DIRECTOR'S REPORT

Much has been written about the extraordinary events that took place in Cambridge, England, 50 years ago that changed biology forever. The discovery of the double-helical structure of DNA ushered in an immediate future for understanding how genes are inherited, how genetic information is read, and how mutations are fixed in our genome. 2003 will appropriately celebrate the discovery and the stunning developments that have occurred since, not only in biology and medicine, but also in fields unanticipated by Jim Watson and Francis Crick when they proposed the double helix. DNA-based forensics is but one example, having an impact in the law to such an extent that some states are now reviewing whether capital punishment should be continued because of the possibility of irreversibly condemning the innocent.

In all the writings and lore about the double-helix discovery, one of the little discussed points that struck me was the freedom that both Jim and Francis had to pursue what they felt was important, namely, the structure of DNA. Having completed graduate studies in the United States, Jim Watson went to Copenhagen to continue to become a biochemist in the hope that he might understand the gene, but he soon realized that biochemistry was not his forte. Most importantly, after hearing Maurice Wilkins talk about his early structural studies on DNA, Jim had the foresight that understanding DNA structure might help understand the gene and therefore he decided to move to Cambridge, then, as now, a center of the field now known as structural biology. Remarkably, although this decision was strongly supported by his mentors, it was not favored by the U.S. funding agency that paid his stipend in Copenhagen. If Jim had followed the suggestions of the funding agency, he would have moved to Stockholm to work with the cell biologist Torbjörn Caspersson, almost certainly ensuring that he would play no role in figuring out the double helix. Support from Salvador Luria, his Ph.D. research mentor, and his new colleagues at Cambridge enabled him to make this important move and essentially ignore funding considerations. Although supposedly working on protein structure, Jim was intellectually free to think more about DNA than protein. Eventually, Luria's and later Max Delbrück's support facilitated funding for Jim to remain in Cambridge. Thus, it helps to have supporters who can influence funding agencies.

Meeting Francis Crick at Cambridge is now the stuff of legend. Francis was pursuing his thesis work on proteins, but he had the freedom and eventual support from his peers to go after DNA when it was clear that building models was the best way to proceed. Individually, they took a big gamble, particularly Jim Watson because failing meant having nothing to show for a substantial amount of time, talk, and energy. However, Cambridge was an environment where risky projects were the norm. At the same time, Fred Sanger was sequencing the first protein (insulin), and Max Perutz and John Kendrew were determining the first three-dimensional structures of protein.

Fifty years ago at Cold Spring Harbor, Al Hershey and Martha Chase had just demonstrated that DNA was the genetic material in phage, the viruses that infect bacteria. Meanwhile, then-director Milislav Demerec yet again played an important role in the development of Cold Spring Harbor Laboratory as a major research center. Immediately after the Second World War, the two laboratories at Cold Spring Harbor that were both directed by Demerec

proposed an expansion of the inadequate facilities, including the addition of a lecture hall and new laboratory buildings and upgrading the grounds. The necessary funds came in 1950 from the Carnegie Corporation and the Rockefeller Foundation. But the events in Korea (some things never change) prevented starting the project until August 1951. Vannevar Bush, then director of the Office of Scientific Research and Development that was responsible for science during the Second World War, opened the new lecture hall in late May 1953, just in time for the annual Symposium. (In 1945, in response to a request for recommendations from President Roosevelt, Bush issued a now-classic report ["Science: The Endless Frontier"] in which he described the importance of biomedical research "for the War Against Disease, for our National Security, and for the Public Welfare.")

Organized principally by Max Delbrück, it was at the first Symposium in the new Bush Lecture Hall in June of 1953, attended by a record 272 scientists, that Jim Watson presented the double helix to a well-prepared audience. Delbrück had distributed copies of the *Nature* paper prior to Jim's talk. A few weeks earlier, Bush, the engineer turned science administrator, stated about biological research, "If I were a young man I am sure that that would be a field I would plunge into. Every day it becomes more attractive; and it touches the lives of all of us in countless ways." Perhaps he had been tipped off about the lecture that was soon to be presented in the hall that now bears his name. He went on, "It is a privilege of you neighbors on Long Island to extend this opportunity to men of great intellect, who can qualify, and who can thus bear the torch for all of the rest of us, in delving into some of the mysteries of life." It is still a happy circumstance that men and women who work at or visit Cold Spring Harbor receive most welcome support and encouragement from our neighbors.

Bush was correct in noting that the field of biology was then at a pivotal time. The double helix was the seed of a revolution that is still ongoing. Although life is no longer mysterious, surprising discoveries continue, such as the recently discovered RNA interference (RNAi) field that scientists at Cold Spring Harbor have helped understand. These new discoveries come from investigator-initiated research that is generously supported by U.S. taxpayers via grants and very importantly by philanthropic donations that provide the catalyst for new ideas.

The modern scientific enterprise depends on appropriate peer review of grant applications, but there are warning signs that the quality of peer review and the mechanisms for distribution of funds need attention. The number of scientists has greatly increased and thus competition for grants is keener now than it ever has been, even in the era when Congress has most strongly supported National Institutes of Health (NIH) funding increases. But the huge success of molecular biology and the wide availability of techniques provide challenges to the Federal funding mechanism. Due to wide dissemination of kit-based techniques, it is relatively easy for individual scientists to string together a series of standard molecular biology methods and propose in a grant application to tackle what is effectively an incremental problem, most likely a problem that many others are also pursuing. When these grant applications are reviewed, they receive enthusiastic support from a panel of peers because the science can obviously be achieved. Grant applications that propose straightforward research do relatively well compared to grant applications that contain really unique and innovative ideas and experimental strategies with fewer preliminary results. Thus, the process of peer review often stifles innovative science, in much the same way as Jim Watson would have been stifled by taking the advice of his funding agency.

Why does truly innovative science fair poorly in grant applications? One reason is that the panel of scientists who collectively review grant proposals tends to make conservative

decisions, even though individual scientists in that group may be very receptive to innovative ideas. Equally important is the sagging quality of peer reviewers. In the past year, I have read many reviews of applications for grants from my colleagues at Cold Spring Harbor and a surprising number defy explanation. In a couple of particularly egregious cases, two of our scientists had separate grant applications in which they proposed research which led them to discover that RNAi-based mechanisms are directly involved in the formation of heterochromatin, the part of the genome that is transcriptionally silent. Incredibly, both of the grant applications not only failed to receive support, but in one case, the review suggested that the whole approach was a waste of time and that the applicant could "improve" his chances of being funded by working on other areas, which the review then went on to suggest. It was obvious to me that the originally proposed science—and more importantly the scientists—were innovative, on the cutting edge, and had a good probability of discovering important new findings. Thus, I found funds from our budget to allow the research to continue. Later, those same two scientists along with another Cold Spring Harbor colleague and others elsewhere were cited by Science as having made the #1 "Breakthrough of the Year" in 2002. This Letterman-like top ten list of scientific accomplishments contains what editors at *Science* consider to be the key important advances in all fields of science made over the past year or so.

All scientists can point to such anecdotes, but my reading of many grant reviews over the past couple of years is that these are no longer isolated cases. What can be done to improve peer review? First, it should be stated that investigator-initiated proposals and peer review of them are the foundation of the success of American science, so the system should not radically change. But there are changes that I believe would greatly improve the current situation.

First among these is improving the quality of reviews. Reviewers who remain anonymous to the applicant should nonetheless be held accountable for the comments that they write into grant reviews. One of the principal roles of the chair of the review panel should be to read the reviews of those grant applications that do not get funded and the response to those reviews made by applicants when they resubmit the grant application. If the applicants write a short, limited response to the reviews and only focus on the important issues, this will not be a difficult task for a panel chair. Although the chair will find many of the applicant's responses an overreaction to the panel's comments, the latter that fit into the egregious category would allow the chair to counsel the reviewer on the appropriate way to review applications. If this mechanism were in place, reviewers who spend four years on a review panel would receive some education about the concept of constructive criticism.

A second improvement could be the reintroduction of a limited number of awards that fund truly outstanding scientists and not specific projects, much like the highly successful mechanism of funding science at the Howard Hughes Medical Institute {HHMI). The NIH had for some time an outstanding investigator awards program that allowed those individuals to use the funds to pursue innovative ideas. A modified version of this mechanism within the NIH structure would go a long way toward giving scientists with a proven record of the highest quality of research the confidence that they could remain innovative, without having to receive HHMI support.

The idea of supporting people and not projects should also be extended to younger scientists in the earlier stages of their careers. All too often, they must apply for research funding for specific projects without the preliminary results that are now so important to obtain an NIH grant. A new mechanism that encourages bright new investigators to be

bold in their initial research would greatly enhance NIH support of our best young scientists who are now in danger of being demoralized by the existing peer review process. Cold Spring Harbor Laboratory has for some years now had a highly successful CSHL Fellows program that enables recent Ph.D. graduates to pursue independent research without any financial burden. Most importantly, they have the freedom to do what they think is best. This program has been very productive and all former Fellows are now leaders in their field of research (see www.cshl.edu:80/public/fellows.html).

Finally, there needs to be a reassessment of the "Request for Application" (RFA) mechanism that has grown so prominent within the NIH. Under current practice, staff within the Institutes at NIH can initiate funding in a particular area of research by advertising an RFA and soliciting grant applications in these areas. They often come with designated funds, thereby limiting the pool of funds available for investigator-initiated ideas. The RFA mechanism works very well when staff in an individual Institute organize a meeting of broad thinkers in a particular field to advise on major new research directions that will be beneficial to science. Good examples are large-scale research projects that the National Cancer Institute (NCI) introduced under the leadership of Richard Klausner when he was Director of the NCI. These projects, such as the mouse models for human cancer, the cancer genome anatomy project, and the development of innovative imaging technologies, were introduced after much thought and debate. They also challenged investigators to think of innovative ideas in new areas of potentially high impact to controlling cancer.

Institute staff initiate RFAs within their portfolio of research funding, but unfortunately, my reading of some of them is that they propose obvious, incremental science. For example, some propose the use of RNAi to study a certain aspect of biology. This exciting new genetic technique has raced around the scientific community and there is no need to encourage its use. Those scientists who are thinking well ahead would have already submitted grant applications using the new technology, leaving those who respond to the RFA to be scientists who would have missed the boat if it had not been for an RFA. Such a mechanism, if allowed to proliferate, will encourage only incremental science by those who cannot be innovative on their own. I believe that there needs to be a reassessment of the whole process of issuing RFAs.

In some ways, research has not changed since the days when Jim Watson and Francis Crick proposed the structure that has become an icon for modern medical research. Today, new investigators in the formative stages of their careers still have many of the best ideas. The MAC-funded Cavendish laboratory and its highly successful successor, The Laboratory of Molecular Biology (LMB), were arguably the most productive research centers in the world, mainly because they supported the careers and visions of talented people, not specific research projects. Fred Sanger, who developed both protein sequencing and DNA sequencing over long periods of time and received two Nobel Prizes for the accomplishments, might not have survived if he had been subject to current NIH peer review. When assuming the Directorship in 1968, Jim Watson in many ways modeled Cold Spring Harbor Laboratory after the LMB. Although dependent on NIH grants, he made sure that we had the necessary funds when peer reviewers turned down some applications that were, nonetheless, worth funding. Such support, still common today, is the reason why Cold Spring Harbor Laboratory remains a leader in the fields we choose to pursue.