On the Frontiers of Cardiology:

AN INTERVIEW WITH EUGENE BRAUNWALD, M.D.

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Eugene Braunwald, MD

Those who attempt to sum up the contributions of Eugene Braunwald, M.D., to research in cardiology run the risk of sounding hyperbolic. Introducing a recent two-part profile, *Circulation Research* Editor-in-Chief Roberto Bolli describes Dr. Braunwald as “the greatest scholar in contemporary cardiovascular medicine.” While Dr. Braunwald himself deflects such compliments by insisting on the sheer number and diversity of individuals who have contributed to

the development of cardiology over the past several decades, it is certainly the case that he and the TIMI Study Group (www.timi.org) of which he is chairman have played an invaluable role in shaping the current practice of cardiovascular medicine and also laying the foundation for future breakthroughs in cardiovascular research and treatment.

As part of its 25th anniversary celebration in 2009, the TIMI Study Group published *The TIMI Trials, 1984–2009*, which documents the group’s first 50 clinical trials and the significant lessons learned through these studies. TIMI projects include clinical registries and trials ranging in scope from phase 1 to phase 4 research and varying in size (the largest involves more than 100,000 patients). As Dr. Braunwald writes in his preface to *The TIMI Trials*, all TIMI efforts are conceived as a means to “enhance the care of patients with coronary artery disease.” From TIMI 1 to TIMI 56 and beyond, Dr. Braunwald and the TIMI Study Group have also achieved the complementary goals of expanding understanding of cardiovascular disease and training new generations of clinical investigators to continue research in cardiovascular medicine.

TIMI 1: From Concept to Clinical Trial

The first TIMI seeds were planted in the 1950s during Dr. Braunwald’s tenure as a postdoctoral fellow at the National Heart Institute (later to become the National Heart, Lung and Blood Institute, or NHLBI) of the National Institutes of Health (NIH) in Bethesda, MD, where Dr. Braunwald worked in the laboratory of physiologist Stanley Sarnoff, M.D., to investigate the determinants of the heart’s consumption of oxygen. When Dr. Braunwald was promoted in 1960 to Chief of the institute’s Cardiology Division, where he split his time between clinical work and research, his lab continued these studies. “By 1967,” he reports, “we had identified the three principal determinants of oxygen consumption”: tension development, velocity of contraction, and frequency of contraction.

When Dr. Braunwald left the NIH in 1968 to become the founding Chairman of Medicine at the University of California,

San Diego, he was joined in this relocation by several members of his NHLBI lab, including Drs. John Ross, James Covell, and Burton Sobel, and their continued research eventually yielded the discovery, described in a 1971 paper, that the size of a myocardial infarction could be influenced by controlling the amount of oxygen required by the heart and the amount of oxygen that could be delivered to the ischemic myocardium. “That, of course, was a very exciting finding,” Dr. Braunwald recalls, “and that pushed me in the direction of devoting a lot of effort in subsequent years toward applying this [discovery] clinically.”

It took about a decade, during which Dr. Braunwald moved to Harvard Medical School and its teaching hospital affiliate, Brigham and Women’s Hospital in Boston, MA, again as Chairman of Medicine, before such clinical applications became possible. By the mid-1980s, the efforts of multiple research groups, including the Brigham group that he headed, had yielded two important developments: the discovery that lytic agents could be administered intravenously rather than directly into the coronary arteries; and the creation in the youthful biotechnology industry of a recombinant form of tissue plasminogen activator (tPA), which serves as a lytic agent. The NHLBI turned to Dr. Braunwald, now external to the institute, to lead a clinical trial that could demonstrate what practices and therapies yielded the best outcomes for patients.

The Thrombolysis in Myocardial Infarction Study Group, which would come to be known as the TIMI Study Group, launched in 1984 and involving 14 hospitals, compared a 40-year-old drug, streptokinase, with the 2-year-old tPA. The study demonstrated tPA’s superiority to streptokinase, and the TIMI data contributed to tPA’s approval by the Food and Drug Administration.

Changing the Scene

The success of the first TIMI trial created a valuable momentum that the TIMI group maintained as proposed new therapies and interventions continued to emerge. Asking whether, once appropriate patients had received tPA, they should all immediately receive an angioplasty, TIMI 2 revealed that in fact a more conservative approach yielded comparable results, and, at the time, with less risk. TIMI 3 went on to explore tPA and invasive and conservative strategies in patients with unstable angina, assessing the outcomes for registry patients based on factors such as race, sex, and age.

By 1986, the research into the role of fibrinolytics that had developed from the work begun 30 years earlier in Dr. Sarnoff’s laboratory on the balance between myocardial oxygen supply and demand was largely complete. Since then, the TIMI Study Group has used its early findings as a foundation for ever more ambitious studies. “We’re still studying myocardial infarction,” Dr. Braunwald emphasizes, but the group is now looking at

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myocardial infarction's connections to diabetes and studying the effects on infarction of intensive lowering of cholesterol levels.

This broader perspective is epitomized by studies such as TIMI 22, also known as PROVE-IT (Pravastatin or Atorvastatin Evaluation Infection Therapy). In this trial, led by Dr. Chris Cannon, M.D., researchers compared the effectiveness of two statins, pravastatin, administered daily at a standard dose, and atorvastatin, given in a larger daily dose as an intensive therapy. The results, Dr. Braunwald

says, "changed the scene." PROVE-IT-TIMI 22 did more than establish that intensive therapy was helpful for patients who had recently experienced an acute coronary syndrome; it also demonstrated that it was safe and even beneficial for such patients to have their low-density lipoprotein (LDL) cholesterol reduced significantly, far below the guideline-recommended 80–100 mg/dL. In fact, Dr. Braunwald notes, the study showed that lowering LDL levels to around 65 mg/dL "produced about a 25% reduction in the adverse outcomes of death, myocardial infarction, and stroke" and succeeded in establishing a new and lower standard towards which doctors and their patients could work.

The success of PROVE-IT-TIMI 22 begged the question: could one safely achieve even lower LDL levels? A retrospective analysis of the data by TIMI co-investigator Dr. Stephen Wiviott, M.D., suggested that some patients had reached LDL levels lower than 40 mg/dL. "If anything," Dr. Braunwald observes, those patients "had an even greater reduction in adverse cardiovascular outcomes." The TIMI Study Group is now embarked on the follow-up study, aptly named IMPROVE-IT, in collaboration with colleagues at Duke University in Durham, NC. Dr. Braunwald reports, "We haven't hit bottom yet," and each step taken to lower LDL cholesterol has improved patient outcomes.

While TIMI has been Dr. Braunwald's major focus, he has also carried out large clinical trials with Dr. Marc A. Pfeffer, M.D., including the SAVE (Survival and Ventricular Enlargement) trial, the first trial that demonstrated the reduction of mortality postmyocardial infarction with an angiotensin converting enzyme inhibitor.

A Career in the Service of the Public

Dr. Braunwald is drawn to the combination of intellectual excitement and potential for human benefit that these projects offer. In his youth he would not have foreseen his career as a clinical researcher, but he was attracted from an early age to the idea of an academic career. While he was still young, he could imagine that such a career might develop in his native Vienna, but Nazi Germany's annexation of Austria in 1938 forced the Braunwald family to flee, first to England and ultimately to New York. In spite of this adversity and the financial hardship that his family faced initially in their adopted country, the young Eugene Braunwald thrived academically and attended the prestigious Brooklyn Technical High School with the intention of becoming an engineer.

As the country and the world emerged from under the shadow of World War II, engineering stood out as "a pretty advanced applied science," Dr. Braunwald recalls. In stark contrast, he says, medicine was "groping." The role of the doctor too often consisted of standing by patients and watching them decline and die.

While engineering looked like a good prospect, Dr. Braunwald was ultimately lured into medicine by its untapped potential. "There was a long way to go," he says, and he saw "tremendous opportunities" to improve patient care. "That was more in the service of people than engineering."

Driven by this idea that medicine could be improved, Dr.

Braunwald was one of only two students in his medical school class at New York University in New York City who performed extended research. During his

study, he worked in one of the country's first cardiac catheterization laboratories, where, he says, one "really analyzed the heart as a pump," and his experience there demonstrated that cardiology was the discipline that effectively combined his engineering interests with his medical focus.

During his medical training, Dr. Braunwald says he received "a lot of positive reinforcement" and had the opportunity to work for excellent people, including Nobel Prize winner Dr. Andre Cournand at Columbia University in New York, NY. "They stimulated me," Dr. Braunwald observes. "A couple of things that we worked on *worked*, so to speak." The ensuing years bore out his prediction that medicine would see "tremendous advances."

Today, given his long and productive career, he has an acute awareness of how far cardiology, in particular, has come. Dr. Braunwald estimates that in 1952, the year that he graduated from medical school, 30% of patients with acute myocardial infarctions died during their initial hospital admission. Another 20% died of heart failure within the following year, and, given the inability of many individuals to reach a hospital, he suspects that the total 1-year mortality rate was around 75%. Considering the developments that have yielded a dramatically different outlook for patients with myocardial infarctions today, Dr. Braunwald reflects, "It has really been so exciting to have been involved in this revolution in care."

Bedsides All Over the World

While participating in this medical revolution, Dr. Braunwald has watched clinical research expand, not just in the sophistication of its methodology and tools but also in its geographic reach. "What has been such a thrilling experience for me is to have participated in this over a 55-year period, beginning at the bench and moving ... to the bedside," he says. "Now the 'bedside' is all over the world."

The TIMI Study Group has grown to reflect this new global reality. After 26 years and more than 55 trials, most of the ongoing TIMI trials involve more than 10,000 patients each, and the group works with more than 1,400 hospitals in 46 countries on every continent. To facilitate collaboration among the many different and geographically diverse sites, Carolyn McCabe, who has been with the group since TIMI 1 and who has served for the past 15 years as the TIMI Director of Operations, introduced a disciplined organizational structure managed on the ground by active lead investigators—"not just figureheads," Dr. Braunwald stresses—in each participating country. These individuals, who are modestly compensated for their work, take part in regular in-person meetings and conference calls in which they report on the performance of the sites under their jurisdiction. Although most of the TIMI trials begin in North America, they have spread

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across the globe to locations in Eastern and Western Europe, North Africa, South America, and now Asia.

As the TIMI Study Group has grown in size and geographic make-up, it has also built up its technical skills and services. At the time of TIMI 1, the only core laboratory service the group could provide was angiography. Now, Dr. Braunwald says, as newer techniques are becoming important and available, “we are adding people with particular skills.” As examples, he cites the group’s active biomarker section under Dr. David Morrow, M.D., and the growing genetics laboratory led by Dr. Marc S. Sabatine, M.D., observing, “If you stay with old technology, you get left behind, and you really cannot continue to contribute.”

This is Research

The global reach, the level of activity, and the number of trials that the TIMI Study Group now regularly maintains (currently eight trials) have been enabled by the recruitment of cardiologists, statisticians, and essential staff. At the TIMI home base in the Cardiology Division in the Department of Medicine at Brigham and Women’s Hospital, physician scientists serve as principal investigators who are each involved in at most two trials and are assisted by a research fellow. Each trial is also assigned at least one experienced project manager and several research assistants.

As a part of Brigham and Women’s Hospital, the group is not for profit. “We’re totally an academic enterprise,” Dr. Braunwald says. “There are no conflicts of interest.” He notes that the group works with industry and respects industry, “but we are not of industry.” All TIMI physician scientists are salaried full-time faculty members of Harvard Medical School, and most of them devote a majority of their time to the TIMI Study Group. “Usually,” Dr. Braunwald explains, “they’re 80% [research in] TIMI and 20% clinical.”

This division of responsibilities is important to Dr. Braunwald: he wants to be sure that TIMI principal investigators have the clinical experience and perspective to help them understand the issues the group is researching, but he also feels strongly that clinical researchers need time to reflect on their research. He says, “I have seen—in other research groups in our institution and elsewhere—when the investigators are under such pressure to see patients that they can’t sit down to think, that they don’t sit in an informal way with each other to bounce ideas around.” For Dr. Braunwald, discussion and reflection are an integral part of the research process. “This is research,” he insists. “It happens to be clinical research, but it’s just as serious as if you were doing the most fundamental biology, and it needs that kind of time.”

An Intellectual Enterprise

Dr. Braunwald’s comparison between clinical research and basic biology is deliberate, a manifestation of his frustration with what he calls academia’s “reductionist approach” in which the more basic one’s research is, the greater its perceived importance. He laments the frequently held belief that “an organ is more important than the entire organism, that ... a tissue is more important than an organ, that a cell is more important than a tissue, that a constituent of the cell is more important than the cell, that the genetic material

is more important than the constituent, and that the structure of the gene is more important than the gene,” a value system that “puts clinical research pretty close to the bottom” of the research food chain. Dr. Braunwald struggled with this issue during his 28 years of chairmanship of three departments of medicine.

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While the situation has improved from three decades ago, he is still troubled by the way this mindset informs much of academic life from institutional promotions to NIH funding.

Another impediment to a clinical research career is the sheer length of training required. The progression of college, medical school, internship, residency, clinical fellowships, and lab work means, Dr. Braunwald says, that “you’re in your thirties before you finish your training.” This training regimen puts a physician scientist about 8 years behind a similarly trained Ph.D. scientist, when the former has family obligations that will require a higher salary that must come from an already small pool of funding. To ensure that individuals are not discouraged from pursuing clinical research, Dr. Braunwald suggests offering a research track that begins during internship and allows trainees to do both clinical work and conduct research and thereby grow simultaneously “in both dimensions.” This track, introduced by Dr. Braunwald at Brigham and Women’s Hospital, boasts some spectacular successes.

Yet another challenge to translational and clinical research, Dr. Braunwald observes, is the time the research takes. A researcher may work for 3 to 5 years on a trial that ultimately yields neutral results, and, Dr. Braunwald argues, “You can’t build a career on that.” The TIMI approach to this difficulty is to see clinical research as, in the TIMI Chairman’s words, “a total intellectual enterprise.” The TIMI Study Group focuses on large trials, invests in core laboratories, and develops hypothesis-driven research that can enhance patient care but also provide scientific information. If the trial results are neutral, “that doesn’t mean that you have wasted [several] years of your life,” Dr. Braunwald explains. “You’re gambling all or nothing if you just do a clinical trial and then count bodies at the end.” Instead, he suggests, it is important to be able to ask “How can we use the trial as the platform to unravel how the genetic makeup influences the manner in which persons respond to the intervention?”

Enormous Mountains

If these are the logistical challenges facing clinical research at large, Dr. Braunwald also sees significant scientific challenges in the near future for cardiovascular research specifically, “enormous mountains” that need to be scaled if patient outcomes are to be further improved. He remarks, “I think that one of the frontiers in cardiology is to come to grips with high-density lipoproteins (HDL).” He wants to see how HDL levels can be safely increased and to investigate whether such increases offer the same beneficial effects as lowering LDL levels. Given that atherosclerosis, the build-up of plaque inside the arteries, represents the basis for 80–90% of heart disease in North America and other developed countries, the question Dr. Braunwald poses is a significant one. He says, “If the answer is positive—and that’s a big if—then I think we can do away with atherosclerosis as we know it today.”

Another area in which Dr. Braunwald sees the need for significant progress is in pharmacogenomics. In the future, he says, “I think we will be selecting drugs and drug dosages based on genetics.” The TIMI Study Group is in the early stages of investigating these issues as well. TIMI physician scientists led

by Dr. Jessica L. Mega, M.D., and Dr. Marc S. Sabatine, M.D., recently published a retrospective pharmacogenetic analysis of data from TIMI 38—known as

TRITON, or “TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel”—that describes the genetic variance of cardiovascular patients who do not respond adequately to the common antiplatelet agent clopidogrel. The overarching goal of this and other studies is to gain a better appreciation of what drugs and what doses are appropriate for individual patients and to avoid giving every patient the same dose, a strategy that, Dr. Braunwald argues, seems overly simplistic, given that “we know we’re all different.”

The Thrill of the Chase

The passion with which Dr. Braunwald speaks of these next frontiers in cardiovascular medicine testifies to his determination to continue to contribute as much as he can to discoveries in these areas. This drive to do more and expand even further an already significant legacy explains—at least in part—the success and longevity of Dr. Braunwald’s career and the spirit that underpins the larger TIMI enterprise.

Over the years, in his work, Dr. Braunwald has been guided by a few basic principles. For the individual researcher as for the larger research group, he believes that research is best accomplished when performed for its own sake. Although he admits it is possible to conduct and even succeed at research with an eye to getting a better job, better pay, or more influence, he feels that pursuing a particular research question because it is “fashionable” does not yield the best results in the long run. The raises and promotions will come to those who have true curiosity, Dr. Braunwald argues, but those rewards should not be the primary motivation for conducting research: “I think the people who really contribute are the people for whom research is [not a means to an end but] an end in itself.”

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For a long-term research career, Dr. Braunwald advises, “you have to feel the thrill of the chase. To me, working on these problems has been really like a hunt.” Nevertheless, he cautions that “people have to realize that the joy [of discovery] doesn’t come along very often, at least for ordinary mortals like me.” Many studies will have

neutral results, but, he contends, “that’s part of it—you’re on the hunt. It’s thrilling to chase after information which could potentially help hundreds of thousands

of people.” That, as Dr. Braunwald well knows, is precisely what is at stake in cardiovascular research.

As a physician scientist who in his research and leadership of the TIMI Study Group has fostered discoveries that have helped a vast number of people, Dr. Braunwald already has much to be proud of. Nevertheless, rather than resting content with his existing legacy, he draws from the accomplishments of his long and prolific career the motivation to keep asking questions about how to improve patient care and continue launching the trials that can provide some answers. After all, says Dr. Braunwald, “There’s nothing that is better than a sense of accomplishment to drive you to do more.”

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SELECTED RESOURCES

1. Williams R. Eugene Braunwald: Escaping death and prolonging lives [part 1]. *Circ Res.* 2010; 106: 1668–1671.
2. Williams R. Eugene Braunwald: Escaping Death and Prolonging Lives [Part 2]. *Circ Res.* 2010; 106: 1786–1788.
3. Braunwald E, McCabe C. *The TIMI Trials, 1984–2009: 25 Years of Clinical Trial Research.* Boston, MA: TIMI Study Group; 2009.
4. Maroko PR, Kjekshus JK, Sobel BE, Watanabe T, Covell JW, Ross J Jr, Braunwald E. Factors influencing infarct size following experimental coronary artery occlusions. *Circulation.* 1971; 43: 67–82.
5. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med.* 1992; 327: 669–677.
6. Mega JL, Close SL, Wiviott SD, Shen L, Walker JR, Simon T, Antman EM, Braunwald E, Sabatine MS. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet.* 2010; 376(9749): 1312–1319.