STRATEGIC HEALTH POLICY INTERNATIONAL

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Access to Medicines: Covenant in Innovation[1]

Innovation in health care appears to be paradoxical: it provides simultaneously hope and fear. Hope to manage to tame at least temporarily disease and death; fear that innovation will raise the cost of health care up to a point where rationing becomes inevitable.

—Claude Le Pen, Director, Health Economics Laboratory, University of Paris-Dauphine[2]

Innovation has progressed beyond providing hope and fear: it now produces anger as well. It was bound to happen. As the investments in modern pharmaceutical discoveries and developments produced solutions for more conditions and as more people needed them, once-small and nearly invisible drug budgets grew at a noticeable rate and to a notable size.

Lilliputian expenditures did not assume Gulliver's girth, but they received the attention of the giant come to town. Perhaps it was because the little pills came from companies that, by comparison, looked like giants alongside patients and other healers. In fact, some of the companies were giants and were bigger than some small nations. Perhaps, as in Gulliver's travels, the townspeople and the giant did not speak the same language or navigate the same waters, the giant having come from a land of research risk, competition, and capital market demands. Speaking those words left the townspeople feeling adrift on lonely, unknown seas, fearing shipwrecks of disease and disability. Perhaps, like Gulliver, it was because the drug giant had traveled the world and had developed the wits to make his way in any country, while the Lilliputians were unaware of lands outside their own. Perhaps the people did not trust the giant's weapons—called prices and patents—fearing they'd be caught in the sights of an uncaring corporation, lacking in compassion for those who needed, but could not buy, the pills. Perhaps it was because…well, whatever the reason, the current relationship between the pharmaceutical industry and those it seeks to serve is no fairy tale.

Recounting the history of the industry and its relationships with governments and patients is unlikely to be of much value and is not my purpose here. Unraveling the mysteries of proprietary information and marketing strategy might be of some investigative interest, but it won't solve today's conflicts. Nor will progress be made by engaging in more finger pointing, blame assigning, or witch hunting, either here or abroad. If the children's tale is instructive,

however, then there might well be a brighter future ahead in the relationship between the pharmaceutical industry and those it serves, after all. Gulliver, you will recall, learns the language of Lilliput. He comes to be of great benefit to the people, prevents an invasion, and saves the palace.

We should all hope that the giants of industry follow in the footsteps of Gulliver and provide us with the benefits we need today in health care. Never before in the history of mankind have so many people, suffering from so many diseases and disabilities, needed so many innovative solutions. As we hope for a future in which we have those innovative solutions on our pharmacy shelves and household medicine cabinets, we need to face the facts: finding and providing these solutions will certainly cost more than today's drug bills. But the price we will pay in early deaths, substantial disabilities, and lost productivity if we choose to stop the search for new treatments and cures will certainly be higher.

Will we find those cures? Without a doubt. Never in history have we been more poised to reap the benefits of decades of research investments nor to grasp the discoveries of the scientific revolution at the frontiers of genomics and biotechnology. Decades of public and private investment in research are paying off. How we should reap the benefits of that research and how much more we can absorb into our health care systems will be among the most pressing questions of this decade. Will we endorse—not only with our voices, but also with our funds—the economics of discovery? Will we continue to support a public-private partnership in innovation? Will we continue to support a for-profit sector within health? Or will we erode the capacity of this nation to be innovative in the same ways that we have eroded our public health systems and crippled physician, nursing, and hospital care—that is, by starving operating programs and ignoring investments that will bring improvements? How will we keep the pipelines flowing with new discoveries, healers, and drugs and assure that those who need the cures get them? Will we, as Americans, come to see the needs of the developing world and recognize the imperative to support the search for solutions there, as well as here? Will other developed nations follow our lead in doing so?

Elsewhere in this book, I have addressed a number of global issues that drive back to the nature of the public policy climate in the U.S. today. I have argued that we practice "health isolationism" and urged against it. We act all too often as if health care in the U.S., including its economics, can be addressed solely within our borders. I have shown how in several ways—the need for subjects for clinical trials, the presence of infectious diseases, the likelihood of pandemics, and the nature of bioterrorism—the U.S. is inextricably linked to other nations. Our fate hangs very much in delicate balance with theirs. In no sector is this truer than in biomedical solutions to today's global challenges. At precisely the time we need the medical innovation industry most, it is under renewed fire.

Shooting the Healer

This is not the first time in history that public ire has been leveled at healers. Healers have always been held accountable within their communities. Dating back to the earliest records, it is clear that they were punished for their misdeeds, not just rewarded for their skills.[3] Misstep,

and the healer was held accountable. This is true in contemporary society as well. In the past several decades, healers in the U.S. have suffered one policy-directed retribution after another. Hospitals and physicians faced this in the 1980s and managed care suffered through hostilities as the millennium clock ticked through midnight. In our dissatisfaction with health care and our attempts to reform it, we selected one healer after another and laid the blame for our discontent at their feet. Spending too much on hospital care? Then certainly the cause must be super-charged fee structures, and the cure would be prospective payment systems that place hospitals at-risk financially in the care-giving process. Implementing those changes brought the industry to its knees and into the red, closing facilities and threatening community care in many locations. Spending too much on physician-driven care? Then certainly the cause was the indiscriminate overuse of resources by clinicians, and the cure would be tighter reign on spending by managed care and its controls. Too difficult to get treatments in managed care? Then certainly managed care was greedy and the cure would be litigation and patients' rights laws. Expenditures still growing? If all else failed, then surely every provider was committing fraud and could be threatened with fines and even jail time and led to see the wisdom of plea-bargaining for lower penalties.

It appears that the next of our healers in line to be demonized is the pharmaceutical industry. Compared to all the others, it is an easier target. It is a visible and, seemingly, the most reprehensible of the players in health care today. Some critics direct their ire at the profitability of the companies others at the promotional tactics of marketing to physicians; many at the interference of healer-patient relationships in direct-to-consumer advertising; and several at the salaries of executives as a basis of contempt. Global public health activists cite the dearth of research and product development for diseases of the developing world, saying that the commercial returns to industry are out of balance with the gains that should be made against the needs of the poor around the world.

Aiming at the Wrong Target

Sadly, however, industry adversaries have not set their sights on drug companies alone. Unwittingly, they have targeted the broader, public-private alliance that produces innovations overall and brings them to us with stunning regularity and predictability. This innovation sector of health care is composed of three interrelated components—first, our biomedical research enterprise; second, our medical education institutions; and third, our pharmaceutical industry. Each depends on the other—and on public and private sector funds and favorable policy—to do an elegant dance of information, financing, and human effort. This interdependent relationship optimizes the contribution they make, through innovation, to our personal and collective health and economy. This is an arena in which the interplay of these players results in a whole that is much greater than the sum of its parts. Cripple any part of this triad and the whole of the innovative machine will grind to a halt—not immediately, for certain, but surely over time. Yet pressures here and abroad threaten to do just that. The consequences will be felt here, and around the world. Consequences that we—and the rest of the world—should not take lightly.

The development of new knowledge is wasted effort unless it is used to develop products that will treat disease, and it is without value unless it is integrated into medical school teaching

programs and results in clinicians that are better-prepared to address the diseases of their patients. The training of new clinicians is incomplete unless they also participate in the development of new knowledge and learn the inquiry skills of research. Pharmaceutical solutions are fueled by these basic research discoveries, and the costliest part of the whole venture—clinical trials—is conducted mainly in medical schools. Medications are hollow promises without an educational system that prepares clinicians for the appropriate selection and use of the therapies. Ample evidence indicates that when these players within our innovative sector cooperate, the results are increased productivity.[4] Collaboration is not the fantasy of rhetoric; it is the reality and backbone of innovation in the U.S. today.

The Paradox of Value

The innovation segment of the American health care industry is on the firing line because of a somewhat unique position, I believe. Not just because of its weaknesses, but because of its strengths. Not just because of its liabilities, but because of its assets. Not because it is potentially a drain on national coffers, but because it is potentially such a boon to those coffers, as well. It has proven itself to be of such value that its discoveries dare not be denied to those in need. It has attracted so many stakeholders, with such keen interests, that the challenge of satisfying all of them may well be impossible unless we rise above our current crises and examine them from new perspectives. As in other areas of health care, the old covenant of grant has outlived its usefulness and is now in danger of destroying a principal engine of health and economic prosperity.

It is a paradox that something so valuable has become so vulnerable in today's health care and economic climate. I'll predict, and frankly without taking much risk in doing so, that the value of medicines will continue to increase and the vulnerability of medical innovation will as well. In fact, the controversies surrounding medical innovation are likely to get much worse before they get better. If these controversies stem the flow of resources into research, the result will be fewer discoveries. If these controversies stem the flow of resources into purchasing these products, the result will be fewer people treated efficiently, and more human suffering and economic loss.

The tragedy is unthinkable for patients in this country, and even more so for those around the world. Alzheimer's disease and congestive heart failure are the scourges of our own society, but the developing world suffers even more from diseases and from the economic consequences they cause. The ink is barely dry on a World Health Organization (WHO) report on the relationship between health and disease, but it should be required reading for everyone involved in crafting health or economic policy today. It demonstrates how defeating AIDS, malaria, and tuberculosis must be a key strategy in building the economies of developing world countries.[5] WHO proposes that investing an additional $27 billion—or .1% of GDP of the U.S., Europe, and Japan—in health programs would save eight million lives and create economic gains of $186 billion. Our innovators have succeeded in developing some pharmaceutical products and public health strategies to combat these three diseases, but none is optimal and more research is needed to reach a more ideal therapy. What is true for these devastating diseases overseas is also true for conditions here. Will we continue to support ventures to find real, simple, tolerable medicines

that will be total cures? Current medicines are the best that early innovation can offer, but they still involve side effects, complicated regimens, and costly public health interventions. Will we ever develop something better for the millions who need help?

If we do succeed, it will be because the healers in biomedical research, medical education, and pharmaceuticals who discover, develop, and integrate innovations in health care have the support of the patients they treat and the communities—in this case the nations—within which they work. This calls for robust funding of biomedical research, adequate use of medicines, supportive pricing policies, and protection of the intellectual property associated with the discovery.

Shining Some Light in the Black Box

Few people today understand the medical innovation sector in the U.S., which is the largest and most productive of all the world's nations. Even those who are a part of it have not grappled well with the interconnectedness of the enterprise. Its ownership is public and private. Its purpose is for-profit and not-for-profit. Its financing comes from private investment capital, philanthropy, and government dollars. Its existence is enabled by the "tangibles" of funds and the "ethereals" of policies. Its organizations are highly decentralized and very complex. In those ways, it is like many of the innovation sectors in other parts of the world. In one way, however, it is fundamentally different. Its method of innovation allows the talent, peer review, and creativity of scientists to pursue new knowledge and develop products, and the marketplace judgment of products to determine their value and willingness to use them. In other countries, research targets are pre-specified and governments set prices that keep product prices down and business investors away. Which is better? The prevailing opinion—and the scorecard of research results—says that, hands down, our model results in more prolific progress. Of the major drugs treating people today and responsible for stunning improvements in health, most were discovered and developed here in the U.S.

This system of discovery and development has been evolving for several hundred years and is reaching its maturity precisely during this time when it is coming under attack. To understand how and to see what is at risk, it is necessary to pull back the curtain and examine the nature of the research enterprise. This will be a simple review, to be sure, but one that is intended to demonstrate what is at stake in the public policies we must forge in this new century.

Federal research capacity is housed in many centers within the health, agriculture, and national defense agencies of the government. The National Institutes of Health (NIH) is the largest of these agencies, with 15,600 employees and an annual budget that has grown from $300 at its founding in 1887 to over $20 billion today. The Centers for Disease Control (CDC) is best known for its contribution to public health, but a number of its 8,500 employees and part of its $4.3 billion budget are devoted to research as well. The Veteran's Administration, the National Science Foundation, the U.S. Food and Nutrition Service, the Agency for Health Research and Quality, and Department of Defense operations at sites such as Walter Reed Army Hospital are also players.[6] Even regulatory and payment agencies, such as the Food and Drug Administration, the Center for Medicare and Medicaid Services, the Environmental Protection Agency, and the

Nuclear Regulatory Commission support biomedical innovation. The work of these agencies is supported by the appropriation of federal funds for research, but direct Congressional funding is not the only way. Regulatory and tax policies also encourage research within the private sector, making the government and taxpayer indirect supporters of that research.

Each government research agency works in partnership with academic medicine. The structure of these biomedical research experts was articulated by Abraham Flexner,[7] whose now-famous report detailed the faculty and facilities necessary to develop a profession of highly skilled clinicians. His proposals have been refined and expanded and today, medical research—along with teaching and clinical care—form the tripartite mission of medical education at the 125 medical schools, 400 major teaching hospitals and health systems, and nearly 8,000 residency training programs in the nation. More than 100,000 faculty, 66,000 medical students, and 98,000 medical residents participate in the training of our next generations of clinical healers. They receive research funding in the range of $12 billion each year—68% from government, 14% from the pharmaceutical industry, and 9% from philanthropic groups. While this is no longer true today, historically, with the tacit approval of those who paid for the health care delivered in medical schools, some patient-care dollars were also used to pay for research. Occasionally extra tests were done to collect data to enrich our understanding of illness, and higher costs for medical center hospitalization provided a funding stream to research university medical centers.

Government agencies and educational institutions, in turn, work cooperatively with the private research-intensive industry. About 50 pharmaceutical companies in this country contribute another $24 billion in research funding in the U.S. and nearly 250,000 jobs. The 1,300 biotechnology companies spend $14 billion and employ 174,000 people. Nearly 90 private research institutions, such as the Coriell Institute for Medical Research, also conduct research, and add another $3 billion.

If the U.S. is a hotbed of innovation, then regions within this nation are the places where the coals burn brightest. The concentration of funding and talent creates synergies in discovery. Companies tend to locate near academic institutions, and near each other. As a result, for example, Philadelphia, home of the nation's first hospital, is now home to more than 350 life sciences companies, employing more than 50,000 workers. It ranks second nationally in pharmaceutical employment, third in biotechnology employment, and fourth in medical device employment. Its universities attract $775 million annually in research, and private investment capital has followed—over $1.1 billion in venture funds since 1995. Support came not only from private and federal government sources, but from the state of Pennsylvania as well. The state invests $65 million per year in its universities, provides $100 million to create Life-Science Greenhouses, and has passed favorable tax and business policy legislation to reduce the costs of doing business and create favorable business climates.[8] Philadelphia is only the entry, however, to a corridor of medical innovation that begins there and stretches to Boston.

Aside from today's benefits of being co-located on the eastern seaboard with other innovators, there are historical reasons why the industry is so concentrated there. The innovation sector began a slow, but steady growth over the past century as the foundational building blocks that support discovery were laid. Philanthropy supported academic researchers until the mid-

1900s, when federal funding began and the great medical research universities developed. Gradually, the small, family-owned—principally European—drug development and manufacturing companies, seeking better opportunities, moved to where the best scientific resources could be found. They came to the U.S., disembarking and settling in New York and Philadelphia, where they could recruit scientists trained in those university programs and work in a climate that rewarded discovery with patents and provided a large market in need of products. World wars required that some of those companies separate from their European parents, particularly if they were German, and demonstrate their loyalty to America as best they could or suffer confiscation of their assets. Loyal they became. They embarked on joint research programs with government to develop and produce penicillin for the fighting forces, and they offered deep discounts to veterans' health care programs after the war as further proof of citizenship and American spirit. For years after the war, they continued their research and development on diseases that were most common—or predicted to be most common—in this country.

Alongside other healers and taken in total, these innovation-sector research investments might appear to be large, but in reality they are quite small alongside other expenditures we make to manage our health and healing enterprise. Compare the total national public and private sector investment in biomedical innovation—$45 billion—to what we, as Americans, spend annually on health care: $1.3 trillion. Or, from another perspective, medical research accounts for less than a nickel of every health care dollar and less than a penny of every federal dollar. That's less than 56 cents per American per day spent on medical research overall in the U.S., with well under half of that amount—19 cents—coming from federal sources.[9] Better yet, compare our research investments to non-health care, and some would say less essential, expenses. We spend more than twice the research investment—$100 billion—on fast food, $24 billion on accessories for our cars and trucks, $20 billion playing golf, and $1 billion on Valentine's Day chocolate**.** The $45 billion for research pales by comparison to the costs of the disease challenges it seeks to address. The annual cost of uncured heart disease is $128 billion; of uncured cancer, $104 billion; of uncured Alzheimer's, $100 billion; of uncured diabetes, $92 billion; of uncured arthritis, $65; of uncured depression, $44 billion. Victor Fuchs has said that each nation chooses its own death rate by its choice of health as compared to other goals.[10] I would agree with him, and add that those choices involve not only what we decide to spend on health care services, but on biomedical research.

Even the cost of uncured disease here in the U.S., however, pales by comparison to the worldwide impact of disease and disability on health and the economy. In the last forty years, life span in the developed world rose by 22 years, largely because of medicines. The developing world has seen improvements as well. In 1950, 15% of children died before their fifth birthday; today only 4% do. Nonetheless, the poorest nations face continuing devastation from several diseases—HIV/AIDS, malaria, tuberculosis, childhood diseases, tobacco-related illnesses, and malnutrition—which alone are responsible for 8 million preventable deaths each year. By 2020, that picture will change. Death rates from these communicable diseases, which are either unknown or largely controlled in our country, will give way to conditions more like ours. Tobacco use will exceed every other disease, including HIV/AIDS. Heart disease, depression, cerebrovascular disease, and lung conditions, such as chronic obstructive pulmonary disease and

tuberculosis, will be the key health global concerns. Depression will cause the greatest burden, worldwide, on quality of life and disability, clearly affecting the productivity of the workforce in every nation.[11]

It is undeniable that health has value for its own sake, and we should care for others for that reason alone. But there are also compelling economic reasons to stem the tide of disease from these conditions. Health provides a workforce with the ability to be productive, and that productivity, in turn, creates better health. The impact would show up not only in annual returns, but would be cumulative as well, of course. For instance, a 20% reduction in deaths from cancer would be worth $10 trillion—double the national debt.[12] Among the working population, for every rise along the rung of the socioeconomic ladder, an individual experiences a corresponding improvement in health and reduction in mortality.[13] Economic development and the reduction of poverty throughout the world are dependent on a healthy population, capable of participating in the growth of an increasingly interdependent world economy.[14] Failure to improve the pace of economic development places us all at risk. Poverty is a growing cause of unrest, leading to threats of increasing violence throughout the world. It affects children disproportionately. As a result, they are malnourished and leave school to work. How can this not have life-long, multigenerational and global consequences?

Is this the concern of the American medical innovation sector? Yes. Why? This nation is a stakeholder—and a key player—in the future of the globe. That is why. As a result, its innovators—who are truly global themselves—are key players and may now be the most beneficial of the assets that the U.S. can offer its global neighbors. The work of the innovation segment of our health care system transcends any national boundary because disease transcends every national border. In my view, the innovation segment of the health care industry is the only true worldwide healer. No other component of health care crosses so many time zones, addresses so many global diseases and national needs, and adjusts to so many regulatory schemes and governmental systems. Interest groups agree, and as a result, a number of them from around the world currently demand the resources of our innovators to solve problems that lie outside our borders, laws, tax systems, and funding. As such, our innovators confront a more complex set of cultural, legal, regulatory, research, marketing, pricing, and disease issues than any other healer can imagine. It is for that reason that the players within the innovation segment of health care—the biomedical research enterprise, the medical education system, and the pharmaceutical industry—should now forge closer ties, recognize the interdependence, and invite those who want their healing into a covenant. It should come as no surprise that the covenant I would envision is a covenant of obligation, replacing the current covenant of grant. As in the case of all other covenants, this covenant must be a conscious, deliberate act of those healers who are the leadership engines of innovation.

Crafting an Innovation Covenant

If we, as Americans, are to do what I suggest and contribute our resources to world health in order to sustain economic development, and even to promote world peace, then we will need to support the ability of our innovators to deliver the solutions to today's disease problems. How might that happen? What would our innovator-healers ask of us in terms of support, and how

would we perform within an interdependent relationship with them? What would be the terms and conditions that each would ask of the other now, given that the covenant was formed long ago and in ways that were not as mature as today's healing and world climates demand?

The innovators are the superior party in this covenant and, as I have argued, the superior parties are the ones who initiate the covenant relationship. Our innovators have articulated what they need in order to continue to heal. Specifically, they have told us that their requirements are resources for research, appropriate product access and use in the marketplace, and protection of the innovative ideas themselves from piracy committed by others.

Resources for Research Ventures

Highest on the list of what innovators say they require for their ventures are resources, both financial and human. On the financial side, innovators need more funds. Recently, Congress decided to meet their request for more financial resources by appropriating higher levels of funding for the National Institutes of Health. In addition to the increased dollars, Congress and disease interest groups also acted on another request: to allow science to drive research projects and limit the "earmarking" of funds for particular projects. Our innovators have argued that following scientific leads is the best way to achieve disease solutions. New knowledge, they have successfully argued, rarely proceeds along a course plotted by politics; earmarks were getting in the way of progress. This, it seems, qualifies as a request within the spirit of a covenant by our healers, and it seems that we, as parties to that covenant, heard them and responded appropriately.

Other financial resources have been provided by partnerships with industry and by capitalizing on the fruits of academic work. These resources for research ventures have come from the collaborative efforts of academic investigators, federal funding sources, and the pharmaceutical industry. Though highly successful, these relationships are currently at risk and the covenant demands that innovators better define and defend collaboration. Collaborative relationships are now suspect, and concerns about conflicts of interest threaten the reputations of scientists and cooperative efforts overall. This is not the first time that researchers have been criticized or have voiced concerns themselves about the challenges of working with new partners.

The alarm sounded by critics today—that industry may have undue influence—is like that made concerning federal government funding of research in the 1950s. In that era, government was beginning to replace private philanthropy as a major source of money for research efforts, raising fears that these funds would distort the research mission. What we take for granted today—that government does and should fund research—was a controversial idea just a few decades ago. Scientists feared that their research ventures would be "directed" by government and that they would no longer be free to pursue their scientific leads as they believed best. As was the case then, and as should be the case now, any threat—real or perceived—should be balanced by the opportunities for a research enterprise that is ever more vibrant and productive, and by mechanisms to ensure that the scientific process proceeds as society would expect it should to develop important innovations. Doing so should not weaken the joint efforts.

In fact, collaboration among various parties—interdependent as they are—should be strengthened, not weakened. Knowledge flows both ways between the bench and the bedside, and only through widespread cooperation among the players will we realize the real value of innovation. Further, though federal support for biomedical research has grown tremendously in the past several decades, it represents a declining share of biomedical research overall. The private sectors of industry and philanthropy—and, in particular, industry—contribute an ever-growing share of the research resources. To ignore that and separate these dynamic forces in discovery from one other is to weaken all the partners.

Those who fear that the universities and government laboratories, and their federal research counterparts, will be at the mercy of powerful companies have only to review the national policies that have encouraged innovators in government and academia to capitalize on their work. These create a balance among the partners and result in additional funding streams for research. Stevenson-Wydler Technology Transfer Act of 1980 accelerated the translation of research results from federal laboratories into commercial products; and the Federal Technology Transfer Act of 1986 provided incentives for federal-industry research. The Bayh-Dole Act of 1980 provides incentives for universities to patent their findings, and income. University licensing income increased from $186 million to $725 million between 1991 and 1997.[15] The Small Business Innovation Development Act of 1982 facilitated the growth of small companies created by scientists dedicated to transferring their discoveries to the market. Some will be critical, regardless of Congressional oversight and pubic accountability, but their arguments, while passionate, do not address the bigger questions of how we, in this nation, will support innovation to solve our own, and the world's, disease problems. The more worrisome issue today is not the occasional conflict in research partnerships; instead, it is the availability of talented scientists able to join in those research ventures in the future. Science—the discovery of the unknown—is no longer attractive to many students, and fewer of them are choosing the difficult and expensive educational path that science requires.

Besides scientists, the other human resource that our innovators require is clinical trial subjects. Traditionally, patient care settings in academic health centers were ideal sources for investigators. The advent of managed care and, in fact, all cost-controlled care changed that. Managed care, while a seemingly natural organizational structure for conducting research, has not embraced any but the most directly cost-relevant studies of health economics and outcomes. Clinical trials have not been a part of the managed care contribution to innovation, even when managed care patients are cared for in the academic health centers that formerly were the clinical trial powerhouses of the world. Though it has never been documented, it is assumed that research-related care is more expensive than other care, and so managed care has shied away. In fact, until recently, and under public pressure and state legislation, some managed care plans refused to pay for any care when the patient was included in clinical research, even if some of the care would have been deemed medically necessary. Further, managed care has not reached out to its members to encourage their participation in research, as numerous clinical trials go begging for subjects. As a result, new organizations—including Physician Based Research Networks (PBRNs) and Contract Research Organizations (CROs)—have emerged to conduct clinical trials and new methods of recruitment—including the Internet—have been used. Despite this, many clinical trials go begging for subjects. Over 41,000 clinical trials are being conducted

today, and of those underway, 80% are not meeting their enrollment deadlines, spending an estimated $1 billion just to recruit patients.[16] Since pharmaceutical companies sponsor more than 80% of the approved clinical trials in the U.S.,[17] the sheer volume of the effort makes the collaboration among these innovators necessary. This, in turn creates yet another target for criticism about the partnership. As a result, the academic health centers that are the mainstay of medical education and clinical research are faced with a double-barreled threat: they lack the financial resources necessary to conduct clinical trials, and they face additional scrutiny and continued oversight because of their relationships with their collaborative partners. Because they are dangerously underfunded, these centers—and the translational research and medical education they provide—are a disadvantaged and threatened partner in the innovation triad.

Protecting the Ideas

Plant a rice field, tend it, grow it, harvest it and sell it. If you're the farmer, the rice you hold in your hands is tangible evidence that you own it. Plant an idea, tend it, grow it, harvest it, sell it. If you're the inventor, there is no real, tangible "stuff" to hold in your hand. Is it yours? Should it be yours? For how long and under what circumstances should you have the rights to it? When might someone else get have rights? Are there ever circumstances when those rights can, or should, be taken from you?

If you are the innovator, your "stuff" is intellectual property and you have a legal right to call it yours. This is true not only in health care innovation, but also in the industrial, scientific, literary, and artistic fields.[18] According to the World Intellectual Property Organization (WIPO), those rights are extended to literary, artistic, and scientific works, performances of performing artists, phonograms and broadcasts, inventions in all fields of human endeavor, scientific discoveries, industrial designs, and trademarks, service marks, commercial names, and designations.[19] Intellectual property, unlike rice, bricks and mortar, inventory, and other corporate assets, is intangible; it does not have physical characteristics. Our innovators tell us that this ownership is critical to maintaining a pipeline of new discoveries. Is intellectual property important? Yes,it is. One study calculated that, on average, 62% of a company's value lies in intangible assets,[20] which are patents, copyrights, or trademarks. In the health care industry, specifically the innovation sector, it is clear why patents are important. It is not the pills in the warehouse that have value, but the knowledge created when they were discovered and developed. Patent protection ensures that innovators have protection against intellectual pirates, similar to the protections farmers enjoy from the theft of crops from their fields.

The U.S. Constitution underscores the importance of patents,[21] and subsequent laws reinforce their value.[22] Internationally, as well, countries agreed to certain obligations regarding Intellectual Property Rights in 1967 with the creation of the WIPO, an agency of the United Nations. Prior to WIPO, many countries excluded pharmaceuticals, considering drugs to be of such great importance to the national welfare that patents should not create barriers to access.[23] Over time, other nations came to recognize that innovation was important and, further, that without protections piracy would plague the vulnerable industries of informatics, entertainment, specialty chemicals, and pharmaceuticals, and so patent protections were provided to the innovators. Recognizing the value of patents is one matter; protecting them as the world changes

is quite another. With the increasing globalization of the world economy, IP rights have emerged as an item of major political conflict among nations and across sectors. Harmonization of IP laws is a key component and central controversy of international trade negotiations, and pharmaceuticals are at issue because they are not considered ordinary goods or products—they are essential goods. As such, they are integral to securing access to health care, a major objective of the World Health Organization (WHO).[24]

Research and development for most industries is grounded in IP protection and the value has been documented in numerous sources.[25] In the case of medical innovation, the discovery enterprise is robust, and the U.S. and its firms lead the way. Over 40% of innovative drugs in the last three decades were discovered in this country,[26] and most of them—94%—by the pharmaceutical sector. Academia and government accounted for only 3.6% and 1%, respectively, of new discoveries.[27] The policies that, in part, fuel this productivity are not without critics. Both here and abroad the greatest concern is that patent protection increases drug costs by allowing powerful companies to have a monopoly over the idea. As a result of high prices, many who might truly benefit from the therapy are unable to afford it.

The results of patent studies will likely always be considered biased toward industry. But the fact is, a number of these studies have found that improving intellectual property protection does not have a measurable impact on prices of existing drugs and that patent-protected products face therapeutic competition. They also found large, powerful customers who bargained well for better prices and, eventually, generic competition.[28] More indicative of the value of patents is the degree to which protection drives investment in risky research [29] and the reality that regions and countries without such protection —including Latin America, South America, Eastern Europe, and India—do not become the incubators for new scientific inquiry and helpful medicines.[30] This is the case even when patent protections are not eliminated, but only "weakened." Canada, for instance, used to apply compulsory licensing to pharmaceuticals. That is, it compelled the patent holder to license rights to a third party to produce and sell a product, with royalties paid back to the innovator as determined by the government. The U.S. International Trade Commission reports that those compulsory licensing requirements had a significant, negative impact on investment levels in the Canadian pharmaceutical industry, particularly investment by research-based companies. Fewer new products were introduced until after 1987, when compulsory licensing was phased out.[31]

Will the U.S.-based innovators—both companies and scientists—convince us that patent protection is the mainstay for future innovation, discovery, and economic growth? The stakes are high, but the outcome is uncertain. Intellectual property is high on the list of concerns for the pharmaceutical and biotechnology industries, but it should be equally important for all those in the innovation sector, and for all of us who will depend on the discoveries they produce for our future health. Patents are not about reaping returns for today's products as much as they are a method to assure funding for tomorrow's products. Society has critical needs that may only be addressed if patent issues are addressed. What can we expect of our innovators in caring for the world? How should national emergencies, which can result in compulsory licensing, be defined and declared? Will patent-free zones be declared? How would they be defined: by disease, by geography, by community? How can our covenant with innovators sustain their work to provide

cures to less-developed countries? Do American innovators or Americans in general have a covenant obligation to countries that do not recognize our patents?

Using the Discoveries

Supporting research ventures with funds and talent and providing for the ownership of the discoveries, however, is only halfway to success unless the technologies that result are used. Medicines are of no value in company warehouses or on pharmacy shelves. We have to use them. When we do, they cost; and increasingly, as so many headlines declare, they are costing us more. We spend more on medicines today. That's undeniable. With more people aging and taking the increasing number of new drugs available,[32] there could be no other outcome. Whether branded prescription drugs or generics, whether over-the-counter drugs or herbals, our interest in and need for a pharmaceutical solution is greater than ever. In 2001, the nation's prescription drug budget was $117 billion, or 9% of every health care dollar we spent. The average drug expenditure per person per day in this country is about $1.19. That is a bit higher than the average $1.15 we spend on telephone service, and shy of the $1.57 spent on auto repairs, $3.75 on clothes, and $8.69 on food. The share of spending was split nearly evenly between generic and patented drugs. The increase in the rate of our spending was driven by several factors: better diagnosis and treatment of diseases, an aging population (the elderly generally consume more drugs), the availability of new drugs, an increase in the number of drugs that patients take, new drugs recently introduced onto the market, and price inflation.[33] We feed our hunger for longer and more pleasant lives with more products, and they are doing better things for our health and economy.[34] Death rates from childhood diseases, sexually transmitted diseases, rheumatic fever and rheumatic heart disease, atherosclerosis, ulcer, ischemic heart disease, and hypertension are down by remarkable levels, all attributable to vaccines and pharmaceuticals.[35]

That drugs are blamed for spending increases is no surprise; they are the most visible of the fruits of research. A researcher who discovers the underlying cause of Alzheimer's disease can bank the cash from medical prizes. A company that develops a drug that reverses the process of Alzheimer's dementia can bankrupt the pharmacy. The spending increase has become so visible and volatile, however, that innovation overall is sometimes blamed for the increasing cost of health care today. It is not the first time that this criticism has been leveled, but it has been a serious enough concern that some policy experts warn, privately, that perhaps Congress should not increase NIH funding as promised because the country can ill afford the cost of the discoveries that will result. These criticisms ignore the fact that the nation and the world cannot afford to stop the progress that biomedical innovation can bring, especially at a time when too many helpful treatments seem so close to reality. Perhaps, as some analysts believe, the root of this spending controversy is the fact that not all patients in the U.S. and overseas today who need access to medicines have reimbursement systems to fund their purchase—as is so often the case with other forms of health care. While the drug budget may be small overall nationally, it can represent a burdensome expenditure for some patients—the 25% of elderly, for example, who lack drug coverage; or the obese person whose drug bills are typically 80% greater than non-obese persons with similar conditions. If access to financing to help those who need it is necessary, then by all means, it should be pursued. Demonizing the innovators, however, is no solution to the problems of financing.

Companies have not only been demonized for drug spending, however. As drugs are used in the marketplace, they are also criticized for conflicts of interest in their collaborations within the innovation sector. In the flow of new knowledge between the researcher, the clinician, and the pharmaceutical industry, the use of a product, once it reaches the bedside, creates even more new insights. Unproven drugs are tested in isolation, in tightly controlled situations, against a placebo. They are not used that way in real patient care. As new products are introduced, research continues and cooperation among the collaborators must continue as well. These studies—sometimes required by regulators, but often pursued by the innovators—help develop better understanding and new uses for the drugs; so much so that the secondary indications of drugs can eventually exceed 40% of revenues.[36] These collaborations, when they involve industry education, are even more suspect. Industry support of education is substantial, reaching over $1 billion each year and accounting for more than 40% of the continuing medical education provided by medical schools. As the number of new drugs increases, so does the level of industry support for continuing medical education, growing 71% since 1996. [37] This happens on the heels of increased industry support of academic research: from 4% in 1960s to 14% by 1997.

As the distance between academia and industry narrowed, some critics believed that the relationship was so close as to contaminate not only the agenda, but the objectivity, of investigators, educators, and prescribers. A number of articles have detailed the risks of conflicts of interest[38] and others have posed solutions to safeguarding objectivity, both for the investigator and the university involved. [39] It would now be wise to determine if the organizational changes suggested by some, including the development of new structures and layers of accountability, are necessary. One proposal calls for the creation of separate new entities to do research and to hold equity and receive royalties. While this might seem useful, it may also only succeed in attracting the best and the brightest away for the teaching and service roles of academic medicine. Other proposals call for industry to cease physician education altogether, claiming that for a company to educate about its product is, a priori, a conflict of interest.

Is this really necessary? Has biomedical research and physician education truly been compromised because of the relationship among the parties? Or is compromise assumed because the private, for-profit sector is involved, and even the prescriber, the academic, and his institution stand to gain financially from discoveries? Is there really an ethical matter at hand, or is it our pervasive discomfort with profit in the healing enterprise? Might this also be just a phase of coming to grips with the costs of new discoveries, and might we all be getting cold feet as the bills of innovation come due?

Enabling Our Innovators to Become Global Healers

We, here in the U.S., might well put our innovation giant to work solving the disease problems of the world, for the needs are great and the giant's talent is immense. As we do, however, we must be thoughtful and strategic. We should sort out where the giant can help and where its girth, regardless of how generous, may not be enough to create the healthy world we would like to enjoy. To begin, we should consider what we—and the giant—are up against. We should address questions such as these:

- How can we better address poverty? Branko Milanovic, a senior World Bank economist, recently assessed world poverty and confirmed what is apparent on the evening news: income disparities are worsening within and between countries.[40] Slower growth in rural areas, generally, and particularly in rural areas of China, India, and Bangladesh, is a major cause. These regions cannot keep up with the more rapid economic development of urban areas and the OECD nations. World inequality is a tension, therefore, between the wealth of the U.S., Japan, France, Germany, and the United Kingdom and the poverty of China and India. The richest one percent—50 million—of the world's people hold wealth equal to the poorest 57 percent—2.7 billion people. It would seem to be self-evident that the poor of the world would have greater health needs and the nations within which they live have fewer resources with which to provide care. Our intuition should be supplemented, however, with the insights into the distribution of goods and services in relation to health. The work of Norman Daniels is instructive here.[41] Daniels describes how the distribution of income, education, political participation, and control of life and work affect health, how inequalities reduce health, and how fair distribution would improve health. He and his colleagues have documented how health correlates with income and other measures of status at the individual level. In other words, it is not just access to care that produces health. Even when a person has access to care, some health conditions have progressed too far for health services to make up for years of physical stress.

  The implications for this should be clear: simply sending medical teams and donating drugs to poor nations will not, alone, solve the problems of poverty and income disparity. Elsewhere in this book, in the discussion of drug donations, I noted the challenges of delivering drug therapies in countries without adequate transportation systems or public education, or in countries where civil disputes, war, and corruption are the norm. Beyond those challenges are those related to economic, educational, and social development that must keep pace with the improving health of the people. Simply providing improved health care will not change the economy of a poor nation, and while our innovation giant may provide solutions to some of the health challenges, it should not be expected to solve the fundamental problems that caused the sicknesses at the outset. We might prevail upon our innovators to provide anti-retroviral medicines for the young women who have been sold by their families into slavery to brothels in the Far East and who now have AIDS as a result, but that will not address the poverty that caused them to become slaves. We might prevail upon other innovators to provide anti-depressant medicines to farmers in the Punjab to stem the rising tide of suicides there, but medicines alone will not alleviate the farmers' poverty by restoring their lands, promoting agricultural diversity, and improving market conditions. Our foreign policy and international aid programs and the domestic agricultural, educational, and development programs must be engaged to address those issues as well.

- How can we better engage our wealth, and that of potential partners, in healing the world? As Americans we should—and we do—decry the poverty of some in our nation, but the work of Milanovic demonstrates how little we comprehend the devastation of poverty worldwide. An American in the bottom 10% of income in this country has greater wealth than two-thirds of the world's population, and those of us in the top 10% (25 million) of income hold wealth equal to the poorest 43% (2 billion) of others in the world. How will we engage our assets to

help others who need it? Will we do this through tax-supported ventures, through philanthropy, through public service, by supporting products in our markets so that our innovators have resources available to research developing-world diseases? Our wealth can be put to work in many ways.

- How can we engage other developed-world commercial markets? American philanthropy and government funding of research are important forms of wealth sharing, but together they cannot sustain the research and development efforts necessary to solve the disease problems of the developing world. Support from the European and Japanese commercial markets is also necessary. Within each of our wealthier markets, we support innovation in what we choose to purchase and how much we are willing to pay for those goods. The choice to purchase care is a choice to support the capital structure of the innovation sector. It infuses capital back into innovation. Doing that encourages investors to likewise infuse their capital—and assume some risk—in the research and development ventures that lie ahead. We need individuals willing to risk nearly a decade of advanced education and six-figure educational debts to become clinicians and researchers. We need individual and institutional investors to risk losing their money on biotechnology and pharmaceutical companies involved in $800 million-per-product discoveries.

- Can we come to peace with profit in health care? In order to convince investors to spend their lives and their dollars—or Euros or Yen—on innovations, an even more fundamental shift is required. We must come to terms with a for-profit sector within health care, including a for-profit sector that works in collaboration with government, academia, and not-for-profits. If we can do this, then we can end many of the unproductive debates of the current day and stem the tide of incursions into intellectual property ownership. The choice, it seems to me, is simple: Do we, as Americans, want to encourage private investors to risk their assets in pursuit of more innovation, or do we not? Do we, as Americans, want to encourage other nations to do likewise? Would we, as Americans, prefer to fund the full cost of education for individuals and take the risks of drug research failure with tax dollars?

- How can we pursue stronger innovation partnerships within this nation? Neither the public nor the private sectors can address the problems of global health alone. Legislated funds for research and public health will never be sufficient to tackle the world's disease problems, and legislated anti-innovation and commercial market policies will only cripple a giant poised to contribute its talent to healing the world needs. Partnership implies more than "doing no harm," however. It implies that the partners will work collaboratively at every stage of the venture. Within the sphere of global caring, this will involve setting an agenda for research, clinical training, and product development and pursuing the critical targets of opportunity and need. It will involve detailing the public and private policies that will support progress, and enumerating the public and private assets that should be engaged to address the needs of the globe, not just our own nation. True, there should be oversight to assure that the public trust is not violated, but that oversight should not impede progress on the road to disease solutions.

- How can we pursue stronger partnerships with other developed nations? Our cross-national

efforts should entail engaging other developed nations in health care innovation and economic development to assure that Americans, alone, do not unfairly shoulder the world's burdens. These discussions will be difficult, particularly as they relate to the support of products in the marketplaces of Europe and Japan. Many developed nations have created unfavorable climates for health care and innovation which have, in part, driven the innovators to the U.S. Some have set product prices that require companies to charge higher prices in the U.S. in order to recoup investment costs and conduct research on new drugs. While there are some hopeful signs that other developed nations—particularly Germany and Ireland—may be willing to reconsider national policies concerning innovation, creating those changes in both the public policies and the prices in commercial markets will not be easy.

- How can we invite partnerships with developing nations? Dependence and independence are aspects of covenant that are immature and unworthy of the healing ventures to which we should aspire. Recognizing and acting within interdependence should be the goal as we deal with any nation, no matter how poor or distressed, just as it is with any patient, no matter how poor or distressed.

- How can we engage our innovators to address the problems of developing world diseases? Some of our most respected scientists, Dr. Anthony Fauci among them, believe that progress made so far in research to combat HIV/AIDS demonstrates that, if applied well, financial and human resources can solve the seemingly unsolvable problems of disease. Yet only 1% of drugs approved in the last 25 years are directed at solving the infectious tropical diseases that comprise so much of the disease burden of the developing world. In a recent study, major pharmaceutical companies indicated they spent less than 1% of their research resources on these diseases, and the public sector is estimated to be spending less than $75 million.[42] Some advocates have advanced proposals to require companies to invest in developing-world diseases,[43] and the government funds an International Center for Tropical Disease Research that issues challenge grants to those who commit their own resources to this arena. The Gates Foundation has emerged as a major funder of developing-world disease innovation, and at a recent meeting of government, industry and academia, our innovators met to assess and correct barriers to research.[44] All these are hopeful signs. Are they enough to address the needs of poor nations for our help, and the needs of this nation to lend it?

The current hostility and mistrust that confront our innovation sector as it attempts to solve our disease riddles are an unfortunate distraction from the task at hand to heal the world. It is my hope that new dialogues can begin. Creating the relationships will require change on the part of all who are involved. For their part, the innovators must become more engaged in telling their story and participating in solving not just the disease, but the health care financing problems. For our part as patients, we must become more involved in appropriately using their discoveries —and being willing to pay for them when we can. As a nation, we must be prepared to fund care for those who cannot afford to pay for it themselves. Most of all, however, we must recognize the consequences of abandoning a century-long tradition of being the most innovative nation in the world. Neither we, nor the world, can afford a kink in the innovation pipeline.

[1] This appeared originally in 2001 in *Covenants: Inspiring the Soul of Healing*. Readers interested in exploring covenants in greater depth can find background in *The Origins of Healing as Divine Gift* and *History and Modern Applications of Covenant Healing Traditions* which appear in this series.

In summary, healing traditions are based on ancient views that healing skill came from the divine. Healers were aligned with divine forces against the terrible, unknowable and sometimes evil forces of illness. As a result, healer-patient relationships were structured as covenants. Covenants differ from contracts. Contracts have a defined beginning and end and specify the duties of the parties in detail. Covenants do not end and do not detail the duties of the parties.

There are two types of covenants, both are relevant in health care and are expressed in oaths taken by clinicians and others in health care. The first type – a covenant of *grant* – defines what one party does for another, without conditions or expectations. Parents have covenants of this type with their children, providing them food, shelter, clothing and protection. The second type – a covenant *of obligation* – involves mutual promises between the parties. Spouses enter into this type of covenant '…for better or for worse.'

The *Oath of Hippocrates*, a classic covenant statement, contains both types. It creates a covenant of *obligation* with other healers, calling for the oath-taker to "…study, learn and teach my fellows…and to treat his sons as my sons." Then, the oath "…grants health…" to the patient. The *Prayer of Maimonides*, an oath created later, contains the same covenant of *obligation* among healers and calls patients into a covenant of *obligation* as well, asking that patients follow medical advice, take prescriptions and avoid the advice of meddlesome friends and relatives uninformed about health and disease.

The book suggests that everyone in health care – not just clinical experts but those in any role in research, management, insurance, health reporting and even policy – are the sophisticated extension of ancient tribal healers. Our societies are more complex, as is our knowledge, our data and information, our technology and our systems of providing care. As a result, as healers we have entered healing streams of an ancient origin. Our patients and communities expect us to ascribe to these covenant values.

In my view – and I am not alone in this – health required the integral relationship among healers, patients and communities. I therefore proposed three steps to transform health: first, a covenant of obligation among all healers, as I broadly defined them; second, a covenant of obligation with patients; and third, a covenant of obligation with communities, as well.

This is an application of those ideas to the policy issues addressed here.

[2] Claude Le Pen, "Innovation and Regulation in the Pharmaceutical Market," in Felix Lobo and German Velasquez, eds., *Medicines and the New Economic Environment*, World Health Organization, Editorial Civitas, Madrid, 1998, p. 213.

[3] Code of Hammurabi

[4] M. Angell, "Is academic medicine for sale?," *N Engl J Med*, 2000,342:1516.

[5] Report of the Commission on Macroeconomics and Health, *Microeconomics and Health: Investing in Health for Economic Development*. Available at http://www3.who.int/whosis/cmh/cmh_report/e/report.cfm?path=cmh. Accessed January 23, 2002.

[6] www.nih.gov, www.cdc.gov, www.dod.gov. Accessed January 30, 2002.

[7] Abraham Flexner, "Medical Education in the United States and Canada," *Carnegie Foundation Bulletin 4*, New York, 1990.

[8] Data provided by the Pennsylvania Biotechnology Association. See also www.pabiotech.org.

[9] Mark Hatfield, Hugo Sonnenschein, Leon Rosenberg, *Exceptional Returns: The Economic Value of America's Investment in Medical Research*, New York: Funding First, 1999. Available at www.fundingfirst.org.

[10] Fuchs, V. *Who Shall Live?* New York: Basic Books, 1974.

[11] Christopher Murray, Alan Lopez, *The Global Burden of Disease*, World Health Organization, Geneva, 1996.

[12] Funding First, *Exceptional Returns: The Economic Value of America's Investment in Medical Research*, available at www.fundingfirst.org. Accessed March 15, 2002.

[13] Michael Marmot, "Health and the psychosocial environment at work," in Michael Marmot, ed, *Social Determinants of Health*, Oxford: Oxford University Press, 1999. See also George Davey-Smith, "Socioconomic differentials in mortality risk among men screened for the Multiple Risk Factor Intervention Trial: White men," *American Journal of Public Health*, 86:489-496.

[14] Report of the Commission on Macroeconomics and Health, *Marcoeconomics and Health: Investing in Health for Economic Development*, World Health Organization, Geneva, 2001. Available at www3.who.int/whosis. Accessed January 23, 2002.

[15] D. E. Massing (Ed.), *USTM Licensing Survey: Fiscal Year 1998*. Norwalk, CT: Association of University Technology Mangers, Inc., 1999.

[16] Kathleen Drennan, "Have the ultimate benefits of clinical trials been maligned beyond repair?," *Drug Discovery Today* 6 (12):597-599.

[17] Medical devices represent 5% of all approved trials and non-drug therapies, such as surgical techniques or radiation, amount to 10%.

[18] *Agreement on the Trade-Related Aspects of Intellectual Property Rights*, WIPO, 1995. Available at www.wipo.org, Accessed March 18, 2001.

[19] Ibid.

[20] World Trade Organization, www.wto.org

[21] Pharmaceutical Manufacturers' Association (PhRMA), "Chapter 8: Global Intellectual Property Protection," *Pharmaceutical Industry Profile 2001* Available at www.phrma.org, Accessed March 17, 2001.

[22] The Drug Price Competition and Patent Term Restoration Act of 1984 recognizes that product testing, development, and compliance with federal marketing requirements can consume some of the patent term, thus reducing marketing time for recovery of research and development costs. The law restores time lost in government review. The law provides that only half of the development time can be restored, the extension can be no more than 5 years, and total patent life cannot exceed 14 years—that is, 14 years of marketing time. The Act also eased requirements and expedited approval of generic products by allowing manufacturers to use the safety and efficacy data from the developing company. In essence the law balanced interests—offering innovators a longer period or protection, but providing generic companies with enhanced market access at the point of patent termination.

[23] F. Scherer, "The Pharmaceutical Industry and World Intellectual Property Standards," *Vanderbilt Law Review* 53(6):2245-2254.

[24] Ibid.

[25] According to the Congressional Budget Office, in 1994, the pharmaceutical industry spent approximately 18% of sales on research and development. It is expected the industry will spend upwards of 20% in the coming years. Comparatively, other U.S. industries spend approximately 4% of sales in R&D. Among European Countries, 1993 figures reveal investment in R&D varies from 7% in Italy to 17% in the United Kingdom. S. Wolf, "Evaluating Damages in Patent Infringement Cases," *Pennsylvania CPA Journal*69(2): 9-12.

Costs, according to the Boston Consulting Group, were estimated at $500 million in 1996. High R&D costs have been associated with a high attrition rate for what is termed "dry holes;" that is, compounds that have been investigated but abandoned during pre-clinical, phase I, and phase II stages for various reasons. TCSDD reports that of the 5,000 compounds in development, only 5 reach pre-clinical testing and, of those, only one may be approved

for sale or become a "blockbuster." Innovative drugs cost more (in both time and money) to develop than modifications to existing compounds. IPP is the means by which companies recover the dollars spent on R&D. In a survey of 100 U.S. firms in different industries, pharmaceutical industries indicated that 65% of medicines would not have been developed or commercially introduced without patent protection. High on the list as well were the Chemical and Petroleum industries, stating that 39% and 25% of their products, respectively, would not have been developed in the absence of IPP. The Boston Consulting Group, *Unleashing Managerial Advantage in Pharma R&D*. Available at www.bcg.com. Accessed April 2, 2001. P. Danzon, *Pharmaceutical Price Regulation–National Policies versus Global Interests*, Washington, D.C.: AEI Press, 1997. Pharmaceutical Manufacturers' Association (PhRMA), op. cit.

[26] P. Danzon, op. cit.

[27] Tufts Center for the Study of Drug Development, *Impact Report*. Available at www.tcsdd.edu. Accessed April 2, 2001.

[28] R. Rozek, R. Berkowitz, "The Effects of Patent Protection on the Prices of Pharmaceutical Products: Is Intellectual Property Protection Raising the Drug Bill in Developing Countries?," *The Journal of World Intellectual Property*, 1(2):179-243.

[29] K. Maskus, "Lesson from studying International Economics of Intellectual Property Rights," *Vanderbilt Law Review*, 53(6): 2219-2239.

[30] J. Revesz, *Trade-Related Aspects of Intellectual Property Rights*. Available at http://bilbo.indcom.gov.au/research/staffrcs/trips/index.html. Accessed April 25, 2001.

[31] USITC, *Prescription Drug Pricing Report*. Available at www.usitc.gov.Accessed April 26, 2001.

[32] H. E. Frech and R. D. Miller, *The Productivity of Health Care and Pharmaceuticals: An International Comparison*, Washington, D.C.: AEI Press, 1999.

[33] R. Dubois, et al. "Explaining drug spending trends: Does perception match reality?," *Health Affairs, 2000*: 19(2):231-239.

[34] F.R. Lichtenberg, *Pharmaceutical Innovation, Mortality Reduction and Economic Growth,* Cambridge, MA: National Bureau of Economic Research, May 1998. Working Paper W6569.

[35] The Boston Consulting Group, "The Contribution of Pharmaceutical Companies, What's At Stake for America," 1993.

[36] D. B. Audretsch and P. A. Stephan, "Company-scientist locational links," *American Economic Review*,86: 641-652. See also: J. Meyer, "*Assessing the Impact of Pharmaceutical Innovation: A Comprehensive Framework*, New Directions for Policy, February 2000. Also available at www.npwnow.org. Accessed March 21, 2002.

[37] A. Holmer, "Industry strongly supports continuing medical education," *JAMA*, April 18, 2001, 285(15):2012-2014.

[38] M. Angell, "Is academic medicine for sale?," *N Engl J Med*. 2000; 342: 1516-1518. See also: C. D. DeAngelis, "Conflict of interest and the public trust," *JAMA* 2000, 284:2237-2238.

[39] H. Moses and J. Martin, "Academic relationships with industry: A new model for biomedical research," *JAMA*, Feb 21, 2001, 285(7):933-935.

[40] Branko Milanovic, "True world income distribution, 1998 and 1993: First calculation based on household surveys alone," *The Economic Journal*, 112:51-92.

[41] J. Cohen and J. Rogers, eds, Norman Daniels[??], *Is Inequality Bad for Our Health?* Boston, MA: Beacon Press, 2000.

[42] B. Pecoul, J. Orbinski, E. Torreele, eds. *Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases*, Geneva: Médecins Sans Frontières/Drugs for Neglected Diseases Working Group, 2001.

Available at http://www.accessmed-msf.org. Accessed January 30, 2002.

[43] M. Angell, "The pharmaceutical industry—to whom is it accountable?," *NEJM*342:1902-1904.

[44] These government programs can be located at the website of the National Institute for Allergy and Infectious Disease (NIAID), Global Health Research. Available at http://niaid.nih.gov/dmid/global. Government and Industry Team up to Battle Infectious Diseases. Available at http://www.niaid.nih.gov/newsroom/releases/challgrants.htm. Summit on Development of Infectious Disease Therapeutics (meeting summary). Available at http://www.niaid.nih.gov/dmid/drug/summit.htm.