I think everyone who evolves in a certain area thinks that area is important. Cardiovascular [work] is important, but other organs are very important too [because] organs are linked together. In reality, on that diagram we talked a lot about heart [and] brain communication. I think that if I had to do it over again knowing what we know now about the heart’s pacemaker, I would go into neuroscience. We're learning how to use the tools of neuroscience as we speak. But from another standpoint, cardiovascular disease is the number one killer in Western society, and cardiovascular aging is the major risk factor. This is also built into my perspective on aging as a disease. The idea is, if you do epidemiology and you want to have a, let's say a list of risk factors, and

let's say the Framingham Heart Study, they have a heart score. Well, you have blood lipids, blood pressure. You know what's the major factor? Age. It swamps out the others. And what they want to do so they could show something important, they say, “Let's take age out of the equation, and we'll focus on all of those other things.” Age is like a silent partner in all of these, and medicine doesn't understand. Your question was cardiovascular, it is the number one disease [and] the number one killer. Age is the major risk factor. At the end of this presentation, “So what's aging?” I tell them the take-home message: If you want to beat cardiovascular disease, beat cardiovascular aging. Those are the subclinical parts that lead to the disease.

Addy: How do you see the field moving forward in general, do you see it based more on aging as the disease, or do you see symptoms-focused research?

Lakatta: I think the message has to be that clinical medicine has to understand more about aging than they do. You know when the National Institute on Aging was formed and when geriatric medicine came into being the internist said, “We know everything. We don't need a sub-specialty of geriatrics.” Same thing with pediatrics. Then, as the information comes in, it becomes important. It takes more time to treat an older person than it does a younger one. But that's not how medicine was being carried out. They viewed older persons as having degenerative diseases. They didn't understand aging was a disease itself. I think that has to become a view of clinical medicine, to start to address [and] invent new therapies that can be applied to something, like the one I was telling you about that may not work with the sensory input. But starting them [the therapies] earlier in life. The whole idea [that] you can't really prolong the human lifespan, [that] we're sort of at the edge of evolution, maybe a couple of million years from now will there'll be 20 more years added on to life for the average [person], but for right now the idea is to preserve health span and the preservation of health span means doing something earlier on before the health span starts to deteriorate, between 50 years and 80 years.

Let's suppose we say, “Okay, 80 is enough, or 90 is enough.” But between that period, we want to be healthy and not have all of these diseases accumulate. What's happening now is they just see older patients mostly, and there are more and more of them because of the demographic impairment, and they walk in with these diseases. There's no major effort. One of the things that is lacking is the translation. There are a number of exquisite laboratories, [including] molecular biology laboratories.

See science proceeds in two extremes: It comes down to personality, again, and how you get your information. The two extremes. It is Jung, who did this [experiment]. [There is also] the Briggs Meyer Personality Inventory that they administer to government employees, a wonderful instrument I think. Let's suppose you're a student in a classroom and the professor puts one piece of a puzzle on a board. Certain people will raise their hands telling what the puzzle is and other people won't say anything until the last piece is in. They [think that] the first person is more intuitive and the other person more sensory. Then you have introversion and extroversion. These qualities, we have in people all throughout life, but in science, if they're left alone, they have to work with each other. You can imagine the intuitive person if he doesn't understand the sensory person. He's talking to the person and the person's not really understanding what the hell he's saying because he has an imagination that links things between the words. That recognition, or realization, has to come in and they have to link to each other. That then plays out in reductionist science. Right now a lot of new information is becoming known about aging in reductionist science—one molecule, a couple of molecules. On the other end there's systems science.

They cannot continue to exist without each other, without converging. With all of the new information that's come out through breakthroughs in aging, the basic biology of aging hasn't been translated into humans. When you ask me, “What should happen in the future?”, that should happen.

Addy: That makes a lot of sense. There have been a lot of new developments and changes that you've witnessed within the NIH and the NIA during your time there. How would you describe the NIH when you first started, and how has it changed?

Lakatta: This reflects my personality. I was in the Public Health Service for 25 years. When I came to NIH, and because I was in Baltimore, I actually didn't know the name of the director of the NIH for 15 years. Well, I didn't lose anything from not knowing. There was no email, right? I could put my nose to the grindstone and do things in the timeframes I wanted to do them [in] and [it] was very successful. What's changed now is “Big Brother” is watching all of the time. If you have an email account, you know that. There are some good aspects to that, and not so. There are so many rules and regulations in NIA. Administration and all of the other rules and regulations were supposed to help the science, [but] now they're getting in the way. A lot are essential, don't get me wrong. Certain parts of it are essential but it just becomes too overwhelming. They have training—you probably had to take all this training too, so I'm preaching to the choir here. They don't check to see if it ever means anything. The NIH is experimental in nature, right? And here you have the administration not paying any attention to good science. They should train half the people and [then] look five years and see if it made any difference. No, they hired a whole lot of people to administer a lot of training, more and more refreshers every year and every day. You got me started on this.

Addy: Anything else to add?

Lakatta: I should have told you that in high school, the teachers that I had inspired me, but I didn't have any role models with respect to careers. We used to take a career preference test. It was a big, thick book, and there would be lines, and you would punch a pin, and then they would put it on a card reader and tell you it was an aptitude test. We would go to the guidance counselor, and I went for my results. He said, “Lakatta, you could be anything you want, but given your personality, maybe you should think about medicine.” After that day I was going to be a doctor, just like that. My other choices were to be a teacher and an entertainer. That's what I'm doing now. I've been able to do that. That's why my job is so wonderful. I mean, I work all the time because it's entertaining to me and I'm glad that they pay me money to do it and I work hard at it. I'm being fulfilled by having new research results that I could teach someone and entertain them while I'm trying to teach them. This is what TED means. [Do] you know about TED talks? The E is entertainment. Technical, entertainment, [and] designs or development, something like that.

Addy: Well, I'm glad that you've managed to combine all three: the entertainment aspect, teaching aspect, and medicine. I've watched several of your lectures, and they're definitely very entertaining and informative. Getting a little bit more into your personal life, how do you feel you've grown as a scientist, and what are your most significant accomplishments you feel that you have?

Lakatta: Well, I think I've grown in science. I [was] initially being trained in clinical medicine and then, thinking the grass is greener, I became a reductionist scientist. When I was telling you about taking those cells out of the heart and looking at signaling mechanisms, I put the two together. I've grown by having both dimensions. In our laboratory, we have very basic research, and we have clinical work, even in the basic research. To give you a concrete example, the field of bioinformatics has really come along. You can do what's called RNA-seq[uence] analysis or proteomics. It's a discovery. You can ask about thousands of genes, transcripts, or proteins, most of which you don't know the names of. You know the names of a couple because you were working in that area. Then you apply that data, and when it comes out you apply it to software programs, for example Ingenuity Pathway, and it tells you, “The genes that were different with aging, or the genes that were different in this transgenic mouse, they fall into these pathways.” Then you look [and think], “Duh! I know about cardiac hypertrophy [except] leukocyte extravasation in B cells." All of these molecules are hovering there. All of these connections [are] called the “systems part,” and people like me who are on the one hand struggling, and on the other hand get very basic with fewer molecules on excitation, calcium release, or [the] coupled clock system. Once we delved into this system biology all of the specific details of the calcium clock and the membrane clock, they're not as exciting as what the hell else is going on in the heart’s pacemaker. The pacemaker cells are just a tiny fraction of the cells. All these other cells are there, and they're talking to each other, and the pacemaker cells can't do anything really well without those others. Yet, they are their silent partners now. That's what I've learned and how I've grown from the beginning, from clinical to basic to systems to reductionist and trying to encompass everything. When I said all those other disciplines, like Epidemiology and Genetics and things, I was never taught any of those, I just learned them and tried to apply them to our research as we go along.

Addy: Amazing. What would you say have been your most significant accomplishments?

Lakatta: I'm going to tell you: I'm known as the Father of Cardiac Aging. All of the studies that we did in humans over a 30-year period were brand new information on how the heart responds to stress. Normally the brain is supposed to keep the heart small and make it beat fast, [but] when you exercise most of your blood is in your veins. When you start to exercise it comes into your central circulation and when it does that it comes into the heart, and it makes the heart initially balloon up. But when you're younger, the input from the brain helps it beat faster and stronger, so it [goes] back to the resting level. With older people, that doesn't happen. They work from a dilated heart at a slower rate, for example. There are many other discoveries like that, cardiovascular aging in humans, and from humans to rodents to molecules to cells and molecules. I think that was a big accomplishment. I think we made a lot of discoveries on receptor subtype signaling in cardiac cells. I think moving into the vasculature and showing that pulse wave velocity is a risk factor separate from systolic blood pressure, and things of that sort. Finally, the coupled clock system I think could be the greatest, but they're all different. Now, I don't think about the dilatation of the heart with exercise. It was on my mind 40 or 50 years ago but now what's on my mind are these other things and how the heart gets demented, how the heart's pacemaker is a brain, that sort of thing.

Addy: What do you most look forward to now within your career and personal life?

Lakatta: I think about [how] in the beginning, I began to attract people into the environment that I created. We worked together with fellows. We worked in a sort of win-win situation because I would outline a project, [and]

the fellow would do it. We would meet, we would become intimate intellectually, and going over the data [we'd] say, "Gee, this means that we should do this next." That was one type of relationship, but then as I got older, beginning about 10 years ago, you see the light at the end of the tunnel. I realized that I wanted to grow up new flowers, these younger people, because when I was given a chance to be exposed to research, even though I never thought I would be involved in it. There's a program now at NIH, and they probably have these at other institutions. I'm a professor of cardiology, medicine, and cardiology, part-time at Hopkins, and a professor of physiology, an adjunct professor at the University of Maryland. I don't get paid for those, but places like that, and [at] the NIH of late, [they] have post-baccalaureate fellowships and I look for people who want to just get exposure. They come in all flavors. I want to say, we need people to continue doing what I was doing, because it [isn't] anywhere near finished. If people don't come to get excited about research, it will just stall or get lost. I'm trying to save people. Some of my children, they [were] a kickback generation, I didn't influence any of them. My grandchildren are going into medicine and whatnot. I think that inspiring younger people to come into the field and sharing with them the thrill of discovery is what it's all about for me now.

Addy: Amazing. Okay, we are coming to the end of our time. I have two more questions. One is personal life-based, we like to end it on an upbeat note. What hobbies do you like to pursue outside of the NIA?

Lakatta: Okay, just the NIA first. You've realized that I'm what you would describe as a perpetual student. That's who I am, but when I'm not doing that, I loved to, until I was about 60 years old, I was playing touch football. I love competition. I love sports. I was pretty good at football. This is two hand touch, but you hurt yourself. Racquetball and things of that sort, I liked that, but I don't do that anymore. We never drank wine in our family; the alcohol consumption was beer. I took some wine courses, and I learned a little bit about it, but initially, they were not that good. I said, "Well, that's a good old substitute for beer, but nothing special." Then when I was in Rochester, New York, the chief medical resident was very much into wines, and he would serve us wines in his apartment. One time I tasted this wine, and the bells were ringing. Then I knew that there was something in wine. It happened to be Château Latour, which is one of the Grand Cru in Bordeaux. I threw away a lot of my medical journals and started subscribing to wine journals. [I] met with people and tasted a lot of wines. I built a wine library in my house. I've been all over the world collecting fine wines, the type that needs about 20 or 25 years [to age]. I have enough of those to last me forever now. Along the way, I'm doing more and more cooking. I've graduated from grilling and smoking things outdoors to making things inside. I just bought a pasta maker last week. My wife and I complement each other on our cooking skills. We spend a lot of time [on it] now. I'm going to be spending more and more time cooking as the years go on now.

At the moment, I want to ask the administration to search for a new laboratory chief so I could be a section chief and focus more on the coupled-clock system and, after a few years, probably retire and become a scientist emeritus and continue to work with the younger people at the NIA.

Addy: Yes, My friend has a pasta maker. She makes it all the time. She got it during COVID. It was like a little hobby that she picked up, but it was really fun to do for parties and stuff. Is there anything that you would like to talk more about or add?

Lakatta: Well, just the thing on the pasta maker. I bought my wife for one of her birthdays, a pasta maker 40 years ago, but it was the kind you crank by hand, and she's been making this pasta and raviolis [where] you roll out the dough and put on the ravioli maker. We ate a lot of that. Now I'm doing it myself. I'm coming of age with respect to that. I don't know that there's anything else to add. I've never been in a hospital actually, [and] I hope that I'm in good health through the remainder of my time on the planet.

Addy: I do as well. Well, it's been amazing talking to you. I've learned so much, and the entertainment part is definitely quality.

Lakatta: You've done a good job at that, during the interview. Thank you.