

## AMERICAN DEMOCRACY AND THE ORIGINS OF THE BIOMEDICAL REVOLUTION

Joan A. Steitz, February, 2001

Last June, headlines blazed with the announcement of the completion of the sequence of the human genome. Craig Venter, head of Celera Genomics and therefore a representative of private interests, and Francis Collins, head of the National Human Genome Research Institute (and incidentally a former Yale School of Medicine postdoc), shook hands with the President and declared the book of life decoded. Despite some ugly aspects to their competition, a rough draft of the sequence of close to 40,000 genes was in hand. Those of us in the know knew that the job was far from done. With only 85% of the sequence of the 3 billion base pairs of the DNA in human chromosomes assembled, a lion's share of the work still remained. Often piecing together the last few percent of a sequence takes as long as determining the first 95%. Nonetheless, this international achievement – resting as it did on the shoulders of literally thousands of participating scientists from academia, industry and government – is a triumph of modern biomedical research.

A third person, who in my opinion should have shared in the handshakes, is Eric Lander. He is Professor at MIT, Director of the Whitehead Institute Center for Genome Research (which contributed roughly one third of the assembled sequence) and the ingenious architect of much of the critical technology that brought the genome project to fruition. He has summed up the promise of this momentous accomplishment as follows, "With the availability of the complete genome sequence, biologists in the 21<sup>st</sup> century will finally be able to see the big picture – health and disease described in terms of the complete symphony of DNA, RNA, and protein variation, both within an organism and across the evolutionary tree. The years ahead will see far-reaching reclassification of disease based on underlying molecular mechanisms and powerful, new therapeutics based on a sophisticated understanding of cellular circuitry."

Even before the Human Genome, the products of the Biomedical Revolution have been increasingly evident in their impact on our lives. DNA forensics, monitoring of the blood supply, prenatal screening, new vaccines, cures for some cancers, treatments slowing the progression of AIDS, and genetically modified foods are but a few examples. With these stunning advances have come legal and ethical concerns: How do we protect against abuses of genetic information? How do we properly design clinical trials of new drugs and therapies? How do we balance reproductive rights against the future of our genetic lineage? These are questions that we all must join in answering – biologist, ethicist, lawyer and citizen. But, they are not the subject of my lecture today.

Rather, I wish to consider a historical question. What is striking about the Biomedical Revolution is that it occurred largely in the US rather than in other countries with comparable intellectual capital. Can we understand how the peculiar form of democracy that is being examined in this series of lectures – American democracy – contributed?

## Origins

The Biomedical Revolution dates its beginnings to 1953. A young American postdoc, James Dewey Watson, and a significantly older English graduate student, Francis H. C. Crick, proposed a model for the double-stranded structure of DNA. At the time it was still controversial whether DNA was in fact the genetic material. Watson and Crick's famous letter to the British journal *Nature* contained no data; the model relied entirely on the results of others – significantly the X-ray pictures of Rosalind Franklin, who died too young to share in the 1962 Nobel Prize. Jim Watson had graduated from the University of Chicago at the age of 19. There he had forsaken his prior love of bird watching and developed an interest in the gene, subsequently earning a PhD in Indiana studying bacterial viruses. During his postdoctoral stint in Europe, Watson's obsession with the nature of the gene and the structure of DNA grew ever greater. Francis Crick, on the other hand, had worked for the British Admiralty developing non-contact mines during World War II and in 1953 was still completing his PhD on the X-ray structure of proteins. The two met in Cambridge, England, and became soul mates in a race to decipher the structure of DNA. Their primary adversary was the famous chemist Linus Pauling of Caltech, who had correctly predicted helical structures in proteins and now had turned his interest to DNA. The structure proposed by Watson and Crick was compelling because of its predictive quality. Their *Nature* paper ended with the famous sentence, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." [*Nature*, 171 (1953) 737-738]. Indeed, the two strands of DNA simply would have to come apart and each pair up with a newly-made strand to give two copies of the original molecule. The model had to be right. And all that has been learned since has only served to confirm it.

The seeds for the growth of a whole new academic discipline had been sown. But beginnings are slow. When I began graduate school at Harvard ten years later, there were still no departments of Molecular Biology. Nor were there textbooks in the field. I enrolled in a graduate program run by the Committee on Biochemistry and Molecular Biology, comprised of a subset of faculty from the Chemistry and Biology Departments. Like a handful of similar programs at other US universities, the faculty all came from other fields. These professors had become entranced by the question of how life works at the molecular level and had allowed their research interests to depart from the standard fare of their departments – usually Biology, Chemistry, or Physics. And here I would like to make my first point about American individualism. These academics were unusual in that they had the courage to stray from the relative security of the discipline in which they had been trained and hired as faculty. Moreover, the university system within which they worked was flexible enough to tolerate this transgression.

At the beginning, all molecular biologists studied bacteria and their viruses. The accepted notion was that one needed to focus on something simple in order to learn anything at all. Biologists who studied more complex higher cells were scorned as wasting their energies on something that was much too complex to make any sense of. These notions were the legacy of the Phage Group, a small cadre of American scientists from various disciplines, including physics, who met in the summers at the Cold Spring Harbor Laboratory on Long Island. As their object of study, they had

chosen what they believed to be the simplest living entities, viruses that infect bacteria (phages). The experimental approaches they developed were based on the belief that genes could be explained by a combination of genetics, physics and perhaps biochemistry. It was a completely reductionist approach. As explained by Leo Szilard, a leading physicist who was among the converts, what physicists brought to biology was “not any skills acquired in physics, but rather an attitude: the conviction which few biologists had at that time, that mysteries can be solved.”

Indeed, the results came pouring in. After the structure of DNA came the discovery of messenger RNA, the middle molecule in the famous Central Dogma, which was first enunciated by Watson and Crick and can now be quoted by schoolchildren: “DNA makes RNA and RNA makes protein”. Next came the elucidation of the genetic code. One of the highlights of my graduate school career was crowding into the back of the ballroom of the Hotel Americana in New York City for one of the plenary lectures of the International Congress of Biochemistry. Excitement was palpable in the hall as we heard of the breakthrough experiment that had at last cracked the genetic code. A year or so later, one of my co-graduate students in Jim Watson’s lab earned his PhD by determining the identity of just ONE base at the end of a bacteriophage RNA genome! And today we have a working draft of the 3 billion bases of the human genome!

In the early years of Molecular Biology (the 1960’s and 70’s), the science was all wonderfully fascinating, but only the very sage could even conceive of the magnitude of its practical implications. Recombinant DNA, developed by molecular biologists in the mid-1970’s, was the keystone that provided the ability to isolate genes and determine their structures. With the subsequent exponential growth of the field, it became acceptable for molecular biologists to study more complex organisms, and the techniques of molecular biology invaded all the related biomedical disciplines. Only several decades later, we have a biotechnology industry worth over \$200 billion that has already contributed dozens of new drugs to treat a host of human illnesses! How and why was this fledgling scientific enterprise supported financially during the early decades when it seemed so esoteric? Why did Molecular Biology flourish primarily in the US rather than in other nations?

### Funding for Basic Research

Money is always key. But its availability is not enough. I would like to contend that the sources and the recipients of funds for basic research, as well as the non-hierarchical structure of our institutions of higher learning, nurtured the growth of Molecular Biology specifically in the US. These significant differences (compared to other developed nations) in how research money is distributed and who gets it are the products of our particular democratic system, which encourages pluralism and rewards individualism.

Let us consider the sources of funding. First, it is very important to understand that US universities do not fund research in the natural sciences even though it is carried out by their faculty on their premises. Instead, research funding is all competitive and comes from outside sources – from agencies of the federal government and private

foundations. The University does provide an environment where a critical mass of scientists are gathered together, fostering creative interactions, and students - both undergraduate and graduate - who in the course of their training participate in cutting-edge research. To give some typical numbers, the current running costs for my Yale department, Molecular Biophysics and Biochemistry (MBB), are somewhat over \$20 million per year, of which less than \$4 million is provided by the University. Altogether there are about 300 people (not counting undergraduate majors) engaged in the research, teaching and administrative functions of the department. The University's portion covers many (but not all) faculty and support staff salaries, set-up costs for new faculty, undergraduate lab courses and partial maintenance of our graduate program. A substantial fraction of the funds acquired from outside are returned to the University in the form of "overhead", which is determined by negotiation between the University and the government to reimburse the space and administrative costs of doing research. Also, graduate tuition is paid to the University. But the salaries of the technicians, graduate and postdoctoral students who execute the experiments, as well as the costs of equipment and supplies, come from non-University sources. What are these sources?

The federal government has been the major source of funding for basic research for the last half century. Before World War II, most basic research in the US was supported by private foundations and federal expenditures for Research and Development were only about 1% of today's, even when adjusted for inflation. Nonetheless, the tradition of the federal government providing funds for scientific research has a long and noble history. Our constitution in fact promotes what the founding fathers called "science and the useful arts". In 1803, President Thomas Jefferson persuaded Congress to appropriate \$2500 to fund an expedition led by Meriwether Lewis to explore the American West. Although Jefferson cloaked the enterprise as economic "for the purpose of extending the external commerce of the US", his real interests were scientific. He saw the expedition as an opportunity "to advance the geographical knowledge of our own continent" and had made certain that Lewis (who had been Jefferson's personal secretary for two years prior to the expedition) was trained in botany, mineralogy, astronomy and ethnology, as well as showing him how to use a sextant. Indeed, the Lewis and Clark journals are a veritable treasure trove, the first systematic survey of the flora and fauna, climate and fertility, and the peoples, their wars and economics, of the American West.

The current era in federal funding for science dawned in 1945 with the report by Vannevar Bush entitled *Science, the Endless Frontier*. Bush had headed the WWII R&D effort and President Franklin Roosevelt challenged him to determine how the unique wartime partnership in research forged between the universities and the government could be sustained in peacetime. Bush's report provided both the intellectual rationale and a blueprint for government support of basic research in areas related to medicine, the natural sciences and defense. To quote from the remarks of President Bill Clinton at the 1999 ceremony awarding the National Medals for Science and Technology:

"Vannevar Bush helped to convince the American people that government must support science, that the best way to do it would be to fund the work of independent university researchers. This ensured that, in our nation, scientists would be in charge of

science. And where before university science relied largely on philanthropic organizations for support, now the national government would be a strong and steady partner. This commitment has helped transform our system of higher education into the world's best. It has kindled a half-century of creativity and productivity in our university life. Well beyond the walls of academia, it has helped to shape the world in which we live and the world in which we work."

To be specific, Bush's report led to the creation of the National Science Foundation (NSF) in 1950 and a system for allocating federal money based on scientific merit. Other federal agencies such as the National Institutes of Health (NIH) and Department of Energy (DOE) have adopted comparable competitive procedures for allocating their funds in support of basic research, and I shall say more about these procedures later. Another boost for federal R&D funding was provided by the launch of Sputnik by the Soviet Union in 1957. It raised anxiety that the US had perhaps slipped in scientific and technical superiority. As a consequence, funding for science and math education achieved double-digit increases annually over the next decade.

To provide some numbers, by 1998, government funding of basic research exceeded that of private industry, \$18 billion compared to \$8 billion. Such publicly-funded research has been critical to private sector innovation. Economic returns on investments in basic research are very high, being widely dispersed and delivered over a lengthy period. A recent study found that 73% of research publications cited by industrial patents were derived from government-funded research. Although occasionally a scientific breakthrough finds immediate application, usually the yields on basic research are realized far into the future. Often, the greatest benefits are the least anticipated. For instance, the War on Cancer of the 1970s has delivered its most significant benefits in the treatment of AIDS in the 1990s. A host of other examples is listed in the article by Silverstein et al entitled "A few basic economic facts about research in the medical and related life sciences."

The most important US institutions that acquire federal funds to conduct basic research are its 200 major research universities. Federal laboratories do exist and do contribute significantly to research in defense, health and energy, but as they are mission oriented (such as the NIH) their impact in basic research has never been comparable to that of universities and in most cases has decreased in recent years. The few high profile biomedical research institutes in the US (the Cold Spring Harbor Laboratory, the Salk Institute, the Whitehead Institute, the Fred Hutchinson Cancer Research Center) are all private, non-profit and have close ties to a university. The migration of US students and young researchers from university to university stirs the mixing pot of ideas and brings fresh insights to the scientific enterprise. It is often said that the best science comes from the bottom up, not from the top down.

A contrasting situation exists in the nations of Europe and the Pacific, where most basic research is conducted in government-supported research institutes. They are staffed by well trained scientists but lack significant input from creative and highly motivated undergraduate and graduate students. Moreover, like their countrymen, foreign scientists tend to stay put, usually working in the same institute for their entire careers. Their science suffers from too much stability and from top-down control.

Equally important for understanding differences between us and other countries is the fact that federal funding for basic research in the US is given to individual scientists, as emphasized by President Clinton, not to their institutions for dispersal. These individual investigators compete directly for government grants, and the vast majority of grant recipients in the US are faculty at our research universities.

Here it is salient that the structure of our universities is quite different from those in Europe and other developed countries. Elsewhere, a department is usually headed by a single professor, who wields absolute power. The system allows (and encourages) the appointment of a cadre of younger academics as assistants (and dependents). They have no choice but to work toward the professor's goals. Often, independent sources of funding for their own ideas are not even available to these younger scientists. And this hierarchical system goes even deeper in some countries. For instance, only now is the Japanese government considering turning the national universities into independent administrative units, freeing them from total regulation by central authority.

In contrast, in a US university there are many professors in every department. Independence in research from other faculty within the department is regarded as a virtue, regardless of whether one is an assistant, associate or full professor. Even the newest assistant professor can (and must) apply for competitive outside grants in order to fund the experiments that will attract students to the lab and produce the publications that eventually lead to tenure.

#### Peer review

Earlier, I referred to Vannevar Bush's blueprint for allocating funds for research based on competitive merit review. This is a system that has been developed principally by the NSF and NIH, but is used by many other federal and non-governmental agencies. It insures open competition for available resources with evaluation of merit by peers. Open competition means that within the framework of an agency's mission, researchers propose their best ideas and anyone may apply regardless of institution or geographic location. The evaluation of applications and awarding of funds by peer review is regarded as primarily responsible for the remarkable quality, originality and success of US basic research. But peer review is largely an American success story. Why?

First, let me tell you how it works. The agency that has issued a request for applications also assembles a "study section", a group of about a dozen active scientists who are specialists in that particular discipline and are willing to serve as reviewers of the grant applications that are sent in. These will be primarily faculty from research universities, but no more than one from any single institution. They will normally serve terms of several years with two or three meetings per year to discuss and rank applications. Study section members receive all the applications to be considered at least a month in advance of the study section meeting. A primary and one or two secondary reviewers are assigned to read and write a critique of each application. At the meeting, these scientists will lead the discussion of that particular

application, mostly focusing on the science proposed and the track record of the applicant, but also including consideration of the appropriateness of the budget request. Then, all members vote. Those applications whose priorities fall above the funding line will receive support, usually after relatively perfunctory review by a higher panel within the organization.

Membership on a study section is voluntary, a lot of work and essentially not remunerated. (The costs of traveling to and attending the study section meetings are reimbursed, with perhaps a token \$200 per day stipend for time spent at the meeting. The much longer preparation time required beforehand is gratis.) Scientists participate because they realize that any other way of allocating funds for research is inferior. One of the important groundrules is that you do not participate in the review of an application from anyone at your own institution or from anyone with whom you have had a close scientific association in the past 5 years. This means as student, mentor or collaborator.

We are lucky that we are so big. Thus, there can be appropriate expertise on your application from someone on the study section with whom you are not closely connected. A relatively impartial decision can be made – essential to the success of the peer review system.

Consider instead the problems with mounting effective peer review in a small country, for instance a Scandinavian nation with a population of 5 million as compared to our 280 million. A famous recent study entitled “Nepotism and Sexism in Peer Review” (1997) examined the reasons why men were twice as successful as females in their application to the Swedish Medical Research Council for post-doctoral positions in 1995. The ‘scientific competence’ of the applicants was judged on a scale of 0 to 4 by the evaluators who comprised the study section. In the published study using multivariate analysis, the competence scores assigned were related to characteristics of the applicants, including their scientific productivity (number and impact of papers, citations in other scientific papers, etc), gender and research field. Three factors were discovered to be independent determinants of high scores for ‘scientific competence’. These were: 1) the applicant’s scientific productivity, 2) gender (males received higher scores than females with comparable productivity; this is matter we will return to later in this lecture), and 3) affiliation with one of the review committee members. For example, applicants who had been supervised by one of the evaluators obtained significantly higher scores for scientific competence than other applicants with comparable productivity. But in a very small country, it is almost impossible to assemble a review group where someone does not have close ties to any of the applicants being reviewed. Thus, peer review has not been a very effective mechanism for distributing funds in most European nations.

Because peer review has worked so well for the US agencies that have used it, a 1995 report from the National Research Council called *Allocating Federal Funds for Science and Technology* has advocated extending competitive merit review as THE method of choice for making future decisions about federal science and technology funding. It advises that merit review should be used not only in ‘extramural funding’ (which is what we have been discussing as the grants that go to faculty at universities)

but also in allocating internal funds for running government laboratories. In recent years, there has also been an active re-evaluation of the criteria study sections use in ranking investigator-initiated proposals. Input from both applicants and study section members has resulted in a new statement of what reviewers should look for in applications for NIH funding. Reviewers are asked “to judge the likelihood that the proposed research will have a substantial impact on advancing our understanding of biological systems, improving the control of disease or enhancing health.” Five criteria are to be assessed: Significance (how will scientific knowledge be advanced?), Approach (is the conceptual framework adequately developed?), Innovation (does the project challenge existing paradigms or develop new methodologies?), Investigator (appropriate training and past record), and Environment (can it contribute to the success of the proposed investigation?).

In summary, the development and extensive use of the peer review system in allocating funds for science has been uniquely successful in the US. Even though it is far from perfect, it a system that embraces equal access, strives for impartiality and rewards individualism. These are principles that reflect the best of the American democratic tradition.

### Funding for Molecular Biology

So far, I have focused on differences in funding and academic structure that have made US universities preeminent in basic research in all the natural sciences. But it is important to say a few words about how the interplay between funding opportunities from multiple sources has enhanced progress specifically in Molecular Biology and the other biomedical disciplines.

Today, the federal government provides about 80% of the dollars spent annually for basic biomedical research at universities, medical schools and nonprofit research institutes. But what happens if a researcher sends a grant off to a federal agency and the study section doesn't give it high enough priority to be funded? Luckily, in the biomedical sciences there are multiple federal agencies whose mission might include our applicant's endeavors, eg the NIH and the NSF, or the NIH and DOE. In addition, there are private foundations that contribute the remaining 20% of the funding; they also employ peer review to disperse their monies for basic research. Since study sections are made up of active scientists, all with their own personal views of what is important, a project that does not appeal to one study section might be viewed enthusiastically by another. This is particularly true of proposals that are highly innovative or out of the mainstream of current endeavor. In most cases a worthy project that is not funded by one agency has a good chance of being funded by another.

Thus, the diversity of funding sources available to a faculty member at an American research university has made the pursuit of truly creative ideas a reality in the US. In contrast, the typical European or Japanese scientist working in a government-funded research institute is likely to be dependent on a single source for support. The administrators in charge of the money may or may not view an innovative project positively.

Although I cannot describe in detail all the sources of funding for biomedical research in the US, I would like to trace the history of three representative organizations, each of which has features that are peculiarly American and reflect certain values of our democratic culture. These are the National Institutes of Health, an example of a federal agency, the American Cancer Society, an example of a mission-oriented voluntary health agency, and the Howard Hughes Medical Institute, an example of a private foundation.

## The National Institutes of Health

Nearly 90% of all federal support for biomedical research comes from funds allocated by Congress to the National Institutes of Health (NIH). Significantly, about half of NIH monies go in the form of investigator-initiated grants to faculty at our research universities, medical schools or nonprofit research institutes. As we have discussed, these funds support the most innovative ideas of the most creative American scientists. A much smaller fraction of the NIH allocation (about 1/10<sup>th</sup> that amount) goes to running its own research laboratories (referred to as the 'intramural program'), located primarily on its campus in Bethesda, MD. How was the tradition established that such a large fraction of NIH dollars should be dispersed off-campus (ie, extramurally)? And why has basic research, rather than only disease-oriented projects, been supported?

The NIH traces its origins to the 1880's, when a one-room laboratory was created in the Marine Hospital on Staten Island, NY, for a young physician Dr. Joseph Kinyoun, who identified cholera bacilli in merchant seamen whose care had been charged to the Hospital. The Hygienic Laboratory, as it came to be called, moved to Washington DC in 1891. In 1901, Congress authorized the building of a new laboratory to investigate infectious and contagious diseases related to public health. Two congressional acts in 1902 allowed the laboratory staff to expand to include PhD specialists, as well as MDs, and charged the laboratory with regulating the production of vaccines and antitoxins (4 years before the landmark Pure Food and Drug Act). Between 1912 and 1930, the laboratory was called the Public Health Service and its officers concerned themselves with such problems as the cause and cure for the dietary deficiency pellagra, the effects of pollution on lakes and rivers, and the basis of anthrax outbreaks at WWI military bases.

In 1930, the name was changed to the National Institute of Health (singular) and further landmark legislation authorized the establishment of fellowships for research into both basic biological and medical problems. Seven years later, the National Cancer Institute (NCI) was created (but only in 1944 designated as a component of the NIH) again with visionary authorization - to award grants to nonfederal scientists for research on cancer and to fund fellowships. Thus the NIH established early three important traditions in its strategy for advancing the health of the nation: 1) funding for basic (rather than exclusively medical) research, 2) support for training (in the form of fellowships), and 3) grants to non-NIH scientists.

The Public Health Service Act of 1944 redefined the NIH in its current form and determined the shape of biomedical research in the modern era. In 1946, the

successful grants program of the NCI was expanded to the entire NIH, and the NIH budget grew nearly exponentially from \$8 million in 1947 to \$1 billion in 1966. Also, in the late 1940s, the NIH was authorized to conduct clinical research, and its new mission oriented sub-institutes, such as the National Heart Institute and National Institute of Dental Research, were created. Today there are two dozen institutes and centers under the NIH umbrella. The scope of NIH activities is extremely varied, including issuing guidelines for animal care, for the use of recombinant DNA, and for the ethical conduct of research, as well as launching special programs like the Human Genome Project (with DOE). For 2001, the NIH appropriation is \$20 billion. (And we will say more later about the annual fights to keep the NIH budget increasing.)

NIH's policy of dispersing nearly half its funds extramurally has paid off handsomely. As one measure of success, more than 80 Nobel Prizes have been awarded for NIH-supported research. Of these, only 5 have gone to investigators in NIH intramural programs.

### The American Cancer Society

The American Cancer Society (ACS) is the largest supporter of basic research among voluntary health organizations, spending on the order of 2% as much as the NIH. It was founded by 15 New York physicians and business leaders in 1913, at a time when mentioning cancer in public was taboo. They set about trying to bring cancer out of the closet by writing for popular magazines and recruiting physicians to educate the public. In 1936, a legion of volunteers whose role it was to wage war on cancer, the Women's Field Army, was created and rapidly expanded to 150,000 people (ten times the original number) by 1938. After WWII, Mary Lasker helped raise \$4 million for the Society to fight what was termed 'the enemy at home'. Remarkably, \$1 million of this was earmarked for the ACS's research program.

In subsequent years, the ACS – although a disease related organization – has spent over \$2 billion on research. It solicits investigator-initiated applications and relies, like the NIH, on peer review carried out by several study sections. Much of the funded research has been very basic, with only tenuous ties to cancer evident at the time. 30 Nobel Prize winners have been recipients of ACS funding, often early in their careers before they received support from other sources.

### The Howard Hughes Medical Institute

The Howard Hughes Medical Institute (HHMI) is a relative newcomer but has recently expanded to become the single largest nongovernmental supporter of basic biomedical research. It currently distributes more than \$500 million annually, about 5% as much as the NIH extramural program. Support to US researchers is not in the form of investigator-initiated grants, but who gets HHMI support is decided by a study section-like mechanism.

The HHMI was founded in 1953 by the eccentric billionaire businessman Howard Hughes. Hughes had long been interested in supporting medical research, but the Institute's mission was framed in impressively broad terms. Its charter states "The

primary purpose and objective .....shall be the promotion of human knowledge within the field of the basic sciences (principally the field of medical research and medical education) and the effective application thereof for the benefit of mankind.” Hughes’ Medical Advisory Board was made up of prominent medical scientists from the most prestigious medical schools. By 1957, 47 investigators, all at major medical schools were being supported by the HHMI.

A new era at HHMI began in 1985, when the trustees sold the Hughes Aircraft Corp. and agreed to disperse 3.5% of its assets (held primarily in the stock market) annually. Since then, the number of investigators has grown to 350 at over 70 locations; they are faculty not only at medical schools and institutes, but also in basic science departments at the nation’s research universities. HHMI is different from NIH or the ACS in that its funds people, not projects. Thus, HHMI investigators are no longer employees of the university where they are faculty, but are nonetheless expected to participate fully (like any other faculty member) in the teaching and training mission of their departments.

New HHMI investigators are appointed in a nationwide competition where every several years the leading US universities and medical schools are asked to propose candidates. Investigators are initially selected and then reviewed every 5 years by a board of peers. They are expected to do innovative, creative research but are not tied to any particular project or field. Thus, HHMI has been instrumental in fostering the growth of certain fields, like structural biology (which was struggling with minimal NIH support in the late 1980’s but now flourishes). Today, HHMI funds do not go exclusively to support the laboratories of the chosen few HHMI investigators. In addition, there are substantial grants to international researchers (such as in the former Soviet Union, Eastern Europe or South America) and for creative ventures enhancing science education in high schools and at the nation’s liberal arts colleges.

#### Other funding opportunities

Although I have chosen to tell you about just three representative American organizations that fund basic biomedical research (the NIH, the ACS and the HHMI), there are dozens of others. Private foundations are particularly prominent on the American landscape, providing a diversity of opportunity for any investigator to obtain support for creative research.

An important category that I have not mentioned is how training in the various biomedical sciences is supported in the US. Here the NIH shoulders the lion’s share of the burden, providing both stipends and tuition for PhD and MD/PhD students at the country’s leading universities and medical schools. NIH training grants are awarded by the same procedures as research grants, based on competitive merit review conducted by study sections. But other sources are contributing increasingly to training and thus to shaping the future of biomedicine. Just a year ago, an important conference on “The role of the private sector in training the next generation of biomedical scientists” was organized by the ACS, the HHMI and the Burroughs Wellcome Fund. The last is an independent private foundation that has made its mark with a funding program that helps outstanding scientists early in their careers to develop as independent investigators. The conference considered the ways that private foundations, even with

limited funds, can have important impact on training at both the undergraduate and graduate levels. Specific attention was given to building bridges between the clinical and basic sciences, as well as to the many new interdisciplinary areas that represent emerging frontiers of research in the postgenomic era.

Once a young biomedical scientist has obtained a PhD or MD degree, there typically remains a minimum of at least three years of training before an independent position can be secured. Funding can come either from the grants supporting the postdoctoral laboratory or from an independent postdoctoral fellowship. In addition to federal agencies (eg, the NIH) and voluntary health organizations (eg, the ACS), there are numerous private foundations that award postdoctoral fellowships, again based on competitive merit review. They provide a (low but livable) stipend and often some additional funds for travel or research supplies. Receiving such a special fellowship is a feather in the cap of the young investigator since it insures a degree of independence while in the host lab and a leg up in acquiring a later position.

Also, within the past several decades a number of private foundations (eg, the Burroughs Wellcome Fund) have developed programs that sponsor the very best new assistant professors, providing both salary and partial research funds. Applications for these prestigious awards, which are limited to a certain number per institution, often require a letter of assurance from the department chair that the faculty position is truly independent. The principle that independence is essential for innovative research has therefore imbued the American funding system at all levels.

## People

Above, we have discussed the history and the workings of US institutions that have provided the funding and infrastructure for molecular biology to flourish in the US. But science is done by people. And US scientists are distinctive in that they have taken more of an active role than scientists elsewhere in shaping environments for doing science and in insuring its funding. I have provided you with the writings of three contemporary American scientists whom I particularly admire – Tom Cech, the newly-appointed president of the HHMI, Harold Varmus, Director of the NIH from 1993 to 1999, and Jim Watson, President and architect of the success of one of the premier US research institutes, the Cold Spring Harbor Laboratory. All three were Nobel Prize winners before they took on their current roles as administrators of science. The flavor of their words reveals features of the Democratic soul that Dean Kronman described in the first lecture as peculiarly American. What is it about American scientists that has led to the enormous success of Molecular Biology, out of which grew the Biomedical Revolution?

## The Role of Liberal Arts Colleges

Surprisingly, graduates of liberal arts colleges are vastly over-represented among American scientists. The numbers are as follows. Whereas only 8% of students attending 4-year colleges or universities are enrolled at liberal arts colleges, they account for 17% of those receiving PhDs in science. Even more impressive, these graduates are disproportionately represented among the most successful American

scientists as judged by election to the prestigious National Academy of Sciences. In a recent two-year period, 19% of newly elected members who were educated in the US obtained their bachelors degree from a liberal arts college.

Do undergraduates experience something special at liberal arts colleges that better outfits them for a scientific career than their peers at a large university? Or, do liberal arts colleges pre-select those students who have an aptitude and a predilection for science? Of course it is difficult to distinguish between the nature versus nurture argument. However, it is salient that of the 20% or so of students that profess an interest in science upon entering college, those attending a liberal arts college are more likely to maintain that interest. Liberal arts colleges graduate a comparable percentage with majors in science, whereas the defection rate is much greater at large universities. Whether it is the more intimate contact with faculty or the critical thinking encouraged by a curriculum that emphasizes the arts and humanities, the “intellectual cross-training” (as Tom Cech dubs it) obtained at a liberal arts college clearly provides an extra edge for success in science.

In contrast, as most of you know, there is essentially no such thing as a liberal arts college in most of the other nations of the world. Post high-school education is almost exclusively government funded and occurs at large universities. These have their advantages, as well as their disadvantages. But the lack of influence from the uniquely American breed of higher education – the liberal arts college - surely contributes importantly to differences in how scientists in the US compared to elsewhere conduct their affairs.

### Representation of Women

Women are under-represented in academia the world over. Science is no exception, with the record worsening the more physical the science. The exclusion of women means that a field is not exploiting its brainpower potential to the maximum.

The problem in the US as elsewhere is a leaky pipeline. Whereas approximately half of undergraduate degrees in the biological sciences are awarded to women, the number drops for PhD recipients and further for those in postdoctoral training. Women account for only about one fifth of the faculty in science and engineering at US universities and 4-year colleges. As you climb the academic ladder the numbers become worse and worse: at the assistant professor level (in all fields) there are about 40% women, dropping to under 30% at the associate professor level, and just over 10% for full professors. Even in medicine, where about half the MD degrees now go to women, the statistics on women faculty in medical schools are no better (and perhaps worse). The causes are complex and currently a topic of much discussion. Some funding agencies have adopted forthright measures to attempt to rectify some of the inequities. For instance, the NSF currently refuses to provide support for running a conference if no women are included as speakers in fields where substantial numbers of women are trained (eg, in subdisciplines of biology where 34% of the PhDs are women).

But the US has done better (about twice as well) at promoting women to academic positions in science, compared to Europe, Japan, and the rest of the world. And molecular biology has done better than other more established disciplines, such as medicine or chemistry or physics. Why? I mentioned above that molecular biology, at least at its inception, was peopled by scientists who had necessarily been trained in other disciplines. These scientists possessed the courage to abandon established research paths and embark on investigations that were viewed as esoteric even when successful. Such adventuresome people are also more willing to acknowledge others based on their contributions rather than on pedigree or status. Thus, women, minorities and other eccentrics have thrived in Molecular Biology. And the inclusive tradition has benefited Molecular Biology in return.

### Scientific Activism

Those of you who have read Harold Varmus's piece in the recommended readings, called "Basic Science and the NIH", will have been struck by several things. First, upon assuming the directorship of the NIH in 1993, Varmus had had no prior administrative experience beyond running his own laboratory (with a budget only one ten-thousandth that of the NIH!). Second, a year earlier (in December 1992) before it was even known that the NIH directorship would be open, Varmus and two of his UCSF colleagues had composed a bold letter of advice, published in *Science* magazine, exhorting the new Clinton-Gore administration to act on eleven concrete recommendations in support of basic biomedical research. Third, in his first public policy talk as Director, Varmus charmingly confessed to considerable political naivete regarding the specifics of some of those recommendations. He quipped "you don't have to live in Washington very long to learn that our proposal to double the budget [of the NIH] by FY '98 is simply not realistic".

Indeed, in the early years of Varmus' leadership at the NIH, with five-year caps on discretionary spending and a monstrous national debt, the struggle was to avoid cuts, rather than even to obtain inflationary increases for the NIH budget. Varmus' 1995 lecture to the Annual Meeting of the Massachusetts Medical Society was grimly titled "Biomedical Research Enters the Steady State". But he did not hesitate to recite the enviable record of scientific accomplishment and remarkable improvements in the nation's health that could be traced to forty-five years of steadily increasing support for the NIH. He ended by asking "Why should the NIH – with its popular goals, productive record, economic benefits, central role in sustaining our universities and training new scientists, and prospects for improving health – be valued any less by the federal government than Social Security and other mandatory entitlement programs?" Varmus did not give up and by 1998, his unrealistic dream of increasing the NIH budget twofold within five years was becoming a reality. A drive to double spending by the NIH is currently underway and reached its halfway point with congressional approval last December of a 14% hike for the third year in a row! [More of Varmus' speeches as former NIH Director can be accessed at [www.nih.gov/about/director.](http://www.nih.gov/about/director.)]

What is incredible about America is that an individual with a vision has the opportunity to step up to a leadership position and see that vision implemented on a huge scale. Harold Varmus, the son of a physician, was an English major at Amherst

College. He had trouble deciding what to do with his life, and “prolonged his adolescence as a graduate student, reading Beowulf and Shakespeare.” Finally he went to medical school, as he says “in part because someone once told Gertrude Stein that it ‘opened all doors,’ in part because medical students seemed more eager than I was to get out of bed in the morning”. Later, while working at the NIH as an alternative to service in Vietnam, he experienced “the intoxicating power” of scientific discovery. More than 20 years later, with his UCSF colleague, Mike Bishop, Varmus showed that cancer genes in viruses are derived from normal cellular genes, which undergo mutations that are the defining events in cancer. The Nobel Prize for the discovery of oncogenes was awarded in 1989. Four years later, when offered the directorship of the NIH, Varmus could not say no. His record in the six years he spent at NIH (taking pride in riding his bike twelve miles to work most days) is enviable.

Jim Watson is another scientist who has never failed to let his opinions be known. His views of the War on Cancer (“The Academic Community and Cancer Research,” 1974), which he participated in initiating in 1971, are both amusing and poignant. Of massive cancer centers, he commented, “No matter how hard you try, you can’t pull qualified specialists out of a hat.” He was not bashful in stating his concern that by granting the new cancer money to large scale programs, “we may be witnessing a transference of power (money) from the research-oriented universities (departments) that have made American biology as it now exists, to a new power base whose past existence was derived from its willingness to work on cancer at a time when most scientists thought it to be an intellectual graveyard.” In “The Necessity for Some Academic Aloofness” (1979), Watson acknowledges the “quiet unease” of the academic environment and cites “a major factor determining the quality of a given institution” as being “the ability of its faculty to reward intellectual success even when it leads to the effective academic redundancy of many of its older members”. He goes on to detail how the immensely important commercial exploitations of recombinant DNA and of monoclonal antibodies can be traced directly back to seemingly esoteric discoveries of pure science. He concludes, “we must never forget that ideas are not only beautiful, but necessary”.

Yet, Jim Watson’s impressive leadership both of the Cold Spring Harbor Laboratory and on the national science scene has been anything but aloof. Subsequent to the DNA structure in 1953, Watson joined the Harvard faculty where his laboratory (he always allowed his students to publish without appending his own name to their papers) made many contributions to uncovering the molecular mechanisms and regulation of gene expression. He wrote the first textbook on Molecular Biology, as well as his startlingly frank account of the discovery of the structure of DNA, the best-seller *The Double Helix*. In 1968, he became Director of the Cold Spring Harbor Laboratory, then a sleepy collection of a few small labs and a summer meeting place (with miserable beds) for molecular biologists. Using his distinctive combination of eccentricity and charm, Watson wooed the affluent Long Island community to get involved in (and provide support for) the affairs of the laboratory. Today the Cold Spring Harbor Lab is known for its innovative research, for its short courses that draw scientists from around the world to learn new technologies, and for its premier meetings on both scientific and ethical topics. The Cold Spring Harbor Press publishes books and journals, the DNA Learning Center provides an introduction to the molecules of life for Long Island

schoolchildren, and the local environment boasts a thriving biotechnology industry spawned by discoveries in the lab. Meanwhile, Watson's vision has spurred the application of molecular biology to the study of the brain and neurological disease. He became the first Director of the National Center for Human Genome Research of the NIH from 1989 to 1992, believing - at a time when few others did - that the sequence of the human genome was achievable. As always, his intuition was correct.

The short article in your packet by A. Moore bemoaning the current crisis in European science ascribes the success of US science policy partly to political lobbying by scientists - "accepted as a rightful activity; almost a professional duty". It exhorts European scientists to follow the example of their American peers to fight the tendency of the European Commission to fund demand-led, short-term science and ignore basic research necessary to lay the foundation for future development and application. My own experience in sitting on scientific advisory boards in Europe is that criticism is invariably delivered with such politeness that it is sometimes difficult to grasp the true message. In contrast, our forthright and often blatant ways of communicating with each other allow no possibility of misunderstanding.

These contrasts in the European versus the American scientific scene seem quite remarkable in the context of one of the chapters by Tocqueville that Dean Kronman slipped onto my reading list. Writing in 1850, Tocqueville found that Americans were "more concerned with the applications than with the theory of science," and that "hardly anyone in the United States devotes himself to the essentially theoretical and abstract side of human knowledge." If I have succeeded in conveying no other message, I hope that I have communicated to you that it is basic research - done because scientists have been in charge of science in the US - that has fueled the Biomedical Revolution. Either Tocqueville was wrong or we have changed!

### Molecular Biology and the Democratic Soul

In my lecture I have tried to paint a picture of the distinctly American institutions, traditions and scientists that together have contributed to the amazing flowering of biology and thus to the Biomedical Revolution in the past 50 years. I have not touched on other, probably relevant contributing factors. For instance, what was the impact of the migration of many European scientists to the US during the WWII era? How important was the devastation of European economies relative to the comparative prosperity that we enjoyed after the war? How has the transformation of southern universities as a result of the civil rights movement contributed? What spurred the origin and explosive growth of biotechnology, which has revitalized the pharmaceutical industry, primarily in the US? Many of you in this room could probably bring more professional insights than I to political, economic or sociological analyses of these questions. But in what I have discussed, the influence of the American entrepreneurial spirit and of the American version of the democratic soul (with its striving for individuality, according to Dean Kronman) is everywhere in evidence.

I would like to end by sharing with you Jim Watson's advice to young scientists. These after-dinner remarks, entitled "Succeeding in Science: Some Rules of Thumb" [Science (1993) 261, 1812-1813], capture the quintessential Watson. He begins by

saying, first “you need some luck.” For instance, he was turned down for graduate school by Caltech (why would they want someone whose undergraduate interest was in birds?) and went instead to Indiana, where his mentor encouraged his passion to understand the nature of the gene. But luck is not enough. Nor does being smart suffice.

Rule 1. “To succeed in science, you have to avoid dumb people.” Watson explains that the goal isn’t simply to win, but to win at something difficult. Hence it is necessary to surround yourself with the very brightest people.

Rule 2. “To make a huge success, a scientist has to be prepared to get into deep trouble.” This means even when your superiors tell you that you are not adequately prepared or qualified to do something, you need to ignore these assessments, regardless of how traumatic that might be.

Rule 3. “Be sure you always have someone up your sleeve who will save you when you find yourself in deep s\_\_\_\_.” Watson contrasts the situation of himself and Crick, who always found someone to help them out of trouble, to that of Rosalind Franklin (their DNA competitor) who had no one to save her and ended being excluded from the race.

Rule 4. “Never do anything that bores you.” If you dislike something, you can’t possibly do it well. Moreover, you need to constantly expose your ideas to informed criticism. You must chat with your competitors, even if you find them objectionable.

Which leads to Watson’s final rule: “If you can’t stand to be with your real peers, get out of science.”

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