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Gene Patents: The Need for Bioethics Scrutiny and Legal Change

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In May 2004, the European Patent Office dealt a serious blow to gene patents by revoking Myriad Genetics's controversial patent on the BRCA1 gene.[1] That patent covered any method of diagnosing a predisposition for breast or ovarian cancer that used the BRCA1 gene sequence.[2] Elsewhere, gene patents are also being challenged in courtrooms,[3] legislatures,[4] and in the arena of public opinion. Numerous international organizations, such as the Council of Europe's Committee on Legal Affairs and Human Rights and UNESCO, view genes as belonging to the common heritage of mankind.[5] Intense opposition to gene patents is also coming from

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1. Press Release, Eur. Patent Office, "Myriad/Breast Cancer" Patent Revoked After Public Hearing (May 18, 2004), http://www.european-patent-office.org/news/pressrel/2004_05_18_e.htm. This type of legal challenge is called an "opposition" to a granted patent under European patent law and allows third parties to challenge a patent's validity within nine months after it is granted. *See* European Patent Convention, art. 99 (1998), http://www.european-patent-office.org/legal/epc/. The revocation was made by the Opposition Division, a panel of three patent examiners and one legal expert, applying current law as set forth in the European Patent Convention. Decision Revoking the European Patent (Art. 102(1), (3) EPC) (Eur. Pat. Office May 17, 2004) (revoking European Patent No. 0699754) [hereinafter Revocation Decision].

2. E.U. Patent No. EP0699754 (issued Mar. 6, 1996).

3. *See* Greenberg v. Miami Children's Hosp., 264 F. Supp. 2d 1064 (S.D. Fla. 2003).

4. *See* Genomic Research and Diagnostic Accessibility Act of 2002, H.R. 3967, 107th Cong. (2002).

5. *Protection of the Human Genome by the Council of Europe*, Council of Eur., Comm. on Legal Affairs & Human Rights Doc. 9002 (Mar. 19, 2001), http://assembly.coe.int/Documents/WorkingDocs/doc01/EDOC9002.htm; *Universal Declaration on the Human*

researchers,[6] politicians,[7] organized religions,[8] indigenous groups,[9] patient groups,[10] and medical professional organizations.[11] Patents covering human genetic material raise a variety of issues related to legal appropriateness, scientific and medical research, and access to health care, as well as issues regarding privacy, autonomy, religious freedom, and reproductive liberty. While there are reasons to celebrate many new developments in medicine and bioethics, patents for human genetic material are an example of a bad policy that needs to be corrected. Gene patents raise bioethical concerns because they can impede access to appropriate health care and violate individual rights.

I. THE UNCOMFORTABLE FIT BETWEEN GENES AND PATENTS

Over two centuries ago, the framers of the U.S. Constitution realized that it was important to create incentives for technological innovation.[12] In return for a patent, the inventor must show the invention satisfies a number of requirements, including a sufficient written description, as well as utility, novelty, and nonobviousness.[13] Yet not all inventions are patentable. For example, products of nature are not patentable.[14]

Genome and Human Rights, UNESCO Gen. Conference (Nov. 11, 1997), *adopted by* G.A. Res. 152, U.N. GAOR, 53d Sess., U.N. Doc. A/RES/53/152 (1999).

6. Declan Butler & Sally Goodman, *French Researchers Take a Stand Against the Cancer Gene Patent*, 413 NATURE 95, 95 (2001).

7. *See, e.g.*, Paul Willcocks, *Canadian Premiers Wade into Gene Patenting Debate*, REUTERS, Aug. 3, 2001.

8. *See, e.g.*, Fred B. Charatan, *U.S. Religious Groups Oppose Gene Patents*, 310 BRIT. MED. J. 1351, 1351 (1995); *see also* Southern Baptist Convention, Resolution on the Patenting of Animal and Human Genes (June 1995), http://www.sbc.net/resolutions/amResolution.asp?ID=570.

9. *See, e.g.*, Letter from Debra Harry, Indigenous Peoples Council on Biocolonialism, to Commissioner of Patents & Trademarks (Mar. 21, 2000), http://www.uspto.gov/web/offices/com/sol/comments/utilguide/ipcb.pdf.

10. *See, e.g.*, Greenberg v. Miami Children's Hosp., 264 F. Supp. 2d 1064 (S.D. Fla. 2003).

11. *See* Ass'n for Molecular Pathology, Clinical Practice Committee, AMP Position on Patenting of Genetic Tests (Nov. 22, 1999), http://www.ampweb.org/PRC/prc-tests.htm.

12. The Constitution gives Congress the power to "promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. CONST. art. I, § 8, cl. 8.

13. *See* 35 U.S.C. §§ 100-05 (2000).

14. Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) (citing Funk Brothers Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948)).

How is it then that genes are patentable? Applicants who seek human gene patents assert that they have isolated and purified a gene or genetic material, thereby producing something new—a product whose non-coding regions have been eliminated, but which still performs the same function as a naturally-occurring gene.[15] While some courts have held isolated and purified products of nature to be patentable,[16] the useful properties of a gene—such as its ability to bind to another complementary strand of DNA for diagnosis or its ability to code for a particular protein—are not ones that the scientist has invented, but rather are natural, inherent properties of genes themselves.[17] Often gene patent holders lay claim to gene segments that actually occur in nature and exist within the bodies of human beings.[18] In fact, one Australian company has acquired global patent protection over non-coding regions of the human genome, amassing millions of dollars in licensing deals with drug companies and universities for the right to use this information in research and drug development.[19]

The patent system is generally designed to incentivize research and innovation, but there are many other incentives for the discovery of

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15. Sheldon Krimsky, *The Profit of Scientific Discovery and Its Normative Implications*, 75 CHI.-KENT L. REV. 15, 26 (1999).

16. *E.g.*, Parke-Davis & Co. v. H. K. Mulford & Co., 196 F. 496 (2d Cir. 1912) (upholding a patent on adrenaline, a natural hormone that was found in animal glands). In *Parke-Davis*, the patent applicant identified, isolated, and purified the active ingredient—adrenaline—creating a product that did not exist in nature in that precise form and that could be used for medical treatment. The U.S. Supreme Court's subsequent *Chakrabarty* decision that allowed a patent on genetically-modified bacteria dealt with a new invention—a genetically engineered life form invented by combining genes in ways that did not occur in nature. Diamond v. Chakrabarty, 447 U.S. 303 (1980).

17. *See* Am. Coll. of Medical Genetics, Position Statement on Gene Patents and Accessibility of Gene Testing (Aug. 2, 1999), *at* http://www.acmg.net/resources/policies/pol-015.asp; Coll. of Am. Pathologists, Gene Patents Detrimental To Care, Training, Research, *at* http://www.cap.org/apps/docs/advocacy/advocacy_issues/Issue_Genepat.html (last visited Nov. 21, 2004).

18. *See* U.S. Patent No. 5,679,635 (issued Oct. 21, 1997) (claiming the genetic sequence of the aspartoacylase gene and protein).

19. Carina Dennis, *Geneticists Question Fees for Use of Patented 'Junk' DNA*, 423 NATURE 105, 105 (2003). That Australian company has entered into licensing agreements with a number of large biotech corporations for between $250,000 and $1 million each. *Malcolm in the Middle*, BIOIT WORLD, Aug. 13, 2003, http://www.bio-itworld.com/archive/081303/firstbase.html. In the United States, two patents covering these non-coding regions are U.S. Patent No. 5,851,762 (issued Dec. 22, 1998) and U.S. Patent No. 5,612,179 (issued Mar. 18, 1997).

genetic sequences. Molecular biologists were attempting to identify genes long before patents were awarded for genetic material. When biologists began the Human Genome Project, they had no idea they would be able to patent genes;[20] they had other reasons to search for genes, namely medical interests and the potential for academic advancement and status.[21]

The discovery of genes does not require the same commercial incentives as drug development. The development of drugs is undertaken primarily with private funds (for which investors expect a commercial return),[22] while the discovery of genes has been undertaken with vast quantities of public funds. For example, national governments and non-profit institutions spent over $1.8 billion of taxpayers' money on genomics in 2000.[23] Myriad, the U.S. genetics company that first patented BRCA1, used over five million dollars from a government agency when researching the patent[24] and utilized sequence data from public databases. Thus, if gene patents continue, the public will pay twice—first for the research and second for the high royalty costs that many patent holders require for subsequent use of their patented gene in a product.

Unlike drug development, gene discovery does not require expensive clinical trials and approval from the Food and Drug Administration. Testing for mutations in a disease gene can begin almost immediately after the gene has been identified.[25] Thus, the need to provide financial compensation to a gene-discoverer through gene patent royalties is not as great as the need to compensate the developer of a drug that must undergo costly clinical trials, especially since only a small number of drugs actually become commercially-viable products.

Moreover, there are fewer drawbacks to granting a patent on a drug or a medical device than granting a patent on a gene. For instance, other

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20. *See* Leslie Roberts, *Controversial from the Start*, 291 SCIENCE 1182, 1185-86 (2001).

21. *See id.* at 1182.

22. PHARM. RESEARCH & MFRS. OF AM., PHARMACEUTICAL INDUSTRY PROFILE 2004, at 7 (2004), http://www.phrma.org/publications/publications//2004-03-31.937.pdf. The high cost of bringing a drug to market includes the salaries for research and development scientists, the expense of animal research and human clinical trials, and the cost of obtaining FDA approval. *See* Joseph DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 152 (2004).

23. Stanford in Washington, Genomics Research Funding 1998-2000, *at* http://www.stanford.edu/class/siw198q/websites/genomics/Gov&nonprofitTotal.htm (last modified Dec. 7, 2001).

24. Bryn Williams-Jones, *History of a Gene Patent: Tracing the Development and Application of Commercial BRCA Testing*, 10 HEALTH L.J. 123, 131 (2002).

25. Jon F. Merz et al., *Diagnostic Testing Fails the Test*, 415 NATURE 577, 577 (2002).

researchers can create alternatives to drugs and devices. In contrast, there are no alternatives to use of the patented human genes for genetic diagnosis and gene therapy.[26]

II. GENE PATENTS CREATE PROBLEMS FOR ACCESS TO APPROPRIATE HEALTH CARE

Under patent law, the patent holder has the right, for twenty years from the date of the application filing, to prevent any other individual or institution from making, using, offering to sell, or selling the invention.[27] The patent holder can choose to license the patented invention to others, can choose to use the patented invention exclusively itself, or can choose to prevent any use of the patented invention by itself or by others. In the gene patent area, the exclusive rights of the patent holder can raise the costs of genetic services, diminish the quality of genetic tests and treatments, and interfere with access to health care.

In some cases, gene patent holders will only let their own laboratories use the test for the patented gene. Exclusive licensing of a gene patent can itself interfere with the development of diagnostics. Various mutations in the same gene can cause a particular disease, but companies that do not let anyone else test for "their" gene make it more difficult for the discovery of other significant mutations in that gene. In countries where the Alzheimer's gene and hemochromatosis gene were not patented, researchers were able to discover previously unknown mutations.[28] These additional mutations are often critical tools for diagnosing individuals who would not otherwise be diagnosed by the patented gene or diagnostic test.

The possibility of inappropriate diagnostics was part of the concern that prompted the French challenge to the Myriad patent.[29] Myriad forbid French doctors from undertaking BRCA1 testing and required the tests to be sent to Myriad's lab.[30] But the sequencing technique by Myriad Genetics fails to detect ten to twenty percent of expected mutations in BRCA1.[31]

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26. Aude Lecrubier, *Patents and Public Health*, 3 EMBO REP. 1120, 1120 (2002).

27. 35 U.S.C. § 154(a)(1) & (2) (2000).

28. Andrea Knox, *Companies Holding Patents to Disease-Related Genes Limiting Access*, PHILA. INQUIRER, Feb. 13, 2000, at A1 (quoting Jon Merz).

29. Press Release, Institut Curie, Assistance Publique-Hôpitaux de Paris, & Institut Gustave-Roussy, Against Myriad Genetics's Monopoly on Tests for Predisposition to Breast and Ovarian Cancer Associated with the BRCA1 Gene 5 (Sept. 26, 2002) (on file with authors) [hereinafter Press Release, Institut Curie].

30. *See id.* at 4.

31. *Id.* at 5. For an example of a mutation that Myriad missed, see Sophie Gad et al.,

Thus, gene patenting runs the risk of directly harming a patient by failing to make available a medical diagnostic procedure that can detect a disease in her genetic make-up. Recent NIH-proposed guidelines recommend wide licensing of patented inventions to nonprofit researchers and public health agencies in order to remedy this problem, stressing that exclusive licensing agreements have "'detrimental short-term and long-term effects on both the quantity and quality of health care.'"[32]

A gene patent allows its holder to charge whatever price it wants. For example, prior to the patent opposition mentioned above, Myriad required that all BRCA1 and BRCA2 diagnostic testing be performed by their Utah laboratory at a cost of $2,975 per test,[33] three times the amount French laboratories charged.[34]

Gene patents can interfere with clinical adoption of genetic tests, potentially compromising the quality of testing by limiting the development of higher quality and lower-cost alternative testing methods.[35] A survey of seventy-two genetic-testing laboratories found that twenty-five percent of the laboratories have been deterred from offering a test due to the enforcement of a patent or license.[36] For example, beginning in 1998, SmithKline Beecham Clinical Laboratories sent letters to labs ordering them to stop performing or developing tests for the hemochromatosis (HFE) gene.[37] The patent holder asked for an up-front fee of $25,000 from academic laboratories and as much as $250,000 from commercial laboratories, plus a fee of twenty dollars per test.[38] As a result, thirty percent of labs that received the letter discontinued testing or ceased development of HFE testing services.[39]

A patent holder might forbid anyone from using the genetic sequence it has patented, even if the patent holder does not itself offer a diagnostic

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Identification of a Large Rearrangement of the BRCA1 Gene Using Colour Bar Code on Combed DNA in an American Breast/Ovarian Cancer Family Previously Studied by Direct Sequencing, 38 J. MED. GENETICS 388, 388 (2001).

32. David Malakoff, *NIH Roils Academe with Advice on Licensing DNA Patents*, 303 SCIENCE 1757, 1758 (2004) (quoting NIH draft guidelines).

33. Andrew Pollack, *Patent on Test for Cancer Is Revoked by Europe*, N.Y. TIMES, May 19, 2004, at C3.

34. *See* Press Release, Institut Curie, *supra* note 29, at 6.

35. *See* Merz et al., *supra* note 25, at 578.

36. MILDRED K. CHO, PREPARING FOR THE MILLENNIUM: LABORATORY MEDICINE IN THE 21ST CENTURY 47-58 (2d ed. 1998) (monograph by Bayer Corp.).

37. *See* Merz et al., *supra* note 25, at 578.

38. *Id.*

39. *Id.* at 577-78.

test using that sequence.[40] This practice could become more prevalent as more pharmacogenomic discoveries are made and inventors sit on their patent rights, prohibiting patients from receiving testing for genetic disease and interfering with the doctor-patient relationship. Most drugs only work on a certain percentage of patients who use them.[41] Genetic testing can help distinguish those patients for whom a drug will work from those for whom it will not. But such tests will also limit the market for drugs. For example, one pharmaceutical company has filed for a patent on a genetic test to determine the effectiveness of its asthma drug, yet does not plan to develop the test or let anyone else develop it.[42] Patent law in Europe, unlike in the United States, provides protections against such actions by requiring that the inventor actually "work" (i.e., use or develop) the invention; if the inventor does not "work" the invention, the inventor may be compelled to license the invention to another entity.[43]

III. SOME GENE PATENTS VIOLATE INDIVIDUAL RIGHTS

A. Informed Consent Issues

In many different settings in the United States over the past thirty years, blood, tissue, and other bodily fluid samples have been collected from individuals and used in genetic research without the person's consent or knowledge.[44] If a lucrative gene was found, it was patented. Once a gene is identified and patented, its availability is often severely restricted, even to the people who provided tissue samples and funding for the genetic research.[45] In one case, the court held that individuals who provided tissue and monetary support to a researcher for the discovery of a particular disease gene could maintain a claim of unjust enrichment against both the researcher and the hospital that patented the gene and charged a fee for

40. *Cf.* Gaia Vince, *Gene Patents "Inhibit Innovation,"* NEW SCIENTIST.COM, July 23, 2002, *at* www.newscientist.com/news/print.jsp?id=ns99992580.

41. *See* Allen D. Roses, *Pharmacogenomics and the Practice of Medicine*, 405 NATURE 857 (2000).

42. Geeta Anand, *Big Drug Makers Try To Postpone Custom Regimens*, WALL ST. J., June 18, 2001, at B1.

43. Yee Wah Chin, *Unilateral Technology Suppression: Appropriate Antitrust and Patent Law Remedies*, 66 ANTITRUST L.J. 441, 450 (1998).

44. Jeffery R. Botkin, *Informed Consent for the Collection of Biological Samples in Household Survey*, *in* CELLS AND SURVEYS: SHOULD BIOLOGICAL MEASURES BE INCLUDED IN SOCIAL SCIENCE RESEARCH? 276, 276-77 (Caleb E. Finch et al. eds., 2001).

45. *See* Greenberg v. Miami Children's Hosp., 264 F. Supp. 2d 1064 (S.D. Fla. 2003).

use of the genetic sequence in testing.[46] But the court also held that the tissue sources had no right to be informed about the potential commercialization of their tissue before they provided tissue to the researcher.[47] This could lead to the anomalous situation where a person's tissue could be used for commercial purposes without her knowledge or consent in ways that violate her personal or religious beliefs, and her only legal remedy would be monetary compensation after the offending act took place.

This is not a trivial concern. Many religion denominations oppose gene patents.[48] Certain religious and ethnic groups have concerns about the use of their tissue for research. In pending litigation, the Havasupai tribe of Arizona is suing researchers for unauthorized use of their genetic samples.[49] The group consented to give blood samples to a particular researcher for diabetes research.[50] They allege that without their consent, their samples were sent to other researchers around the country for research, which they had not approved, including research that might lead to discrimination against them as a group (such as schizophrenia research) and research that could contradict their religious beliefs (such as research on the purported origins and migrations of the group).[51]

In Europe, concern about informed consent of patients whose tissue is used in developing a gene patent is so important that it is mentioned in European patent provisions. Directive 98/44/EC of the European Parliament and Council of the European Union, created as a means to ensure uniformity in intellectual property rights as applied to biotechnological inventions throughout the European Union, states that where "an invention is based on biological material of human origin or if it uses such material . . . the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law."[52] If such a policy were in force in

46. *Id.* In extreme instances, the biobank that unjustly enriched itself might be required to disgorge all of its profits to the tissue sources. *See* Univ. of Colo. Found. v. Am. Cyanamid Co., 153 F. Supp. 2d 1231 (D. Colo. 2001) (requiring disgorgement of patent royalties in an unjust enrichment context).

47. *Greenberg*, 264 F. Supp. 2d at 1070.

48. Southern Baptist Convention, *supra* note 8.

49. Larry Hendricks, *Havasupai Tribe Files $50M Suit Against ASU*, ARIZ. SUN, Mar. 16, 2004, at A1. The case was filed in Coconino County Superior Court on March 12, 2004 (Case No. S-0300-CV-20040146).

50. Hendricks, *supra* note 49.

51. *See id.*

52. Council and Parliament Directive 98/44/EC of 6 July 1998 on the Legal Protection

the United States, it would protect individuals whose blood samples were used without their consent in genetics research and served as the basis for patent applications.

B. Reproductive Liberty Issues

Since a gene patent holder has the power to forbid all use of that specific gene or mutation for the lifetime of the patent, the patent holder can limit its use entirely in certain situations, such as by forbidding prenatal diagnosis for that particular gene. The company that holds patents on mutations in the BRCA1 and BRCA2 genes has indicated that it will use its control to forbid prenatal testing for breast cancer, perhaps due to the controversial potential for selective abortion.[53] However, such a stance interferes with a woman's reproductive liberty, a right guaranteed by the U.S. Constitution.[54] Because the issuance of a patent is a state action, even when issued to a private party, it might be deemed to infringe on reproductive rights where it limits the availability of genetic testing needed for a woman to make an informed decision. In *Lifchez v. Hartigan*, a federal judge struck down an embryo research ban as unconstitutional because it interfered with a woman's right to use innovative prenatal screening.[55] The judge said, "The cluster of constitutional choices that includes the right to abort a fetus within the first trimester must also include the right to submit to a procedure designed to give information about that fetus which can then lead to a decision to abort."[56]

IV. TOWARD A NEW POLICY HORIZON

There is growing interest in the U.S. Congress in dealing with the problems created by patents on genetic sequences.[57] There are several potential policies that could be adopted. Genes could be declared

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of Biotechnological Inventions, 1998 O.J. (L 213) 14, recital 26, http://europa.eu.int/eur-lex/pri/en/oj/dat/1998/l_213/l_21319980730en00130021.pdf.

53. LORI ANDREWS & DOROTHY NELKIN, BODY BAZAAR: THE MARKET FOR HUMAN TISSUE IN THE BIOTECHNOLOGY AGE 44 (2001).

54. *See* Eisenstadt v. Baird, 405 U.S. 438 (1972); Griswold v. Connecticut, 381 U.S. 479 (1965).

55. Lifchez v. Hartigan, 735 F. Supp. 1361, 1377 (N.D. Ill. 1990).

56. *Id.*

57. *See* Consolidated Appropriations Act, 2004, Pub. L. No. 108-199 § 634, 118 Stat. 3, 101 (2004) ("[N]one of the funds appropriated or otherwise made available by this act may be used to issue patents on claims directed to or encompassing a human organism.").

unpatentable subject matter. Another potential remedy is to allow doctors to perform diagnostic testing on patients without deeming the procedures to be infringement of the relevant gene patent. For example, Congress enacted a statutory provision exempting licensed medical physicians from infringement for use of a patented medical or surgical procedure.[58] Enacting a similar amendment for gene patents would permit doctors and laboratories to use patented gene sequences in diagnostic tests without having to pay a royalty or obtain a license.[59] Alternatively, the government could impose compulsory licensing for all uses of gene patents. Under this system, patent holders would have to grant licenses to researchers and physicians to use a patented genetic sequence in return for a reasonable fee to the patent holder.[60]

CONCLUSION

Gene patents create problems for health care, medical research, and individual rights. While it might be appropriate to award patent rights to a genetic diagnostic kit or a genetic therapy, it is not appropriate to award protection over an isolated sequence or a clone of a gene. Prohibiting the patenting of genetic sequences is not inimical to patent law. Rather, it would be permissible in the United States and around the world under the public health exceptions in the World Trade Organization's TRIPS Agreement.[61] It is crucial for high quality health care and individual autonomy that the United States reexamine its gene patent policy.

58. 35 U.S.C. § 287(c)(1) (2000) (noting that infringement actions "shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity").

59. *See* Genomic Research and Diagnostic Accessibility Act of 2002, H.R. 3967, 107th Cong. (2002).

60. For a more comprehensive discussion of this proposal, see Lori B. Andrews, *The Gene Patent Dilemma: Balancing Commercial Incentives with Health Needs*, 2 HOUS. J. HEALTH L. & POL'Y 65, 103 (2002); *see also* Jon F. Merz, *Disease Gene Patents: Overcoming Ethical Constraints on Clinical Laboratory Medicine*, 45 CLINICAL CHEMISTRY 324, 328-29 (1999).

61. Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, LEGAL INSTRUMENTS—RESULTS OF THE URUGUAY ROUND vol. 31, 33 I.L.M. 81, art. 27 (1994).