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2015 Association of American Physicians Presidential Address Medicine in 2055

Paul B. Rothman

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AAP Presidential Address

Part 1: Introduction Good morning, and thank you all for being here today. It's a true honor to address this esteemed group and to follow in the footsteps of so many outstanding leaders in academic medicine who have delivered this address over the past 130 years. Before I begin, I wanted to note how privileged I have felt over the years to work with so many outstanding people in our field. I sometimes worry we lose sight of the talent and commitment of those around us. There are few, if any, other fields that we would be surrounded by those whose lives are committed to improving the lives of the world around us and are willing to work countless hours to achieve this goal. In planning today's talk, I took some time to listen to past AAP presidential speeches and found them informative and refreshingly varied. The talks that I found most engrossing were those that took a somewhat narrow theme — the practice of humanistic medicine or communicating about science to the public — and really delved into the nuances of the issue with telling data points and smart insights. Well, today I am going to do the opposite of that. No, I don't mean that the talk will be insight-free, although I can't make any promises! Instead of […]

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Part 1: Introduction

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No, I don't mean that the talk will be insight-free, although I can't make any promises! Instead of carving out a focused, manageable theme, I've decided to tackle the "big picture." The stated purpose of the AAP is "the advancement of scientific and practical medicine" (1). So I thought, why not assess "the advancement of scientific and practical medicine" — both in terms of how far we've come and where we may be going in the future.

It seemed a tad ambitious to start at the very beginning of modern medicine, so instead, I'll go back to the early days of my own career. I'll start by touching on a few of the major triumphs I've had the pleasure of witnessing over the past 40 years of biomedical science — areas where discovery has revolutionized clinical practice. Then, I'll spotlight some of the current advances being driven by academic medical centers around the country in our collective quest to eradicate disease and help people around the globe lead longer, healthier lives. Finally, I'll look ahead to the next 10–20 years. Today's scientists are making staggering progress in many disease areas, but I'm going to focus on just a handful of conditions that are being dramatically changed through new technologies, new discoveries, and emerging treatment options — areas where I truly believe we will be able to offer new hope for patients over the next decade or two. For this portion of the talk, I asked all of my department chairs at Johns Hopkins Medicine to weigh in, so the predictions reflect their views as well as my own.

Finally, when it comes to the pursuit of cures, we are in the midst of an era of unprecedented opportunities in science, but we're also butting up against unprecedented challenges in the environment for doing science. I'll spend a little time addressing these barriers to innovation and what we can do to overcome them.

Part 2: Lewis Thomas, David Baltimore, and falling in love with science

I made up my mind to become a scientist when I was still in high school. It was 1975, and I was sitting in my AP biology class in Bayside, Queens, probably sporting an awful pair of plaid bell-bottom trousers. David Baltimore had just won the Nobel Prize for his discoveries concerning recombinant DNA. Although my previous heroes had been Tom Seaver and Joe Namath, the ability to isolate and manipulate genes got me excited about science. When I resolved to become a scientist, Dr. Baltimore was the major reason I set my sights on MIT, where he was a professor at the time. Anyhow, I had this fantastic teacher, Mr. Yohalem, who managed to get a bunch of restless teenagers excited about the intricacies of biology and the limitless possibilities of science.

One day, my teacher, who knew I was really fascinated by this stuff, gave me a new book called *The Lives of a Cell* by Lewis Thomas (2). Some of you are probably familiar with his work, but for anyone who isn't, Lewis Thomas was the biology world's resident poet-philosopher in the '70s and '80s. At the time this book was published, he was president of the Sloan-Kettering Cancer Center in New York. *The Lives of a Cell*, which won the National Book Award in 1975, is a brilliant collection of short essays — musings on biology, death, medicine and technology — which were originally published in the *New England Journal of Medicine* in a monthly column called "Notes of a Biology Watcher." Interestingly, the *NEJM* didn't pay Lewis Thomas to write the column, but they gave him 1,000 words and promised not to edit him — an offer many of us would find hard to pass up!

In the book, Thomas laid out an argument that has stuck with me throughout my entire career. He provided a lens through which it's possible to evaluate medical progress in any disease area by distinguishing between three different kinds of medical technologies:

The first category, he calls "supportive therapy." This is the care physicians provide to tide patients over through diseases we don't really understand and whose progress we can't really halt — think: multiple sclerosis, pancreatic cancer, ALS. These therapies are not true technologies but, more accurately, the absence of effective technologies.

Any person who has watched a family member slowly succumb to Alzheimer's knows how frustratingly little is understood about the disease. This category of care involves lots of nursing and hospitalizations, a lot of bedside engagement, and ultimately, a lot of defeat, and it accounts for a hefty portion of our health care spending in this country.

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The second category is "halfway technology." These are the steps we take to minimize the impact of a disease or alter its course in the absence of sophisticated understanding of what causes the disease and how to prevent and/or cure it. In this category, you find organ transplantation, therapies for heart disease, and arthritis drugs.

Cancer, too, falls in this middle category. Most of what we still do to treat cancer is aimed crudely at taking out cells that are already cancerous: chemo, radiation, surgery. We do have some fundamental knowledge of what causes cancer, and our therapies are getting more precise. But the idea of the cancer stem cell is only 5–10 years old. There are very few forms of cancer where we clearly understand the biological mechanism involved and we can knock out the disease.

Thomas refers to the next level up as the "decisive technology of modern medicine." The emblematic tale he tells here has to do with the eradication of polio disease. At Hopkins in the 1940s and '50s, a researcher named David Bodian and his colleagues identified the three strains of poliovirus and developed an early vaccine. As a result of the global vaccinations efforts kicked off in the 1980s, most of the world's population now lives in areas completely free of polio.

I find this to be a useful framework for thinking about medical interventions, especially in this era of heightened cost-consciousness in health care. Much of what will occur over the next few years in the health field will be getting inefficiencies out of the system. Several decades of fee-for-service reimbursement for medical expenses where costs were easily passed on to a third-party payer has led to lots of waste and inefficiency. You have seen over the past 5 years, and will see over the next 5 years, healthcare delivery systems eliminate this waste as price pressures and new reimbursement systems will put tremendous pressures on the revenue side and will lead to a much more efficient health care system. I will not talk about this today. What I will focus on today are the disruptive scientific advances that fundamentally alter how we understand and treat diseases.

Ideally, we'd like to be able to understand the underlying cause of a disease to effectively treat it; otherwise, we devote a disproportionate chunk of our finite resources to treating manifestations of disease.

The public is always clamoring for more "translational" research. The trouble, as you all know, is that we can only get to Thomas's third category — the "decisive technologies" — by answering countless individual questions in basic science, many of which don't have evident practical applications.

It's the accretion of that basic work, most of which ends in failure, that gets us closer to cures, and it's up to us to defend that work to the naysayers and the purse-string holders.

Part 3: Forty years of progress inching toward "decisive technologies"

Over the past 40 years since Lewis Thomas's book was published, I've had the pleasure of witnessing stupefying advances in medicine — progress that has had enormous impact on how we deliver health care and conduct health-related research. I'd like to talk briefly about how the practice of medicine has changed since I entered the field, and then assess the really dramatic transformation that's underway in areas like cancer and regenerative medicine as we look ahead to the future of medicine.

In 1984, I graduated from the Yale School of Medicine and went on to an internship at Columbia-Presbyterian. The hospital I went to work in as a first-year resident was full of AIDS patients. I remember how baffled the attendings were when 20-year-old guys started coming in with forms of cancer and pneumonia that had almost never been seen in healthy young adults. Eventually, these patients would get emaciated and confused and die slow, painful deaths, and there was almost nothing we could offer, aside from some paltry "supportive therapies," to use the Lewis Thomas lexicon.

Remember, in these early years of the epidemic, after the first cases were reported in 1981, we didn't even know what HIV was. We thought it was an autoimmune disease. It wasn't until researchers discovered, in 1984, that it was an infectious disease caused by human retrovirus that the medical community could focus on developing an antiretroviral drug. Three years later, AZT (azidothymidine) was approved, and a seminal moment came in the late '90s, when a cocktail of AZT and other meds turned HIV into a chronic condition.

Fast forward to the present day, and doctors — including my colleagues Bob Siliciano and Deborah Persaud — are developing new strategies to prevent latent HIV reservoirs as a way to achieve viral remission, where the virus isn't detectable in the blood even after a patient stops drug treatment. Because we understand the disease and know how to halt its progress and its spread, we are almost at Lewis Thomas's point of decisiveness, although we still haven't arrived at an effective vaccine or a true cure. Nonetheless, it is astonishing to witness how far we have come in three decades.

While HIV/AIDs stands as one of the most dramatic examples, there are plenty of other cases where decades of research and clinical experience have elucidated previously obscure diseases and propelled us forward along Lewis Thomas's continuum.

For instance, think about how we treat stomach ulcers. Back in the '80s, we still thought peptic ulcers were caused by stress or spicy foods. We tried to ease the symptoms with milk and antacids — treatments that, we later learned, actually worsen the problem by stimulating the stomach to make more acid. Now we know that ulcers are triggered by helicobacter pylori attacking the stomach lining. We know this because Barry Marshall and Robin Warren both intentionally ingested and infected themselves with the bacteria in an effort to prove the link to a skeptical science community. Knowing that bacteria is the underlying cause of ulcer has allowed us to treat the condition quite effectively with antibiotics.

Cardiovascular disease is another great example of how quickly treatment protocols can change as new findings emerge. If you had arrived at the hospital with a heart attack in the '70s or '80s, we probably would have given you morphine to knock you out. Assuming you survived, the next morning, you would have awakened to orders for weeks of strict bed rest and a greasy breakfast of bacon and eggs.

Then, in 1980 came the first big paper linking cholesterol levels to coronary heart disease, from the Framingham study. Next, Michael Brown and Joseph Goldstein's groundbreaking work on cholesterol metabolism led to the first statin, approved for use in 1987. We still really don't know why a person develops atherosclerosis. But we know that it correlates with LDL levels and that, if you alter these levels, you

affect disease. As we began to understand risk, we could intervene early. In 1988, the National Cholesterol Education Program began establishing targets for cholesterol levels. And many people who would have died from heart disease in the past are living longer because we've convinced them to quit smoking or exercise more. Even if one does have a heart attack today, we have good tools at our disposal — coronary angioplasty, stents, blood thinners, statins, etc. — and we'll get you up and moving quickly. From 1984–2004, the death rate from cardiovascular disease in the U.S. fell 41% — one of the most celebrated success stories of 20th-century medicine.

We've made remarkable progress in our efforts to thwart cancer, as well. Over the past two decades, we've arrived at a much more sophisticated understanding of the genetics and molecular and cellular processes involved in cancer-cell growth. That has led to game-changing treatments, such as drugs that interfere with those specific molecular targets — Herceptin for breast cancer or Tarceva for lung. There are even cancers where we can overcome the disease entirely. In chronic myelogenous leukemia (CML), 95% of patients have the Philadelphia chromosome leading to the BCR-ABL oncogene. In the 1990s, Novartis came out with Gleevec, which binds to and inactivates BCR-ABL. Today most patients with CML enjoy a near-normal life expectancy, and accordingly, Gleevec remains the sort of Holy Grail of cancer R&D.

Of course, none of this would be possible without DNA sequencing, the most obvious accelerator of discovery in cancer and other areas. DNA sequencing has grown exponentially faster and cheaper since it first arose in the 1970s. The next-generation sequencing methods that began cropping up in the 1990s have yielded extraordinary insights by revealing the variations/mutations that cause disease. Over the past decades, Bert Vogelstein and others have cracked the genetic codes of dozens of forms of cancer, making it possible to detect tumors early.

Amazing leaps in facilitating technology have served to spur many of these advances, from methods for amplifying a piece of DNA very quickly (PCR/taq polymerase) to the development of green fluorescent protein (GFP).

Increasingly sophisticated tools and technologies like these make this an incredibly exciting time to be a scientist. With our ability to obtain and rapidly analyze complex data sets, we are on the verge of some truly breathtaking breakthroughs. The combined application of electronically searchable phenotypes and genetics will give incredibly precise insights into therapeutic pathways. Fields like metabolomics and proteomics are exploding. We are learning much more about the human microbiome and the role it plays in health and disease, as well as the impact of environmental factors. We're even harnessing the power of the patient's own immune system to fight off disease. With the convergence of all these innovations, we're poised for some major leaps forward over the next two decades.

Part 4: The next 10–20 years

Category 1: Regenerative medicine. The first category where we can expect to see spectacular progress over the next decade or two is regenerative medicine.

In the U.S., roughly 80% of people over 65 suffer from osteoarthritis of the knee because the cartilage cushion at the ends of the bones has deteriorated over time. The difficulty with cartilage, of course, is that it doesn't heal itself. But the good news for future arthritis sufferers is that we may in fact be closing in on the metaphorical "fountain of youth" when it comes to joint regeneration, thanks to stem cell technology and induced pluripotent stem cells (iPSCs).

We hope that within a decade or two, advances in stem-cell biology will lead to the ability to regenerate certain tissues, from cartilage to cardiac muscle cells. If we can implant stem cells in the area of cartilage damage that are instructed to generate cartilage-like tissue and signal the body to produce normal cartilage cells, then we could greatly reduce the impact of joint degeneration in a long-lasting way. It's a really exciting time for the orthopedics field because this technology may not be too far off, and researchers around the country are working hard to bring this to fruition. Beyond degenerative joint disease, the ability to regenerate tissues could lead to improved outcomes for other conditions, such as cardiomyopathy, spinal muscular atrophy, and ALS.

The same may be true for macular degeneration, the most common form of blindness in the elderly. Stems cells open up a lot of exciting new avenues for cures, where previously we would have relied on Band-Aid–type therapies. In stem cell technology, one exciting story that's come out of Johns Hopkins in the last couple of years is the artificial retina.

Using iPSCs from humans, Johns Hopkins researchers in our Department of Ophthalmology have created a 3-D retina in a dish that not only has the architectural makeup of the retina, but also has the ability to generate electrical signals when stimulated by light. In other words, these lab-grown retinas, with their functioning photoreceptors, behave like normal, healthy retinas. This achievement, which was years in the making, may ultimately lead to technologies that restore vision in people with retinal diseases. The hope is that it could eventually enable retinal cell transplants that halt or even reverse the onset of blindness.

Category 2: Gene therapy. What's fascinating about the human body is that one tiny defect in a gene can have devastating, life-altering health consequences. Now that we can sequence a whole human genome in a day, we can identify these mutations much more rapidly. The next step is to see if, using gene therapy and perhaps gene editing, we can correct these defects. For instance, I'm excited about novel applications of technology like CRISPR — a technique for directly editing DNA which involves removing cells from sick people, editing the faulty chromosome, and then returning the modified cell to the patient. CRISPR is something that we need to study because there's the possibility of correcting thalassemia or sickle cell or hemophilia in hematopoietic stem cells. Again, we're not there yet. The technology is still nascent. But DNA-editing techniques offer great promise that perhaps we'll devise some decisive technologies for some of those diseases.

In the meantime, scientists are devising a technique for partially matched (haploid-identical) bone marrow transplants, which can completely wipe out sickle cell disease in some patients. A preliminary clinical trial of these transplants has demonstrated the potential to bring cures to a majority of sickle cell patients who need them — elimi-

nating the need for a lifetime of pain medications and blood transfusions. One way or the other, I believe sickle cell disease will be curable within the next 10 years.

Category 3: Cancer. And then there's cancer, which truly is "the emperor of all maladies."

At AMCs, we are knee-deep in the difficult work of analyzing genetic, epigenetic, and lifestyle factors and using that information to make decisions about how to treat and prevent cancer.

One of the most exciting stories in medicine right now is the tremendous progress being made around personalized healthcare, or precision medicine. We are mining massive amounts of electronic patient information to yield medical strategies tailored to the individual. Over the next decade, personalized medicine will have a rapidly growing impact on tumor diagnosis and treatment. Targeted therapies based on genomic tumor sequencing — as opposed to simply the organ of tumor origin — will become the standard of care.

We are looking toward the future and identifying opportunities to unleash the huge potential of informatics and use "big data" to tackle medical problems. Another major theme in cancer today is early screening. Molecular diagnostics for cancer and other diseases clearly will only increase. Increasingly sensitive assays targeting recurrent mutations will be employed for early cancer detection, particularly when it comes to breast, ovarian, and colon cancer screening. For instance, common colon cancer will be diagnosed by screening in blood or stool. Many forms of cancer (e.g., colorectal, melanoma, liver, etc.) will be detected at a very early stage and be amenable to surgical cure. We've already seen preliminary success in the development of an early blood test for pancreatic cancer, a disease that is often deadly because it's detected late, after it has already spread.

Scientists at the Kimmel Cancer Center also have developed a test to detect ovarian and endometrial cancers using cervical fluid obtained during routine Pap tests. In a pilot study, the PapGene Test, which relies on genomic sequencing of cancer-specific mutations, accurately detected 100% of endometrial cancers and a substantial portion of ovarian cancers.

I'm similarly excited about some of the strides the medical community has been making in a third area, cancer immunology, by gearing up the body's own immune system to boost defenses and attack cancerous cells. The best-known prophylactic vaccines are those that guard against microbes that put one at risk for developing cancer, e.g., Gardasil and Cervarix for human papilloma virus. In 2010, the FDA approved the first cancer treatment vaccine, Provenge, to prolong survival in men with metastatic prostate cancer.

Around the world, there are active clinical trials of cancer treatment vaccines underway in every type of cancer. At Hopkins, our pancreas cancer program director, Elizabeth Jaffee, tells me she has seen patients who were given a life expectancy of six months go on to survive six years with a vaccine she's testing. It's an incredibly exciting time.

Over the next ten years, it is safe to say that a whole range of emerging immunotherapies — including cancer vaccines, PD1 inhibitors, CAR T-cell therapies, etc. — will have a dramatic impact of a range of cancers, curing currently incurables ones and converting others into chronic disease.

Part 5: Funding woes and waning support for young investigators

So what are the major hurdles to accomplishing all the spectacular innovations I've predicted today?

Obviously, the first one is funding. We all know that the NIH has lost one-fifth of its purchasing power over the last decade and that competition for grants is fierce. This austerity makes it challenging to get innovative new projects up and running. At the same time, all the efforts underway to rein in healthcare spending in this country are putting downward pressure on our clinical revenues, which historically have helped subsidize our research and education missions. Many academic medical centers will struggle to sustain all parts of the mission, to keep doing the important work of advancing medicine for the benefit of humanity.

Concurrently, public support for science is not as strong as it has been in years past. A Pew study conducted in August 2014 found that 24% of U.S. adults believe that government investment in basic science is "not worth it." In other words, nearly a quarter of adults in this country don't believe the money the federal government puts into cancer research, genomic research, etc. benefits society in the long run. That is a mind-boggling statistic when you think of all the progress that's been made over the past 40 years alone.

The Pew Foundation also polls scientists. Every five years, the research center polls thousands of scientists about the environment for conducting research in the U.S. They ask about the perceived challenges for launching a research career and the problems interfering with the conduct of high-quality research. In the most recent poll, published in January, only 50% of scientists polled said they think this is a good time for science, down from 74% in 2009. That's a steep and troubling decline.

I won't spend a lot of time talking about funding, but I do want to say that it's imperative that all of us in this room are vocal proponents of change: that we are on the Hill asking Congress to reverse the NIH cuts, that we seize opportunities to speak to the public and the media about science and the current climate for science, and that we team up with patient groups to advocate for more awareness. We need to push these issues.

But there's a second issue that has many of us increasingly concerned, and that's the lack of support for up-and-coming scientists. William Osler, one of the founders of this professional organization, once wrote that "the effective, moving, vitalizing work of the world is done between the ages of 25 and 40." Some of us in this room might take umbrage at that, but you have to remember that life expectancy for men in Osler's time was around 50 years! Nonetheless, there is something to be said for the drive and creativity that accompanies youth — the combination of gusto and intellectual independence that is necessary to produce paradigm-shifting ideas. Young scientists are a precious resource, and I worry we are stripping them of the ability to do great science.

David Baltimore was just 32 when he discovered reverse transcriptase in 1970. It's hard to imagine a scientist that age making such an immense contribution today. In fact, the likelihood of accomplish-

ing a Nobel-worthy discovery in the sciences by age 30 has fallen to almost zero, according to a recent analysis by economist Bruce Weinberg (a professor at Ohio State). These days, the average Nobel winner in medicine is 45 at the time of the prizewinning breakthrough. Moreover, today's scientists with medical training do not receive their first major research project grant from the NIH until age 45, on average. In 1980, the average age of first RPG was 38.

Why the delayed liftoff? Well, for one thing, there's a lot more to learn. The science has gotten so much more complex, requiring many years of training and experience to accrue the mastery needed to forge an independent career. In fact, the average time to graduation for MD/PhDs is now 8 years, up from 6.6 years in the 1980s.

In addition, young physician-scientists are spending more time on direct patient care, which detracts from their scholarly research output. Finally, the NIH grant review system itself — with its tendency to fund sure-bet ideas from proven investigators (i.e., those of us sitting in this room) — disfavors the young.

Young investigators today are caught in a sort of catch-22: they lack the preliminary data required to secure the grant funding necessary to generate the data. Thus, the number of NIH principal investigators in the under-36 bracket has fallen to 3% today, down from 21% in 1980.

So what are we sacrificing by failing to fund the work of up-and-comers at this pivotal moment in their careers? It turns out, we might be losing out on something critically important: innovation.

A report summarized in *Nature* in February analyzed 20 million biomedical papers and found that young scientists are much more likely than senior ones to publish in cutting-edge areas and emergent fields. Moreover, seasoned researchers are more likely to publish on hot topics when they are overseeing the work of early-career scholars.

This pipeline problem is front and center for academic medical centers. When young scientists struggle to launch their own labs, they seek positions overseas or veer off the academic path into industry, threatening a "brain drain" for universities. To maintain our U.S. preeminence in biomedical research, we need to make careers in science more attractive and more viable.

Recent working groups have been formed on this issue by the NIH and the National Academy of Sciences. In January, Johns Hopkins University President Ron Daniels published his own suggestions for improving the system in an article in the *Proceedings of the National Academy of Sciences*. He called for strategic federal investment via creative new grants tailored to young investigators, reforms to the peer-review process, and more investment in visionary individuals rather than in specific proposals.

We have to provide ample mentoring and advising for our young faculty on a path to a biomedical career, especially at transition points. There are different ways to go about this. At Hopkins, we have encouraged all our departments to form presubmission grant-review committees, and we urge departments to enforce protected research time for junior researchers with training grants so that they can establish the robust body of work needed to win the backing of the NIH.

Finally, we must help our young faculty minimize their reliance on federal funding. Creating internal research awards is one way, but we also must encourage our budding investigators to pursue dollars from other sources, including foundations, commercial partners, philanthropists, and nongovernmental organizations. Now is the time to test bold new ideas for refueling our academic research engine.

In preparing for this talk, I looked back to the AAP presidential addresses delivered by two of Hopkins' founding fathers: William Osler (1895) and William Welch (1901). There's a line that stood out from Welch's speech. Speaking about any young man who chooses a career in one of the scientific subjects, he says this: "If he succeeds in winning his spurs, he can look forward with reasonable assurance to securing a desirable position as a teacher and a director of a laboratory of his special branch of science."

Young scientists today might not have "reasonable assurance" of becoming directors of their own labs or tenured professors, but we can make sure they have fulfilling and productive careers that help move medicine forward.

Part 6: Conclusion

In conclusion, I'm going to give you one more Lewis Thomas quote. Lewis Thomas wrote, in *The Lives of a Cell*, "Everyone forgets how long and hard the work must be before the really important applications become applicable. Generations of energetic and imaginative investigators exhausted their whole lives on the problems. You need the intelligible basic facts to begin with, and these must come from basic research." With this audience, I'm preaching to the converted; we all believe that. We believe that understanding the basic mechanisms of disease will lead the transition from supportive therapy to halfway technology to definitive technology. And despite all the headaches in our work today, I think most people in this room will agree that there's nothing we'd rather do than dedicate our lives to medical science. Thank you for listening.

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