Impact Through Discovery: A Global Challenge
Presidential Address at the American Heart Association 2011 Scientific Sessions

Gordon F. Tomaselli

“He who has health has hope; and he who has hope has everything.”

—Arabic proverb

Good afternoon; on behalf of the American Heart Association and American Stroke Association, welcome, colleagues and friends from around the globe, to Scientific Sessions 2011. Whether you are in clinical care, research, or education, I thank you for joining us. It is truly an honor to be in the company of those engaged in the noblest of endeavors, the improvement of human health. I would like to take a moment to personally thank those of you joining us from around the world. Approximately 100 nations are represented at Sessions this year. That is only fitting because global prevention of cardiovascular disease and stroke is a major focus of our meeting. To succeed in global prevention, we must all be part of a united front.

I am going to discuss how our research world reaches far beyond the laboratory and the clinical setting. We will explore the crucial differences it makes in human health, in addition to how vital biomedical research is to economies and societies around the world. And we will discover some of the perils we will face globally if we do not find ways to fund more research.

The community of cardiovascular practitioners and researchers has much to be proud of. The trends in mortality from cardiovascular disease and stroke having increased over the first half of the past century have significantly declined since the 1960s. Much of the decline is in the reduction in mortality from coronary heart disease. The decline is attributed to dramatic advances in the acute and chronic treatment of atherosclerotic coronary artery disease. The recognition of the importance of control of risk factors such as tobacco use, blood pressure, cholesterol and glucose control, diet, and exercise have resulted in improvements in both primary and secondary prevention of coronary artery disease. Despite these advances, heart disease and stroke remain the number one and number four killers of Americans and the leading cause of death in the world. Cardiovascular diseases. The discoveries we need for this fight are most likely to come from a broad range of scientific research.

Some nations recognize the importance of this more than others. In this country, I am very concerned about the decrease in research support in general—and the declining share of publically funded research across science disciplines. This is extremely troubling for future innovation. If the history of science and medicine has taught us anything, it is the difficulty of predicting the next breakthrough or paradigm-shifting discovery.3

The contemporary era of investment in biomedical research has produced a number of breakthroughs that have fundamentally changed the way we treat patients with cardiovascular disease and stroke. Many of these breakthroughs were made possible by complementary public and private funding. What is notable about many of these research milestones such as cardiac transplantation, anticoagulant and antithrombotic therapy, cardiopulmonary bypass, and the links between dietary fat, cholesterol, and atherosclerosis (Table) is that nearly all are derived from a basic science finding that was translated to the bedside.

My home institution’s history features a significant number of important advances. Many Johns Hopkins investigators were funded by the American Heart Association and the federal government, including Peter Agre, the discoverer of

Table. Advances in Cardiovascular Medicine

| Anticoagulant and antithrombotic therapy |
| Cardiopulmonary bypass |
| Cardiac catheterization |
| Cardiac pacing |
| Cardiopulmonary resuscitation |
| Defining the relationship between dietary fat and atherosclerosis |
| External defibrillation |
| Functional genomics |
| Heart transplantation |
| Regenerative medicine |
| Stem cells |

Moreover, awareness and management of risk factors are low, particularly in the young and minorities who are disproportionately affected by adverse health factors, have less access to care, and are less aware and thus less likely to be treated. We have an obligation to our patients, our countries, and to ourselves to discover new ways to promote and improve health, reduce health care costs, and fight the leading cause of death in the world, cardiovascular diseases. The discoveries we need for this fight are most likely to come from a broad range of scientific research.

From the Department of Medicine, Division of Cardiology, Department of Cellular and Molecular Medicine, Johns Hopkins University, Baltimore, Maryland.

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Correspondence to Gordon F. Tomaselli, MD, Department of Medicine, Johns Hopkins University School of Medicine, 720 Rutland Ave, Ross 844, Baltimore, MD 21205. E-mail gtomasel1@jhmi.edu (Circ Res. 2012;110:12-16.) © 2012 American Heart Association, Inc.

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aquaporins. Among the other innovators were the investigators who initiated the development of the contemporary management of congenital and heritable heart and vascular disease.

Johns Hopkins has been at the center of many seminal developments in the management of sudden cardiac death, which is my own area of interest and investigation. In fact, the modern era of cardiopulmonary resuscitation began at Johns Hopkins. That is where the landmark development took place in the 1950s—when William Kouwenhoven, James Jude, and Guy Knickerbocker, who were studying cardiac defibrillation, resuscitated a dog using chest compressions followed by open chest defibrillation. Cardiopulmonary resuscitation and defibrillation are obviously major advances, but far from perfect solutions for sudden cardiac death (SCD). The work of these men was soon followed by another critical advance, the development of external defibrillation.

Although defibrillation was highly effective for the treatment of cardiac arrest, defibrillators were rarely available for most patients who needed them. What was really needed was not just a small portable defibrillator, but one that could automatically detect an abnormal cardiac rhythm and correct it on its own. This was a revolutionary idea at the time, discounted by many and at times ridiculed. But one tireless scientist believed in it. His name was Michel Mirowski—and I am proud to say that I currently hold the chair named in his honor at Johns Hopkins. Mirowski was a remarkable man. He fled Nazi Germany as a teenager and was the only member of his family to survive the Holocaust. He studied medicine all over the world and was driven to invent the internal cardioverter defibrillator (ICD) by the tragic death of his mentor, Dr Harry Heller. This inspired Mirowski to create the International Classification of Diseases without significant financial support but with plenty of determination. He and colleagues, including Morty Mower, started developing it from concept to clinical use while working at the Sinai Hospital in Baltimore, Maryland. In 1980, it all paid off when Dr Levi Watkins performed the first human implantation of an ICD at Johns Hopkins. Mirowski saw thousands of lives saved by his breakthrough before his death in 1990.

It is instructive to consider Mirowski’s story in the context of publically funded research. How many lives could have been saved throughout the 1960s and 1970s with government support of Mirowski’s cutting-edge work? People were dying throughout the world; one man had an idea that might save them. Yet his idea did not garner significant financial support. I want you all to remember this story when you are urging government agencies to fund more research. There may well be more Michel Mirowskis out there somewhere—investigators who only need a financial jump-start to save thousands of lives.

International Classification of Diseases technology is without question the first line of therapy for survivors of sudden cardiac arrest and patients at high risk for SCD. Of course, the International Classification of Diseases provides expectant therapy. Minimizing risk and prevention of SCD altogether is a far preferable strategy.

In an effort to prevent rather than promptly treat sudden cardiac arrest (SCA), research from around the world, including work from our own laboratory, has provided insights into the fundamental nature of excitability of the heart. It also provided the foundation for another important step, the pharmacological treatment of cardiac arrhythmias, which are the primary cause of sudden cardiac death in most cases. Detailed clinical investigation over decades highlighted not only the important benefits but also the limitations of drug therapy for the prevention and treatment of sudden cardiac death.

The confluence of research in physiology and the genetic revolution have contributed enormously to our understanding of the molecular basis of inherited and acquired cardiac arrhythmias. An intriguing example comes from our own laboratory. We were evaluating a patient with syncope whose abnormal electrocardiogram (ECG) suggested he was at risk for a serious heart rhythm problem. We diagnosed Brugada syndrome with a type 1 ECG and a mutation in the cardiac sodium channel gene, SCN5A. The mutation caught our attention because it was in a region of the channel that is involved in regulating channel function in response to stressors. Some of these stressors may be triggers for lethal arrhythmias. We created DNA vectors containing SCN5A carrying the disease-causing mutation. We expressed and isolated the mutated channel peptide. Unlike the wild-type peptide, the mutated channel peptide could no longer be modified by protein kinase A, one of the main enzymes that is activated by the sympathetic nervous system. We then expressed the channels in tissue culture cells and recorded currents using patch clamping. We found that under basal conditions, the mutant currents were the same as currents through wild-type channels. But with stress, wild-type channels exhibit a robust increase in the current that may be protective against arrhythmias and is not present in the mutant channel. This is consistent with the clinical situation in this patient, and in others with this syndrome. Arrhythmias are typically triggered in patients with Brugada syndrome when there is stress of various kinds, prominently fever.

It is now possible to take fibroblasts from such patients and reprogram them to become heart cells. These are called induced pluripotent stem cells. Reprogramming is a very powerful technique that allows us to study the effects of a human mutation in its native context. Induced pluripotent stem cells are a platform for drug testing in a human cellular model and may, in the future, be a method applied to regenerative medicine. This is just one example of the enormous potential of research that ranges from the clinic to the bench and back.

But why is it that this young man had syncope and an abnormal ECG while his sister and mother who carried the same mutation were completely without symptoms or the ECG signature of the syndrome? This question reinforces the concept that even the most straightforward disease mechanism is an incredibly complex systems biology problem. The reasons are the enormous dynamic range of the expressed genome and the incredible connectivity of apparently divergent pathways in the human body. Appropriately, a major effort in the postgenome era is applying systems biology methods to understanding the clinical implications of rare and common variations in the human genome.
There are a number of other gaps in our understanding of the mechanisms of heart disease and stroke, translation of the science into practice, and the effect of diagnostics and therapeutics on the public health. Addressing these gaps will require more investment in research. But great possibilities lie ahead. Of course, exploring those possibilities can be very expensive. China, Japan, and the European Union have increased funding in recent years.\(^4\) The European Union recently voted for a 77% budget increase in innovation and research.\(^5\) Germany in particular has heavily invested in the biomedical research sector, serving as an example to other developed nations. However, in the United States, research funding has not kept pace. Importantly, in recent years, research spending by the U.S. government has decreased when measured in constant dollars. Even at the peak of the National Institutes of Health (NIH) budget-doubling period, when measured in constant dollars, this spending was only 0.23% of the gross domestic product,\(^6\) 6 In the past few years, the private sector share of research and development has increased.\(^7\) And while that may sound like private industry is going to save the day, that is not the case at all. In fact, it is folly to assume that any great extent of fundamental research funding will come from the private sector. For industry, short-term returns are critical, and those are far less likely in basic research. It is important to recognize the interrelationship between federally funded and private sector-sponsored research, the former often serving as the foundation and informing the latter, producing an effective and complementary synergy. However, if we wish to continue our progress against cardiovascular diseases, governments worldwide must increase research support.

What kind of return does the world get? The most obvious long-term gain is in human health. NIH Director Francis Collins told the U.S. Congress this year that NIH research has been largely responsible for a gain of approximately a year of longevity every 6 years since 1990. He noted that a child born in America today will live an average of 78 years—nearly three decades longer than a child born in 1900. Collins also testified about how significant research developments have helped prevent heart attacks, control blood pressure, reduce cholesterol, and dissolve clots.\(^8\) These developments have played a significant role in the decline of cardiovascular disease deaths in the United States. While it is still the leading cause of death, mortality rates from heart disease have decreased by 50% over the past 30 years alone.\(^2\)

The correlation between those death rates and federally funded research is profound. Manton and his colleagues at the Center for Demographic Studies at Duke University estimated the economic impact of NIH funding to tax revenues by considering mortality reduction and the decline in disability rates that resulted from research.\(^6\) They found increased funding directly and dramatically correlated to declining death rates for heart disease and stroke. They showed a similar correlation for declining cancer and diabetes deaths.

In addition, there is a noteworthy correlation with economic impact. Manton estimated the economic impact of NIH funding on tax revenues. He did this by considering the research-associated decline in mortality and disability rates resulting in a larger number of taxpayers. The total gain in tax revenue alone is estimated to be $885 billion over 10 years.\(^6\) These savings alone would nearly be enough to triple the NIH budget over the same 10 years. Estimating the additional economic value of healthier workers to the gross domestic product is difficult, and then there is still the direct economic benefit of the research work itself and Medicare savings. Adding it all together, an economic benefit of more than $1 trillion to the U.S. economy seems conservative.

The economic benefit of funding of research is clear and far reaching. Direct NIH funding produced approximately a half a million U.S. jobs in 2010. Sixteen states added more than 10,000 jobs. That means jobs and revenue to workers and their families, more tax revenue, and less cost to states to support the unemployed. This analysis does not even consider the economic impact of the research work itself.\(^9\)

A recent report by United for Medical Research considered the relative benefits of investment in research in the context of the current fiscal deficit. The deficit feedback effect of government spending describes the potentially deleterious effect of growing the deficit on private sector investment. However, there is good evidence that investment in basic research by the NIH, rather than shrinking private investment, serves as a catalyst for such investment by contributing to the intellectual and physical infrastructure that supports innovation. The spending on research is an investment, and not simple spending without return. This fact was recognized by a study of the bipartisan congressional Joint Economy Committee, which concluded in a report published in 2000,\(^10\) that federal and private investments in biomedical research are
complementary. An independent analysis by the National Bureau of Economic Research in 2009 concluded the each dollar of NIH research support led to a 32-cent increase in privately funded medical research emphasizing the same point.\(^7\)

The long-term benefit of federal research funding is clearly seen in the NIH’s impact on the medical and biotech sectors of the economy. Nearly a million U.S. citizens work in this wide-ranging sector, producing $84 billion in wages in 2008. In 2010, this sector exported $90 billion worth of various goods and services, including pharmaceuticals, medical equipment, and supplies.\(^9\) Investment in research leads to additional basic and important societal benefits, but these can be easy to overlook. This investment supports education and training—vital components in any society’s ability to thrive. Government investment enables new technologies and new economic sectors. The Internet, genetic engineering, and biotechnology are just a few examples.

There is room for debate about the magnitude of the economic benefit of investment in biomedical research, but in the final analysis investment in research not only is good for human health but also is a boon for national economics. A failure to invest, however, will have unfortunate consequences and economic benefits can easily disappear. Education would suffer because research supports and enhances technologies used directly in education and training. Research underwrites some of the cost of running universities and creates a highly trained and affordable workforce. From a science standpoint, large gaps in the knowledge base will remain and probably will grow. When funding becomes difficult, risk-taking in research and translation is stymied. And this slows the development of new diagnostics, treatments, and cures. A lack of funding means a loss of young investigators to other careers. Important opportunities are lost.

How can we, as clinicians, researchers, and educators, ensure this investment happens? We need to make ourselves more available as role models in science and medicine. This will enable us to find and develop the next generation of leaders in science and medicine. We must provide the motivational message that I think is at the core for most of us: science and medicine are remarkably fulfilling careers, and they enable us to positively impact humanity.

The American Heart Association clearly understands the importance of investing in research, and in fact has been the largest funder of research in cardiovascular diseases and stroke outside the federal government. We have a very rich history in this area, having funded 12 Nobel Prize winners. At the American Heart Association, we continually work to grow the research portfolio and increase financial support for investigators and supported more than $3.3 billion in cardiovascular and stroke research. Although the specific programs have changed since the first research committee was convened and led by Dr Louis Katz in 1949, the fundamental tenets remain consistent, to support the individual investigator, to recognize the importance of a wide spectrum of scientific disciplines, to promote collaboration, and to invest in young scientists. Indeed, within 15 years of the beginning of the American Heart Association research program, there was at least one funded American Heart Association investigator in every medical school in the United States and many outside the United States.

We must maximize our communication sources, including meetings such as Scientific Sessions, scientific journals, the Emerging Science Series, and social networking. The American Heart Association also has a role in accelerating translation of discoveries into clinical solutions. This can help us convince the public and policymakers about the importance of fundamental science. Our new Science Accelerator program can bring science and business together in an effort to more quickly turn research findings into clinical solutions. It will be collaborative, not competitive, with other programs such as the NIH National Center for Advancing Translational Sciences and other translational research programs at universities and in private sectors around the globe.

Perhaps most importantly, as a community we must become more vocal. We need to overcome our reticence to talk about the importance of our work. We tend to be analytic and reserved, but we must remember our larger obligation. We have to change the tenor of the conversation. We must make our elected officials understand that this investment builds healthy lives and healthy economies. We must all advocate for research support.

I believe science and professional organizations need to redouble our efforts to advocate for more government funding. I urge everyone here to get involved. Become a member of the American Heart Association and the American Heart Association’s “You’re the Cure” network. Or join another specialty science, medical, or professional society around the world. No matter where you are from, make sure your government knows how important this is. Get out there and be heard.

Moreover, both individuals and organizations have to think and work outside the traditional advocacy lines. A few years ago, Alan Leshner, chief executive officer of American Association for the Advancement of Science, proposed what he called a “glocal” science advocacy approach to complement and enhance traditional methods.\(^11\) I think the sentiment is correct, although there are many glocal approaches. In essence, the approach is to take a global issue and make it meaningful to a community or society at a local level. Operationally, scientists, physicians, and advocates recruit nonscience and medicine community members to promote and lobby elected representatives and other decision-makers, such as city councils, school boards, and other community groups. The approach is grass-roots advocacy and complements less frequent but regularly more massive advocacy efforts inside the Washington beltway. This will require a major engagement of the science and medicine communities in advocacy, education, and communication outside of the university, hospital, and laboratory. Indeed, all physicians and scientists need to recognize that advocating and educating the public about the work that they do is part of the job. This needs to be recognized and supported by leaders of schools, institutes, departments, and divisions, as well as peers.

Despite the enormity of this challenge, I have faith in the community where I have made my professional life and I...
remain optimistic. I come by that optimism and that faith in medicine honestly. You see, I am a physician and a researcher, but I also have benefitted personally from scientific discovery. Nearly 30 years ago, my mother, at age 49, needed a new heart. She was suffering from dilated cardiomyopathy complicated by sudden cardiac arrest. She waited 19 days, and it was a very tense time for our family; fortunately, she finally got a new heart. I remember her miraculous transformation; one day she was breathless from the simplest tasks like bathing, and a few days later she was riding an exercise bike. From there, Patricia Tomaselli went on to live a rich full life. She watched her children get married; she welcomed her grandchildren into the world. She saw those grandchildren graduate and even saw some get married. The extension of my mother’s life was to my family a true miracle. And it was possible because of science, discovery, and translation into practice. So you can see why I remain optimistic about the future of cardiovascular research despite the obstacles we face. I have personally experienced how research can save and improve lives.

References
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Gordon F. Tomaselli

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