The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation

HAROLD EDGAR and
DAVID J. ROTHMAN

Columbia University

AS A POLITICAL AND GOVERNANCE INSTITUTION, nothing in the regulatory domain resembles the institutional review board (IRB). To invert the classic story about God delegating authority to a committee to perfect His creations and getting a giraffe in return, the IRB *is* the giraffe, so odd is it when compared to other creatures in the jungle.

Despite its many idiosyncrasies, over the past two decades IRBs have transformed the conduct of research projects involving human subjects. Unquestionably, their very existence has tempered the inevitable propensity of researchers to pursue investigations without dispassionately weighing the risks they are asking others to assume or fully informing their subjects of them. Indeed, IRBs have been so successful as to set an international standard for monitoring clinical research.

Nevertheless, in the American context, the very proliferation of these committees, to the point where they are to be found in every type of institution conducting research, raises critical questions about uniform standards and performance. Is it truly the case that a "one size fits all" approach works well? Are the same general procedures for appointing members and defining their obligations appropriate for reviewing research conducted not only at the Central Intelligence Agency (CIA), the Bureau of Prisons, and the National Institutes of Health (NIH), but also at for-profit hospitals, local community hospitals, and university-affiliated, tertiary-care centers? Does it make sense to give the leadership of an institution, which by its very nature cannot survive without the funds and fame brought in by clinical research, the responsibility for appointing the membership of a monitoring committee? Or, more broadly framed, is the local and institutional basis of IRB organization still appropriate? Are the assumptions that initially underlay that choice still valid? The goal of this essay is to suggest that the answers to these questions may well be no, and to provide some modest, but potentially important, recommendations for change. IRBs can take credit for remarkable accomplishments, but it may be time to revise the framework governing human experimentation.

The Milbank Quarterly, Vol. 73, No. 4, 1995

The IRB Structure

The IRB system rests on two sets of federal regulations. The first commits various agencies of the U.S. government to securing IRB approval before research is conducted on human subjects, either in house or through the grants they fund for outside projects. Government-supported biomedical research is the paradigm case.[1] Before any federal money can be expended on research involving human subjects, the regulations require that a protocol must be approved by this institutionally based committee, with a membership of no less than five persons, at least one of whom must not be affiliated with the institution. The IRB's central charges are, first, to review whether the benefits of the proposed research outweigh the risks, and second, to make certain that the investigators have explained all the relevant issues so as to secure the subject's informed consent. Although the federal regulations that establish the IRB system apply only to federal activities and federally funded grants, many states require IRB review for all research performed within their jurisdiction, no matter how it is funded. Moreover, the vast majority of academic institutions choose to review all their research protocols through an IRB, rather than reviewing some, but not others, on the basis of who is providing the funding.

[1] 45 Code of Federal Regulations § 46.101 et seq.

Contrary to what many people presume, IRB regulations do not require the review of *all* innovations in medical practice, let alone all instances of physicians following their preferred treatment strategies without ascertaining whether their approach works better than someone else's. The IRB focuses exclusively on activities intended to gain generalizable knowledge, and to the extent that someone, a surgeon for example, forswears an interest in general knowledge and presumes that the best way to treat Parkinson's disease is to burn the brain's pallidum—to take an illustration from the *Wall Street Journal*'s headline story of February 22, 1995—that surgeon need not bring his new technique before an IRB.[2]

Independent of federal funding regulations, the Food and Drug Administration (FDA) requires that protocols involving human subjects and new drugs or medical devices must be approved by IRBs. For example, were a surgeon to use a new commercial medical device in order to accomplish a proposed intervention, FDA procedures would be triggered. Insofar as testing new drugs on human subjects is concerned, FDA regulations are in important respects the same as those imposed by the Department of Health and Human Services (DHHS) on research institutions seeking grants. Yet FDA oversight differs in several important respects. FDA reviewers themselves examine the merits of the protocol and do not leave all decision-making to the IRB. Thus, in ways that overlap or supersede an IRB finding, FDA reviewers may reject research that they consider too risky or may compel investigators to carry out more animal studies before beginning clinical trials. At the same time, the FDA may impose strict regulations on the manufacture of drugs and biologics *before* they are tested, again going well beyond the IRB's usual safety concerns.

The FDA procedures do provide a degree of national oversight for clinical research. In addition, some funding agencies may conduct their own reviews of a protocol's research ethics; NIH study groups, for example, have been known to do this on occasion, rejecting a proposal on ethical grounds that a local IRB has already approved. But many human experiments do not come under either FDA or NIH study group purview, leaving decisions about the ethics of research solely in the hands of the IRB.

[2] On the IRB and FDA regulatory process see, in general: 39 *Federal Register* 18917 (May 30, 1974); National Research Act of 1974, P.L. 93-348, 88 Stat. 342 (Title II), *U.S. Congress and Administrative News*, 93rd Cong., vol. 1, p. 379; and 46 *Federal Register* 8386 (January 26, 1981).

Thus, the power to approve or disapprove research on ethical grounds is granted to a local institutional committee, composed of members of the same institution (with the one necessary exception) that is seeking the funding. Moreover, by all reports, the members who dominate the IRB discussions are these insiders, not the outsiders (who are everywhere a distinct minority). So, in effect, the key decision-makers on the IRB are colleagues who must live with any disappointed applicants whose protocols they have rejected. Furthermore, most IRB committee members are themselves researchers and the standards they set for others will come back to bite them too.

To be sure, the IRB is uniquely well protected from formal institutional domination. Unlike most committees, which are structured to exercise power delegated by a parent and are ultimately responsible to that parent, an IRB decision to disapprove research may not legally be overturned by the institution. For example, if it believes it has grounds to do so, an IRB can effectively terminate a researcher's career at a particular institution by rejecting his protocols or by insisting on such close supervision that it becomes impossible for him to carry out investigations. At one institution, a researcher, whose casual attitude toward consent was notorious, was required by the IRB to have one of its members present whenever he obtained consent from a subject. The requirement proved so onerous, causing innumerable delays, that the investigator left the institution within months.

Nevertheless, the IRB's autonomy and isolation are largely theoretical, in that no federal controls or regulations exist on how the institution decides who gets appointed to the committee, how long those persons stay, or on what grounds a member may be dismissed or not reappointed. Indeed, powerful people within an institution have a myriad of largely untraceable ways for punishing an obstructionist IRB member: from withholding or delaying promotion to blocking his or her access to other grants—a fact that no IRB member can fail to recognize. Similarly, there are no formal controls on the selection of the outside and unaffiliated members, whose professional qualifications thus may not always be clear. While many of these outsiders may understand and appreciate the scientific or ethical dimensions of research, there is no way to ensure that they are anything other than a friend of a trustee, looking for an opportunity to participate in an institutional activity.

Finally, not only the formal structure but also the actual workings of

the IRB leave room for dissatisfaction. Despite the amount of time that IRBs devote to examining the language of the consent form, they are not required to investigate whether the consent language they hammer out either is actually used on the floor or serves to educate the patient about the nature of the research he or she has consented to. It is rare for an IRB to leave the confines of its committee room and examine what actually occurs in the consent process.

In effect, then, the regulations governing the IRB are, to say the least, a permeable shield, with no strong framework to ensure that subjects' interests take precedence over institutional ones. The judgments that will be made on this basis need not be so flagrant as to eventually provoke a scandal. Balancing research risks against benefits is complicated, and a committee that consistently makes the calculus in favor of the research will hardly ever be identified. On occasion, a glaring miscalculation will command headlines; the decision of the UCLA IRB to allow investigators to withdraw medication from schizophrenic patients in the course of a trial may be one such instance. But the overriding point is not how typical the UCLA actions are, but how the IRB system provides so few bulwarks against this tilt in decision making (Office for the Protection from Research Risks 1994).

To put the case bluntly, if one were to look at the IRB exclusively in terms of formal structure and organizing principles, it would seem to be a paper tiger. An individual serving on the body and an institution organizing it may fulfill the highest ethical standards; any one participant may claim, with full justice, that his or her IRB is exemplary in its functioning. Nevertheless, there are very few provisions in the regulations that protect against bodies that might be sloppy, venal, or subservient to the institution. Put another way, the quality of an IRB's work depends to an inordinate degree on the conscience and commitment of its volunteer members. The fact that the NIH has created an Office for the Protection from Research Risks (OPRR) in no way mitigates this point. OPRR is empowered to review the membership roster on local IRBs, but because the formal requirements are so minimal, such review is of limited effect. Nor does OPRR have the funds or personnel to conduct regular and ongoing examinations of how individual IRBs normally function. If OPRR does learn about a particular case (either through the institution, the press, or the grapevine), it will investigate the incident. In 1994, however, the office made only 10 site visits (Burd 1995).

The Dark History of Human Experimentation

When and why did the IRBs assume this peculiar structure? Why were such bodies created in the first place, and why was their organization so locally based?

The story opens in the early 1960s, when those charged with administering research funding, particularly at the NIH, took note of the public furor generated by exposés of gross abuses in medical research. These included the uncontrolled promotional distribution of thalidomide throughout the United States, labeled as an experimental drug; the administration of cancer cells to senile and debilitated patients at the Brooklyn Jewish Chronic Disease Hospital; and the uncontrolled distribution of LSD to children of several prominent families at Harvard through Professors Alpert and Leary. Most important, of course, was Henry Beecher's 1966 article in the *New England Journal of Medicine*, detailing 22 protocols of dubious ethicality, and declaring that the roster had been winnowed down from a longer list culled more or less from periodicals crossing his desk (Beecher 1966; Rothman 1987, 1991). NIH officials, as administrators of government funds, were deeply concerned about the impact of these scandals and moved in preemptive ways to ensure that Congress would not curtail research funding.

What accounts for the extraordinary capacity of medical experimentation abuse to be perceived as a major scandal, even when the provable physical harms that resulted from it were small, certainly when compared to the harms done by impaired physicians (an issue that has never sparked public furor)? The answer lies in the unique combination of events that made human experimentation a symbol for the two great nightmares of twentieth-century life. The first is the frightening power of some political ideologies to demand that no private interest impede the accomplishment of the public good. The second is the acute fear that man must adapt to whatever science produces, and that science is ultimately beyond social control.

In imprinting the first nightmare, the significance of the crimes committed by the Nazi doctors cannot be overstated. The U.S. government used the war crimes trials to teach that there must be limits to government power. One could not justify maiming and killing by claiming that the state required answers to pressing medical questions. Even an institution once as prestigious as German medicine was corrupted by succumbing to an ideology that state interests trump other considerations. And

this, of course, was precisely the basis on which America fought the ideological contest in the difficult years of the late 1940s and early 1950s, when the communist movement threatened to win elections in Italy and France and indeed throughout Western Europe (Annas and Grodin 1992; McNeil 1993).

From an American perspective, a maximization of collective welfare was not a legitimate basis for imposing harms of whatever magnitude upon individuals. Theories of individual rights set a limit on government authority, even if the community was then less well off, a position that was taken seriously at a time when the rate of Soviet economic growth allegedly surpassed our own. Although it took some 20 years for Nuremberg to become synonymous with the horrors of human experimentation—what caused the initial period of silence and why it came to an end is still not well understood—by the mid-1960s, and even more prominently in the 1970s and 1980s, the lessons to be drawn from the Nazi experience became widely recognized and shared.

These events represent a fascinating twist in the history of political theory in America. The intellectual leadership of the United States before World War II was profoundly committed to general utilitarian values. For example, one way to characterize the fight over the New Deal was as an argument by opponents that the proposed reforms violated traditional property and contract rights, which was countered by proponents with the claim that such rights should be limited by public needs. In effect, conservatives were defending individual rights and liberals were ready to restrict them in the name of collective well-being. Similarly, such seminal legal thinkers as Oliver Wendell Holmes and Felix Frankfurter were forever extolling the need for general legal standards and for imposing such requirements on people whether or not they could measure up to them. Holmes wrote that he would tell a person about to be executed, who might have had no power to avoid his wrongful deed, that he should regard himself as a soldier in the cause of general deterrence of crime.

This persistent and powerful strain of ideological positivism in the United States was brought into disrepute in the postwar era because it provided no sure stopping point whenever those in power believed a course of action to be absolutely necessary for collective well-being. Indeed, recall Justice Holmes's decision in *Buck v. Bell*, justifying the sterilization of the mentally infirm, and his remark that the sacrifice asked of the woman involved was small compared to that expected of others. Three generations of imbeciles were enough: that is, enough for the

community. The case of *Buck v. Bell*, not surprisingly, was frequently invoked by German defense lawyers at Nuremberg.[3]

The experience of convicting Nazis has had the ironic result that the victors' earlier confidence in general utilitarian theories was largely superseded by the victors' intelligentsia, in favor of ultimately deontological theories such as John Rawls's *Theory of Justice*. These theories trace their intellectual provenance to Kant, and to the German tradition, which was itself a nineteenth-century rejection of English utilitarian writers like John Stuart Mill and Jeremy Bentham. The result of this change was that medical experiments and social policy toward them became, in our society, the symbol of our acknowledgment of absolute limits on the claims the collective can make on the individual, and the rejection of a principle that anything goes so long as we are persuaded that more will gain than some will lose.

These are not, of course, the only alternatives by which experiments may be judged, but so powerful is the symbol of clinical research without consent that we approach them with extreme reluctance. The controversy over whether to permit experiments in emergency situations, where no consent is feasible, illustrates the attitude. And the recent fervor over the radiation experiments that government agencies conducted during the 1940s and 1950s on unknowing subjects suggests that medical experimentation has lost none of its symbolic power (Burd 1994).

If Nuremberg was one critical underpinning for public attitudes toward human experimentation, the second was the social awareness that new medical breakthroughs affected not simply the individual patient, but also human life more generally, and, given the dimensions of the potential transformations, the innovations had to be reviewed and authorized by someone other than the particular investigator. The rapid growth in transplant procedures was one dramatic instance: do we as a society want to promote a medical technology that makes the body into a collection of spare and reusable parts? Moreover, physicians themselves were often eager to share responsibilities in decision making, not only so as to alert the public to what was going on, but also to share the responsibility for allocating the novel resources. The most noteworthy case was that of the Seattle doctors' move to establish a lay kidney dialysis committee for the purpose of deciding who received the life-saving benefits. The negative reference point, of course, was the fate of physics and phys-

[3] *Buck v. Bell* (274 U.S. 200, 47 S. Ct. 584, 71 L. Ed. 1000).

icists who thought about Sanskrit poems as they watched the mushroom cloud, realizing they had altered the course of history without securing a societal consensus about the wisdom of doing so. Indeed, it was the development of nuclear weapons that encouraged biologists to convene the Asilomar Conference and to delay recombinant DNA research until a broader consensus about its safety could be secured (Rothman 1991).

The Local Character of the IRBs

Although the scandals in human experimentation drove the decision to regulate research, they hardly explain why the results placed such heavy reliance on local, institution-based procedures. One major reason was that the research community was ahead of the curve of public demand, regulating itself before others did so. Local, institutional review was the least intrusive means of allaying public fears. Ask anyone in the pharmaceutical industry whether they fear more their review by an IRB or their fate with an investigational new drug (IND) at the FDA, and you will learn that the IRB is vastly more flexible than the FDA. An IRB is far more apt to communicate quickly what troubles it and how those troubles may be overcome. The public interest, it should be noted, often gains significantly from this flexibility, but it comes, as we shall see, with a price.

The preference for localism drew as well on a whole set of assumptions about the research enterprise and those who conduct it. First, when the IRB mechanisms were put into place over the 1970s, everyone, at least at the NIH, assumed that funds were readily available to do research. The inevitable result of IRB review was to delay things, but the costs of delay could be absorbed in a generous overhead allotment; moreover, the researcher who had to move more slowly on project A could always find support for project B. In other words, by making review local, the penalties of regulation were minimized.

Second, regulators presumed that IRBs would almost always operate within a university teaching hospital where a shared commitment to the ideals of good science would far outweigh any tendency for persons to trade favors or elevate concerns for the financial viability of the institution above their loyalty to the integrity of science or the well-being of subjects. The accepted premise was Robert Merton's persuasive argument that the universal principles of science override narrow academic allegiances. Thus, once science incorporated ethical principles in human experimentation into its own system, scientists would effectively enforce them, offsetting any dangers in localism. Moreover, the forces motivating researchers were promotions, prizes, and grants, all of which depended upon the respect of peers. No one would, therefore, risk imperiling the prestige of his or her institution by letting sloppy or unethical research slide by. Thus, it seemed as though the local character of IRB review secured all the advantages that came with being close to or part of the action, without running the risk of having regulators captured by the regulated.

Third, the designers of the IRB system expected that the subjects themselves were likely to be suspicious about human experimentation, adopting a cautious, self-protective stand against involvement. Participation was perceived as both burdensome and risky; experiments were dangerous, and subjects were fully alert to the implications of being a guinea pig. Discussion of research ethics spoke of the need to distribute fairly the *burden* of participation, not relying on and exploiting the poor. All the while, the attention devoted to the specific wording of consent forms was a way to guarantee that subjects would be able to act so as to promote their own self-interest. Well-informed subjects would never put themselves at undue risk. Where subjects were for one or another reason not capable of giving consent (owing to the debilitating effects of illness, mental disability, youth, or confinement to a prison), it seemed right to bar them from being used as subjects. The one exception was in the event that they had a special stake in the research mission; research on retardation, for example, might well require that persons with retardation be the subjects—even then, additional protections had to be employed. Research carried such danger that, although the policy was rarely made explicit, women, particularly women of child-bearing age, also seemed to require special protection. The fair sex should be protected, and even more, the fetus should be protected, lest some experiment adversely affect embryonic development.

The Limits of Localism

Each one of these three premises has now been substantially undercut, with the end result that the localism of the IRB appears to generate more problems than it solves. The confidence that IRB delay or disapproval carried no penalties because a surfeit of research opportunities was available has weakened—really disappeared. Money for research has become

very scarce, and researchers have no confidence that there will always be another grant if this one is delayed.

Even more important, many potential subjects no longer regard participation in experiments as a dangerous activity. The line between experiment and therapy has blurred, and human subjects do not necessarily greet departures from accepted procedures, even exceptionally risky ones, with suspicion. Accordingly, the IRB presumption that a well-crafted consent form was a meaningful protection has weakened: subjects may well be simply too eager to obtain what they see as the most advanced and potentially therapeutic intervention. The shock troops leading the assault on the traditional perspective of risk were persons with AIDS. Their perspective is now being shared by advocates for those with Alzheimer's disease, advanced breast cancer, and indeed, for all those with a deadly illness (Edgar and Rothman 1990; Rothman and Edgar 1992).

All the while, new medical technologies continue to move society in totally new directions, with no systemic review of their desirability. Take, for example, the recent announcement from George Washington University that its investigators have begun experiments that may lay the groundwork for human cloning. The research received the approval of the institution's IRB. (It turns out that the IRB approved the protocol without knowing that the investigators had already conducted the research. When it learned of this breach, the IRB penalized the investigators, compelling them to withdraw an abstract of their findings. For our purposes, the critical point is that the local IRB did ratify the protocol and would have allowed the research to go forward [Schwartz 1994]. Those interested in giraffes may note, however, that a committee established pursuant to federal law directed academics not to publish their research, and no widespread discussion of First Amendment implications has ensued.) But precisely who vested George Washington University with the responsibility for deciding whether human material should be so used? Indeed, by what processes were the men and women chosen who made the ultimate determination to approve it? And what did they hear by way of opposition to the researchers' request to go ahead? Surely, some alternative or supplement to such local decision-making seems in order (Fackelman 1994).

So too, the proportion of research that is industry-funded, rather than government supported, has increased dramatically, which carries several critical implications for IRB reviews (National Institute of Health 1993). Researchers may have entrepreneurial interests in products being tested

at their home universities. Indeed, the academic institutions face major issues of conflict of interest because medical entrepreneurialism has become a goal of the university itself. For example, whereas Harvard University used to prohibit patenting of medical innovations as contrary to the public interest, it now has established an in-house investment company to provide seed capital for ideas worthy of commercialization, and the proceeds of such commercialization are to be returned to the university and distributed to the inventor, to his or her laboratory, and to research more generally (Gupta 1994). Increasingly, universities take equity positions in faculty-created start-up companies. Although no data are available to ascertain the frequency with which medical institutions hold equity in companies whose products are tested in their facilities, or how often researchers have a substantial financial stake in the products they are investigating, both phenomena now occur, and are all the more likely to occur in the future.[4]

Indeed, some institutions now function economically as packagers of patients with rare diseases. The concentration of patients at the institution makes feasible corporate-sponsored research protocols that could not otherwise be done; the institution profits handsomely by providing experimental options to those sponsors, in effect matching sponsors and volunteers who would not otherwise efficiently find one another. To these ends, a pharmaceutical company recently purchased an advanced cancer treatment center, with the hope, we presume, that along with whatever other benefits the center might bring, it would provide a site for clinical trials. While the results of these trials may well contribute to improving medical treatment, the concern is whether the institution's financial stake in research has grown so great as to jeopardize the independence of locally based IRBs.

In fact, for these reasons, and others as well, the academic center, which served as a paradigm for the IRB, is likely in the future to lose what was once a near monopoly over research. Its role is being usurped from at least two sides. One the one hand, huge multistate and international trials have been, and will be, organized, bringing thousands of patients into a single trial, run by a coordinating group. With research becoming more national, ethics review on the local level makes still less sense. Second, the managed care plan provides a perfect site for many trials. To the extent that health maintenance organizations and other

[4] 35 United States Code, §§ 200–12 (annotated).

providers develop information bases linking different physicians' treatment patterns to patient outcomes, they are the natural place to conduct research on how much of a difference, if any at all, an intervention brings. Indeed, if we are prepared to insist as part of the managed care revolution that cost-containment measures be researched rather than imposed (which we may not be), then an in-house IRB model is hardly equipped to serve as guardian of patient interests (Freedman 1994).

One final point about the locus of research activity has recently assumed exceptional importance. The original 1960s assumption that the university was the site of most human experimentation minimized the importance of the fact that a number of government agencies, including the Department of Energy (DOE) and the CIA, were already heavily invested in such activities. Although there were discussions and hearings on whether so local and internal a system made sense in this context, and these agencies in time did agree to come under the regulations and establish their own IRBs, not until the 1994 exposé of cold war radiation research did the disadvantages of this arrangement become the center of public attention and policy analysis. Is it truly meaningful for the DOE or the CIA to run its own IRB? In light of what we now know about their activities, the local basis for the regulation of their human experimentation seems less satisfactory.

Taking the "I" out of the IRB

If the old paradigms no longer hold, what revisions should be made in public policy? Where do we go from here?

The IRB system has worked reasonably well, and to dismantle it would be a mistake. Nonetheless, IRBs were a "one size fits all" solution. Obviously, no single reform or institutional structure will be able to provide adequate oversight of all biomedical innovations. Accordingly, public policy innovations should move forward simultaneously on a number of fronts. We mention three.

IRB procedures are completely inadequate to protect the public interest from the ends of research, or to assure sufficient lead time to permit political focus on the limits, if any, that should accompany the development of new technologies. Mechanisms must be found to assure that proposed research that crosses frontiers achieves public visibility and provides opportunity for political choice before it is implemented. In contemplating how to accomplish this end, one is drawn inevitably to the establishment of a "super" committee or committees, charged at the minimum with a monitoring function, at the maximum with the right to veto research deemed unacceptable.

How can this be done? Throughout the world, various countries have established national ethics committees to serve as ongoing advisors on difficult ethical issues associated with research, and medical practice more generally. Numerous bills have been put forward to establish such a committee in the United States, and the Clinton Administration has expressed interest in such a proposal. But, in the past, initiatives have floundered on the question of who gets to appoint whom to do what, particularly when everyone knows that the issue of abortion may lie in the background (Office of Technology Assessment 1993).

Three principal and interrelated issues must be addressed in the design of an overarching monitoring mechanism:

First, whether to constitute one committee, endowing it with visibility and prestige because of its singularity, or several committees, distributing responsibility among members selected for their particular expertise. The NIH's recombinant DNA advisory group is the prototype of the special committee. And it has worked. Researchers complain about its delays, but it has had a profound impact on securing public consensus that gene research is an appropriate end, and one that can be safely pursued. Such committees should not, however, be appointed ad hoc, as the recent experience with the special committee established to advise the NIH on embryo research demonstrates. The President rejected out of hand a key recommendation—to permit the occasional creation of embryos for limited research purposes—before it was even considered by the NIH. Had procedures been in place that had earned credibility over time, it might not have been possible to dismiss a proposed policy in such politically expedient fashion.

Second, to determine how expansive a committee's jurisdiction should be: whether it will be limited to reviewing funded grant proposals and issuing advisory opinions, leaving the ultimate decisions to local IRBs and researchers, or whether its approval will be required before research is undertaken.

Third, to decide who should appoint such a committee, and what kind of staff it should have, questions that obviously become more or less sensitive depending on what powers the committee is granted.

Our own preference is to seek multiple committees of specialists, appointed by DHHS–NIH officials, whose responsibilities would extend to their particular fields of research—neurobiology, genetic therapy, reproduction—without regard to the sources of the research funding, governmental or private.

After considerable hesitation (and an initial difference of opinion between us), we would not grant the committee formal power to halt research. Adding another layer to the review of human investigation would incur too much expense and delay. Instead, we prefer to have such committees stay abreast of research methods and issues, making public the significant questions and providing general guidance to local IRBs about particular protocols. Yes, investigators who can persuade their own IRBs of the propriety of their work will be able to take the first research steps in advance of such review (the George Washington University cloning research is a case in point). But two considerations seem to us to reduce the potential risks. For one, frontier research is usually incremental, in the sense that the relevant professional community knows who is involved with research near the boundary and what the likely pace of advance will be. The presence of professional leaders on a committee with high visibility will encourage people in the field who have doubts about their own or their colleagues' agendas to ask whether and to what extent the issues that concern them have already been analyzed and considered. For another, expert committees will have ready access to the media and to policy makers, for biomedical research is (and will continue to be) in the public spotlight. Accordingly, expert committees will have time to foster debate about the research and ultimately provide the opportunity for an informed political decision on its desirability. In short, controversies about the stopping points in particular lines of research—whether they involve cloning, genetic enhancement, or other novel procedures—will have to be decided ultimately in the political arena, and administrative mechanisms cannot avoid that fact.

The second broad area of reform involves improving the present IRB system to take account of the newly entrepreneurial character of biomedical science that we have described.

Many of the concerns we raised are the appropriate object for formal legal rules. For example, conflict-of-interest guidelines can, and should, specify the limits on researchers and institutions that are simultaneously financially invested in the development of products and the testing of

those products. We would, for example, preclude investigators from recruiting patients and conducting clinical evaluations where the product being tested is one in which they hold a commercial stake.[5] So too, patients should be told of any financial commitments that would motivate the investigator to select this treatment for the patient rather than the others on hand (Rodwin 1993).

The third direction that reform must take is to strengthen the "outside" elements of the IRBs, while leaving review based in the institution itself. Localism has the advantage of accomplishing review not only more quickly but also with the knowledge, informal as it is, of the character of the investigators. Most important, it greatly facilitates learning that something is going wrong: nurses, residents, physicians do not have to cross institutional lines to inform someone of their concern that a protocol is not being followed.

IRBs processing a substantial number of protocols should, however, include experts drawn from scientific groups outside the institution. Moreover, there must be more focus on the appointment and renewal process. We should also seek to quasi-professionalize the role of outside members, linking them in groups that could come together to study common issues, so that there might be greater uniformity given to concepts like minimum risk. (The programs for IRB members run by such organizations as Public Responsibility in Medicine and by the Office for the Protection from Research Risks itself provide the beginnings of a model for such an effort.) The proposition that outside members can represent a relevant "community" has always seemed suspect to us; and we would prefer to see on each IRB a member who felt loyalty to a newly constituted community of research ethics advisors.

These stipulations about strengthening the outside role in IRB review take on special importance when the research is being conducted by the government itself. To make certain that such bodies as the DOE and the CIA remain well within the bounds of ethical research, it is vital that outsiders play an even more important role in their reviews than elsewhere. To accomplish this change would not be easy, not only because these bodies are very insular, but because outsiders also might well require security clearances and have to assume burdens of confidentiality that would hamper their effectiveness in bringing abuses to light. But

[5] A final Public Health Service rule has just been announced. See 60 *Federal Register*, 35810, issued July 11, 1995.

were a commitment to extrainstitutional review made, strategies for at once protecting the national interest and the subjects' well-being could be designed.

Finally, and almost certainly, we should have far more effective oversight mechanisms. It would be entirely feasible, for example, for an NIH office to sample (in the technical sense) protocols from research settings (not only universities, but also companies and government agencies), and to include in this effort interviews with the subjects of the research (reviewing the process by which they gave consent, what they understood the experiment to be, and how the research itself was conducted). The very existence of such a procedure might help improve IRB performance.

In sum, it is time to take the superintendence of human research to a different, and more national, level. Whether this change can be accomplished within the current political climate is debatable. The necessity for such a shift is not.

References

Annas, G., and M. Grodin. (Eds.). 1992. *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation*. New York: Oxford University Press.

Beecher, H.K. 1966. Ethics and Clinical Research. *New England Journal of Medicine* 74:1354–60.

Burd, S. 1994. U.S. Will Coordinate Rules on Obtaining Research Subjects' Informed Consent. *Chronicle of Higher Education* (July 13):A22.

———. 1995. Research by the Rules. *Chronicle of Higher Education* (April 14):A32.

Edgar, H., and D. Rothman. 1990. New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process. *Milbank Quarterly* 68 (suppl. 1):111–42.

Fackelman, K.A. 1994. Cloning Human Embryos. *Science News* (Feb. 5): 92–5.

Freedman, B. 1994. Multicenter Trials and Subject Eligibility: Should Local IRBs Play a Role? *IRB* 16 (Jan.–April):1–6.

Gupta, U. 1994. Hungry for Funds, Universities Embrace Technology Transfer. *Wall Street Journal* (July 1):A1, A5.

McNeil, P.M. 1993. *The Ethics and Politics of Human Experimentation*. Cambridge: Harvard University Press.

National Institutes of Health. 1993. *NIH Data Book* (DHHS pub. no. 93-1261). Bethesda, Md.

Office for the Protection from Research Risks. 1994. *Evaluation of Human Subject Protections in Schizophrenia Research Conducted by the University of California, Los Angeles* (issued May 11, with attachments A–F). Washington.

Office of Technology Assessment. 1993. *Biomedical Ethics in U.S. Public Policy*. Washington: U.S. Congress.

Rodwin, M.A. 1993. *Medicine, Money and Morals: Physicians' Conflicts of Interest*. New York: Oxford University Press.

Rothman, D.J. 1987. Ethics and Human Experimentation: Henry Beecher Revisited. *New England Journal of Medicine* 317:1195–9.

———. 1991. *Strangers at the Bedside* (chaps. 1–5). New York: Basic Books.

Rothman, D.J., and H. Edgar. 1992. Scientific Rigor and Medical Realities: Placebo Trials in Cancer and AIDS Research. In *AIDS: The Making of a Chronic Disease*, eds. Elizabeth Fee and Daniel M. Fox. Berkeley: University of California Press.

Schwartz, J. 1994. Cloning Experiments Violated GWU Policies. *Washington Post* (Dec. 7):A26.

Address correspondence to: Dr. David J. Rothman, Center for the Study of Society and Medicine, Columbia College of Physicans and Surgeons, 630 West 168th Street, Black Building 101, New York, NY 10032.