LAW AND PUBLIC POLICY IN HUMAN STUDIES RESEARCH

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Laws embody public policies which, in turn, reflect generally accepted standards of behavior. When conflicts exist or very sensitive issues must be resolved, commissions are frequently created to seek a consensus on what public policy ought to be. As I will explain, there has been good concordance throughout the 20th century between U.S. law and bioethics.

Previous papers have discussed the Nuremberg Code, which of course was the culmination of a criminal trial [1]. But there are other court cases that have been landmarks in the United States and form the backdrop for any discussion of bioethics and public policy, because what ought to be done—or ought not be done—must be viewed within the parameters of what the law permits or requires.

Historical Cases

Lawyers usually begin reviews of cases on human studies research by quoting Judge Cardozo, who in 1914 wrote that "every human being of adult years and sound mind has a right to determine what shall be done with his own body and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages" [2]. Since 1914, that principle has been reaffirmed in many of the landmark cases involving patients' rights in the context of (for example) contraception, abortion, and the right to refuse treatment [3].

Other cases in the decades since 1914 have further elaborated the principle of informed consent in the area of health care, which of course is what Judge Cardozo was referring to in *Schloendorff*: physicians may not perform medical procedures on patients without their consent. In the 1950s, a case against Stanford University more particularly described the physician's duty to inform, and made clear that consent based on inadequate information is not valid [4].

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A 1965 Canadian case, *Halushka v. University of Saskatchewan*, is the first in which the plaintiff was a normal volunteer [5]. While participating in research involving heart catheterization under general anesthesia, Halushka experienced cardiac arrest. He survived—but with cognitive impairments that resulted in his withdrawal from the university. Evidence at trial revealed that he had not been told of the risks of general anesthesia, nor had he been told that the catheter (which he understood was going into his arm) would be advanced all the way up to and into his heart. Accordingly, the court ruled in his favor, finding that the duty to inform a research subject is as great, if not greater, than the duty to inform a patient receiving medical care.

At about the same time, physicians at the Jewish Chronic Disease Hospital in New York injected cancer cells into patients for research purposes [6]. The research was supported in part by a Public Health Service grant, and therefore required informed consent based on a full explanation of the purpose, risks, and methods of the research. The New York Attorney General brought a license revocation proceeding against the physicians who conducted the research, and the licensing board concluded that: "These patients and their families have the human right to decide what would be done with their bodies" (paraphrasing Cardozo). As a result, the physicians' licenses were suspended for one year, but the suspension was stayed and they were put on probation.

The next landmark decision was a 1972 Washington, D.C., case, *Canterbury v. Spence*, which shifted the information standard for consent from that which a physician in that same specialty and location normally would disclose, to that which a reasonable patient would want to know in order to decide whether to accept a proposed treatment [7].

Federal Policies and Regulations

The NIH policies have been in the forefront in the protection of human subjects since 1953, when the NIH Clinical Center introduced prior review by medical committees of all research that would involve human subjects [8]. That requirement was extended to extramural research by the Surgeon General in 1966, when he made it a condition of the research award [9]. Since then, all applicants for a research grant or contract from the Public Health Service have been required to submit their research proposals to local committees whose mandate is to protect the rights and welfare of human subjects. These committees, now known as institutional review boards (IRBs), consider the acceptability of the proposed research in terms of the procedures for soliciting informed consent and an assessment of the risks and anticipated benefits of the research.

In 1971, the *Institutional Guide to DHEW Policy on the Protection of Human Subjects*, better known as the "Yellow Book," was created by Donald Chalkley in the NIH Division of Research Grants [10]. (There was no Office for

Protection from Research Risks (OPRR) in those days.) The Yellow Book established the requirement that the members of institutional review committees have varying backgrounds, to bring different perspectives to the review of proposed research. The Yellow Book was converted into regulations, with minor modifications in 1974 [11].

Congressional Hearings

One of the reasons that the NIH began to convert its Yellow Book policies to regulations was that Senator Edward Kennedy was holding hearings on research abuses [12], and officials in the Department of Health, Education, and Welfare (HEW) thought that regulations addressing the concerns raised would reassure Congress and the general public that everything was under control. Senator Kennedy's concern had been triggered by the Tuskegee studies (in which black Americans were deprived of treatment for syphilis in order to observe the natural progression of the disease) and the Willowbrook studies (in which a vaccine for hepatitis was tested on mentally retarded children in New York). In addition, commentators had challenged the so-called resurgence of psychosurgery and the ethics of fetal research. The Supreme Court decision that legalized abortion in certain states, *Roe v. Wade* [13], had provoked fears that some women might become pregnant and then have an abortion in order to provide fetuses for medical research.

The National Commission for the Protection of Human Subjects (1974–1978)

As a result of Senator Kennedy's hearings, Congress enacted legislation creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [14]. By law, members of the commission represented a variety of disciplines (e.g., law, public policy, medicine, basic science, and ethics) as well as the general public.

Mandate

The commission operated under a very broad mandate. It was asked to do the following things:

- Identify the basic, ethical principles that should underlie the conduct of biomedical and behavioral research;
- Determine the boundaries between research and practice;
- Evaluate the effectiveness of institutional review boards (IRBs);
- Consider the need for additional protections for children, pregnant women, fetuses, prisoners, and "the institutionalized mentally infirm" who are invited to become subjects of research;

- Determine the conditions, if any, under which psychosurgery should be performed; and
- Consider the implications of new advances in biomedicine.

The legislation also required that the commission submit its reports to members of Congress, to the President, and to the Secretary of HEW. The Secretary's responsibility was to publish the commission's reports and, within a reasonable length of time, to implement its recommendations. If the Secretary decided not to adopt one of the commission's recommendations, then the Secretary was obliged to publish an explanation in the *Federal Register.* Thus, he was required either to implement what the commission recommended, or explain why not.

Regulatory Impact

The work of this commission is evident in the current regulations of the entire federal government for conducting research involving human subjects. The commission revised the regulations governing IRBs to reduce the requirements for review of minimal-risk research and thus permit the IRBs to spend more time on those protocols presenting more than minimal risk. It was largely because the IRB members testified to the commission that they needed relief from reviewing trivial kinds of research, that the commission recommended what is now called "expedited review" of minimal risk research and exemptions for categories of research so designated by the Secretary. In addition, new subparts of the regulations implement the Commission's recommendations for research involving children, fetuses, pregnant women, products of human in vitro fertilization, and prisoners.

Regrettably, the commission's recommendations for special protections for "those institutionalized as mentally infirm" were never adopted. There were conflicts, apparently, amongst different interest groups as to which patients with mental disorders or cognitive disabilities should be covered by any such regulations. And as a result of the conflicts, there are still no regulations specifically protecting people whose capacity to consent may be compromised by emotional or cognitive disorders.

The most often cited product of the National Commission is the Belmont Report, which identified the basic ethical principles that should underlie the conduct of research with human subjects [15]. The three principles identified by the commission are:

1. *Respect for persons*—which supports individual autonomy through the process of informed consent;
2. *Beneficence*—which is interpreted in this context as promoting the welfare of human subjects and minimizing harm; and

3. *Justice*—which requires that the burdens and benefits of research not go disproportionately to any one group of people, and that those who would derive the benefits of the research should share in the burdens.

The commission debated, but never endorsed, the concept of prioritizing the three ethical principles. Some commentators had suggested that autonomy, or respect for persons, should trump beneficence and justice; but the commission declined to establish any order of priority.

The commission also broadened the definition of risk that must be considered by IRBs to encompass not only medical or physical risks but also psychological, social, legal, and economic risks [16]. Nonmedical risks frequently are related to the possibility that someone might breach confidentiality, and people with no connection to the research would learn the identity of individuals participating in studies concerning sensitive topics such as drug abuse, AIDS, or child abuse. That knowledge in turn could result in loss of employment, denial of insurance coverage, social stigma, family disruption, and (in some cases) criminal prosecution.

Analysis of Protections Provided by Other Federal Agencies

Commission staff surveyed the regulations of 21 federal agencies that conduct or support research with human subjects and prepared a report summarizing the kinds of research that the other agencies were supporting and the policies and procedures in place to protect human subjects. It appeared that most of the agencies had adopted the HEW regulatory scheme, but with minor variations. For example, some agencies required that the IRB chair sign a certificate of IRB approval, while others required that the entire IRB sign such a document. Although these may seem to be trivial differences, they resulted in unnecessary complications for IRBs, in part because it is often not clear which agency ultimately will fund the research under review, and sometimes two or more agencies support the same research. This regulatory review laid the foundation for a similar study by the President's Commission (see below) and recommendations for a single, government-wide set of rules.

Dispelling Conventional Wisdom

In November 1975, to better understand the involvement of prisoners in research, commission members and staff visited several prisons, including the State Prison of Southern Michigan at Jackson, at which large-scale pharmaceutical research was being conducted. They toured the prison, spoke with the prisoners and prisoner representatives, met with prison wardens, and interviewed drug company personnel. What they found refuted the conventional wisdom that prisoners had limited opportunities to earn

money and that drug firms offered payments to research subjects that far exceeded what could be earned in prison jobs.

By contrast, the commission found that many prisoners genuinely wanted to participate in research, or at least to volunteer, because it was the only way to get a thorough medical examination. In fact, prisoners relinquished better paying jobs within the prison, and lost priority in the job ladder, in order to volunteer for drug company research projects, because they knew they would get a good medical examination and possibly, follow-up treatment [17]. This insight became the basis for the Commission's decision not to prohibit research involving prisoners, because the prisoners didn't want that. Instead, the Commission required that there be adequate medical facilities and personnel available in the prisons doing research. Although the Commission recognized that improvement of the prison system was not part of its mandate, it set standards for health services in prisons wishing to do clinical research that few—if any—prisons could meet. The result was a significant curtailing of research involving prisoners in the United States.

Legacy

An important aspect of the Commission's work was that it operated entirely in public, providing broad access to the process of developing public policy. Open meetings were required by law, the agenda was announced in advance, and all documents sent to the commissioners were available to anyone who requested them, for whatever reason [18]. (Generally, two large binders of materials went to the commissioners each month over a period of four years.)

In addition, the Commission's minutes routinely were sent to hundreds of people on the mailing list, and the Commission held public hearings not only in Bethesda, but also in other regions of the United States. Members of the public could address the commission on any issue under consideration. There were no requirements that speakers represent a formal organization or that they be a physician, scientist, research administrator, or other professional. Anyone who asked to address the commission could do so. In addition, the commission received many letters and postcards, every one of which was photocopied and included in the agenda books distributed to the commissioners before each meeting. Thus, concerned citizens, unable to attend an open hearing, could make their views known to the commission and participate in the process of developing public policy.

An important practice established by the commission was to deposit one set of all its materials in the Kennedy Institute of Ethics Library at Georgetown University. Documents provided included minutes of all the meetings, transcripts of the meetings, agenda books that went to the commissioners on a monthly basis for four years, draft reports of recommendations and conclusions, correspondence, and, of course, the final reports.

It is a publicly available resource for scholars who want to examine the history of research with human subjects and the development of public policy in this country.

During its four-year term, the National Commission demonstrated the importance of involving diverse constituents in the development of public policy and the feasibility of deliberating about sensitive topics in public which, in turn, enhances credibility of the process and promotes acceptance of the product. These important aspects of the National Commission's activities paved the way and set the standards for other commissions that followed.

HEW Ethics Advisory Board (1978–1980)

The HEW Ethics Advisory Board (EAB), which began when the National Commission ended in 1978, was established to review problematic protocols that could not be approved by an IRB under regulations that were adopted in response to the National Commission's recommendations. The Ethics Advisory Board is probably best known for its report on "Human in Vitro Fertilization," prompted by a research proposal from Vanderbilt University. Shortly thereafter, Baby Louise Brown was born in England, setting off a firestorm of public concern very similar to the more recent response to the cloning of the sheep "Dolly" [19]. Some people feared the creation of human-animal chimeras, which they believed would be the next scientific "advance."

The Ethics Advisory Board's report on human in vitro fertilization was published by HEW Secretary Califano in 1979, on his last day in office [20]. Since then, every secretary of the department of HEW (now HHS) has failed to act on the report. It simply disappeared into the proverbial black hole, and the principal investigator whose grant application started it all died without ever receiving an answer from the department. But the proposals that the Ethics Advisory Board made for consent by both of the donors of the ova and the sperm, IRB review, and other aspects of human in vitro fertilization were adopted in their entirety by the American Fertility Society, and are followed for the most part by in vitro fertilization (IVF) clinics in the United States [21].

The Ethics Advisory Board also issued a report on HEW support of fetoscopy as a technique for prenatal diagnosis of sickle-cell disease and other disorders [22].

The President's Commission (1980–1983)

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research operated under a mandate similar to that of the National Commission in the research area; but

it also had obligations to consider various matters related to health care. Thus its reports included: *Securing Access to Health Care, Deciding to Forego Life-Sustaining Treatment, Screening and Counseling for Genetic Conditions, Splicing Life, Defining Death,* and *Making Health Care Decisions* [23].

The President's Commission sponsored the first workshop on scientific misconduct, an issue raised initially in the context of violations of IRB requirements [24]. (There had been a spate of incidents of scientific misconduct in the late 1970s and early 1980s, all of which involved research with human subjects.)

An important legacy of the President's Commission includes the government-wide "Common Rule," which incorporates Subpart A of the HHS regulations and was adopted in 1991 by 17 federal departments and agencies that conduct or support research with human subjects [25]. It took only 10 years to accomplish. (Those of us who are waiting for a common definition of "research misconduct" can draw reassurance from that.)

The President's Commission also developed the first official *IRB Guidebook,* which is a large, loose-leaf binder containing materials designed to help principal investigators and IRB members understand the public policies behind the federal regulations, and how the rules should be applied in various situations. The *Guidebook* is now in its second edition. Finally, the Commission proposed improving federal oversight of IRBs through periodic site visits by teams of IRB members from other institutions (similar to the accreditation process of the Joint Commission for Accreditation of Healthcare Organizations). This recommendation was never formally implemented.

Current Challenges

Concerns have been raised recently about studies of relapse in psychiatric illness, research involving cloning, and issues relating to confidentiality of medical information and biological materials. It is imperative that the scientific community participate in these debates. Otherwise, legislation may unintentionally prevent important research, by forbidding access to biological materials that are archived and to data from medical records that are not personally identifiable to the researcher.

Several issues discussed at the NIH symposium persist in the present. For example, I was called recently by a client, the parent of a teenager who needs a heart transplant. The parents had first called me several years ago because they were concerned that their son's place on the waiting list for a new heart might be jeopardized by the fact that he has Down's syndrome, and they thought that they might need a lawyer to persuade hospital authorities that it would be improper to take the child's disability into account. Several years ago, we had persuaded a hospital that Down's syndrome should not prevent an otherwise qualified patient from receiving a

heart transplant. The father called me again because his son was now in a different hospital, and the parents had been told (again) by a surgeon that he would talk with the other surgeons, but he anticipated there would be resistance by some who would not want to give a valuable organ to a patient with Down's syndrome. Apparently, concerns about "lives not worthy to be lived" or "those not worthy to receive scarce medical resources" are still with us.

Another example, which you may have read about in *Nature*, is the fact that the "visible man," that wonderful computer construct that is available on the Internet, was created from the body of an executed prisoner [26]. That fact provoked vigorous debates as to the propriety of using the body of a condemned man for such a purpose. The prisoner's lawyer said that the prisoner gave a free and informed consent, because he genuinely wanted to give something back to society. He thought he was donating his body to science, perhaps for organ transplants. The prisoner had never been told, however, just what might be done with his body. He clearly was not informed that everyone in the world would be able to examine his body on the Internet. Curiously, the journal that reported the incident also published the name of the condemned prisoner.

There is an urgent need for guidelines for involving individuals with cognitive impairments or—as they now say, "decisional incapacity"—in research. We need those guidelines so that research on dementias and serious mental disorders can proceed for the benefit of those who suffer from such conditions.

Other problems recur, from time to time. A year or so ago, human cloning research at a local university won a prize at the annual meeting of the Fertility Society. It was later revealed that the researchers had not sought IRB approval until after they had completed their experiments, and that no consent forms were signed by the donors of the sperm and ova (both patients of an IVF clinic) for use of their fertilized eggs in research [27].

In 1996, a college student died from a lethal overdose of lidocaine, received while participating as a normal volunteer in research that involved bronchoscopy. After the volunteer's death, an investigation revealed that the consent form had not listed death as a possible, albeit rare, event; the protocol had not established a maximum dose of the lidocaine for healthy subjects; and incremental changes to the protocol had not been reported to the IRB [28].

This brings us to the need for further improvement in the IRB system. We need better federal oversight of IRB performance. In IRBs that I have audited, I found that IRB members are conscientious but seriously overburdened. They have many more protocols for which they are responsible than they can handle. As a result, they tend to spend most of their time and energy on the initial review of new protocols and skimp on the continuing review of protocols that they had previously approved [29]. The

problem with that, of course, is that the IRB may not be carefully reviewing adverse events that have accumulated over the last year or so, and may not realize how many subjects have died or withdrawn from the protocol, and why. Consequently, the IRB is not in a good position to know if and when one arm of a clinical trial is clearly superior to the other(s), so that everyone can benefit from the investigational treatment, or conversely, whether there have been so many adverse events in one arm of the clinical trial that the trial ought to be halted. Without a careful continuing review, IRBs cannot protect research subjects in the manner contemplated by the regulations and expected by the general public.

A standard form for requesting continuing review would be very helpful to assure that certain information is always provided for annual review. The IRBs also must pay attention to the items on the form, and send the forms back if essential information is missing. I have found that sometimes the staff or one IRB member will review the applications for continuing review and present them to the convened IRB in a batch, to be approved without any substantive discussion. Similarly, sequential changes to protocols are not always reported, or they are not fully appreciated by the IRB, because continuing review is so abbreviated.

Clearly, there still are plenty of issues for the National Bioethics Advisory Commission to address.

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