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LEE E. FARR LECTURE

Reflections on a Life in Biomedicine: Leading Change

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Dr. Elizabeth Nabel delivered the following presentation as the Lee E. Farr Lecturer on May 7, 2013, which served as the culmination of the annual Student Research Day at Yale School of Medicine. Dr. Nabel is President of the Brigham and Women's Hospital in Boston, Massachusetts, and Professor of Medicine at Harvard Medical School. Her lecture to Yale medical students portrayed her own personal and professional journey through medicine as a series of opportunities. Dr. Nabel focused on the roles and responsibilities of physicians to recognize need and to make change through focused advocacy.

LEE E. FARR LECTURE

Today I'll share with you my career journey, and some lessons I've learned along the way. My main message is that the ride is full of opportunities. At every juncture, it's a good idea to see what might be done to continually grow and improve — both personally and professionally and also for societal benefit.

A life of science alone is rarely itself enough to fulfill us as humans. I maintain many distractions to keep me happy, sane, and balanced. I wear a lot of hats. I am a scientist, a physician, a wife, a mother, and an administrator. I am married to another physician scientist, and together we have raised three children, all of whom seem headed to careers in science, medicine, or both. How thrilling it has been to "mentor

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†Abbreviations: NHLBI, National Heart, Lung, and Blood Institute.

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at home" and see my children find their own dreams in this 21st century world.

YALE AS A MODEL

I'd like to highlight a few heroes in your midst that make Yale a special place. The late Dr. Lee Farr, namesake of this lecture, trained here at Yale, and then shared his ideas and talents in various ways and at several institutions across the country. His pioneering work in nuclear and environmental medicine has been central for many subsequent efforts and discoveries — among them the design of the first nuclear reactor to be used for medical purposes. Where would we be today without those forward-looking individuals like him who saw the importance of conjoining physics and biology in exploring health?

Scientists like Dr. Farr are emblematic of the so-called academic triple threat — an individual that excels at patient care, research, and education. These three pillars remain the vision of academic medicine, even if many of the processes and details have changed over time and will continue to change. One of your alumni, Abraham Flexner, whose 1910 report set the stage for our current model of integrating medicine and medical education, focuses on a blended experience of science and clinical care, bridged through analytical thinking in both realms [1]. Academic medical centers like Yale are especially unique with the strong emphasis on critical thinking in a nongraded, noncompetitive environment that requires students to write a thesis based on original research.

That, of course, is the focus of this special lecture, and I would like to recognize publicly this year's prize-winning students and projects:

• Benjamin Himes: "siRNA therapy in glioblastoma stem cells: Identification of target genes and potential therapeutic implications"

• Sounok Sen: "Understanding costs, value, and patterns of care of new radiation technologies among older women with breast cancer"

• Kevin Koo: "Male-partner participation in the prevention of mother-to-child HIV transmission in South Africa"

• Michael Peluso: "Biological and clinical markers of neuronal injury in primary and chronic HIV-1 infection"

• Rachel Rosenstein: "Innate immune sensing of allergens"

MY CAREER JOURNEY

Although I am not a Yale graduate, I am one of you. I am a veteran of academic medicine, although I have taken some interesting detours. All of these experiences have taught me valuable lessons. Within my own career journey, there is a thread worth noting. It is the role of advocacy, in the broadest sense — continually observing your surroundings, recognizing problems as opportunities, and then driving change.

My life began in Minnesota, as Midwestern as it gets. Growing up, I was surrounded by family —generations intermingled to offer stories, humor, and advice. I learned many lessons from my grandparents and parents. My mother was a schoolteacher and homemaker, the daughter of a "country" lawyer. She had a sense of pragmatism that came with that life and that quality is something she passed on to me. My father was a research scientist at 3M, and he was a tinkerer, an inventor — as a chemist, he developed a number of compounds for 3M such as Scotchgard and adhesives for products such as Post-it Notes. He loved science, and he loved to talk about science. My siblings and I loved that and couldn't help but fall in love with science ourselves.

But as a girl in the 1950s, in this conservative Midwestern culture, girls weren't expected to like science, much less actually want to pursue it as a career. So I faked it: despite loving technical subjects, I would purposefully get things wrong on exams so that I would not be at the top of the class or get the highest marks. It's a little embarrassing to admit this, but it does provide a good example of how far we've come as a society, although there is still room for improvement.

I went to St. Olaf College, and then ultimately, I decided to go to Weill Cornell

Medical College in New York City, in large part because views toward women in medicine were more progressive on the coasts. This was a time in the 1970s when the feminist movement was coming to the fore with the likes of Betty Friedan and the "feminine mystique," Gloria Steinem, and Ms. magazine.

I gather that some of you have met your life partners during your training here at Yale. I met my husband, Gary, when I was a resident at Brigham and Women's Hospital and he was an intern. Our first date was to settle a bet about a patient diagnosis. He won. We went out for dinner at a lovely restaurant in Cambridge's Central Square and — I am not making this up — ended up in the middle of an armed robbery at the restaurant. What a beginning! Just a little over a year later, we got married. Managing two careers, maintaining our marriage, and raising three children have been a wild ride. But it has been so rewarding because we believe in each other and in what we do.

After our training, Gary and I both got our first faculty jobs at the University of Michigan in Ann Arbor. There, we worked together on some of the first gene therapy studies in cardiovascular disease and cancer, each in our respective labs. We loved the nurturing, yet academically stimulating environment that Ann Arbor offered. It was a wonderful place for us to be at that time. We flourished scientifically and even started a company. I remember a funny incident there that involved our son Chris, who at the time was 5 years old. We participated in a family interview for the Ann Arbor News. The journalist asked Chris what he wanted to be when he grew up. Chris replied, "A cell doctor." The journalist then said, "Don't you want to be a heart doctor?" Chris replied with a startled expression on his face, "Why no, only girls are heart doctors!" Chris is now as an MD/PhD student at the University of Pennsylvania, and his grandfather would be very proud!

Then, in 1999, when Gary was recruited to become the director of the National Institutes of Health Vaccine Research Center, a new branch at NIH that focused on developing an HIV vaccine, we had to think seriously about making a change. Despite having a great set-up for work and family in Michigan, we took a risk in moving, and it ended up a good opportunity for me, too. Although I had been recruited to NIH to be the National Heart, Lung, and Blood Institute's (NHLBI†) Scientific Director of Clinical Research, a few years later, I had the opportunity to become NHLBI Director. That was a terrific experience that I will tell you a bit more about in a few minutes.

HOW FAR WE'VE COME

In 1982, I was in your shoes. I was ready to begin the incredible journey that is a life in science and medicine. As a new intern, I was full of dreams. I was ready to care, ready to learn, and ready to be an instrument of change as a 20th century doctor. Now, the passing of a few decades feels more like a few centuries. The breakneck pace of change in biomedicine certainly contributes to this perception.

It is truly amazing how far we have come. Our nation's investment in biomedical research has been a wellspring of knowledge about human health and disease. We've gone from Watson and Crick's initial model of DNA [2] to whole-genome sequencing. We're quickly moving away from one-size-fits-all medicine toward precision medicine. The particularly promising field of regenerative medicine offers genuine hope that re-growing injured and damaged organs will be part of routine care in the next decades.

Consider that the first organ transplant was performed by the late Dr. Joseph Murray in 1954, when he led a group of physicians at the Peter Bent Brigham Hospital in Boston in performing the world's first successful human organ transplant — a kidney between two twin brothers [3]. This first, risky step was truly a giant leap for transplantation in general, and in the 60 years since then, organ transplantation has saved thousands of lives. I was truly lucky to have interacted with Joe Murray over the years and treasure the mentorship he provided to me and to so many others.

Building on this pioneering work, 58 years later in 2011, a team of more than 30 doctors, nurses, and residents at the Brigham performed the nation's first full-face transplant [4] on Dallas Wiens, a young father from Texas who lost his entire face in a horrific accident that occurred while he was painting a roof and brushed a high-voltage overhead electrical wire. Led by an incredibly innovative plastic surgeon, Dr. Bo Pomahac, the medical team worked for more than 15 hours to replace his nose, lips, facial skin, facial muscles, and the nerves that provide sensation. He has had many follow-up procedures and rehabilitation since. No one thought he would even survive the accident, and that he has come this far is truly remarkable. In fact, as you may have heard, Dallas was married just last month to a burn survivor — what a beautiful love story!

OPPORTUNITIES FOR MAKING CHANGE

Certainly, a life in academia is a life of learning, as well a series of chances to extend knowledge for the public good. I've had the extraordinary opportunity to make change in several ways.

Women's Heart Health

An early instrument of change for me was a young 35-year-old African American woman whom I cared for as a junior resident in the Brigham's emergency room. She came to the emergency room feeling tired and short of breath. We did a number of tests and couldn't find anything specific, so we sent her home thinking she had the flu. Two days later, she returned, having suffered a full-blown heart attack. She was 35 years old. How could this be? I had completely missed the early signs two days earlier.

Such a fate wasn't possible in a young woman, I reasoned, since I had been taught that heart disease was a "man's disease." The role of a woman was to take care of her spouse, father, or family member, but women didn't get heart disease until they were very old, and then you didn't or couldn't do much about it. But her case was a hidden story waiting to be told — and an action that needed to be taken — to change the thinking about heart disease.

As we now know, heart disease is the number one killer of women, and it is not just a man's disease. Luckily for her (and for me), we saved this woman's life with interventional therapies, and she got a second chance. That woman, and that experience, pointed me to a goal I've been working toward ever since. I realized that women of all ages and from all walks of life need to understand the importance of protecting their hearts. My experience with that patient lit a fire in me. I recognized the need to raise awareness about women's heart health. I saw that we needed to help women understand that heart disease is a serious threat, but that it is largely preventable and that there is a lot that women can do to protect their hearts.

We know this from research that began in the mid-20th century, which followed residents of the small Massachusetts town of Framingham. Those studies defined the main risk factors for cardiovascular disease: high cholesterol, smoking, hypertension, and diabetes. Framingham Heart Study results set in motion a number of things. Public education campaigns taught Americans the importance of these risk factors, and scientists performed Nobel Prize-winning work that resulted in the development of life-saving statin medications to manage cholesterol. All of this contributed to a strong evidence base about the causes, progression, and successful management of heart disease [5].

Sometime later, as director of the NHLBI, I leveraged my position to drive change by building The Heart Truth® awareness campaign [6] that used a red dress as a symbol of women and heart disease. We partnered with many professional and advocacy organizations, including the American Heart Association, the American College of Cardiology, and Women Heart. Because we wanted to leverage our awareness, but knew that as a federal government agency our reach would be limited, we partnered with the fashion industry and created a fashion show that featured celebrity models wearing designer red dresses during New York's

fashion week. First Lady Laura Bush was our national ambassador who did many events with us, and she embraced women's heart health as one of her causes as First Lady. We also partnered with Diet Coke®, which was a risky thing to do at the time, due to perceived endorsement of the food and beverage industry. But we did it because we knew that Diet Coke would be able to reach women through brand recognition, and they could really deliver our message to women throughout America. They have accomplished this goal, as you may have seen with the red dress symbol appearing on Diet Coke cans. This experience taught me that advocacy for one's passion can be achieved by personal commitment that is strengthened through forming innovative partnerships.

Global Health Leadership

I also had the opportunity, while leading NHLBI, to recognize another area ripe for advocacy: the global epidemic of noncommunicable diseases that is raging in the developing world. Here, the need was clear, and the global scientific community has really come together to address it. As with women's heart health, in this case, "treating the problem" was less about finding a good drug or a doing a clinical trial. It was about teaming up to share knowledge and to engage partners in and outside the health sector. In June 2009, I was fortunate to help launch the Global Alliance for Chronic Diseases [7,8], in which six of the world's foremost health agencies, collectively managing an estimated 80 percent of all public health research funding, formed an alliance to collaborate in the battle against chronic, noncommunicable diseases. For the last couple of years, this alliance has made great progress, focusing mainly on the needs of low- and middle-income countries and on those of low-income populations of more developed countries. From my participation in this effort, I have learned that it really is possible to translate research findings into sustainable solutions.

More recently, at the Brigham, I've had the opportunity to work on a global partnership with the nation of Rwanda [9]. Here is a country with incredible public health needs — a place with six doctors for every 100,000 people, a war-torn land with significant infrastructure deficits. What we've focused on in Rwanda is capacity-building. We have partnered to bridge gaps in infrastructure, we have shared medical personnel, and we have enjoyed many opportunities for training and cross-learning. Truly, the benefits of this endeavor — a direct alliance with the Rwandan government — have been bidirectional.

If most of this advocacy sounds difficult and non-medical — and indeed a lot of it is brokering deals through lots of meetings and travel — everything makes sense when you get to see the results close-up. I had the recent experience of visiting two hospitals in Rwanda that the Brigham has helped build and staff in collaboration with Partners in Health and the Ministry of Health in Rwanda. In 2009, I had first met Justine, a lovely 11-year-old girl who was suffering from very bad heart failure. She had rheumatic heart disease, something we rarely see in the United States anymore. Rheumatic heart disease results from untreated strep-throat infection, and because we have good access to antibiotics, few Americans develop this type of heart condition. But that is not the case in the developing world. Fortunately, through collaborative efforts, Justine received corrective heart surgery in 2009, and she and her mother were provided new housing and a garden so she could focus her efforts in school. In 2012, I returned to her village in Rwinkavu, and got to see Justine again. Now, she is a robust, 14-year-old young woman, thriving in school, and aspiring to go to medical school. Making a difference starts with one individual at a time, but the success builds as real change happens.

Common Knowledge from a Rare Disease

My last example will be about scientific investigation. This is an amazing story of translational research, a story about a very rare disease, Hutchinson-Gilford Progeria Syndrome, abbreviated as proge-

ria. The phenotype is devastating, encompassing a range of symptoms that affect the whole body: hair loss, diminished subcutaneous fat, growth retardation, skeletal abnormalities, and cardiovascular disease. The psychological impact is perhaps the biggest of all: people with progeria age prematurely and are robbed of the normalcy of childhood. Children who have this disease age prematurely such that they physically resemble people much older, in their 80s and 90s. There is no cure, and typically these children die early, in their teens. I was fortunate to get involved in collaborative research project with Dr. Francis Collins, who is now the NIH Director. The project has been an extraordinary effort involving inventive genetic sleuthing, a dedicated and creative interdisciplinary team, a rich foundation of protein biochemistry, cutting-edge cell biology, and a representative mouse model [10,11].

Under the leadership of Drs. Leslie Gordon and Mark Kiernan, we were successful in recruiting about three dozen young patients who have this condition from all over the world and who came to Boston to receive an experimental therapy born of biochemical experiments [12]. Possibly the most surprising twist in this story is the finding that the genetic error in progeria also corresponds to some aspects of normal aging. Research in this area remains active and exciting!

OPPORTUNITIES FOR CHANGE: HEALTH CARE REFORM

I want to conclude today by telling you about something to which I have been dedicated — but it is actually an opportunity for all of us. It is about the key roles we as physicians will play in health care reform as it unfolds throughout America. I know I don't have to tell this audience that biomedical research is a jewel in the crown of this country; it undergirds the many incredible advances we know about. Academic medical centers are the bedrock of this whole effort, held up by the three pillars that I spoke about before: excellent patient care; innovative, high-impact research; and high-quality education. We must all continue to press for the vitality of biomedical research — not just for health, but for growth in our 21st century knowledge-based economy. I also don't have to tell all of you that this is a very challenging time for our biomedical community. We are in a period of economic hardship, trying to emerge from a recession. We can and should use the urgency of the national dialogue on health care as an opportunity to focus on the role of biomedical research and medical discovery in laying the foundation for better human health.

In early 2010, as new president of the Brigham, having come from Washington, DC, and knowing health care reform was on the horizon, I immediately saw the need to redesign care and bend the cost curve at our medical center. I knew that doing so would be hard, and that it would be unpopular. Yet, I knew it had to be done and I would have to be the one to lead the change. So I set about to draft a strategic plan to chart this course. I talked, but mainly I listened. And I worked hard to engage all facets of my organization, from patients to residents to nurses to doctors and to housekeeping staff and many others. I tried to be as transparent as I could be and to be responsive to the needs of the many people that make up a teaching hospital community — most importantly, the people we serve.

This process led us to some really important changes, and we have been able to cut costs without compromising quality. That is critical, because at the end of the day, if as a health care organization we cannot say that patients come first, what is it all worth?

MOVING TOWARD THE FUTURE

Remember one thing if nothing else: Modernizing and adapting to new environments must not corrode the vision of academic medicine. Patient-centered care, evidence-based medicine, and training the best doctors are what we do. Today's academic triple threat may look different from

that we saw in people like Dr. Farr. Today, our science is complex and multidisciplinary. Our problems intersect science and society. Today's triple threat must encompass vision, passion, and team play. Today, we are part of a new world in medicine, one driven less by static knowledge but by knowing how to recognize and lead change. Through our smartphones and iPads, most of us have the world's biggest library in our pockets 24/7. The coming changes in health care will certainly affect how we do business, toward a more patient and family-centered model of care. To best meet the needs of our patients, we will need to use a team-based approach that involves a range of healthcare providers — nurses, pharmacists, physician assistants, mental health specialists, and many others. Modern academic medicine is a partnership of higher education, health care, patients/families/communities.

Advocating for the right change for our patients, our institutions, and our communities will shape the future environment in which we practice medicine. As you move through your own scientific and medical journeys, keep these thoughts paramount. Be clear on what you believe. Build partnerships and permit uncommon alliances to catalyze action. Be willing to take a stand, and don't be afraid to be different or unpopular to get something important done.

As you cross the threshold toward the next phases of your lives, I wish all of you the very best. Know that we are counting on you to find your voices and speak out for the things that will benefit all of us.

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