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The Economics of Human Gene Patents

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ABSTRACT

The author examines patents on DNA sequences, including data on gene sequence grants issued by the PTO during a 33-month period from 1998 to 2001. Policy supporting patents on DNA sequences and other elemental information that are far "upstream" in the product development pathway is contrasted with the economic bases and rationale for patents to pharmaceuticals, which require a protracted and expensive process of development and testing but that can be relatively cheaply and competitively imitated once they are approved and disclosed. How to allocate appropriately the economic returns among the upstream and downstream inventors is a challenging problem for economic theory, as well as for contemporary biomedical research, and is perhaps most familiarly embodied in licensing and cross-licensing disputes involving "reach-through" and "reach-back" rights. Such disputes can generate enormous transaction costs. They may become increasingly frequent and vexing with respect to the scope and overlap of patent claims on human gene sequences. On the basis of his analyses, the author argues that genome patent claims should be interpreted narrowly. He is particularly concerned with ensuring that the development of new (therapeutic) products is not blocked or retarded by a multiplicity of prior patent claims, but he is pessimistic that the diversity of participants in biotechnology will provide a "sufficient community of interest to organize comprehensive low-royalty cross-licensing" regimes. Accordingly, he suggests mandatory arbitration as one mechanism for resolving such problems.

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In the millennium year 2000 two teams, one organized through the public sector and one privately financed, completed preliminary sequence maps of the human genome, encompassing an estimated three billion DNA base pairs. Current estimates, still subject to considerable uncertainty, suggest that the human genome includes 30,000 to 40,000 distinct gene sequences that may in combination express 100,000 proteins. The United States Patent and Trademark Office has been accepting patent applications for individual human genome sequences whose "utility" can be shown by links to particular genetically-based diseases, genetically expressed proteins whose function in the human body can be identified, and/or medical diagnostic methods. As of 1999, nearly 3,000 patents of this nature had been issued, and a considerable backlog of applications is said to exist.[1] Whether, or under what circumstances, patents on human genome sequences should be issued has become a highly controversial issue both in the United States and in the European Community.

There are three main ways to approach this issue—precedential, ethical, and utilitarian. The precedential approach asks whether the intent of Congress in enacting patent laws under Article I, Section 8, of the U.S. Constitution was to allow patents for the identification of phenomena such as gene sequences already existing in nature. The ethical approach asks whether any individual or organization should have the exclusive right, limited to be sure in time, to control the commercial uses of phenomena that are as fundamental to human life as gene sequences. These are questions on which economists, who are more like plumbers than philosophers, have no comparative advantage. This paper, therefore, emphasizes a utilitarian approach, asking what benefits might arise from granting human gene sequence patents under diverse circumstances, what the costs might be, how the costs and benefits balance out, and how the benefits and costs are distributed among the diverse affected parties. The question is an extraordinarily difficult one, and readers

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should not expect a precise quantification of benefits and costs. The best that can be done is to survey what we know about the extent to which patent protection plays a role in accelerating (or impeding) the progress of science and technology, especially in the domain of human health, identify the relevant benefit and cost proclivities, and show how they are interrelated.

This paper begins by laying out what is known about the role patents play in providing incentives for research and development investments. Three narrower patent effect domains are explored further: pharmaceuticals, the commercialization of inventions made under government contracts, and biotechnology (which is distinctive in the large number of startup companies performing research and development). Evidence is marshaled on the kinds of organizations, public and private, performing basic research in biology, the characteristics of U.S. patents that embody DNA sequence claims, and the organizational origins of surveyed DNA sequence patents. From that empirical base, the paper focuses conceptually on the tradeoffs faced in awarding patents at diverse stages of a multi-stage discovery and development sequence for a representative therapeutic product. Finally, the empirical and conceptual threads are pulled together in an attempt to draw broad implications for public policy.

Before we begin, it is important to recognize that genomic research leads to improvements in health therapy through a complex multi-stage process. One first stage is the identification of a genome sequence. A second stage may follow, in which the functioning of the sequence in expressing proteins or (when there are mutations) causing or curing health problems is discovered. These two stages may be reversed; e.g., scientists may identify a health problem or a protein and then work backward to find the specific DNA sequence that is associated with it. The next stage entails conceiving a practical embodiment of this knowledge in the form of synthesized proteins, protein fragments, or other chemical molecules affecting them, diagnostic tests, or the like. Once a specific therapeutic modality or diagnostic approach is defined, clinical tests must be carried out to ensure that it actually works in human subjects. Regulatory hurdles must be cleared before the sequence of discoveries, inventions, and tests can be applied to improve human health and welfare. The multi-stage character of this process is a recurring theme in what follows.

THE PATENT GRANT AND ITS ALTERNATIVES

A fundamental rationale for patent grants is to impede the emergence of competitors to some newly-invented product or process, thereby allowing the inventor to realize, or at least expect to realize, profits that will on average repay the cost of its inventive efforts. The underlying theory is illustrated in Figure 1. Suppose a new product is invented and developed to the point of commercialization. The market demand for the new product is characterized by the solid line in Figure 1 labeled "Initial Demand Curve." The demand curve for any product is a schedule of units that might be purchased in a given time period, i.e., per year, depending upon the price charged, arrayed in descending order of consumers' ability and willingness to pay. Thus, some consumer would be willing to pay at most $19.36 for a single unit (where the demand curve meets the vertical axis); the 100 thousandth unit would find a consumer willing to pay no more than $14; and the 400 thousandth unit a consumer willing to pay just a bit less than $4. Readying a new product for the market also entails working out production methods, which are assumed to entail a cost of $4 per unit produced, shown by the horizontal cost curve marked "Cost per Unit" in Figure 1. At first the firm marketing this new product is the only seller of its product—in economic terms, a monopolist. It can choose the price that maximizes its profits —in Figure 1, $10.95 per unit, which will lead to the purchase of 160,000 units per year. Selling 160,000 units at a price of $10.95 per unit, and with production costs of $4 per unit, the firm will realize an annual profit of $1.112 million, shown as a diagonally shaded rectangular area in Figure 1. If all goes well, this profit will, over a sufficient period of time, repay the innovator's research and development costs plus accumulated interest to compensate for the time lag between the sinking of research and development (R&D) costs and their recoupment.

Even though the new product is priced monopolistically, consumers are also better off as a consequence of its availability. The extent to which they benefit is calculated by the difference between what they would be willing to pay, read as a descending schedule from the demand curve, and the price they must actually pay. That surplus of "willingness to

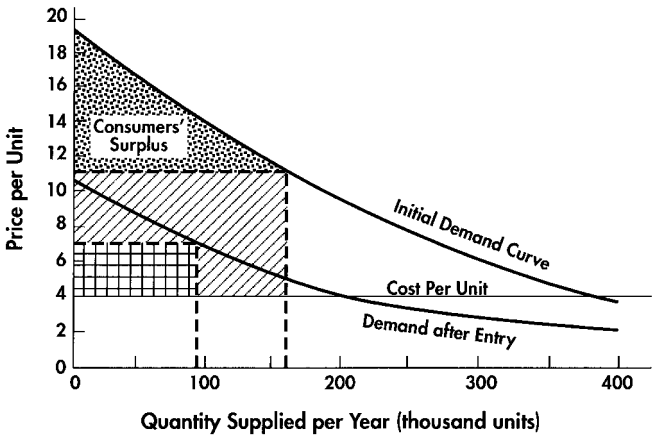

Figure 1. How competitive entry erodes the profits of an innovator.

pay" less the price actually paid is called consumers' surplus. It is shown as the nearly triangular dot-shaded area in Figure 1. As illustrated, it amounts to approximately $640,000 per year. Thus, both inventor-developers and consumers gain from the new product. In the case of life-saving medical products, consumers' willingness to pay may be very high indeed, leading to particularly large consumers' surpluses.

Sooner or later, the new product's profit potential will stimulate other firms to imitate the product and offer their own competing versions. When this happens, the demand curve remaining for the original innovator will shift downward and to the left, e.g., to the solid line labeled "Demand after Entry" in Figure 1. Making the best of its new and less advantageous situation, the innovator will reduce its price to $7.00 and sell 93,000 units per year, realizing a profit of ($7.00 − 4.00) × 93,000 = $279,000, shown by the cross-hatched rectangular area in Figure 1). If the required R&D expenditures are, for example, several million dollars, a reduced profit of this magnitude may be insufficient to recoup them. If rapid erosion of its profits by competitive imitators is foreseen, the would-be inventor–innovator may choose not to make the necessary investment in research and development, and so the product will not be brought into existence. This would be unfortunate, since, absent competitive entry, the combined benefits to participants in the economy, that is, profits plus consumers' surpluses (which amount to at least $1.75 million per year) would be more than sufficient to cover the requisite R&D investments, and so having the new product is economically worthwhile.

The role of patents is to retard competitive imitation sufficiently to let inventors and developers of potentially beneficial new products or processes expect net profits from their R&D investments. Even in the limiting case of an R&D investment so costly that it would not be made unless the innovator were guaranteed a perpetual monopoly of the new product, there is a net economic gain from having the product, since the monopoly profits needed to repay initial R&D costs are augmented by consumers' surplus; thus, total consumer plus producer benefits exceed R&D and production costs.

Alternative Barriers to Competitive Imitation

An important limitation of this rationale for the patent system is that patent protection may generate incentive "overkill," providing more protection from competitive imitation than a would-be innovator needs to justify its R&D investment. This would be so, for example, under the conditions described by Figure 1 if the innovator's head start in marketing its new product ensured that it would be free of competitive imitation for at least a year, and if the R&D costs required to make the innovation totaled (after appropriate risk-adjusted interest cost adjustments) less than the $1.112 million of profits realizable during the first year of new product sales. If the innovation would be made without patent protection, the additional monopoly profits protected by patents impose an unnecessary burden upon consumers, who, in the absence of patents, would, after competitive imitation, enjoy lower prices and larger consumers' surpluses than they would if the new product continued to be protected by patents after its R&D payback period.[2]

A head start is one "natural" barrier to rapid imitation. It is likely to protect the innovator's profits more, the longer it takes for an imitator to duplicate the innovator's product. That in turn depends in part upon how long it takes would-be imitators to recognize that there is a product worth imitating and also upon the duration and cost of R&D or other investment required to market an imitative product. Front-end imitation costs vary widely. To copy software or recorded music, the cost of imitation is close to zero; one needs nothing more than a compact disc burner. To imitate a commercial airliner design, the second mover may have to incur R&D costs close to those of the innovator, replicating detailed design drawings, prototype fabrication, and extensive prototype testing (since small design variations may render the aircraft structurally unsound or aerodynamically unstable).[3] If R&D replication costs are high and the market is too small to yield profits sufficient to cover twice-original R&D costs, imitation may not occur at all in airliner-like innovation cases.

Recognition lags may be especially long, and R&D duplication costs particularly high, for new production processes that can be kept secret from imitators, e.g., by restricting access to production sites. Secrecy during the R&D phase also enhances the innovator's head start advantage for new products, since the imitator is unlikely to begin its own R&D program until the innovator's product has been successfully launched into the market.

The advantage of a head start is magnified for products such as semiconductors and aircraft, whose production cost falls with increased experience as a result of "learning by doing." In the typical case, unit production costs fall by 20–30% with each doubling and redoubling of cumulative output up to substantial output thresholds. For a typical integrated circuit, this means that the producer who has produced 10,000 chips may incur costs of $20 per chip, while the firm with experience producing a million chips incurs a cost of only $2.25.[4] With a head start down the learning curve, the innovator can take advantage of its lower costs to charge modest but still profitable prices that render an imitator's operations unprofitable. The expectation that this could happen might sway a would-be imitator's decision toward not imitating, thereby extending the innovator's head start.

Especially for consumer goods, being the first to offer a new product also confers significant advantages in the form of difficult-to-dislodge brand loyalty and a favorable image that allows the innovator to charge premium prices even when numerous imitative substitutes are available.[5] These "pioneering brand" advantages are seen inter alia in the large price differences typically prevailing between originally branded and generic prescription drugs.

Survey Evidence

Two large-scale surveys have attempted to assess the extent to which patent protection, as compared with other barriers to competitive imitation, is important to would-be innovators hoping to capture the benefits from their technological innovations. They yield generally similar insights.

The first, the so-called Yale University survey by Richard Levin et al.,[6] elicited judgments from 650 U.S. industrial research and development laboratory managers about the relative effectiveness of several means for protecting the competitive advantages from new products and processes. The responses, on a seven-point scale, could range from 1 (not at all effective) to 7 (very effective). The average scores for various mechanisms across 130 industry groups were as follows for *new and improved products* and for *new and improved processes*, respectively:

- Patents to prevent duplication 4.33 and 3.52
- Patents to secure royalty income 3.75 and 3.31
- Secrecy 3.57 and 4.31
- Being first with an innovation 5.41 and 5.11
- Moving quickly down learning curves 5.09 and 5.02
- Superior sales or service efforts 5.59 and 4.55

Only secrecy was deemed less effective than patent protection on average in capturing the benefits from new and improved products; for new processes, patents were considered the least effective of six alternative mechanisms. The average scores varied widely, however, across industries. Among the 65 industry groups in which more than three responses were obtained, "patents to prevent duplication" had the highest average scores in agricultural chemicals (6.88), pharmaceuticals and biologicals (6.55), and industrial organic chemicals (6.05). Indeed, in those industries, patent protection was considered the most effective means of capturing the benefits from product innovations.

An even more extensive survey of 1,478 U.S. R&D laboratory managers was conducted from a Carnegie–Mellon University base by Wesley Cohen et al.[7] The authors asked their respondents to estimate inter alia the percentages of product innovations on which various mechanisms were effective in helping capture the benefits from those innovations. Across the 34 industry groups for which results have been reported, the average scores for alternative means of capturing the benefits from product innovations were as follows:

- Secrecy 51.0%
- Patents 34.8%
- Other legal instruments 20.7%
- Lead time 52.8%
- Complementary sales and service effort 42.7%
- Complementary manufacturing capability 45.6%

Thus, on average, patent protection was considered the second least effective means of capturing profits through product innovation, leading only "other legal instruments" (such as copyright and trademarks). Among the 34 industry groups, the highest average scores for product patent protection were recorded for medical equipment (54.7%) and drugs and related products (50.2%). For drugs, however, secrecy, which received much more emphasis in the Carnegie-Mellon survey than in the Yale survey for reasons that are unclear, had an even higher average score (53.6%) than patent protection, which in turn was followed closely by lead time (50.1%) and complementary manufacturing capability (49.4%). For medical equipment, the average score for drugs was exceeded by the lead time variable (58.1%). For no reported industry did patent protection hold first place among the alternatives.

A less extensive survey asked 100 U.S. industrial R&D executives what fraction of the inventions they developed during 1981 through 1983 would not have been developed had the companies been unable to obtain patent protection.[8] The R&D expenditure-weighted average for 12 industry groups was 14%. By far the largest estimated loss of developments, 60%, was projected by pharmaceutical industry executives.

The Special Role of Patents in Pharmaceuticals

The survey evidence is consistent: patents are not a very important means of capturing the benefits from innovation, and hence a stimulus to R&D investment, in most industries. But the pharmaceutical industry, whose products may be based upon human gene sequence information, is an outlier, attaching especially great importance to product patent protection. There are three probable reasons for this emphasis.

- For one, in pharmaceuticals, as in organic and agricultural chemicals, patent claims tend to define products especially precisely. If one atom is replaced by some other atom in a

defined organic molecule, the product may not perform its intended function.

- Second, once a particular molecule is identified as a potentially effective therapeutic medium, it must be carried through expensive clinical trials to prove its safety and efficacy. For new chemical entities first tested in human beings in the United States between 1970 and 1982, the average clinical trial cost, including the cost of molecules dropped in failed trials, was $60 million per approved drug (assuming 1993 general price levels).[9] When clinical trial costs were capitalized at a 9% interest rate to the date at which commercial sales began, the average estimated cost rose to $93 million. For that cohort, pre-clinical discovery costs directed toward finding molecules worth testing were of roughly the same magnitude as capitalized clinical costs when failed efforts are averaged in.[10] A more recent survey of molecules introduced into clinical testing between 1983 and 1994 by main-line pharmaceutical firms yielded an estimate, including capitalized pre-clinical, clinical, and failed-molecule costs, of $802 million per approved drug (assuming price levels for the year 2000).[11] Most of the cost increase relative to prior survey estimates was attributable to more extensive and more costly clinical trials. Compared with earlier surveys, pre-clinical costs were a smaller fraction of total capitalized costs.
- Third, absent patent protection or regulatory barriers to imitation,[12] imitators might spend a very few million dollars on product formulation, process development, and clinical trials (typically on 24 human subjects) required to prove therapeutic equivalence and bring their generic substitutes onto the market in competition with the company that has incurred huge discovery and clinical testing costs. Most of the innovators' costs are incurred to provide information that a drug in fact works and is safe, information on which generic competitors can then take a free ride. Thus, the disparity between the investments of innovators and those of imitators is particularly large in pharmaceuticals—almost as large as when software pirates simply copy the diskettes of an innovator.

It is for these three reasons together that patents are accorded such high importance by pharmaceutical manufacturers. Similar reasons underlie the importance attached to agricultural chemical patents, since new products must be tested extensively for environmental safety before receiving marketing approval.

The emphasis traditional pharmaceutical manufacturers placed on patent protection had important consequences for patterns of drug development during the early 1960s.[13] Up to 1962, academic investigators performing research under grants from the National Institutes of Health (NIH) turned to private-sector pharmaceutical firms to screen thousands of newly-synthesized organic chemical molecules. If those entities showed promise of therapeutic efficacy, which occurred at frequencies above the average for company-synthesized compounds, the pharmaceutical firm secured exclusive rights to the molecule and proceeded with further pre-clinical and, when appropriate, drug development work. Beginning in 1962, however, the Department of Health, Education, and Welfare (HEW) imposed more stringent invention-reporting requirements for academic grant holders and required private-sector firms screening grant-based molecules to certify their acceptance of HEW patent policies, under which the screening company could be deprived of exclusive rights to the screened molecules and possibly also to related molecules developed in-house. When the new policy was adopted, pharmaceutical companies are said to have rejected the revised patent agreements "almost unanimously" and to have withdrawn completely from screening NIH-grant–based molecules.[14] As a consequence, academic investigators were forced to seek other ways of testing their new molecules. The best alternatives were the cancer and malaria drug screening programs operated by the NIH and Walter Reed Hospital, but they covered only a narrow spectrum of possible therapeutic uses. As a result of this stalemate, many new molecules were not screened at all or screened inadequately, making it unlikely that they would lead to new drugs and limiting researchers' publication outlets to those that did not require evidence of therapeutic merit. Collaboration between academic researchers and drug companies is said also to have ebbed. The stalemate was ended in 1968 when the Department of Health, Education, and Welfare amended its patent rules to allow the assignment of exclusive rights in grant-based patents.[15] Legislative support followed with passage of the Bayh–Dole Act in 1980. The history of the episode is a warning, however, that the emergence of new therapeutic entities could be impeded when patent-conscious private-sector firms fear that their investments in clinical testing might lack sufficient intellectual property protection.

Related Evidence

The refusal of pharmaceutical companies to screen molecules resulting from federal grant–supported research during the 1960s was one of the most extreme cases investigated by the Committee on Government Patent Policy on how patent rights affected the further development of inventions made under government contracts or grants. That committee, on which I served as economic adviser, explored on a much broader plane the links between patent rights stemming from government-supported R&D and commercial utilization. At the time of its study, some agencies of the government regularly allowed their contractors to take exclusive rights to contract- or grant-related inventions, while others pursued

the opposite policy. From this "natural experiment" it was possible to analyze statistically the relationships between patent rights and commercialization for 1,720 patented inventions made by for-profit government contractors, the majority holding defense and space contracts, for which complete survey information was obtained.[16] Among those 1,720 inventions, 11.8% had been utilized in civilian market applications by the original contractor, 4.3% had not yet been utilized commercially but were expected to be, and 2.4% had been put to civilian market use by one or more licensees. An important contingent variable affecting utilization was whether the contractor had prior experience working in the civilian sector to which the invention pertained. A two-way classification revealed the following commercial utilization percentages:

- For contractors who had prior experience, utilization rates were 23.8% with exclusive rights and 13.8% without.
- For contractors who lacked prior experience, utilization rates were 6.6% with exclusive rights and 2.2% without.

Prior experience was apparently more important than exclusive patent rights in encouraging commercialization. However, both with and without prior experience, commercialization rates were higher with exclusive rights than without them. It was not possible to tell definitively from the evidence in which direction causation ran: to what extent good commercialization prospects led contractors to bargain more vigorously for exclusive patent rights, and to what extent exclusive rights facilitated investments in commercialization. From further analysis of the quantitative data and numerous case studies, I concluded that having exclusive rights on inventions made under private-sector government contracts was more apt to turn the tide toward civilian utilization

- when the firm making the invention was small both absolutely and in relation to the relevant civilian market;
- when the inventing firm had no prior commercial position and had to either break into the field itself or find a licensee;
- when substantial technical development costs and risks remained before commercialization could occur; and
- when the relevant market was small in relation to expected development costs.

The committee's work was a forerunner to passage of the Bayh–Dole and Stevenson–Wydler Acts in 1980.[17] Those acts created presumptions in favor of granting exclusive patent rights on inventions made by government contract and grant recipients and to firms carrying out the commercial development of inventions made in-house by government employees. To achieve administrative simplicity, however, they do not attempt to account for the nuances associated with the four points itemized above.

Small Firms and High-technology Startups

My inference from the committee's research was that patent rights contributed with special force to commercialization of inventions made under government grants or contracts for relatively small and/or newcomer firms. More recently, many inventions originating under government-funded research have been developed for commercial use by new high-technology ventures, typically financed in their early growth stages by organized venture capital intermediaries and then by initial public stock offerings (IPOs). With rare exceptions, such start-up firms are small in their early years. In 1996, venture capital providers disbursed an estimated $663 million to biotechnology firms and in 1997, $966 million.[18] In 1999, $1.24 billion (out of total disbursements to all industries of $50 billion) were disbursed by venture capital firms to 207 biotechnology companies.[19] In 1998, some 327 biotechnology companies had crossed the IPO threshold and had common stock listed on U.S. securities markets.[20] Their market capitalization at the time was $97 billion; their product sales $13.4 billion, and their research and development outlays $9.9 billion, or an astonishing 74% of sales. With such high outlays, aggregate biotech industry losses amounted to $5.1 billion. Indeed, according to *Business Week*, only 13 publicly listed biotech companies reported positive net profits in 1998; 22 were expected to do so by the year 2000.[21]

How important patent rights are in attracting investment to new high-technology ventures generally and, in particular to biotech ventures, is not entirely clear. From 14 case studies of technologies licensed by universities to private firms, usually small, Hsu and Bernstein reported that "many of our case study entrepreneurs, regardless of the size of the particular technology in question, would not have licensed their technologies without an exclusive license. The threat of direct competition in a niche market is usually too daunting for the licensee."[22] However, they identify exceptions, notably, the semiconductor industry, in which patent protection was considered less important. That raising venture capital is facilitated in many fields, and perhaps especially in biotechnology, when exclusive patent rights either exist or can be anticipated, appears to be the prevailing view.

The availability of venture capital has been highly cyclical. Danzon et al. show that when venture funds are forthcoming in only small amounts on capital markets, biotechnology startup firms tend to compensate by entering cooperative arrangements with and receiving funding from traditional pharmaceutical manufacturers.[23] From a survey of 118 U.S. startup companies, Gans et al. found that biotech-

nology companies entered into alliances—defined as either cooperative research, testing, and/or marketing agreements with larger incumbent firms, or outright mergers—far more frequently, in 55% of the cases, than did startups operating in other technological fields.[24] Sixty-five percent of the surveyed startup companies had at least one U.S. patent; the average number of patents per firm was 7.68. Gans et al. reported furthermore that firms with at least one patent to license or sell were significantly more likely to enter into alliances than firms without patents, holding other variables such as the field of technology and the source of initial financing constant. Thus, patent protection appears to facilitate access to capital not only directly but also through inter-firm alliances.

Against this evidence we must consider a conflicting strand from the Carnegie–Mellon survey of 1,478 industrial R&D executives.[25] As we have seen earlier, patent protection was not considered a very important means of securing the benefits from company product innovations in the average industry, although the pharmaceutical industry, including biopharmaceuticals, was an exception. However, Cohen et al. observe that larger firms found product patents to protect their innovations more effectively on average than did smaller companies. When they eliminated from their sample all responding firms with sales of less than $500 million, patent protection turned out to be the most important means of securing the benefits from product innovations in seven broad industrial groups (including drugs) out of 33. Their tentative rationalization of this result is that the "costs associated with patents, particularly their defense, disproportionately dissuade small firms from availing themselves of patent protection."[26] From this conclusion one might speculate that the relatively high propensity of startup firms possessing patents to enter cooperative relationships with better-established enterprises may stem not only from the need for funds, but also from perceived vulnerability vis à vis the patent portfolios of larger rivals.

For investments to develop new pharmaceutical and biological therapies, it seems clear that having patent protection is in most cases quite important. Without it, startup firms lacking robust internal cash flow are likely to have difficulty financing their research and testing programs. And for more mature enterprises, the cash flows foreseeably available to be invested inter alia in R&D would almost surely be limited, leading to lower R&D investments.[27]

PATENTS AND BASIC BIOLOGICAL RESEARCH

The emphasis thus far has been on the role of patent rights in encouraging the commercial development of inventions from their early inchoate stages, and in particular, in carrying out the expensive clinical trials necessary to market new therapeutic entities. However, the principal concern in this report is not whether promising molecules should receive patent protection, but whether patent rights should be extended to cover human gene sequences, which may, among other things, provide a pattern for the synthesis of useful molecules, i.e., one or two steps earlier than the drug development stage. Thus, we must explore how patent rights affect incentives to carry out research on gene sequences and their links to subsequent therapeutic entities, and how the existence of genome patents affects investment in those "downstream" entities. We begin with the first of these questions.

A map of the human genome provides scientific knowledge about the endowments of nature. Scientific knowledge is viewed by economists as the quintessential public good, that is, something whose use by one individual does not necessarily reduce the amount available for consumption by others, and whose use by anyone, once it is made known, is difficult to prevent except through special legal institutions such as patents. This view of knowledge as a public good was not original to economists. Two centuries ago, Thomas Jefferson fully anticipated the notion[28]:

> If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea, which an individual may exclusively possess as long as he keeps it to himself, but the moment it is divulged, it forces itself into the possession of every one, and the receiver cannot dispossess himself of it. Its peculiar character, too, is that no one possesses the less, because every other possesses the whole of it. He who receives an idea from me, receives instruction himself without lessening mine; as he who lights his taper at mine, receives light without darkening mine. That ideas should freely spread from one to another over the globe, for the moral and mutual instruction of man, and improvement of his condition, seems to have been peculiarly and benevolently designed by nature.

From this, it is reasonable to infer, Jefferson, whose duties as Secretary of State made him the first U.S. patent examiner, would have been skeptical about awarding patents on such basic scientific discoveries as the detailed structure of the human genome.

Jefferson lived, however, in a time when science was mostly a low-cost avocation pursued by amateurs. Now science, especially biological science, is a highly-organized enterprise pursued at considerable expense by both profit-oriented and nonprofit institutions. The presumption against patenting basic information about natural phenomena might be overcome if the prospect of securing exclusive property rights in scientific discoveries for a limited period of time served as a necessary or important incentive to making investments in scientific research, and in particular, if it served

to elicit discoveries that would not otherwise be made or to accelerate the pace at which scientific knowledge advances.

Scientific research directed toward advancing knowledge per se has tended to be the province of academic institutions and government laboratories. In 1980, only 2.8% of all research and development performed by U.S. industrial enterprises was reported to be basic scientific research. By 1998, the basic research share of industry's total R&D outlays had risen to 6.4%.[29] In 1980, industrial enterprises performed 13.7% of all reported basic scientific research in the United States; by 1998, their share had risen to 28.4%. Increases in biological research probably played a substantial role in this heightened industry attention to basic research. How large that role was is uncertain because of sparse data. From the available data on pharmaceutical and biotech company[30] R&D expenditures, and assuming that 20% of biotech specialists' R&D outlays were for basic research, I estimate that total industrial basic research expenditures in pharmaceutical and biological therapy areas in 1998 amounted to roughly $4 billion, a not inconsiderable amount. Better estimates will be possible when the National Science Foundation publishes industrial biotech R&D data, sought for the first time in its survey covering calendar year 2001.

Industrial enterprises pursue basic scientific research not only to secure priority in identifying promising product development candidates, but also to maintain capabilities that complement and enrich product development efforts, to attract superior talent, and to open up windows to the outside scientific world through ongoing surveillance of relevant scientific advances and direct contacts with academic investigators. Some unknown but undoubtedly considerable fraction of these motives for performing industrial basic research would exist whether or not scientific discoveries could be patented.

The other main source of support for basic research is government. In 1999, the NIH obligated an estimated $8.63 billion for basic research. Of this total, approximately $1.4 billion was for intramural research, most of the remainder going to support academic research or ($360 million) basic research in industry.[31] In the same year, 40.6% of the NIH research budget is said to have been focused on biology (as distinguished, e.g., from medical sciences and chemistry).[32] Thus, I estimate that the NIH devoted roughly a half billion dollars to intramural basic research on human biology in 1999.

In 1999, federally-funded expenditures on basic and applied research in the biological sciences at U.S. academic institutions totaled $4.23 billion.[33] An additional $1.8 billion of biological research at academic institutions was funded by non-federal sources, including state governments (e.g., from general state university support funds), university overhead, grants from industry, and grants from foundations (which probably did not exceed $30 million).[34] A large fraction of these expenditures undoubtedly entailed basic research, although the exact proportion may be unknowable, since distinctions are difficult to make. It seems clear, however, that in the biological sciences, academic basic research effort has been on the same order of magnitude as my estimate of industrial basic research effort, a marked departure from the more typical preponderance of academic over industrial basic research activities.

In the biological sciences, the fraction of all academic R&D funded by the federal government declined from 72.6% in 1979 to 67.4% in 1986 and 64.3% in 1997.[35] The proportion financed by other sources obviously had to rise to fill the gap, although no detailed breakdown is available. In 1975 grants from private industry to academic institutions lagged far behind three other sources. However, industry funding grew more rapidly than the other sources, at an average rate of 7.8% per year, so by 1998, it was almost as important as state and local governmental funds, contributing 7.2% of total academic R&D support.

For academic investigators working under government research grants, patent rights are relevant not only because they make it possible to license out commercially promising inventions for private-sector development, among other things yielding royalties and other payments shared between inventors and university budgets, but also because they encourage information sharing between academic and industry groups and financial support from industry. Since the Bayh–Dole Act was passed, a host of universities have established technology licensing offices to screen the inventions of university staff and negotiate licenses with outside firms. Between 1980 and 1998, the number of U.S. invention patents awarded per year to American universities rose from 390 to 3,151.[36] A survey of 112 business units licensing university inventions between 1993 and 1997 revealed that firms that had increased their licensing of university inventions during this period doubled their research grants to universities over the same interval.[37] Selecting from a menu of reasons to explain why they had increased their funding of university research, the surveyed companies emphasized what they perceived to be a change in universities' receptiveness to licensing and research agreements. Thus, the relatively rapid growth of industrial financial support for academic R&D during the past two decades is probably due in part to the changes in university patenting practices triggered by the Bayh–Dole Act. In this respect, an indirect link from patent rights to the support of research that yields scientific discoveries, which in turn facilitate commercial developments, is seen. However, since industrial enterprises financed 4.1% of academic R&D outlays in 1980, before the Bayh–Dole Act had its effects, the funding increment attributable as of 1998 to patent policy changes would appear at most to have been on the order of three percentage points.

RESULTS FROM A SURVEY OF GENE SEQUENCE PATENTS

In order to determine the extent and technological coverage of genome patenting, an analysis of recent patent grants was conducted. The U.S. Patent Office's computerized database was searched for all patents issued between September 1, 1998, and June 5, 2001, whose abstracts contained the terms "DNA" plus "sequence," or "nucleic acid" plus "sequence."[38] Altogether, 1,770 such patents were retrieved, 1,199 from the DNA plus "sequence" search and, after elimination of duplicates, 571 from the "nucleic acid" plus "sequence" search.[39]

To keep the analysis within feasible bounds, and because U.S. policy concerns focus primarily on the R&D incentives of domestic actors, the first step in the retrieval procedure was to separate out patents assigned to non-U.S. entities. However, some of those foreign-assignment inventions were made by U.S. inventors. Those for which at least half of the listed inventors were U.S. residents were kept within the domestic sample; those with more than half of the inventors residing abroad were considered foreign. After this division, 620 of the patents were classified to be of foreign origin and 1,150 of U.S. origin. The foreign-origin patents came from a total of 24 nations, with counts for the six leaders as follows:

Japan	151
Canada	78
France	73
Great Britain	64
Germany	49
Denmark	46

An attempt was made to classify the foreign-origin patents according to the types of organizations to which they were assigned. An estimated 65% came from companies, 18.3% from free-standing laboratories (usually government-owned and/or nonprofit), and 8.1% from universities. The university share, we shall see, is much lower than the comparable share for U.S. universities, no doubt reflecting the differential impact of the Bayh–Dole Act on U.S. universities' propensity to seek patents.

For the U.S.-origin patents, a much richer three-way classification was attempted. From inspection of the published patents, each patent was placed within one of several categories: those pertaining to the human genome, to animal genomes, plant genomes, or microorganism genomes (e.g., viruses, bacteria, and fungi); those that were methods of sequencing DNA and related genetic material; plus an "other" category that encompassed mainly uses of oligonucleotides and DNA or RNA primers (i.e., short nucleotide sequences). For patents that pertained directly or indirectly to humans, further distinctions were made among DNA sequence claims with or without expressed proteins; preventive inventions (e.g., pertaining to vaccines); diagnostic inventions; gene therapy inventions; other human treatment inventions; and a catch-all category. Since many patent specifications anticipated multiple uses, multiple codings were frequently made. From the patent assignee names, patents were classified as to whether they were assigned to a company, a university, a hospital or nonprofit research institution; or a federal, state, or local government agency; or were retained by the inventors themselves (presumably because an employer chose not to exercise its assignment rights). Within the company category, further breakdowns utilizing standard business reference works were made among *Fortune 1000* corporations, other companies large enough to be covered in *Moody's Industrials*, (mostly) smaller companies whose stocks were traded over-the-counter, companies with no known publicly-traded stocks, and foreign companies (usually, since most or all of the inventors were U.S. residents, for inventions made by their U.S. branches). Because the sample began with patents issued in late 1998, the company type distinctions were made to reflect company status as of early 1999.

Figure 2 shows the distribution of sample patents by broad use categories. Among the 1,150 U.S.-origin patents, 414 were coded as primarily for human use. The second-most-frequent-use category comprised methods of analyzing and sequencing DNA, i.e., research tools. Only two of these were found to have direct applicability to human beings. To be sure, better research tools have important indirect implications for human welfare; no attempt was made to speculate on them in the codings. Human-use implications were more frequent, but not ubiquitous, with patents on microorganisms. Other microorganism uses include industrial fermentation processes. Within the microorganism category, patents

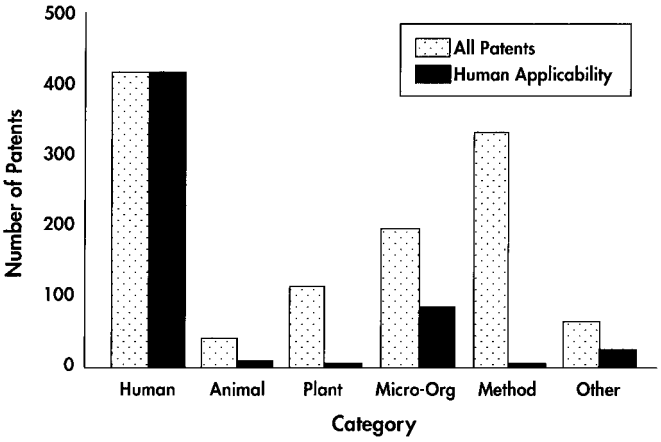

Figure 2. Distribution of patents originating in the United States, by broad categories.

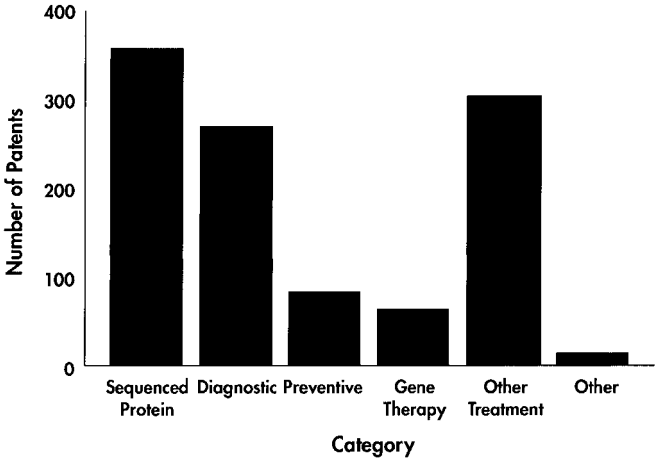

Figure 3. Distribution of human-use patents by specific use.

pertaining to virus structure had the largest fraction (60%) of anticipated human uses.

Altogether, 528 patents, or slightly less than half of the total U.S.-origin sample, were coded as having potential human uses. Figure 3 displays how these uses were distributed. Since multiple coding was allowed, 1,116 human-use applications were coded altogether for the 528 patents.

The cohort of most direct relevance to the question of whether genome sequence patents should be granted is that pertaining directly to human gene sequences, in nearly all cases, with the proteins the sequences were believed to express included as part of the patent specification. Three hundred sixty-three patents, or a bit less than a third of all sampled U.S.-origin patents, claimed human genome sequences. Among these, only six came anywhere near claiming a DNA sequence without additional expressed protein or other utility claims, but none was without some assertion of potential therapeutic or other utility. For the 363 human DNA sequence patents, 255 were coded as also having treatment applications, 212 as having diagnostic applications, 40 as having application in gene therapy, and 24 for preventive applications. Sixty-eight claimed human genome sequences, usually with expressed proteins, without any additional explicitly coded human uses.

The other most frequently claimed uses of the inventions were for treating illnesses, both through gene therapy (65 patents) and by other means, and for diagnosing genetic defects or other maladies. Preventive applications, such as the development of vaccines, were cited in a total of 84 cases.

Figure 4 shows the shares of patents originating from the various kinds of organizations to which the sample patents were assigned. The R&D advantages traditionally attributed to "big business," including "Big Pharma," are not in evidence for our sample. Companies listed among the *Fortune* 1000 for the year 1998 and/or included among the large companies covered by *Moody's Industrials* originated relatively small shares of the sample patents. The principal exception was for plant DNA patents, in which Monsanto plays a leading role. Most of the foreign companies receiving patents within the U.S.-origin group were also relatively large, or at least, large enough to maintain laboratories in the United States. Their greatest relative strength also materialized in plant DNA patents (e.g., Novartis of Switzerland), followed by patents on microorganisms (in which Novo Nordisk of Denmark is a world leader).

Universities led in the receipt of human-use patents (the

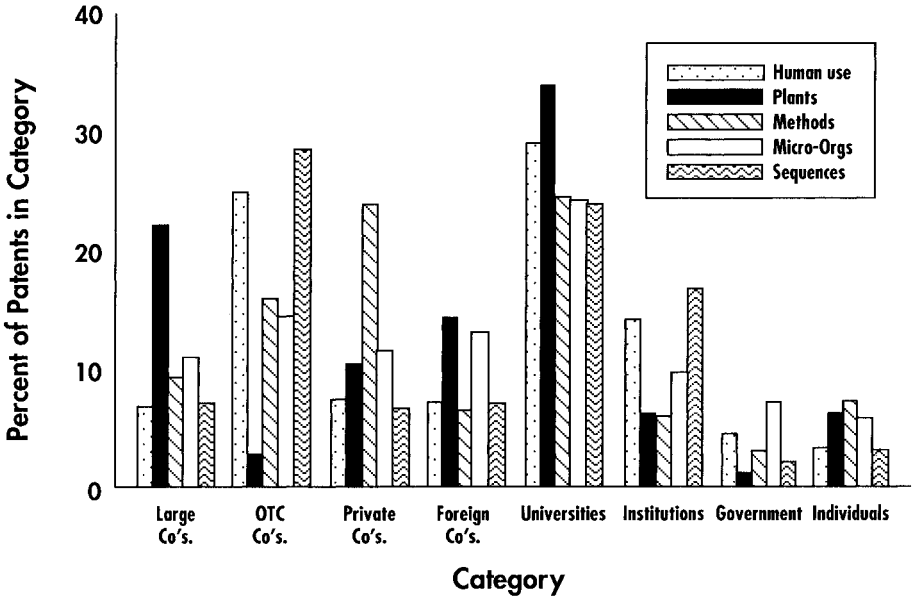

Figure 4. Organizational shares of patenting activity, by category.

first bar in each organizational cluster), which includes some patents double-counted under other categories of Figure 4, and indeed in all categories but one. In second place as originators of human-use patents, with 137 patents, were companies too small to be listed in the *Fortune* 1000 but well enough established to have their shares traded on the NASDAQ OTC market.

The OTC companies were the most prolific originators of patents that included human DNA sequence claims, with 108 such patents. The second rank among DNA sequence patents was held by universities (91 patents); third rank by hospitals and nonprofit research institutions (63 patents), fourth place by the U.S. affiliates of foreign corporations (29 patents), fifth place by large U.S. corporations (26 patents), and sixth place by private companies without publicly traded securities (24 patents).[40] The private-company group appears to have a noteworthy comparative advantage in generating DNA sequencing method, i.e., research tool, inventions.

The following list extracts from the organizational data in a different way, listing the leading eight corporate patent assignees in descending order of the total number of U.S.-origin sample patents received. The list presents both total patents and human-use patents.

Incyte Pharmaceuticals:	58 total, 56 human use
Human Genome Sciences:	35 total, 35 human use
Novartis (Switzerland):	17 total, 0 human use
Monsanto:	16 total, 0 human use
Novo Nordisk (Denmark):	15 total, 1 human use
Genencor:	15 total, 0 human use
Bayer (Germany):	13 total, 13 human use
Roche (Switzerland):	13 total, 3 human use

The largest number of patents went to Incyte Pharmaceuticals, traded over-the-counter, whose Worldwide Web home page claimed that the company is a leading provider of genomics information. Incyte was also said to be leveraging its database to make significant therapeutic discoveries. In second position was Human Genome Sciences, also traded over-the-counter, whose home page states that the company intends to commercialize novel compounds for treating human diseases based upon the identification and study of genes.[41] The posture of OTC-listed Genencor, with no human-use patents, seemed puzzling at first glance. However, its home page explains that the company's main products are industrial enzymes used, e.g., to reduce cellulose and grains, even though Genencor also works on human immunology problems. Although Hoffmann–LaRoche is best known as a leading pharmaceutical and vitamin supplier, its DNA patents (not including those assigned to its partly-owned Genentech subsidiary) were distributed across a broad array of functional categories.

The prospect of obtaining patent protection is probably most important to the financing and R&D investment incentives of small companies without publicly traded securities. Next most sensitive in this respect are likely to be the companies with securities traded on OTC markets. Here, however, a distinction should be made, which could not be made in the organization type codings, between fledgling companies with no commercial products providing internal cash flow and those (such as Chiron and Genzyme) with well-established product sales.[42] From the evidence at hand, it would appear that at most about 36% of the DNA sequence patents, or 132 patents in total, and 34% of the human-use patents defined more broadly, originated from these especially patent-sensitive organizations. Since some of the OTC companies have strong internal cash flows and interest in ensuring their survival through vigorous R&D programs, the realm of high patent dependence is probably smaller than these estimates.

To be sure, some research and hence patents from universities and not-for-profit institutes, which together dominate the surveyed patent categories, may depend upon R&D grants from industry, which in turn may be conditioned by the expectation of patent licenses, often exclusive. On this the direct evidence from our survey is sparse. Fifty-two of the patents in our U.S.-origin sample had multiple assignees, which means that the underlying research was jointly conducted or that a second assignee provided important financing. Among the 37 jointly-assigned patents in which a university was one assignee, the other assignees were private domestic companies in 14 cases, foreign companies in one case, other universities in eight cases, hospitals or free-standing research institutions in 14 cases, and government agencies in two cases. Among the 19 jointly-assigned patents with a hospital or research institute as one assignee, private companies were a second assignee in two cases. Thus, the cohort of not-for-profit institutional patents with direct private company co-assignment is small. It is certainly much smaller than the domain of all university and hospital R&D financed by industry, since split patent rights assignment is neither necessary for, nor customary in, the financing arrangements linking not-for-profit and private-sector industrial organizations.

One further element of perspective must be added. As we have seen, our survey covering 33 months of patent issues yielded 1,770 patents with the required combination of "DNA" or "nucleic acid" plus "sequence" terms in their abstracts. This, of course, is a subset of all patents resulting from biological research and development. It is difficult to tell how large the relevant patent universe is. Statistics from the U.S. Patent and Trademark Office reveal that in calendar years 1999 and 2000, 10,124 patents were issued in the four patent classes most closely corresponding to our sample:

class 435 (molecular biology and microbiology), 436 (immunological testing), 504 (plant protecting and regulating compositions), and 530 (natural resins, peptides, proteins, lignins, and reaction products thereof).[43] Excluded from this count are the large number of patents in traditional pharmaceutical classes, including class 424 (bio-affecting and body-treating compositions, with 5,844 patents). Within our sample, 1,185 patents were issued during the comparable years 1999 and 2000. Thus, our sample encompasses at most only one tenth of the biotech patent universe, and our sample of DNA sequence patents, one thirtieth of the relevant universe. Assuming no differences in the propensity to patent per million dollars of R&D, a point on which little information exists,[44] the research and development from which our sample of patents stemmed must also have been a relatively small fraction of all the R&D, academic and industrial, carried out in the biological disciplines. Clearly, as debate proceeds over how much patent protection human DNA sequences should receive, it must be recognized that it directly affects only a modest fraction of all research and development activity in biology.

INSIGHTS FROM ECONOMIC THEORY

During the past three decades numerous articles and books have been published on the economics of patent policy. Many ask how patent grants might be fine-tuned under specific conditions to secure the maximum surplus of economic benefits from innovation, after deducting production, R&D, and legal costs. In practice, there is far too much uncertainty, and the institutional apparatus is far too clumsy, to follow the fine-tuning guidance provided by this theoretical work. Nevertheless, some useful but crude insights can be extracted.

The pioneering contribution was by William Nordhaus, now at Yale University.[45] Nordhaus asked how, assuming that innovators maximize the discounted present value of their expected profits from process (i.e., cost-reducing) innovations, government might set a patent life that maximized the surplus of *social* value (i.e., the combined surpluses realized by consumers and producers) less R&D costs. He found that the optimal patent life varied widely from one to 34 years, depending upon how easily cost reductions flowed from R&D efforts and the price elasticity of demand for the product whose production process was being improved. The "easier" it was to achieve cost reductions and the more price-elastic product demand was, the shorter the optimal patent life.

Prospect versus Rent-seeking Models

Nordhaus' initial theoretical model has been extended to deal with questions of optimal patent breadth (or scope), compulsory licensing regimes, and much else. The most important extension for our present purposes was the questioning of Nordhaus' implicit assumption that inventors had what Edmund Kitch later called exclusive "prospect" rights to undertake their inventions.[46] That is, Nordhaus assumed that the firm conducting R&D on a particular problem was the only such firm working on the problem, and it could therefore choose the intensity of R&D effort that maximized the time-discounted surplus of what economists call quasi-rents (i.e., the surplus left over after production and marketing costs are subtracted from product sales) over alternative levels of R&D investment. This implied that the firm in question did not have to worry about other firms conducting parallel R&D and possibly preempting its invention.

An alternative view of the R&D world was first proposed by Yoram Barzel.[47] He argued that inventors had to compete with other inventors for priority and hence temporary monopoly profits from the relevant invention. Invoking an assumption from the theory of competition in price-setting, this inter-firm competition would drive R&D costs upward until the aggregate net profit from inventive activity, netting the probability-weighted costs of the losers against the gains of the winner, would on average be zero. This perspective falls under a larger set of contributions known as the theory of rent-seeking. However, the standard view of rent-seeking is unfavorable, e.g., visualizing lobbyists increasing their costly efforts to secure a particular legislative outcome until the net gains are zero. This view, I shall argue in a moment, is too pessimistic, and so one might characterize Barzel-type R&D escalation as virtuous rent-seeking.

Early applications of the Barzel view to the Nordhaus theory assumed to the contrary that rivalrous and pejoratively duplicative R&D activity was purely wasteful.[48] From this perspective, the profit (or more precisely, quasi-rent) gains from extending patent lives and spurring more expenditure on R&D were mostly dissipated as costs, and with smaller net gains, much shorter patent lives—e.g., in the range of a half year to one year—were warranted.

It is almost surely wrong, however, to view the competitive escalation of R&D as intrinsically wasteful. Especially at the early concept-forming stages of technological research, there is likely to be substantial uncertainty about the approach that will both yield technical success and best meet consumer demands.[49] The pursuit of multiple research paths increases the likelihood that good solutions will be found, and for both statistical and behavioral rivalry reasons, it accelerates the achievement of an acceptable solution. The greater the payoff from finding a solution, the larger is the optimal number of parallel paths, especially when ex ante uncertainties are substantial.[50] Thus, in the top-priority U.S. atomic bomb development program during World War II, five costly parallel paths to the separation of fissionable ma-

terials and two approaches to bomb design were pursued. Progress toward therapy for AIDS patients was undoubtedly accelerated by the large number of researchers attracted to the problem because of its enormous social importance. Also, since different researchers are likely to pursue qualitatively different approaches to a problem, competition among groups makes it likely that superior solutions will be found, or in the case where numerous solutions have merit, that the diversity of consumer wants will be more completely satisfied.[51] The large number of molecules with which anti-AIDS drugs can be formulated provides an example.

An Aggregate Perspective

Figure 5 provides a schematic illustration of the two polar theoretical models, their implications, and the implications of weaker or stronger intellectual property regimes. The heavy solid line labelled *C(RD) Function* is what William Nordhaus originally called an invention possibilities function. It shows how the number of new biological entities (NBEs) carried successfully through clinical testing depends upon the amount or cost of R&D done. With no warranty that the parameters chosen are correct, it is drawn to exhibit diminishing returns in the R&D–NBE relationship, at first weakly and then strongly. Diminishing returns set in because at any moment in time the progress of science offers a limited menu of promising therapeutic strategies, and as the level of R&D effort is increased, there will be more near-duplication of others' efforts and the pursuit of less promising technical possibilities, in both instances leading to a smaller incremental new product yield.

Three alternative quasi-rent regimes are illustrated, one (Q_1) assuming relatively weak intellectual property laws, another (Q_2) patents of longer duration and broader scope, and the third (Q_3) an extension of the intellectual property regime from the developed nations to the entire world, as under the TRIPS section of the Uruguay Round treaty. All three are also subject to diminishing marginal returns, since, despite huge uncertainties, profit-seeking enterprises will try to target first the biological entities with relatively large prospective payoffs and address lower-payoff projects only with relatively generous R&D budgets.

Under a Nordhaus or "prospect" view of the world, firms choose projects without competitive challenge so as to maximize their net profits, shown as the horizontal distance between the R&D cost function C(RD) and the relevant quasi-rent function (the dot-dot-dashed lines). With low-payoff quasi-rent function Q_1, the profit-maximizing equilibrium (at point N_1) entails R&D spending of roughly $1.5 billion, leading to seven new products per year and quasi-rents of $2.6 billion, with net discounted profits of $1.1 billion. As potential quasi-rents rise to Q_2 and then to Q_3,

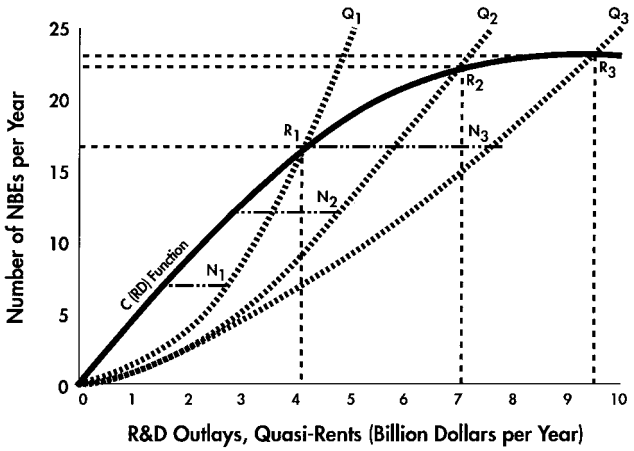

Figure 5. Illustration of how stronger patent rights affect NBEs (new biological entities) discovery. The horizontal axis measures two variables, both scaled in billions of dollars per year-the amount spent on biopharmaceutical research and development (R&D) and the discounted quasi-rents (i.e., therapeutic agent sales less costs of production and marketing) resulting from that R&D. The vertical axis measures the number of NBEs entering the market per year as a result of R&D.

R&D spending rises to $2.75 billion and then to $4.1 billion, leading to 13 and 17 new products per year at equilibrium points N_2 and N_3, respectively, with net profits of $2.0 billion and $3.4 billion.

R&D competitive in the Barzel sense leads to substantially more R&D, indeed up to the point where quasi-rent and R&D cost functions intersect so that their net value is zero, at equilibria R_1, R_2, and R_3. More new products will therefore be forthcoming on average, but with diminishing returns —e.g., 17 per year in the relatively weak intellectual property regime Q_1, 22.5 in regime Q_2, and one additional product in the regime Q_3 with the most wide-ranging scheme of intellectual property rights.[52]

Nearly-simultaneous Discovery

Between these two polar extremes, the rent-seeking model is almost surely the more realistic. An implication deserves repeated emphasis. Especially in those areas of potential therapy with high possible payoffs—i.e., where anticipated quasi-rents are well in excess of expected R&D costs—there is likely to be a good deal of what appears to be simultaneous or near-simultaneous discovery and a considerable number of NBEs meeting similar but not identical therapeutic needs. Indeed, the histories of science and technology are replete with additional chronicles of basic discoveries and technological inventions made more or less simultaneously—so much so that the distinguished sociologist Charles Ogburn suggested that some basic inventions might be "inevitable."[53] The work that led to the discovery of nuclear fission by

Hahn and Strassmann was being pursued along similar tracks in numerous research centers, leading physicist Robert Wilson to remark that "nuclear energy was a time bomb set for the human race, and eventually the human race would have had to reckon with it."[54] James Watson and Francis Crick correctly perceived themselves to be in a race to discover the structure of DNA with Maurice Wilkins and Rosalind Franklin at the University of London and Linus Pauling at California Institute of Technology.[55]

To conclude from this "softly deterministic"[56] view of the discovery process that *most* discoveries will be made fairly quickly by someone else if the credited discoverer were absent from the scene goes too far. Even in modern times, the genius of a Newton or an Einstein could make a difference of decades in at least some cases. But it is fair to say that the greater the salience attached to a problem by the scientific or technological community, determined in part by the importance of the problem and in part by the agenda-setting effect of prior knowledge advances, the more likely it is that a solution will emerge from one group or another within a few years. Exceptions include those challenges, such as counting the flux of neutrinos, exploring Mars, or harnessing the power of hydrogen fusion, requiring such enormous resources that at most one or a very few teams can work simultaneously, and then only if the climate of political and hence financial support is favorable. I consciously exclude the case of sequencing the human genome, on which the presence of high-stakes competition appears to have advanced the inevitable by at most a few years.

Sequential Invention and Patents

Mapping human genome sequences is important in the worlds of medicine and commerce because it helps point the way toward useful inventions—the synthesis of therapeutic molecules or the repair of existing molecules, probes to identify and perhaps correct genetically-based diseases, etc. The chain of discovery might also be reversed, e.g., from the identification of a genetically-based disease, one can pinpoint the genome sequences shared by persons with that disease and hence target the search for corrective therapies more narrowly. In either case, later discoveries and inventions, to paraphrase Newton, build upon the shoulders of prior discoveries. Scientific and technological advances are temporally linked.

The relationship between discoveries from basic research and the development of commercialized follow-on inventions is particularly close in biology. Surveying 108 business enterprises, Edwin Mansfield asked research laboratory heads what percentage of their new products introduced between 1986 and 1995 "could not have been developed (without substantial delay) in the absence of recent academic research."[57] For all surveyed industries, 15% of the new products were related in this strong way to prior academic research. In drugs and medical products, the proportion was 31%, the highest for any of seven reported industry groups. An additional 13% of commercialized drug and medical products were said to have received "substantial aid" from recent academic research.

A schematic view of these dynamic linkages is provided by Figure 6. Consider a key precipitating discovery, *A*, emerging from either academic or industrial basic research efforts. *A* itself undoubtedly builds upon the shoulders of predecessor discoveries, indicated by the dotted arrows to the left of *A*. But what is of most immediate interest is the impact *A* has on the subsequent discovery and/or development of B_i (and other products $B_1 \ldots B_N$, which are ignored here). How *A* affects *B* can vary over a two-dimensional spectrum: at the extreme, *B* may be impossible without *A*, or in less extreme variant cases, the existence of *A* can speed the development of *B* or lessen the cost of developing *B*, or both. *B* in turn sets the stage for further improvement developments, shown by the dotted arrow to the right of B_1 but these too are ignored here.[58]

The crucial question is, How do varying degrees of patent protection affect incentives for discovery and development at the sequential stages of this model?[59] The problem begins with recognition that *A* confers upon the developers and users of *B* (and subsequent inventions) what economists call "external benefits," that is, benefits that would not be realized in a regime of no intellectual property rights by an entity whose work gave rise to *A* but not subsequent innovations. In other words, the benefits are realized externally from whatever commercialization *A* achieves. If *A* is indispensable to the development of *B*, a correct assessment of the benefits from *A* includes not only any net benefits from the sale of products based directly upon *A*, but also the total surplus of consumer plus producer benefits less R&D and production costs from subsequent innovations such as *B*. If *A* merely accelerates the development of *B* or reduces the cost of developing *B*, the external benefits from *A* include the value to consumers of having *B* earlier and/or the (ap-

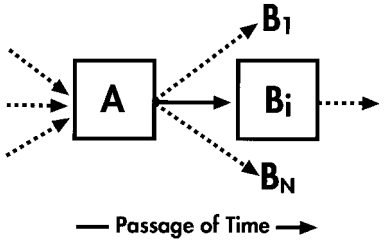

Figure 6. Time phasing of interdependent sequential interventions.

propriately discounted) reduction of *B*'s underlying R&D cost.

A fundamental proposition of economics is that in the presence of such "externalities," markets may fail to send the signals needed for a proper allocation of resources. An extreme case arises when, as is not uncommon in scientific discovery for the reasons articulated by Thomas Jefferson, *A* has no commercial value in its own right, but is valuable only because of the inducement it provides to the development of *B*. Or in an only slightly milder case, the commercial exploitation of *A* alone yields profits (or more accurately, quasi-rents) too small to warrant the investment needed to discover *A*, but which, when added to the external benefits from *B*, more than justify that investment.

Instruments used by government to help solve this problem include research and development subsidies and the awarding of intellectual property rights. A principal rationale of the research grants system is that scientific discoveries confer substantial social benefits that cannot be "internalized" by the persons performing the desired research, which therefore has to be supported by an entity—the government or a philanthropic institution—that can take a broader society-wide view. As we have seen, roughly half of recent U.S. basic research in biology has been supported in this way. An alternative is to bestow upon the entity investing in the discovery of *A* intellectual property rights of sufficient breadth and duration to let the rights holder extract enough of the benefits from *B*'s commercialization to repay or, to compensate for uncertainty, perhaps more than repay, its investment in *A*. These rights could be minimal, e.g., a natural head start toward developing *B* protected by temporary secrecy or non-transferable know-how from work on *A* that gives *A*'s research team an advantage over others in the development of *B*.[60] Or they might be embodied in patents whose scope and duration cover improvement inventions such as *B* along with the immediate subject matter of *A*. It is here that the controversy over human gene sequence patents reaches its most acute focus.

One possible rights-based solution is to give the discoverer of *A* sufficiently broad and enduring rights totally to exclude others from commercializing derivative inventions such as *B*. Under the "prospect" theory of patent rights, the organization discovering *A* would have exclusive rights to "prospect" for *B*-type inventions, often with the further explicit or implicit assumption that by virtue of having discovered *A*, that entity is most competent to do the follow-on work. This view is almost surely wrong. For one, the kinds of competence needed for follow-on work may be quite different from what was needed to make the initial discovery. The different capabilities of university researchers as compared with industrial R&D teams are an obvious example. Biotech startup firms are relatively strong in basic research and discovery activities, but commonly lack clinical testing and (especially) marketing skills. This imbalance leads them to license their patents to, cooperate with, or sell out to well-established pharmaceutical enterprises. Also, the directions in which a discovery may be applied are often myriad, and a single entity is not likely to perceive and back financially all the various derivative development possibilities.[61] It is more the norm than the exception in the history of technology for the firms introducing significant derivatives of and improvements upon a basic discovery to be other than the original discoverer.[62] To ensure that all valuable commercial derivatives of a discovery are exploited, there is no better maxim than that of Mao Tse-tung, "Let one hundred flowers bloom."

A solution to this problem is to confer patent rights that cover follow-on *B*-type developments, but to allow or even (through governmental policy) encourage the licensing of rights to utilize the science or technology underlying *A* to other entities wishing to build upon *A*'s shoulders.[63] Licenses might be non-exclusive, as in the licensing of the basic Cohen–Boyer gene splicing patents by Stanford University to several hundred users,[64] or exclusive, as might be necessary when development of a therapeutic molecule—requiring clinical testing outlays measured in the tens of millions of dollars—follows directly from a scientific discovery. Here too, however, bad things can happen. Determining the division of rents between the original discoverer and follow-on developers requires bargaining, and solutions may materialize that either stalemate further progress or undermine incentives for additional private investment in basic discovery.[65] Bargaining stalemates are especially likely when the discoverer of *A* has broad rights covering follow-on developments, but when *A*, like many basic scientific discoveries, has little or no commercial value by itself.[66] Then the follow-on developer, which may have to invest substantial sums in development and testing, may insist upon the lion's share of the economic rents attributable to its undertaking, while the discover of *A*, with the power to block development completely, demands an incompatibly large share. Merges and Nelson document numerous important cases in which such patent stalemates significantly delayed, or without permissive regulatory interventions could have blocked, desirable technological advances.[67] If the balance of power lies too much on the side of the stage-*A* discoverer and too little on stage-*B* developers, there could be too little investment in practical implementations $B_1 \ldots B_N$ and too much (at least in relative terms) in early-stage research. We address in a subsequent section the kinds of government policy interventions that might minimize the resource allocation distortions resulting from such problems.

The A → B schema, however, may present too simplified a picture of the relationships between early-stage discovery

and commercialization of the derivative inventions. A National Science Foundation–backed study of the scientific and technological "events" that led to five new technologies, including the first oral contraceptive pill, demonstrated the large number of research streams that had to converge to yield ultimate practical embodiments.[68] For "the pill," approved in 1960 by the Food and Drug Administration, many of the antecedent events occurred between 1940 and 1960, and if they had received strong patent protection, the patent assignees might have been in a position to block or levy a heavy toll on the final development effort. The compression of time spans between scientific advance and commercialization since then means that even more potentially blocking events might occur, each with 20-year patent rights extending into the period of feasible commercial innovation for biotechnological advances.

When numerous patented technologies are precursors to an innovation, each seeking to extract substantial royalties from derivative efforts, the combined demands could accumulate to a level at which investments in commercialization or next-step research are seriously impeded.[69] The problem is analogous to conditions on the Rhine River during the 18th Century. Over the 85-kilometer stretch between Mainz and Koblenz in 1780, there were nine toll stations, and from there to the Dutch border, there were 16 more.[70] Each acted as a partial monopolist over the rights of traffic to travel the Rhine by its fortified *Raubritter* (robber baron) castle, seeking to extract the profit-maximizing toll from passers-by. The multiplication of tolls suppressed most of the traffic that otherwise would have traversed that artery—absent tolls, the least costly means of travel in an era of hopelessly bad roads —and thereby impeded German economic development. Not until 1831 were treaties concluded that allowed essentially free navigation and hence full development of the waterway's potential.

One way of breaking such impasses is for the participants in an industry to enter into cross-licensing accords under which each patent holder contributes its patents to a generally available pool, with or without modest compensation, on the understanding that all others will behave similarly. This was done at government insistence in the early years of the aircraft and semiconductor industries.[71] More recently in semiconductors, cross-licenses have again been the solution to a logjam comprising thousands of patents, any of which might emerge to challenge or even enjoin a firm's right to produce a complex microprocessor or application-specific integrated circuit.[72] In biotechnology, the asymmetry of relevant actors' positions—ranging from university scientists through genome-researching firms, vector providers, and instrumentation makers to specific biopharmaceutical developers—is likely to make it more difficult to find a sufficient community of interest to organize comprehensive low-royalty cross-licensing.[73] Even in semiconductors, market power and utilization asymmetries between general-purpose semiconductor producers, microprocessor specialists, and computer makers led to bitter and expensive litigation, resolved in part through Federal Trade Commission intervention.[74] Thus, there is a genuine danger that strong and extensively overlapping patent positions could impede the progress of therapies based upon molecular biology.

POLICY OPTIONS

Various alternative policies might be pursued toward the patenting of human gene sequences. Thus far, it would appear, the U.S. Patent and Trademark Office has not been issuing patents for human DNA sequences without additional claims showing their utility, e.g., through identification of the proteins they express or the medical treatments they enable. It is doubtful that allowing the patenting of DNA sequences without additional utility proofs would be beneficial to anyone other than persons who have such applications pending. Preliminary sequencing of the entire human genome has been completed, partly through a government-sponsored effort and partially at private initiative. Offering patent rights cannot motivate what has already been done; it can only confer windfalls for past investments made without the clear expectation that patent rights could be secured. Unless errors are found in the two existing sequence sets, any non-pathological sequences discovered in the future are likely to be barred from patentability by the existence of prior art. Therefore, changes toward more permissive patent standards are unlikely to induce positive effects, but could cause damage by impeding further research on links between gene sequences and medical treatment modalities.

Under the policies that have been adopted by the Patent Office, thousands of patents have been issued on human genome sequences and their claimed links to proteins, diseases based upon genetic defects, diagnostic probes, and the like. It is unknown how well founded the claims of utility are. Not allowing such patents in the future would discourage some research supported by private-sector investment. How much discouragement there would be is highly uncertain. As we have seen, the kinds of patents that did satisfy Patent Office criteria between 1998 and 2001 were only a small subset of all patents generated by industry and academic research in the biological fields—almost surely, after pharmaceutical patents are counted, less than 5–10% of the universe. At most half of the underlying research within that subset was by institutions whose efforts depend significantly upon patent protection; the rest was financed by government grants and/or motivated by well-financed companies' need to remain competitive by staying abreast of the relevant science and introducing new products. And if some research were

discouraged by policies that lean on the side of withholding basic genome sequence rights, it would not necessarily mean the perpetual loss of life-saving therapies. It is more likely that the seminal inventions would be delayed, not lost forever. To illustrate hypothetically, assuming a discount rate of 7%, a five-year delay in the availability of a key invention implies a social loss on the order of 30% relative to the discounted benefits that would be realized if the invention were available immediately.[75]

To ensure that promising future lines of research are not impeded, existing genome patent claims and any claims allowed in the future ought to be interpreted narrowly. In ruling whether basic patents have been infringed, the courts sometimes apply a doctrine of equivalents that permits a broad reading of the scope of the subject patents with respect to follow-on inventions,[76] and thus allows the original patent to extract royalties from, or even to enjoin, covered follow-on inventions. Alternatively, when a follow-on invention entails a substantial advance in the state of the art, the courts have the option of applying a reverse equivalents doctrine, construing earlier patents narrowly and hence finding no infringement. The technological achievements that will be built upon knowledge of the human DNA structure are likely to be so important to human welfare that it would appear preferable to interpret existing and future utility-based claims narrowly. For instance, there is reason to believe that a single DNA sequence, perhaps in combination with other sequences, will define more than one protein. If a patent claims a DNA sequence and some protein with proven or suspected functions in the human body plus "all analogous proteins that might be expressed," the benefits from ensuring that all new therapeutic opportunities are thoroughly explored would argue for a narrow interpretation of claims and the exclusion of speculative "analogous" claims. Construing claims broadly could block important avenues of research or appreciably increase their cost and risk.

Because it is vital to keep future research possibilities open to the maximum possible degree, legal precedents that exempt from injunction and the payment of royalties the use of patented technologies solely for research purposes are highly desirable. Their continuation apparently stands in jeopardy as a result of new appellate court interpretations.[77] The research exemption is an imperfect policy because of its asymmetry: the use of patented concepts or methods in research may carry no royalty burden, but patented research instruments, vectors, and the like are purchased at prices elevated by whatever monopoly power patent grants confer. And as our survey has revealed, a considerable fraction of the patents relevant to genome sequencing cover research tools. However, as has long been recognized, perfect intellectual property policies are unattainable. When research that has been exempted from patent claims leads to commercialized products whose production requires the use of others' patented technology, those patent holders will presumably be able to reach through and collect their toll on product sales.

Even when patent claims are interpreted to bind upon new and improved products developed by entities other than the patent owner, it is important to ensure that new product development is not blocked or severely retarded by a multiplicity of prior patent claims. Developing new products that enhance human health and welfare should not be like walking through a mine field, with risk of severe consequences should a loosely-related patent claim be infringed, or like cruising along the Rhine River in the 1770s, with toll collectors every few kilometers. Means of breaking possible bargaining stalemates should be in place. One possible policy, consistent with the Federal Trade Commission's settlement of the *Intel* case, would be to prohibit outright injunctions against drugs that have been accepted by the Food and Drug Administration for clinical testing and/or approved for marketing to humans. Rather, all disputes would be settled with a determination of damages, if infringement were found to have occurred. A stronger and preferable policy would be to require that disputes threatening the availability of new therapeutic modalities be settled through mandatory arbitration, with the standard of damages for infringement being "reasonable royalties" rather than the "lost profits" standard applied in infringement cases.[78] Therapeutic innovators found to be infringing background technology patents could be required to provide a cross-license to their own product improvement patents in exchange for a royalty-bearing license to the earlier background technology. This approach would strengthen the rewards to original patent holders while facilitating the maximum diffusion of biological technology for medical purposes.

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ENDNOTES

[1]"Profiting from the Human Genome," *Harvard Magazine*, July–August 2001, p. 70.

[2]In the limiting case of purely competitive pricing, with price equal to the $4 per-unit cost, consumers' surplus would be approximately $2.4 million per year, compared with $640,000 under monopoly pricing.

[3]See Edwin Mansfield et al., "Imitation Costs and Patents: An Empirical Study," *Economic Journal*, vol. 91 (December 1981), pp. 907–918.

[4]See F. M. Scherer, *Industry Structure, Strategy, and Public Policy* (New York: HarperCollins, 1996), p. 211.

[5]The original research pinpointing this phenomenon was Ronald Bond and David Lean, *Sales, Promotion, and Product Differentiation in Two Prescription Drug Markets*, Federal Trade Commission staff report (Washington: February 1977); and Robert D. Buzzell and Paul W. Farris, "Marketing Costs in Consumer Goods Industries," in Hans Thorelli, ed., *Strategy + Structure = Performance* (Indiana University Press, 1977), pp. 122–124.

For some underlying theory, see Richard Schmalensee, "Product Differentiation Advantages of Pioneering Brands," *American Economic Review*, vol. 72 (June 1982), pp. 349–365.

[6]Richard Levin, Alvin Klevorick, Richard R. Nelson, and Sidney Winter, "Appropriating the Returns from Industrial Research and Development," *Brookings Papers on Economic Activity: Microeconomics* (Washington: 1987), pp. 783–820.

[7]Wesley J. Cohen, Richard R. Nelson, and John P. Walsh, "Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)," working paper, Carnegie–Mellon University, January 2000.

[8]Edwin Mansfield, "Patents and Innovation: An Empirical Study," *Management Science*, vol. 32 (February 1986), p. 175.

[9]Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, and Louis Lasagna, "Research and Development Costs for New Drugs by Therapeutic Category," *PharmacoEconomics*, vol. 7 (February 1995), p. 165. The estimates assume 1993 general price levels.

[10]Since these outlays precede clinical testing outlays, and hence occur from 8 to 15 years on average before the ultimate products are marketed, their magnitude is raised much more than clinical testing costs by capitalization to the time of marketing.

[11]Tufts University Center for the Study of Drug Development, News Release, November 30, 2001, summarizing results presented at a November 30 conference in Philadelphia attended by the author. Although the survey included seven biological entities (out of a total of 68 entities), all were originated by traditional pharmaceutical enterprises. Because therapeutic substances originated during the 1980s and early 1990s by biotechnology firms required on average fewer human test subjects and shorter testing periods than traditional "small molecule" entities, the average capitalized cost of approved biotech-based pharmaceuticals would undoubtedly be found to be lower than $800 million. See Tufts University Center for the Study of Drug Development, News Release, July 16, 2001.

[12]E.g., the seven-year period of marketing exclusivity accorded orphan drugs in their orphan indication(s).

[13]This account is based upon the Harbridge House report, "Effects of Government Patent Policy on Drug Research and New Product Development," prepared under a contract with the Committee on Government Patent Policy, Federal Council for Science and Technology (Boston: May 1967), especially Sections I and IV.

[14]*Ibid.*, p. I-2. The nearly unanimous rejection is puzzling, given evidence that average clinical testing costs were much lower then—roughly $1 million per successful drug—than after testing requirements escalated following passage of the Kefauver–Harris Act in 1962. See Edwin Mansfield, "Comment," in Joseph D. Cooper, ed., *The Economics of Drug Innovation* (Washington: American University, 1970), p. 151.

[15]See Rebecca S. Eisenberg, "Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research, *Virginia Law Review*, vol. 82 (November 1996), pp. 1682–1683.

[16]The summary here is drawn from my monograph, *The Economic Effects of Compulsory Patent Licensing*, New York University, Monograph Series in Finance and Economics, Monograph 1977-2 (New York: 1977), pp. 79–82. See also Harbridge House, Inc., *Government Patent Policy Study*, volumes I–IV (Boston, 1968).

[17]On the complex history of the acts, see Eisenberg, "Public Research and Private Development," pp. 1662–1727.

[18]*Venture Capital Yearbook: 1998* (Wellesley Hills, MA: Venture Economics Inc., 1999), p. 58.

[19]"Disbursements per Company by Industry: 1999," *Venture Capital Journal*, April 2000, p. 45.

[20]"Move Over, Dot-Coms, Biotech Is Back," *Business Week*, March 6, 2000, p. 120, citing data collected by Ernst & Young.

[21]*Ibid.*, p. 118.

[22]David H. Hsu and Tim Bernstein, "Managing the University Technology Licensing Process: Findings from Case Studies," *Journal of the Association of University Technology Managers*, vol. 9 (1997), pp. 1–33.

[23]Patricia M. Danzon, Jeffrey McCullough, and Sean Nicholson, "Efficiency in the Market for Biotech-Pharmaceutical Alliances," working paper, University of Pennsylvania, June 2001.

[24]Joshua S. Gans, David H. Hsu, and Scott Stern, "When Does Start-up Innovation Spur the Gale of Creative Destruction?" National Bureau of Economic Research working paper 7851 (August 2000).

[25]Cohen et al., "Protecting Their Intellectual Assets."

[26]I am reminded of how General Georges Doriot, president of the first modern high-technology venture capital fund, responded when I told him that our research group at Harvard Business School would study the impact of patents on corporate R&D decisions: "Patents are just a weapon with which big firms bludgeon my startup companies," he said. On the other hand, in an analysis of the first 148 patent infringement cases decided by the Appellate Court for the Federal Circuit, created in 1983, I found that firms with sales of less than $25 million did not experience disproportionately unfavorable outcomes. "Changing Perspectives on the Firm Size Problem," in Zoltan J. Acs and David B. Audretsch, eds. *Innovation and Technological Change* (Harvester Wheatsheaf: 1991), pp. 34–35.

[27]See, e.g., F. M. Scherer, "The Link from Gross Profitability to Pharmaceutical R&D Spending," *Health Affairs*, September/October 2001.

[28]From an 1813 letter to Isaac McPherson reproduced in John P. Foley, ed., *The Jeffersonian Cyclopedia* (New York: Russell and Russell, 1967), p. 433. Jefferson goes on to recognize the ambiguous case for providing patent protection on the ideas embodied in inventions.

[29]National Science Board, *Science and Engineering Indicators: 2000*, pp. A-16 to A-25.

[30]See especially *Business Week*, March 6, 2000, p. 120.

[31]National Science Board, *Research and Engineering Indicators: 2000*, pp. A-60 and A-72; and U.S. National Research Council, Board on Science, Technology, and Economic Policy, *Trends in Federal Support of Research and Graduate Education* (Washington: pre-publication version, 2001), p. 122. The figures from the first source have been adjusted to reflect the more recent benchmarks reported by the second source.

[32]National Research Council, *Trends in Federal Support,* p. 139.

[33]National Research Council, *Trends in Federal Support*, p. 128. This estimate undoubtedly contains a substantial but unknown fraction of the research done in university-affiliated hospitals.

[34]National Research Council, *Trends in Federal Support*, pp. 144–145.

[35]National Science Board, *Science & Engineering Indicators: 2000*, p. A-319.

[36]U.S. National Science Board, *Science and Engineering Indicators: 1996*, p. 249; and *Science and Engineering Indicators: 2000*, p. A-476. A search by Lucent Technologies revealed 46 cases in which universities asserted their patents through law suits against private firms. Testimony of Jim Finnegan at the National Academies Board on Science, Technology, and Economic Policy workshop on Academic IP, April 17, 2001, p. 40 of the proceedings transcript.

[37]Jerry G. Thursby and Marie C. Thursby, "Who Is Selling the Ivory Tower? Sources of Growth in University Licensing," National Bureau of Economic Research working paper 7718 (May 2000), pp. 15–17. On the response of Stanford and the University of California, see David C. Mowery and Arvids A. Ziedonis, "The Effects of the Bayh-Dole Act on U.S. University Technology Research and Technology Transfer," working paper, July 1999.

[38]The author is indebted to Andrew Mulcahy, a biology major at Princeton University, who carried out the search.

A parallel search of pending patent *applications* published between March 15, 2001, when the Patent Office began publishing applications, and August 10, 2001, retrieved only 29 applications. A curiosity of this meager trove was that few disclosures revealed the ultimate patent

assignee, which will make it difficult to obtain early insight into individual companies' inventive activity from published patent applications.

[39] Statistical analyses revealed that European firms were more likely to use "DNA" than "nucleic acid" in their patent abstracts. Patents received by hospitals and nonprofit research institutions, patents with direct implications for human health, and methods patents were more likely to use "nucleic acid" than "DNA," all else equal.

[40]This category is subject to some imprecision because information about such firms' structures is sparse. It is possible that some small companies with foreign home bases were classified as private U.S. companies.

[41]The Web page for Incyte Genomics, Inc., corporation is ⟨http://www.incyte.com⟩, and that for Human Genome Sciences, Inc., is ⟨http://www.hgsi.com⟩ (both accessed August 29, 2002).

[42]Biotech specialists Amgen, Calgene (controlled by Monsanto), Genentech (partly owned by Hoffmann-LaRoche), and Genetics Institute (controlled by American Home Products) were counted in the large-company group.

[43]U.S. Patent and Trademark Office, Information Products Division/TAF Branch, Web site report, "Patent Counts by Class by Year: January 1977–December 2000," March 2001. The largest number of patents, 7,530, were issued in class 435.

[44]See F. M. Scherer, "The Propensity to Patent," *International Journal of Industrial Organization*, vol. I (March 1983), p. 110, showing that the pharmaceutical industry received 1.93 1976–77 patents per million dollars of 1974 R&D, compared with 1.70 patents for all U.S. industrial firms combined.

[45]William D. Nordhaus, *Invention, Growth, and Welfare: A Theoretical Treatment of Technological Change* (Cambridge, MA: MIT Press, 1969), Chapter 5. For an early elaboration, see F. M. Scherer, "Nordhaus' Theory of Optimal Patent Life: A Geometric Reinterpretation," *American Economic Review*, vol. 62 (June 1972), pp. 422–427.

[46]Edmund W. Kitch, "The Nature and Function of the Patent System," *Journal of Law & Economics*, vol. 20 (October 1977), pp. 265–290.

[47]"Optimal Timing of Innovations," *Review of Economics and Statistics*, vol. 50 (August 1968), pp. 348–355.

[48]See Michael Berkowitz and Y. Kotowitz, "Patent Policy in an Open Economy," *Canadian Journal of Economics*, vol. 15 (February 1982), pp. 1–17; and the debate between Donald McFetridge and M. Rafiquzzaman on one hand and Roger Beck in John Palmer, ed., *Research in Law and Economics*, vol. 8 (1986) (Greenwich, CT: JAI Press), pp. 91–129.

[49]On the financial outcomes of innovation projects, see F. M. Scherer, Dietmar Harhoff, and Jörg Kukies, "Uncertainty and the Size Distribution of Rewards from Innovation," *Journal of Evolutionary Economics*, vol. 10 (2000), pp. 175–200.

[50]The earliest modern theoretical demonstration of that point was F. M. Scherer, "Time–Cost Tradeoffs in Uncertain Empirical Research Projects," *Naval Research Logistics Quarterly*, vol. 13 (March 1966), pp. 71–82. There is reason to believe that the same insight was presented a century ago by philosopher Charles Sanders Peirce, but no citation is available.

[51]See, e.g., Burton Klein, *Dynamic Economics* (Harvard University Press, 1977); Michael Spence, "Product Differentiation and Welfare," *American Economic Review*, vol. 66 (May 1976), pp. 407–414; and F. M. Scherer, *International High-Technology Competition* (Harvard University Press, 1992), pp. 35–40 and 178–181.

[52]The small incremental gain from R_2 to R_3 comes from the severely diminishing returns assumed in the *C(RD)* function's final segment. They may be exaggerated. This is a point on which we have sparse empirical evidence.

[53]William F. Ogburn and D. S. Thomas, "Are Inventions Inevitable?" *Political Science Quarterly*, vol. 37 (1922), pp. 83–98. See also Robert K. Merton, "Singletons and Multiples in Scientific Discovery," *Proceedings of the American Philosophical Society*, vol. 105 (1961), pp. 470–486; Merton, "Priorities in Scientific Discovery: A Chapter in the Sociology of Science," in Bernard Barber and Walter Hirsch, eds., *The Sociology of Science* (Glencoe, IL: The Free Press, 1962), pp. 447–485; Thomas S. Kuhn, *The Structure of Scientific Revolutions* (University of Chicago Press, 1962), Chapters VII and VIII; and Abbott P. Usher, *A History of Mechanical Inventions*, rev. ed. (Harvard University Press, 1954), Chapter IV.

[54]From a book review in the *Scientific American*, December 1958, p. 146.

[55]James D. Watson, *The Double Helix* (New York: Atheneum, 1968).

[56]The term is Usher's, following William James.

[57]Edwin Mansfield, "Industry–University R and D Linkages and Technological Innovation," paper presented at the annual meetings of the American Economic Association, January 1996, updating "Academic Research Underlying Industrial Innovations: Sources, Characteristics, and Financing," *Review of Economics and Statistics*, vol. 77 (February 1995), pp. 55–65. "Recent academic research" was defined as research within 15 years of the relevant innovation's commercialization.

[58]For a pioneering analysis of the multi-stage invention problem that has been almost totally ignored in more recent scholarship, see C. C. von Weizsäcker, *Barriers to Entry: A Theoretical Treatment* (Berlin: Springer, 1980), Chapters 8 and 9. Von Weizsäcker's principal conclusion is that in an environment of rapid technological change and obsolescence, the series-relatedness of inventions calls for stronger intellectual property protection of inventions at any given stage. He recognizes that variations upon his stylized model can lead to different inferences, as we shall see here.

[59]For seminal treatments of this problem, see Suzanne Scotchmer, "Standing on the Shoulders of Giants: Cumulative Research and the Patent Law," *Journal of Economic Perspectives*, vol. 5 (Winter 1991), pp. 29–41; and Jerry Green and Suzanne Scotchmer, "On the Division of Profit in Sequential Innovation," *RAND Journal of Economics*, vol. 26 (Spring 1995), pp. 20–33.

[60]Secrecy with respect to fundamental concepts as a more lasting source of advantage to the discovers of *A* seems a less practical alternative. Universities such as Harvard permit their staffs to delay publication of research results, e.g., while patent protection is being sought, by at most a few months. See the testimony of Wesley Cohen at the National Academies workshop on Acedemic IP, transcript p. 158, which estimates the average publication delay at 4.7 months. Business firms in fields such as biotechnology would find it difficult to recruit able staff if they sought to delay indefinitely the publication of scientific discoveries.

[61]As Jack L. Tribble, patent counsel to Merck & Co., observed in the National Academies Academic IP workshop, "99 percent of everything exciting that happens will happen outside of your own research labs." Workshop transcript p. 113.

[62]See, e.g., John Jewkes, David Sawers, and Richard Stillerman, *The Sources of Invention*, 2nd ed. (New York: Norton, 1969); Willard F. Mueller, "The Origins of the Basic Inventions Underlying DuPont's Major Product and Process Innovations, 1920 to 1950," in the National Bureau of Economic Research conference volume, *The Rate and Direction of Inventive Activity* (Princeton University Press, 1962), pp. 323–358; Clayton M. Christensen, *The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail* (Harvard Business School Press, 1997); and Klein, *Dynamic Economics*, Chapter 5.

[63]Another alternative is an R&D joint venture between the discover of *A* and a follow-on developer. For its advantages, see Scotchmer, "Standing on the Shoulders of Giants." One of many possible problems is that when a would-be co-developer approaches the original patent holder with its commercialization idea, the basic patent holder may choose not to grant the necessary rights but to start its own solo development effort.

[64]See Susan Aldridge, *The Thread of Life: The Story of Genes and Genetic Engineering* (Cambridge University Press, 1996), pp. 104–108.

[65]This point is powerfully argued by Robert P. Merges and Richard R. Nel-

son, "On the Complex Economics of Patent Scope," *Columbia Law Review*, vol. 90 (May 1990), pp. 839–916.

[66]Merges and Nelson, p. 866.

[67]*Ibid.*, pp. 884–908.

[68]Illinois Institute of Technology Research Institute, *Technology in Retrospect and Critical Events in Science* (the *TRACES* study), vol. 1 (Chicago: December 1968), Figure 8.

[69]That this problem exists at a serious level in biotechnology is argued by Michael A. Heller and Rebecca Eisenberg, "Can Patents Deter Innovation? The Anticommons in Biomedical Research," *Science*, vol. 280 (May 1, 1998), pp. 698–701.

[70]Elliot Forbes, ed., *Thayer's Life of Beethoven* (Princeton University Press, 1967), p. 38.

[71]See Merges and Nelson, "On the Complex Economics of Patent Scope," pp. 890–896.

[72]See Rosmarie Ham Ziedonis and Bronwyn Hall, "The Effects of Strengthening Patent Rights in Firms Engaged in Cumulative Innovation: Insights from the Semiconductor Industry," University of Pennsylvania and University of California at Berkeley, May 2001.

[73]On the differences between academic and industrial laboratories, see the testimony of Jim Finnegan at the National Academies Academic IP workshop, transcript pp. 40–41.

[74]Federal Trade Commission, *In the Matter of Intel Corporation*, Agreement Containing Consent Order, Docket No. 9288 (March 1999). The author was economic expert for the FTC in the proceedings that preceded consent settlement.

[75]It is assumed that once the key invention is made, the benefits do not reach their full potential immediately, but achieve $(1 - e^{0.2T})$ of their potential in early years, where T is the number of years from the initial availability of the invention. Thus, by year 10, they have reached 86% of their potential.

[76]See Merges and Nelson, "On the Complex Economics of Patent Scope;" and Merges, "Intellectual Property Rights and Bargaining Breakdown: The Case of Blocking Patents," *Tennessee Law Review*, vol. 62 (Fall 1994), pp. 75–106.

[77]*Embrex Inc. v. Service Engineering Corp.*, 216 F. 3d 1343 (2000) (Court of Appeals for the Federal Circuit).

[78]On the differences between royalty standards, see F. M. Scherer and Jayashree Watal, "Post-TRIPS Options for Access to Patented Medicines in Developing Nations," J International Law. 2002.