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to the
Subcommittee on Science, Technology and Innovation, Senate Committee on Commerce, Science and Transportation
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Chairman Kerry, Ranking Member Ensign, and Members of the Subcommittee, I am grateful for this opportunity to describe our research to those who support it. I will give a brief account of the research, its significance, and future prospects. Then I wish to explain some of the challenges we face and how they may be overcome.

The control of gene expression

Our research has to do with genes, which direct the formation and the activities of our bodies. Every cell in our bodies contains a complete set of genes. Which subset of genes is used in a particular cell determines whether it becomes nerve, muscle, blood, liver and so forth. The goal of our research and that of many others has been to understand how this controlled use of genetic information is accomplished. The practical implications are enormous. All infectious disease entails genetic control. Cancer results from a breakdown of control. Therapeutic approaches such as stem cells require intervention in genetic control.

Genetic information has been likened to a blueprint or a book. In order to use the information, the book must be opened and read. Our work has uncovered principles of both the opening and the reading of genetic information. We are now close to understanding genetic control.

The nucleosome, fundamental particle of the chromosome

Genetic information is contained in a long thin molecule of DNA. Human DNA is a meter in length and must be compressed to a micrometer in our cells. This might be accomplished in an organized way by spooling, as is done for sewing thread or garden hose. The problem is that to gain access to a gene in the middle, the entire length must be unspooled. Nature has solved this problem by the use of mini-spools. I proposed in 1974, and it has since been verified, that DNA is wrapped around a set of eight protein molecules in a particle known as the nucleosome. A million of these particles are strung together in a human chromosome. For access to a gene in the middle, only a few particles need be unspooled, while the rest are left undisturbed. Unspooling is a key control point for gene activity, and is already a promising target of anticancer drugs.

RNA polymerase, the gene-reader in our cells

Once DNA is unspooled, the genetic information can be read. The gene reader is a protein machine known as RNA polymerase, which copies the genetic message into a related form called RNA, in a process known as transcription. RNA directs the synthesis of proteins, which perform all bodily functions.

In work done over the past 25 years, we have obtained a picture of RNA polymerase in the act of transcription. RNA polymerase is composed of 30,000 carbon, oxygen, and nitrogen atoms. Our picture shows the precise location of every atom. In this picture, we see the DNA double helix entering the polymerase machine and the RNA product as it is formed and released. This picture has revealed the basis for readout of the genetic code, and how occasional mistakes are corrected. It has already been employed for the design of new antibiotic drug. Structure of RNA polymerase in the act of gene transcription. Chains of protein building blocks are shown in white and orange. Gene DNA, in the form of a blue and green double helix, enters from the right. RNA, shown in red intertwined with one DNA strand, exits from the top.

The future: A molecular computer for the control of gene expression

RNA polymerase does not act alone in the readout of genetic information. An additional 50 protein molecules participate directly in transcription. We discovered, in particular, a giant assembly of 20 proteins called Mediator that serves as a kind of molecular computer. Mediator receives information from inside the cell and from the environment, which it processes and delivers to RNA polymerase. A major objective for the next decade of our work is to determine the atomic structure of Mediator and to understand the control of transcription. We already know that mutations in genes encoding Mediator can cause cancer. Knowledge of Mediator structure will enable us to correct many such problems and to intervene more generally in the control of gene expression.

The challenge of funding basic research

Our work has been supported almost entirely by the NIH. The cost was about \$20 million over 30 years, mostly for the stipends of the more than 80 graduate and postdoctoral trainees involved. Due to current constraints on the NIH budget, virtually none of our work would be funded today. I can say with certainty that ***a grant application for the research leading to the discovery of the nucleosome, fundamental particle of the chromosome, would not be approved.*** The reason is simple: I had no idea at the outset of what I might find, and no good idea of how to go about it. Our ***RNA polymerase structure work was supported by NIH only after it became clear it would succeed.*** When we began, the prospects for success were virtually nil – no way of producing the RNA polymerase, no hope of forming the crystals needed for imaging, and no technology for deriving the image.

The reason for the disconnect between funding and discovery is clear: funds are awarded for compelling ideas, supported by preliminary evidence, creating a high likelihood of success. But **discoveries are by their nature unanticipated, completely unknown**. They cannot be sought out in a deliberate manner. They cannot be proposed to granting agencies or evaluated by review groups. So how are discoveries made in the American system? The answer is by risk-taking. Scientists supported to do straightforward research may divert some of their funds for testing new ideas. If they succeed, then the results form the basis for new grant applications. If they fail, they may be in trouble and be unable to continue even with their original research.

The risky nature of truly innovative research is both the strength and the Achilles heel of our system. In the past, when NIH funded approximately 20% of new grant applications, most capable investigators could obtain support, some of them would conceive of and try new ideas, and occasionally an important discovery was made. Today, with funding levels at 10% or less, many fine investigators have lost their support, few will take risks, and the pace of discovery will fall dramatically.

In the March 23, 2007 issue of Science magazine, Senator Arlen Specter is quoted as asking the reasonable question "What's going to happen to NIH if the budget is cut by \$500 million?" The answer is that the number of publications from NIH-sponsored research will decline accordingly, by about 5%, but innovation will be stifled across the board. The chilling effect of funding cuts ripples through the system, deterring bold action and creativity on the part of established investigators, and discouraging young scientists from entering the system. This has already happened. My European colleagues have noted a reverse brain drain already occurring now.

There is another way in which small budget cuts can have a disproportionate effect. Research is highly synergistic. One part depends on others. For example, my own determination of the RNA polymerase structure was critically dependent on the work of hundreds of physicists and engineers, on synchrotrons such as that at the Stanford Linear Accelerator and on cutting edge photon physics.

Of all the adverse effects of flat-funding or even cutting the NIH budget, the disillusionment of young people is the worst. The choice of a career in science already represents a great sacrifice. A passion for science must be weighed against a long period of training - 10 or more years of postgraduate study at low wages - and the possibility of no career at the end. The importance of young scientists cannot be overstated. To paraphrase an illustrious politician, it's the people, stupid! Progress in science, and discovery in particular, is the work of the best young minds. America has taken pride in the Nobel class of 2006, present here today. If we do not take action now to restore enthusiasm for the pursuit of science, there will be no American class of 2026.

Discovery as a driving force of progress

Much has been said about the value of basic research, and I am sure the arguments are well known to you. I would like to add some points not so often stated. Scientific medicine is comparatively new, just over a hundred years old. The advances already made have impacted the lives of us all. Every major advance can be traced to a discovery made in the pursuit of basic knowledge, not for a medical or economic purpose. Some examples are X-rays, antibiotics, magnetic resonance imaging, recombinant DNA, and structure-based drug design. Future advances, including the prevention or cure of cancer, AIDS, Alzheimer's, and other dread afflictions, will come from new discoveries and new information. Efforts currently targeted towards these and other worthy ends are unlikely to succeed. I recall the words of Lyndon Johnson to the effect of "life-saving discoveries locked up in the laboratory." This serious sentiment was mistaken. Application of existing knowledge is not the limiting factor. The knowledge itself is limiting.

It has been remarked that we know 1% of everything about the human body. A small fraction of a percent would probably be more accurate. But consider how enormous have been the benefits to our health and our economy from what little we know now. Imagine how great would be the benefits of knowing the remaining 99%!

There is a further overarching purpose to basic research. An urge to explore is a part of our nature. It was a major factor in the evolution of our species. It has motivated us to go to the moon and to outer space. The exploration of inner, human space is no less grand. It is also an expression of the human spirit.