For more than half a century, the American system of science has received credit for more major discoveries in basic biomedical science than that of any other society. But as we reflect on the history of science over the last century and a half, we observe that the center of science has shifted periodically from one society to another.[1] The center of science in the mid and late eighteenth century was France, but subsequently it was Germany, then Britain, and ultimately the United States. In France, Germany, and Britain at the height of their success, as in the United States today, there was a widely held view—within each country's scientific community and abroad as well—that the system of science was performing extremely well. But in retrospect, we observe that in each of these countries, at the peak of their scientific strength, some of the decline in the quality of their system had already set in. Discussions about the duration of American hegemony are particularly relevant as China becomes increasingly powerful economically, politically, militarily, and in science [see July 24, 2008 issue of *Nature*].

These observations raise the questions, in what direction is American science headed? Might some of the key factors which have led to the excellence of the American system of science already be evaporating? Despite the fact that a substantial proportion of major discoveries continue to be made in the United States, how long will this trend be sustained? Can we identify fundamental problems that are already emerging which over time will diminish the quality of American science? And if so, can they be corrected?

Obviously, these are very difficult questions to answer, in part because we can never with any accuracy forecast the unfolding of complex historical processes. Actors are always moving forward as if in a fog, but the better they understand the path on which they have been traveling, the greater their potential insight about where they are moving. Thus, with greater understanding of historical changes in science in other nations, and threats to American scientific prowess, it may be possible to make some "mid-course" corrections.

The literature on path dependency reminds us that even though systems are always changing, they are usually constrained by their evolutionary trajectory. It is very rare that a society or its system of science departs fundamentally from its past. Even revolutionary systems—despite their enormous change—tend to maintain a great deal of continuity, at least in the short run. Thus, when pondering the future of the American system of science, we can be confident that it too will continue on a trajectory influenced by its past.

---

1 See the third essay in this volume, "The Rise and Decline of Hegemonic Systems of Scientific Creativity," for a discussion of scientific hegemony.

To understand the trajectory along which each national system of science moves, it is useful to be mindful that a society's system of science is part of a larger social system, which influences its scientific practices as well as many other sectors. Thus far, in other essays, we have focused primarily on how the structure and culture of research organizations influence the making of major discoveries. In giving primary attention to scientific organizations and their characteristics, we have made relatively few comments about the role of a society's larger social system in shaping scientific practices. Yet the social system in which a society's scientific practices are embedded plays an important role in shaping scientific practices. When we attempt to understand why scientific practices in Japan, the former Soviet Union, or France have differed so much from those in the United States, it is important to understand the differences in the larger social systems of which systems of science are a part. Every society is made up of multiple subsystems—e.g., economic, political, educational and science systems—and each social system and its constituent parts are linked together with a distinctive logic.

Thus, the key to understanding the developmental path of any society's science system is to comprehend the logic of development of its larger social system. Over time, a society's social system undergoes chance effects and may even develop imbalances. Some scholars have suggested that there is a tendency across social systems for parts of a social system to resemble one another.

In any society the culture in which scientific research is embedded is the glue for linking its levels and segments together. But a society's culture and its social processes have a high degree of path dependency. There are marked differences in institutions and culture between societies and thus in the structures and cultures of their research organizations, and these differences persist across time in a path dependent manner. Changes in the societal culture bring about changes in the science system.

5.1 The Path Dependent Nature of National Systems of Science

At a general level of definition, the subject of path dependency is "tricky business." Scholars who use the term path dependency vary in the meaning they attach to it. At one extreme is the view that path dependency refers mainly to the causal relevance of events in some type of temporal sequence. In short, history matters: what actors do today is shaped by what they did yesterday. Hardly anyone is a strict determinist, assuming that actions of today are totally determined by choices made in the past or by the institutional and/or organizational environment in which they are embedded. If social systems were strictly deterministic, and if

societies operated according to fixed rules, we would have the ability to better understand the trajectory of a society's science system.

Many commentators, in using the term path dependency indicate their meaning to be that once a country, organization, or individual has started down a track, there are multiple choice points, but certain institutional arrangements obstruct easy reversal of the initial choice. The costs of exit—or of switching to some plausible alternative—can be large and daunting. The farther along a path a society or an organization is in developing a set of practices, the more difficult it becomes to shift to alternative paths. As a result, extensive movement down particular paths, whether at the societal or organizational level, tends to have "lock in" effects.

A critical issue in using the term path dependency is to understand *how* history matters. In studying the environment in which scientific research is embedded, we include the following as relevant to the definition of path dependency [Hollingsworth, 2004; Pierson, 2000: 252; Arthur, 1994]: (1) small events often have major consequences, (2) specific courses of action—once introduced—are very difficult to reverse, (3) there is a great deal of chance and contingency to the unfolding of history, and (4) the timing and sequence of events are very important in shaping longer-term social processes and outcomes.

There is also a path dependent aspect of scientific discoveries. In brief, if you are too late in making a specific scientific discovery your chance of obtaining widespread recognition for the discovery is decreased, even if your work on the discovery is quite advanced. Scientists give considerable emphasis to priority in the discovery process. Being early in developing a novel technique, adopting a new type of instrumentation, or developing a new discipline often makes a great deal of difference in shaping the recognition for the scientist and the subsequent trajectory of his scientific research. Scientists who adopt a process or instrument or establish a particular kind of disciplinary-based department at a later date may be of little consequence in the competitive discovery process.

When it comes to designing research organizations, actors generally have no way of knowing a priori the consequences of their actions. Experienced and wise decision makers are generally aware that they are gambling, that they may well be introducing components and processes which will later prove to have undesirable consequences or which over time will require major adjustment. Unfortunately, many policy makers and administrators tend to be overly optimistic, rational, and functionalist in administering research organizations and to exaggerate their ability to gauge the consequences of their actions [Langer, 1975].

Most institutional and organizational change unfolds in processes which are somewhat blind and random. Societies that excel in being innovative in various sectors or spheres over extended periods of time do so because of their good fortune in having an institutional environment which offers them the capacity

to perform well. Some of the excellence in innovation stems from planning, some from accident. At best, we can hope to discern retrospectively what the regularities were which influenced high performance in science. Generally, we cannot predict what processes will definitely lead to particular outcomes, but we can hope to specify which ones are most likely not to lead to particular types of scientific outcomes. In retrospect, we can see what *kinds* of organizations and laboratories were successful in the past, and what *kinds* were unsuccessful in making major discoveries.

5.2 The Path Dependency of Institutional Environments

The institutional environment of organizations provides resources for organizations that play a major role in shaping their behavior. How resources are allocated to organizations is inextricably bound up with the relationship between organizations and their institutional environments. In our approach to the study of major discoveries across societies and over time, we generally focus on four aspects of institutional environments that constrain the behavior of research organizations. These are environmental or external control over (1) the appointment of scientific personnel, (2) whether or not a particular scientific discipline will exist in a society's research organizations, (3) the level of funding for the society's research organizations, and (4) the type of training needed for appointment in research organizations. On the basis of these characteristics, we classify societal or institutional environments as weak or strong. As noted in other essays in this book, these processes change over time, and in turn influence the behavior of research organizations.

In those societies in which external controls over organizations were highly institutionalized and strong, there was less variation in the structure and behavior of research organizations. In such instances, the connectedness between research organizations and their institutional or external environments was so strong that research organizations had low autonomy to pursue independent strategies and goals. For example, increases in funding for science from the central government have led to increases in the size of research organizations, new types of organizations, and new scientific missions.

Conversely, the weaker the society's institutional environment in which research organizations were embedded, the greater the variation in the structure, behavior, and performance of research organizations. Moreover, where the institutional environments were more weakly developed (*e.g.*, the United States), organizations generally had greater autonomy and flexibility, factors which contributed to their ability to foster the development of new knowledge.

Hence, in those societies (*e.g.*, France) where institutional environments were most developed and rigid (*i.e.*, strong), and where there was less organizational autonomy and flexibility, fewer radical innovations in basic and applied science emerged over the past century. French scientists made more major discoveries in biomedical science before World War II than in the second half of the twentieth century. But on the other hand, the French did make many incremental innovations in basic and applied biomedical science throughout the twentieth century.

The data on the institutional environments of France, Germany, Great Britain, and the United States suggest that there is a high degree of complementarity among the four concepts for describing institutional environments: when one was weak, the others tended to be weak. Similarly as there was change in one concept, there was change in the others.

Even though there are prototypes of strong and weak institutional environments, there have been exceptions to the way institutional environments affect organizations, even in the same society and over time. For example, the performance of German universities has been greatly constrained by their being embedded in a relatively strong institutional environment. But in the same society, Max Planck Institutes have had much more organizational autonomy and partially as a result have performed quite well [Mayntz, 2001; Ash, 1997]. The achievements of a number of German scientific organizations were especially notable in the early twentieth century. In a weak institutional environment such as that in Britain, there are some research organizations operated by governmental departments which have been operated in a very bureaucratic manner, and have been heavily and directly dependent on Whitehall (which determines personnel policies, research plans, and financial resources). In this regard, the Laboratory of Molecular Biology (LMB) in Cambridge has been a major exception with regard to the practices of government research laboratories in that it has enjoyed considerable autonomy over the years. In contrast to Whitehall-dominated units, British universities historically had much greater organizational autonomy and more independence to shape their own personnel and research policies, a situation that has changed markedly in the last thirty years, even at Cambridge and Oxford [Ziman, 1987].

Historically, modern societies have had a scientific sector which gives priority to the production of public goods (*e.g.*, communal science), where the norms of "open science" have prevailed. These have been celebrated in the writings of various historians and sociologists of science.

But during the process of end-of-the-twentieth-century modernization, a for-profit sector has also produced science and technology and this has grown at an accelerating rate. In this sector, the incentives have been primarily monetary in nature. During the past fifty years, the process of industrialization has tended to

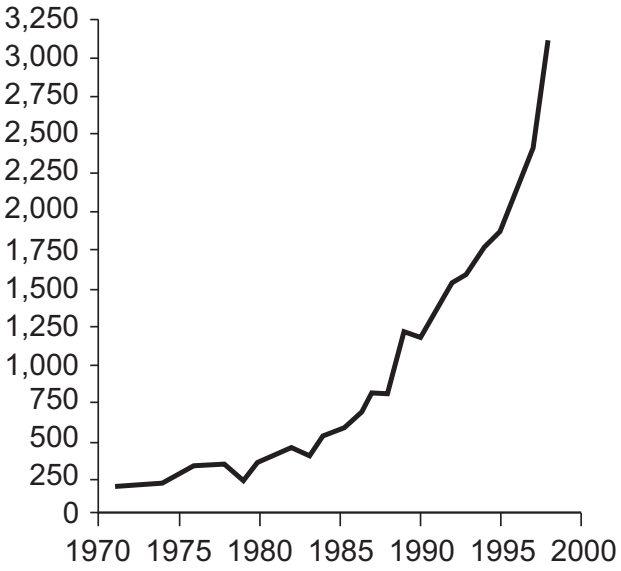
diminish the proportion of individual scientists pursuing communal obligations and the production of public knowledge, and has tended to increase the proportion of scientists engaged in the pursuit of pecuniary gain. This process is one of the most important forces transforming the American social system of science. As the for-profit world has increasingly influenced universities, they have become more preoccupied with reaping rewards from patenting, licensing, and other forms of property rights for scientific and technological knowledge (interview with Greenspan). The first essay in this volume has given some attention to this.

However, these trends should not be exaggerated. The American system of science has garnered worldwide attention since the end of World War II for its excellence in communal-type science. To give a few examples, since 1945, Nobel Prizes in Physiology or Medicine have been awarded to almost ninety scientists who did their research in the United States and there have been over sixty Nobel Prizes in Chemistry for work done in the United States. There have been over eighty Nobel Prize-winning physicists who did their prizewinning research in the United States. About forty to fifty percent of all Nobelists across the twentieth century did their research in the United States. The number of published scientific papers by United States authors leads the world, even compared with all countries of the European Union combined. These markers of achievement, together with the influx of foreign students seeking American training, have been widely noted for fifty years. Excellence, however, is never permanent, as global changes in trade patterns and financial flows indicate. Moreover, as a society's social system changes, there is change in the system of science. The remarkable American system of science now faces a variety of difficult challenges. The fact that the American system of science is embedded in a larger social system that is changing its characteristics and encountering serious economic problems poses serious challenges for maintaining its level of scientific achievement.

Given the larger social system in which American science is embedded and the rate and types of changes in the economic system, one should not be surprised that the for-profit sector of science has been expanding throughout the twentieth century. As emphasized in the first essay, the Bayh-Dole Act of 1980 permitted universities to use research funded by the federal government to obtain and own patents. The sector's rate of growth has dramatically increased during the past several decades. The act accelerated the expansion of the for-profit sector in universities [see Figures 5.1 and 5.2]. Some scholars have suggested that Bayh-Dole was but the tip of the iceberg and that the pressures for American science to turn toward profit had been profound even prior to 1980 [Mirowski, 2011]. Under the act, intellectual property resulting from federally funded research in universities could be patented, and universities and their researchers would be the beneficiaries of any resulting patent

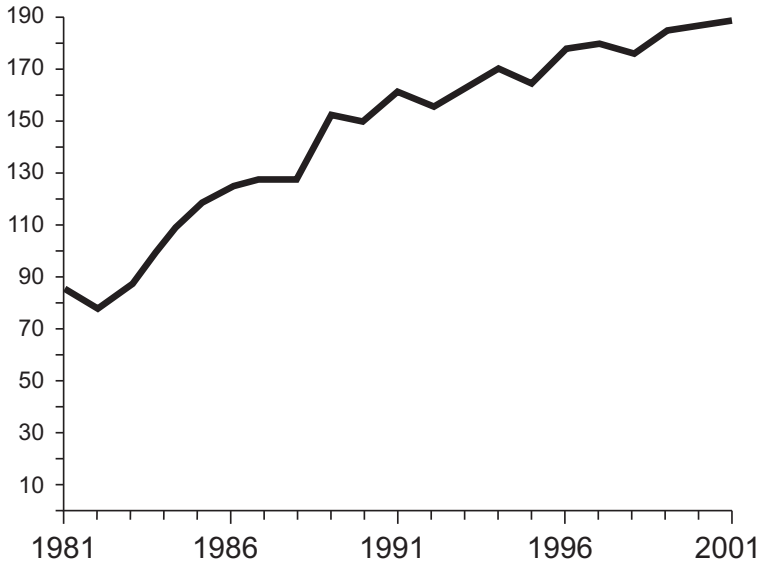
royalties. Moreover, university linkages with industry have increased dramatically during the past three decades. Subsequent to the Bayh-Dole Act, Congress passed much additional legislation to foster university-industry relationships, resulting in considerable profits for many universities [Washburn, 2005].

FIGURE 5.1 **United States Patents Granted to United States Academic Institutions 1971–1998**



Source: *National Science Board, Science and Engineering Indicators* [1996; 2004]

FIGURE 5.2 **Number of Academic Institutions Granted United States Patents 1981–2001**



Source: *National Science Board, Science and Engineering Indicators* [1996; 1998; 2004]

As National Institutes of Health overhead rates were adjusted downward, universities struggled to support research laboratories with their own funds [Stephan and Ehrenberg, 2007: 11; Slaughter and Leslie, 1997]. In the period following the passage of the Bayh-Dole Act, the historical relationship between public sector and for-profit sector science was significantly altered, bringing about a transformation in the culture and behavior of American universities.

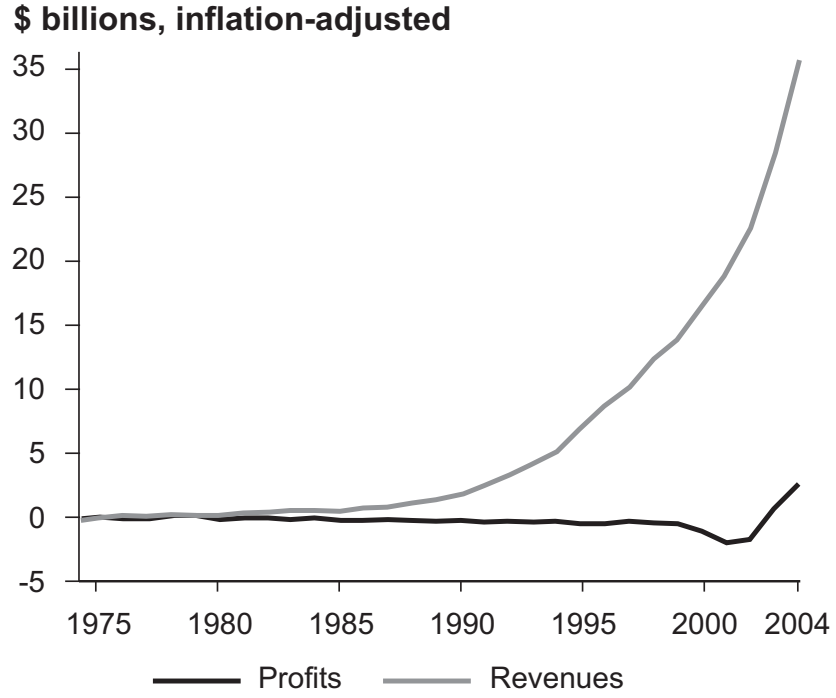
Historically, universities were sites primarily concerned with producing science as a public good, while for-profit firms were primarily engaged in producing science and technology as private goods. The distinctions between these types of organizations were not always clear. Indeed, the University of Wisconsin began to engage in patenting as early as the 1920s, with patent royalties flowing to the Wisconsin Alumni Research Foundation (WARF).

Of course, the Bayh-Dole Act was just one of numerous factors which have led to an increasing commercialization of science within American universities. Another has been the change in the structure of American universities, which has meant a more "management" style of leadership. As universities have increased dramatically in size and have become more fragmented and bureaucratic, their deans, provosts, chancellors, and presidents have suffered a diminishing ability to make good assessments about the quality of the science produced by scientists in academic positions. In compensation, quantitative measures have tended to become increasingly important indicators of academic quality [Whitley, 2007]. For years, the number of scientific publications was used as a major indicator of quality, as most individuals holding high "management" positions in American universities could not evaluate the quality of specific scientific publications. In more recent years, this quantity of publications measure began to be supplemented by measures of the amount of money an individual scientist generated in grants, patent royalties, licensing agreements, etc. Increasingly, special rewards to scientists within universities have tended to go to those who generate the most revenue.

As this has occurred, the role model for young post-docs in scientific fields has been changing. For a young investigator, the dominant role model is no longer the senior scientist [*e.g.*, Niels Bohr, Linus Pauling, Howard Temin, Frederick Gowland Hopkins] who made a fundamental discovery which might alter the way scientists think about important problems. Rather, the contemporary role model has become the senior scientist who has multiple extramural grants, is part owner of one or more for-profit firms, and owns not only a BMW but also a Mercedes. The emphasis is on scientific problems which can quickly be solved and which can lead to the next grant or to a new patent—essentially short-term profit maximization.

Increasing numbers of scientists have become involved directly with for-profit efforts, frequently starting their own firms, with the hopes that their firms will become publicly traded firms, or be absorbed by larger firms. Whatever the amount of investor interest in science-based business firms (and it has been considerable), the recent study by Gary Pisano of the publically listed biotech firms in the late twentieth and early twenty-first centuries showed that although there was an enormous increase in biotechnology sales, in aggregate the profits had been stable—virtually zero—suggesting that many of those investing in the sector had unrealistic expectations [see Figures 5.3]. While most of the biotechnology sector has been independent of universities, an increasing portion of the sector has been intricately tied to universities. Indeed, many universities have become venture capitalists.

FIGURE 5.3 **Revenues and Profits in the Biotechnology Sector 1975–2004**



Source: Pisano [2006, 5]

These processes in turn are leading to further changes in the behavior of American universities. Some universities are beginning to resemble holding companies. The successful scientist is increasingly an entrepreneur who operates his/her own small firm within the university. As long as one can generate sufficient revenue, the professor has a very high level of independence, with teaching and other university obligations becoming ever more irrelevant.

There is some evidence that in the short term the increasing commercialization of the American university is contributing to a very modest level of economic productivity and growth for the entire society. Clearly, a robust for-profit science sector has been an important stimulus to the American economy in the late 1990s and the early twenty-first century.

We fear that the increasing commercialization of science and bureaucratization of research universities will discourage young investigators from engaging in high-risk research [Whitley, 2010]. For many years there has been considerable debate about how advances in technology influence the agenda for fundamental and basic science. [Landau and Rosenberg, 1986; Rosenberg, Landau, and Mowery, 1992]. What is not sufficiently appreciated is that for the continuation of economic growth in highly industrial societies, a sustained abundance of underlying advances in fundamental or basic knowledge is necessary [Belfiore, 2009]. Indeed, many fundamental advances in basic knowledge had consequences which were realized in the marketplace only after long periods of time. Moreover, most consequences were usually unintended [Comroe and Dripps, 1976; Illinois Institute of Technology Research Institute, 1968]. "Scientific research is above all a process that has to remain open to the serendipitous, the unexpected, the incongruous, the unanticipated" [Mirowski, 2011: 289], which in some research areas has helped to make possible in only a few hours the selection and duplication of extremely small samples of DNA by a million-fold [Judson, 2004: 38].

Thus, it is appropriate to seek perspective on the implications of our findings for sustaining major discoveries in American research organizations. The commercialization of science is increasingly shaping the style of scientific research in American universities, resulting in a tendency for many of our society's most talented scientists to be driven less by inquiry as an end in itself, and rather to engage in non-controversial inquiry, research which is incremental and likely to reap financial rewards. As the costs of science have risen, senior American scientists find that they must spend an increasing proportion of their time raising money for research. Numerous senior scientists have informed us that they spend at least a third of their time seeking funding for their labs. But as they succeed in raising money, they must then devote more time as a manager—recruiting graduate students, postdocs, other scientists, as well as technicians. The battles within their own research organizations with colleagues in other labs and administrators over space never end and consume even more time. The net effect is that many of society's most senior and respected scientists have less and less time to engage in deep and serious thinking.

At present, the problem of obtaining funding for laboratories in America's leading research universities is not as difficult as in most other highly industrialized

societies. During the 1990s and in the first few years of this century, unprecedented sums of money flowed into American universities. Numerous universities waged major fundraising campaigns which yielded hundreds of millions of dollars. In the past two decades, a few universities mounted campaigns to raise in excess of a billion dollars. In 2010, twenty universities received gifts of over $250 million apiece, as listed in Table 5.1, a pattern similar to that in other recent years.

TABLE 5.1 **Gifts to Twenty United States Universities, 2010**

	$ Millions		$ Millions
1. Stanford	599	11. UCLA	340
2. Harvard	597	12. Wisconsin	312
3. Johns Hopkins	428	13. Cornell	308
4. USC	426	14. Berkeley	308
5. Columbia	402	15. MIT	307
6. Pennsylvania	382	16. Washington	285
7. Yale	381	17. UCSF	269
8. NYU	349	18. UNC Chapel Hill	257
9. Duke	345	19. Michigan	252
10. Indiana	343	20. Chicago	251

Source: Council for Aid to Education annual Voluntary Support of Education survey [2010]

As a result of dozens of interviews with senior scientists and administrators in America's largest research universities, it has become quite obvious that most high level administrators have little understanding of the most effective ways of investing this money to generate high quality research. The presidents of numerous major research universities resemble the CEOs of major American banks in the early twenty-first century. Their organizations have become too complex to be managed. According to Tainter [1994], complexity in advanced industrial societies poses serious impediment to sustaining good organizational performance [Sornette, 2000]. Every major research university in the United States has a development office which engages in enormous public relations activities and makes oftentimes exaggerated claims as to how its funds are being channeled to cure a long litany of diseases. Development offices have spent countless hours conducting investigations about potential, wealthy donors to determine if they had a close relative or friend afflicted with a major disease, so the organization can then target the donor with the right hype—all to enhance fundraising. The courtship of major donors has become a serious and time-consuming activity; development offices have become major centers in the nation's leading universities.

5.3 Size of Research Organizations and Commercialization of Biological Science

It is hardly surprising that the American systems of business and science would increasingly share many of the same characteristics. As one of Harvard's most respected biologists, Richard Lewontin [1991: 3–4] reminded us, science as a social system is embedded in and influenced by most of the other social systems of a society. While small firms and small-scale science are still quite pervasive throughout American society, advanced industrial capitalism in the twentieth century has made it difficult for small firms to survive, just as big biological science is making it increasingly difficult for small science institutes and small-scale science to obtain the sufficient resources for survival. The American business system is witnessing an erosion of trust and the spread of greed and is increasingly immersed in an ethos of aggressive advertising. Meantime, some of these traits are diffusing to and emerging in the American system of science. While the two systems seem to be converging in some respects, the similarities should not be exaggerated. Indeed, there are profound differences in the two systems.

In the past, funding for biological science had been targeted for specific diseases. Now, new strategies have been developed to attack numerous diseases. This was, in large part, a response to the rapid advances in genetics and molecular and cell biology, as well as to a host of new technologies which aided scientists in analyzing numerous diseases in greater detail. As this occurred, ever more research funds have been needed, and as the biomedical science community has promised to make many more rapid scientific advances, funding has increased, ironically leading to demands for even more funding.

Promising advances in biomedical science raised the hopes and expectations of the American people that cures for numerous diseases were just around the corner. By 2010, the United States spent more money than any other country on healthcare and research, not only in absolute dollars but as a percentage of GNP. Health expenditures, defined broadly, rose from approximately five percent of GNP shortly after World War II heading toward a projected twenty percent in the year 2020. The American health sector had become the most expensive part of the economy. In the biomedical sector, powerful lobbying groups have emerged, some of the most powerful in American society, supported by pharmaceutical and biotechnology firms, biomedical research groups, insurance companies, manufacturers of large and small medical instruments, professional associations, and universities. The medical-industrial complex had become comparable to the military-industrial complex about which President Eisenhower had warned a half-century earlier. The process had been somewhat self-organizing—almost

beyond control—posing serious problems to American national security [Cook-Deegan, 1994]. One might point to many areas of biomedical research as examples, but we focus briefly on only a few.

One of the most interesting was the Human Genome Project (HGP), which came to great visibility in the late 1980s, at the time the largest biomedical research project ever launched. From the beginning, this was an international project, though in personnel and money, American scientists were dominant. Ultimately the HGP involved twenty centers in several countries including France, Germany, Great Britain, Japan, and the United States. In the United States much of the early initiative for the project was led by lobbying efforts of three powerful scientists, James D. Watson, Walter Gilbert and Leroy Hood. Implementation of the program was lead by a handful of major centers: three funded by the National Institutes of Health (the Whitehead Institute in Cambridge, Massachusetts, the Washington University School of Medicine in St. Louis, and the Baylor College of Medicine in Houston); the Joint Genome Institute in Walnut Creek, California (funded by the United States Department of Energy); and the Sanger Institute in England. The cost of the project was several billion dollars. Early on, some of its chief supporters attempted to legitimate the project by giving it religious overtones. Nobel laureate Walter Gilbert [1993] wrote a widely circulated essay characterizing the project as "A Vision of the Grail." Daniel Kevles and Leroy Hood in their introduction to The Code of Codes wrote, "Unquestionably, the connotations of power and fear associated with the Holy Grail accompany the genome project" [Kevles and Hood, 1992]. Harvard biologist Richard Lewontin observed that many of the key advocates of the project characterized it with metaphors from medieval Christianity: DNA was said to be the Grail, molecular biology a religion, and proponents of the Human Genome Project were its prophets [Lewontin, 1992]. When most of the project was completed, there were huge celebrations held on June 26, 2000, with participation by President Bill Clinton and Prime Minister Tony Blair, both of whom spoke in symbolic tones as though the scientific community had finally discovered the Holy Grail. To add legitimacy to the Human Genome Project, its evangelists prophesied that as a result of their endeavors, it would soon be possible to locate on human chromosomes the defective genes responsible for most diseases, and it would then be possible to understand their causes and to devise therapies for their cure. A few distinguished scientists predicted that the completion of the Human Genome Project would quickly lead to the cure of many diseases [Collins and McKusick, 2001; McElheny, 2010].

The Human Genome Project was an interesting commentary on the times. The complexity of the program exceeded all previous scientific research projects—including the development of the atomic bomb at Los Alamos during World

War II. Many of the Americans and British prominently associated with the Human Genome Project had strong ties to universities, biotechnology firms, the National Institutes of Health, the Department of Energy, the Medical Research Council in Britain, private American foundations, the Wellcome Trust, and the manufacturers of materials used in sequencing research [Sulston and Ferry, 2002; Preston, 2000].

The Human Genome Project fed the appetites of many scientists, journalists and policy makers who were keen to acquire new information about the frontiers of biomedical science. However, most had limited ability to interpret or understand the Human Genome Project. By the time the Human Genome Project came to an end, many in biotech firms, the investment community and elsewhere suddenly awakened to the fact that the HGP was not going to lead to quick cures of disease that many had promised as being just around the corner. Norton Zinder, a distinguished geneticist in the United States and senior professor at Rockefeller University who had previously with great vigor promoted HGP, was attempting by 2000 to cool down the irrational exuberance about the project by suggesting that it was not nearly as important as its chief advocates had led the public to think: this is simply "the beginning of the beginning ... The human genome alone doesn't tell you crap ... With the human genome, we finally know what's there, but we still have to figure out how it all works. Having the human genome is like having a copy of the Talmud but not knowing how to read Aramaic" [Quoted in Preston, 2000: 83].

By the beginning of the new century, Richard Lewontin observed that most in the molecular biology community had realized that the Human Genome Project had never been the appropriate target for large-scale biological research; rather the scientific community should have been concentrating on the "proteome, the complete set of all the proteins manufactured by an organism. Although the devotees of the genome project kept assuring us that genes make proteins and therefore when we had all the genes we would know all the proteins, they now say that, of course, they knew all along that genes don't make proteins, genes only specify the sequence of amino acids that are linked together in the manufacture of a molecule called a polypeptide ... The sequencing of the DNA of a gene is technologically trivial in comparison with the determination of the three-dimensional structure of a protein" [Lewontin, 2001: 190–192].

Nobel Laureate John Sulston, who had headed the Sanger Center in England on genome research, warned the public that the biological community was still very ignorant about the processes of life. Sulston and Georgina Ferry echoed the sentiments of Zinder that "we are right at the beginning, not at the end; we don't know what most of the genes look like, or where they are expressed ... Once we've found the genes, we need to work out what proteins they produce and to

understand the time and place of expression. And until this is done, the linkage between genes and disease will be poorly understood" [2002: 248, 256–257].

To understand the linkage between genes and most common diseases, there now began to be a "mad rush" of scientists attempting to understand the sequence of proteins—a far larger project than the HGP, one involving many more scientists and literally billions of dollars. Though the genome provides only the "recipes" for the making of proteins, it is the proteome that constitutes the building blocks of cells. It is the proteome which differentiates various types of cells. The proteome is much more complex and difficult to understand than the genome. Whereas the DNA alphabet is made up of few chemical bases (*i.e.*, A, C, G, and T), proteins are constructed among twenty amino acids. Although genes do specify which amino acids are strung together to form a particular protein, even if scientists know the amino acid sequence of a protein, it is very difficult to determine what the protein does or what other proteins it interacts with. Moreover, it is exceedingly difficult to determine accurately the three-dimensional structure of a protein. While genes are linear, proteins fold into very complex and unpredictable shapes. And whereas the scientific community is of the opinion that the genome consists of between twenty thousand and twenty-five thousand genes, a typical cell makes hundreds of thousands of different proteins.

Within a very short period of time, proteomics became one of the fastest growing areas of biological science, not only in the number of people doing research in the field but also in the level of funding. By 2005, it was estimated that at least $5.6 billion was expended simply on proteomic instruments, supplies, and services. Many of the world's leading pharmaceutical firms began to rely on proteomics to revolutionize their drug development programs. By 2002, one American company alone had raised almost $1 billion for its proteomics program. Universities on both sides of the Atlantic competed with each other in establishing huge proteome research organizations [Ezzell, 2000; 2002].

The field of proteomics has contributed extraordinarily to furthering knowledge of the biological world, knowledge which is accelerating at a very rapid rate. With advancements in X-ray crystallography, two-dimensional gel electrophoresis, and mass spectrometry, scientists have made phenomenal advances in understanding the precise three-dimensional structures of proteins. But the process of understanding what a protein does or what other proteins it interacts with is proving to be far more difficult than believed to be the case by scientists a few years ago. With new visualization techniques, scientists have many more images with which to enhance their biological insights. All of this research is permitting individual laboratories to characterize individual proteins of interest and to study not only large proteins but also protein complexes. But whereas a few years ago there were predictions that a revolution in the

pharmaceutical industry was around the corner, that in only a few years drug companies would be able to customize or tailor a drug to the special needs of a patient, these predictions have proven to be illusory. Similar to the way President Richard Nixon's war on cancer was quickly going to bring an end to cancer in the 1970s, the HGP and proteomics have brought about very important advances in diagnostic tools, but cures for most diseases have proven to be far more difficult than many proponents had led the public to believe.

Just as some of the scientific exuberance over the human genome project and proteomics cooled off, many in the scientific community and the public jumped on the bandwagon of stem cell research. This quickly became one of the most promising areas of biomedical research in our time, but it, too, was fueled by unrealistic expectations.

An example of the scientific exuberance for stem cell research was a grandiose scheme launched in California by a group of private citizens who placed a referendum—Proposition 71—on the ballot in November 2004. The proposition, strongly endorsed by California voters, created the California Institute for Regenerative Medicine which quickly became one of the world's largest financial supporters of stem cell research. The money was to be raised by the issuance of $3 billion in public bonds which would provide $300 million for each of ten years for stem cell research in the state of California. Including interest, the bonds would eventually cost approximately $6 billion—coming from the state's general fund—which was already in great fiscal difficulty. The most vocal supporters of the bonds alleged that the research institute would be self-financing, as the bonds' principal and interest would be paid from patent royalties and licensing fees derived from stem cell research, and from savings in the state's swelling medical costs as stem cell research brought about cures. Proposition 71 had very little provision for legislative or public oversight of how the money would be used. Moreover, neither the legislature nor the executive branch of California government was given authorization to end the annual funding or to shift the funds to other purposes.

Almost immediately, there was a "gold rush excitement" among many in the California scientific community. Evan Snyder, director of stem cell biology at the Burnham Institute in San Diego, proclaimed that California was going to become the stem cell center of the world, not just the United States. There were promises that stem cell research would become a huge, new California industry, creating thousands of jobs and bringing in millions of dollars in patent royalties. Indeed, the California project was the largest single initiative ever undertaken by a sub-national government to fund a new industry. Because California was already a state with many high-quality universities, well-established venture capitalists, and entrepreneurs, the California proposition was immediately perceived as a threat to other centers across the country. Irv Weissman at Stanford announced

even before the passage of the proposition that he was going to undertake a vigorous recruiting campaign in the East to bring many of the nation's most senior stem cell scientists to California. Meanwhile, scientists at the University of California San Francisco, University of California San Diego, Caltech, the Burnham Institute, the Salk Institute, and elsewhere announced their intentions of getting Proposition 71 funds for their own institutions. Even biotech firms which had not previously been involved in stem cell research indicated their intention to get in on the action. As Martin McGlynn, chief executive of the biotech firm Stem Cells announced, "There's an old maxim in the biotechnology industry that when they are passing around the hors d'oeuvres, help yourself whether you're hungry or not" [Pollack, 2004; McElheny, 2010].

Shortly the threat from California generated defensive measures among stem cell researchers across the country. A few firms announced that they would establish a branch in California in order to obtain some of the funds. Harvard, which already was a major center of stem cell research, indicated that it would attempt to raise $100 million for a stem cell institute [Pollack, 2004]. Several other states approved plans and raised large sums of money in order to develop programs for research on stem cells in their states.

5.4 Research Strategies

Readers of this essay will undoubtedly vary in the policy implications they derive from it and previous chapters. After all, science is a part of the broader societal system. We do feel obliged to express our judgment about a few of its implications.

Large-scale and expensive science projects are here to stay. Just as industrial and financial institutions continue to increase in size and complexity, this is also true with universities. These tendencies are likely to be irreversible. However, we believe that the findings of our research on four countries over a period of a century suggest that research organizations and their component parts are likely to be more creative in fundamental, basic science when they have a high degree of flexibility and autonomy and are not constrained by highly complex bureaucratic environments. Research organizations tend to be more creative when (1) there is a great deal of intellectual interaction among their diverse parts, and (2) leaders at every level of the organization have a good grasp of the direction in which science worldwide is moving, and the capacity to make highly informed judgments about the scientists being recruited and the research they are conducting. Contrary to much contemporary thinking, great science flourishes when distinguished leaders are given the opportunity to operate paternalistically.

In this connection we are reminded of the environments in which Niels Bohr flourished in Copenhagen; Simon Flexner, Herbert Gasser, Detlev Bronk, and Torsten Weisel at the Rockefeller; Lawrence Bragg and Ernst Rutherford at the Cavendish; Michael Foster and Frederick Hopkins at Cambridge; Salvador Luria at MIT; Max Delbrück and George Beadle at Caltech; Max Perutz at the Laboratory of Molecular Biology; and Bill Rutter at the University of California San Francisco. Not everyone may agree with our evaluations of each of these scientists, but our judgments are based on in-depth analysis of each of these scientists and the environments in which they worked and which they contributed to creating. Others may argue that the organizational characteristics which we have described associated with major discoveries are a phenomenon of the past, that future discoveries and creativity are much more likely to be parts of large-scale science—organizations with large laboratories and projects involving hundreds of scientists which must of necessity become complex bureaucracies because of their large scale. Large-scale science is more likely to be embedded in large organizations led more by managers than by distinguished scientists.

Some results of our larger body of research suggest that large-scale research organizations are necessary for science to flourish. Some biological science projects were loosely modeled along the lines of huge physics projects (*e.g.*, the Human Genome Project). And in the latter half of the twentieth century there were a series of major discoveries in particle physics from experiments performed on large accelerators, several of which resulted in Nobel Prizes. However, throughout the twentieth century excellent science in physics has been and is still occurring within small groups, often consisting of very few senior investigators, each having only two or three young assistants. Throughout the last century there was a great deal of similarity between biology and physics, in that much work of both tended to occur in small research settings. Physicist Per Bak made the argument a few years ago that the dominance of large-scale physics projects has ended. Observe that some of the Nobel Prize winners in physics over the last thirty years did their work in very small settings: Klaus von Klitzing's [1985] work on the quantum Hall effect in semiconductors; the research of Alexander Muller and Georg Bednorz [1987] in Zurich for their work on superconductivity in ceramic materials; Gerd Binnig and Heinrich Rohrer [1986] of the IBM Labs in Zurich for their design of the scanning tunneling microscope; and Pierre-Gilles Gennis [1991] of the Collège de France for his discoveries about liquid crystals and polymers—all of which were followed by a number of other Nobel Prizes toward the end of the century also involving small-scale science [Nobel Foundation Directory, 2001; Bak, 1996: 35–36]. But it was not just Nobel laureates in physics who were able to do excellent work on a low budget. For example, at the relatively small Rockefeller University two of

the world's most creative physicists, Mitchell Feigenbaum and Albert Libchaber, worked virtually alone in fields related to chaos theory and small-scale fluid experiments [Gleick, 1987].

We live in an era in which both large-scale and small-scale biological science is desirable. But the great danger to the future of excellence in basic biomedical science comes from the paucity of an endangered type of research organization—the small independent scientific institute and the highly autonomous small institute within a much larger organization. Here we have in mind such outstanding organizations as the Neuroscience Institute in La Jolla, California, under the direction of Gerald Edelman, and the Basel Institute of Immunology. Our society must strive to recreate the small-scale science institute modeled after the structure of the Rockefeller Institute for Medical Research in the first half of the twentieth century, the Salk Institute in its first twenty years, the Cavendish Laboratory at the University of Cambridge in the first half of the twentieth century, the Laboratory of Molecular Biology outside Cambridge during its first thirty years, and the physics institute at the University of Göttingen in the first third of the twentieth century. Moreover, a number of contemporary Max Planck Institutes are relatively small and are doing excellent research. Unfortunately, across the globe small research organizations are threatened with extinction.

But even if these kinds of environments were conducive to extraordinarily high performance in the past, why should we not conclude that in the future important advances in the biological sciences are most likely to occur in our largest research organizations—especially in large American research universities?

Theories about performance in complex organizations are valid across space and time. There is a great deal of theory and empirical evidence demonstrating that research organizations which focus on a particular core competency and which focus broadly on a single domain (*e.g.*, basic biomedical science) are likely to perform much better than an organization internally differentiated into dozens of scientific disciplines. In the United States, many corporate organizations which formerly were engaged in numerous industrial sectors have in recent years reduced their diversity and have concentrated on their core competencies resulting in much improved performance. Research on complex organizations has demonstrated that the same principles apply to research teaching organizations. With high diversity and great complexity, it becomes difficult for research organizations to be at the frontiers of excellence in scientific research, teaching, and service to society. Although all of these are laudable activities, it is very difficult to achieve excellence in all three simultaneously. Small research organizations with high flexibility and autonomy, and the type of leadership discussed in the first essay of this volume have much greater potential for making major discoveries than large organizations at the opposite end of the continuum on each of the variables discussed therein.

Large-scale projects are here to stay in virtually all major fields of science. We will continue to need large research enterprises developing huge data sets. However, our societies will also have a continuing need for small institutes of the type which can provide scientists opportunity and time for deep thinking (interviews with Nurse, Wiesel, Blobel, Edelman, Perutz). Large-scale scientific research projects can be indispensible for providing vast quantities of data for creating descriptions of nature. But once in possession of large data sets and rich descriptions, science needs to advance to hypothesis development and formulating new understandings. This kind of activity is more likely to occur in small institutes where scientists in diverse fields may have frequent and intense interaction with one another.

At one time, it was necessary in many research areas for scientists to have access to large computing facilities in order to address many problems, and these facilities tended to exist primarily in large organizations. But with the great advances which have taken place in computing facilities, powerful computing capability now resides in the offices of most scientists. It was not so long ago that many scientists had to travel considerable distances to gain access to a supercomputer. Today, thousands of researchers throughout the world have easy access to the functional equivalent of a supercomputer. In the United States, supercomputing facilities throughout the country stimulated the development of a national network called the NSFnet, linking researchers to remote supercomputers as well as to thousands of other scientists. Today, desktop computers can serve as windows into an international system of computers. For most practical purposes, a scientist may bring the supercomputer into the office and use it "as if it were sitting inside his or her desktop machine" [Kaufmann and Smarr, 1993: 20]. Moreover, the three-dimensional interactive graphics available on a graphics workstation can create a scientific visualization far beyond the capacity of the most advanced supercomputer center of only a few years ago—enabling scientists to determine the structure of molecules, atoms, and atomic nuclei. All of these advances are making it possible at relatively low cost for computational biologists to work at the frontiers of their field from their offices. Also within a small institute, scientists can now combine these technologies with amazing microscopes, making it possible to identify the shapes of molecules and to examine how things work in living cells. Scientists can color proteins so that with a microscope they can see red, yellow, or green proteins moving around a cell. Moreover, they can now witness a time and space dimension within a cell.

With all of this new technology, it is not necessary to have a huge research laboratory in order to conduct research at the frontiers of science. Indeed, in a small research environment, it is possible to have rich interactions with other scientists without continuous interruptions which tend to occur in large research

universities where a scientist must constantly and desperately search for a few minutes to engage in deep thinking. Moreover, in many small research institutes scientists are subjected to fewer pressures to write numerous grant proposals in order to fund a sizable stable of postdocs, and fewer postdocs are exiting or being recruited all the time.

As suggested above, experiences of a number of small research institutes suggest that small institutes may make an enormous difference in the world of science. An additional twelve to eighteen small and truly distinguished institutes the size of the Laboratory of Molecular Biology would have an enormous impact on the world of science. Instead, philanthropists are pouring hundreds of millions of dollars into huge research centers (*e.g.*, Harvard, Stanford, UCLA, Yale, etc.). While the majority of this money is indeed put to constructive purposes, an extra hundred million dollars for a large institution such as Harvard, Yale, or Stanford is hardly going to mean more than a minor dent in the history of these institutions or to the larger world of science. Of course, wealthy donors may desire to have buildings or endowed professorships named after them, and thus derive a great deal of status and gratification from such an exchange. We need both large and small institutes, and small institutes with a high degree of autonomy certainly may still exist within large organizations. The Howard Hughes Medical Institutes at many large American universities are examples of such. The existence of both large and small research organizations unquestionably enhances the richness of the scientific enterprise.