PRESIDENT'S REPORT

Cold Spring Harbor Laboratory continues to produce breakthrough science and provide outstanding science education. Of particular note, 2012 saw the recruitment of six new faculty, two of whom, David Tuveson and Gholson Lyon, are not only outstanding scientists, but are clinicians who see patients. David Tuveson will oversee our exciting new Cancer Therapeutics Initiative and focus his research on pancreas cancer, melanoma and carcinoid tumors. He will also work closely with the nearby Lustgarten Foundation that focuses on pancreas cancer, where he will head its science program. Gholson Lyon works in pediatric neurology and studies inherited neurological disorders, principally in families in Utah. Molly Hammell, Jesse Gillis, Dan Levy, and Ivan Iossifov strengthen our basic science research, notably in the field of genomics and in quantitative biology, an area that has emerged as a strong component of our research portfolio. CSHL continues to be recognized by Thomson Reuters as the leading institution in the world in molecular biology and genetics, evidence that our fundamental research is having great impact. One example is Adrian Krainer's years of dedicated inquiry on how genes are differentially expressed—basic research that has now resulted in a promising drug he co-developed for the children's genetic disorder spinal muscular atrophy, which now enters Phase 2 clinical trials.

As 2012 drew to a close, however, the United States approached the edge of a financial precipice popularly called "the fiscal cliff." Amid the fractious partisan politics surrounding that term and the unresolved issue of our federal budget deficit, the implications were clear for the Laboratory. We faced the prospect of yet another year in which our elected national representatives would not find a way to pass a budget, once again leaving in doubt the status of federal support for basic research.

We entered the current year, therefore, acutely aware of the urgency of attracting substantial new philanthropic contributions in order to avoid the possibility that critical cancer, brain and plant biology research be curtailed, even for a moment. That would mark an historic and tragic retreat. Although American philanthropy leads the world in support of basic and applied science, it cannot replace the substantial, stable and predictable support that historically has been provided by the federal government. Unfortunately, stagnant or even declining federal support of science is now the norm. If Cold Spring Harbor Laboratory is to remain at the forefront of research in molecular biology and genetics, we need a larger endowment as a buffer to variations in federal funding that are now occurring and will likely occur for at least the next decade.

Our nation has been without a budget for 4 years. To pay bills since approving its last budget in April 2009, Congress has passed a series of what lawmakers euphemistically call "continuing resolutions." Failing to provide the fundamental guidance and stability that an annual budget provides, our leaders have thus defaulted on a constitutionally specified responsibility to the electorate. This failure has had a deleterious impact on many aspects of national life, including the pursuit of new knowledge in the biological and life sciences. These reductions are also coming at a time when private industry has dramatically cut back on fundamental and basic scientific research, in favor of primarily supporting applied research that leads directly to commercial products. American industry is increasingly looking to academia to carry out the basic research and discovery that will benefit our economy.

For our Laboratory and other research institutions, the absence of macro-level budgetary guidance has had two broad effects. One has been an implementation of fiscal austerity, by default. The other is that the lack of guidance from the federal government has thrown into limbo attempts by the scientific community to plan the course of future, long-term research projects.

In 2012, federal support for research at CSHL, mostly through grants to individual investigators by the National Institutes of Health (NIH) and the National Science Foundation (NSF), amounted to $53.9 million, over 49% of the total funding that we received in support of research

from external sources. To state the obvious: One cannot effectively prepare a plan for future work when a key funding source cannot make choices and plans of its own. Even after the 112th Congress in its waning hours passed a tax package that averted the "cliff," a budget still was not forthcoming. We therefore once again had to guess at the expected level of support for research, essentially figuring out how to deal with uncertainty, including the issuance of some grants on a 6-month basis (normally grants are awarded for 4 years and funds release 1 year at a time). Any scientist can tell you that half a year of funding means nothing when the experiments you are conducting will take several years to plan and execute.

American science will fall behind, without a doubt, if the current situation continues into the future. That much is certain.

My purpose in this letter is to report the present situation and to make suggestions about how federal funding for research might be dispensed on a more stable and predictable basis. I want to discuss not only the federal role in sustaining our common enterprise, but also to encourage members of the research community to help strike a crucial balance by acknowledging our own responsibility to make realistic plans for future work, in view of the ongoing fiscal constraints.

I also want to appeal to philanthropy, to those private individuals who are able to provide much-needed support to CSHL in these austere times to fulfill the vision held by Carnegie, Rockefeller, and other great American philanthropists: that helping to advance science will secure the future strength of the society that our children will inherit. Fortunately for Cold Spring Harbor Laboratory, our Trustees and supporters have recognized this need, but we do need to broaden our base of philanthropic support.

Endless Frontier, Finite Funding

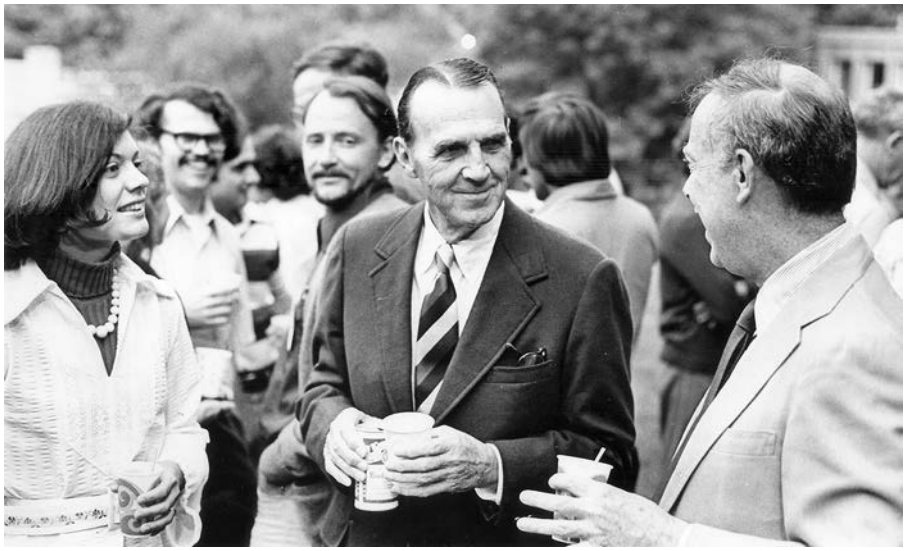
Science is indeed the "endless frontier," as the great American proponent of federally supported basic research, Vannevar Bush, successfully argued the year the Second World War was won. But no one, including Bush, ever said that public funds to support the exploration of the scientific frontier would be limitless.

We in the research community must acknowledge that public funding is finite. Yet in the area of basic and applied biomedical research, as channeled through the NIH, it is important to establish that funding has been essentially frozen since 2003. In that year, legislators from both parties could boast that over the previous 5 years they had authorized a doubling of NIH funding. Spurred by excitement over assembly of the complete human genome sequence and the practical benefits that many expected quickly to materialize from that work, the doubling was an example of lay enthusiasm running ahead of scientific and economic common sense.

What biological scientist would *not* favor a doubling of the main source of research-grant funding? Actually, many of my colleagues and I were not sanguine about the prospect, much preferring instead a federal commitment to a steady and predictable increase in basic research funding each year, while keeping up with or slightly exceeding biomedical cost inflation, which tends to run higher than the national consumer price index.

What some feared in 2003 has come to pass: Federal funding for the NIH has flatlined since the completion of the doubling. Measured from a 1998 baseline, the 2003 NIH appropriation of over $27 billion represented a 100% increase in nominal dollars. But since that time, now nine funding cycles in the past, the NIH appropriation has actually *declined* over 16%, taking biomedical cost inflation into account: the $30.86 billion appropriated for NIH in 2012 was over *$5 billion less* than the 2003 figure, when inflation is factored in.

If we had possessed the foresight and nerve in 1998 to eschew the doubling concept and had instead secured commitments for modest 3% annual increases in federal support for NIH, while pegging base funding to inflation, the NIH budget in 2012 would have exceeded $32 billion—



The Laboratory has always prospered because of philanthropic foresight and civic mindedness. Charles Robertson, seen here with the Watsons in 1974, seeded our endowment.

about $1.5 billion, or 5%, more than the actual 2012 estimate. These numbers assume continued funding of science during the dramatic financial crisis in 2008, but over $10 billion was added to the NIH budget in 2009 from economic stimulus funds, which would not have been necessary if continuous and predictable funding had instead occurred. With such steady support, scientists could have planned long-term projects with confidence. As the situation exists now, many scientists are closing their laboratories because of lack of funding since the sudden spurt of NIH funding has withered and was not sustained. Fortunately, at Cold Spring Harbor our sources of private support have so far prevented shutting down research laboratories. Indeed, philanthropic support has even enabled starting new initiatives that have had a major impact on cancer and autism.

My point is one that prudent financial advisors have been making for as long as capitalism has been around: a simple compounding at modest rates of annual increase is very likely to be more powerful than an occasional fiscal surge, inspired by what are often unrealistic expectations of near-term payoffs. "Slow and steady wins the race"—in science as in building a nest egg.

There are powerful reasons behind this argument as it applies to research funding, and they are not only about numbers. It is instructive to look back for a moment at the history of how our federal government came to vigorously support basic science. Prior to the Second World War, federal contributions were minimal, as weighed against funds provided by the nation's great philanthropists. Most biomedical research was then conducted by scientists based in universities that were supported by endowment income, special research funds, and foundation grants. The year before the start of the Great Depression, The Rockefeller Institute had since its founding in 1902 received some $65 million in endowment funds from the estate of John D. Rockefeller. As noted by the historian Paul Starr, this alone was many times the amount spent by the federal government on medical research during that same interval.[1]

Early in the 20th century, it was the Department of Agriculture that received the lion's share of the government's research attention. To the very limited extent that it invested directly in medical research, the federal government focused on the Hygienic Laboratory, once part of a hospital

[1]Paul Starr, *The Transformation of American Medicine* (Basic Books, 1982), 339.

in Staten Island, and later, after moving to Washington, D.C., the forerunner of the U.S. Public Health Service (PHS). Just after the turn of the 20th century, allocations were less than $50,000 a year. During the Progressive Period, the PHS began to study infectious diseases. In 1930, the Hygienic Laboratory was renamed the National Institutes of Health, and in 1938 it moved to its present location in Bethesda, Maryland. A year prior to that, the government had established the National Cancer Institute (NCI). And in a major departure in 1944, for the first time the NCI authorized federal funds to be allocated to basic researchers not directly in the government's employ. This was the precursor of the modern extramural grant program that provides core research funds for CSHL and many other American research institutions.

On the eve of America's entry into World War Two, the NCI's cancer grants and all other PHS activities received less than $3 million in total federal support. The Department of Agriculture's research budget was almost nine times greater. The war, of course, turned the tables. Vannevar Bush's Office of Scientific Research and Development (OSRD), which played an historic role in developing advanced technologies that made possible the Allied victory, was split in two sections, one dedicated to defense technologies, the other, under the Committee on Medical Research (CMR), focusing on technologies to help meet the medical problems occasioned by war. From a new way to treat malaria, to the isolation of blood derivatives like gamma globulin, to the development of means of mass-producing penicillin, the CMR achieved triumphs that would support arguments following the war for a greatly augmented federal role in biomedical research.[2]

Among the proudest moments in the history of Cold Spring Harbor Laboratory are those chronicling the roles of Demerec, Bryson, and others in laying the foundations for critical advances in penicillin production. Vannevar Bush drew a very important lesson from this and other wartime research efforts. It concerned the society and system that had given rise to academic research institutions like ours where wartime advances were made. The United States was a nation that had granted autonomy to scientists. Open-ended, investigator-initiated basic research had generated the pool of intellectual property from which real-world products were rapidly developed in the urgent wartime context.

Bush's famous report, "Science: The Endless Frontier," written in 1945 in fulfillment of a request from President Franklin Roosevelt, was, however, not an argument for federal funding of *applied* research, but instead the kind of *basic* research that had provided the intellectual capital to fuel those wartime innovations. The war made clear to Bush that only the federal government had sufficient economic power to sustain a world-class basic-science research establishment. Upon this foundation the nation would prosper financially and militarily. But also, importantly, the health and welfare of its citizens would steadily improve. This is the vision behind our modern NIH and NSF.

When Bush later recollected that "[t]he war . . . proved that things could be accomplished in a hurry, given *unlimited* funds, the intensity of war, and most important, a background of basic scientific knowledge ready for application,"[3] he did not mean to suggest this was a reasonable expectation for a nation in peacetime. The question in ordinary times was whether enough funds would be allocated and enough freedom be granted scientists so as to keep new discoveries coming. Today, the NCI budget represents about $16 per person per year for the support of all cancer research and therapy development. About the same amount per person supports all neuroscience research, including all research on Alzheimer's, Parkinson's, all other neurodegenerative diseases, all psychiatric disorders such as autism, schizophrenia, depression, acute disorders such as stroke and trauma, as well as basic brain science. So the annual investment per person is not substantial.

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[2]ibid., 340–342.

[3]G. Pascal Zachary, *Endless Frontier: Vannevar Bush, Engineer of the American Century* (MIT Press, 1999), 288.

Taking Responsibility

At this moment our nation is clearly limited in its capacity to finance basic science. Things that might be done today in areas in which much progress has recently been made, cancer therapeutics being the most notable, are not getting done because of the scarcity of resources, both public and private.

What can we reasonably expect? I would be pleased to see a federal commitment to present levels of NIH and NSF funding, adjusted for inflation plus 3% per year. This would place CSHL and peer institutions on an even keel during the next decade, in which austerity is likely to prevail. It is imperative that we keep up with and at least somewhat exceed the rate of biomedical cost inflation. Otherwise, the nation's science is certain to enter a period of decline. We will not be able to plan, as I have noted. Nor will we be able to support, and therefore will not be able to attract, first-rate minds to enter scientific research. According to a recent report of the NIH-sponsored Biomedical Workforce Committee, of which Cold Spring Harbor's Leemor Joshua-Tor was a member, the number of doctoral students in basic biomedical science continues to soar, with over 15,000 Ph.D.s granted annually. With the success of our science, this number has risen quickly, from a base of about 6500 new Ph.D.s a year in the mid-1980s. The number far exceeds the numbers exiting basic science. In contrast, other fields of science such as chemistry, physics and behavioral and social science do not produce increasing numbers of active Ph.D.s. At the same time, the number of all principal investigators under age 36 in biomedicine who are receiving career-sustaining NIH grants has declined from 18% 2 decades ago to less than 4% today. The number of applications, meantime, for a shrinking number of NIH grant awards of all kinds continues to rise. Nationwide, fewer than 1 application in 6 is successful. Based upon my experience in reviewing grants, I estimate that 1 in 4 or 1 in 3 are of the highest quality and warrant funding. At Cold Spring Harbor, the success rate of proposals by our faculty is more than twice the national average, partly due to the philanthropic support that sustains science through times when federal funding is not obtained and partly due the fact that at Cold Spring Harbor, philanthropic support supplements federal grant support.

Under these circumstances it is imperative for research institutions to take responsibility for their future. The administrative team at Cold Spring Harbor Laboratory provides an example of how ambitious yet realistic planning 5 to 10 years out, combined with a constant effort to husband scarce resources, can yield a program in basic science that—as the statistics continue to show—places our faculty's output at the very top of the field. As mentioned, CSHL's research is the most influential in molecular biology and genetics, as measured by the impact of faculty publications.

The so-called NIH salary cap determines the maximum salary support that scientists can receive. It has been reduced substantially in recent years, and may be reduced some more. We and other institutions must make up the difference if we are serious about retaining faculty, for the NIH cap does not come close to the level of salary that we must pay our senior scientists. We do provide such support to all of our senior faculty, while supporting full salaries for at least the first 5 years for all junior faculty. We also pay for a large portion of our infrastructure costs, in part to meet conditions set but not paid for by the federal government, but mostly to keep the infrastructure capable of supporting cutting-edge science.

How do we manage this? Science at CSHL cannot be done without the proceeds from our fundraising efforts plus annual spending from our endowment. The latter is frankly still too small to provide us with breathing room. So, we have tried to plan our future science programs on the basis of what we can realistically budget, given all the current constraints. It is now time for our political leaders do their part to keep federal support for research predictable. But as I have intimated, the needs of the research community will certainly exceed the government's ability to provide, probably for a decade or more. At Cold Spring Harbor, we are very fortunate to receive generous support from many foundations and individuals. These sources, together with our

endowment draw, covered 50% of our research expenditures in 2012. Such a ratio of federal to private funding of research may have to be the norm for all institutions in the future, not just Cold Spring Harbor and other like-minded research institutions. Medical schools will have to provide more to their scientists, but this change also comes at a time when clinical income is dropping at a rapid clip.

The Power of Philanthropy

Philanthropic support has been a fundamental part of what makes Cold Spring Harbor Laboratory successful. It is clear to all our scientists that federal grant support provides the core funding needed to maintain a research program and its key infrastructure, but it is philanthropic support that allows our scientists to do their most innovative research. Thus we must increase philanthropy, growing our endowment so that key funds can be allocated when needed, not in the year or two that it takes to secure a federal grant, long after a new idea is stale.

Part of the logic for increasing support to Cold Spring Harbor is our track record: we have a long history of major accomplishments and great influence in both research and science education—all achieved through prudent use of very limited funds. The seeds of our success were sowed by the great philanthropists of the last century. The estate of Andrew Carnegie launched our genetics research and sustained it for 60 years. The Carnegie Institution of Washington put the Laboratory on the map as one of the world's leading centers of genetics research. CSHL's future Nobelists Al Hershey and Barbara McClintock were beneficiaries of the Carnegie largesse. When Carnegie monies were withdrawn in the early 1960s, the Laboratory very nearly was forced to close. Not long after that, Jim Watson came to Cold Spring Harbor as Director. The history of the intervening years was possible in large measure because of Jim's great ability to make the case for philanthropic support. He also appreciated the value of defined research focus, most notably cancer research. This research expertise brought in institutionally stabilizing federal funding, much of it via the NCI. Since 1987, we have been designated by NCI as a National Cancer Center for basic research in cancer.

The reality of today, however, is that we have arrived at a point at which, even with an endowment in excess of $300 million, we have little margin for disappointment, whether in the performance of our endowment portfolio or in levels of federal support, or, indeed, in the success of our fundraising efforts. CSHL has prospered because of philanthropic foresight and civic-mindedness: that of Mr. Carnegie and his administrators, but also our local heroes including the Jones family, Louis Tiffany, William K. Vanderbilt, Walter Jennings and George Pratt, Marshall Field III, and J.P. Morgan. Without them, the Delbrück Laboratory would never have been built. Without them, Demerec and Hershey and McClintock, not to mention summer visitors like Salvador Luria and Max Delbrück, also both Nobel laureates, or the then young turks like Norton Zinder and Jim Watson, might never have had the opportunity to change history, right here on the grounds we walk each day.

Charles Sammis Robertson's philanthropic spirit provided the foundation for our current endowment and changed the face of the institution, giving us an endowment and the opportunity to create the Banbury conference center, where small private gatherings of people with the power to change the course of science have been held regularly for over 3 decades. More recently, we have been privileged to have truly major support from the Simons Foundation and the Stanley Medical Research Institute, philanthropic support that has literally changed how we understand the cause of certain psychiatric disorders. Today, we are fortunate to have many other individuals, particularly our current Trustees, who provide significant support to Cold Spring Harbor Laboratory and provide us with the funds that will ensure that we remain a leader in the life sciences. But to maintain our leadership in research and science education we will have to expand greatly the number of such loyal supporters.

"Surplus wealth is a sacred trust which its possessor is bound to administer in his lifetime for the good of the community." That was Andrew Carnegie's "Gospel," and it is one that I fervently hope a civic-minded few will now take to heart so that our great institution might safely navigate some very treacherous fiscal waters. Perhaps our nation's leaders will also smooth out the fiscal waters for research funding, and together, a public-private partnership will continue to ensure that American science remains the most innovative in the world.

Bruce Stillman, Ph.D., F.R.S.
President and Chief Executive Officer