PATENTS, ETHICS, HUMAN LIFE FORMS

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OUTLINE

INTRODUCTION

It might be supposed that morality operates as a side constraint on patentability. On this view, even though a process or device might meet conceptual and scientific criteria for recognition as an invention, moral considerations might override so as to deny a patent. Or again, it might be held that morality, genetics, and biotechnology so intertwine that whenever we construct criteria of patentability with respect to "genetic inventions," we perforce impose some moral view.

EXPLOITATION AND MONOPOLY OF CLONED DNA SEQUENCES

Whereas U.S. patent authorities formerly declined to issue patents on gambling devices and phony medicines, the U.S. Patent Code of 1952 dissociates law and morality. It leaves to other laws the matter of restraining the use of inventions. Efficiency alone commends this division of labor, since many patents are never exploited. For example, Pasteur obtained a U.S. patent in 1873 on a yeast for making beer. But, so far as we know, he never developed a commercial product (1). If immorality of use does not count as an objection to a patent application in general—even if the proffered device be mischievous—should immorality of use count as an objection to patents on life forms?

We might answer this with another question. If a patent on a gene or other human life form confers ownership over something human, and if, on moral grounds, we reject claims to own humans, are not patents on genes and human substances illegitimate? This question probes not an invention's use but the appropriateness of the patent privilege itself. A patent lawyer will reply, reprovingly, that a patent does not confer ownership, that a patent merely grants for a term of twenty years the privilege to exclude

others from making, using, or selling an invention. This reply does not end the discussion. For various circumstantial reasons any policy on biological patents brings moral controversy in its train. In the first instance, allowing commercial entities to wield even limited monopolies on things human will seem morally problematic to many observers. Some will regard such privileges as threats to the autonomy of persons (as discussed below for clinical settings). Others will point to various economic consequences of wielding patents, among them high prices and restricted output of end products. When a DNA sequence patent issues but the patentee fails or declines to introduce a product predicated on the sequence, the only benefit of the patent, if one may call it that, is to prevent the patentee's competitors from exploiting the sequence. It may be granted that for some the welfare loss of squandering an opportunity to improve beer production, especially for a mere scientific career, is cause for lament. But if a patentee shelves a human gene patent and denies society an opportunity to develop beneficial drugs or to perform gene therapy, the cost may be human suffering. As we shall see, good reasons obtain to resist the generalization that biological patents enhance aggregate welfare. In respect of the foregoing concerns, one hears not merely the voices of patent examiners and courts—unlikely arbiters of morality in any event—but a variety of moral views held among citizens to whom accountability for governmental decisions is owed.

Because the decision to award a patent may be publicly perceived as at least implicitly a decision to condone any and all uses of the invention, it may behoove us first to resolve objections concerning morally problematic uses of certain biotechnological innovations before we attempt a consensus on monopoly of the innovations. If prudence commends this two-part agenda in the United States, the European patent system demands it. The European Patent Convention of 1963, whose criteria of patentability are otherwise roughly coincident with the American, proscribes patents on inventions whose commercial exploitation would be "contrary to *l'ordre publique* or morality." This phrase was long considered so vague as to lack teeth. But as adopted in 1998, the Directive on the Legal Protection of Biotechnological Inventions of the European Parliament (the "European Directive," or "ED") declares unpatentable, on the ground that their commercial exploitation would be contrary to *l'ordre publique* or morality, the following: human germ line intervention, "cloning" humans, commercial use of embryos, and both somatic and germ line genetic intervention in animals that is "likely to cause suffering without any substantial medical benefit to man or animal" (2). To this the ED curiously adds, "exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation."

Anticipated Benefits of Transgenesis

Mankind has bred plants and animals for millennia. Since Mendel, breeders have exploited knowledge of dominant and recessive alleles. Moral controversy about genetic engineering stems not from manipulation by breeding, but from recombinant DNA. It is not that recombinant techniques clearly violate any moral view in particular. Rather it is the case that recombinant DNA technology poses questions not previously raised within any traditional moral theory.

Transgenesis consists in isolating a gene of one living being and inserting the gene at an early embryonic stage, before somatic and germ cells separate, in such a way that the gene enters the germ line of another living being of a different species. The insertion may be accomplished by introducing the foreign gene into (i) a retrovirus that infects an embryo, (ii) a plasmid microinjected into the pronucleus of a zygote, or (iii) cultured embryonic stem cells injected into the cavity of a blastocyst. The inserted genes are usually few and manifest themselves in only a small subset of an animal's phenotype. Transgenesis enables improvements in the growth, heartiness, and yields of animals and plants as sources of food, vaccines, and other compounds, affords models for study of diseases, the immune system, and gene regulation and expression, holds promise for direct therapeutic use in humans, allows the "pharming" of animal organs so that,

upon transplant to humans, they will not be rejected, and allows production of cotton, plastics, and other industrially valuable compounds. A vaccine-enriched transgenic banana holds promise as a vehicle for surmounting economic and practical obstacles to vaccine delivery in many regions of the world.

Reservations Concerning Transgenesis

As encouraging as these prospects may be, they are not without their detractors. Objections to transgenesis include the following. Even if genes insert at a targeted locus, in animals the effect of transgenesis may be suffering, a theme frequently rehearsed in European discussions. The usual defense of animal experimentation (as in the ED) adverts to collective human benefit. A net increase in aggregate human preference satisfaction is all that need occur to satisfy a utilitarian; the second form of Kant's categorical imperative permits using even humans as means so long as they are not used solely as means. But risk-averse humans worry about their own welfare in eating transgenic plants and animals—even assuming full disclosure in the grocery store. To introduce a vaccine into a banana crop raises questions about imposed risk-taking and paternalism when informed consent may not be feasible. Risk of human suffering is sometimes cited as a consideration against human gene therapy. Risks about where and in how many copies genes insert and whether a procedure will otherwise work are chanced by any single recipient of somatic cell therapy; to this germ line intervention adds the risk that an untoward result may burden future generations who, it may be said, have no voice in what is done to their ancestors' genomes. Even when gene therapy achieves an intended result, the long-term effect may be a population less diverse, a gene pool that is diminished. A suite of controllable genetic characteristics may eventually generate a canon. By reference to that canon, persons lacking certain traits may be treated by others as inferior. Perhaps indeed we shall cavort down a slippery slope from disease-related therapies to frivolous enhancements. To engage in germ line intervention, it is decried, is to "play God."

Defense of Human Germ Line Intervention

A defense of human germ line intervention might run as follows. Genetic engineering may be a way to improve man's contribution as co-creator in God's work (3). One might argue that God would wish caring physicians to use it. Gene therapy will not invent discrimination, a practice already thriving with respect to many traits. We should not count even against enhancement that someone will be born with a trait more desirable than another trait. Instead a temptation to be invidious should remind us, as do Kant and many religions, to recognize the dignity of each person. As for an effect on descendants, that is not a new category of moral responsibility. Future generations are already affected by innumerable influences on one's germ cells of how one lives. One may imagine a complaint of wrongful life by someone born with a genome adversely affected by something that went wrong in a gene therapy procedure, but in another case, the same tort might be committed by failing to attempt gene therapy. It would appear dubious to bar a physician from using an available method of averting disease in a consenting patient's offspring if, for example, the odds of the method's success exceed those of any treatment after birth. It is also difficult to expect a family or society to forgo eradicating a lethal gene if that be possible. A few decades from now, germ line intervention may be considered routine, its provision the duty of a competent physician, its inclusion a requirement of the health care a just society ought to provide.

The slippery slope to enhancement is not fairly ascribed to gene therapy (though perhaps to recombinant DNA). Recombinant human growth hormone, for example, is already dispensed. At least at present, the imagined efficacy of gene therapy is limited to diseases involving single genes, and among those, to diseases mediated by recessive genes, because an inserted gene's locus may not be controllable and any dominant defective gene remains in the patient. On the other hand, someday prospective parents may be speaking of a "designer child" polymath 9′ basketball player. In any event a

distinction between "therapy" and "enhancement" may not be sharp or necessary. If a slippery slope connects therapy and enhancement, the transition from first violation of any ban on genetic enhancement to widespread violation thereof may be an avalanche. A treaty presented for adoption by members of the European Union bans enhancement (4). As of this writing, human germ line intervention for enhancement purposes is not feasible, but upon its availability, one may expect the following. Though a government may ban genetic enhancement, as soon as one person manages to procure an enhancement, others acting rationally will likely rush to procure enhancement in order to remain competitive (5). These aspirants will either violate the ban or migrate to a sovereignty that lacks one. Sovereignties will likely behave the same way, rushing to follow the first innovator for fear of being dominated by superiors. Unless one contemplates intrusive "audits" comparing parental and progeny DNA, a ban on enhancement seems unenforceable.

The foregoing brief account reveals moral concerns about uses that insinuate themselves into discussions whether to approve monopolies of uses. We may now turn to moral concerns about a patent privilege itself.

Autonomy and Patent Claims Against Parents and Children

The effect that a patent might exert on individual autonomy may be studied through a dramatic example. This first requires that we explain the rationale for patents on transgenics.

Patented Transgenic Organisms Although Pasteur's yeast long before gained a patent, modern recognition of a nonplant life form as patentable occurred in a decision with respect to a bacterium into which were introduced plasmids rendering the bacterium capable of decomposing oil (6). Patentability was later confirmed for multicellular organisms (polyploid oysters) (7). A furor ensued over ethical concerns, and for a time, the U.S. Patent and Trademark Office ("PTO") imposed a moratorium on animal patents. Thereafter the PTO issued a patent on the Harvard mouse (8).

Designed for the study of cancer, the Harvard mouse contains DNA sequences, comprising an oncogene such as *myc* and a promoter, that effect a high proclivity to form tumors when the mouse encounters carcinogens. The introduction and expression of the *myc* gene in the mouse was innovationary. One could not have presumed that a zygote acquiring the oncogene would survive its insertion and expression, or if the zygote did survive and a mouse were born, that the offspring would be fertile. The Harvard mouse invention was exhibited for patent purposes by deposit of DNA in a plasmid. But the patent extends not merely to the inserted DNA, not merely to the oncogene's introduction and expression, but to the whole "oncomouse."

Why should a patent embrace an animal? Two arguments might be mustered. First, there has endured throughout the history of patents the notion that patents should not be available on nature's extant treasures—in a phrase attributed to Thomas Jefferson, on any "product of nature"—but should be available only on what humans manufacture. The discovery of uranium garnered no patent, but the PTO issued a patent to Glenn Seaborg on curium and isotopes of americum, transuranic elements believed to exist on earth only in a cyclotron or reactor as a result of human efforts. Of course such elements may be abundant in stars. A precise statement of patent eligibility would not exclude from patentability every naturally occurring thing. Rather we may state patent eligibility by the following proposition, which we may call the "unpatentability of nature": to be eligible for a patent, a thing must be such that there obtains only a very low probability that, without human intervention, the thing exists near the surface of the earth or on other astronomical bodies to which humans travel. What constitutes a "very low" probability requires specification. Since patent lore speaks confidently of things that "exist" or "do not exist," no guidance on probability may be found within it.

It is logically possible for there to evolve an organism whose genome is identical to some modern transgenic organism. Exchange

of genes across species occurs and any mutation is possible. Yet the probability may be extremely low that a creature will contain genes of two given organisms that do not mate. In such case a patent examiner may treat a transgenic genome as if it does not naturally occur. An animal possessing such genome is then seen not as an unpatentable product of nature but as a patentable "manufacture" or "composition of matter" (9). With respect to the European Patent Convention, it would be said that such an animal is not an unpatentable "variety" (10). In general, the fruits of breeding programs are considered varieties, but transgenic animals are not considered varieties because transgenesis was unknown in 1973 when the European concept of a variety was introduced.

Second, when introduced into a recipient's germ cells, transgenes pass to descendants. A transgene will not be expressed in all offspring of the first generation, but those in which it is expressed will be selected for further breeding. Were a patent to cover only cells expressing a trait, it would not capture the invention, which, by virtue of being genomic, appears in every cell. Were a patent to cover only an inventor's process of introduction and expression, anyone who purchased one transgenic animal could breed others without infringement; natural reproduction is not the same process as laboratory transgenesis. A purchaser of transgenic agricultural livestock could breed the livestock through unlimited generations. Hence inventors are accorded the protection of a patent on the transgenic genome, which is effectively a patent on the animal. Breeding descendants of a patented transgenic animal without license would just as clearly constitute infringement as would duplicating a patented laboratory process for inserting transgenes into an embryo. The patent system assimilates reproduction, whether natural or artificially aided, to "making" a duplicate.

The Human Qua Infringement A moment's reflection reveals that if the foregoing two grounds (a claim to originate a manufacture; self-reproducibility of a recipient) entitle an architect of transgenesis to a patent on recipient and progeny, then in the case of human germ line intervention, infringement claims will lie against the birth and existence of humans. To call human birth or life a "patent infringement" seems perverse. But on what principled grounds should we reject such claims? Even in the somatic cell case, as scientists perfect the manufacture of yet more human enzymes and other proteins, as they progress to substantial tissues, should society continue to grant patents on human "parts"? Manufacture of a liver or other major organ, or someday even of a brain, may confound previous thinking.

Abjuring the Human Qua Infringement To resolve the solecism of the human qua infringement, we may reason as follows. We do not imagine infringement claims against any plant or animal. Instead we recognize claims against people who control breeding. We do so because we recognize a farmer's ownership of plants and animals. When the "designer" of a transgenic organism applies for a patent, the contest concerns only which humans (or corporations they represent) own property in the nonhuman species. When the issue is which of two humans owns a human, we say that humans own themselves. They do not own each other. Human births, we hold, are not analogous to breeding, to manipulation by owners of mating subjects. Hence we may decline to recognize property rights in humans.

The premise that humans do not own each other, that we each enjoy a "bodyright" (11), is not categorically held in all societies, and given that the common law describes an adolescent's maturity as "emancipation," perhaps it is not unequivocally held anywhere. Defense of the premise often comes round to some distinction between humans and animals. According to a Cartesian distinction, man is a singular creature possessed of reason. According to Kant, only man and angels are capable of reason. To say that a human being's existence infringes property rights would seem inconsistent with the second and third forms of the Kantian categorical imperative, which together enjoin that we treat each person not solely as a means but as an end-in-himself in a kingdom of ends. If we allow an ownership claim on a person,

we condone treating the person solely as a means. We condone interfering with the person's autonomy. Were someone to assert an ownership claim that purportedly extended to only part of a person, the claim would appear indistinguishable from a claim on the whole. Bodily parts are integrated. For the same reasons, conception and birth, the instantiation of human nature, may be held immune from claims of others. We may also say that conception and birth are private.

Distributive Justice and Patent Claims on Extracorporeal Compounds

Although we may thus deny the permissibility of exerting dominion over, impairing the autonomy of, or disrespecting an individual, a different case, actual in biotechnology, is the following. There is adduced a substance that is human in the sense of being found in the human species, but which has been made outside the human body and is not ascribable to any individual. Were a patent to issue on that substance, the patent would not appear to interfere with any individual.

To this it must be added that it is not easy to steer clear of the DNA sequences that distinguish an individual or that make any individual akin to another. Only about three million of the three billion base pairs in the human genome account for individual differences, but the genetic code is redundant, the most interesting traits are polygenic and beyond present understanding, and mutation never ceases. For now, individual identity, to the extent it is genetic, is genomic. We have not demarcated a nonindividuating subset of the genome that we may cede. We do know that individuality is greatly affected by a relatively small number of regulatory sequences that control which genes are expressed. Such sequences are indeed used in biotechnology manufacturing unless a bacterium's or other host's regulatory sequences effect expression.

Let us assume for the moment that it is possible to grant monopolies on proteins and DNA sequences without there resulting any interference with the autonomy of any individual. The PTO effectively allowed as much when it began to grant patents on human DNA sequences despite its earlier declaration that a patent on a human would violate the prohibition of slavery in the Thirteenth Amendment to the Constitution of the United States. It contravenes common usage to say that a nonpossessory interest in a protein or gene constitutes slavery.

Were one confident that a system of limited monopolies would lead to advances that prevent or alleviate human suffering, one might decide that the conceptual coherence of the patent system should give way to the promotion of aggregate welfare. If patents on genes contravene the unpatentability of nature, so much the worse for that premise. It seems that one perforce resorts to that stance for the defense of patents on plant antibiotics. One might go so far as to say that there should issue any patent, even if the patenting process is purely piecemeal, that results in net aggregate welfare gains.

Whether compromise with intellectual purity be systematic or piecemeal, and even assuming any contingent results that an advocate of such conceptual indulgence predicts, this talk of welfare effects presupposes a criterion for discerning improvements in welfare. That in turn implicates some version of a social welfare function. A social welfare function is a function that yields or induces a positioning of possible resource allocations on which one may predicate a claim such as "α is a welfare improvement over β." The specification of a social welfare function is the main problem of distributive justice. For this reason, what begins as a moral problem concerning respect for personal autonomy, which arguably is tractable by virtue of the ability to eschew interfering with any individual, endures as a challenging problem of collective morality.

To the extent that patents are distributive mechanisms, this problem arises within an economy in respect of any patent. But concerns abound with respect to the welfare effects of biotechnology patents. Some may espy unacceptable burdens and risks for the human species as a whole from various patents on molecular or structural human life forms. For instance, when a patent owner sets what seems an exorbitant price for a vital drug, one observes an arguably undesirable effect of market power conferred by an unqualified government-created monopoly.

PRODUCT PATENTS ON HUMAN DNA SEQUENCES

Supposing that the prospects of collective benefit or some other morally persuasive consideration have justified the alteration and use of life forms, why confer exclusive control on one party? The orthodox *quid pro quo* of a patent is that, instead of keeping an invention a trade secret, the patent teaches the details. When a patent expires, the invention will be in the public domain, and even during its term, what others learn from its teaching may foster other innovations. Whether the patent's revelations are in fact valuable will depend on whether one may easily infer the invention by reverse engineering (12). An alternative and more familiar rationale asserts that a patent provides an incentive that fosters ingenuity and effort. Or as Bentham put it, "He who has no hope that he shall reap will not take the trouble to sow" (13).

Isolation-Purification Rationale for DNA Product Patents

Organic compounds found in humans are, *ipso facto*, naturally occurring. Suppose that an organic chemist discovers a way to synthesize a protein in a purified form not found in humans. If the protein appears extractable from another organism, then perhaps we should not regard the protein as distinctively human. But in fact the human version of a given protein is unlikely to be identical with that of another organism. Through mutations in duplicate genes, species have evolved a variety of genes coding for different versions of proteins that we call by single generic names. The notion of isolation and purification (a creature of case law, not statute) was popularized by product patents on inorganic chemicals. (In patent parlance, a "product patent" is a patent on a thing as opposed to a patent on a process.) The notion was then borrowed in support of patents on the products of biological processes, including purified human adrenalin, prostaglandins, vitamin B_{12}, and, most recently, human DNA sequences. For the last, investigators' counsel have persuaded patent examiners that investigators have "isolated and purified," which is to say cloned, human genes.

There is reason for scepticism whether a patent must be available in order to induce a given result. "The large amount of research that has already occurred when no researcher had sure knowledge that patent protection would be available," noted the Supreme Court of the United States in affirming the patent on the oil-eating bacterium, "suggests that legislative or judicial fiat as to patentability will not deter the scientific mind from probing into the unknown any more than Canute could command the tides" (6). There arrived for filing a spate of plant patent applications in Europe, many presumably from European companies, quickly after the first plant patent was allowed there in 1989, which suggests that the research had long before been done. And rivals face effort and expense to follow a first entrant into the market. In the United States the lead time that an imitator of a drug or medical device would need to obtain approval from the Food and Drug Administration ("FDA") for selling the product provides a period of *de facto* exclusivity to the product's originator once the originator obtains approval. There may also be observed a tendency after a favorable experience for physicians to continue prescribing, and consumers to purchase, the first drug of a genre. Assertions about the necessity of incentives can be facile, but evidence is lacking.

Inventions concerning nonliving phenomena make use of materials that mankind has long exploited with an aplomb perhaps attributable to the mistaken belief that we cannot alter earth's vastness. Biological inventions obviously effect alterations of nature. If we approve the engineering of some protein, we might view the circumstance that it is found in humans as a reason against monopoly. Hence the isolation–purification rationale originated for chemistry in general cannot be assumed to carry the day for human compounds. One might add that to adopt such construct for humans would not follow the model of chemistry faithfully enough. Patents have been granted to those first to synthesize chemicals, but courts tend to find evidence that chemical patents have been infringed only insofar as a patentee's process has been copied.

The probable benefits of recombinant innovations may in a given case outweigh the acknowledged detriments. But each wave of innovation evokes a new comparison of risks, costs, and welfare gains.

Unpatentability of Nature and DNA Patents

An enduring challenge for the molecular biologist is to understand a disease or bodily function, to identify a protein related to it, to ascertain the nucleotide sequence of a gene coding for the protein and the protein's amino acid sequence, to locate the gene on a chromosome, and to explain the gene's regulation and expression. Once sequenced, a cloned gene may be preserved as complementary DNA ("cDNA") in a vector. When vectors transform and infect, not only do they multiply an inserted gene, but the gene can integrate into the transformant genome, causing such host to produce the protein for which the gene codes. It is by growing such transformants under suitable conditions that a biotechnology manufacturer may produce a protein in high volume.

A typical patent claims at least three inventions: (a) an isolated and purified DNA sequence encoding some protein, (b) any vector that contains that sequence and any transformed host possessing that sequence, and (c) one or more processes. The patent system indulges the notion that the cloning of genes produces "inventions" that do not naturally occur. By contrast, a detailed examination of what occurs in the laboratory, though providing ample evidence to confirm our admiration for scientific achievements, reveals no *entity* that mankind creates (14).

A gene encoding any human protein exists in nature. It is embodied in a chromosome. Its transcript also exists in mature messenger RNA ("mRNA"), a single strand of DNA-complementary nucleotides. Transcription of DNA into mRNA, followed by splicing that eliminates introns, is nature's own "isolation" of the coding sequence (with uracil in place of the thymine of DNA). This alone seems to tell against the argument that only an inventor has achieved isolation. Is "purification" then the inventor's trump over nature? The process of making cDNA is not thought to occur naturally in humans (though many viruses that infect humans make DNA from RNA). But once a gene is known, the laboratory process of making cDNA can be routine. Perhaps then vector and host deserve credit as the ingenious embodiments of purification? Where a host and a donor of foreign DNA are members of species that do not mate, asserted Stanley N. Cohen and Herbert W. Boyer in teaching the first recombinant process, a recombinant host "could not exist in nature" (15). This imagined impossibility of course is an exaggeration. Any mutation is possible. As Bernard D. Davis observed in debating the hazards of recombinant DNA research, bacteria absorb foreign DNA from lysed cells of their host, including the human gut. The rate of bacterial absorption of foreign DNA is low, but the number of bacteria in the gut is enormous, and bacteria have thrived for millions of years. There is some probability for any given human gene that it has already occurred in a bacterium. We may not observe that gene today, since the gene may have conferred no selective advantage on the bacterium, and the strain vanished (16). On the other hand, what is the likelihood that a plasmid or bacterium naturally contains a given human gene? That probability may approximate that of unicorns existing. Cohen and Boyer evoked a sense of mythological improbability when they called an altered plasmid a "chimera."

When a patent claims a chimera and host, the two are usually notable only in one respect: they contain a DNA sequence that the applicant purports to have invented. The plasmid and host are effectively the sequence's housing and factory. Once an investigator has selected a sequence as described above, the process of cloning it, and hence the "invention" of the sequence in a vector and transformed host, is mechanistic. Advanced techniques for sequencing proteins may make straightforward the selection of probes and primers, and hence the discovery of a known protein's gene. The "invention" of a protein variant may also follow straightforwardly from a variant, experimentally achieved, of a gene sequence. An investigator who finds naturally occurring genes and proteins merits accolades. But it remains to be

shown why a patent should issue, and if so, on what.

What Should Suffice for a Biotechnology Product Patent?

As necessary conditions for award of a product patent, consider the following: (*1*) a claimed invention is such that it is highly improbable that we shall find it as such on earth or on any other astronomical body to which human travel is possible, and (*2*) the invention is ingenious. The "as such" phrase in (*1*) would allow some particularly convenient forms (e.g., a vector with a foreign DNA insert) to gain recognition apart from a natural form. In (*2*), "ingenious," which shares an etymological root with "genetics," is a placeholder for what constitutes an invention, of which more later. Sequences fail (*1*) if they are found in chromosomes and mRNA. Chimeras, transformed hosts, and cDNA meet (*1*) but fail (*2*) when they are mere mechanistic steps from discovery of a sequence. The vectors and hosts of microbiology are not as fastidious as the species united in mythological chimeras: they accept DNA inserts regardless what creature originates them.

An "artificial gene" may satisfy both (*1*) and (*2*). In theory such a gene may be constructed of any codon-containing sequence one likes; in practice the amino acid sequence of a protein may inspire the sequence. Some caution may be needed in characterizing a sequence as "artificial" because if a sequence codes for a human protein, then either that sequence, another differing only by substitution of alternative codons for the same amino acids, or yet another that is insignificantly different exists somewhere in the genome. Because of the phenomenon of overlapping genes, the sequence may also be part of another gene that its discover has not even envisioned. On the other hand, it may be that an "artificial gene" meets (*1*) and that its gene product is in some sense superior. (The artificial gene product might, for example, lack contaminants usually found in the natural gene product.) Not every such sequence will be ingenious. Courts have often declared DNA sequences inferred from protein sequences to be obvious (17, p. 50).

In view of patents on algorithms—a departure from previous conventional wisdom that ideas are not patentable—one might appeal to the notion of patents on information as a defense of DNA patents. But this defense would seem to fail insofar as any information encoded in cDNA is encoded in naturally occurring DNA and mRNA.

Adverse Welfare Effects of DNA Patents

If the autonomy of no one in particular is threatened by a product patent, the autonomy of everyone together might be.

The PTO in 1987 granted a product patent on isolated and purified natural erythropoietin. Merely four months later it granted a second patent to another party relating to a recombinant DNA technique for making the protein. The second patentee had cloned the gene after screening a genomic DNA bank with two sets of probes. It then produced the protein in transformed hamster ovary cells. The first patent blocked the invention of the second. This portended that patients would be deprived of a recombinant method of producing erythropoietin in high volume at low cost. As a group, patients were saddled with the first patentee's production method (extracting extremely low yields of the protein from thousands of gallons of urine). When, four years later, the first patent was invalidated on unrelated procedural grounds, the second became a barrier against any better recombinant process employing the claimed sequence (18). Similarly did a biotechnology firm discover the human gene for factor VIII:C by probing a human cDNA bank, inserting the gene in plasmids, transforming hamster kidney cells with the plasmids, and producing factor VIII:C. This recombinant advance was blocked by an earlier patent on factor VIII:C itself (19). The patentee's process not only required enormous amounts of donated blood plasma for a small yield, but in contrast with the recombinant method, it risked contamination. Contamination was a critical risk because many hemophiliacs who received contaminated factor VIII:C died of AIDS. The recombinant's manufacturer protested unsuccessfully that the patentee had not invented factor VIII:C (though, given the

chance, the manufacturer might have argued for its own invention of the recombinant). The erythropoietin and factor VIII:C episodes illustrate how product patents may frustrate society's interest in encouraging, at the same rapid pace at which biomedical research is otherwise moving, helpful innovations in processes for making therapeutically valuable human compounds.

Farmers raise the specter that, burdened by the high cost of patented animals and crops, they may turn to cheap unpatented strains, that crops will become less diverse, and that more crops will succumb to pests. In transgenesis, often an investigator cannot control the place within a genome at which a foreign gene inserts or the number of copies that insert, or in the case of plants, the weeds or other unwanted plants to which a transgene may migrate via airborne pollen. We also have reason to rue "blind promotion of technological innovation" (20). Agriculture, after all, is an industry afflicted with overproduction. A patent granted by the European Patent Office on all manner of genetically engineered soybeans has been criticized on the ground that soybeans are among the world's most important crops and monopoly of soybeans will threaten "world food security." Suppose that a patent on a critical crop, organism, or substance has been conferred on an enterprise that becomes bankrupt. Or suppose that the patent is acquired by some foreign entity that is involved in international intrigue, that uses the patent as leverage for some disreputable purpose, or that otherwise seems to control output contrary to the common good. As exemplified by experience with the anti-AIDS drug zidovudine (or "AZT"), the price of a patented product is a monopolist's price.

Scientists have become acutely aware that availability of patents on DNA sequences may be generating a patent race that misallocates resources and delays publication of results. This would run contrary to the hope underlying the Human Genome Project that disseminating chromosomal mapping and sequence data will foster growth in collective knowledge. It took four years after a gene implicated in breast cancer, *BRCA1*, was mapped to chromosome 17 before one of twelve rival collaborations found the gene, a feat they all recognized as a "discovery" (21). Yet the winner immediately sought a patent on *BRCA1* and related diagnostic processes. About a year later, one of the competing groups contributed to a public database the sequence of a large portion of chromosome 13 where *BRCA2* was thought to repose. "It will not be helpful to medicine," the scientist John Sulston was quoted as saying, "if, by the year 2003, control of every single gene is tied up by one company or another for twenty years. That would be an enormous ball and chain. . . .[F]or the good of humanity, we should try to keep these things in the publicly exploitable domain" (22). The group contributing the chromosome 13 sequence data urged that DNA sequences be public information. Within a month thereafter, *BRCA2* was found (23). This seemed to exemplify the rapidity of progress when results are shared. Thereupon the discoverers of *BRCA1* filed for a patent on *BRCA2*, launching a dispute over who found *BRCA2* first. Seemingly ignored was the untenability of claiming to invent parts of nature's storehouse.

One cannot dismiss objections to product patents as the outpouring of any single, disputed moral view. Even without an appeal to morality, it may be argued on exclusively scientific and economic grounds that patents on human DNA sequences violate the unpatentability of nature. Many moral views assign significance to the aggregate welfare consequences of that violation. In such case the moral case against human DNA sequence patents reprises the scientific.

ALTERNATIVE INCENTIVES FOR BIOTECHNOLOGICAL INNOVATION

Measures for Holding onto the Availability of Product Patents

The legal criteria for patentability are that a "process," "manufacture," or "composition of matter" be "new," "useful," and "nonobvious" (24). According to a conservative article of faith espoused by patent practitioners, these criteria possess such protean qualities as to suffice for the resolution of all questions that arise from time to time. The criteria

need only be interpreted by the courts. In reply to this, it must be said that, under prevailing interpretations, "new" and "useful" erect only minimal thresholds. "New" eliminates from patentability only what has already been published. "Useful" eliminates from patentability only the utterly useless, a rare creature among proffered inventions anyway. (Scientists at the National Institutes of Health, NIH, dramatized the weakness of the "utility" requirement in 1991–1992 when they ostensibly satisfied the criterion by citing a seemingly trivial use for parts, "expressed sequence tags," of cDNA sequences. The applicants conceded ignorance about the feature of usual biological interest, viz., what the sequences encode or regulate, and ventured only that the tags could be useful as genetic markers, primers, or probes in diagnostic kits for unnamed diseases. But any DNA sequence may be a marker in genomic mapping.)

To resolve a question of patentability, two sobriquets, "manufacture" and "nonobviousness," must carry most of the load. In fact nonobviousness must do all the work. For it is considered settled in U.S. patent law that cloned DNA sequences, as fruits of "isolation and purification," constitute a patent eligible genre. Being a "product of nature" is now seen as no impediment to patent eligibility; the question is whether a sequence constitutes a new, useful, and nonobvious manufacture or composition of matter (25). Thus stood on its head is Jefferson's use of "product of nature" for the unpatentable. But the point is only semantic: since every extant thing's ingredients are naturally occurring raw materials, every extant thing may be called a "product of nature" in some sense. The semantic point entails no practical consequence if some other provision insures the unpatentability of nature. (As defined earlier, the unpatentability of nature is the premise that to be eligible for a patent, a thing must be such that there obtains only a very low probability that without human intervention, the thing exists near the surface of the earth or on other astronomical bodies to which humans travel.) We might think that the statutory term "invent" secures the unpatentability of nature. But instead for the domain of biotechnology though not for others, we observe patent examiners and courts effectively either rejecting the unpatentability of nature or exhibiting remarkable restraint as they construe the premise. The DNA sequences that they pronounce patentable are sequences that *chromosomes of living beings contain*. The only apparent way to reconcile this with some version of the unpatentability of nature is to emphasize that a given cDNA sequence corresponding to a chromosomal sequence differs from the chromosomal sequence insofar as the chromosomal sequence is littered with introns. Still it must be said that the chromosomal sequence *includes* the cDNA sequence. That is to say nothing of the chromosomal sequence's uninterrupted transcript in the form of mRNA. Courts and patent examiners keep faith with only a weak version of the unpatentability of nature.

Given that DNA sequences are recognized as a patentable genre, whether a given sequence garners a patent turns on whether the sequence is deemed obvious. When courts first struggled with arguments about recombinant DNA technology, it seemed obvious that what was obvious was not obvious. As courts came to recognize recombinant techniques as commonplace, they bent over backwards to conclude that newly discovered cDNA sequences were nonobvious. If the prior art did not enable a method of finding a proffered sequence "with a reasonable prospect of success," a court would pronounce the sequence nonobvious. (This move vindicated a patent on the sequence encoding erythropoietin, a sequence found by screening a genomic DNA bank with two fully degenerate sets of oligonucleotide probes.) As further reasons to sustain a verdict of nonobviousness, courts have even recognized circumstances extraneous to the intellectual process of discovery and invention, including commercial success, long-felt need, failure of others, unexpected results, and the scepticism of rivals (17, p. 19). As critics would have it, one influential judicial decision saves the day for cDNA patents only by tortuously construing "obvious" so as effectively to declare patentable *per se* any DNA sequence found to encode a protein (26). According to one observer, the obviousness of many purported

cDNA inventions is betrayed "in the very attitude of the persons skilled in the field. Today, if a researcher discovers a new protein and its probable properties, he usually does not publicize the information until he has found the corresponding gene. How to explain this in a community whose motto is 'publish or perish' save that it would be obvious to another research team to pick up the information, and clone the gene?" (17, p. 90). In hopes of securing future DNA patents against a tide of progress that may render ever fewer cDNA sequences nonobvious, it has been suggested that the nonobviousness requirement, to the extent not already emasculated by the aforementioned judicial decision, might be weakened. If the steeplechase jump proves too high for the average contestant, lower the bar. Where a nucleotide sequence is itself a drug, as with anti-sense RNA or the use of a DNA sequence to achieve expression without integration into the genome, it has been suggested that obviousness might be replaced with superiority over prior art in therapeutic efficacy (17, pp. 141–143, 148). Without some such move, it is urged, future application of the obviousness standard may thwart the availability of product patents on the expectation of which the biotechnological industry arose. Here an appeal is made to the biotechnologist's familiar prediction that a world without DNA patents will be a world without therapeutic innovation. But rehearsing that prediction does not provide evidence for it.

The issue remains whether, all things considered, more DNA product patents should issue. By virtue of considerations mentioned earlier, the answer may be in the negative. In such case, what might replace such patents?

Categorical Prohibitions

In the Biotechnology Patent Protection Act of 1995 (27), procured at the behest of the biotechnology industry to allow a biotechnology process claim to piggyback on a product claim, precedent was set for legislation that speaks in biological parlance about patents concerning molecular biology. Despite the supposed protean generality of the patent conceptual scheme, the door has been thrown open to discipline-specific rules. What most commonly seems to flow through that door is a stream of *ad hoc* prohibitions, usually categorical and often embracing uses as well as monopolies on uses. One favorite in the U.S. Congress and the European Parliament is a moratorium on a given sort of patent or research. Sometimes the rationale for a prohibition will appear to assimilate a property interest in an extracorporeal molecule to invasion of personal autonomy, which earlier we found reason to distinguish. As the portion of the human genome claimed by patents expands, motivation arises to prohibit any more such patents. Were a ban imposed, the control experiment of life without patents would run in real time. Biotechnology firms would compete with no intellectual property save for trade secret protection of whatever they managed to keep secret. Such competition might produce salutary results. It might also diminish aggregate welfare unless some mechanism replaces at least some of the incentives fostered by product patents.

Compulsory Publication of DNA Sequence Data to Thwart Patents

When without first filing for a patent, a scientist publishes a DNA sequence, no one may obtain a patent on the sequence. Mere citation of that publication as prior art will spike anyone's claim that the sequence is "new." Mindful of this, some scientists acting of their own volition and other scientists acting in compliance with funding mandates have promptly and systematically released DNA sequence data as discovered. A concerted effort so to publish could thwart most new DNA patent applications. Thereupon it becomes open season for any and all to explore therapies predicated on all unpatented portions of the genome. The benefits of expanding the universe of potential investigators would seem apparent. To the extent that research motivated by profit may contribute applications that might not flow from academic laboratories, incentives must now be sought elsewhere.

Subsidies

When a public good is underprovided, as is familiarly the case in perfect competition (e.g., as to education and national

defense), government may step in to provide it. Valuable public ideas are intellectual public goods. Suppose then that no further patents issue on DNA sequences other than artificial sequences. Instead, the government systematically subsidizes biotechnological research. Subsidies are awarded not only to academic institutions but to nonprofit biotechnology research centers. Specifically organized for the pursuit of applied as well as basic research, these centers tackle applications that might not be pursued, or pursued with less zeal, in academic laboratories. This scheme could implement coordinated decisions, reached with benefit of expert extramural advice, concerning which fields of fundamental biomedical and biotechnological research should be pursued and to what extent. The scheme entails substantial expenditures and may importune taxes earmarked for research (20). But the subsidies assure that society gains the benefit of valuable innovations.

Were it widgets that society sought to encourage, subsidies for institutional laboratory research might not succeed in coaxing the same innovations as would market incentives for entrepreneurs experimenting in their shops. When the desired innovations are biotechnological, it happens that academic laboratories constitute society's most fertile source of ideas. What academic laboratories do not pursue by way of applications may be pursued in the research centers. Were a share of sales revenues promised to any laboratory originating an end product, market incentives could also be brought to bear within both academic laboratories and research centers.

In the marketplace, with valuable discoveries being contributed to the public domain and available for exploitation, firms would now compete less on the basis of their discoveries and more on their efficiency in production. As with any subsidy, it may be difficult to ascertain whether the extent of biotechnological innovation induced is optimal. But one could at least compare the extent of technological innovation during the present era of product patent availability with the extent of technological innovation under a new regime.

Exclusive FDA Approval for a Term of Years

A government may also engraft an incentive mechanism upon the process by which, with a view to public safety, the government grants approval for the sale of medical products and devices. The Orphan Drug Act (28) affords a model for such an incentive scheme. According to that statute, if the FDA grants a manufacturer approval to sell a drug targeted at a disease that affects fewer than 200,000 persons in the United States, or whose likely sales cannot reasonably be expected to recoup the costs of development, the agency must refrain, for seven years after such approval, from approving sale of the drug by anyone else for use against that disease. Routine delay in obtaining FDA approval for any drug affords to the first party who gains FDA approval some period of *de facto* postapproval protection against imitators; in respect of an orphan drug, the first party to gain approval enjoys seven years of *de jure* postapproval exclusivity. The orphan drug scheme is not without its complications. For purposes of identifying which compounds are blocked for seven years by an approved orphan drug, it has been necessary to define what constitutes "the same drug." The FDA defines a new drug to be the same as a previously approved orphan drug if the new drug has the same "principal molecular features"—unless the new drug is "clinically superior" to the approved orphan drug (29). This seems to rehearse, though with variations, a judicial patent doctrine that a claimed invention is obvious if the prior art includes a structurally similar compound—unless the claimed invention possesses an unexpected property (17, pp. 145–148).

This incentive scheme could be extended. From orphan drugs it could be extended to any genre of products that seem likely to serve the public interest—indeed to any and all biotechnology products. To specify the genre of products for exclusive approval, the government could rely on advice from extramural scientific panels. Such a scheme would spare the costs, burdens, and uncertainties of patents. It would reward the development of valuable products without tying up the human genome with property claims. It

would respect the unpatentability of nature. The number of years and other terms of the exclusive sale privilege are of course variable. One might also replicate the provison of the Orphan Drug Act that allows the FDA to approve sale of an orphan drug by a second applicant if the original manufacturer "cannot assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition" (30).

Human Methods Patent

Ambivalence between patents on products *vis-à-vis* patents on processes has been evident since recombinant DNA technology began. The Cohen-Boyer patent protects a process. It was followed, as the technology developed, by many process as well as product patents (31). The Cohen-Boyer application also sought claims on recombinants, but no product patents issued until 1984 (on plasmids) and 1988 (on plasmid-transformed hosts). Stanford University's licensing of the process patent thrived beginning in 1981 before Stanford acquired any product patent (32).

A possible resolution of the ambivalence would be to require hereafter that to secure a patent pertaining to a DNA sequence, one must invent some new process that can be performed in respect of the sequence rather than claim to have invented the sequence or its gene product. A new form of patent predicated on this principle has been proposed (14) in the following statutory phrasing:

> There shall be allowed a patent pertaining to a human life form (a "human methods patent" or "*HMP*"), the scope of which patent shall not exceed the least inclusive description of an ingenious process. Such a process may consist in the production, use, alteration, amplification, or attenuation of human life forms outside the human body. An *HMP* may include an additional claim on nonhuman reproduction of any transgenic and its progeny if and only if (a) the ingenious process produces such transgenic, (b) such transgenic produces a human life form, and (c) without reference to such human life form, the process would not be patentable.
>
> No product patent shall be allowed on a human life form or anything in which it is included. The foregoing shall not preclude a patent on a synthesized, fully explicated nucleotide sequence or protein that is not present, consecutively or otherwise, in the human body.
>
> Research in a nonprofit institution for nonprofit purposes shall be exempt from any claim of infringement.

The significance of an *HMP* may be made more clear by the following observations.

(i) Interspecies homology is only similarity to a degree, not identity of nucleotide sequences. Absent evidence of identity with a nonhuman form in a given case, "human life form" may be assumed distinct.

(ii) The confinement of an *HMP* to the least inclusive description of an invention protects against the detriment of overbreadth as illustrated by experience with erythropoietin and factor VIII:C. Such limitation would depart from the law's tendency to allow contributors a claim on a whole—as when a farmer obtains a claim on grain in an elevator with which the farmer's is commingled, or a security interest in a part attaches to a mass in which the part is commingled or assembled. Reasons for parsimony obtain concerning the human genome.

(iii) Suppose that an *HMP* claims "a method for obtaining DNA sequence $b_1, b_2, \ldots b_n$ from genomic DNA as follows: . . . ," and describes the ingenious method by which the sequence was discovered. Without more, such a patent would afford little protection. Everyone may now read the sequence disclosed by the patent. Free of infringement, anyone may then obtain the sequence by employing any process, including the polymerase chain reaction, other than the patented process. To avoid this vulnerability, the discoverer might seek to claim "cloning of the sequence in vector v and transformation by v of host h that results in production of protein p_i as follows: . . . ." Perhaps this investigator has ingeniously devised a way to use a new v to produce p_i in some mammalian h never before used to produce human substances. In general, it will not be ingenious to clone an identified sequence, nor to produce a protein by means of a known gene. The principle of least inclusiveness allows a claim on only so

much of the process as is ingenious. The discoverer's successors may find it unnecessary to use the process first used to discover the thing, and may proceed to "event around" the process. This is true about the discovery of any natural thing. Successors may also invent methods by which to use, alter, or promote or attenuate the effect of the thing.

Process patent opportunities still await—in protein chemistry, insertion of foreign DNA, transformation and infection, gene expression, and protein-manufacturing techniques. One process might describe a technique for making a protein, another how to use it. Or a firm might use knowledge of a gene not to produce but to curtail the effect of a given protein, including a newly discovered protein.

(iv) It may be possible to state certain minimal conditions for work to be ingenious. If a claimed method is predicated on a human life form, it may be unlikely to exhibit an advance over present knowledge unless the life form is fully explicated. "Fully explicated" entails, in the case of DNA, that a specific nucleotide sequence (the "explicated sequence") is identified, including all regulatory sequences necessary for any exons in the explicated sequence to be transcribed into RNA and for a gene to be expressed, that all such sequences have been inserted into a vector or maintained in some stable form, that it is known what the explicated sequence encodes or regulates (or perhaps only that it is implicated in the etiology of a disease), and that the process succeeds in expressing or preventing expression of such gene. For a protein, full explication would embrace biological function, amino acid sequence, and encoding gene sequence.

(v) One could circumvent a patent thus far described if, for example, one were to pay a royalty in order to perform a patented transgenic process of producing a human hormone in a pig, and then, without paying any more royalties, one were to breed a line of pigs. Thereby one could obtain copious amounts of the hormone. Natural breeding of course produces naturally occurring progeny, and, except for plants in the United States, such progeny would seem unpatentable. To prevent the foregoing circumvention, which would defeat an inventor's reasonable property expectations, the *HMP* allows a claim on growing or nonhuman breeding of a transgenic if the transgenic is a result of the invented process and the transgenic produces some human life form without reference to which the process would not be patentable. The additional claim may be defended as a claim on reproduction of an "unnatural" organism, one not likely to be found in nature. Such scheme resolves the predicament to which the self-reproducibility argument for the Harvard mouse patent is directed. It allows no claim on a human life form itself. Nor may the additional claim encompass human reproduction. Should the invented process happen to be one of artificial human reproduction, remedies may be provided (as discussed in the next section) against infringing providers, but never against a parent or child as such.

Whether an "artificial gene" or the protein it encodes will qualify for an *HMP* is contingent on how close a variant or equivalent the gene may be to what is found in the human genome. Will this contingency discourage fruitful research on the genome? Significant disincentives seem unlikely unless firms so greatly prefer product to process patents that they choose to pursue the more difficult task of sequencing proteins rather than finding naturally occurring genes encoding for proteins. Where proteins may be sequenced automatically, a disincentive may occur. But if the therapeutic value of an artificial gene product is not sufficient, it will not be an appealing product no matter what the patent availability. At least the products of naturally occurring genes have known worth.

Objections to the *HMP* and replies thereto include the following. Industrialists preferring product patents often contend that recombinants are more potent and free of contaminants, that recombinants thus differ from natural isolates and from each other, and hence that product patents will not prevent new advances from reaching the market. This conjecture seems belied by the history of erythropoietin and factor VIII:C in particular, and in general by the hegemony of any product patent over improvements. Whichever industrialist happens to be first in

time will often hoist another on the petard of contradiction. In scientific publications and in advertising, sellers of recombinants are wont to describe their products as virtually identical to the corresponding natural isolates. But when forced to defend against a claim of patent infringement, the same sellers may be heard invoking the "reverse doctrine of equivalents," which, under U.S. patent law, excuses some literal infringements if the accused product displays differences in specific activity and purity from the patented product. (The doctrine of which this is called the "reverse" sustains a claim of infringement against an accused protein somehow differing from a patented protein if no functional differences obtain between them.)

A more orthodox industrialist objection to the *HMP* would be to say that without product patents, businesses will not invest the millions of dollars needed to find a gene and to produce a protein by recombinant methods. This bluff is handy because it is counterfactual. As earlier indicated, when one looks at the relatively scant evidence of inventive behavior without patents, and then conjectures about what happens if only process and not product patents are available, one may be sceptical about the claim that biotechnology cannot thrive without product patents. The effective protection afforded by process patents depends on how easy it is to design around a process. Large, complex proteins found in humans may be more difficult to design than, say, pharmaceuticals. Biotechnology patents are replete with process claims. It appears that firms have found ways to protect their intellectual property even though patent examiners vary in their view of product *vis-á-vis* process claims, and even though, given how often courts invalidate them, the status of any product patent is contingent. It must be granted that process patents are often less convenient to enforce because a patentee must show what transpired in a rival's plant. Even so, if a patent has been issued on a recombinant process, ordinarily the recombinant result has only a very low probability of naturally occurring. The patent holder may invoke this probability to refute a defendant's claim to have bred transgenics without using a patented process and without using offspring of the patented process.

One previous motivation for a U.S. product patent is now obviated. When the Harvard mouse emerged, anyone could avoid infringement of a U.S. process patent by performing the patented process in a foreign country outside the reach of U.S. law and then importing the end product into the United States; no such move would defeat a product patent. A statutory amendment changed this by declaring that any such importation is an infringement of the process patent (33). By virtue of the Biotechnology Patent Protection Act, one may obtain a process patent on a recombinant process that uses or makes a patented product, although this piggyback rule will be moot if product patents become unavailable. Instead of this piggyback rule, it might better be declared that a patent is available on an invented process if what the process uses or produces would be patentable but for the fact that the product is a human life form. Such is the effect of the *HMP*. It allows a process claim to be predicated upon a human life form while allowing no claim on the life form itself.

It remains necessary to show an ingenious process. An industrialist may object that there seem to be few new processes to invent, that current biotechnology employs standard processes that differ only by genes expressed. Mere substitution of a different gene in a known process may indeed be perfunctory. It would not seem to state an argument for product patents to say that innovation is difficult. Opportunities for process innovations abound. The Cohen-Boyer patents expired in 1997. It may simply be that the challenge of finding genes commands more attention at present.

The *HMP*, subsidies, and a period of exclusive FDA drug approval could be implemented separately or together.

ANCILLARY MECHANISMS

Compulsory Licensing

A patent subjects society to the vagaries of a monopolist's choices and fortunes. A possible protection against such risk with respect to biological patents is compulsory licensing according to which anyone may use a patented process upon payment of no more than some reasonable royalty. Another protection is ceilings on the prices of goods made by patented processes. As early as the federally supported Cohen-Boyer research, the NIH considered seeking patents on funded innovations. NIH asserted patent rights to AZT based on the research contributions of NIH intramural scientists, all with the declared purpose of restraining prices of products. This prompts the suggestion that a government agency other than the patent office be empowered to determine what events trigger, and the royalty rate of, a compulsory license established as a condition of any biotechnological patent. A further condition might empower the agency to set maximum prices on goods produced and processes performed in the practice of the patent. An ideal scheme would foster commercial incentives and allow a reasonable return on investment while preventing exorbitant prices.

Such a scheme, it may immediately be objected, would interfere with markets. The industrialist might contend that governments should not restrain returns on genetic inventions since they do not restrain prices of patented artificial hearts or organ transplants. One might reply that when a government grants the privilege of selling a drug or medical product, or of enjoying a monopoly on anything importantly related to human health, the public interest may justify conditioning the privilege on end product price restraint. Compulsory licensing would also protect against disasters with respect to things other than price. As earlier noted, the patentee of the sole therapy for a serious disease could become bankrupt or for other reasons decline to practice or license the invention. The common weal may demand that the invention be available. The industrialist's appeal to the case of an organ transplant does not provide a persuasive counterexample against a compulsory license because organs are donated and recipients pay only for services. An artificial organ is not perfectly analogous to a gene since the organ lacks person-defining genetic information. In any case there may be good reasons to interfere concerning any commerce in human parts.

Expert Guidance

A U.S. patent is only presumptively valid. Since courts often invalidate patents, no one knows for sure that a patent is valid until and unless it is upheld in court. Consider how numerous are the courts within the sovereignties that comprise the international biotechnology market. Trial courts decide only questions placed before them by a flow of cases that is nearly stochastic. The same is true for appellate courts on which depend the prospects of resolving conflicts among trial courts. In contrast to scientists for whom dialogue is a way of life, judges of different courts do not, as a matter of decorum, communicate with each other on pending cases. The science on which they rule is also limited to that practiced a few years, if not a decade, before trial. This obtains because time of invention is the reference point for what is obvious. Hence judicial decisions provide uncertain guidance about patentability of today's scientific processes. Moral issues, as we earlier saw, are not even tackled.

It seems improbable that any one word such as "nonobviousness" or "ingenuity" can bear the load of defining what is a sufficient feat to merit a monopoly. For instance, a claimed invention might be a *tour de force* of genetic engineering, even though the investigator knows neither a sequence's chromosomal locus nor the sequence's coding or regulatory function, if the investigator correctly infers that the sequence is involved, by homology or otherwise, in the etiology of a disease. To transform "ingenious" from placeholder to admission ticket, we may have to settle for a notion of family resemblance. For if ingenuity were to admit of precise definition, would anything be ingenious?

To meet the difficulty of recognizing ingenuity as science progresses, to overcome the lag between research and adjudication, and to

improve upon the limited expertise brought to bear in patent adjudication, a mechanism could be confirmed for introducing scientific expertise. A government agency, otherwise involved in scientific research, could exercise authority continually to revise published standards for patenting life forms in reliance on recommendations of expert scientific panels. For purposes of judicial review, the law could preserve the practice of judging a patent by the standards in effect at the time of alleged invention. From such expertly framed standards, the biotechnology industry could obtain guidance more current and systematic than case law or statute is likely ever to be.

IMPLICATIONS OF PATENTS IN THE CLINIC

Introduction of Human Substances Outside the Germ Line

Ex vivo somatic intervention involves removing patient cells (e.g., tissue-infiltrating lymphocytes or bone marrow stem cells), growing them in culture, transferring genes into them using nonvirulent retroviruses or otherwise, and reintroducing the cells into the patient's body, not necessarily at the site of their effect. *In vivo* intervention is exemplified by the introduction of retrovirus vectors containing human genes at the site of the condition to be overcome. The ED, which would allow patents on substances isolated from the human body, would permit, while the *HMP* would deny, a patent on such cultured cells or vectors. They are ineligible for an *HMP* because they are or contain human life forms. Indeed the cultured cells are grown from the patient's. Except for attempted enhancement, the cultured cells would be unlikely candidates for "inventions" anyway. They are not intended to be innovations. The goal of therapy is to insert a normal gene. The ultimate achievement is homologous recombination. Thereby a normal gene replaces a defective one rather than entering the genome at an indeterminate locus.

Somatic interventions involve medical procedures on patients. Medical treatment, surgery, and diagnosis are not patentable in Europe (34). Their eligibility for U.S. patents has been dubious since 1862 when a patent was sought on the use of ether. It has seemed to many that it would be wrong to discourage physicians, on pain of infringement, from deploying in the relief of human suffering the most efficacious procedures they can muster under the exigencies they face. Hence one might conclude that the only processes of somatic intervention that may qualify for an *HMP* are ancillary laboratory processes. Similarly might patents be confined to laboratory processes with respect to tissues or organs grown in cell culture—especially if, as may be typical to avoid rejection, the cultured cells are grown from the patient's. Opportunities for process innovations would appear abundant when one apprises present difficulties in somatic cell therapy and the challenge of growing tissues and organs.

A contrary moral view might be that the foregoing is too generous. Suppose that one opposed patents on reproduction of any sort. One might assimilate the culturing of cells to reproduction, thereby reversing the patent law's assimilation of reproduction to manufacture. One might add that a laboratory process ancillary to a medical treatment is indistinguishable for these purposes from the treatment. The contention that human reproduction cannot be an infringement does not entail any claim about what is human reproduction. One might conclude that a patent on growing cells outside the human body does not threaten any patient's autonomy so long as there is no claim on the cells themselves. The difficulty of developing successful methods of somatic cell therapy, and of cultivating tissues and organs, suggests the benefit of patent incentives. One need not claim that laboratory processes ancillary to medical procedures are in general nonmedical. One need only allow some of them to be patentable.

Human Germ Line Intervention

Germ line intervention affects reproduction in two ways. (a) It alters the genome, an offspring's complement of genes that appear in all cells including the gametes. (b) In order to achieve (a), it is performed before germ and somatic cells of an individual differentiate, i.e., on zygotes and early stage embryos. A moral objection might be lodged against

a patent on any such method because of these links to reproduction. As noted, the ED would allow no patent on any method of human germ line intervention. Again a reply may be that collective benefit could result from creating patent incentives on certain laboratory processes. It is also noteworthy that a patent on gene therapy would not be a patent on *in vitro* fertilization. Therapy is subsequent to fertilization. The choice to conceive may be seen as a different choice than the choice whether to intervene genetically for the health of a child whose conception has been chosen, even if the former is contingent on the latter. On the other hand, the opposite may be the case if eggs fertilized *in vitro* are screened for genetic defects or traits, thereby exercising a choice of which shall live. Two *in vivo* methods also merit mention. One consists in altering an embryo *in utero* by retroviral infection. Another consists in causing adult testes or ovaries to produce genetically engineered gametes (35). A requested European patent on the latter technique was criticized as contrary to *l'ordre publique* or morality (36). For these also one may ask whether the prospect of collective benefit suffices to warrant property claims on ancillary laboratory processes of medical procedures.

If government grants patents on any germ line interventionary process, does that comport with the stance that human reproduction cannot be infringement? The answer lies in stipulating that no remedy will lie against a parent or child as such. Damages and preconception injunctive relief could be made available against unlicensed providers of patented processes. If Mr. and Mrs. Thurston, learning of Mendipulate Inc.'s patented technique for germ line manipulation, arrange with their physician for the technique but no one pays the royalty, a damage remedy may lie against the providers. We can scarcely imagine a suit by Mendipulate against Mrs. Thurston, her daughter or granddaughter, or their physicians or hospitals, complaining of the conception of a child, not to mention injunctive relief, i.e., an order for an abortion. Mere pragmatism makes clear that Mendipulate's interests require no remedy against a patient. Drug manufacturers do not sue patients who infringe by "using" an infringing drug. They sue rival manufacturers and distributors who "make" and "sell" the drug in quantity.

Mendipulate may protest that if it cannot obtain a product patent, every Thurston descendant will benefit from Mendipulate's invention without paying for it. Mendipulate is correct that the *HMP* allows claims on reproducing the progeny of transgenesis only for nonhuman reproduction. But consider that Mendipulate will advertise a patented process of germ line therapy as a method to remedy a genetic defect. It cannot tenably assert that if it had a product patent, many Thurston descendants would become good-paying customers when they inherit the defect! Moreover, whether the process is therapy or enhancement, Mendipulate's twenty years of monopoly will run before any transgenic Thurston reaches adulthood. Mendipulate may still complain that if Mr. or Mrs. Thurston undergoes a patented Mendipulate process that causes them to produce genetically engineered gametes, no more compensation will be gotten by Mendipulate if the Thurstons have a dozen children than if they have one. This of course overlooks the difference between having children and copying a patented contraption for profit. People are not motivated to have children because they can copy a gene for free. Mendipulate may anticipate fecundity when it prices the royalty for its laboratory process.

Since interventions will be performed by physicians, enforcement of a process patent will require showing what happened in the doctor's office. To Mendipulate this will seem inconvenient. It would prefer a product patent whose infringement it could establish by comparison of parental and progeny DNA. Such a comparison would be peculiar, to say the least, as it would be mustered in support of a complaint that a child is healthy or possessed of some enhancement. It should suffice to protect Mendipulate that licensed specialists may generally be expected to pay royalties on patented processes. What would be troublesome would be the enterprising move of a patient who sells gametes that contain

altered genes. This concern may be minimized for the moment by realizing that only enhancement genes, not corrected disease-causing genes, would be likely to be marketable.

Society might deem the collective benefit of enhancement to be insufficient for allowing a patent. If concerns about playing God and discrimination prevail, refusing patents on enhancement would be a means to discourage the practice. A contrary view might be that if we demarcate certain interventions to be outside the physician's armamentarium for maintaining health, no public policy will be disserved by a patent.

There remains possible a product patent on a synthetic gene nowhere found in humans. To use such a gene might depart from the present vision of installing normal in lieu of defective genes. The prospect of such departures no doubt explains the habitual mention of Frankenstein when observers discuss germ line intervention. Regardless, the immunity of parents and children as such from claims of infringement would control. The inventor of a human genetic intervention surrenders the product of the process for integration into an unownable being. If a process alters an early stage embryo, integration occurs into a human in gestation. If alterations are made in gametes or the means of their production, integration occurs into the body of the patient.

CONSISTENCY OF POLICY FOR PLANTS AND ANIMALS

Unless policies about forms of life evince a consistent understanding of innovation and reflect generalizable moral principles, a stable consensus seems unattainable. Conditions (*1*) and (*2*) above stated for a biotechnology product patent—low likelihood of finding the claimed invention in nature, and ingenuity—appear applicable to any life form patent. Some transgenic plants and animals may be improbable of natural occurrence and recognizable as the products of ingenuity. Others may possess transgenes from members of their own species for which the odds of acquisition by mutation are better than trivial, or as to which the process of transgenesis is not ingenious. Where a product patent would be unwarranted, a process patent could be available. As may an *HMP*, a process patent could claim a process by reference to an identified plant or animal life form. It could add a claim on the breeding of any plant or animal that the patented process produces and without which the process would not be patentable. Such an additional claim would obviate the self-reproducibility rationale for a transgenic product patent.

One may argue for bounding a patent's enforceability by operation of a "farmers' privilege," a derogation imposed for plants in the United States and often proposed for animals there and in the ED. This permits a farmer to breed patented animals to the extent needed to replenish stocks on the farm, or to plant seeds generated by transgenic plants grown on the farm. A farmers' privilege would avail a typical farmer who does not seek to compete with breeders in selling varieties as such but who wishes to sell what is raised on the farm. The derogation would entail that, as Mendipulate must do concerning the Thurstons, commercial breeders must collect their royalties on the first generation.

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See other entries Human Genome Diversity Project; Medical Biotechnology, United States Policies Influencing its Development; Ownership of Human Biological Material; see also Patents and Licensing entries.