During the twentieth century, a fruitful union developed between medical science and the global pharmaceutical industry. This union survived two devastating world wars, numerous political revolutions, and a bitter, extended cold war between the forces of communism and the capitalist democracies. It survived as well major shifts in the nature and the primary locations for cutting-edge scientific research and for pharmaceutical R&D. It survived the uneven development of government programs for the purchase of pharmaceuticals and the delivery of healthcare. This amazingly successful union of science and industry survived even though for most of the century, the activity in science was intrinsically global and transparent in nature, while the innovative activities in the pharmaceutical industry were intrinsically national and proprietary in nature.

We remind you of the durability and flexibility of the union between medical science and pharmaceuticals so that you will, we hope, appreciate
the optimism with which we approach the twenty-first century that stands before us. We were both trained as historians. We were not trained to develop predictive social science models or grand prophecies. But we do believe that the past can provide us with rough guidelines to the future. Especially when history offers examples of enduring institutions and the kind of flexible, innovative behavior that has enabled complex relationships like those between pharmaceuticals and medical science to survive a century of dramatic changes.

A QUICK GLANCE AT THE PAST CENTURY

Reflect for a moment on how dramatic those changes were. The first great wave of change, which began in the late nineteenth century and extended through the Second World War, involved what philosopher Alfred North Whitehead famously described as “the invention of a new method of invention.” Beginning in the coal-tar dye industry in Britain and Germany in the 1860s and 1870s, and in Thomas Edison’s Menlo Park laboratory in the United States, manufacturers and entrepreneurs began to appreciate the value of trained scientists and engineers in developing a systematic new approach to science-based product development. The new institution of the industrial research laboratory soon spread beyond coal-tar dyes and electric
lights to companies in telecommunications, petroleum, chemistry, photography, and pharmaceuticals, owing in large part to the convergence of several trends at the turn of the century – the development of new knowledge in physics and chemistry, the emergence of research universities and cadres of trained PhDs eager for jobs in which they could apply their expertise, and the rise of large corporate enterprises with the scale, scope, and resources to be able to take the risk of supporting the new laboratories. Within a generation, the inventor-entrepreneur of the late-nineteenth century, epitomized by men like Edison, Joseph Swan, and Leo Baekeland, gave way to the “industrialization of invention,” with corporate laboratories administered by leaders like Kenneth Mees at Kodak, Willis Whitney at General Electric, and Frank Jewett at AT&T.

In the pharmaceutical industry, this institutional evolution involved the interaction between germ and later viral theory in academic science and organic chemistry and later vaccinology on the part of industry. In the course of the long era of innovation that followed, the primary locus of scientific innovation ultimately shifted from Continental Europe and England to the United States. Similarly, the primary centers for pharmaceutical innovation gradually moved westward, from Germany, France, and England to the Western Hemisphere. Following World War II,
there was some drift westward in pharmaceutical production and distribution, but nationalistic political economies and theories of import substitution ensured that production/distribution would remain more globally dispersed than research and development (R&D).

The rise of the United States as the world’s leading innovator in both medical science and pharmaceutical R&D was accelerated by European developments leading up to, during, and immediately following the Second World War. The top-flight medical scientists who sought refuge in the United States played significant roles in America’s rise to prominence in new drug development. This shift –mirrored in other areas of academic science and industrial innovation -- was sustained by American developments, both public and private. The United States invested billions of public dollars in support of medical research; we refer not merely to the federal money but also to the state and foundation support for research universities and training programs for young scientists. A large, extremely diverse, enormously expensive system of public and private higher education, with porous boundaries and intense internal competition for money and scholars, provided the base for this new U.S. system. One of the unique characteristics of the U.S. science establishment was the large role
played by a private nonprofit sector that included some of the nation’s leading research universities.

Patent protection for intellectual property and a market without price controls or, with some exceptions, government monopsony in the post-World War II era encouraged American pharmaceutical manufacturers to steadily increase their investments in R&D. This largely private system of new drug development was deeply embedded in the public/nonprofit basic research networks mentioned above--there was and still is a high degree of functional specialization in this system. Private firms did almost all of the work of new drug development. They also developed innovative systems for production and distribution. Tomorrow’s dollars for pharmaceutical R&D could not be acquired if firms—howsoever innovative their laboratories were—could not sell their products effectively in national and international markets.

Vaccine innovation followed a slightly different course, with the public and nonprofit sectors playing a larger role in the development of new pediatric vaccines and in their distribution. Here too, however, the private sector handled most of the production and, after the 1950s, more and more of the discovery process.
By the 1960s, this complex and varied system for new drug and vaccine development was firmly established and supported throughout the industrialized nations. The leading pharmaceutical innovators were all situated in technologically and scientifically advanced nations, and within most therapeutic categories, a small number of large firms led the way in new drug development.

The first major challenge to this global system for innovation came not from the marketplace but from laboratories in both Europe and the United States. Biochemistry and enzymology in the 1950s and 1960s produced a new understanding at the molecular level of disease and the means of preventing, curing, or at least controlling disease. This breakthrough had an impact upon both science and industry comparable to the new understanding arising from the germ theory of disease. There was potential here for another major shift in pharmaceutical innovation, and indeed, one of the first major breakthroughs on the commercial front came from the work of Dr., later Sir, James Whyte Black in England, who discovered the role of beta-blockers in fighting heart disease. German science as well seemed poised to provide that nation’s pharmaceutical firms with competitive advantages in using biochemistry and enzymology in drug development.
For industry, the challenge was to use the new science without losing capabilities in organic chemistry. The old and the new had to be blended together effectively, a managerial process that sounds easy but in practice was extremely difficult to do successfully. Without mentioning names, we assure you that not all research directors were equally successful and not all firms made the transition smoothly. This was true in the United States as well as Europe. The process on the industry side involved adding an entirely new layer of expensive scientists who were not always as tolerant of the old style of research as they should have been. At this crucial point in the industry’s evolution, British and German firms slipped further behind their U.S. competitors in the process of innovation. In the British case, the major problems appear to have developed at the interface between the firm and the science establishment. As a result, British firms did not initially make full use of Black’s breakthrough. In the German case, the science establishment was probably still too underdeveloped as a result of World War II. Whatever the causes, the U.S. industry’s prominent position as the world’s leading pharmaceutical innovator was strengthened.

Alas, there was no opportunity for any pharmaceutical innovator to rest on the accomplishments logged in cardiovasculars, antibiotics, and neurological therapies. A third wave of change overlapped with the
biochemistry/enzymology revolution and forced pharmaceutical innovators in the United States, as well as Europe and Asia, to add another layer of scientists to their laboratories. By this time, Japan had emerged as an aggressive competitor in a number of important therapeutic categories. In Japan, the United States, and Europe, molecular genetics and rDNA technology forced every firm in the industry to add to its research staff, while developing alliances with small biotechs in various specialized areas of research. The impact of these new development was felt in both small molecule and large molecule research. We have analyzed these changes in another published paper and will not dwell on them here. But they were obviously one of the driving forces behind the combination movement that rippled through pharmaceuticals in the 1990s and continues to transform the industry today. A larger corporate base and larger revenues were needed to sustain a larger R&D operation, and to balance it, larger marketing and sales teams.

Two aspects of the consolidation movement interest us: first, we find telling the speed with which the pharmaceutical sector transformed itself; and second, we find equally telling the manner in which all of the large research-driven firms in the industry had established and acquired capabilities in molecular genetics and rDNA technology by the end of the
1990s. This latter development was especially important because by that
time combinatorial chemistry and bioinformatics were again changing the
R&D landscape, offering new economies of scale and scope in research.

As should be evident, we are cataloguing a century-long period in
which the pace of change in the medical sciences has accelerated (very
rapidly of late) and in which the leaders in the pharmaceutical industry have
remained flexible enough to accommodate to those changes in their
scientific networks. Not all firms have prospered. Not all have been able to
maintain their organizations without being absorbed by more innovative and
wealthy companies. But the history of this industry displays no period of
Schumpeterian “creative destruction” comparable to that experienced by the
British dye industry in the nineteenth century or the U.S. tire industry in the
post-World War II period. This is the historical foundation on which we
build our optimistic scenario for the next century.

A GLANCE INTO THE FUTURE

Globalism! Or, as one astute commentator put it, “Globality,”

presents itself as the most likely central theme for any prophetic
pronouncements. But we think not. While we acknowledge that certain
aspects of a new global economy have emerged in recent years (and we will
discuss some of these changes), we believe the dominant factors that promise to change the science-industry nexus in this case will be regional. We see one major regional entity already well defined in the European Union. We see another beginning to take shape as a Western Hemisphere free trade and common currency area begins to coalesce and expand. We see a third beginning to form in Asia, although in this case the outlines are vague and the future very much in doubt. One can not even tell which of the Asian major powers will provide leadership in that regional bloc. But in our view Asia will be encouraged to move further toward regional consolidation as the two other major blocs become more firmly established.

How will these regional blocs change the links between science and industry in the biomedical case? In our best-case scenario, they will provide enlarged fiscal foundations to support the vibrant, productive science establishments needed to exploit more fully the research frontiers that have opened up the past two decades. If the acceleration of medical-science innovation continues—and we assume it will—only very large players will be able to fund the basic research opportunities that exist and will arise in future years. Nation states—even the most wealthy nation states—will no longer be able to provide the necessary financial resources. We have already seen some evidence of this in cooperative space research and cooperative
research in particle physics. We have seen public and private cooperation in successfully mapping the human genome. In brief, medical science is outgrowing the resources of the nation state and only regional institutions will be able be players in the decades ahead.

Regionalization will be important because it will provide the opportunity for existing science institutions organized along national lines to specialize and not to attempt in each case to cover the entire range of scientific opportunities. Specialization of function is one of the keys to scientific and economic progress in the past three centuries. The First, Second, and Third Industrial Revolutions were all accompanied by higher and higher levels of specialization and professional differentiation. Our current Information Age Revolution is certainly no exception, and it provides particularly intriguing opportunities for specialization and the cooperation, the interdependency, that is the other side of the specialization coin. Adam Smith long ago pointed out that the breadth of the market determines the degree of specialization. And we would add that the breadth of the market for knowledge in the Information Age determines as well the degree of coordination and cooperation required to make any society function successfully.
Regional platforms in science policy will be able to finance the next great surge of basic innovations in the medical sciences and make optimal use of particular national and local cultures and talents. Take biotech as a good example. In the current setting, many nations are attempting to duplicate the U.S. success in employing molecular genetics and rDNA technology in drug discovery. These efforts on the public side—and they normally have an important public component—seem to assume that there is one good path to success. But what is evolving (in some cases with which we are familiar) is a series of national patterns of specialization. In Germany, as Hannah Kettler and Steve Casper have pointed out, the biotech industry is specializing in platform technologies, while the U.K. industry is following the more generalized U.S. model and emphasizing the search for new drugs. While in this instance, specialization may be a product more of political (the particular nature of government subsidies) than economic factors, we believe this type of development is the wave of the future within large regional economic blocs.

The regionalization that we foresee will further enhance the protections provided to intellectual property, a crucial factor promoting innovation in pharmaceuticals. This is likely to happen first within the blocs and then between them and nations in the less developed parts of the world.
Within the blocs, there will be steady pressure to standardize protection across the various nation states. The pressure (as with social policy in the EU today) will be exerted upward, with the goal of bringing all of the nations up to the standard of those providing the most protection to the intellectual properties of their most innovative firms. The blocs will have substantial bargaining power to exert on nations that fail to protect such rights. Access to the markets of the blocs will be too valuable to lose in order to pirate pharmaceuticals or other similar products.

Is regionalization likely also to promote increasing reliance on markets, rather than government programs for the delivery of healthcare, including pharmaceuticals? There are several reasons to believe this may be the case. The public/private balance in the United States has clearly promoted innovation, and there is substantial interest in Europe, for instance, in achieving similar progress in new drug development. In general, regionalization in Europe has already accelerated the decline of state-owned enterprises and put increasing pressure on national governments to live within their means in funding public programs. Privatization has become a major movement throughout the world, with activities as varied as telecommunications, water supply, and transportation shifting from the public to private sectors in Europe and the United States. All of these
developments suggest that a similar shift could take place in the provision of healthcare.

A crucial determinant of the pace of change in healthcare will probably be the degree of success achieved in the other areas subjected to privatization, as well as in the America healthcare situation. If in Europe the privatized telephones don’t work or cost too much for many of the people to afford, if the trains don’t run on time or run safely, if too many people have their water supply cut off, then market failure will quickly bring about a movement to re-regulate these activities or shift them back into the public sector. Similarly, if the United States is unable to increase the number of its citizens covered by health insurance and unable to provide the assistance that many persons on maintenance medicines need to purchase their essential drugs, the drift from the public to the private sector elsewhere is likely to slow or stop.

There are encouraging developments in the United States in recent years. These include the increasing use of health maintenance organizations and the development of technologically advanced systems for providing affordable pharmaceuticals to a large percentage of the population. This latter reference is to the pharmaceutical benefit managers (PBM). One of these, Merck-Medco, has organized an automated pharmacy capable of
dispensing more than 5,000 prescriptions per hour and 550,000
prescriptions per week with a 99.9996 percent error free rate. Orders are
received via the internet as well as the telephone. Such a system offers
efficiencies and conveniences that are attractive to payors and patients alike.

In our best-case scenario, regionalization will promote many other
efficiency-enhancing innovations in new drug development and in
production and distribution as well. Regionalization will ensure more
funding for basic research. It also seems likely to promote continued
consolidation in the industry. There is every reason to believe that small
biotechs will continue to develop new products and platform technologies.
We do not expect to see them all absorbed by large pharmaceutical
companies, if only because the large firms can more economically and
flexibly employ licensing and alliance strategies to achieve the same
objectives as merger and acquisition. Innovation in new drug development
can thus remain dispersed, even though innovation in production and
distribution become more highly concentrated in the global industry.

**SOME TENTATIVE CONCLUSIONS**

Is our best-case scenario likely to develop? The forces working
against this outcome will certainly be powerful. There will be considerable
political capital during this century (as there was in the last) in mounting
attacks on greedy corporations—especially those producing life-saving or
life-enhancing pharmaceuticals. There are obvious incentives for nations to
continue to violate intellectual property rights. There is every reason for a
person receiving subsidized healthcare in any part of the world to oppose
privatization. They have in the past; they will in the future.

But regionalization will, we think, counter and ultimately overcome
these pressures to preserve the status quo. The promise of new therapies
will be great. The opportunities for economic growth through innovation in
new drug development, production, and distribution will be appealing.
Larger regional markets will increase the economies of scale and scope,
while promoting further specialization of function. If the industry responds
to this challenge as it has in the past, large pharmaceutical firms will add to
their R&D capabilities; develop new forms of corporate organization, and
experiment with novel styles of company governance suited to a world with
global markets, international scientific networks, and regional systems of
political economy. The potential to achieve this outcome is before us. We
will in the years ahead see whether the requisite determination, flexibility,
and political statesmanship are forthcoming in Europe, the Americas, and
Asia.