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SPECIAL ARTICLE

The Legends Colloquium

A Conversation Between Eugene Braunwald and Valentin Fuster

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This conversation between Eugene Braunwald, MD, and Valentin Fuster, MD, PhD, was held at the 18th meeting of the Valentin Fuster Society on September 14, 2023, at the New York Academy of Medicine. Deepak L. Bhatt, MD, MPH, and Martin E. Goldman, MD, served as moderators (Figure 1).

Dr Deepak L. Bhatt (DLB): There has been excitement about artificial intelligence (AI) for the past decade, and now the FDA has approved clinical applications. What do you think the impact of AI will be on cardiac clinical care 5 years from now?

Dr Eugene Braunwald (EB): Before addressing your question, I need to say something about Valentin. Marty Goldman mentioned what Valentin has accomplished as the Editor-in-Chief of *JACC*. We all know the saying, "Imitation is the sincerest form of flattery." Valentin started with the podcasts and the central figures of articles in *JACC*, and now all the leading cardiology journals have followed these 2 leads. It is an example of his enormous impact on the entire field.

Also, I should be a member of the *VF Society*, because my first cardiology fellowship, from 1953 to 1954, was at the Mount Sinai Hospital. Simon Dack was in charge of the fellows, but formal cardiology training programs had not yet been initiated anywhere in the United States. I was given enormous opportunities that year. I started in the cardiac catheterization laboratory. Then I had the chance to make the first measurement of pressure gradients across the mitral valve in patients with mitral stenosis before and after mitral valvotomy. And, I was a coauthor of a paper published in the *Journal of Clinical Investigation* on the hemodynamics at various stages of pregnancy, as well as one of the early papers on C-reactive protein. So, I am enormously grateful to Mount Sinai for getting me started as a clinical investigator in cardiology.

As far as AI is concerned, when new technical developments come along, there are usually 2 groups of people who take strong positions on them. One group who is suspicious and mired in the past, and those who are looking into the future. When Laënnec developed the stethoscope in 1816, it changed clinical cardiology. Many naysayers thought that it was a bad idea because it put doctors physically at a distance from their patients. They were used to listening to the patient's heart with their ears directly on the chest. Others saw this as an important device to move the field forward. Twenty years ago, the human genome was completed, and everyone thought that this was going to be an enormous advance in cardiology and in all of medicine. Others were very skeptical. It turned out to be somewhere in between. The same thing occurred with the development of computers. At first, there were a lot of critics, and it took a while, but now we cannot practice medicine without them.

AI will enhance diagnosis and estimate prognosis. If you feed in the phenotypic information and conduct a polygenic risk score early in life (further amplified in the following text), AI will aid in establishing the diagnosis and prognosis and this information can optimize treatment. I do think that this will change the practice of medicine—but these changes will not occur overnight. The human genome didn't change anything overnight when it was first described but it is certainly having a rapidly growing impact today.

Dr Valentin Fuster (VF): Well, thank you Gene for your kind words. It is an honor to be here with you, and I have appreciated your sage advice over the

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FIGURE 1 **Drs. Valentin Fuster, Deepak L. Bhatt, Martin E. Goldman, and Eugene Braunwald**

Drs. Valentin Fuster, Deepak L. Bhatt, and Martin E. Goldman are seated, and Dr. Eugene Braunwald appears live on screen.

years. Frankly, I see AI as, like the discovery of electricity, something that will have a huge impact in the world. There are 3 aspects that will affect cardiology. First is the clinical aspect. I agree with you completely that there will be a great impact on patient diagnosis and prognosis. Second, from the educational point of view, I am concerned that it may hamper our independent cognitive skill, particularly the physician-patient interaction. Today's education of fellows-in-training is very digitally oriented. Will AI affect independent thinking? Lastly, AI has already impacted research and investigations. As editor of a journal, when papers come from AI and they add ChatGPT, you cannot always understand where the data came from. There are very positive aspects of AI, but we need to be cautious and exercise oversight. I certainly think AI is here to stay and will be very, very important in our lives.

MEG: Following up on the same question, AI is certainly going to change the way we practice medicine. Patients already bring in Dr Google's report or their ChatGPT report on their clinical condition. They have access to their reports before we do.

Would you still recommend your children or grandchildren go into medicine and specifically cardiology?

EB: I have 7 grandchildren, and I have not recommended that any of them go into medicine. I am very disappointed with what is happening to our profession, which has changed largely into a business. The idealism that existed when I trained and during the first 30 years after I graduated from medical school is disappearing. We are ranking hospitals, doctors, and journals using flawed metrics. Health care is now extremely competitive, and it is killing the idealism. If any of my grandchildren decide to go into medicine, I will obviously support their decision wholeheartedly, and counsel them about the excitement of cardiology, but our specialty will be very different from what it is today.

The cardiology of the future probably will focus a great deal on prevention. Valentin has been, and remains, a world leader in preventive cardiology, particularly in childhood with his studies focused on children between 4 and 7 years of age. There will be a secondary branch of cardiology that will focus on patients who are critically ill. It is very likely that ventricular assist devices are going to play an even greater role in the treatment of end-stage heart failure with devices that are safer, smaller, and less expensive.

VF: My son is a musician, which has nothing to do with what I am doing, and my daughter is an architect. I exposed them to everything and then I saw what was attractive to them.

EB: Well, I certainly agree with that approach.

DLB: Much like in AI, there has been a lot of excitement in genetics, particularly in cardiovascular medicine for certain conditions like long-QT syndrome. But, what are your thoughts about genetics when applied to common cardiovascular conditions? Dr Braunwald mentioned the polygenic risk score, but beyond that, do you think genetics will actually be useful for common diseases like atherosclerosis?

EB: Yes, I do. For example, the PCSK9 story is one about a gene that is associated with elevated low-density lipoprotein cholesterol (LDL-C) and the efforts that are being made to silence the gene that encodes PCSK9. This could have a very profound effect on the lowering of LDL-C as well as the incidence of ischemic heart disease, still the major cause of cardiovascular death. In monogenic disorders, the silencing of the offending gene will occur. The work on gene editing in hypertrophic cardiomyopathy looks quite promising in this regard. The polygenic risk scores are being refined, and they can be obtained at birth or even before birth, and the results can be used to optimize diet and lifestyles of the offspring in childhood.

VF: Well, when somebody asks me about the future in cardiology, I say a new word: "*imago-genomics*." Imaging and genomics are going to really transform our specialty. Genetics is evolving very rapidly, not only related to risk factors like LDL-C, aorta, or cardiomyopathies, but also on aspects that we were not

aware of, like clonal hematopoiesis, which affects 35% of adults, related to monocytes from the bone marrow that mutate and are not defending us anymore. The polygenic approaches—for example, to coronary artery disease—have a low specificity. Thus, because coronary disease is very heterogeneous, at present, we have to be very careful not to overemphasize this aspect.

MEG: Dr Fuster spoke a few years ago in one of these meetings about cigarettes and how we have not been successful in banning them. Certainly, cigarettes and alcohol are major health care risks. What would be the best tactic for the doctors in this room and future cardiologists to try to have an impact on the politicians and reduce those major risk factors?

VF: Well, I have 3 comments. The future is of concern. The NHANES (National Health and Nutrition Examination Survey) study shows that the national risk factor profile is going to increase. In the United States, cardiovascular mortality had decreased, reached a plateau, and is now going up. Again, the world of excess consumption, the world of stress, the world of making you to do what you are not supposed to do, is increasing. Societal pressures are so stressful that you go to drink and smoke, overeat at night, and you do all the things that you are not supposed to do.

As a second point, frankly, this is why I am so involved with children. I personally think that only early education can really get into the real roots of the problem. If you start in the school system, with kids 3, 4, 5, 6, or 7 years of age, teaching quality of life and prioritizing health is how we may begin to change the culture. This is why I am so involved with children's health education. The third point is about politicians: we all hope politicians may change aspects of health, such as the food and soft drink industry, etc, but by and large they do not. The fact of the matter is that we have to start with the family and with the school system. We have to create a culture.

EB: That is the case because many politicians are supported by lobbyists who work for companies that sell cigarettes, alcohol, fast foods, and the continued reliance on fossil fuels. All of this is supported by social media and frequently exaggerated advertising. This accelerates climate change and coronary risks. To break this vicious circle, you have to start somewhere, and Valentin's selection of the school system is probably a logical place to begin.

DLB: What do you think about the potential for gene editing? Is it going to be possible in the future to provide a therapy and cure conditions such as hypercholesterolemia effectively and safely?

VF: Certainly, a breakthrough is going to be in gene editing. Why? Very simple. Because you can develop genes of embryological primitive cells that can overcome a problem. It is going to be fascinating. This is one of the most exciting fields in medicine.

EB: I agree with that. There are a lot of studies in primates going on with positive results and some early human studies that look quite promising.

MEG: Currently, we have medications and PCSK9 inhibitors to significantly lower cholesterol. I remember as an intern when someone asked you how low is low for low-density lipoprotein (LDL), you said 50 mg/dL! So how low to go with LDL, and at what age would you start treating patients?

EB: You cannot have too low an LDL-C! In the 4-S (Scandinavian Simvastatin Survival Study) that broke new ground with statins, the baseline LDL was 185 mg/dL, and now we are looking at goals below 15 or 20 mg/dL. The only thing we see as we progressively reduce the LDL-C is that clinical outcomes seem to improve. I go back to the idea that you simply cannot have too low an LDL-C. I would say that if 50 mg/dL was outrageously low 40 years ago, I would now like to see it below 20 mg/dL for both primary and secondary prevention. Certainly, if you look at preclinical studies and at human populations who rarely get atherosclerosis, their LDLs are in the 40 to 60 mg/dL range. Observations in TIMI (Thrombolysis In Myocardial Infarction) have shown no problems with LDLs under 15 mg/dL, and that is the direction in which we are headed.

VF: There is good evidence that subclinical disease begins at age 20 years, and LDL-C higher than 70 mg/dL facilitates subclinical disease. So, to me, the normal LDL-C for somebody who never had any cardiovascular events should be below 70 mg/dL. However, the guidelines are problematic because they only deal with heart attacks, strokes, and people over 40 years of age. I predict we will begin to treat elevated LDL-C beginning at age 20 years. I hope the therapeutic subcutaneous approach twice a year will improve adherence. Over the next 10 years, there will be treatment earlier and reach even lower levels. Again, the culture will evolve when people realize that subclinical disease is dictating late cardiovascular events, not disease that is already manifested.

EB: My motto is "the lower the LDL-C the better and the earlier you start the better." That is why I am interested in the concept of polygenic risk scores at birth, because the LDL tracks beyond that, and we can identify trends early before they become risk factors.

DLB: Well, it has been a real privilege getting to interview 2 giants of medicine. You have each made immeasurable contributions to the field in terms of scholarship and mentorship. Dr Fuster, what do you think is the greatest contribution of Dr Braunwald?

VF: Well, I am biased, because as he knows, when I left my training in Edinburgh, I asked for a job to work with him. I was offered the position from Dr Ross in San Diego and then I had a visa problem. So, I could not go to UCSD, but fortunately, I was recruited at the Mayo Clinic.

Why was I so excited to work with Dr Braunwald? He was a giant in the field already in the early 1970s, and it was amazing. He was very involved in physiology of the circulation, which fascinated me. He developed the concept of left ventricular ejection fraction and defined what leads to contraction. He developed the concept of dP/dt in the early 1970s.

Dr Braunwald has shown leadership in all the areas of cardiovascular disease over the last 40 years through the TIMI studies, which he started in the early 1980s. He has been incredible. One study after the other. I remember the first one, which I think was streptokinase vs TPA, then the discovery of the role of ACE inhibitors in heart failure with Dr Marc Pfeffer.

DLB: Dr Braunwald, what do you think is the greatest contribution of Dr Fuster?

EB: Well, that is a real tough question because his contributions to cardiology have been and remain so broad and so deep. It was our loss when he could not join us in San Diego, and he did extremely well by going to the Mayo Clinic. That is where Dr Fuster became interested in coronary thrombosis and the role of platelets, which really changed cardiology. I give him enormous credit for that. And, some of his early studies with aspirin following coronary bypass surgery have withstood the tests of time and have prolonged many lives. The other area I referred to earlier has to do with prevention of cardiac disease and the work that he has done and is continuing with children. These 2 areas are quite different, and he has really made key observations in both.

MEG: Again, we are inspired by today's discussion because Dr Fuster and Dr Braunwald have changed medicine and the way we practice cardiology. No 2 people will ever have the impact they have had again. So, the question I have for both of you: what inspires you to continue to do what you do? To what do you attribute your longevity and cognitive acuity that allows you to have such great productive careers?

VF: Our lives are all driven by motivation. And I have the motivation of science, the motivation of understanding that something you may discover could make lives better, and that is a motivation. As you know, I go to Madrid once a week because I have a center of research there [*The Centro Nacional de Investigaciones Cardiovasculares (CNIC)*] with 400 investigators. I get the young people as excited as I am with new ideas and so forth. So, that is what it is. But furthermore, I love patient care, the aspect that has triggered my clinical research career by opening questions to investigate.

MEG: And to what do you attribute your cognitive acuity that allows you to be that productive and that energetic?

VF: Well, we go into the genes again. My mother died at age 102 years, and she was going from the north to the south of Barcelona by bus at the age of 95 years. The bus drivers all knew her. She went shopping by herself. So, I inherited something, and this is the reality of our lives. When you have inherited something, you can only give thanks. I constantly give thanks to society because I have been a very lucky guy, very lucky.

EB: I have remained as interested and excited about cardiology as I had been during my cardiology fellowship here at Mount Sinai Hospital 70 years ago! I take enormous pleasure in watching everything that we are doing in cardiology today, how it is changing. I lived through a time when there were no useful antihypertensive drugs, no cardiac surgery, and no echocardiography or other imaging. I have enjoyed a ring side seat to observe these and other developments and, in a few instances, even participated in them. If you can contribute to the development of a field, even if it is just adding a single brick to the construction of a large, important building, the impact may be quite satisfying. This has driven me through all of these years and what is continuing to do so now.

DLB: Dr Braunwald, what one question do you have for Dr Fuster?

EB: Valentin, though you have accomplished so much in cardiology, we still have an enormous number of sudden cardiovascular deaths, and we have not really done much in that area of cardiology. I wonder whether you have any ideas how we can overcome this?

VF: Well, going back to the issue that we have been discussing, we have to completely change our view to prevent all of this and go much further to understand health. The answer to your question is not just prevention, culture, and education, but investigation has to be done with the most modern tools in understanding health and enhancing the mechanisms that make us healthy. Prevention has to be driven by science with the most modern technology to understand health. Prevention of sudden cardiovascular death fits with these concepts.

DLB: And Dr Fuster, what one question do you have for Dr Braunwald to answer?

VF: What is next for you, Gene? What is your next project?

EB: My next project is simply to put one foot in front of the other and continue with what I am doing right now. I feel very fortunate to work on my textbook, *Heart Disease*, which is a way of educating cardiologists (and me!), and to working in the TIMI Group with a new generation of brilliant, devoted young clinical investigators.

MEG: Last question: if you could have dinner with any 3 characters, fictional, real life, alive or not here anymore, who would those people be?

VF: Mr Winston Churchill. He is the one I would like to know. He was a genius and somebody that I would like to understand much more. Lots of books have been written about him on different aspects, but he was the 1953 Nobel laureate in literature. He was a fantastic politician. He decided to take approaches that everybody really thought were crazy. He is a fascinating person that I would have loved to know, of course with Plato and Aristotle as well. And with Dr Braunwald!

EB: The 3 people with whom I'd love to have dinner are Leonardo da Vinci, Charles Darwin, and of course, Valentin Fuster.

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