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Can Patents Deter Innovation? The Anticommons in Biomedical Research

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The "tragedy of the commons" metaphor helps explain why people overuse shared resources. However, the recent proliferation of intellectual property rights in biomedical research suggests a different tragedy, an "anticommons" in which people underuse scarce resources because too many owners can block each other. Privatization of biomedical research must be more carefully deployed to sustain both upstream research and downstream product development. Otherwise, more intellectual property rights may lead paradoxically to fewer useful products for improving human health.

Thirty years ago in *Science*, Garrett Hardin introduced the metaphor "tragedy of the commons" (*1*) to help explain overpopulation, air pollution, and species extinction. People often overuse resources they own in common because they have no incentive to conserve. Today, Hardin's metaphor is central to debates in economics, law, and science and is a powerful justification for privatizing commons property (*2*). Although the metaphor highlights the cost of overuse when governments allow too many people to use a scarce resource, it overlooks the possibility of underuse when governments give too many people rights to exclude others. Privatization can solve one tragedy but cause another (*3*).

Since Hardin's article appeared, biomedical research has been moving from a commons model toward a privatization model (*4*). Under the commons model, the federal government sponsored premarket or "upstream" research and encouraged broad dissemination of results in the public domain. Unpatented biomedical discoveries were freely incorporated in "downstream" products for diagnosing and treating disease. In 1980, in an effort to promote commercial development of new technologies, Congress began encouraging universities and other institutions to patent discoveries arising from federally supported research and development and to transfer their technology to the private sector (*5*). Supporters applaud the resulting increase in patent filings and private investment (*6*), whereas critics fear deterioration in the culture of upstream research (*7*). Building on Heller's theory of anticommons property (*3*), this article identifies an unintended and paradoxical consequence of biomedical privatization: A proliferation of intellectual property rights upstream may be stifling life-saving innovations further downstream in the course of research and product development.

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The Tragedy of the Anticommons

Anticommons property can best be understood as the mirror image of commons property (*3*, *8*). A resource is prone to overuse in a tragedy of the commons when too many owners each have a privilege to use a given resource and no one has a right to exclude another (*9*). By contrast, a resource is prone to underuse in a "tragedy of the anticommons" when multiple owners each have a right to exclude others from a scarce resource and no one has an effective privilege of use. In theory, in a world of costless transactions, people could always avoid commons or anticommons tragedies by trading their rights (*10*). In practice, however, avoiding tragedy requires overcoming transaction costs, strategic behaviors, and cognitive biases of participants (*11*), with success more likely within close-knit communities than among hostile strangers (*12*–*14*). Once an anticommons emerges, collecting rights into usable private property is often brutal and slow (*15*).

Privatization in postsocialist economies starkly illustrates how anticommons property can emerge and persist (*3*). One promise of the transition to a free market was that new entrepreneurs would fill stores that socialist rule had left bare. Yet after several years of reform, many privatized storefronts remained empty, while flimsy metal kiosks, stocked full of goods, mushroomed on the streets. Why did the new merchants not come in from the cold? One reason was that transition governments often failed to endow any individual with a bundle of rights that represents full ownership. Instead, fragmented rights were distributed to various socialist-era stakeholders, including private or quasi-private enterprises, workers' collectives, privatization agencies, and local, regional, and federal governments. No one could set up shop without first collecting rights from each of the other owners.

Privatization of upstream biomedical research in the United States may create anticommons property that is less visible than empty storefronts but even more economically and socially costly. In this setting, privatization takes the form of intellectual property claims to the sorts of research results that, in an earlier era, would have been made freely available in the public domain. Responding to a shift in U.S. government policy (*4*) in the past two decades, research institutions such as the National Institutes of Health (NIH) and major universities have created technology transfer offices to patent and license their discoveries. At the same time, commercial biotechnology firms have emerged in research and development (R&D) niches somewhere between the proverbial "fundamental" research of academic laboratories and the targeted product development of pharmaceutical firms (*7*). Today, upstream research in the biomedical sciences is increasingly likely to be "private" in one or more senses of the term—supported by private funds, carried out in a private institution, or privately appropriated through patents, trade secrecy, or agreements that restrict the use of materials and data.

In biomedical research, as in postsocialist transition, privatization holds both promises and risks. Patents and other forms of intellectual property protection for upstream discoveries may fortify incentives to undertake risky research projects and could result in a more equitable distribution of profits across all stages of R&D. But privatization can go astray when too many owners hold rights in previous discoveries that constitute obstacles to future research (*16*). Upstream patent rights, initially offered to help attract further private investment, are increasingly regarded as entitlements by those who do research with public funds. A researcher who may have felt entitled to coauthorship or a citation in an earlier era may now feel entitled to be a coinventor on a patent or to receive a royalty under a material transfer agreement. The result has been a spiral of overlapping patent claims in the hands of different owners, reaching ever further upstream in the course of biomedical research. Researchers and their institutions may resent restrictions on access to the patented discoveries of others, yet no-

body wants to be the last one left dedicating findings to the public domain.

The problem we identify is distinct from the routine underuse inherent in any well-functioning patent system. By conferring monopolies in discoveries, patents necessarily increase prices and restrict use—a cost society pays to motivate invention and disclosure. The tragedy of the anticommons refers to the more complex obstacles that arise when a user needs access to multiple patented inputs to create a single useful product. Each upstream patent allows its owner to set up another tollbooth on the road to product development, adding to the cost and slowing the pace of downstream biomedical innovation.

How a Biomedical Anticommons May Arise

Current examples in biomedical research demonstrate two mechanisms by which a government might inadvertently create an anticommons: either by creating too many concurrent fragments of intellectual property rights in potential future products or by permitting too many upstream patent owners to stack licenses on top of the future discoveries of downstream users.

Concurrent fragments. The anticommons model provides one way of understanding a widespread intuition that issuing patents on gene fragments makes little sense. Throughout the 1980s, patents on genes generally corresponded closely to foreseeable commercial products, such as therapeutic proteins or diagnostic tests for recognized genetic diseases (*17*). Then, in 1991, NIH pointed the way toward patenting anonymous gene fragments with its notorious patent applications on expressed sequence tags (ESTs) (*18*). NIH subsequently abandoned these patent applications and now takes a more hostile position toward patenting ESTs and raw genomic DNA sequences (*19*). Meanwhile, private firms have stepped in where NIH left off, filing patent applications on newly identified DNA sequences, including gene fragments, before identifying a corresponding gene, protein, biological function, or potential commercial product. The Patent and Trademark Office (PTO), in examining these claims (*20*), could create or avoid an anticommons.

Although a database of gene fragments is a useful resource for discovery, defining property rights around isolated gene fragments seems at the outset unlikely to track socially useful bundles of property rights in future commercial products. Foreseeable commercial products, such as therapeutic proteins or genetic diagnostic tests, are more likely to require the use of multiple fragments. A proliferation of patents on individual fragments held by different owners seems inevitably to require costly future transactions to bundle licenses together before a firm can have an effective right to develop these products (*21*).

The editors have asked selected members of the scientific community to respond to the Policy commentary by J. J. Doll and the Review by M. A. Heller and R. S. Eisenberg. Their remarks are available at www.sciencemag.org/feature/data/980465.shl

Patents on receptors useful for screening potential pharmaceutical products demonstrate another potential "concurrent fragment" anticommons in biomedical research. To learn as much as possible about the therapeutic effects and side effects of potential products at the preclinical stage, firms want to screen products against all known members of relevant receptor families. But if these receptors are patented and controlled by different owners, gathering the necessary licenses may be difficult or impossible. A recent search of the Lexis patent database disclosed more than 100 issued U.S. patents with the term "adrenergic receptor" in the claim language. Such a proliferation of claims presents a daunting bargaining challenge. Unable to procure a complete set of licenses, firms choose between diverting resources to less promising projects with fewer licensing obstacles or proceeding to animal and then clinical testing on the basis of incomplete information. More thorough in vitro screening could avoid premature clinical testing that exposes patients to unnecessary risks.

Long delays between the filing and issuance of biotechnology patents aggravate the problem of concurrent fragments. During this period of pendency, there is substantial uncertainty as to the scope of patent rights that will ultimately issue. Although U.S. patent law does not recognize enforceable rights in pending patent applications, firms and universities typically enter into license agreements before the issuance of patents, and firms raise capital on the basis of the inchoate rights preserved by patent filings. In effect, each potential patent creates a specter of rights that may be larger than the actual rights, if any, eventually conferred by the PTO. Worked into the calculations of both risk-taking investors and risk-averse product developers, these overlapping patent filings may compound the obstacles to developing new products.

Stacking licenses. The use of reach-through license agreements (RTLAs) on patented research tools illustrates another path by which an anticommons may emerge. As we use the term, an RTLA gives the owner of a patented invention, used in upstream stages of research, rights in subsequent downstream discoveries. Such rights may take the form of a royalty on sales that result from use of the upstream research tool, an exclusive or nonexclusive license on future discoveries, or an option to acquire such a license. In principle, RTLAs offer advantages to both patent holders and researchers. They permit researchers with limited funds to use patented research tools right away and defer payment until the research yields valuable results. Patent holders may also prefer a chance at larger payoffs from sales of downstream products rather than certain, but smaller, upfront fees. In practice, RTLAs may lead to an anticommons as upstream owners stack overlapping and inconsistent claims on potential downstream products. In effect, the use of RTLAs gives each upstream patent owner a continuing right to be present at the bargaining table as a research project moves downstream toward product development.

So far, RTLAs have had a mixed reception as a mechanism for licensing upstream biomedical research patents, but they appear to be becoming more prevalent. When Cetus Corporation initially proposed RTLAs on any products developed through the use of the polymerase chain reaction (PCR) in research, they met strong resistance from downstream users concerned with developing commercial products (*22*). Later, Hoffmann–La Roche acquired the rights to PCR and offered licenses that do not include reach-through obligations (*23*). The resulting pay-as-you-go approach increases the upfront cost of a license to use PCR, but it decreases the likelihood of an anticommons emerging.

More recently, some universities and other nonprofit research institutions have balked at terms DuPont Corporation has offered for licenses to use patented oncomouse (*24*) and cre-lox (*25*) technologies, although others have acquiesced to the license terms (*26*). These patents cover genetically engineered mice useful in research that could result in products falling outside the scope of the patent claims. DuPont has offered noncommercial research licenses and sublicenses on terms that seem to require licensees to return to DuPont for further approval before any new discoveries or materials resulting from the use of licensed mice are passed along to others or used for commercial purposes (*27*). DuPont thereby gains the right to participate in future negotiations to develop commercial products that fall outside the scope of their patent claims. In effect, the license terms permit

DuPont to leverage its proprietary position in upstream research tools into a broad veto right over downstream research and product development.

As RTLAs to use patented research tools multiply, researchers will face increasing difficulties conveying clear title to firms that might develop future discoveries. If a particularly valuable commercial product is in view, downstream product developers might be motivated and able to reach agreements with multiple holders of RTLAs. But if the prospects for success are more uncertain or the expected commercial value is small, the parties may fail to bargain past the anticommons.

Transition or Tragedy?

Is a biomedical anticommons likely to endure once it emerges? Recent empirical literature suggests that communities of intellectual property owners who deal with each other on a recurring basis have sometimes developed institutions to reduce transaction costs of bundling multiple licenses (*28*). For example, in the music industry, copyright collectives have evolved to facilitate licensing transactions so that broadcasters and other producers may readily obtain permission to use numerous copyrighted works held by different owners. Similarly, in the automobile, aircraft manufacturing, and synthetic rubber industries, patent pools have emerged, sometimes with the help of government, when licenses under multiple patent rights have been necessary to develop important new products (*28*). When the background legal rules threaten to waste resources, people often rearrange rights sensibly and create order through private arrangements (*12–14*). Perhaps some of the problems caused by proliferating upstream patent rights in biomedical research will recede as licensors and licensees gain experience with intellectual property rights and institutions evolve to help owners and users reach agreements. The short-term costs from delayed development of new treatments for disease may be worth incurring if fragmented privatization allows upstream research to pay its own way and helps to ensure its long-run viability. Patent barriers to product development may be a transitional phenomenon rather than an enduring tragedy.

On the other hand, there may be reasons to fear that a patent anticommons could prove more intractable in biomedical research than in other settings. Because patents matter more to the pharmaceutical and biotechnology industries than to other industries, firms in these industries may be less willing to participate in patent pools that undermine the gains from exclusivity (*29*). Moreover, the lack of substitutes for certain biomedical discoveries (such as patented genes or receptors) may increase the leverage of some patent holders, thereby aggravating holdout problems. Rivals may not be able to invent around patents in research aimed at understanding the genetic bases of diseases as they occur in nature.

More generally, three structural concerns caution against uncritical reliance on markets and norms to avoid a biomedical anticommons tragedy: the transaction costs of rearranging entitlements, heterogeneous interests of owners, and cognitive biases among researchers.

Transaction costs of bundling rights. High transaction costs may be an enduring impediment to efficient bundling of intellectual property rights in biomedical research. First, many upstream patent owners are public institutions with limited resources for absorbing transaction costs and limited competence in fast-paced, market-oriented bargaining. Second, the rights involved cover a diverse set of techniques, reagents, DNA sequences, and instruments. Difficulties in comparing the values of these patents will likely impede development of a standard distribution scheme. Third, the heterogeneity of interests and resources among public and private patent owners may complicate the emergence of standard license terms, requiring costly case-by-case negotiations. Fourth, licensing transaction costs are likely to arise early in the course of R&D when the outcome of a project is uncertain, the potential gains are speculative, and it is not yet clear that the value of downstream products justifies the trouble of overcoming the anticommons.

Even when upstream owners see potential gains from cooperation and are motivated to devise mechanisms for reducing transaction costs, they may be deterred by other legal constraints, such as antitrust laws. Patent pools have been a target of antitrust scrutiny in the past (*30*), which may explain why few, if any, such pools exist today. Although antitrust law may be less hostile to patent pools today than it was in 1975 when a consent decree dismantled the aircraft patent pool (*31*), the antitrust climate changes from one administration to the next (*32*). Even a remote prospect of facing treble damages and an injunction may give firms pause about entering into such agreements.

Heterogeneous interests of rights holders. Intellectual property rights in upstream biomedical research belong to a large, diverse group of owners in the public and private sectors with divergent institutional agendas. Sometimes heterogeneity of interests can facilitate mutually agreeable allocations (you take the credit, I'll take the money) (*33*, *34*), but in this setting, there are reasons to fear that owners will have conflicting agendas that make it difficult to reach agreement. For example, a politically accountable government agency such as NIH may further its public health mission by using its intellectual property rights to ensure widespread availability of new therapeutic products at reasonable prices. When NIH sought to establish its co-ownership of patent rights held by Burroughs-Wellcome on the use of azidothymidine (AZT) to treat the human immunodeficiency virus (HIV) (*35*), its purpose was to lower the price of AZT and promote public health rather than simply to maximize its financial return. By contrast, a private firm is more likely to use intellectual property to maintain a lucrative product monopoly that rewards shareholders and funds future product development. When owners have conflicting goals and each can deploy its rights to block the strategies of the others, they may not be able to reach an agreement that leaves enough private value for downstream developers to bring products to the market.

A more subtle conflict in agendas arises between owners that pursue end-product development and those that focus primarily on upstream research. The goal of end-product development may be better served by making patented research tools widely available on a nonexclusive basis, whereas the goal of procuring upstream research funding may be better served by offering exclusive licenses to sponsors or research partners. Differences among patent owners in their tolerance for transaction costs may further complicate the emergence of informal licensing norms. Universities may be ill equipped to handle multiple transactions for acquiring licenses to use research tools. Delays in negotiating multiple agreements to use patented processes, reagents, and gene fragments could stifle the creative give-and-take of academic research. Yet academic researchers who fail to adopt new discoveries and instead rely on obsolete public domain technologies may find themselves losing grant competitions. Large corporations with substantial legal departments may have considerably greater resources for negotiating licenses on a case-by-case basis than public sector institutions or small start-up firms. This asymmetry may make it difficult to identify mutually advantageous cross-licensing arrangements. Patent owners are also likely to differ in the time frames they can tolerate for recouping current investments in transaction costs.

Owners are also likely to differ in their willingness and ability to infringe the patents of others, resulting in asymmetrical motivations to negotiate cross-licenses. Use of a patented invention in an academic laboratory or a small start-up firm may be

inconspicuous, at least if not described in a publication or at a scientific meeting. Patent owners may be more reluctant to sue public sector investigators than they are to sue private firms. Differences in institutional cultures may make academic laboratories and biotechnology firms more tolerant of patent infringement than large pharmaceutical firms. Owners who do not feel vulnerable to infringement liability may be less motivated to enter into reasonable cross-licenses than owners who worry more about being sued.

Cognitive biases. People consistently overestimate the likelihood that very low probability events of high salience will occur (*36*). For example, many travelers overestimate the danger of an airplane crash relative to the hazards of other modes of transportation. We suspect that a similar bias is likely to cause owners of upstream biomedical research patents to overvalue their discoveries. Imagine that one of a set of 50 upstream inventions will likely be the key to identifying an important new drug, the rest of the set will have no practical use, and a downstream product developer is willing to pay $10 million for the set. Given the assumption that no owner knows ex ante which invention will be the key, a rational owner should be willing to sell her patent for the probabilistic value of $200,000. However, if each owner overestimates the likelihood that her patent will be the key, then each will demand more than the probabilistic value, the upstream owners collectively will demand more than the aggregate market value of their inputs, the downstream user will decline the offers, and the new drug will not be developed. Individuals trained in deterministic rather than probabilistic disciplines are particularly likely to succumb to this sort of error (*37*).

A related "attribution bias" suggests that people systematically overvalue their assets and disparage the claims of their opponents when in competition with others (*38*). We suspect that the attribution bias is pervasive among scientists because it is likely adaptive for the research enterprise as a whole. Overcommitment by individuals to particular research approaches ensures that no hypothesis is dismissed too quickly, and skepticism toward rivals' claims ensures that they are not too readily accepted. But this bias can interfere with clear-headed bargaining, leading owners to overvalue their own patents, undervalue others' patents, and reject reasonable offers. Institutional ownership could mitigate these biases, but technology transfer offices rely on scientists to evaluate their discoveries. When two or more patent owners each hope to dominate the product market, the history of biotechnology patent litigation suggests a likelihood that bargaining will fail (*39*).

Conclusion

Like the transition to free markets in post-socialist economies, the privatization of biomedical research offers both promises and risks. It promises to spur private investment but risks creating a tragedy of the anticommons through a proliferation of fragmented and overlapping intellectual property rights. An anticommons in biomedical research may be more likely to endure than in other areas of intellectual property because of the high transaction costs of bargaining, heterogeneous interests among owners, and cognitive biases of researchers. Privatization must be more carefully deployed if it is to serve the public goals of biomedical research. Policy-makers should seek to ensure coherent boundaries of upstream patents and to minimize restrictive licensing practices that interfere with downstream product development. Otherwise, more upstream rights may lead paradoxically to fewer useful products for improving human health.

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