Research in biological science is advancing so rapidly that those of us fortunate enough to participate in discovery are swamped with information. As a result, we specialize, engaging deeply in one or two areas of science and relying for the rest on other specialists who condense complex ideas into short review articles in the journals. If motivated—perhaps by an unexpected discovery—we can either read further in the literature or participate in conferences and talk directly with experts in a field. Because this is how progress in science is made, the approximately 24 research meetings held each year at Cold Spring Harbor Laboratory add greatly to our intellectual environment and provide scientists working here with a constant flow of new information and fresh ideas.

The rapid pace of modern research is also making a social impact as people try to understand particular diseases or come to terms with issues that have an ethical or moral dimension, such as stem cell research. It is important for the public to keep abreast of developments in science, but it is not easy. There is broad support for the use of tax dollars to fund medical research, but many individuals want to know how research spending will help them directly. It is often a hard question to answer. Research seldom yields advances that have a direct and immediate impact on human lives. More often, practical benefits take years to develop.

Take as an example the recent outbreak of the SARS virus in 2003. Within a few months of the first reports of infection and its subsequent spread to several widely separated countries, the virus was identified and its biology understood well enough to make possible its containment. This success prevented what might have been the spread of a disease that, at best, would have wreaked economic havoc and, at worst, could have been a global medical tragedy. It is not widely enough appreciated that the ability to propagate coronaviruses and identify the genetic makeup of the infectious agent relied on basic research done in the 1960s and 1970s. And this research was not specifically geared to tracking down an emerging virus. The ability to clone and sequence the virus genome, for example, came from cancer research as much as from infectious disease investigations.

Today, vigorous advocacy for disease-targeted research drives much of the funding for basic research in biology. This phenomenon became a significant force in the 1980s, following grassroots calls for special funding initiatives to deal with AIDS and breast cancer. Although neither condition has been cured, anti-HIV drugs that emerged from an understanding of the basic biology of the virus have enabled people to live longer with chronic infection, and breast cancer mortality is dropping, mostly due to early detection.

It is almost certain that public advocacy has driven the recent increases in federal research spending. The National Institutes of Health (NIH), a collection of mostly disease-focused research institutes, supports the vast majority of basic and applied biology and medical research in the United States. The individual Institutes fund research that is done primarily in universities or research institutions such as our own. From 1999 to 2003, the NIH budget doubled to a level that is now about half the annual amount spent on defense research, not including other defense-related research on space, energy, and transportation. But increases in NIH appropriation have slowed and now are only just keeping up with inflation. Because much of its funds are already committed to multiyear grants, there will be less money for new research proposals in the next five years. Furthermore, the emerging large federal budget
deficits will greatly reduce the ability and the will of Congress to support health-related research. In such times, it is even more important for scientists to ensure that the public and Congress understand and appreciate our research enterprise.

This probable decrease in funds comes at a time when there is much more to do in medical research than even the current budgets will support. With the completion of the human genome sequence in the past year, the pace of research is faster than ever. New and completely unexpected biological phenomena are being discovered. One extraordinary example is the ability of short fragments of RNA—like DNA, a nucleic acid—to silence the expression of individual genes. The emerging understanding of “RNA interference” or RNAi, in which Cold Spring Harbor scientists are prominent, has caused us to reassess our ideas about how genes are regulated.

Eventually RNAi, like many of today’s discoveries, is likely to revolutionize how medical conditions such as cancer, diabetes, and obesity are treated. But the processes required to develop drugs that are effective and safe to use take many years. With only a limited understanding of the path from the laboratory bench to the patient’s bedside, the public needs a longer-term perspective on basic research and scientists have largely failed to get this across.

A particularly informative example is the history of the development of monoclonal antibodies as drugs. As part of their immune system’s defense against infection, animals and humans have a population of cells (B lymphocytes) capable of producing tens of thousands of different antibodies. A single B cell secretes a single antibody that recognizes a small, specific part of a protein, and it was a long-held dream of scientists to isolate and clone one B cell and thus obtain large quantities of its specific (monoclonal) antibody. In 1975, in Cambridge, U.K., Georges Köhler and César Milstein achieved this goal with a technical innovation that produced continuously growing B cells secreting an antibody with a single specificity. Their work was immediately hailed by the press and the scientific community as revolutionary and within ten years justifiably gained Köhler and Milstein the Nobel prize. Almost as immediately, monoclonal antibodies were talked about as “magic bullets” that could cure diseases by targeting proteins located exclusively on abnormal cells such as tumors. Optimism and expectations were high, but then reality set in.

The first monoclonal antibodies were produced from mouse cells and some were approved for human therapeutic use. The first was Orthoclone OKT3, intended to prevent cells of the immune system from rejecting transplanted kidneys. But the mouse antibody, itself a protein, was found to produce an immune reaction when injected into humans, limiting the value of the therapy and possibly causing further disease. Much more work was needed, using recombinant DNA technology, to manipulate mouse antibodies and make them unrecognizable by human immune systems. It was not until 1997, more than 20 years after the initial basic research discovery, that true monoclonal antibody therapy became a reality.

A major application was in the treatment of the B-cell cancer non-Hodgkin’s lymphoma (NHL), in the form of a drug known as Rituxan®. Directed against a protein on the surface of the lymphoma cells, the monoclonal antibody initiated selective destruction of the cells. Recently, the drug Zevalin®, a monoclonal antibody linked to a radioactive molecule, has been approved for the treatment of NHL. ReoPro®, also approved in 1997, was an early success in preventing platelet cell clogging of arteries after angioplasty. The number of monoclonal-antibody-based drugs is growing and includes Enbrel® and Remicade® for rheumatoid arthritis, Herceptin® for breast cancer, Erbitux® for colon cancer, and most recently, Avastin® for blocking the blood supply to tumors of the colon. One of these drugs, Erbitux® is at the center of the current insider-trading scandal that has seen a CEO imprisoned and a popular media and television personality convicted. Yet despite considerable news coverage about this drug, the public is largely ignorant of the real processes that produced it. Far removed
from the headlines and misplaced euphoria about magic bullets is a much more complex story involving the extensive search to find suitable applications for monoclonal antibodies, the difficulty of academic laboratories to develop drugs all the way to the clinic, and the reluctance of the pharmaceutical industry to pursue completely novel approaches to drug development until the academic community provides proof of principle that the approach works.

Another example of the effective but lengthy translation of research discoveries into therapeutics is the development of the remarkable drug Gleevec® for early stage chronic myeloid leukemia (CML) and rare stromal tumors of the gastrointestinal tract. This “first in its class” drug targets a protein produced as a result of a genetic abnormality in myeloid blood cell precursors in patients with CML. A translocation between two chromosomes (9 and 22) in patients with CML was first observed in 1960, but it required the development of recombinant DNA technology 13 years later to provide the tools that enabled identification the BCR-ABL gene that resulted from the chromosome translocation. It took a further ten years, until the mid 1980s, to show that the product of BCR-ABL was a tyrosine kinase, an enzyme that modifies other proteins through addition of a phosphate group. And finally, in the mid-to-late 1990s, it took the focused efforts of a single dedicated clinical scientist, Brian Druker, with access to drugs made by Novartis to demonstrate the therapeutic potential of compounds that inhibit tyrosine kinase activity. It was not until 2001 that the FDA approved the use of the inhibitor of BCR-ABL kinase activity known as Gleevec for human cancer treatment.

Gleevec's success has prompted a rush to develop other drugs based on the genetics of human cancer. But it will take time, and unfortunately sometimes a long time, for cutting-edge research to move into the clinic, despite help from the biotechnology industry in speeding the process. Shortening the time will be a challenging task requiring improved interactions between industry and academia, changes in how applied research is supported and more funds for such research, and amendments in how intellectual property from basic research is handled. This last step could involve making it mandatory for basic research patents to be licensed nonexclusively to industry, but since changes in the law would be required, it is unlikely to happen.

The completion of the Human Genome Project and other recent advances have suffused academia and industry alike with optimism about a renaissance in basic and clinical research. Almost every day the popular press announces new discoveries that may lead to new therapies. As scientists we should be careful not to over-hype the results we report. Even if it doesn’t sell newspapers or suit the needs of sound-bite television, it would be more accurate if scientists, institutional public relations staff, and the media present “breakthroughs” in the clinic not as new discoveries but as the result of a long and often frustrating research process. This kind of public education about how science works must first and foremost be the responsibility of scientists themselves. If we cannot set the tone for a broader understanding of what we do, we risk losing credibility with a public that supports science but is conditioned to expect immediate results. People must be better informed about the painstaking journey of discovery, not just the results obtained and their future potential.

In this respect, Cold Spring Harbor Laboratory was particularly active in 2003. The year in which we celebrated the 50th anniversary of Jim Watson and Francis Crick's discovery of the structure of DNA was an opportunity to inform as well as rejoice. Our Dolan DNA Learning Center created the DNA Interactive Web site (www.dnai.org) that accompanied a five-part television series called DNA: The Secret of Life about the development of DNA science and its impact on society. The series had an accompanying book of the same name, written by Jim Watson and Harvard’s Andrew Berry. These three projects, all inspired by Jim Watson, reached for the same goals, not simply a celebration of the double helix and other great
accomplishments in biology and medicine, but an imaginative and powerful demonstration of science as a human activity that raises vital ethical, legal, and social issues.

The Dolan DNA Learning Center (www.dnalc.org), initially established in 1986 to teach modern biology to nearby high school students, now has a global presence through its Internet-based education programs. Its current suite of Web sites, and those that are planned, permit students and their families to learn about research and its results. *DNA From The Beginning* outlines in simple terms the history of genetics from Mendel to the Human Genome Project (www.dnaftb.org). It profiles scientists who did important work, but more importantly, it describes how they made their contributions. The *Your Genes, Your Health* Web site (www.ygyh.org) is a striking collaboration between those affected by diseases, scientists, clinicians, and the Learning Center's educators. Other Web sites deal with the origins of humans and with the thorny history of science gone awry during the 20th century eugenics movement. These individual sites complement each other and share material, and several are in development, including one on cancer. Perhaps there should be a site describing the timeline for developing drugs from basic research to the bedside. Focusing on approved and successful drugs and working back to the ideas and techniques that lead to treatment, we would learn valuable lessons about how basic research and medicine intertwine and about the timelines that are necessary to deal with complicated human diseases.

The type and level of biology and medicine now being taught in the middle grades of high school with the assistance of the Dolan DNA Learning Center’s Web sites are exactly what the public at large must understand to participate effectively in national dialogs about disease research and issues such as human stem cell use. These sites are supported through numerous short-term grants because there is no endowment to support the Learning Center. It is a priority to seek such support. The Learning Center is one of several means by which Cold Spring Harbor Laboratory is pioneering science education, and whether or not you are a scientist, browsing the virtual world of biology and medicine may be well worth your while.

Education about the research behind existing drugs will aid in public education, but it will not advance current research. A recent *Fortune* magazine cover story by Cliffton Leaf argues that current research is not winning the fight. The claim is that academics are focusing on basic research and not applied science. Leaf also argues that there is a lack of focus on the main problems such as metastasis and early detection. The academic community, however, is very well aware of problems that need to be studied, and in this respect, the article presented little new information. For example, it has been well known that early detection of cancer increases the effectiveness of current therapy and because of this, the National Cancer Institute (NCI) leadership initiated a large program on early detection in the mid-1990s, a point not made in the article. I am now on an NCI committee to advise on the discovery and application of new technologies for cancer early detection, diagnosis, and therapy, and new approaches will emerge from such deliberations.

We know what to do—the problem is how best to achieve results. Current NIH funding mechanisms limit the amount of support each scientist can receive, and such funds cannot be pooled to make the research enterprise more efficient or goal orientated. Each pot of funding is restricted to the aims of individual grants. Funding mechanisms are needed that allow teams of our scientists to join together and work with sufficient financial resources to achieve defined goals. Without new NIH funding mechanisms, we must solely rely on long-term and significant philanthropic support. With such support, scientists at Cold Spring Harbor Laboratory can make a real difference.