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Introduction of Elizabeth G. Nabel

Eugene Braunwald

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AAP Kober Medal Presentation

A brief biography Our honoree, Dr. Elizabeth (Betsy) Nabel, was born in St. Paul, Minnesota, into a family with strong Midwestern roots. Her father was a scientist at 3M and her mother a schoolteacher. They instilled into her a powerful value system — a love for family and learning, hard work, integrity, and a deep obligation to serve the wider community. She, her sister and two brothers looked forward to family dinner when their father would describe his interesting work as a chemist and inventor — translational research is what it's called today. He transmitted an excitement about science to Betsy and her brother, Tom, who became an academic pharmacologist. Betsy was a summa cum laude graduate of St. Olaf College, a small, excellent Lutheran college in Northfield, Minnesota. After graduation, she was ready to leave this somewhat sheltered environment and to "try her wings" in the wider world. She was awarded a Rockefeller Brothers Fellowship to attend the Union Theological Seminary in New York City. After additional training at Columbia University, she entered Cornell Medical College. As a senior medical student, she spent a month's elective in cardiology at the Brigham and Women's Hospital (the Brigham). As a consequence of that relatively brief experience, she made two decisions that would lead ultimately to the successful professional life that brought […]

2014 Association of American Physicians George M. Kober Medal

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A brief biography

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As a senior medical student, she spent a month's elective in cardiology at the Brigham and Women's Hospital (the Brigham). As a consequence of that relatively brief experience, she made two decisions that would lead ultimately to the successful professional life that brought her here today, as well as to a fulfilling personal life. Her first decision was to return to the Brigham for her house staff training in internal medicine because she became strongly attracted to the interplay between clinical medicine and research that she observed. The Brigham had not yet become a large hospital, and the basic science laboratories, clinical research laboratories, and patient floors were close together, both physically and intellectually, with the faculty moving back and forth easily between these areas. Her second key decision was to select cardiology as a specialty because it was the field in which she felt that she could make the greatest difference to patients by using both her head and her hands.

Betsy graduated from Cornell in 1981 with no fewer than 5 scholarship prizes (Figure 1). During her medical residency at the Brigham, she was regarded as a superb and compassionate physician who was greatly admired by both her attendings and medical students. Betsy was a very hard worker; if she were a house officer today, she would have great difficulty confining her work week to 80 hours. By returning late in the evening to check on her patients and meeting with their families, as was her custom on her "nights off," she would threaten the accreditation of the program. But, of course, that was not an issue in 1981.

During her residency she met Gary, an intern with an MD/PhD in Immunology from Harvard, who was an outstanding member of our highly selective research residency track. Betsy tells the story that their first date was to settle a bet about a patient's diagnosis; Gary won. They went out for dinner to a restaurant in Cambridge and ended up in the middle of an armed robbery. She admired the cool way in which Gary handled the situation. A year later they were married.

Following his residency, Gary took his postdoctoral fellowship in David Baltimore's laboratory at MIT. Betsy stayed at the Brigham for a fellowship in Cardiology. The Nabels have three children (Figure 2): Chris, who is completing an MD/PhD at the University of Pennsylvania; Elisa, who is in an MD/PhD program at Mt. Sinai; and Katherine, who majors in biology at Stanford.

In 1987, on completion of their fellowships in Boston, the Nabels moved to the University of Michigan, where Betsy ascended rapidly through the academic ranks to Professor of Medicine and Physiology and Director of a new, interdepartmental, and multidisciplinary Cardiovascular Research Center. She became Chief of the Cardiology Division as well. As a visitor to her program in 1998, I came away with four impressions. First, she was intimately acquainted with every detail of the research, teaching, and clinical activities in her large and thriving Center and Division. Second, she was intensely interested in providing her trainees and junior faculty with the tools for future success. Third, she

Figure 1
Elizabeth G. Nabel at graduation from Cornell Medical College, 1981. Photo courtesy of Elizabeth G. Nabel.

Conflict of interest: The author has declared that no conflict of interest exists.

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Figure 2
The three Nabel children: Elisa (left), Chris (middle), and Katherine (right). Photo courtesy of Elizabeth G. Nabel.

was quite active, running a large clinical service and caring for her own patients. Fourth, I was impressed with her thorough understanding of academic finances, a skill that she acquired early in her career and that has subsequently served her well.

After 12 enormously productive years in Ann Arbor, the Nabels moved to the NIH. Betsy's first position was as Scientific Director of Clinical Research and Chief of the Vascular Biology Section in the intramural program of the National Heart, Lung and Blood Institute (NHLBI). Gary, a member of this Association, became Director of the Vaccine Research Center in the National Institute of Allergy and Infectious Diseases (NIAID), which he transformed into a center of great excellence. In 2005, Betsy became Director of the NHLBI.

In 2010, Betsy returned to the Brigham and Women's Hospital as President and Professor of Medicine at Harvard. Gary became Chief Scientific Officer of Sanofi, based in Cambridge. In addition to overseeing a multicontinental and multibillion-dollar research enterprise that plays to his immense strengths in science, Gary is continuing his own vaccine research, in which he remains immensely productive.

Research

Betsy's first paper during her cardiology fellowship at the Brigham was on experimental renal hypertension (1). One of her coauthors was Gary H. Gibbons, who would become her immediate successor as Director of the NHLBI, and the other was Victor J. Dzau, then an Assistant Professor in the Department of Medicine and now President of the Institute of Medicine. As a fellow, Betsy also became interested in and played a critical role in the effort to characterize silent myocardial ischemia. She and her colleagues reported that ambulatory electrocardiographic monitoring of most patients with symptomatic angina showed that they also had surprisingly frequent and prolonged episodes of silent ischemia, both at rest and during ordinary activities. This led to an important concept, namely that it is the total ischemic burden, expressed as the duration and severity of ischemia, both symptomatic and asymptomatic, that is an important determinant of clinical outcome in patients with chronic coronary artery disease (2).

Her findings also suggested that coronary vasoconstriction plays a significant role in the development of silent ischemia. This led to her desire to understand the mechanism of vascular smooth muscle contraction. For this she turned to the basic science laboratory of the late Tom Smith, a distinguished member of this Association, and she collaborated with Brad Berk, who was in her intern group and is now also a member. They showed that the Na^+-Ca^{2+} exchange that occurs in cultured vascular smooth muscle cells is a determinant of the free intracytoplasmic [Ca^{2+}], which in turn is a major determinant of smooth muscle contraction and thereby of the coronary lumen (3). This is the first of many examples of how Betsy has approached research: one, begin with a clinical observation (silent ischemia); two, measure it precisely under a variety of circumstances (ambulatory electrocardiography); and three, identify the responsible mechanism in the basic science laboratory (ionic movements in cultured cells).

The Nabels arrived in Michigan at the height of interest in fibrinolytic therapy for acute myocardial infarction. Betsy collaborated with Eric Topol, Bert Pitt, both members of this Association, and others in an important trial, which showed that in patients with acute myocardial infarction, the addition of an angiotensin-converting enzyme inhibitor to tissue plasminogen activator (tPA) improved the function of the salvaged myocardium (4). The concepts presented in this seminal paper have stood the tests of time, as, by the way, have Betsy's other research contributions.

Consistent with her earlier approach to move from the bedside to the bench, Betsy wanted to apply the tools of modern biology to what was then the relatively new field of vascular biology. She enlisted the collaboration of Gary, by this time a card-carrying molecular biologist and Howard Hughes investigator in the Departments of Biochemistry and Medicine at Michigan. They began a series of elegant studies in molecular genetics, and gene transfer in vascular smooth muscle. In one of their first experiments, they transfected endothelial cells in tissue culture with a retroviral vector expressing β-galactosidase. The genetically modified endothelial cells were then successfully introduced into the pig's ileofemoral artery (5). This was one of the first examples of successful gene transfer into mammalian endothelium.

The Nabels and their collaborators then investigated the expression and function of recombinant FGF by gene transfer of a vector encoding FGF on blood vessels. They demonstrated that FGF stimulated endothelial hyperplasia, capillary formation and intimal thickening, reproducing the pathologic findings observed in the vascular injuries that lead to atherosclerosis and the restenosis that occurs after vascular injury (6). In related studies, they reported that transfer of TGF-β1 into porcine arteries increased production of the extracellular matrix and hyperplasia of the intima and media (7).

In the 1990s, coronary artery stenting became widely used around the world.

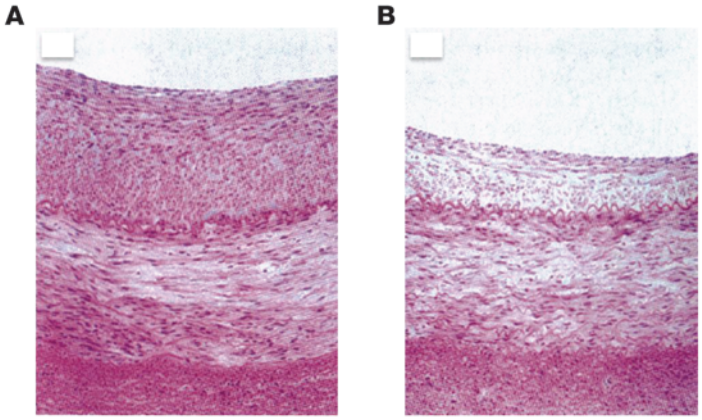

Figure 3
The greatly thickened intima of a porcine ileofemoral artery after balloon injury (**A**), and the marked reduction of intimal thickening after gene transfer of p21 (**B**). Figure reproduced with permission from *Proceedings of the National Academy of Sciences of the United States of America* (9). Copyright (1996) National Academy of Sciences, U. S. A.

Restenosis, which was characterized by intimal cellular proliferation, became a common clinical problem. Betsy and her colleagues investigated whether expression of recombinant genes in atherosclerotic arteries after balloon injury could inhibit this proliferation. They reported that in atherosclerotic rabbit arteries subjected to balloon injury, transfer of a thymidine kinase gene with the nucleoside ganciclovir prevented cellular proliferation (8). In an effort to limit intimal cell proliferation in response to arterial injury, Betsy and her colleagues found that gene transfer of p21, a cyclin-dependent kinase inhibitor, reduced intimal cell proliferation (Figure 3 and ref. 9). This important study showed that it is indeed possible to limit cellular proliferation following arterial injury, providing the biological framework for the subsequent development of drug-eluting stents, which inhibit intimal proliferation and are currently in use worldwide.

When she was at the NIH, Betsy collaborated with Francis Collins, the 2015 Kober Medalist, in the study of the Hutchinson-Gilford progeria syndrome (HGPS; Figure 4). This very rare condition leads to death due to myocardial infarction or stroke at an average age of 13 years. It is characterized by reduced vascular compliance, hypertension, joint contractures, and alopecia (10). Theirs was a natural collaboration between a geneticist and a vascular biologist. Both had enormous administrative responsibilities, but simultaneously led excellent and productive research teams. This appears to be the first collaboration between two consecutive Kober Medalists.

In 2003, the Collins laboratory discovered the genetic etiology of HGPS (11); namely, a point mutation in the lamin A gene, leading to a deletion of 50 amino acids in lamin. The shortened protein, aptly named progerin, leads to disruption of the nuclear membrane. Normally, the maturation of lamin A requires cleavage of 15 amino acids, including a farnesyl group. In HGPS, farnesyl cleavage fails to occur, causing disruption of the nuclear lamina, DNA damage that leads to dysregulation of gene transcription, and impaired DNA repair (12). The two teams went on to create a transgenic mouse model of HGPS (13). The carotid and femoral arteries of these mice had no smooth muscle or endothelial cells, but instead showed considerable collagen and proteoglycan deposition, similar to what had been observed in patients with this condition (14). The administration of a farnesyl transferase inhibitor (FTI) to the transgenic mouse model prevented both the onset and progression of cardiovascular disease (15). These observations, as well as the availability of an orally active FTI, provided the stimulus for conducting clinical trials of this agent in HGPS. These trials are ongoing.

How and why did HGPS, a devastating but very rare event, become a focus of intense interest of two important laboratories? It is because it may shed some light on the normal biology of aging. The premature aging that is characteristic of both HGPS in children and of normal aging in adults may share a common molecular and cellular basis (14). The progressive telomere loss in senescent normal cells leads to the production of progerin. This altered protein has been found in the skin of normal elderly persons and in the diseased coronary arteries of non-HGPS individuals, suggesting that it may play a role in the progression of coronary artery disease in the elderly.

Director, NHLBI

In 2005, Betsy became Director of the NHLBI. One of her first actions was to set up a vigorous communication plan with her many anxious constituents. It was multipronged, and involved special articles in the journals of the cardiovascular, pulmonary, and blood communities; presentations at their national meetings; and countless one-on-one or small-group meetings. The conversations were bidirectional. She kept her finger on the pulse of grantees, present and future, as well as on the leaders of professional societies and key members of the Congress and their staffs.

Betsy published a series of "Notes from the Director." In the first of these, she presented her vision of the future, very clearly and simply: "I believe strongly that we must protect and nurture investigator-initiated research. The NHLBI will continue to invest in the most talented scientists conducting the highest-caliber research" (16). A lot of people were relieved to learn of this commitment from the new Director. It was also a time when concern had arisen about the future of young investigators. Betsy paid more than

Figure 4
Sampson Gordon Berns, a patient with Hutchinson-Gilford progeria syndrome. Figure reproduced with permission from *Lancet* (22).

Figure 5
The formal start of the Global Alliance for Chronic Diseases, with Elizabeth G. Nabel signing for the US. Figure reproduced with permission from *Science* (20).

lip service to the support of this critically important group. She wrote: "[W]e need to create a better springboard to launch junior investigators into independent careers . . . . The Institute has increased the RPG payline for new investigators by 5 percentile points . . . . [T]he NHLBI will enable an expedited review for new investigator RPG applications . . . ." (17). I believe that the NHLBI was the first institute to take this important action.

Under Betsy's strong and decisive leadership, the institute increased support of studies of the genetic mechanisms of disease, genomic analyses of population-based cohorts, and the use of genomics to guide diagnosis and treatment (18). The formation of the Progenitor Cell Biology Consortium brought together 18 research teams across heart, lung, and blood fields to focus on basic studies of progenitor cell biology. The Cardiovascular Cell Therapy Research Network, established by Betsy, initiated clinical trials of cell-based therapies for ischemic and other heart diseases. Alan Guttmacher, Betsy, and Francis Collins established the database of Genotypes and Phenotypes, termed dbGaP (19), the first open-access database at the NIH. It included data obtained from all NIH-supported Genome-Wide Association Studies as well as the Framingham and Jackson Heart Studies, and the Women's Health Initiative. dbGaP remains in full operation and has been a model for data sharing with other biomedical research funders.

Betsy considered the NHLBI Directorship to be a platform from which she could advocate for public health issues. She focused on three areas: global health, women and heart disease, and obesity. She became one of the founders of the Global Alliance for Chronic Diseases, including cardiovascular disease, cancer, type 2 diabetes, and chronic respiratory diseases, conditions that cause more than half of all deaths worldwide (Figure 5 and ref. 20). The alliance is a partnership between investigators in a developed country and investigators in a developing country. It coordinates a consortium of research projects on hypertension prevention and control. Currently, it is considering responses to an RFP for diabetes and is preparing an RFP in chronic lung diseases.

Heart disease has been the most common cause of death in women in the US for many years. However, until relatively recently, heart disease was seen by the public as primarily a man's disease. Betsy brought together several public and private organizations and developed the Heart Truth campaign, in which the Red Dress became the symbol for women and heart disease. Betsy engaged First Lady Laura Bush to be the National Ambassador of the Heart Truth campaign. Mrs. Bush and Betsy did many events together, both at the White House and around the country, to raise awareness of the importance of heart disease to women. This campaign has been one of the most successful health awareness programs ever.

President, Brigham and Women's Hospital; Professor of Medicine, Harvard Medical School

These are challenging times for teaching hospitals. Given the chaos in the health care field, especially in reimbursement for services provided to the uninsured or underinsured, leaders of these institutions are increasingly judged by the bottom line they achieve. Most of these leaders have backgrounds in hospital administration, business, and finance, and while they often talk a good game about academic values, when the chips are down, their primary concern is with the bottom line. Presidents of the Harvard teaching hospitals are particularly challenged because in addition to hospital operations, they are also largely accountable for the research and postdoctoral training programs in their institutions, and they are expected to be academically qualified to be full professors at the medical school.

Those of us who knew Betsy during her six years of training at the Brigham knew that a deep appreciation of science had been "baked" into her DNA — because her father had been a scientist. The entire hospital community was thrilled when she assumed the presidency of the hospital four and a half years ago. It had not been a single step "from Resident to President," as some have joked. As summarized above, there had been many accomplishments and rungs on her professional ladder between the time that she left the Brigham and returned. However, in addition to having a leader that shared their highest academic aspirations, our faculty needed someone whose feet were planted solidly in the fiscal realities of the day, and who understood the maxim "no margin, no mission." Betsy had shown as Director of the NHLBI that it is possible to prioritize expenditures and move the organization forward despite a static budget.

Probably the most important task of a hospital President in our system is the selection — in concert with the Dean — of new department chairs and to review the performance of the sitting chairs. Thus far, Betsy has created two new academic departments, has recruited their chairs, and has recruited three of the 15 chairs who have retired; she is completing the searches for a fourth and

fifth. Betsy has shown that she is a discriminating judge of "academic horseflesh." The new chairs are physician-scientists of note, and we are confident that other new chairs in the "Nabel era" will be of similar caliber.

Betsy is transforming the Brigham by leading the effort to develop multidepartmental, multidisciplinary centers. Within weeks of her arrival, she began work on a Heart and Vascular Center, which is now operating quite smoothly and successfully. A Neurosciences Research Center is next, to be followed by a Musculoskeletal Research Center. She is successfully gathering the resources to enhance the Brigham's academic mission and is now constructing new facilities to replace many of our laboratories, which, while of excellent quality, are scattered in leased space around the campus. In addition, she has acquired the last parcel of unoccupied land in the very congested Longwood area for future development. An important accomplishment has been enhancement of the relationship between the Brigham and the Dana-Farber Cancer Institute, which is led by Ed Benz — like Gary Nabel, an alumnus of the Brigham research residency and a distinguished member of this Association. Perhaps most remarkable of all, Betsy has coauthored a paper with Peter Slavin, the President of the Massachusetts General Hospital. This is a historic first, and reflects the close collaborations between these Harvard Medical School–affiliated hospitals within the Partners HealthCare system (21).

Betsy's numerous honors include membership in the Institute of Medicine, on whose Council she served; Fellowship in the American Academy of Arts and Sciences; as well as honorary doctorates from distinguished universities in the US and abroad.

The Kober Medal, the Association of American Physicians' highest honor, was awarded for the first time in 1925. Since then it has been awarded to 85 men and just two women, Drs. Helen Taussig and Helen Ranney. This year it is awarded to Dr. Elizabeth G. Nabel, a brilliant scientist, an inspiring teacher and talented mentor, a strong leader of academic and research institutions, and a vigorous proponent of science and global medicine.

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Acceptance of the 2014 Association of American Physicians George M. Kober Medal

Giving back

Elizabeth G. Nabel

Thank you, Gene. To be honest, I never thought I would be considered for this award. I was totally surprised when Warner Greene called me. I am deeply honored, and I thank you, Larry Jameson, the AAP, my colleagues, and of course my family.

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Dr. Eugene Braunwald

I cannot begin to express my gratitude to Gene Braunwald. Gene, you have been my hero, since 1981, when as an intern, I presented cases to you in morning report or rounds. Your commitment, your intelligence, your standards, and your values have shaped and transformed my life in medicine.

Several years ago, Gary and I hosted Gene at our home in DC, along with the Sarnoff fellows. Chris and Elisa were in high school at the time. I recall introducing Gene to Chris and indicating that Gene was his academic grandfather. I said to Chris, "If Gene didn't have such a terrific training program, your Dad and I would never have met!" So, Elisa and