A powerful perception that innovation has stagnated persists in the biomedical research community. In a series of Commentaries—three in this issue and more in future issues—diverse professionals engage in a critical dialogue on innovation that explores whether novel ideas continue to emerge and whether their implementation continues to create value. The authors also discuss ways to resuscitate innovation through new risk-benefit analyses, correction of funding follies, monitoring conflicts of interest, defining the roles of public and private institutions, and the teaching of innovation.

WHY INNOVATE?

A persistent mantra fueled post–World War II America—that the fostering and harnessing of novelty would create value, improve our quality of life, restore and prolong health, and provide security to society and growth to communities. Now grafted onto this engrained philosophy is a drop-off in the metrics of novelty and the perception that creation has stagnated—at least in biomedical science. As we are well into the 21st century, it behooves scientists and policy-makers not only to assess the accuracy of this impression but also to validate the long-accepted mantra. Specifically, all stakeholders must now determine whether truly novel ideas continue to emerge, whether value continues to be created by the implementation of these ideas, and, finally, whether pursuit of the former necessarily leads to the latter. This need for assessment immediately raises the question of how different professionals define innovation. To some, innovation is restricted to the conception of ideas; to others, the entrepreneurial spirit defines innovation—and many would hold that innovation is optimized when both are present (Fig. 1).

Irrespective of definition, the questions that surround the notion that innovation is at risk, especially in the United States and in particular in medicine, is of such concern to biomedical scientists and engineers that thought leaders from the widest spectrum of disciplines and domains gather to discuss them. In a series of Commentaries—three in this issue and more in future issues—diverse professionals dissect many of the elements of this critical dialogue on innovation: risk-benefit analysis, funding follies, conflicts of interest (COIs), the roles of public and private institutions, and the teaching of innovation. Most importantly, these comments coalesce around a debate of the two seminal questions posed above.

Fig. 1. The creation of technology.

IS INNOVATION REALLY DEAD?

If innovation is the creation of value, and value is measured not in dollars but in community health, security, and happiness, would we still decry a crisis in innovation? The age and health of the American population have increased and improved, respectively. Advances in cardiovascular medicine and technology have reduced morbidity and mortality from the leading cause of illness and death sixfold over the past 40 years. Thrombolytic agents and endovascular scaffolds (stents) in heart attack victims, implantable defibrillators, and valve replacement therapies have significantly reduced mortality in people with cardiovascular diseases. Cancer death rates fell 21% among men and 12.3% among women during 1991 to 2006 and continue to decline as a result of early detection, targeted cancer treatments, and a growing understanding of the connection between life-style and cancer risk, all of which make use of modern innovations. Advances in imaging and diagnostics have dramatically enhanced early detection, especially in breast and colorectal cancer. Racial disparities remain, and not all elements of society have equal access to technology—a problem in dispersal, not development.

Despite these strides, concern over innovation has risen exponentially: In 1980, there were only 168 papers on the topic available on PubMed; in 2011, the number will likely exceed 4000. Why? A collection of troubling statistics has caused growing anxiety among researchers who anticipate that current trends threaten the future of biomedical research and, therefore, the refinement of clinical medicine.
FEAR OF RISK STIFLES INNOVATION

Threatening future trailblazers. The current crisis in public funding of biology-related research threatens all spheres of biomedical creativity. The 2011 budget for the U.S. National Institutes of Health (NIH)—the United States’ prime public funder of biomedical research—is $30.7 billion, $260 million below the 2010 level (a 0.8% cut) (1). Contrast this number with the cost of maintaining the U.S. health care system [the United States spent ~$2 trillion on health care in 2008 (2)] or with expenditures for international security [the current Department of Defense base budget alone is >$500 billion, and the Department of Homeland Security budget is $43.2 billion (3)], and the relative investment in biomedical science is all the more staggeringly unbalanced. As the cost of science soars, the expendititure for federal grant awards for U.S.-based university research remains flat or, worse, dips into the negative; relative to cost, awards are lower than they have been since the foundation of NIH.

These conditions threaten an entire new generation of scientists and, therefore, innovation. Young investigators are forced into longer training periods and greater employment uncertainty. In 2007, the average age of an NIH-funded principal investigator was ~50 years, up from 38 years in 1980 (4). And between 1980 and 2007, the age at receipt of first R01 research project grant—the predominant mechanism for individual investigator research funding from NIH (5)—rose ~1 year of age for every four years of funding, from ~38 to 39 years to ~44 years of age for those with an M.D. or M.D.-Ph.D., and from ~37 to ~42 for those with a Ph.D. (6). Considering that tenure decisions are made well before these ages (usually between the ages of 35 and 37), many cases are decided for faculty candidates with little hard research funding.

More senior investigators who have committed to academic careers risk losing funding and the inevitable spiral of loss of space and inability to retain a critical mass of students and fellows—another threat to future innovation. University faculty members then are forced to seek alternative funding just when institutions are applying draconian regulations restricting industrial-academic interchange. In this issue of Science Translational Medicine, Andrew Marks presents an overview of the current federal funding environment and suggests new funding models that support high-risk research in academia. He makes specific note that NIH cites innovation as a critical component of its evaluation criteria for grant funding and yet seems not only to have fewer funds for all ideas but also to force investigators to shy away from risk in research and toward certainty in results. Marks proposes a means to reward originality and foster novel thought so as to make innovation a central point of how the practice of science can have the greatest impact on the future practice of medicine.

Reviving intrepid industry. If submitted patents and emerging products are measures of creativity, then the United States is losing ground dramatically compared with past U.S. and current world efforts. U.S. academicians submitted ~30% of worldwide patents in 2002 and roughly half that number in 2006 (7). Although the total number of patents granted in 2010 was twice that in 2000, unique patent numbers have remained flat at ~800,000 per year; this is because the greatest growth in awards has come from patents that protect or “picket-fence” existing technology (7). Similarly, the number of new diagnostic products, devices, and drugs approved has fallen off substantially. For example, the number of applications for New Molecular Entities received by the U.S. Food and Drug Administration (FDA) dropped from 45 in 1996 to 23 in 2010 (8). The health of established and start-up companies in the biomedical industry is faltering. Venture funding is paralyzed and inadequate (9). In the last five years in Silicon Valley alone, start-up valuation slipped 55%, funding of healthcare-related companies dropped by 52%, and the number of venture capitalist groups and private equity funds fell by 25% and 65%, respectively (10, 11).

In their Commentary (also in this issue), Bernard Munos and William Chin review the industrial landscape of innovation and describe the current schema that rewards “bad risk” as a system “doomed to failure.” The authors envision the emergence of a renewed focus on translational research designed to yield mechanistic insight and suggest that success “must start with breakthrough science that forges paths along which innovation can flourish.”

Rethinking regulatory standards. At the basis of all innovation in the United States is the funnel and filter of the FDA. This agency regulates what foods, drugs, and devices may transition from research concept to the medical clinic, and all acknowledge that the move from bench to bedside is taking longer, costs more, and is increasingly uncertain. Regulatory evaluation time lines, long viewed as metrics of innovation efficiency, are slipping. From 2003 to 2007, it took an average of three months to obtain clearance for lower-risk medical products through the 501(k) process and 15 months to receive premarket approval (PMA) through the more rigorous scientific review process required to ensure the safety and effectiveness of new devices. In 2010, the former rose ~45%, and the latter nearly doubled to ~30 months (10, 12, 13). Richard Stack and Robert Harrington propose in their article (which will appear in a future issue) that these numbers reflect a societal aversion to risk and can only rise further unless we understand that risk is associated with innovation and not always synonymous with harm.

Such notions are not new or even modern; they date back to the beginning of therapeutics when intervention first was tempered by primum non nocere—above all, do no harm. Interventional medicine clashed with religion at every level. Healing rituals without mechanistic insight challenged the divinity of the priests, and therapies that were evidence-based were deemed contrary to the will of the supreme being, who imposed disease, or were viewed as interfering with the evolutionary movement from one world to the next. In a fascinating twist, a dialogue developed among practitioners of multiple religions, who came together even during a time of great strife. In the 12th century, the philosopher and physician Maimonides proposed a resolution that sought to distinguish between legitimate medical treatment and magic: To be considered valid, a treatment must either be based on scientific (mechanistic) understanding, or there must be empirical evidence that illustrates the treatment’s efficacy even if the mechanism of action is not understood (14). These two criteria sanctioned the pursuit of science, the understanding of nature, and the healing of man. Today, many would propose the same requirements—rushing to understand can prevent harm done from rushing to treat—and would consider such insight as a holy pursuit; however, most would also acknowledge that waiting to comprehend may delay therapy indefinitely. This balance challenges us all.

SECURING THE FUTURE

As one might expect, in academia the drumbeat of concern for the power, promotion, and proliferation of innovation grows ever louder. Most universities now have an innovation center, and many have entire pro-
programs dedicated to teaching innovation and well-financed initiatives designed to translate ideas into products and drive concepts to communal benefit. Curricula devoted to innovation exist not only in business schools but also in schools of engineering and the physical and biological sciences. Scholarly works on innovation abound, and faculty positions in innovation sciences are now available. States vie for innovation through tax code breaks and funding incentives, and all recognize the importance of innovation in creating jobs and products both for enhancing the practice of medicine and for export.

In a future issue, Paul Yock et al. explain that innovation can be taught and, when taught, can generate not only concrete new ideas but also a perpetual source of such ideas that flow from a newly created generation of innovative leaders. The authors describe two major streams of educational theory that have shaped innovation programs in bioengineering: design thinking and entrepreneurship education. Further, Yock and colleagues expound on the renewed responsibility for innovating in all sectors of industry and academia and reinforce the notion that robust scientific investigation spurs innovation on all fronts. This handshake between industry and university, while seemingly natural, as the former provides leaders for the latter and the latter translates the work of the former, is increasingly deemed problematic and rife for conflict of interest and abuse. Barbara Bierer and Lita Nelsen describe these very issues and how they can not only be managed but also used to foster innovation in this era of translational medicine (also in a future issue).

SEEK TO UNDERSTAND

The recurring themes of the papers in this series are that innovation drives the engineering of our society and a better quality of life and that human beings suffer when innovation is fettered. Yet, we must not hold innovation alone as sacrosanct. We must temper primum succurre (rush to treat), not necessarily with primum non nocere but perhaps with primum sciere (seek first to understand). Promotion of mechanistic investigation can drive innovation and ultimately improve clinical medicine. But even here we must be cautious, for often the time line of comprehension well exceeds the time line of conception and even implementation. Indeed, Hippocrates himself warned that “we ought not to reject the ancient Art [of the practice of medicine], as if it were not, and had not been properly founded, because it did not attain accuracy in all things, but rather, since it is capable of reaching to the greatest exactitude by reasoning, to receive it and admire its discoveries, made from a state of great ignorance, and as having been well and properly made, and not from chance” (15).

There must then be a middle ground, a common desire to make all lives better without sacrificing some through inappropriate haste at introducing untried technology or by holding back important findings. This series of articles offers some answers for carving our path forward. Stakeholders must reconnect with the realization that risk is a driver of pioneering discovery. And we must find ways to teach and support innovation without falling prey to conflicts of interest, without confusing innovation with greed-directed entrepreneurship, and, above all, by embracing the notion that innovation forms the fiber of modern society and shapes the soul of modern man.

REFERENCES AND NOTES


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Elazer R. Edelman and Martin B. Leon

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