DIRECTOR'S REPORT

At the time of this writing, we are in the midst of celebrating several significant anniversaries for Jim Watson. It was 50 years ago that Jim, as a young graduate student working with Salvador Luria, first arrived at Cold Spring Harbor to spend the summer with that year's phage group. Twenty years later, in 1968, Jim, returned to the Laboratory as its new Director and began the remarkable revitalization of the Laboratory's facilities and research activities. By choosing to study the cancer-forming DNA tumor viruses, simian virus 40 (SV40) and adenovirus, Jim placed the Laboratory and its scientists in an excellent position to make seminal contributions to cancer research and to fundamental aspects of eukaryotic cell and molecular biology. Jim arrived here with his new bride, Liz, and together they have perfected one of the most attractive centers for research in the world, combining historic and architectural taste with an unparalleled love for the beauty and history of Cold Spring Harbor and its environs. All of us owe a great debt to both Jim and Liz, and we are happy that they continue to devote much of their time to the continued success of the Laboratory.

Science has changed profoundly in the past 30 years. The year 1997 marks the 25th anniversary of the publication by Paul Berg and his colleagues of the first joining together of DNAs from different sources; they combined SV40 DNA with either bacteriophage λ DNA or *Escherichia coli* DNA. The next year, Stanley Cohen, Herb Boyer, and their colleagues reported the first functional recombinant DNA. Twenty years ago, Fred Sanger and his colleagues reported the sequence of the complete genome of bacteriophage ϕX174 (5375 nucleotides), and they published the new chain-terminating method for sequencing DNA. Today, this technique is the basis for sequencing the entire genome of many organisms, including the human genome, which consists of about 3 billion base pairs. These accomplishments, together with the innovative use of restriction endonucleases by Kathleen Danna and Dan Nathans to map the SV40 genome in 1971, heralded a new age in biology. Soon, Cold Spring Harbor Laboratory scientists, quick to master the new science, made important advances that contributed to the emerging recombinant DNA age. Biologists were no longer limited by techniques, but only by their imagination.

One of the significant developments to come soon thereafter was the establishment of the first biotechnology companies, which used the new biology to produce contemporary pharmaceutical products and reagents more effectively. The biotech companies, with their significant resources provided by venture capital, would soon produce recombinant human growth hormone, recombinant insulin, blood cell growth factors, and other important new drugs. Company scientists realized that they had to be in the business of basic research to be the first to discover new drug targets and proteins. The initial successes of the biotech companies attracted collaborations with increasing numbers of academic researchers because their biotech colleagues often had equipment and facilities that were the envy of the academic community. Collaborations to sequence proteins and clone cDNAs that encoded important cell surface receptors and other signaling molecules became the norm. Often, the biotech companies won the race with academic laboratories to obtain key genes. But even with all its resources, the biotech industry did not surpass the quality of research in the universities and institutions like our own, for it was not always obvious where the next important and useful discovery would emerge. With few exceptions, the great discoveries in biology during the past 20 years emerged from academic laboratories, including Cold Spring Harbor Laboratory.

The relationship between academic research and biotech research has evolved over the years, and today, a happy synergy exists that greatly benefits society as a whole. Publicly funded academic research is still governed by peer review, is published for all to see, and is focused primarily on the issues that society and individual scientists deem important. A large percentage of public funds continue to support fundamental, rather than directed, discovery. For example, many of the dramatic advances in the development of combinations of drugs against HIV relied on basic studies of many retroviruses and their interactions with the cell. Techniques and facilities for protein crystallography that ultimately played an important role in the development of the HIV pharmaceuticals were developed to understand the structure of proteins that had little if any medical or commercial value. And without recombinant DNA technology, it would have been far more difficult to develop strategies to fight the AIDS epidemic. There remains much to do in HIV research, but it is already clear that because of the vigorous support of basic academic research, scientists had the tools to deal with HIV when it surfaced. Basic research had provided an infrastructure on which to build, and although it was often frustrating that progress was not faster, the pace of dealing with the disease was relatively rapid when compared to epidemics of the past.

Biotechnology companies now play an important role in the larger biomedical research enterprise. In addition to their contributions to basic and applied research programs, they have become a very effective conduit for translating the basic research discoveries made in academic laboratories into drug discovery and, ultimately, clinical uses. In the past, basic research discoveries that might have languished for many years are now rapidly picked up by the biotech industry and incorporated into their own research programs.

Many biotech companies, in turn, seek collaborations with the much larger pharmaceutical companies that have the financial and technical resources to develop promising leads into the clinic or to the market. In a sense, the pharmaceutical industry can choose from the large number of projects put forward by the smaller biotech companies and have greater confidence that a project may go all the way to the clinic. Collaborations between the biotech and pharmaceutical companies are important because the cost of developing a new drug that will become an FDA-approved pharmaceutical is extraordinarily high, often running into the hundreds of millions of dollars. As a result of the academic–biotech–pharmaceutical collaborations, completely new approaches for the treatment of cancer are entering clinical trials at unprecedented rates, with real expectations that significant inroads to treating the disease may occur in the not too distant future.

Collaborations between academic institutions such as Cold Spring Harbor Laboratory and the biotech industry can also fulfill another need that large pharmaceutical companies may not address. Many diseases, although devastating to patients and their families, are not economically feasible for large pharmaceutical companies to pursue, principally because the market will not be large enough to justify the expense. Biotech companies, particularly the newer enterprises, are more likely to pursue these targets because they offer an opportunity for a biotech company to achieve its first independent clinical success. In some cases, where the clinical need is demonstrable but the economic incentive is absent, public funds from the National Institutes of Health and other government agencies might be money well spent. Thus, the relationship between the biotech industry and public funding might come full circle to yield clinical success.

The number of biotechnology companies continues to grow at a rapid rate, and I suspect that we are at the beginning of a significant expansion and further evolution of this industry and its relationship to academic labs. Public funding for science is increasing because every informed person realizes that extraordinary research opportunities now exist. We also know from experience that the academic community is best positioned to make the important advances that are unexpected, primarily because the goals of basic research are very different from the research conducted in industry. At the same time, however, industry cannot afford to ignore these basic discoveries and has equipped itself with the technologies to rapidly take advantage of new developments. Today, the biotech and pharmaceutical industry laboratories are much more well equipped for modern biology than are the academic laboratories; they cannot afford not to be.

The cost of modern biological research in academic laboratories is increasing with the complexity of the tasks. Unfortunately, public funding for equipping academic laboratories has not kept pace with the cost of the equipment. It is common these days to spend many hundreds of thousands of dollars on a single item of equipment for a single investigator, and federal funds are not easy to obtain in a timely and efficient manner, if they can be obtained at all. To ensure that the academic research laboratories do not fall behind the well-equipped industrial laboratories, the National Institutes of Health and the National Science Foundation should establish better mechanisms for providing infrastructure support. It would be very dangerous to create a wide gulf between the academic labs and the industrial labs because of the lack of equipment support in academia. Such a gap would eventually lead to a weakening of the process of innovative discovery that is the hallmark of academic research. One kind of funding mechanism for improved infrastructure might be to provide competitive, peer-reviewed, multi-year block grants to institutions that would then have access to these funds immediately. Although Cold Spring Harbor Laboratory spends a considerable amount of its resources obtained through fund-raising to equip its labs, we cannot keep pace with the constant demand for new equipment. This is, in part, because the equipment is more expensive, and also because the techniques in modern biology are more complex than they were 20–30 years ago.

The existing relationship between biotechnology and academia is a healthy one for society as a whole, as long as the potential conflicts of interest are declared and understood by the public, research institutions, and scientists. The vast majority of such interactions, and certainly all of those occurring at Cold Spring Harbor Laboratory, benefit without compromising the goals of publicly funded research. We have in place a very effective subcommittee of the Board of Trustees that oversees interactions with private companies and enforces strict guidelines on the nature of the collaborations.

This year saw the completion of an agreement that allows Westvaco, Novatis, and Monsanto Corporations to provide infrastructure support for our research in plant biology and to help us develop a database of gene-trap and enhancer-trap lines of *Arabidopsis*, one of our favorite plants for biological investigation. Without the support of these forward-thinking companies, we would not have the resources to pursue this research, which will ultimately benefit the entire plant biology community. This year also saw the completion of agreements with Hoffmann La-Roche Inc., OSIP (formerly Oncogene Sciences), and Helicon Corporation to study learning and memory and with Tularik Inc. to identify new cancer gene loci. These arrangements will enable our scientists to pursue their research projects and have access to resources that otherwise would not have been available.

Because future interactions between biotech and academic laboratories will be an integral part of the larger scientific picture, we have taken steps to help establish a Biotech Park on Long Island near the Laboratory. Centers of modern biological discovery such as

Cold Spring Harbor Laboratory often have attracted biotech companies to locate nearby because the proximity fosters scientific interactions and aids in recruiting scientists to their companies. The Laboratory has been involved in transferring technology to many start-up biotech companies, but most of these are located in places other than Long Island. Three of these companies, however, exist nearby and we are keen to see that they remain. To facilitate this, the Laboratory sought advice and help from New York State, and we were pleased to learn recently that Governor Pataki and the State Legislature will support the establishment of a Biotech Park adjacent to the nearby State University of New York, Farmingdale campus, a short distance from the Laboratory. Although the Biotech Park will be a separate entity from Cold Spring Harbor Laboratory, we will help guide the facility to become a nationally recognized center of excellence in biotechnology. It is hoped that a nearby Biotech Park will attract many outstanding companies that will create a broader scientific environment on Long Island and at the same time benefit the area economically. John Cleary did much to guide us in our support of this important project; for this, and for many other matters on which he has provided sound counsel, we are very grateful.

Our own growing technology needs require that we provide an off-grounds facility to accommodate the increased DNA sequencing and gene-based research that is such an essential component of modern biological science. As the Laboratory expands its genome sequencing and related gene technologies, we need space that would best be provided by a large building located off campus. In addition, the success of our neurobiology research program has created new demands for mouse behavior facilities that cannot be incorporated into our existing infrastructure. As part of a solution for these urgent needs, we expect in the near future to acquire a sizable building that is located a short distance from the Laboratory, on the way to the Biotech Park. There, we will establish a state-of-the-art DNA technology center large enough to accommodate the expanded genome projects that we began 2 years ago, as well as behavior rooms that will do justice to the exciting neurobiology research.

Another development this year that should broaden the intellectual community on Long Island and take the Laboratory to new heights was the decision this year by our Board of Trustees to explore the possibilities of establishing a Graduate School of Biological Sciences. We already have a very expansive education program at the Laboratory, including the elementary and high school programs at the DNA Learning Center, a sizable contingent of graduate students from the State University of New York (SUNY) at Stony Brook, and our advanced courses and meetings program that constitute postgraduate training for scientists. We see the possibility of starting our own graduate school, while maintaining the very valuable programs and interactions we have with SUNY Stony Brook, as very exciting. It is particularly pleasing that Winship Herr is developing the new graduate school that will take Cold Spring Harbor Laboratory into a new era.

As the pace of biological discovery evolves, so too, does the Laboratory. Any research institution must adapt to the sometimes dramatic changes in modern biological research. The projects and thinking I have outlined are all essential for our research institution to remain dynamic. At the same time, we must make sure that our scientists are supported to the fullest extent possible and that the research remains of the highest possible quality, in the new academic style.