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INVITED EDITORIAL
Rethinking Risks to Human Subjects in Genetic Research

Philip R. Reilly

Shriver Center for Mental Retardation, Waltham, Massachusetts

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Although the concern of biomedical researchers for the well-being of human subjects is as old as research itself, the modern era has a well-defined beginning. The horrors conducted by the Nazi doctors under the name of research led directly to the drafting in 1946 of the Nuremberg Code (1949; Annas and Grodin 1992). Only 500 words long, the document holds a hallowed place in western culture. Not unlike the Emancipation Proclamation that ended slavery in the United States, the Nuremberg Code firmly rejects for all time the notion that humans may be treated as objects in clinical research. The fundamental principle of the code is in its first line: "The voluntary consent of the human subject is absolutely essential" (p. 181).

The 1950s and 1960s largely predate the emergence of bioethics as a formal discipline. In some quarters, however, efforts were made to disseminate the principles embodied in the Nuremberg Code and to emphasize to investigators that they had an ethical obligation to protect human subjects. For example, the 1961 handbook of the NIH Clinical Center describes hazard to the subject as always a "primary concern" (NIH 1961). In those years, however, the doctrine of informed consent, now a cornerstone of research, was not yet fully developed, and virtually no thought was given to the ethical issues that arise in research involving vulnerable populations. A seminal event in the history of research ethics occurred when Dr. Henry Beecher, a professor at Harvard Medical School, published an influential article criticizing the treatment, by clinical investigators, of human subjects, as described by the researchers themselves in dozens of scientific papers published after World War II (Beecher 1966). One of the most troubling examples concerned efforts to develop a vaccine for hepatitis, that included deliberately infecting retarded children at Willowbrook, a state-run institution located on Staten Island, New York. This occurred with parental consent, but the consent process was clouded because parents who agreed were able to move their (often severely retarded) children to the top of the list of persons waiting for admission. Soon after Beecher's paper was published, the 37-year history (1932–69) of the Tuskegee syphilis study garnered national attention. Here, the central ethical concern was that many persons with active syphilis were not offered penicillin therapy when it became available because to do so would undercut a key research goal: careful documentation of the natural course of the disease (Jones 1981).

In the 1970s, the research community and the federal government began to formalize rules for the ethical conduct of clinical research trials. In 1974, the federal government issued its first regulations concerning the protection of human subjects (Federal Register 1974). That same year, enactment of the National Research Act created the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research and charged it to identify the "basic ethical principles" that should underlie research involving humans (Public Law 1974). On August 8, 1975, regulations were implemented that paid special concern both to research involving particularly vulnerable populations (fetuses and pregnant women) and to in vitro fertilization (Code of Federal Regulations 1975*a*). The commission worked for 4 years, an effort that culminated in the Belmont Report (1979), a succinct document that has stood the test of time and, like the Nuremberg Code, should be in the office of every scientist who conducts research with human subjects.

The 1975 regulations created the system of institutional review boards (IRBs) that are now such a familiar feature of the research process in the United States. Perhaps not fully appreciated is the dramatic change effected when the federal regulations made institutions share responsibility with investigators for the ethical conduct of human-subjects research. In reviewing research proposals, each IRB was charged to determine that (1) the risks to the subjects were outweighed by the potential benefits of the research, (2) the rights of the

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Address for correspondence and reprints: Dr. Philip R. Reilly, Shriver Center for Mental Retardation, Inc., 200 Trapelo Road, Waltham, MA 02452. E-mail: preilly@shriver.org

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subjects would be adequately protected, and (3) "legally effective informed consent will be obtained by adequate and appropriate methods" (Code of Federal Regulations 1975*b*).

During the period 1975–90, the process of providing ethical review of proposals to conduct research involving human subjects matured. The major areas of IRB concern were the assessment of *physical* risk, the protection of vulnerable populations (including children and adults with limited mental capacity), and the quality of the consent process. Beginning in the early 1990s, there emerged an important new theme in the ethics of biomedical research: that gene-discovery studies posed the threat of genetic discrimination—that there is a risk of *informational* harm associated with participating in studies that elicit genetic information from which one might infer health status.

The growth and magnitude of concern over genetic discrimination during the 1990s has been significant. Despite the fact that the corpus of published literature that purports to document such discrimination (usually in the form of denials of access to health insurance, life insurance, or employment) against otherwise healthy persons on the basis of genotype is small (Billings et al. 1992; Geller et al. 1996), a large fraction of the American public and their legislators currently perceive such economic discrimination to be a genuine risk. To give one measure of the current level of interest in averting the threat of genetic discrimination, consider that, from 1975 through 1990, only one federal bill intended to regulate the use of genetic information was introduced in Congress, whereas, since 1995, >20 such bills have been filed.

In the mid-1990s, those who had focused largely on the potential abuse of clinically derived genetic information enlarged the scope of their warnings to include research studies. To my knowledge, no reports of informational harm due to deliberate or inadvertent violation of research databases stimulated this change. At least two developments did influence the new concern. The first was the realization that there were many inchoate DNA databases—large collections of tissue samples that had been collected in earlier years, pursuant to multicenter trials for which permission to conduct genetic tests had not originally been sought—that might have greater value if genotyping could be combined with existing demographic and clinical data. The second was the increasing amount of research by gene mappers who studied small, highly self-defined populations because they appeared to have a high prevalence of a particular phenotype—thus suggesting the presence of an influential predisposing allele (McKeigue 1997). The first led to a sustained but now resolving debate about the proper use of archived material (Clayton et al. 1995). The second has raised a new bioethical concern: that the model of informed consent that is bedrock to the conduct of research involving human subjects may not be adequate when a highly defined branch of the human family is the focus of the genomic research.

This later concern also arose in part because the representatives of and advocates for indigenous peoples around the world began to express suspicion that the scientific community in the wealthy nations intended to acquire and use genetic facts about them to create wealth in which they, the indigenous peoples, would not share (Taube 1995; Friedlander 1996). In effect, the argument was that researchers were behaving in a manner that recalled the 19th century colonialism of European powers seeking new markets. This concern has been heard by the community of nations. Recently, the United Nations Educational, Scientific and Cultural Organization (1997) adopted a "Declaration on the Human Genome" that strongly supports the principle that indigenous populations are not merely a resource to be genetically mined by rich scientific teams from western nations. The ideas embodied in Articles IV and V of the UNESCO Declaration recognize a community interest in genetic research that operates on a different plane and has different implications than does the process of enrolling a subject.

Foster, Bernstein, and Carter (1998 [in this issue]) suggest that, in conducting genetic research with some ethnic groups, researchers must, before attempting to satisfy the standard imposed by the principle of informed consent, first meet a new ethical obligation. They argue that, in certain populations, *community* discourse is an important antecedent to the standard consent process that defines the relationship between the investigator and the *individual* subject. Their paper recounts the process by which they sought understanding and community consensus for a genetic study involving an Apache tribe in Oklahoma. They point out that the individuals they sought to enroll as subjects are part of a small group that has been and still is the object of discrimination by members of larger groups in our culture. They posit that, because evidence that Apaches are genetically predisposed to a particular disease could reinforce discriminatory behavior, research conducted on *some* members of the tribe could lead to knowledge that, once disseminated, might harm *any* member of the tribe, whether or not the individual had participated in the research.

Foster et al. (1998) describe how they successfully addressed this issue among the Apache, and they propose a model that they think is generalizable for other researchers working with members of other cultures. The essence of the model is that research should be preceded by careful efforts to understand how decisions are made in the particular culture. Success in understanding the relevant decision-making units in the society should permit the investigators to identify appropriate represen-

tatives who can foster discourse with the community. If community consensus favoring the research is reached, evidence thereof should be submitted to the IRB. Once the IRB has determined that consensus has been reached (and if the proposed study survives other analysis), the IRB can permit the standard efforts to recruit subjects.

I have little criticism of the approach advocated by Foster et al. (1998), so long as I accept their premise. I do, however, have some doubts about the premise. They state that "[t]he primary risk [arising from research in a socially identifiable population] is that laypersons may misuse scientific findings" (p. 000). In effect, they argue that publication of a paper announcing the discovery of an allele that predisposes to adult-onset diabetes in the Apache tribe could become grapeshot for the guns of prejudice. I agree that, among those who harbor strong prejudice against Native Americans, some might use a genetic predisposition to diabetes to rationalize their own feelings and to propagate prejudice among others. I doubt, however, that this would lead to a discernible increase in intolerance. On the other hand, there may be some kinds of genetic predisposition (say, to addictive behavior) that, if demonstrated to be disproportionately common among a particular ethnic group, could fan the fires of hatred in a significant way. Foster et al. (1998) seem to back off from this concern when they assert that the larger risk is discrimination *within* the Apache by one individual against another.

Even if we accept the premise that there are ethnic groups in which all members could be threatened by misunderstanding or deliberate misuse of new genetic information and that such groups should be afforded the opportunity to have a dialogue with investigators, the solution suggested by the authors still raises significant operational issues. Their model of community participation and approval seems workable only with small groups that have a well-defined leadership structure. The challenge of seeking community approval within a tribe of a few hundred is imaginable; the challenge of seeking consensus among larger groups is not.

Over the last few years, driven in part by reports indicating that as many as 2.5% of Ashkenazi Jews carry a germ-line mutation that predisposes to ovarian and/or breast cancer (Struewing et al. 1997), some members of that community have become deeply concerned about genetic discrimination. Given the horrors perpetrated against Jews over the centuries, especially the Holocaust, the concern must be respected. Yet, it is worth noting that much of the research concerning genetically influenced diseases among Ashkenazi Jews is both conducted by Jewish scientists and supported by Jewish organizations (Waldman 1998). The capacity for hatred is part of human behavior. No matter what new knowledge is discovered, there will be someone ready to twist it to serve a terribly wrong goal.

The approach used by Foster and his colleagues raises several issues. First, their decision to conduct ethnographic interviews with 150 members of the Apache tribe as a preliminary step in developing community consensus around the research could, if generalized, create a significant new cost to gene-mapping studies. Second, the creation of a community-based (tribal) IRB that, in addition to its other activities, assumed the task of negotiating a subcontract with the University of Oklahoma (the institutional home of the investigators) to determine the allocation of the rights to the potential wealth from intellectual property created by the research could be viewed as creating a possible conflict of interest. Third, the suggestion that comparative DNA studies could discover information about Native American migration patterns that is in conflict with Apache origin narratives raises an unusual problem in informed consent. Should a potential subject be warned that one or more findings may challenge his religious beliefs? This strikes me as beyond the appropriate boundaries of the duty to warn, for it suggests that scientists must censor their inquiries if conducted in the shadow of religion. When Galileo trained his telescope on the heavens and saw four moons orbiting Jupiter, he set in motion forces that would destroy the narratives built around a geocentric universe—no doubt upsetting the world views of a lot people.

Foster et al. (1998) suggest that the Apache tribe is similar to other vulnerable populations (children, pregnant women, and prisoners) that have been singled out for special protection by the federal regulations that govern research with human subjects. This argument opens the door to a line of reasoning that makes me uneasy. Adult members of the Apache tribe are autonomous persons who (with rare exceptions, such as those with mental retardation) have the capacity to decide whether or not to participate in a study. To suggest otherwise invites the paternalistic suggestion that the tribe needs a special layer of protection, an idea that is inherently demeaning.

The authors assert that the approach they developed to conduct genetic research among the Apache is generalizable. In their words, "Everyone is a member of one or more socially identifiable populations" (p. 000). It seems to me that few of us belong to just one such clearly defined population. Could not most of us claim membership in two or more ethnic groups (Irish, Italian, Jew)? And who among us can identify an obvious public or private entity within those groups that is socially empowered to speak for the rest? The recent concern raised among Ashkenazi Jews about the dangers of genetic research elicited sharply differing responses among different groups that purport to speak for portions of that community in the United States (Wadman 1998).

I think the notion that clinical research among socially identifiable populations should proceed only if the in-

vestigators have educated the community and achieved consensus should be viewed as a laudable goal, but not as an ethical or legal obligation. The successful work with the Apache will not be so easy to replicate in other cultures. Efforts to proceed in a similar fashion elsewhere could lead to great expense and long delays and could, possibly, chill some research. They could also lead to a new kind of forum shopping, as investigators try to determine which population would be easiest to work with. The real issue at hand is how to ensure that, when persons who are members of socially identifiable populations decide whether or not to participate in research, they do not have to weigh the risks of genetic discrimination for themselves or their community.

There are no easy cures for prejudice, but a deeper understanding of genetics may be more likely to combat prejudice than to support it. Thanks to advances in molecular genetics, we have learned that each of us shares ~99.9% of our nucleotide sequence with even our most geographically dispersed neighbors and genetically distant cousins. This information would gratify the great geneticist, Theodosius Dobzhansky. Twenty-five years ago, he argued that the 2,000-year effort to enforce a caste system on the Indian subcontinent was a complete failure because the genetic diversity retained among different social groups made it impossible to create meaningful genetic differences between them (Dobzhansky 1973).

The major value of the contribution by Foster and his colleagues (1998) may not be in the dissemination of a model agreement for obtaining community consensus for genetic research, although that is certainly helpful. Their paper reminds us that we are dealing with extraordinarily powerful information in the use of which we must take the utmost care. Geneticists must be aware that information they discover can lead to harm in ways that are difficult to anticipate. Among the most pernicious risks is that genetic information could be twisted to rationalize ethnic or racial prejudices that already so deeply threaten the human family.

References

Annas GJ, Grodin MA (1992) The Nazi doctors and the Nuremberg code. Oxford University Press, New York

Beecher H (1966) Ethics and clinical research. N Engl J Med 274:1354–1360

Billings P, Cohn M, de Cuevas M, Beckwith J, Alper J, Natowicz M (1992) Discrimination as a consequence of genetic testing. Am J Hum Genet 50:476–482

Clayton E, Steinbuerg K, Khoury M, Thomson E, Andrews L, Kahn M, Kopelman L, et al (1995) Informed consent for genetic research on stored tissue samples. JAMA 274: 1786–1792

Code of Federal Regulations (1975*a*) 45 CFR 46

Code of Federal Regulations (1975*b*) 45 CFR 46.102(b)

Dobzhanzky T (1973) Genetic diversity and human equality. Basic Books, New York

Federal Register (May 30, 1974) 39:18914

Foster M, Bernsten D, Carter T (1998) A model agreement for genetic research in socially identifiable populations. Am J Hum Genet 63:000–000 (in this issue)

Friedlander J (1996) Genes, people and property. Cultural Survival Q 20:22–24

Geller L, Alper J, Billings P, Barash C, Beckwith J, Natowicz M (1996) Individual, family, and societal dimensions of genetic discrimination: a case study analysis. Sci Engineering Ethics 2:71–88

Jones JH (1981) Bad blood: the Tuskegee syphilis experiment. Free Press, New York

McKeigue PM (1997) Mapping genes underlying ethnic differences in disease risk by linkage disequilibrium in recently admixed populations. Am J Hum Genet 60:188–196

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) The Belmont report: ethical principles and guidelines for the protection of human subjects of research. Department of Health, Education, and Welfare, Washington, DC

NIH (1961) Handbook on the utilization of normal volunteers in the clinical center. NIH, Bethesda

Nuremberg Code (1949) Trials of war criminals before the Nuernberg military tribunals under control council law no. 10, vol. 2. U.S. Government Printing Office, Washington, DC

Public Law (1974), 93-348

Struewing J, Hartge P, Wacholder S, Baker S, Berlin M, McAdams M, Timmerman M, et al (1997) The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 336:1401–1408

Taube G (1995) Scientists attacked for "patenting" Pacific tribe. Science 270:1112

United Nations Educational, Scientific and Cultural Organization (1997) Declaration on the human genome

Wadman M (1998) Jewish leaders meet NIH chiefs on genetic stigmatization fears. Nature 392:851

Waldman L (1998) Jewish gene studies pose no threat. NY Times (April 26)