

## The 2016 American Society for Clinical Investigation Presidential Address

### Believe the miracles: of biomedical science and human suffering

Levi A. Garraway

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#### ASCI Presidential Address

Let me begin by thanking each of you for this distinct honor. It has been one of the great privileges of my professional career to serve as President of the American Society for Clinical Investigation. I am also deeply grateful to the ASCI Council, which has offered such rich guidance, wisdom, and friendship as we addressed a range of challenges and opportunities for the ASCI over the past few years. In addition, it is deeply gratifying to pay tribute to the wonderful men and women who have led this esteemed organization over several generations. One past ASCI President, Dr. Edward J. Benz, Jr., has also led my home institution (the Dana-Farber Cancer Institute) for many years. Naturally, I read his presidential address with particular interest. In a now classic vignette about why he enjoyed being ASCI President, Dr. Benz wrote: "The duties are few; the effort required is modest. It is well documented that no ASCI president has ever suffered excessively from overwork due to the demands of the office" (1). I can't help but wonder whether Dr. Benz would have written the same words if he had experienced the "joys" of presiding over the founding of a new ASCI scientific journal! Over the years, ASCI presidents have noted that preparing this address proved vexing at times, and I agree. [...]

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Over the years, ASCI presidents have noted that preparing this address proved vexing at times, and I agree. Not only does this occasion beckon us to wax philosophical regarding the state of the physician-scientist — as opposed to our typical lectorial mode of describing scientific results from the podium — it also does so while dangling that age-old, Solomonic contingency: “There is nothing new under the sun.” Nearly everything insightful that can



**Figure 1. Ancestral roots.** (A) Levi Watkins, Sr. (B) Levi and Lillian Watkins with three of their six children, Annie Marie, Pearl, and Levi Jr. (C) Annie Marie (Watkins) Garraway. (D) Michael Garraway. (E) The Garraway family in the mid-1970s. Photographs courtesy of the author.

be said about the state of the MD scientist has already been articulated repeatedly and eloquently by past presidents over several decades. Some past speeches lament the threatened plight of the physician-scientist. Others bemoan the sense that the gener-

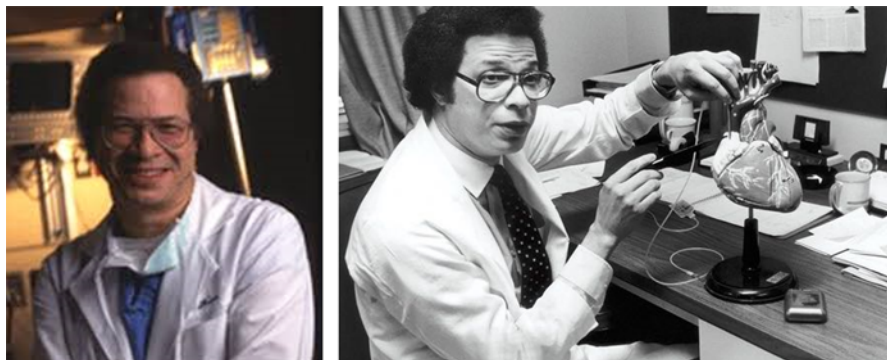
al population does not fully understand or value biomedical science. Still others decry the lack of funding, tepid support of clinical departments, or incompatible demands on our time. Each new treatise on these matters makes it that much more difficult to articulate an original viewpoint the next time around. Moreover, while these very real obstacles may indeed be top of mind, they can also be somewhat depressing.

An “aha moment” occurred when I came across a recent op-ed piece by

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**Figure 2. Dr. Levi Watkins Jr., the first African-American to attend and graduate from Vanderbilt Medical School, and the first African-American cardiac surgery chief resident at Johns Hopkins.** Photographs courtesy of the author.

the French philosopher and ethicist Pascal-Emmanuel Gobry entitled: “Why so many scientists are so ignorant” (2). Gobry argues that many scientific elites in our society claim vast intellectual authority while glibly dismissing entire disciplines (e.g., philosophy or theology) as inferior or even irrelevant. To Gobry, this intellectual arrogance bespeaks a sparse knowledge of the rich tradition of ideas on which our civilization is built.

After reading that op-ed, I considered the gauntlet to be thrown down. For this address, I resolved neither to dwell on the negative nor to settle for lack of novelty. (After all, I need to get this address accepted to the *JCI* or at least *JCI Insight!* There’s got to be some novelty.) In no way do these omissions signal disregard or indifference about the many challenges we face. Rather, my hope is to offer an uplifting narrative that celebrates our distinctive calling and epic journey as physician-scientists across history. This is a story we all know well, perhaps told in a different way. In the telling, let it not be said that this address lacks ideas gleaned from other scholarly disciplines in addition to medical science (though their inclusion here is admittedly somewhat risky). Finally, since this audience consists of so many students and junior investigators, a specific goal is to encourage them as they endeavor to carry our torch into the future.

### Standing on extraordinary shoulders

My own part in this journey starts with my grandfather, Levi Watkins, Sr. (Figure 1A). He earned a college degree. This

accomplishment seems ordinary, but it was attainable by only approximately 1% of African-Americans during the 1930s. Afterwards, he married a preacher’s daughter (they had six children, three of whom are shown in Figure 1B). Throughout his career, he worked tirelessly in support of educational opportunities for African-Americans — first as a teacher in rural Kansas, and eventually as President of Alabama State University. My grandfather’s life exemplified three basic attributes: education, faith, and hard work.

Those traits were passed to my mother, Annie Marie Garraway (Figure 1C), as though they were monogenetic. She made her children go to church. At home, education reigned supreme: my mother and father both had PhDs (she in mathematics and he in plant biology). Whatever else we did, my two sisters and I were clearly not going to be viewed as truly successful by our parents unless we too earned PhDs (we all did).

My father, Michael Garraway (Figure 1D), was an émigré from the Caribbean. Dad brought additional dimensions that proved decisive for my own path. Foremost among these was his passion for his work as a scientist and professor at The Ohio State University (and for their college football team — that particular variant was translocated to a super-enhancer locus when it was passed to me!). Dad’s passion for science was dwarfed only by his passion for his family (Figure 1E) and for life. Unfortunately, that life was cut short just four years after he was diagnosed with an aggressive form of prostate cancer. His tortuous journey through the

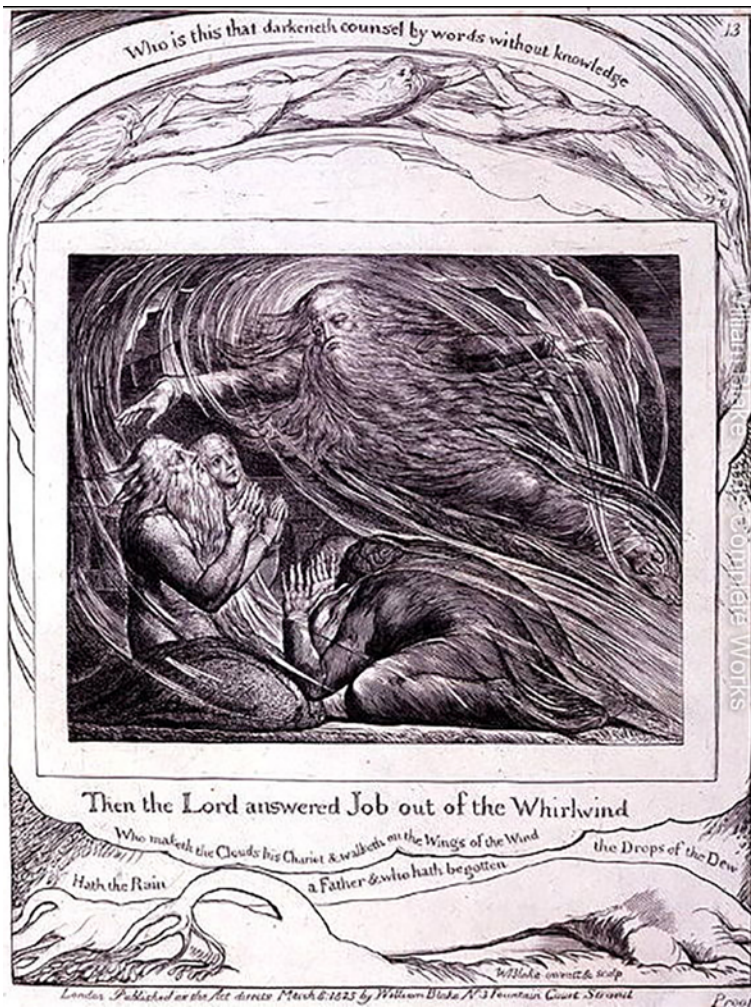
pain and suffering induced by metastatic disease, the sequelae of cord compression, and the toxicities of failed treatments left me with the grim conviction to pursue cancer research as a career.

My decision to pursue academic medicine stemmed from my grandfather’s first son and namesake: Dr. Levi Watkins, Jr. (Figure 2). My “Uncle Levi” lived a life of “firsts.” Not only was he the first in our family line to become a doctor, he was also the first African-American to attend and graduate from Vanderbilt Medical School. He was the first African-American cardiac surgery chief resident at Johns Hopkins. In the 1980s, he performed the first surgery to implant a cardiac defibrillator. Throughout his life, he was intensely hard-working as a cardiac surgeon and associate dean at Johns Hopkins, and as a champion for social justice. He died tragically almost exactly one year ago. Uncle Levi would have enjoyed being here today. And, I certainly would have enjoyed prodding my distinguished Hopkins colleagues to get him inducted into the AAP!

Having graciously indulged this brief sojourn into my family history, you might now infer certain things about who I am and how I see the world. At one level, the mere fact that I stand here today represents a convergence of unlikely events across many decades, together with the intense effort and sacrifice of many people. Equally, the opportunities afforded to my family seem remarkable for being unremarkable. We all know that success may be attained through education, hard work, and holding fast to certain bedrock principles. Even so, it feels particularly gratifying and humbling to reflect on a personal family legacy in which the ordinary become extraordinary.

### Remembering who we are

By analogy, reviving the genesis of our collective physician-scientist narrative may help us visualize and embrace anew our identity and opportunity. Somewhere near the beginning of our forays into medicine and science, each of us was asked: “Why do you want to be a doctor?” For most of us, the answer probably revolved around a deep-seated desire to help people. But what did we mean by that? A simplistic answer might be: “Help them recover from — or manage — their diseases.” But while



**Figure 3. Job seeking a rationale for his suffering.** An illustration from William Blake's 1825 Illustrations of the Book of Job, object 13 (Bentley 421.12) "Job's Evil Dreams". Courtesy of [www.william-blake.org](http://www.william-blake.org).

that answer is true to a point, it doesn't quite capture the imagination.

If we peel off the layers of that question until we reach its radix, "helping people" really means something much more foundational: it means taking our stand against the facet of human suffering that manifests itself through disease. Philosophically speaking, the problem of human suffering is perhaps the oldest and most vexing question in human history. Like its twin, the problem of evil, human suffering seems at once indomitable and intolerable. It angers us, frustrates us, evokes despair, and foments doubts regarding our livelihood, our security, and the existence of any meaningful transcendence.

To frame this in another way, disease represents one mechanism whereby the chaotic flares up within human existence. In both Ugaritic mythology and the sacred

texts of the Judeo-Christian tradition, the chaos that is bound up in nature and in human experience is often depicted symbolically as a seven-headed sea monster named Lotan or Leviathan. When viewed through this ancient literary lens, disease arguably comprises at least one head of this mythical seven-headed beast from the deep that wages its cosmic battle against humanity from generation to generation.

And yet, the pervasiveness of suffering in our world seems to awaken an elemental moral imperative inside the best of us. First, suffering and chaos impel us to ask the grand question of *why*. A famous ancient depiction is found in that classic scriptural narrative wherein a man named Job seeks a rhetorical showdown with the divine regarding a rationale for his suffering (Figure 3 and the Hebrew Bible, Job, chapters 38–41). When that showdown

finally transpires, the divine discourse is as confusing as it is poetic. However, two aspects stand out. On the one hand, an epic portrayal of the Leviathan creature by YHWH offers a strikingly honest acknowledgement of the ravages of chaos across creation. On the other hand, the sweeping lyrical tapestry that precedes this grim imagery reminds us equally of the superabundant beauty, goodness, and wonder in this world.

In addition to evoking the question of why, the desecrations caused by suffering and chaos demand a response. We *must* oppose them — ideally while leveraging and embodying the goodness that is in the world. Taking a stand against suffering, however tentative and frail that stand might be, represents an absolute moral good — the ultimate in nobility and dignity. Chaos indeed presents a formidable challenge, but it need not be our only reality. Actively opposing suffering is simply the right thing to do.

Therefore, discerning and countering the suffering that manifests as human disease anchors the root cause of why most of us became physician-scientists. This moral imperative also helps explain why we persist even when patients are ungrateful, our treatments are woefully inadequate, our research findings are ambivalent, and our grants just miss the pay line. Moreover, the physician-scientists whom we revere most have, in some fashion, triumphed over these existential challenges. They have asked the question "why" in a manner that might be addressed through reason. And, by tackling the big questions of disease with scientific rigor and tenacity, they entrench themselves in audacious defiance of the "chaos monster" that is human disease.

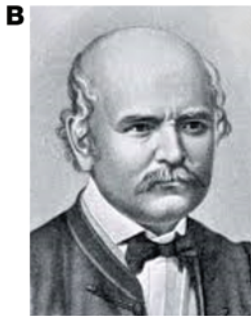
*This is who we are.*

### From miracles to medicine

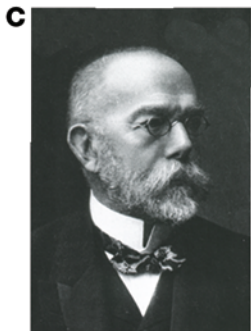
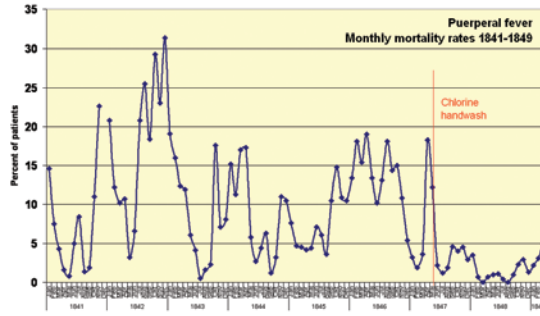
Throughout most of human history, both its root causes and the very notion of opposing chaos caused by human disease were typically relegated to the realm of the magical or miraculous. Physical and mental afflictions were often believed to have been brought about through the whims of gods, spirits, or demons, perhaps as punishment for some overt or hidden personal transgression against the divine. Conversely, cures of debilitating illnesses were dramatically portrayed as rare,



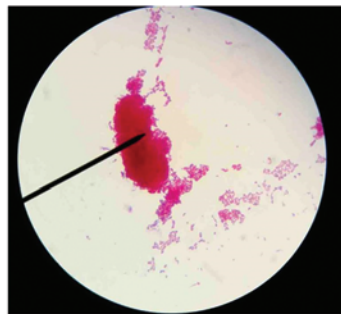
Edward Jenner: Insights into vaccination



Ignaz Semmelweis: The effect of handwashing on reducing rates of infection



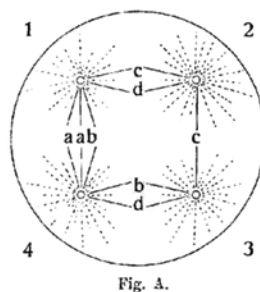
Robert Koch: Development of tissue-staining techniques to identify new pathogens



Wilhelm Roentgen: The discovery of X rays and their potential medical application



Theodor Boveri: Studies that established the chromosomal basis for inheritance

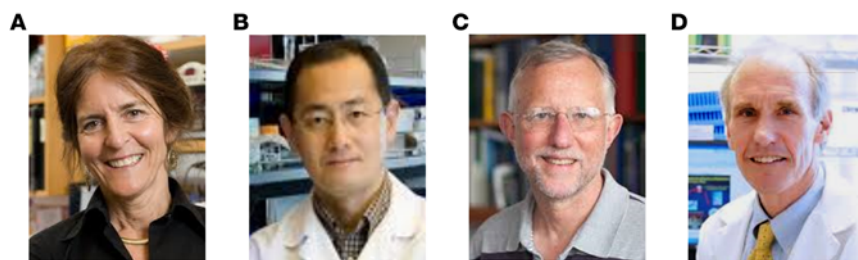


**Figure 4. Medical science begins to render the miraculous into the commonplace.** (A) Edward Jenner’s experiment paves the way for the first human vaccine. James Gillray’s 1802 caricature of Jenner vaccinating patients (right). (B) Ignaz Semmelweis’s recognition that handwashing with chlorinated lime water could dramatically reduce the incidence of puerperal fever in maternity wards. Puerperal fever monthly mortality rates for the First Clinic at Vienna Maternity Institution 1841–1849 (right). (C) Robert Koch’s use of new tissue staining techniques to demonstrate that tuberculosis was caused by a novel bacterial pathogen. (D) Wilhelm Roentgen’s grasping of the significance of cathode rays on a paper screen in a dark room. (E) Theodor Boveri’s studies established the chromosomal basis for inheritance and first suggested that disordered chromosomes might cause diseases such as cancer. Image credits: Edward Jenner by James Northcote, © National Portrait Gallery, London, England (A, left); Wikipedia.org (A, right; B, right; and E, left); National of Library of Medicine (B, left; C, left; D, left and right); Science Prof Online Science Image Library (C, right); Boveri, T. “Zur Frage der Entstehung maligner Tumoren” Jena, Gustav Fischer, 1914 (E, right).

extraordinary events — this is perhaps best exemplified by the miracle narratives of the Christian tradition.

And then, slowly but inexorably, medical science began to render the miraculous into the commonplace. In the vast majority of those famous cases we all know well, the key advance began with a curious physician or scientist paying close attention to observations from nature and asking big questions that could be addressed feasibly through experimentation. Observations that domestic farm workers exposed to cowpox were resistant to the scourge of smallpox prompted Edward Jenner to conduct a simple but powerful experiment in people that paved the way for the first human vaccine (Figure 4A). The recognition by Ignaz Semmelweis that handwashing with chlorinated lime water could dramatically reduce the incidence of puerperal fever in maternity wards (Figure 4B) transformed mortality rates and eventually fueled Louis Pasteur’s work to define the germ theory of disease.

This pattern of tackling major medical questions through observation linked to experimentation quickly took root in several other areas of biology and medicine in the run-up to the 20th century knowledge explosion. Among many exam-



**Figure 5. Recent speakers at the AAP/ASCI/APSA Joint Meeting.** (A) Jean Bennett, whose research is extending the prospect of restoring sight to some patients. (B) Shinya Yamanaka, whose pluripotent stem cell discoveries hold promise in reversing certain types of paralysis. (C) Charles Rice, whose research could enable curative therapy for hepatitis C. (D) Carl June, whose work epitomized the advent of cancer immunotherapy.

ples, Robert Koch leveraged new tissue staining techniques to demonstrate that tuberculosis was caused by a novel bacterial pathogen (Figure 4C), and followed this Nobel Prize-winning discovery with a series of mechanistic postulates capable of determining whether particular bacterial agents were causal for infectious disease. Wilhelm Roentgen grasped the possible significance of the unexpected effects of cathode rays on a paper screen in a dark room and, soon afterward, discovered the existence and medical applications of X-rays (Figure 4D). The systematic studies of Theodor Boveri in model organisms established the chromosomal basis for inheritance and first suggested that disordered chromosomes might cause diseases such as cancer (Figure 4E). In each of these instances, we have curious investigators whose training conditioned them to recog-

nize a major possibility in human disease biology or unmet clinical need, to conceive of an incisive and feasible experimental approach to address this question, and to exert the discipline and tenacity needed to execute this approach.

One of the most gratifying aspects of the joint ASCI/AAP annual meeting for me personally over the years has involved listening to leading biomedical scientists from across the spectrum whose transformative discoveries are extending this legacy into unprecedented treatment avenues. For example, in recent years this meeting has included talks by people like Jean Bennett (Figure 5A), whose research into the use of gene therapy to treat genetic causes of blindness is extending the prospect of restoring sight to some patients. Or by Nobel laureate Shinya Yamanaka (Figure 5B), whose pluripotent stem cell discoveries hold out the promise of reversing certain types of paralysis. Charles Rice (Figure 5C) presented research that could enable curative therapy for hepatitis C. And, the work of Carl June (Figure 5D) epitomized the advent of immunotherapy and its ability to literally snatch some metastatic cancer patients from the jaws of death, giving them a new lease on life. These advances, and so many others like them, call to mind that timeless prophetic quote: "...the blind receive sight and the lame walk, the lepers are cleansed and the deaf hear, the dead are raised up..." (New Testament, Matthew 11:5). Are the medical science advances we have brought forth as a field really so different from those miracle narratives of old?

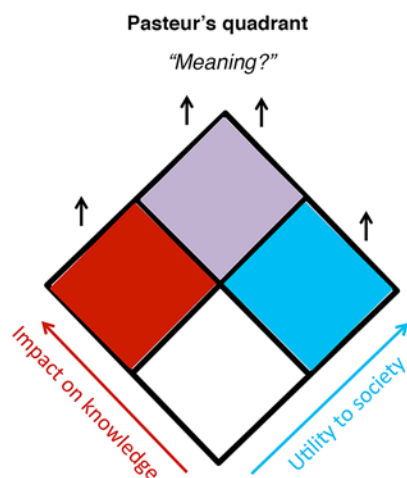
The vignettes I shared about my family were intended to convey my sense of amazement regarding the extraordinary opportunities I have experienced, because

they resulted in large part from antecedent lives lived in "ordinary" ways (e.g., through education, faith, and hard work). In a sense, the story — indeed, the wonder — of medical science represents the converse: a continuing saga of extraordinary benefits to humanity that have been made increasingly ordinary — at least in the Western world. In every case, intellectually curious individuals stared down baffling aspects of the suffering and chaos of human disease, asked the question why, and made unprecedented inroads through rigorous scientific investigation. Nobel laureate Francois Jacob describes this eloquently in his autobiography, *The Statue Within*: "In science, the great man is, first of all, the one who knows how to spot the right problems at the right moment, while there is a chance of solving them" (3).

### Biomedical science and meaning

Elsewhere in his autobiography, Jacob makes an even more profound statement: "What man seeks, to the point of anguish, in his gods, in his art, in his science, is meaning." Although Jacob himself did not unpack this comment, it seems intuitively obvious that the ultimate objectives of medicine and biomedical science discussed earlier hover near a coalescence of paths to meaning extolled by various branches of philosophy, theology, and psychology. For example, we can readily perceive alignment between the aims of medical science and the utilitarian's "greatest happiness principle," the secular humanist's "greater good," the existentialist's "worthy goal," the logical positivist's legacy of achievements, the postmodernist's mechanistic deconstruction, the Confucianist study of basic human existence, the Judaic elevation of the world ("Olam HaZeh"), the Christian love ethic, the Islamic pillar of charity ("Zakah"), the Hindu "thou art that" ("Tat Tvam Asi"), and the positive psychologist's dedication to something greater than oneself.

Given these fundamental alignments, it stands to reason that we are most likely to find fulfillment in our investigational careers by making sure to tackle research questions that really matter. The esteemed cancer biologist Robert Weinberg once said: "It is as hard to work on an uninteresting problem as it is to work on an inter-



**Figure 6. A variation of Pasteur's quadrant, a visualization of investigations as they contribute to fundamental knowledge or utility to society.**



Figure 7. “Destruction of Leviathan,” an 1865 engraving by Gustave Doré.

esting problem.” (I actually think uninteresting problems are even harder — they require a lot of extra motivation!)

Of course, notions and debates about rendering meaning from scientific inquiry are not new. Prioritizing the most important questions seems axiomatic in biomedical research. Variations on this theme have often been depicted graphically using Pasteur’s quadrant (Figure 6), which bins investigative pursuits based on their impact on fundamental understanding versus their utility to society (4). Implicit in most such illustrations is that the top quadrants contribute to value and meaning, whereas the bottom quadrant (low impact and low utility) is to be avoided at all costs.

Unfortunately, however, it is surprisingly easy to slide into a staid incrementalism in biomedical science. This phenomenon often becomes apparent when reviewing grants or browsing scientific journals that are perhaps less widely read

than the *JCI* or *JCI Insight*. Over time, there can be a tendency for some biomedical scientists to become increasingly conservative scientifically, to the point where their research programs no longer make meaningful contributions. When this happens, insecurities begin to take root, further stifling intellectual creativity and risk-taking. Curricula vitae gradually become populated with publications that may technically count toward the next R01 renewal, but fail to take bold steps or break new conceptual ground. Grant proposals may “check all the boxes” while presenting no real chance of “moving the needle” in the field. Eventually, this “incrementalist” cycle may produce a scholarly entrapment devoid of substantive impact.

The drift toward incrementalism is inevitably accompanied by a cynicism that grows over time. For example, a few years ago I was discussing an innovative research grant application with several

faculty members. I mentioned that I had erred on the side of being bold and ambitious in what I had proposed, and that I hoped this would not backfire during the review process. One of the senior faculty members looked at me condescendingly and said: “You don’t put anything bold in a grant proposal — you propose something safe and tell them it’s innovative!” Eventually, this mentality may breed an Absurdist dissonance within physician-scientist ranks, because it operates as though the big, unanswered questions of human biology and disease matter less than the petty gamesmanship of academic standing. Worse yet, it is no fun!

Practically speaking, we all maintain some degree of balance between high-risk/high-reward projects and safer, more certain research directions. At the same time, we must fight avidly against the entropic drag toward incrementalism in our investigative pursuits lest we risk eroding their larger meaning. This requires considerable effort. Grasping the crucial unanswered questions in our respective fields and developing bold but feasible investigational paths to address them requires protected time for contemplation and study, prioritizing of limited resources, forging effective partnerships to engage complementary expertise, rallying trainees to our cause, and old-fashioned hard work — punctuated periodically by doses of inspiration and good fortune. No one can expect such a path to be easy. Allegorically speaking, we are still waging a daunting battle against the fabled chaos monster that is human disease — only, it turns out that the reality is vastly more complex than the Leviathan myth!

As I said at the beginning, I do not intend to dwell on the negative. On the contrary — there has never been a more exciting time for physician-scientists to deploy their curiosity, rigor, and imagination. The explosion of technology, computational power, and experimental capacity make the ground fertile for unprecedented discoveries. Not only does our training position us uniquely to lead, in some cases, we are the only ones who have the expertise needed to accelerate knowledge and improve health around the world.

This is why the ASCI and AAP remain such crucial professional societies. Together, they provide a distinc-

tive venue where esteemed physician-scientists may convene across disciplines to remember and celebrate who we are. They galvanize us to refocus on the big questions of our field and how we might address them experimentally. During my time as ASCI President, we founded *JCI Insight*, which endeavors to provide a new avenue for our members to communicate their discoveries while also facilitating innovations in form and subject matter. And, both of our societies provide many living examples of individuals whose accomplishments inspire all of us to reclaim our legacy of confrontation with and, increasingly, triumph over human suffering caused by disease.

When ASCI was founded, the very premise of doing clinical science through studies of living systems seemed revolutionary. Now, biomedical research is not revolutionary at all. It is part of the establishment. In fact, the larger community may view our chic offices, ivo-

ry towers, and state-of-the-art labs and ask: “Why hasn’t more progress against disease been made? Why are so many people still dying of cancer? Why can’t we make more progress against neurological diseases such as Alzheimer’s and stroke?” Therefore, our challenge and mission is no longer simply to do biomedical research as trained clinicians, but instead to identify and address head-on the big challenges in our fields — challenges that seem impossible, that others might shy away from, but where advances would change the world once again. If not us, who will rise up to confront the monster?

In conclusion, it has been my honor to serve ASCI as President, and it remains my cherished privilege to be a part of such a distinguished and dedicated group of physician-scientist leaders. I am deeply inspired by the miracles that biomedical science has brought to medicine. Yes, the path is tortuous and many setbacks clutter the road behind us and the road

ahead. Nonetheless, we stand defiantly in the face of chaos (Figure 7), ever aspiring toward that vision articulated by the psalmist of old: “... to crush the heads of Leviathan and give him as food to the creatures of the desert” (Hebrew Bible, Psalm 74:14).

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