

INTERVIEW

Extracting Knowledge From Science: A Conversation With Elias Zerhouni

Revolution and innovation in basic science, not changes at the margins, are what it will take to really improve health care.

by **Barbara J. Culliton**

ABSTRACT: National Institutes of Health (NIH) director Elias Zerhouni is pushing hard for innovation and the risk taking required to make major leaps in medicine. Fully attuned to cutting-edge work that crosses disciplines, he cites nanotechnology, clinical databases designed to answer research questions, systems biology, and an openness to radical ideas among his top priorities. The NIH director's job, he says, "is to have a vision." This requires leveraging NIH funding so that money is spent more wisely and has a cumulative effect on population health. Knowledge can be extracted from science, and health system transformation is made possible. [*Health Affairs* 25 (2006): w94–w103 (published online 9 March 2006; 10.1377/hlthaff.25.w94)]

EDITOR'S NOTE: Increasingly, contemporary biomedical science is an interdisciplinary endeavor. Real innovation often requires collaboration among traditional bench researchers, computer scientists, scholars talented in writing complex mathematical algorithms, and bioengineers, among others. Genomics and all the other "-omics," nanotechnology, modern epidemiology to fight novel infectious disease, and health information technology (HIT) are interdisciplinary by nature. And they are surely innovative.

In an effort to bring information from the world of research to the readers of Health Affairs, and to introduce biomedical scientists to the world of health policy and economics, Health Affairs is initiating a series of interviews with leading innovators in the biomedical sector. The series is sponsored by the not-for-profit Institute for Health Technology Studies, or InHealth, which recognizes that innovation in medical technology plays a vital role in better and more cost-effective health care. Its goal is to provide solid, unbiased information to the public, as well as to policymakers,

and scholars in all areas of medical technology. Health Affairs is pleased to announce this new collaboration.

The series will focus on individuals who are either innovators in their own right or in a position to foster novel research. We begin with a conversation between Elias Zerhouni, director of the National Institutes of Health (NIH), and Barbara Culliton, a Health Affairs deputy editor. Zerhouni, a native of Algeria, became NIH director in May 2002. Formerly executive vice dean at the Johns Hopkins University School of Medicine, he is also an innovator in medical imaging who was chair of the Department of Radiology and Radiologic Sciences and professor of bioengineering at Hopkins. As the following interview reveals, he is deeply committed to fostering research that will lead to the very best innovative technology for medical care and the health care system. Zerhouni's "Roadmap" for NIH makes it clear that real interdisciplinary research will be essential for major advancement in science and medicine.

Elias Zerhouni is director of the National Institutes of Health in Bethesda, Maryland. Barbara Culliton is a deputy editor of Health Affairs.

Emphasis On Innovation

Barbara Culliton: Innovation is of great interest to the health policy community and also to the biomedical community. The NIH Roadmap that you and your colleagues developed to stimulate new research at the National Institutes of Health [NIH] is focused in many ways on innovation. Could you give me some examples of what you think have been the most important areas of innovation in recent years? What innovations in medicine or research are making an important difference?

Elias Zerhouni: First of all, let me make sure we get the context right, because I think some of the readers and authors of *Health Affairs* think that NIH is doing irrelevant research. It's not true. You mentioned that *Health Affairs* is preparing a special issue on cardiovascular disease. There has been significant progress in the management and treatment of heart disease in the past decade. Many people do not know how much NIH-funded basic research lies at the foundation of this success.

In terms of innovation overall, I think we're at an inflection point. We're in a different regime right now from biomedical sciences and the implications for research, and there's going to be a new approach to a lot of NIH priorities that will have major importance to health. Just to give you an example, if you looked at the medical team caring for one patient in 1960, you probably had the doctor and nurse and part-time work from a laboratory person—two and half people. Today, to render the care we're rendering, you're talking about seventeen, eighteen, or nineteen people per patient per encounter. Today, a patient is likely to get services from radiology and pathology, plus an internist or other specialist, and drugs, plus administration, billing, and things like that. Health care has become, if you will, an activity that has grown to a sort of mass customization, with many tests and consultations.

The most expensive way to practice medicine is to do it the way we do it, where every interaction can involve as many as twenty people. So the transaction costs are enormous. My view is that we are going to have to make major changes, not changes at the margins. Better

information systems—electronic medical records—are important, but they are at the margins. They're going to be critical, no doubt about it, but they're not going to truly revolutionize health care in the twenty-first century or improve our health in the twenty-first century to a degree that would be desirable.

So then you have to say, OK, if that's the view, what strategies do I need to think about, and what knowledge do I need to extract from science, to make a difference? If we keep practicing the medicine we know today the same way for twenty-five years, we will have lost the game.

There's no doubt that marginal improvements in any part of the system are insufficient. We're going to need revolutionary improvements. They can't come unless we have the ability to understand not only terminal phases of a disease process but, more important, the entire life cycle of the disease process. What do I mean by this? Think of it this way. In any disease process you can think of, you have normal biology, and then something is happening biologically that you're not aware of—it's called the preclinical phase, right? And then, all of a sudden, you're aware of what's happening because some symptom appears, which tells you, "Hey, this is not right. I have high blood pressure." It's not right to have it. You compensate for it. It's called the compensated phase of the disease. And eventually the disease progresses somewhat. Most people intervene at that interface—for example, when they have chest pain. That's when patients are willing to pay anything to get back to the "compensated" phase, where they can handle what's going on. But, frankly, when you look at that curve of loss of health, you realize that your strategy should be to minimize that loss, right? But you also realize that the cost of doing so is the highest at that interface between compensative and decompensative. When you have chest pain, you go and get angioplasty, and then you get surgery. It costs \$100,000, and if that doesn't take care of it, you might get a heart transplant, for all you know. So what we need to do is to understand the life cycle of the disease much earlier—on a preclinical basis,

not a symptomatic basis.

Culliton: How do you propose to do this? It is easier to describe than accomplish. If you look at the NIH Roadmap, you see some startling suggestions for setting research priorities, certainly compared with former plans for redesigning the research infrastructure. The roadmap is very contemporary; it focuses on all the new sciences, many of them with elements of the physical sciences woven into biology. I think it's the most radical plan for NIH that I've ever read. If you really implemented this plan—

Zerhouni: You'd make a huge difference.

Culliton: Yes. A lot of the currently funded grants that, in effect, are making differences at the margin, including some duplicative research, would have to go. Because something's going to have to go. You do not have infinite resources, despite the fact that the NIH budget has doubled during the past five years to \$27 billion.

Zerhouni: Right. And that's the point. So what is the core issue that I see? If you want to transform medicine, it has to be from something other than the curative paradigm: Wait until you're sick and then come and see me, and I'll do what I can. That has been true for 5,000 years. Now we have to do something different.

Culliton: Agreed.

Zerhouni: The reason we have not been able to change earlier is because we were ignorant. We just didn't know what happened at the very primal event that leads from health to disease—you know, when the first molecule in a cell or neuron does what it does to go off track.

Culliton: Don't you think we're still fairly ignorant?

Zerhouni: We are. So that's my point. That's why the NIH Roadmap is helpful: It points in the direction of knowledge, which is where good science needs to go. It's what I tell people: At the edge of science, between the known and the unknown, everybody's ignorant. And if anybody says they know, they're not scientists.

From Prevention To Preemption

Culliton: When you talk about understanding the disease process early, you're posing a different paradigm than what we usually think of as prevention.

Zerhouni: Oh, yes. It's different.

Culliton: That is important, because we think we know more about disease prevention than we do. We're really very ignorant there.

Zerhouni: It's really what is called preemption. Prevention is stopping something you know is there. We don't know exactly why it's there, but we correlate the early signs of disease with something and say, "Gee whiz, you could prevent it." Preempting is removing the initial molecular event—precluding the possibility of that thing even happening. That's different. And that's the concept I'm promoting. But how

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do you get there? You go from the curative paradigm and you say, OK, what is next? Everybody talks about personalized medicine. Just as an aside, in Seattle recently, I talked about personalized medicine. I said that in twenty years we're going to have what I call the "three-Ps medicines": predictive, personalized, and preemptive. That's my vision. And I really think that's where science is going. A reporter then said, "Personalized—you mean that finally, in twenty years, I'll have my own personal doctor?" No. That's not what I meant: Tailored, individually tailored. But the key word is not personalized. The key work is preemptive. That's different.

Culliton: And to get preemptive medicine, you need to focus on the new technology you describe in the roadmap and count on a totally new form of innovation?

Zerhouni: Yes. You need new tools for understanding biology as systems. We need to get away from the reductionist approach: One gene or one event causes disease. So then, the question is, How do you get there? What has happened that allows us now to think that we can understand systems? Well, obviously the

technologies spawned by the genome—genomics, proteomics, and so on. People will give you that list of things they can identify and say, well, you see, we can do it. The whole field of biomarkers is really developing.

Academic And Industry Research

Culliton: This line of discussion raises the matter of the relationship of basic academic or NIH-funded research to research in the biotechnology or pharmaceutical industries. The biotech industry is founded, in many ways, on basic research. The NIH Roadmap talks about promoting collaboration. At the same time, policy discussions have arisen about whether this is appropriate or not. Why do you think these collaborations are important?

Zerhouni: Public-private partnerships permit the leveraging of the NIH's clinical and scientific resources with a wide variety of private entities, including research institutions, patient advocacy groups, professional organizations, foundations, and industry. This is part of the NIH's mission—one aspect of the roadmap that we think will hasten the translation of basic discovery to medicine for the public.

Important Innovations

Culliton: OK. Back to where we were. We were talking about the importance of innovation in science. What are the most important innovations, in your view?

Zerhouni: One of the most important discoveries of the past decade has been the phenomenon of RNA interference, and regulation of RNA at the molecular level. Why is that important? The beauty of that discovery is that it gives us a tool that allows us to turn off a given gene on a very specific basis—a cancer gene, for instance.

We know that some disease processes begin when a single gene is turned on inappropriately. The developing technology of RNA interference enables us to selectively block gene activity. It's also known as gene silencing. If you have the right RNA code, you can stop the gene you're aiming for, and that gene only. Never in the history of mankind has this ever been possible. Can you imagine?

It's almost like trying to understand cell

phones, but you are an alien and you don't know how they work. Then, all of a sudden you discover that, hey, they respond to a given number. And if I can send that number, I can basically talk to that cell phone and not the other ones. Can you imagine the power of that tool? And sure enough, we're already seeing the progress with RNA interference.

A lot of the work is still in the laboratory, but I bet it will not be for long. For instance, people working on *C. elegans*, the roundworm, have identified ways to interfere with muscle and with the genes that regulate fitness and fatness. They have identified some genes in model organisms whose function in human genes is unknown. We don't know what they do. So, to me, understanding RNA interference as system is a core message of the roadmap, which is aiming at really advanced problems. The frontier is what I call biological complexity on a predictive basis.

So, when I see an inflection point or phase transition—I'm sure you will understand that—what does that mean in terms of scientific exploration? It means that we've gone from the typical reductionist phase of science, which is a step ahead of descriptive biology, to the point where we can now envision the most integrated understanding of systems biology. For this, you can see that you can perform a whole new type of experiment. We will need the collaboration of biologists, computer scientists, mathematical modelers, and so on to understand not just a particular molecule but groups of molecules interacting with each other. And to do that, you need to work on the tools that allow you to turn the genetic switch on, off, on, off and see what the regulation and the pathways are. I think that's possible today. The next challenge is creating the ability to test it in a human population.

Translational Research

Culliton: This is an ideal segue into another major feature of your plan for NIH: namely, special emphasis on translational and clinical research, the sciences that take basic studies into human beings. You have said that it has become quite clear that available animal mod-

els of human disease are often inadequate, necessitating even more research on human populations and biological samples. So suppose you want to go use RNA interference and go from experiments in *C. elegans* to people. Obviously, you are right to say that the pool of researchers skilled at translational and clinical research needs to be rebuilt. You are also suggesting that there should be more research in people because some studies simply cannot be done in laboratory models. It is inevitable that some of this research will be risky, and we seem to be a society that is not comfortable with risk when risk means losing rather than winning. How do you think this will play out?

Zerhouni: It's hard enough to propose risky research for patients with acute, terminal illnesses. It's even more difficult when it's a chronic disease, yet chronic disease is far more prevalent and, therefore, far more expensive to the health care system than it used to be. People are willing to accept more risk if it's an acute disease—there's a risk tolerance that's different.

I think there was a dream not too long ago that we would be able to model any human disease in animals. And that's where we've had progress—for instance, cancer in mice, whereby you insert human cancer genes to cause human cancers in mice. We have immune models, and they are very helpful, very important. But it isn't enough. Someone said we can cure every cancer in mice already.

Culliton: Judah Folkman at Harvard has said that if you have a mouse with a tumor, he can cure it. People have jumped to the conclusion that, therefore, he and others can cure human cancer. But it's not so.

Zerhouni: So that tells you already that we put too much hope in mice. Plus we have no basis to say that just because something does not work in mice, it will not work in humans. We don't know enough to say that, so we have to think carefully about how much weight we give to these studies, valuable as they are. We

don't even have that loop closed. So clearly we need to have a different construct when it comes to translational research; we need to reinvent it. And we need to reinvent it with the new tools of genomics and bioinformatics and others. For example, nanotechnology is going to be very, very important in our ability to conduct clinical research—what we call MEMS, micro-electronic mechanical systems, “labs on chips” concepts. That's going to be very important in transforming clinical research because, as I've noted, we're dealing with chronic diseases primarily today in our population. I imagine using nanotechnology as a way of tracking the course of disease in people at home, under natural conditions. We will be able to monitor the effect of our interventions (drugs or whatever) and see what perturbations are critical to success or failure.

The connection of nano devices to an information system that can track a population over time is going to be critical. The correlation of that to samples of blood, or whatever tissue, is also going to be critical. So, you see that I'm envisioning a very different world of clinical investigation.

The job of the NIH director is to be the visionary who says, We are the edge of science, and to provoke a change—be a provocateur, not the manager of the status quo. It's extremely hard. The key thing, though, is if you don't have a framework for a vision, nobody moves in a really new direction. Today there are genuinely new opportunities, but the new science will require interdisciplinary collaborations. That will be key.

Culliton: What, in your terminology, is the difference between translational science and clinical science?

Zerhouni: It's really two aspects of a better approach to understanding human disease. Translational is when you're taking research that you've learned at the bench and taking it to the bedside, in clinical trials or whatever. Clinical research is something else. I'll give you

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an example. You have drug A—I'm just going to give you a simple one—drug A, drug B, drug C. What is the best dosing for these in the human population? That's what I would call clinical research.

But translational science for me would be that you discover that Vincristine had anti-tumor characteristics, and you ask, Why does it have that? Or Taxol. It seems to affect the cell life of the tumor cell. Why does it have an effect? OK, let's make sure we can make that happen. Then you take it from yew bark, where we found it originally, and make a synthetic version, which will be consistent every time you give it. That's translational science. Clinical research, on the other hand, is optimization. So, I think we're traveling to a new world where we will have to intervene well before disease strikes.

Culliton: But you will need a large team to conduct the research under this model.

Zerhouni: Right.

Culliton: Elaborate more on your vision. How are you going to implement it?

Zerhouni: At the fundamental level, we need to continue to invest in basic science at an accelerated rate. That's why we need to look at the NIH Roadmap. Sixty percent of it is directed at basic science. It's not clinical science, although people misunderstand that. It's stimulating and provoking people in moving from a reductionist phase of science to a phase of science where they can understand not one molecule at a time, but micromolecular assemblies—understand not one pathway at a time, but how pathways interact with each other. It's what we were talking about before: biology as a complex system.

Culliton: Complex in time and space. We've only recently been able to think seriously about understanding physiology in time and space.

Zerhouni: Exactly. Time and space.

Culliton: So it doesn't matter that you have a gene somewhere: You need to know when it's turned on, when it's turned off, and what other genes are in contact with it.

Zerhouni: Exactly.

Culliton: And you need to know what turned that gene on or off.

Zerhouni: And you need to know in a quantitative way—more quantitative biology.

Culliton: You find that the characteristics of the clinical investigator need to be redefined.

Zerhouni: Exactly. And of basic science, too. Because at the end of the day, you need to import all of these discoveries—RNA interference, large-scale mass-spec determination of protein changes over time, nanotechnology—all these will have to be applied in a clinical environment, because we need to design new disease models that will predictably model disease in humans. At least we don't know how to do that. We have

transgenic mice, for instance, and that's important, but we can't rely on that forever.

Culliton: In other words, those animal models are no longer sufficient.

Zerhouni: Right, they're not good enough. And they tend to focus on one gene at a time.

Culliton: And now science now needs to focus on many genes interacting with each other?

Zerhouni: Yes, that's right.

Culliton: Will this new science, which brings a component of the hard sciences and mathematics to biology, change medical school?

Zerhouni: Yes, it will change medical science education in medical schools. I don't know that it will change basic physiology and the like. And its effect will vary. Because medical schools are diverse—when you've seen one, you've seen one; there's a spectrum of activities in medical schools. But the key message here is that medical school science needs to accept a major shift in thinking, not looking at one molecule over and over again, but looking at systems of molecules interacting. If you look at a

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disease molecule by molecule, you get an interesting result only one out of 5,000 times. And that's why the pharmaceutical industry is so ineffective—because that approach is just not predictive enough. And the understanding of this in terms of positive action, and of determining safety, are the twin stones of making sure that you get to something that will have an effect. Reinventing translational science is the other side of the coin.

Culliton: So that's why you're saying this is still an enterprise that requires a lot of basic research.

Zerhouni: A lot of basic research. But you see, that basic research has a leveraging ratio that is enormous in the population. Why? Let me give you an example. You've already given the example of cardiovascular disease, so you know the impact of that. But let's look at HIV/AIDS. Remember that in the mid-1980s we had no treatment—nothing; 50 percent of the patients were terminal AIDS patients.

Culliton: Yes.

Zerhouni: And when we made our predictions for the future (I was at Johns Hopkins then), we predicted that 80 percent of all medical beds would be occupied by AIDS patients by 1995. In this country, we were successful in finding the value of AZT and of the protease inhibitors. That was basic science, and now we have medicines that work.

Culliton: And the blood tests to detect the virus and keep the blood supply safe.

Zerhouni: Sure. Without all of that, we would have about 200,000 patients right now in U.S. hospitals, and the equivalent number on the steps of Capitol Hill screaming at us because we haven't done anything for them. But we made progress because of the basic science. The basic science cost, as I look back, was about \$10 billion in the ten years between time zero—the identification of the virus—and the implementation of therapies that started to lower the death rate. People look at that and say, Well, all right, it affected a few people. But the gain in leveraging is this: That \$10 billion saved \$1.4 trillion in health care expenditures—\$1.4 trillion. That's what it would have cost to care for all of those AIDS patients, if

you figure in nursing, supportive care, and hospital care. That would have been tragic. You could have had that, or you could have invested \$10 billion in science, which we did, and ultimately it saved us \$1.4 trillion. But still people complain. They say, Oh, the cost of these drugs—\$12 billion a year! Right, now the patient is alive because of expensive drugs. And many are productive. But you know what? I'd pay that \$12 billion a hundred times over instead of having 200,000 dying people in my hospital. That basic science investment paid off 140 to 1. That's what I mean by leveraging.

Information Sharing And Open Access

Culliton: Let's shift the conversation back to innovation, which I know is high on your agenda, especially nanotechnology—clearly a science that requires researchers with many different skills and a lot of imagination. Earlier you said that using nanotechnology, physicians will eventually be able to implant what we might call nano-tracers in a patient, and determine when the disease process is just beginning. There is another aspect of this kind of science altogether, and it has to do with taking information such as you're describing and putting it into vast shared databases for research purposes—a national project in epidemiology like we've never seen before. Right now we don't have huge clinical databases that can be used for research. One issue here is creating the right databases and the algorithms that can ask the right questions to mine the data. The other is open access. You are promoting a plan to have all NIH researchers deposit raw data in an NIH-managed database. Would this create an entirely new research tool, a way to look at physiological changes in large numbers of people over time?

Zerhouni: Right. If you go back to the NIH Roadmap, there's one subtopic that we call NECTAR—the National Electronic Clinical Trials and Research network. And the reason we picked that word is that when the bees come, they pollinate the flowers that make the honey. That's the nectar. So we extract the nectar of knowledge.

Culliton: Very poetic.

Zerhouni: Very poetic, yes. I'm proud of that one. But the idea was exactly that. We're doing all these trials that record information that is never used again. We're doing all these experiments that don't work. We have no one place where the integration of the information can be used as a powerful hypothesis generator as well as a powerful way of understanding the change in phenotype or the change in response, whatever you can think of.

Culliton: Does this require creating a new database, analogous to GenBank [the NIH genetic sequence database] or some of the other major databases that are widely used by scientists from all over the country and the world?

Zerhouni: Well, you should definitely build the platform, then test it and pilot it. One of our problems is that when you get so big, you have so many vested interests in their little piece that you basically can't pioneer anything new. So that's why the roadmap is different: It fosters innovative research.

Rewarding Innovation

Culliton: What other ideas are you trying to get off the ground?

Zerhouni: One is what we call the Pioneer Award. It is going to fund truly innovative work, not anything that is already going on. You'd think that would be welcomed. But everybody said, Oh, no, we're already pioneering. We don't need a pioneer award program. But I said, We'll do an experiment. We'll see. It turns out that one of the first pioneer award-ees was a nanotechnologist, who in one year developed a barcode for identifying biological traits. In one year. That's fantastic. Six of the nine Pioneer Awardees in the first year had never done anything for NIH, and they were all in different fields—new fields for us, including the hard sciences and bioinformatics.

Culliton: That speaks to the point about interdisciplinary science and its relevance to biology and medicine.

Zerhouni: Yes. Let me give you an example. This award winner had an idea, and he said, If I use my nano particle and I combine it with multiple DNA strands that I know the code of,

and then I attach to that a detector for the Alzheimer's protein in the cerebrospinal fluid (CSF), maybe I will find markers from patients with Alzheimer's disease. Boom. One year. He had it. We had been looking for a CSF marker for early Alzheimer's disease for years. So that's a case in point showing that if you open up the possibility and you pilot it, it may happen. And so far, I've been right. But, you see, this is what I thought: I thought we were too conservative. And our process of peer review sometimes is too conservative.

Culliton: That's why I'm looking for examples. I've been following NIH for a long time, and in many ways it is conservative in selecting grants for support. In a former plan to bring clarity to the NIH administration and grant giving, there's a paragraph, deep in the middle of the document, that suggests that NIH start a new study section for "innovative ideas." At the time, no one seemed to grasp the implications of that paragraph. They didn't get the fact that that suggestion implied that they were not supporting a whole lot of innovative ideas or you wouldn't need a study section for innovative ideas.

Zerhouni: For twenty years we talked about funding an innovative research award, but nothing got done. So, it's one thing to say you're conservative and so on. Another thing is to do something about it. It's easy to sit back and be a critic. What is not easy to do is to have the vision: OK, what do we do about it? We created this parallel process for the Pioneer Awards. I understand now why it took twenty years—because the counterarguments I had about this were enormous. And the first reason was, "Wouldn't that be an admission that we're not innovative?"

Culliton: It could be interpreted that way.

Zerhouni: Wouldn't that be a waste of money because any crazy idea out there would be innovative? I said, no—we'll try a different peer review process.

Culliton: How much money did you put into the Pioneer Award program?

Zerhouni: It's pretty large; Each award is \$500,000 a year for five years. That's two and a half million dollars per award. The first year,

the institute directors said, Let's do seven to try it out. And the first year we had so many good ones, we did nine. The second year, we decided to do fourteen. And now we're talking about expanding it even more.

The key thing is to do the pilot. You prove that it's valid. And the process has opened new attitudes. Now, when novel applications go directly to one of the institutes, a lot of institutes say, Gee, I like that idea. So there are lots of new grants that got funded not within the Pioneer Award program per se, but because of new attitudes. For example, the Dental Institute saw a proposal from this fellow who said, "I can diagnose through the saliva many of the conditions that would be of interest to oral health and so on and so forth." So they picked it up. I want to create an aura around the Pioneer Awards, but I don't want a hundred of them. They have to be highly selective, highly prestigious. But I want the idea to spread through our culture.

Culliton: It sends a message that it's OK to take a risk.

Zerhouni: Right. And that to me is more important than the amount of money. Because I know that these innovative people come in, and their ideas get picked up. It might not receive a Pioneer Award, because Pioneer Awards, frankly, are highly selective. It's like the mini-Nobel for young investigators.

Now, go back to your question about databases for clinical research—the same thing is true. You need a pilot project to get people to respond. So, for example, through the roadmap we have a funded project called Informatics for Integrating Biology and the Bedside (i2b2), based at the Brigham [Brigham and Women's Hospital, in Boston, Massachusetts, one of the founding hospitals of Partners HealthCare, which includes the Harvard teaching hospitals and community hospitals in the Boston area]. We asked them, What can you do to test the idea of tracking a population through medical records? A lot of people would say, You won't be able to do this unless you reform the entire health care system. Great. But that's not very pragmatic.

Leveraging Research Results

Culliton: So this is a way to think about using data from papers written with NIH funding to create a new approach to doing a kind of epidemiological research that wasn't possible without new computer and bioinformatics technology.

Zerhouni: Right. It's the same thing. People tell me, If you really want to do this, you're going to have to reform NIH. Forget that. That's a lifetime, and that's not practical. What you need to do is conduct defining pilots. RNA interference didn't happen because all of us thought it was a great idea. It happened because a couple of very smart scientists had an insight, and then everybody else adopted it. So the i2b2 program, which is ongoing right now, is going to collect all the files in the Partners HealthCare system—two and a half million electronic records. Within a few years, the answer to your question will be known to us through the i2b2 project. There was a national competition to become the site for this project; it wasn't easy, but the Brigham got it. We now have the same concept with the Kaiser Permanente system, too, looking at their approach. The science and knowledge have to be extracted by tracking patient populations over time with very precise phenotyping information correlated with lab tests and so on. If we see value, then that justifies further investments.

Culliton: If you had large clinical databases to which lots of researchers contributed, you could not only ask so-called informed questions, you could also ask the computer to generate correlations that one might not even anticipate, by writing algorithms that ask random questions. This would add another new dimension to the use of large databases to develop information about patients and disease, or health for that matter.

Zerhouni: Right. I hope you can capture the enthusiasm I have for the possibilities. We've never had so many possibilities, really—the changes that I'm seeing at fundamental level. To me it's a scale issue. If you look at the history of medicine, 5,000 years ago, we understood the empirical observation: You look red;

you look pale. We understand so much more now, in depth, that was completely unknown back then. Neuroscience—there's another frontier of science, which is why we included a neuroscience blueprint in the NIH Roadmap. But as you try to crystallize it for a nonscientific reader, we're exploring, essentially, at different lower and lower levels of scale and higher and higher levels of complexity. So, when you look, for example, at structural biology, we now know that all of the things that happened in life systems are related to interactions of proteins and very precisely modulated. We know that. But we have no clue how these structures do that. Sometimes we don't even know about one protein, let alone multiples together. Here's an example. We knew 2,000 protein

structures ten years ago. Today we know 35,000. The problem is that we only know 2,000 that are bound to the membrane of cells. And you ask, How much do we need to know? It's about a million. So, big jump. If you look at the scale, it's exponential. But there are thousands more protein structures to learn.

Culliton: Genomics is another example.

Zerhouni: Yes, genomics is the same way. And it will get us somewhere, but maybe not right away. Just as nanotechnology will. You know, what's really emerging is that we're made of nano-machines. We are nano-machines that have been put together. And we don't understand how you go from one scale to the other. We have to understand all the little nano-machines and the genotype. That's the challenge of science today. But at the end of the day, if we're not predictive, we're not individually targeted, and we're not preemptive, medicine is not going to work in a society that requires twenty people to take care of one person at any one time. It's just not going to be economically viable. Little changes aren't going to do us much good.

Even in a nationalized health care system, because you have no billing and no administration, you will gain another 5 percent. That's

not enough to make a dent. No. You need what I call the leveraging effect of science. Go from 1 to 140 in value, as in AIDS. That is the game. And you have to innovate to be there, and you have to be on the edge of science. That means that you don't know the answers. And you have to push it. People talk about the NIH budget at \$28 billion being a lot. But frankly, it's \$96 per American per year. For all of cancer, it's \$16 per person per year. Yet we know that half of our population is going to suffer from cancer. So, just to give you an example, for any one person, if I invest at the current level for fifty years, it's \$800—less than half a day of cancer treatment. You follow the argument?

Culliton: Yes.

Zerhouni: The leveraging effect is enormous, but obviously, there is a lot more to do. And we are in the transition. We have to learn how to spend money early in the life cycle of disease. The money that has been the least productive—the least productive—is the money that's invested at the end of the life cycle of a disease process. That is not productive. To have that grow by 10–15 percent a year as a nation, spending \$600 billion on that part of the disease life cycle instead of investing in all up front, is, I think, a waste.

We can't slow the pace of research because "Oh, we don't have enough money," so we just won't do anything new. That is the kiss of death. That's exactly when you need strong leadership and when you need to provoke people into looking into different directions.

Culliton: I gave a talk to the AAMC [Association of American Medical Colleges] annual meeting about fifteen years ago and told them that, in fact, there was no reason that the NIH budget needed to increase.

Zerhouni: Oh, my God. I would have hated you for that.

Culliton: I said that what you have to do is spend the NIH budget better.

Zerhouni: Well, now I think we're spending it better.

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