

# Chapter 7

## Legal and Regulatory Issues



## Legal and Regulatory Issues

---

Basic legal tenets govern experimentation and biomedical research on human beings (see box 7-A). This chapter addresses the legal issues raised by neural grafting, including protection of recipients, protection of donors, informed consent, and Federal and State regulation.

### PROTECTION OF NEURAL GRAFT RECIPIENTS

Recipients of neural grafts may often be individuals needing special protection. Both the Federal and State Governments have recognized this need and have sought to provide protection through statutes and regulations. The relevant Federal and State legislation is outlined below.

#### *Coverage by Department of Health and Human Services Regulations Governing Research*

Department of Health and Human Services (DHHS) regulations apply to all research with human subjects that is conducted or funded by DHHS [45 CFR 46.101]. These Federal regulations have potentially widespread application. The Federal budget for the National Institutes of Health (NIH) alone represents over one-third of all money spent on health-related research in the United States (63). In addition, the reach of these Federal regulations extends well beyond federally funded research, since the regulations are used widely as guidelines in institutions that do not receive Federal funding (19).

The DHHS regulations apply to both therapeutic and nontherapeutic research and define research as “a systematic investigation designed to develop or contribute to generalizable knowledge” [45 CFR 46.101-46.409; 21 CFR 50.1-50.48; 45 CFR 46.102 (e)]. Some types of research are exempt from Federal regulations under certain conditions, for example educational research and research involving survey or interview procedures [45 CFR 46.10 l(b)(l) and (3)].

All Federally funded human research projects must be reviewed and approved by an Institutional Review Board (IRB) [45 CFR 46.103(b)]. IRBs are required to conduct continuing review,

which can include third-party observation [45 CFR 46.109(e)]. The intervals of continuing review are contingent on the degree of risk involved in the experiment but must not be less than once per year. The regulations also provide that risks of the proposed research must be minimized and must be reasonable in relation to anticipated benefits [45 CFR 46.110(a)(l), (2)], and they provide for expedited review of research that involves minimal risk [45 CFR 46.110(a)(2)]. “Minimal risk” means that the risks of harm anticipated in the proposed research are not greater than those encountered in daily life or during the performance of routine physical or psychological tests [45 CFR 46.110(a)(3)]. Research activities involving no more than minimal risk include, for example, collection of hair and nail clippings, recording of data that do not involve invasion of the subject’s privacy [46 FR 8392], and minor changes in approved procedures [45 CFR 46.110(b)].

Federal regulations require that selection of subjects be equitable [45 CFR 46.110(a)(3)] and that informed consent be obtained from each subject [45 CFR 46.116]. The regulations stipulate the basic elements that must be included in informed consent and require that such consent be documented and provided in language the subject can understand. They further provide that neither the researcher, the institution, nor the sponsor may be released from liability through the subject’s oral or written consent. DHHS regulations specifically address research involving fetuses, pregnant women, and human *in vitro* fertilization [45 CFR 46.201]. Moreover, separate provisions are included for research with children [45 CFR 46.401 (a)].

#### *Coverage by State Laws and Regulations*

*In* research programs where there is no Federal involvement or influence, government oversight will depend on whether there are State statutes. Where DHHS and Food and Drug Administration (FDA) regulations overlap State statutes, the Federal regulations are not intended to preempt applicable State or local laws [45 CFR 46.10 l(g); 21 CFR 50.25(c)]. Few States have statutes that address human experimentation specifically. At least six address human research as part of patients’ rights

### Box 7-A—The Genesis of Medical Research Ethics

Many legal principles in the area of medical research ethics have been developed in response to abuses of research subjects in Nazi Germany. Examples of unethical research in the United States further stimulated public discussion and policy considerations. The most well-known examples of research abuses in the United States are the Willowbrook hepatitis study and the Tuskegee syphilis study. In the 1960s, institutionalized mentally disabled children at Willowbrook Institution were infected with live hepatitis virus in an effort to develop a vaccine. The scientists justified their procedures by noting that hepatitis ran rampant through the institution and that all of the children would eventually contract the disease. From 1932 to 1972, scientists conducting a U.S. Public Health Service study of 400 black men suffering from syphilis deliberately withheld treatment from them in order to study the effects of allowing the disease to take its course, even though penicillin had been found to be an effective treatment. At least 28 of perhaps as many as 107 men died as a result of this study.

In the trials of Nazi physicians, the court set forth standards that should be met before and during research. The Nazi physicians tried to defend themselves by pointing out abuses in research that had occurred elsewhere, including those in the United States. However, this defense did not succeed, and 15 of the 23 physicians were found guilty of war crimes and crimes against humanity. Those standards, subsequently adopted by the United Nations General Assembly, are known as the Nuremberg Code. The tenets of the code significantly influenced subsequent State laws. For example, the preamble to the California human experimentation law states that the law was necessary since the Nuremberg Code was not codified and thus is unenforceable [Cal. Health & Safety Code 24171(b)]. Federal regulations in the United States dealing with research were likewise influenced.

The Nuremberg Code provides guidelines for ensuring that participation in research is voluntary and that the risks of research are minimized. It provides that:

- . certain basic research and animal research must be done before human research is undertaken;
- . the research must be well designed;
- the research must be undertaken only by scientifically qualified individuals;
- . the potential results must justify the risk involved in the performance of the research; and
- . those results must not be procurable by other means of study.

The central principle of the Nuremberg Code is that participation in research must be voluntary, informed, and uncoerced and that subjects have the right to bring the experimentation to an end. The code also requires that risks be minimized through appropriate design and conduct of the research as well as adequate preparation and facilities to protect the subjects. Research is forbidden if there is an *a priori* reason to believe that death or disabling injury will occur (although the code does allow an exception if the scientists also serve as subjects), and ongoing research must be stopped if there is reason to believe that its continuation will lead to the injury, disability, or death of the subjects.

In applying the ethical principles enunciated in the Nuremberg Code to the issue of neural grafting, the question of whether there has been sufficient animal research may arise. Fetal grafts in rodents and in monkeys have been studied, but some experts in the field believe that more animal research is necessary. They also believe that certain additional information is needed about the nervous system. They argue that eventually, however, human subjects must be involved.

SOURCES: Office of Technology Assessment, 1990; based on L. Andrews, *Medical Genetics: A Legal Frontier* (Chicago, IL: American Bar Foundation, 1987); B. Barber, "The Ethics of Experimentation with Human Subjects," *Scientific American* 234(February): 25-31, 1976; A.M. Capron, "Human Experimentation," *BioLaw* 10:217-229, 1986; T. Gill and R. Lund, "Implantation of Tissue into the Brain: An Immunologic Perspective," *Journal of the American Medical Association* 261:2674-2676, 1989; S. Golby, "Experiments at the Willowbrook State School," *Lancet* 1:749, 1971; R. Greenwald, M. Ryan, and J. Mulvihill, *Human Subjects Research: A Handbook for Institutional Review Boards* (New York, NY: Plenum Press, 1982); J. Jones, *Bad Blood: The Tuskegee Syphilis Experiment* (New York, NY: Free Press, 1981).

statutes. Some States have statutes protecting particular groups of research subjects (e.g., the mentally disabled), while others have a professional ethics statute that mandates obtaining patients' consent to experimentation. The provisions range from a simple statement that individuals have the right to refuse to participate in experimental research to statutes

that list the requisite elements of informed consent. Some statutes simply prohibit human experimentation that involves any significant risk of physical or psychological harm. Often, the statutes use the terms "human research" and "human experimentation" interchangeably. Table 7-1 lists State regulations covering human subjects in experimentation.

Table 7-I-State Regulations Pertaining to the Protection of Human Subjects in Experimentation

Alaska regulates human experimentation with the mentally ill; limits experiments to those that pose no hazardous risk.	Nevada provides that prospective subjects in human experimentation have the right to refuse to participate.
Arizona requires informed consent before a person may participate in a research project as a human subject. Regulates human experimentation with the developmentally disabled.	New Hampshire requires IRB approval for any research involving human subjects.
Arkansas regulates human experimentation with the mentally ill; provides that patients have the right to refuse to participate.	New Jersey regulates experimentation with the mentally ill and mentally retarded; provides that mentally disabled patients have the right to refuse to participate and requires that the research be intended to benefit the mentally ill subject. Court approval is mandatory if the disabled patient is declared incompetent.
California has a comprehensive statute regulating experimentation involving novel therapy and research on human subjects. Requires Institutional Review Board (IRB) approval and informed consent for any research involving human subjects; requirements for informed consent include an explanation of procedures, possible side-effects, information about alternative therapy, and subject's right to withdraw consent at any time during the experiment. Regulates human experimentation with the mentally ill; informed consent of the patient or guardian is required, and the research must be intended to benefit the mentally ill subject. A grievance mechanism is provided should the experiment go awry.	New Mexico regulates human experimentation with the developmentally disabled and the mentally ill; requires informed consent of the patient or guardian.
Colorado requires informed consent before a person may anticipate in a research project as a human subject. Regulates human experimentation with residents of facilities for the developmentally disabled; informed consent of the patient or guardian is required.	New York has a comprehensive statute regulating experimentation with novel therapy on humans and research on healthy human subjects. Requires IRB approval of any research with human subjects; requirements for informed consent include an explanation of procedures, possible side-effects, alternative therapies, and subject's right to withdraw consent at any time during the experiment. Makes specific mention of these rights with respect to the mentally ill.
Connecticut provides that prospective subjects in human experimentation have the right to refuse to participate.	North Carolina regulates human experimentation with the mentally ill, the retarded, and substance abusers; requires informed consent of the patient or guardian.
District of Columbia requires informed consent before a person may participate in a research project as a human subject. Regulates human experimentation with the mentally ill and developmentally disabled; requires informed consent of the patient or guardian and that research be in the best interests of the patient. A court order is mandatory for psychosurgery, sterilization, medical/behavioral research, or pharmaceutical research on resident of a facility for the developmentally disabled.	North Dakota requires informed consent for participation in research projects. Regulates human experimentation with the mentally ill and developmentally disabled; requires informed consent of the patient or guardian and that research be in the best interests of the patient. A court order is mandatory for psychosurgery, sterilization, medical/behavioral research, or pharmaceutical research on resident of a facility for the developmentally disabled.
Delaware regulates human experimentation with the mentally disabled; informed consent of the patient and IRB approval are required. The requirement for informed consent may be waived in cases where an attempt to obtain informed consent from the patient has failed, no other therapy exists or the patient has not responded to accepted therapies, the research would be in the best interests of the patient, and the waiver has been approved by the IRB and the patient's legal guardian or next of kin.	Ohio regulates human experimentation with the mentally ill; requires informed consent of the patient or guardian. A court order is required for unusually hazardous treatment procedures if the patient is legally incompetent or involuntarily committed to a mental institution.
Florida requires informed consent before a person may participate in a research project as a human subject. Regulates human experimentation with the developmentally disabled; informed consent of the patient or guardian is required. Physician may request court approval when unwilling to act on developmentally disabled patient's consent and the guardian is unknown or cannot be located.	Oregon requires informed consent for participation in research projects.
Hawaii regulates human experimentation with the mentally disabled; states that patients have the right to refuse to participate.	Rhode Island requires informed consent for participation in research projects.
Illinois regulates human experimentation with the mentally ill and developmentally disabled; informed consent of the patient or guardian is required.	South Carolina regulates human experimentation with the mentally ill and the developmentally disabled; states that mentally disabled patients have the right to refuse to participate.
Kansas requires informed consent for participation in research Projects. Regulates human experimentation with mentally ill inpatients; requires informed consent of the patient and his or her guardian.	South Dakota requires State review board and informed consent of the patient or guardian before the mentally ill may participate in research.
Maine requires informed consent before a person may participate in a research project as a human subject. Regulates human experimentation with the mentally retarded; informed consent of the patient or guardian is required.	Texas provides that prospective subjects in human experimentation have the right to refuse to participate.
Massachusetts provides that prospective subjects in human experimentation have the right to refuse to participate.	Vermont provides that prospective subjects in human experimentation have the right to refuse to participate.
Michigan provides that prospective subjects in human experimentation have the right to refuse to participate.	Virginia has a comprehensive statute regulating experimentation with novel therapy on humans and research on healthy human subjects. Requires IRB approval of any research with human subjects; requirements for informed consent include an explanation of procedures, possible side-effects, alternative therapies, and subject's right to withdraw consent at any time during the experiment. Specifically regulates human experimentation with the mentally ill; experiments are limited to those that pose no hazardous risk.
Minnesota requires informed consent for participation in research projects.	Washington requires informed consent for participation in research projects.
Missouri requires IRB approval for research with the mentally disabled, informed consent of the patient or guardian, and that the research be intended to benefit the mentally ill subject.	Wisconsin regulates human experimentation with the developmentally disabled, mentally ill, and substance abusers; requires informed consent of the patient and his or her guardian and IRB approval.
Montana requires State review board approval and informed consent for research with the mentally disabled.	Wyoming requires informed consent for participation in research Projects. Regulates human experimentation with the mentally ill; informed consent of the patient or guardian is required.

SOURCE: Office of Technology Assessment, 1990.

Only three States have enacted comprehensive legislation that applies specifically to medical research with human subjects—California, New York, and Virginia [Cal. Health & Safety Code 24170-24179.5; N.Y. Public Health Law 2440-2446; Va. Code 37.1-234-37.1-241]. The statutes of both California and New York affirm that human experimentation is vital for the benefit of humankind but require that it be undertaken with due respect for the rights of individuals to determine what is done with their bodies. The New York and Virginia statutes provide that researchers conducting experimentation in compliance with Federal regulations concerning protection of human subjects are not subject to the State requirement. California provides that researchers conducting investigations within institutions receiving Federal funding and who obtain informed consent as required by Federal regulations are exempt from all State requirements except the provisions requiring that the subject receive a list of subjects' rights and a list of any penalties that may attach for violation. The list of subjects' rights does not include information beyond that required in the Federal regulations. As noted earlier, compliance with Federal regulations does not render State or local laws inapplicable [45 CFR 46.10 l(g)]. Therefore, in States that do not make provisions for the overriding applicability of Federal regulations, researchers must observe both Federal regulations and any State or local statutes or regulations.

All three of the comprehensive State statutes appear to regulate experimentation involving novel therapy on patients as well as research on healthy subjects. Each defines human experimentation (research). Virginia defines "human research" as any medical research that departs from established methods using human subjects who might be exposed to possible injury as a consequence of their participation. This appears to encompass therapeutic experimentation. California and New York define "human experimentation" as experiments that are not necessary for treatment nor of direct benefit to the subject. Although these statutes appear to be aimed primarily at experimentation on healthy subjects, both include as an element of informed consent a requirement that the individual receive information concerning appropriate alternative procedures. As this information would not be relevant to the subject of purely nontherapeutic experimentation, it could be argued that these statutes also apply to therapeutic experimentation.

Although Federal regulations and the statutes of California, New York, and Virginia specifically address the elements of informed consent, some States merely provide that informed consent be obtained. In all, statutes of 24 jurisdictions contain provisions requiring some kind of informed consent before a person may participate in a research project as a human subject. Of these statutes, 11 apply to research with the mentally disabled. Eleven of the informed consent statutes do not specify what information must be provided. Many States have general medical consent statutes that would apply to recipients of neural grafts. Of the remaining statutes, 10 provide only that the prospective subject has a right to refuse to participate in human experimentation. Four of these statutes apply only to research with the mentally disabled.

The California human experimentation statute provides fines and terms of imprisonment for anyone who violates its requirements. Liability extends to persons who are primarily responsible for conducting medical experiments and representatives or employees of pharmaceutical companies who are directly responsible for contracting with the subjects.

### ***Role of Institutional Review Boards***

There has been concern that research proposals be reviewed in advance by groups uninvolved with the research project itself. This has led to the formation of IRBs to assess the ethical ramifications of proposed research. IRB approval is necessary before a project can receive Federal funding [45 CFR 46.103(b)]. Federal regulations and some State laws provide for advance review of research proposals by IRBs. This mechanism arose out of concern for the rights of human subjects who participate in medical research (5,53) and the fear that relying on the investigator's sense of professional responsibility was an insufficient safeguard of the subject's rights (45). There is an inherent conflict between the researcher's goals in undertaking the experiment (which may lead to acquisition of knowledge, enhanced professional status, or commercial gain) and the patient's rights (53). Because of this conflict, it was thought necessary to ensure that proposed research is reviewed by an impartial body. When functioning properly, IRBs prevent premature experimentation with human subjects (by monitoring whether appropriate laboratory and animal research has been con-



Photo credit: Gregory Robertson, Howard University

An Institutional Review Board voting on approval of a protocol involving human subjects in research.

ducted to support the scientific design and safety of the study) and ensure that the subject has given fully informed consent.

Currently, the Federal Government requires that any product for which marketing approval is sought from FDA and all research involving human subjects that is conducted or funded by DHHS be reviewed and approved by an IRB [45 CFR 46.101-46.409; 21 CFR 56.107, 56.108]. Similarly, four States—California, New Hampshire, New York, and Virginia—require IRB review of any research involving human subjects. Seven States and the District of Columbia provide for IRB approval of any research with the mentally disabled.

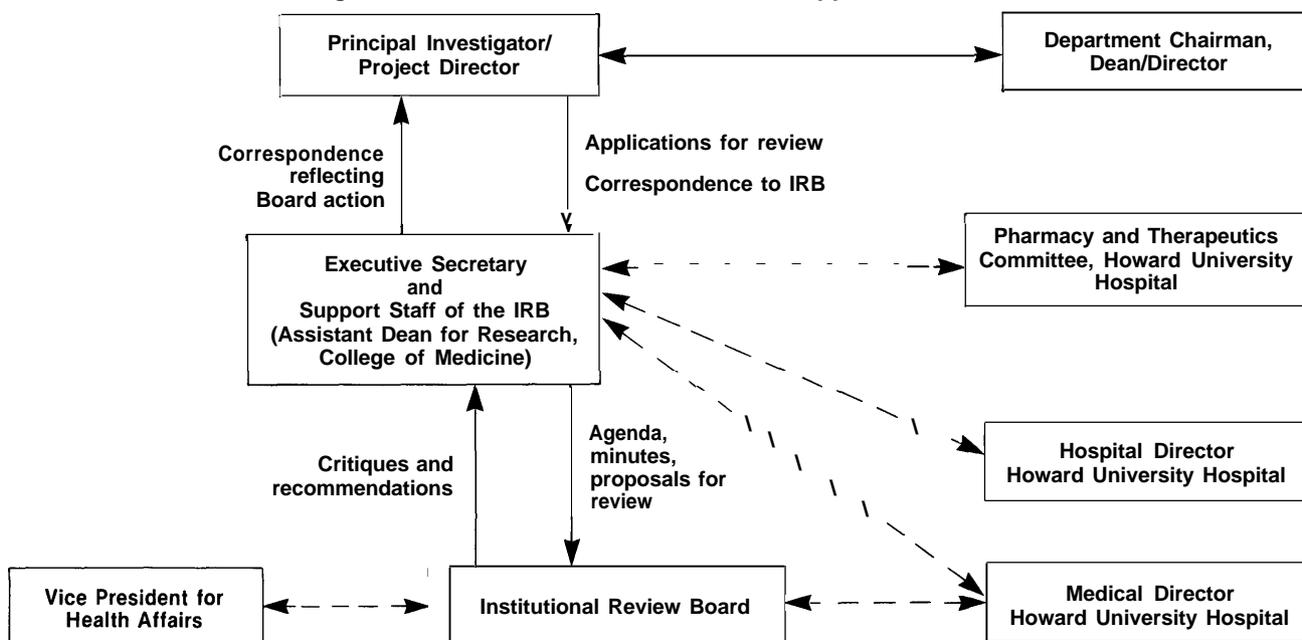
Federal regulations and New York and Virginia statutes set forth duties of an IRB, which include evaluating risks and benefits to the prospective subject and ensuring that risks are outweighed by potential benefits to the subject or by the importance of the knowledge to be gained. An IRB must take the following factors into consideration in deciding whether or not to authorize human research:

- the adequacy of the researcher's description of the potential benefits and risks involved;
- the adequacy of the methodology of the research;
- whether any nontherapeutic research presents a hazardous risk to human subjects;
- whether risks to human subjects are outweighed by potential benefits to the subjects;
- the adequacy of the informed consent form; and
- whether the informed consent is to be obtained by adequate and appropriate methods.

IRBs are also charged with deciding whether the persons proposing to conduct human research are qualified and competent, and they must periodically investigate each project to ensure that it is being carried out according to the original proposal [N.Y. Public Health Law 2444; Va. Code 37.1-236]. Figure 7-1 illustrates the procedure for obtaining IRB approval for projects involving human subjects at one research institution.

In any IRB review, the fundamental ethical guidelines for determining whether a therapy

Figure 7-I—An Institutional Review Board Approval Process



These interactions shall occur as the need arises, such as projects involving drugs (PTC); inpatients at Howard University Hospital (Hospital and Medical Directors); adverse reaction (Medical Director, Hospital Director, and Vice President for Health Affairs); annual reports (Vice President for Health Affairs).

Procedure for obtaining Institutional Review Board approval currently in use at one research institution.

SOURCE: Howard University, Institutional Review Board, Washington, DC.

may be experimentally used on humans is to hold each person fundamentally entitled to respect as an individual (70) and to proceed only if there is a favorable ratio of benefits to risks (1). Specifically, this standard requires a thorough assessment of the probable outcome (in both its helpful and harmful aspects), which is weighed against the results of not using the proposed treatment. For example, if a patient has a fatal disease and there are no known mitigating treatments, a therapy previously untested in humans that was not likely to cause serious or lethal harm to the patient might be approved for experimental use in the patient.

Only the Federal regulations [45 CFR 46.109; 21 CFR 56.108] and the statutes of Delaware, New York, Missouri, and Virginia set forth the composition of an IRB. Under Federal law each IRB must include:

- . at least five members with varying backgrounds (including racial and cultural backgrounds);
- . a combination of men and women;

- . a member from a nonscientific discipline, such as a lawyer or an ethicist; and
- . a member who is not otherwise affiliated with the institution [45 CFR 46.107].

Problems may arise if members of the IRB are associated with the institution. Such individuals may not be able to be completely objective because of their identification with the researcher, their loyalty to the institution, and the fact that any possible success may accrue indirectly to associated review board members (45). One way to avoid this problem would be to require that the IRB include as members only individuals who have no connection with the research institution. Some commentators argue that this proposal may promote unwarranted public interference with medical research (45) and that membership on an IRB could become a political appointment, which might threaten the academic freedom of researchers (56). However, it has been suggested that the possibility of political interference should be outweighed by the necessity for objective input. The principle underlying IRBs is that protection of the rights of human research subjects overrides the absolute freedom of the

researcher to perform unrestricted experimentation (56).

### Requirements for Informed Consent

The doctrine of informed consent is based on the right of every individual to participate in decisions about his or her own medical care (17). Informed consent means the ‘knowing’ consent of a person or, if the person is not competent to consent, his or her legally authorized representative (24). An individual cannot consent to be an experimental subject without understanding what that may entail. Adequate informed consent requires that the researcher transmit to the prospective subject, in language the subject can understand, any information that might influence the subject’s decision to participate or not participate (24).

Potential problems with attempting to convey all updated information to subjects have been noted (69). Studies are statistically designed to have sufficient power to accept or reject a given hypothesis; however, unplanned interim analyses may be invalid and may not provide sufficient, reliable information. Early disclosure of benefits (or lack of benefits) may be unfair to patients recruited early in the study. Such patients consent to participate without any preliminary data. Patients acquired after the study has been under way may be at a distinct advantage if they are provided with benefits gleaned from data (or lack of data) derived from the earlier patients. However, it would be reasonable to update the informed consent by providing information concerning new risks or alternative therapies (69).

Some of the likely recipients of experimental neural grafts, persons with Alzheimer’s disease, for example, may have impaired mental functioning, which may or may not affect their ability to give informed consent. Thus, it is likely that some subjects in this field may be incapable of giving consent for themselves (11,64,65). Various guidelines have been suggested for research on subjects who are incapable of consenting. There is general agreement that such individuals should be allowed to participate in therapeutic research the intent of which is to provide a health benefit to them. With respect to nontherapeutic research, some commentators suggest that it should not be undertaken on people who cannot personally give valid, informed consent (49). Others suggest that it should be

permissible to undertake important, nontherapeutic research on incompetent individuals, provided there is proxy consent and there are minimal or no risks (32).

Discussion of research in the four decades since adoption of the Nuremberg Code has highlighted some additional ethical concerns. The concern that selection of subjects for research be equitable has been incorporated into the Federal regulations [45 CFR 46.111(a)(3)]. For example, a particular class or race of persons should not serve as subjects for research that primarily benefits persons of another class or race. Some commentators suggest that this should be particularly true in the case of subjects incapable of consenting (e.g., research on an incompetent, elderly subject should benefit other elderly people).

The adequacy of consent for experimental therapy raises more questions than that for proven treatment because less is known about the efficacy and risks involved in an experimental procedure. Although no absolute guarantee exists that an established treatment will be effective and will cause no harm, even fewer and possibly no guarantees exist when the proposed therapy is experimental. Therefore, a prospective subject must be made aware that little is known about the possible risks and consequences involved in participation in the experiment (15). As the New York human experimentation law provides, “Every human being has the right to be protected against the possible conduct of medical or psychological research on his body without his voluntary informed consent” [N.Y. Public Health Law 2440].

Federal regulations and laws in California, New York, and Virginia provide that the information given for proper informed consent must include the following:

- an explanation of the procedures, drugs, or devices to be used in the experiment;
- a description of any possible risks and discomforts that might be expected;
- an explanation of possible benefits;
- a disclosure of appropriate alternative procedures, drugs, or devices;
- an offer to answer questions that the prospective subject may have concerning the experiment and its effect; and



Photo credit: Gregory Robertson, Howard University

Clinical investigator counsels patient prior to obtaining informed consent for her participation in human subjects research protocol.

. an instruction that the individual's consent to participate in the experiment maybe withdrawn at any time, without prejudice [Cal. Health & Safety Code 24172; N.Y. Public Health Law 2441; Va. Code 37.10234; 45 CFR 46.116].

There is virtually no disagreement concerning the requirement of these elements for informed consent. Federal regulations require, in addition, that informed consent include a statement describing the extent to which the confidentiality of the subject will be maintained, the expected duration of the subject's participation, and an explanation as to whether any medical treatments or compensation are available in the event of injury.

When the subject is also a patient, it is important that a realistic assessment of the expected results of the therapy be provided. Patients may tend to overestimate the benefits they will experience with an experimental treatment. To counter that tendency, it may be useful to provide information, when applicable, about the extent of previous research on the experimental treatment in animals and humans.

Informed consent must also include a statement of whether any alternative treatments exist. The subject should be told if the use of the experimental treatment will foreclose any of those alternatives. An example of this would be when the subject's disease will have advanced too far after he or she has received experimental therapy to treat it with traditional therapy (30).

The use of aborted fetal tissue for neural transplantation raises a unique issue about consent. The recipient should be told the source of the

tissue—that it was from an aborted fetus—since that information may be material to the recipient's decision whether or not to consent to the transplant (57). Another commentator goes further, stating that disclosure should be made concerning all animals used in preclinical studies (10).

There are concerns about what should happen if the human subject is harmed in the study. According to Federal regulations and California law, the subject should be given an explanation of the availability of medical therapy in case of injury incurred as a result of the experiment [45 CFR 46.116(a)(6); 21 CFR 50.25(a)(6); Cal. Health & Safety Code 24172(f)]. If compensation for research injuries is not provided for, the prospective subject should be so informed. If a subject has not been specifically informed that he or she bears the financial cost of potential physical injury, the informed consent is, arguably, not complete (53).

Research subjects must also be given an assurance that they are free to refuse to participate or to withdraw their consent at any time and to discontinue participation in the project without penalty or loss of benefits to which they are otherwise entitled [45 CFR 46.116(a)(8); 21 CFR 50.25(a)(8)]. All ethical codes stipulate that subjects must be able to withdraw from an experimental project at any time, without prejudice or penalty (30). The right to withdraw is derived from the premise that the subject is doing something for the benefit of others and that such acts are generally not obligatory (30).

If researchers do not provide adequate information to a subject before the study is undertaken, they can be sued for damages if harm results (26). In addition, physician-researchers who do not obtain informed consent may be disciplined for unprofessional conduct. In the Jewish Chronic Disease Hospital case, 22 debilitated patients were injected with live cancer cells without first having given their informed consent (45). The Attorney General of New York brought an action against the principal investigators to the Board of Regents Discipline Committee, which found the doctors guilty of fraud, deceit, and unprofessional conduct. The doctors were punished, not because they performed experiments that resulted in harm to the patients, but because they did not obtain informed consent before proceeding. California law also provides penalties for violation of the informed consent provision, including damages up to \$1,000 for

negligent failure to obtain informed consent, damages up to \$5,000 for willful failure to obtain informed consent, and damages up to \$10,000 and up to 1 year in jail for willful failure to obtain informed consent that exposes the subject to substantial physical or psychological risk. Additional protections are provided regarding drug companies. A representative or employee of a pharmaceutical company who knows of substantial physical or psychological risks of an experiment and does not disclose them can be imprisoned for up to a year and freed up to \$10,000 [Cal. Health & Safety Code 24176(a)].

#### Handling of Grievances and Nonrelease From Liability

The California statute provides a grievance mechanism for patients when an experiment goes awry. It requires that the subject be given the “name, address, and phone number of an impartial third-party, not associated with the experiment, to whom the subject may address complaints about the experiment” [Cal. Health & Safety Code 24173 (c)(lo)].

Like the Federal regulations [45 CFR 46.116; 21 CFR 50.20], the **statutes** in California, New York, and Virginia provide that any attempted or purported waiver of an individual’s legal rights is void. The New York and Virginia **statutes state** that it is impermissible to release any individual, institution, or agency and any agents thereof from liability for negligence [Cal. Health & Safety Code 24176; N.Y. Public Health Code 2442; Va. Code 37.1-235].

#### Protections for Particularly Vulnerable Subjects

Some statutes and regulations cover research on particularly vulnerable groups, for example children or the mentally disabled. Statutes concerning research on the mentally disabled may be relevant to experimental neural grafts into subjects with disorders that affect their mental functioning. Federal regulations provide that IRBs shall add appropriate additional safeguards if the potential subjects suffer from acute or severe physical or mental illness [45 CFR 46.116(b)]. Although the regulations do not describe what these additional protections might be, NIH has introduced guidelines covering intramural research (20). The guidelines include a procedure for obtaining proxy consent as well as additional oversight for research that involves more than minimal risk. The guidelines prohibit research of

more than minimal risk if the patient is incapable of choosing a proxy decisionmaker and has no next of kin to seek court-appointed guardianship.

Twenty-five States and the District of Columbia specifically regulate experimentation on the mentally disabled (see table 7-1). Other States regulate experimentation on residents of nursing homes [Mo. Ann. Stat. 198.088(l)(b)(c); Or. Rev. Stat. 441.385]. The abundance of State legislation reflects a general concern that institutionalized persons are frequently used as experimental subjects because they are “administratively convenient” to the researcher (30) and that they are often taken advantage of, either because of their mental deficiencies or their guardians’ lack of interest in their welfare (2). That State laws tend to pay close attention to the issue of informed consent for mentally ill patients is due to concerns not only about voluntariness, but also about the capacity of these persons to comprehend information (76).

Of the 25 jurisdictions that provide statutory guidelines for experimentation on the mentally disabled, 14 States and the District of Columbia require that informed consent of the patient or patient’s guardian be obtained. Kansas and Wisconsin require informed consent of both the mentally disabled person and the guardian [Kan. Stat. Ann. 59-2929(6); Wis. Stat. Ann. 51.61]. Five States provide only that mentally disabled patients have the right to refuse to participate in experimentation projects.

In some States, the permissibility of research on mentally disabled individuals turns on both its purpose and its level of risk. At least two States, Alaska and Virginia, limit experimentation on the mentally deficient to that which poses no hazardous risks. These statutes authorize an administrator to determine what procedures are both experimental and risky. Four States, California, Missouri, New Jersey, and North Dakota, require that the research be intended to benefit the mentally ill subject. A similar approach, with more stringent provisions, is taken by the Delaware statute, which prohibits the participation in experimental research of mentally ill persons who are incapable of giving voluntary consent—except under the following circumstances [Del. Code Ann. Tit. 16,5172, 5175]:

- an attempt to obtain informed consent from the patient has failed;

- no other therapy exists or the patient has not responded to accepted therapies;
- the research would be in the best interests of the patient; and
- the waiver has been approved by the IRB and the patient's legal guardian or next of kin.

The proposed waiver must then be approved by a court, which may deny approval for any reason it deems appropriate.

Other statutes specify a particular review mechanism that must be followed. Six States require prior review and approval of any research projects by an IRB, while three jurisdictions require review and approval by State boards before experiments are conducted on mentally disabled persons. Florida, New Jersey, North Dakota, and Ohio require some sort of judicial determination of the necessity of an experimental procedure before it maybe used on an incompetent person. Florida, New Jersey, and North Dakota require that the patient be physically present at such a judicial hearing, represented by counsel, and provided the right and opportunity to confront and cross-examine witnesses. These three States also place the burden of proof on the party alleging the necessity of the treatment.

### *FDA Regulation of Neural Grafting Materials*

*Neural* grafting presents a number of issues for would-be recipients. A potential patient might be concerned about what material is to be grafted into his or her brain and whether that material is safe and effective. These issues are likely to come within the jurisdiction of the FDA. Any description of the FDA's role in regulating the safety and efficacy of neural grafting materials is complicated by the fact that there are several different types of materials, each of which raises slightly different questions. In addition, neural grafting materials (and materials that could potentially be used for neural grafts) represent developing technologies that have not yet been directly addressed by the FDA. A final complicating factor is the developing nature of FDA policies for the regulation of biological products that may be analogous to neural grafting materials and the resulting lack of published regulations or decisions in this area.

The FDA is responsible for regulating the distribution of drugs and devices under the Federal Food, Drug, and Cosmetic Act (FFDCA) [21 U.S.C. 321 *et seq.*] and has been delegated authority to regulate the

commercial distribution of biologics under the Public Health Service Act (PHSA) [42 U.S.C. 262]. In addition, the Coordinated Framework for the Regulation of Biotechnology [49 FR 50856; 50 FR 47174; 51 FR 23302] delegated authority for the regulation of human drugs, medical devices, and biologics produced by biotechnology to the FDA. As described in chapter 4, materials used in neural grafting are varied and may come from various sources. Neural grafting ranges from implanting tissue obtained from the patient's own body to implanting genetically engineered cells from a cell line developed and maintained in a laboratory. The risks inherent in using each type of material have yet to be assessed by the FDA, but it is possible to outline the issues that the agency is likely to consider, based on its statutory mandate, existing regulations, and decisions with respect to similar materials.

Neural grafting materials present challenges at the cutting edge of developing FDA policy because these materials are sometimes analogous to tissue transplants and sometimes to products of genetic engineering. The principal questions regarding neural grafting materials are:

- Is the FDA likely to regulate the manufacture and distribution of the product?
- If the answer to the first question is yes, will the product be regulated as a drug, device, or biologic?

FDA jurisdiction with respect to drugs, devices, and biologics is described below. Areas in which the law is unclear as it may apply to neural grafting materials are described, and issues in the potential regulation of specific types of neural grafts are presented.

### FDA Jurisdiction

**Drug**—The FFDCA defines “drug” in part as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. . .” and “articles (other than food) intended to affect the structure or any function of the body of man . . . but does not include devices or their components, parts, or accessories” [21 U.S.C. 321(g)(1)]. The classification of a product is thus based in part on the use intended by the manufacturer. A product may not be classified as both a drug and a device, but it maybe regulated as both a drug and a biologic. The Supreme Court has sustained the

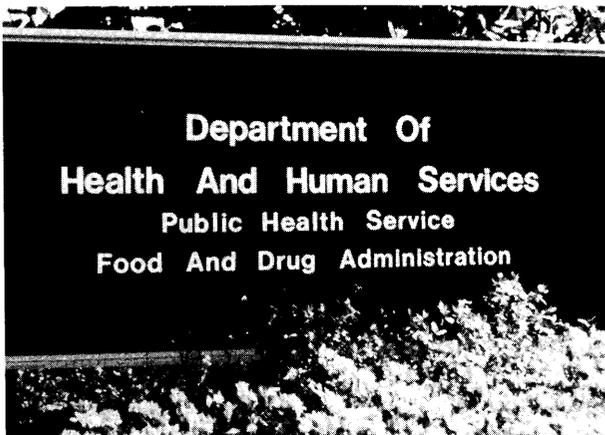


Photo credit: Food and Drug Administration

FDA's authority to interpret the FFDCA'S definitions broadly, in view of the broad public health objectives of the legislation (60).

**Device**—The term “device” is defined in the FFDCA as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article. . . which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease” or which is “intended to affect the structure or any function of the body” and “which does not achieve any of its principal intended purposes through chemical actions within or on the body” and “which is not dependent on being metabolized for the achievement of any of its principal intended purposes” [21 U.S.C. 321(h)].

The items listed as devices in the statute imply that Congress intended the term to refer to man-made products. Aside from implants and in vitro reagents, the items in the list are synthetic products that are generally made of materials such as metal or plastic. The legislative intent underlying the definition of device is probably limited to artificial implants (66). Some products that may otherwise fit the definition of drugs or biologics are regulated as devices because they are considered accessories to or components of a device. A product may be classified as both a biologic and a device.

**Biologic**—The law that authorizes Federal regulation of biological products for human use was enacted in 1902 and was revised in 1944 as part of the recodification of the PHSA, (now codified at 42 U.S.C. 262) (39). The PHSA establishes requirements for “any virus, therapeutic serum, toxin,

antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of diseases or injuries of man” [42 U.S.C. 262]. At present, the scope of the term “analogous product” is unclear. It has not been extensively reviewed by the courts (71), nor did Congress clarify the term in 1970, when, in response to conflicting positions by the courts on whether blood was an analogous product, it amended the PHSA to specifically include blood, blood components or derivatives, and allergenic products [Public Law 91-515]. It is therefore unclear whether courts would uphold FDA regulation of neural grafting materials under the PHSA without the enactment of specific language to add such materials to the statute.

The initial question, then, in determining whether the FDA has jurisdiction to regulate neural grafting materials is whether a particular material meets the definition of a drug, device, or biologic. All biologics are considered either drugs or devices as well as biologics (71). However, an article proposed for use as a neural graft cannot simultaneously be both a drug and a device. The question of how to categorize neural grafting materials will be considered further later in this chapter.

#### FDA Regulation of Safety and Efficacy

The FDA regulates product safety and efficacy in a number of ways. Under the FFDCA, a drug or device is deemed to be adulterated if it consists of a filthy substance or if it has been prepared under unsanitary conditions such that it may have been contaminated with filth or rendered injurious to health. Drugs and devices are considered adulterated if the methods used in manufacturing, storing, or packing them do not conform to current good manufacturing practice or if the container is made of a substance that may render the contents injurious to health. Drugs are also adulterated if their strength, purity, or quality is less than is represented [21 U.S.C. 351].

A drug or device is misbranded [21 U.S.C. 352] if its labeling is false or misleading or if adequate directions for use or adequate warnings against unsafe use are omitted from the label. Any drug or device is misbranded if it is dangerous to health when used in the dosage or manner or with the frequency or duration described in the labeling.

Owners or operators of establishments for the manufacture, preparation, propagation, compounding, or processing of drugs or devices must register all places of business with the FDA [21 U.S.C. 360] in order to facilitate inspection and enforcement of FDA regulations. Several types of operations are exempted from the registration requirement. These include pharmacies dispensing prescription drugs or devices on prescriptions of licensed practitioners prescribing for patients in the course of professional practice [21 U.S.C. 360(g)(1)], practitioners licensed by law to administer drugs or devices and who manufacture these items solely for use in their professional practices [21 U.S.C. 360 (g)(2)], and persons who make the products solely for use in research, teaching, or chemical analysis and not for sale [21 U.S.C. 360 (g)(3)].

Premarket approval of a new drug application (NDA) is required for new drugs [21 U.S.C. 355]. A “new drug” is one that is not generally recognized by qualified experts as safe and effective for use under the conditions prescribed in the labeling [21 U.S.C. 321(p)(1)]. An application for premarket approval (PMA) is required for some devices [21 U.S.C. 360(e)], but all manufacturers of devices are required to at least notify the FDA 90 days before introducing a device into the market [21 U.S.C. 360 (k)].

An exemption from premarket approval may be obtained for shipment of products intended solely for investigational use by filing an investigational new product application. This submission is either an investigational new drug application (IND) [21 U.S.C. 355(i); 21 CFR Part 312] or an investigational device exemption [21 U.S.C. 360(j)(g); 21 CFR Part 812]. The FDA reviews the submission to protect the safety of investigational subjects and to ensure that the research design is adequate for the purpose of testing safety and effectiveness in the event that an NDA or PMA is filed. The study must be approved by an IRB in each institution or area in which the drug or device will be tested.

The FDA requires manufacturers of approved drugs and devices to make prompt reports of adverse events and periodic reports on safety and effectiveness [21 CFR 314.80, 314.81, and part 803] after the products have been distributed for use.

Biologics are subject to all of the FDCA requirements listed above except the premarket approvals. Instead of an NDA or PMA, both

biologics and the establishments that produce them must be licensed (product and establishment licenses are required prior to marketing). In addition, biologics are regulated for false labeling under the PHSA [42 U.S.C. 262(b)].

The FDA can enforce its requirements in a variety of ways. Administrative mechanisms include inspections to monitor compliance, revocation of approved marketing applications (NDA, PMA, or product licenses), and recalls. Judicial actions that may be sought by the FDA include seizures of adulterated, misbranded, or unapproved drugs or devices (including biologic), injunctions against shipping, and criminal prosecutions (71).

#### Possible Limits on the FDA's Regulatory Authority

Two legal concepts, interstate commerce and the practice of medicine, may limit the FDA's jurisdiction over some types of neural grafting materials. Arguments on both sides of each concept are summarized here, although the courts have generally allowed the FDA broad authority to carry out its statutory mandates. The success of the arguments outlined below will depend, however, on the facts and circumstances of the cases in which they may arise.

*Interstate Commerce-One* argument against Federal regulation is that if the material is produced and distributed within a State, the interstate nexus required for Federal regulation does not exist. For example, cells obtained from one patient that are cultured and then grafted into the brain of another patient within the same hospital do not appear to be involved in interstate commerce.

The FDA has successfully mounted several arguments that enabled it to regulate products that were not shipped interstate. First, some of the statutory requirements for drugs, devices, and biologics do not require the showing of an explicit interstate nexus. Examples of these are registration of producers of drugs and devices [21 U.S.C. 360] and regulation of false labeling of biologics [42 U.S.C. 262(b)] (61). In addition, the Medical Device Amendments of 1976 [Public Law 94-295] authorize seizure of misbranded or adulterated devices without proof of interstate commerce (39).

A second argument used successfully by the FDA has been that if a component of the drug travels in interstate commerce, the interstate nexus has been

**satisfied.** An analogous argument could be made about the solutions in which tissues are preserved or the petri dishes or media in which cells are cultured.

Finally, section 361 of the PHSA [42 U.S.C. 264] authorizes the Surgeon General, with the approval of the secretary of DHHS, to make and enforce regulations to prevent the transmission or spread of communicable diseases. This authority has been delegated to the Commissioner of the FDA for fictions related to FDA-regulated products [21 CFR 5.10 (a)(4)]. The power of the FDA to ban the *intrastate sale* of small turtles in order to prevent the *interstate* spread of Salmonella was upheld pursuant to this provision in *State of Louisiana v. Mathews* (58). The FDA also relied on section 361 as a primary source of statutory authority to regulate blood in intrastate commerce in order to prevent the spread of syphilis, hepatitis B, and HIV (71).

**Practice of Medicine**--Traditionally, the FDA has not interfered with the practice of medicine. The FDA does not regulate the use by physicians of approved drugs for unapproved purposes (62,72), and physicians practicing medicine are specifically exempted from the registration requirement imposed by the FFDCRA [21 U.S.C. 360(g)(1)(2)]. The new technologies involved in neural grafting present difficult questions of what constitutes the practice of medicine, whether there are circumstances under which the FDA would decide to regulate what might be called the practice of medicine, and the circumstances, if any, under which FDA jurisdiction to do so would be upheld.

The traditional exemptions serve several purposes. Approved drugs are presumably safe when reasonable doses are prescribed and contraindications are observed. In fact, the freedom of physicians to prescribe as they see fit can lead to the discovery of important new uses for existing products. The U.S. District Court in *United States v. Evers*, concerned about regulation of the intrastate practice of medicine, stated that restricting the medical profession (here a licensed physician) from using a drug for a purpose not contraindicated on the label would exceed the powers of Congress (62). The court opined that malpractice claims provide appropriate protection for the patient. Another reason for the traditional exemption of the practice of medicine might be the difficulty of trying to regulate the practices of individuals relative to the ease of regulating manufacturers, who are likely to be

shipping large quantities of products in interstate commerce. Finally, the fact that the practice of medicine usually overlaps the issue of intrastate commerce (because physicians have generally practiced on patients within their States) may have influenced the position of the FDA with respect to individual practitioners.

Neural grafting materials and other tissues or products of biotechnology raise new questions about FDA regulation and the boundaries of the practice of medicine. What is the boundary between product and process? For example, should the safety and efficacy of neural grafting be seen as a function of the quality of the grafting material, the storage of the material (e.g., tissue banking), or the grafting process? Is the grafting process the practice of medicine? If so, will the FDA regulate the process?

In practice, the decision to regulate will probably depend on the perceived dangers of the product. For example, concern about HIV infection through blood products led to an innovative process for the regulation of blood banks. At the Federal level, blood is regulated as a service rather than a product. This has the effect of decreasing the liability of blood banks and hospitals from strict liability for a dangerous material to malpractice liability for negligence. Some persons believe that tissue banks should be similarly regulated.

Genetically engineered materials present the option of customized biologics, or therapeutics tailored to each individual patient (34). This is a very different situation from that of traditional biologics, such as vaccines, which were produced in large quantities and distributed to large portions of the healthy population in order to prevent disease. Cells, for example, might be genetically engineered in a laboratory at the same hospital where they will be grafted into the patient. Is this the practice of medicine? The label "practice of medicine" does not necessarily preclude FDA regulation. Rather, it indicates a gray area in which the FDA may find enforcement difficult and physicians may protest regulation. Products of biotechnology such as genetically engineered cells present safety hazards unlike those of traditional drugs or biologics. Manufacturing problems include difficulty in product characterization and potency, nonreproducible products, difficulty with product stability, and the presence of adventitious agents and contaminants (intrinsic and

acquired). Scientific problems include the absence of feasible animal models for preclinical testing for safety, efficacy, or both (38).

The problems outlined above present both a reason for the FDA to be concerned about the safety of neural grafting materials derived from biotechnology and a challenge to its present regulatory scheme. The development of these products and their use by physicians may present a challenge to the traditional exemption of the practice of medicine from FDA regulation.

### Regulation of Neural Grafting Materials

The principal questions with respect to FDA regulation of materials used in neural grafting are:

- Will FDA regulate the material?
- If so, how will the material be categorized (drug, device, or biologic)?

The decision as to whether the FDA will regulate neural grafting materials depends largely on whether the FDA determines that the product fits within the statutory definition of drug, device, or biologic. Another consideration is whether the FDA has reason to be concerned about the safety of the material. Finally, the question of whether or not the product is intended for commercial distribution may be relevant. The terms of the PHS Act are “sale, barter or exchange” [42 U.S.C. 262], which may allow for regulation even where commerce is not involved. As described earlier, the Commissioner of the FDA is empowered to promulgate regulations to prevent the transmission or spread of communicable diseases, without regard to interstate commerce [21 U.S.C. 264].

The second question is how neural grafting materials will be categorized. At present, there are no published regulations to help answer this question. The FDA has issued “Points to Consider” for manufacturers of ex vivo-activated mononuclear leukocytes and for cell lines used to produce biologics. Points to Consider do not have the force of law, nor do they represent formal FDA policy, but they do indicate the current thinking of scientists at the FDA. Points to Consider for somatic cell therapy are likely to be relevant to neural grafting materials, but they have not yet been approved for distribution by the FDA. Tissue products and products of biotechnology are regulated on a case-by-case basis in order to allow flexibility with respect to new technologies.

Decisions about whether a given product is a drug, device, or biologic and which administrative center at the FDA will regulate it depend on the intended use of the product, who in the agency has the requisite expertise, and what analogous products are regulated in each center. This means that the situation will change as similar materials are regulated, making it impossible to predict with confidence how neural grafting materials will be regulated by the time they are actually considered by the FDA. As more tissue and biotechnology products are developed and regulated by the FDA, however, the agency could develop consistent regulations, as it did for blood products. As mentioned earlier, it is unclear whether a court would find neural grafting materials ‘analogous’ to blood products and therefore subject to regulation under the PHS Act without the enactment of more specific statutory language.

There are many different types and sources of neural grafting materials (see ch. 4). The following classification scheme will be used here to describe the issues the FDA is likely to consider in deciding whether and how to regulate these materials:

- autografts of tissue,
- allografts of tissue or cultured cells,
- autografts of genetically engineered cells, and
- genetically engineered cells distributed to patients.

The discussion which follows is subject to the caveat that there are no formal regulations specifically describing the role of the FDA with respect to these materials. Considerations that are salient today could become less important by the time the FDA is actually confronted with the need to regulate neural grafting materials.

*Autografts of Tissue*—This refers to tissue obtained from the patient’s own body (e.g., the adrenal medulla) and grafted into his or her brain. This material is least likely to be regulated by the FDA because there is minimal manipulation of the tissue, there is no increased risk of transmission of communicable disease, and the procedure is within the traditional practice of medicine. The FDA does not, for example, currently regulate bone marrow autografts.

*Allografts of Tissue or Cultured Cells*—The source of this same-species graft material could be, for example, fetal tissue or cells from another person. This category is a gray area in which it is

unclear what the FDA will decide. The FDA is likely to want to regulate for safety purposes (e.g., to prevent the spread of communicable diseases such as HIV infection). The considerations here could be analogous to those surrounding blood banks, leading to regulation of tissue banking and distribution.

The FDA has recently decided to regulate implants of dura mater, the tough, outer membrane covering the brain and spinal cord, because of concern about the possible transfer of Creutzfeldt-Jacob disease or human retroviruses. Dura mater is regulated as a device because it does not achieve any of its principal intended purposes through chemical actions within or on the body or through metabolism. To the extent that tissue grafts for mitigation of Parkinson's disease are intended to act by releasing dopamine, they are more likely to be regulated as drugs than as devices. Tissue grafts used to patch injured neural systems may be more analogous to dura mater and therefore regulated as devices. Similarly, certain cell lines that are cultured in vitro and used for skin transplantation and in wound and burn therapy are regulated as medical devices (74). This suggests that cell lines used as neural grafting material for the purpose of mechanically bridging the traumatized or injured central nervous system could be regulated as devices. It is most likely, however, that such cell lines would be considered biologics, because the neural bridging function is dependent on the biological activity of the cells (75).

Cells that are cultured, modified, or otherwise expanded in vitro are regarded by the FDA as biological drugs and are believed to be subject to regulation under the PHS Act (74). The regulatory status of in vitro-cultured cells that are not shipped in interstate commerce is not clear, but in most instances such cells are administered with investigational biologics, necessitating an IND application (74). If an investigator were to produce cells without additional investigational agents, the role of the FDA in regulating the therapy under the IND regulations would be less clear (73).

***Autografts of Genetically Engineered Cells—*** Cells that are prepared by a patient's personal physician for infusion back into the same patient may be considered "practice of medicine" and therefore may not be subject to FDA regulation (74). However, safety issues arise in therapies that make

use of genetically engineered cells because of the unknown effects of the foreign genetic material on the patient and persons in contact with the patient (74). In addition, cells may synthesize a drug or biologic. The FDA might therefore choose to assert jurisdiction despite the practice of medicine issue. A clinical trial begun under an IND at NIH recently set a precedent for FDA regulation of an autograft of genetically engineered cells. The FDA is concerned that when using a virus there is a small chance of recombination with a virus already existing in the body (25).

***Genetically Engineered Cells Distributed to Patients—***This category includes cells from animals or humans other than the patient which are engineered and then grafted into the patient. Given the safety considerations and the precedent established for autologous grafts of engineered cells described above, it is likely that the FDA would seek to regulate engineered cells in wider distribution.

### ***Regulation of New Surgical Procedures***

The previous section described briefly the complex regulatory scheme developed by Congress and the FDA as it might apply to neural grafting materials. That intricate system of regulation to ensure the safety and efficacy of articles intended for use in the diagnosis, treatment, or prevention of disease in humans contrasts sharply with the absence of any direct Federal regulation of new surgical procedures developed for the same purposes.<sup>1</sup> Whether considering biomedical articles or procedures, the problem is where to draw the line between safety and efficacy, on the one hand, and encouragement of biomedical innovation, on the other.

This section describes the implications of the absence of direct Federal oversight for the development of neural grafting procedures. Indirect mechanisms for regulating new surgical procedures are outlined, and a mechanism for potential Federal involvement in the assessment of safety and efficacy of new surgical procedures is described. The intent is to describe the current situation and ways in which it could be modified, if that is deemed desirable.

While Congress and the FDA have recognized the need for careful consideration before moving from animal studies to controlled clinical trials

<sup>1</sup>This section is concerned with new surgical procedures that are not part of federally funded research.

involving gradually increasing numbers of patients for assessment of new products, there is no analogous regulation of the move from animal studies to human trials for surgical procedures. An IRB will only approve protocols that demonstrate some hope of benefit to the subject and the absence of long-term negative effects, but there are no specific criteria for moving from animal studies to human research.

Of the neural grafting procedures, only techniques meant to alleviate the symptoms of Parkinson's disease have progressed to human trials. Grafts of tissue from a patient's adrenal medulla have been performed for Parkinson's disease patients in Sweden, Mexico, China, Canada, England, Spain, Portugal, Cuba, Colombia, Chile, and the United States. Implants of human fetal tissue have been performed in Sweden, Mexico, England, Spain, Cuba, China, and the United States (18). A few studies have been done privately in the United States despite the ban on federally funded transplantation research that uses fetal tissue obtained from induced abortions. Although these trials are already under way, debate continues as to whether the results of animal studies justify them. Some believe that animal research has already produced sufficient information to justify limited human trials. In the words of one scientist, "animal research is the key to initial understanding and refining techniques, but never solves all the problems" (4).

Persons who question the wisdom of advancing to human neural grafting trials at this stage of research question whether the animal (and the few human) trials that have been done provide evidence of the absence of long-term adverse immunological effects or the presence of beneficial effects. Others argue against progressing with human trials on the grounds that no one has been able to identify the etiology of Parkinson's disease and it is therefore not known whether the same disease processes that caused the initial neuron degeneration could also produce degeneration of grafted neurons (23). A neurologist who has used the procedure and identified adverse side-effects stated: "This is an area in which we've done too much too fast" (40). A neurobiologist advised even greater caution: "I'm not convinced the procedure is ready for humans. . . if we move ahead too soon, the results can be overinterpreted" (40).

While well-controlled human research using methods such as randomized clinical trials is essential to the development of new drugs, the feasibility and utility of such methods for evaluating the efficacy of new surgical procedures is controversial. Some surgeons argue that surgical procedures differ from drugs in ways that render the results of randomized clinical trials of surgical procedures useless, if not harmful, to the development of surgical treatments (8, 9, 68). The outcomes of surgical procedures, according to this view, are so dependent on the skill and experience of the individual surgeon and the circumstances of the individual patient that research which generalizes across patients and physicians will be meaningless. Other physicians and surgeons believe that controlled clinical trials are important for determining whether an innovative surgical therapy is of value (6, 31) and when an accepted surgical procedure of unproved value should be discontinued (21).

The absence of well-controlled clinical studies and of standards for deciding when to move from animal to clinical studies may lead to several problems. First, physician-investigators may be encouraged to take large risks in order to be among the first to perform new surgical procedures. This encouragement takes the form of publicity, funding, and professional attention for bold new efforts to save lives. While the surgeon may risk his or her professional reputation, the greater risks are to the patient, who may not be able to give truly informed consent because of the combination of chronic or terminal illness and lack of information about benefits and risks of the new surgical procedure. The physician and patient may believe that any procedure is better than certain death or prolonged, severe disability, even if the benefits and risks of the procedure are unknown. This logic was used to justify liver transplantation in 1983, before there were adequate data supporting its efficacy (51). In the absence of well-controlled clinical trials, procedures may be widely accepted clinically even if they are not actually effective.

A study of the introduction of four new surgical procedures found that, with the exception of one procedure which was evaluated through the FDA drug approval process, the procedures were introduced without controlled clinical trials or well-designed observational studies (12). This means that the procedures which were performed did not contribute to an overall evaluation of their efficacy

and that future patients will not have adequate information on which to base their decisions about treatment. In addition, when effectiveness is still in question, tension is likely to develop about the extremely high costs of some new surgical procedures (51).

A three-stage procedure for the evaluation of new surgical procedures has been suggested (12). First, the physician-investigator should develop the new procedure and define diagnostic criteria to evaluate it. The second stage would be collaborative clinical trials in which formal research protocols are followed and quantitative evidence is collected and analyzed according to predetermined statistical criteria. Finally, after efficacy is established, the procedure could be released for more general use.

#### Indirect Regulation of New Surgical Procedures

New surgical procedures are regulated indirectly by third-party payers, which decide whether or not to reimburse for them. The number of patients who undergo a procedure is determined in part by the extent to which coverage is provided by insurers. Federal insurers of medical care include the Health Care Financing Administration, Department of Veterans Affairs, and the Department of Defense. Safety and efficacy determinations are sometimes part of the process by which insurers decide whether a surgical procedure is experimental or accepted treatment and, ultimately, whether they will cover the procedure. Discussion of the means by which each Federal and private insurer assesses safety and efficacy in the course of deciding the status and coverage of procedures is beyond the scope of this report. The very different processes by which decisions were made about the status of liver, kidney, and heart transplantation have been described (51).

Other forms of indirect regulation of surgical practice include hospital standards set by the Joint Commission on Accreditation of Healthcare Organizations, professional standards of practice from specialty societies, State licensing laws, and medical malpractice claims. IRBs exert the most direct control over research on new surgical procedures. While research protocols are often submitted to local IRBs, there is no Federal requirement that this be done unless the research receives Federal funding or takes place as part of an FDA application. In addition, IRBs will have difficulty

evaluating a protocol in the absence of risk-benefit information.

#### Potential Federal Role

Concern about rising health-care costs and the safety and efficacy of new medical procedures has led to increasing congressional interest in the evaluation of such procedures. While direct regulation of the practice of medicine may strain the regulatory authority of the FDA, the Federal Government could play a role in the evaluation of new procedures and could promulgate standards of practice for purposes of consumer information and decisionmaking by physicians and third-party payers.

Neural grafting may eventually be considered as a treatment for some debilitating neurological disorders that affect large numbers of vulnerable patients with chronic or terminal illnesses. It is essential, therefore, that the clinical development and use of the procedures be based on well-controlled research on safety and efficacy rather than on desperate hopes of cures for these patients. The methods of assessing the safety and efficacy of liver transplants prior to 1984 (51) are a model of what to avoid in assessing new surgical procedures.

The newly created Agency for Health Care Policy and Research [Budget Reconciliation Act of 1989, Public Law 101-239, sec. 6103] is charged with promoting research on selected surgical procedures in order to assess their appropriateness, necessity, and effectiveness. This agency could be charged with assessing the development of clinical neural grafting procedures, still in their infancy, to ensure that the use of these procedures develops in accordance with data from well-controlled studies, rather than in response to factors external to the actual efficacy of the procedures.

## PROTECTION OF DONORS OF FETAL TISSUE

Since embryos and fetuses are among the proposed sources of tissue for neural grafts (23), Federal regulations and State laws governing embryo and fetal research may apply. Some of these laws appear to be sufficiently restrictive to forbid experimental transplants using fetal tissue in certain States. However, if neural grafting becomes standard medical therapy, current embryo and fetal research laws would no longer prohibit the procedure. In legal

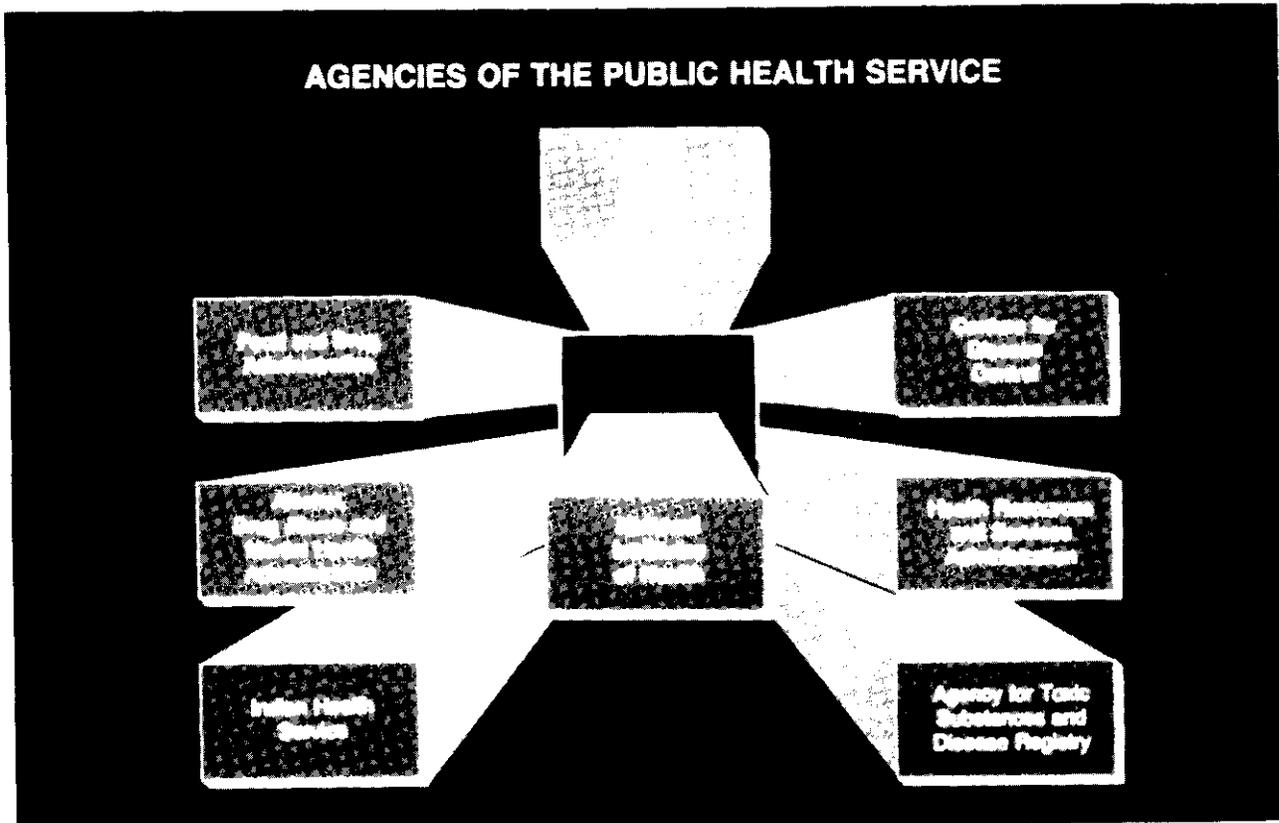


Photo credit: National Institutes of Health

contexts, the term “embryo” has been used to refer to the conceptus from fertilization until the end of the eighth week, and the term “fetus” has been used to refer to the conceptus in all stages of development.

The use of fetuses as a source of tissue for neural grafts raises complicated issues. In most instances, the tissue will come from fetal cadavers, although the tissue itself may still be living. Abortuses of between 8 and 12 weeks’ gestation are presently considered appropriate sources of tissue for grafting. However, there may also be instances in which physicians intend to remove tissue from live, nonviable fetuses (fetuses incapable of surviving outside the womb). Moreover, some experimental interventions might involve the pregnant woman and her living, in utero fetus; for example, a woman might be asked to undergo an alternative abortion procedure in order to better preserve fetal tissue or to postpone the abortion until the fetus is more developed (36). Different laws will apply, depending on whether the fetus is dead, alive ex utero, or alive in utero and depending on whether the experiment presents risks to the pregnant woman as well.

Further issues are raised regarding maternal consent. These center on whether a pregnant woman should have the right to prohibit or authorize the use of her fetus for experimentation. Some laws address this issue, as well as the role of the father in the consent process. An additional issue addressed by fetal research laws is whether women should be allowed to receive payment for fetal tissue. Some laws banning compensation would extend to payment of third-party intermediaries as well.

### *Development of Federal Policy on Fetal Research*

Federal activity with respect to the issue of fetal research has been extensive. In 1974 Congress passed the National Research Act [Public Law 93-348]. This legislation established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, whose first charge was to investigate the scientific, legal, and ethical aspects of fetal research. The statute prohibited all federally funded nontherapeutic research on fetuses prior or subsequent to an abortion until the

Commission made its recommendations and regulations were adopted. In 1975 the Commission made its recommendations (46), and in 1976 the Department of Health, Education, and Welfare (now the Department of Health and Human Services) adopted regulations for the Federal funding of fetal research [45 CFR 46.201-211]. Under these regulations, which for the most part comport with the recommendations of the Commission, certain types of fetal research are allowed, with constraints based on obtaining parental consent and minimizing risk to the pregnant woman and the fetus.

In 1985, Congress again acted on the issue of fetal research. It passed a law forbidding Federal conduct or funding of research on viable ex utero fetuses [42 U.S.C. 289]; however, there is an exception for therapeutic research and for research that "will pose no added risk of suffering, injury, or death to the fetus and the purpose of which is the development of important biomedical knowledge which cannot be obtained by other means" [42 U.S.C. 289g(a)]. It also provides that, for research on living fetuses in utero, Federal regulations must require the standard of risk to be the same for fetuses that will be aborted as for fetuses that will be carried to term. Simultaneously, Congress passed legislation creating a Biomedical Ethics Board, composed of six members of the Senate and six members of the House of Representatives, with an outside advisory committee [42 U.S.C. 275]. Fetal research was the first order of business for the group. Under existing Federal regulations, the Secretary of DHHS may authorize research that does not comply with the regulations in instances of great need and great potential benefit [45 CFR 46.211]. A recent statute, however, suspends that authority until the Biomedical Ethics Advisory Committee (BEAC) conducts a study of the "nature, advisability, and biomedical and ethical implications of exercising any waiver of the risk provisions of the existing Federal regulations on fetal research" [42 U.S.C. 289g(c)]. As of autumn 1989, the activities of the BEAC had been suspended, and it seems that no report on fetal research will be undertaken.

Federal attention again turned to the issue of fetal tissue transplantation research in 1988. The Director of NIH requested permission to fund projects using fetal tissue for transplantation. On March 22, 1988, the Assistant Secretary for Health denied the request on the grounds that the use of fetal grafts raised ethical and legal issues that should be addressed by

an advisory panel and imposed a moratorium on Federal funding of human fetal tissue transplantation research using tissue from induced abortions. Such an advisory panel was convened and subsequently published its recommendations in the *Report of the Human Fetal Tissue Transplantation Research Panel* (67). The panel recommended lifting the moratorium and emphasized that commercialization should be prohibited and that the abortion procedure should be separated from the procedure using fetal tissue. (See app. A for a discussion of the DHHS moratorium on fetal tissue transplantation research.)

### *Federal Regulations Governing Fetal Research*

Federal regulations define the term "fetus" as a conceptus after implantation. They defer to State and local laws on the subject of research with fetal cadavers [45 CFR 46.210]; however, there is some dispute about whether another section of the statute, which does not specifically apply to dead fetuses, should be read to apply in the context of research (3). That section provides that "[n]o inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the [research] activity" [45 CFR 46.206(b)]. Even if this section on inducements were read into the Federal law about research on fetal cadavers, it would not necessarily preclude experimentation involving neural grafts from abortuses. Although some commentators have alleged that the possibility of donating fetal tissue for experimental transplantation might lead women to undergo abortion (3) and thus is an inducement, others have suggested that there is little evidence that women would do so if there were prohibitions on payment for fetal tissue and on donation of tissue to a relative (54). These persons have noted that informing women who are ambivalent concerning abortion about the chance to donate tissue would not be an inducement unless it were specifically aimed at convincing the woman to abort, particularly if no valuable consideration is offered (54). Moreover, there is support for the position that the term "inducement" means valuable consideration and that the possibility of participating in research, without compensation, would not be considered valuable consideration (54).

With respect to research on live fetuses, Federal regulations provide that appropriate studies must be done on animal fetuses before human studies are

carried out [45 CFR 46.206(a)(2)]. When research involving live human fetuses is undertaken, the consent of the pregnant woman and prospective father are required (unless the prospective father's identity or whereabouts are not reasonably ascertainable, he is not reasonably available, or the pregnancy resulted from rape) [45 CFR 46.208(b), 46.209(d)]. Some persons criticize the requirement that the prospective father's consent be obtained (54). To protect the pregnant woman and the fetus, the research must not alter a pregnancy termination procedure in a way that would cause greater than minimal risk to either [45 CFR 46.206(a)(3) (4)].

To protect the fetus, the researchers must not have a role in either the determination of what procedure is used to terminate the pregnancy or the assessment of whether the fetus is viable [45 CFR 46.206(a)(3)]. In utero fetal research may be undertaken if the research is designed to be therapeutic to the particular fetus and places the fetus at the minimum risk necessary to meet its health needs [45 CFR 46.208(a)(1)]. It may also be undertaken if the research imposes minimal risks and "the purpose of the activity is the development of important knowledge which cannot be obtained by other means" [45 CFR 46.208(a)(2)].

Where it is unclear whether an ex utero fetus is viable, that fetus may not be the subject of research unless the purpose of the research is to enhance its chances of survival or the research subjects the fetus to no additional risk and its purpose is to develop important, otherwise unobtainable biomedical knowledge. Research on a living, nonviable, ex utero fetus may be undertaken if the vital functions of the fetus will not be artificially maintained, experimental activities terminating the heartbeat or respiration will not be employed, and the purpose of the research is the development of important, otherwise unobtainable biomedical knowledge [45 CFR 46.209(b)].

### *State Laws Governing Embryonic and Fetal Research*

*The* overwhelming majority of State legislatures have yet to address the issues associated with experimental neural grafting using fetal tissue. Only Missouri and Pennsylvania have enacted legislation directed specifically at fetal tissue transplants. The Missouri law makes it a crime for any physician to perform an abortion knowing that the woman is

seeking it for the purpose of donating the fetal tissue for implantation, or for anyone to offer consideration for the conception of a fetus which will be aborted and used for transplantation. In Pennsylvania no fetal tissue or organs may be obtained for transplant purposes without the written consent of the pregnant woman. No payment of any kind may be offered, and consent is valid only if obtained after the decision to abort has been made. All persons who participate in the procurement, use, or transplantation of fetal tissue or organs, including the recipients, must be informed of the source of the tissue or organs (e.g., stillbirth, miscarriage, ectopic pregnancy, abortion, or other means). The person giving consent to the procurement or use of fetal tissue or organs may not designate the recipient. Violation of these provisions may result in civil penalties.

A proposed law in California takes a similar approach (59). While allowing the donation of a fetus for "medical research or therapeutic application," this law incorporates many guidelines first suggested in 1987 in a forum on fetal tissue transplants convened by Case Western Reserve University School of Medicine (35) and suggested by the Human Fetal Tissue Transplantation Research Panel in its report (67). The proposed law prohibits consideration as an inducement to undergo an abortion for the purpose of donating the tissue, the naming of a specific recipient, and doctors "participating in the procedures resulting in the loss of a fetus" from participating in any research using tissue from that fetus.

Although other States have not specifically addressed the question of neural tissue grafts from fetuses, the general fetal research laws in effect in 25 States may bear on it. Table 7-2 lists and describes State regulations. State laws governing fetal research are not as precise as Federal law. Some contain no definition of fetus, death, or research. Indeed, "the uncertainties surrounding the reach of such State regulatory regimes may both create a dangerous chilling effect on even peripheral research, and leave the regimes exposed to constitutional attack" (59).

Only one State, New Mexico, has adopted a law patterned on Federal regulations pertaining to fetal research. Other States have enacted a variety of regulatory approaches, with the permissibility of fetal research depending, in part, on the following factors:

Table 7-2-State Regulations Pertaining to the Use and Procurement of Fetal Tissue for Grafting Research

<b>Arizona</b> regulates research using fetal cadavers and live ex utero fetuses; prohibits research with fetal cadavers (except for pathological examinations and autopsies) obtained through a planned abortion; prohibits experimentation on live ex utero fetuses.	<b>Indiana</b> regulates research with fetal cadavers and live ex utero fetuses; prohibits research with fetal cadavers (except for autopsies and pathological examinations) obtained through a planned abortion; with fetal cadavers not obtained from a planned abortion, research can be undertaken on tissues or cells with the consent of one parent; prohibits research with live ex utero fetuses.
<b>Arkansas</b> requires maternal consent for research using fetal cadavers obtained through planned abortions; bans nontherapeutic research involving live ex utero fetuses. Prohibits the sale of tissue from fetal cadavers.	<b>Kentucky</b> bans research using live ex utero fetuses. Prohibits donation of live fetus for experimentation; prohibits sale of tissue from live or viable fetuses for research purposes. Prohibits sale or purchase of a child for adoption or any other
<b>California</b> regulates research using live ex utero fetuses and fetal cadavers obtained through planned abortions; prohibits nontherapeutic research with live ex utero fetuses. Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue; prohibits sales and purchases of an organ or tissue when the organ or tissue is to be removed after the death, as well as the use of an organ known to have been transferred for valuable consideration; prohibits the sale of unclaimed bodies.	<b>Louisiana</b> prohibits farming in vitro fertilized fetuses for research or for any use other than to create a pregnancy. Prohibits sale of in vitro fertilized embryos prior to implantation; prohibits purchases and sales of all bodies and parts for valuable consideration.
<b>Connecticut</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue, as well as the donor's expenses of travel, housing, and lost wages; prohibits trafficking in dead bodies.	<b>Maine</b> prohibits research on live ex utero and live in utero fetuses. Prohibits sale or donation of fetal tissue from live fetuses for research.
<b>District of Columbia</b> has no regulations directly addressing use of fetal tissue. Prohibits offering valuable consideration for organs; nothing is excluded from definition of valuable consideration.	<b>Massachusetts</b> regulates research using fetal cadavers, live ex utero fetuses, and live in utero fetuses; requires mother's consent for research with fetal cadavers; bans research on live ex utero fetuses and live in utero fetuses which is nontherapeutic for the fetus when the fetus is to be the subject of a planned abortion except for diagnostic and remedial measures to preserve the life or health of the mother); when fetus is not to be the subject of a planned abortion, study of in utero fetuses is allowed, providing the procedures do not substantially jeopardize the life or health of the fetus. Prohibits donation of a fetus for experimentation; prohibits the performance of an abortion in cases where "part or all of the consideration for said performance is that fetal remains may be used for experimentation"; prohibits sale of fetal tissue for research; prohibits purchase and sale of bodies.
<b>Delaware</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits organ donor from receiving compensation for disposition of his or her own body; however, payment to mother for fetal tissue is not prohibited.	<b>Michigan</b> regulates research using fetal cadavers, live ex utero fetuses, and live in utero fetuses; requires mother's consent for research with fetal cadavers; bans research on live ex utero fetuses and live in utero fetuses which is nontherapeutic for the fetus when the fetus is to be the subject of a planned abortion (except for diagnostic and remedial measures to protect the life of the mother); when fetus is not to be the subject of a planned abortion, study of in utero fetuses is allowed, providing the procedures do not substantially "jeopardize the life or health of the fetus. Prohibits donation of a fetus for experimentation; prohibits the performance of an abortion in cases where" art or ail of the consideration for said performance is that fetal remains may be used for experimentation"; prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the expenses of removal of the organ, use of the organ, and donor's losses and expenses (this statute would require regulatory action to cover brain tissue).
<b>Florida</b> bans nontherapeutic research on live in utero and live ex utero fetuses when done in connection with a planned abortion. Bans the selling, purchasing, or transferring of a human embryo for valuable consideration. Prohibits the offering of valuable consideration for organs, but excludes from "valuable consideration" the expenses of removal and use of organ (this statute would require regulatory action to cover brain tissue); prohibits the purchase and sale of unclaimed bodies.	<b>Minnesota</b> prohibits nontherapeutic research using live ex utero and live in utero fetuses. Prohibits sale of tissue from live fetuses for any purpose. Prohibits sale of living conceptuses or nonrenewable organs, but allows the buying and selling of a cell culture line from a nonliving conceptus.
<b>Georgia</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits buying or selling a human fetus or fetal part; this prohibition does not apply to donations under the Uniform Anatomical Gift Act (UAGA), reimbursement of a living donor's actual expenses, or payment of costs associated with collecting, storing, and implanting a donated part; prohibits the purchase and sale of bodies.	<b>Missouri</b> prohibits nontherapeutic research using live ex utero or live in utero fetuses obtained through a planned abortion. Prohibits physicians from performing an abortion knowing that the woman will donate tissue for implantation; prohibits monetary inducement to conceive with the intention of aborting the pregnancy and using the tissue for experimentation or tissue implantation; prohibits knowingly offering or receiving valuable consideration for organs or tissues of an aborted fetus other than payments for burial, other final dispositions, and pathological examination.
<b>Hawaii</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue; prohibits sales and purchases of an organ or tissue when the organ or tissue is to be removed after the death; prohibits sale of dead bodies.	<b>Montana</b> bans nontherapeutic research on live ex utero fetuses.
<b>Idaho</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue; prohibits sales and purchases of an organ or tissue when the organ or tissue is to be removed after the death.	<b>Nebraska</b> bans research using live ex utero fetuses obtained through a planned abortion (except for diagnostic and remedial measures to preserve the health of the mother). Prohibits sale of tissue from live or viable fetuses for research when fetal tissue is obtained through a planned abortion.
<b>Illinois</b> prohibits research with fetal cadavers except for autopsies and pathological examinations) obtained through planned abortions [the Federal District Court recently ruled that this law is unconstitutional]; with fetus not obtained from a planned abortion, research can be undertaken on its tissues or cells with the consent of one parent. Prohibits sale of fetal tissue for any purpose; prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue.	

Continued on next page

**Table 7-2—State Regulations Pertaining to the Use and Procurement of Fetal Tissue for Grafting Research—Continued**

<p><b>Nevada</b> prohibits anyone from using or making available the remains of an aborted embryo or fetus for commercial purposes; prohibits contribution of organs for valuable consideration, but excludes from “valuable consideration” expenses associated with removal and use of donated organ as well as expenses incurred by the donor.</p>	<p>Rhode Island regulates research with fetal cadavers, live ex utero fetuses, and live in utero fetuses; requires mother’s consent for research with fetal cadavers; bans research on live ex utero fetuses and live in utero fetuses which is nontherapeutic for the fetus when the fetus is to be the subject of a planned abortion (except for diagnostic and remedial measures to preserve the life or health of the mother); prohibits abortion if main motivation is procurement of tissue for research; prohibits donation of fetus for experimentation. Prohibits sale of fetal tissue for experimentation.</p>
<p><b>New Mexico</b> prohibits nontherapeutic research or research that poses a greater than minimal risk to the fetus on live ex utero and live in utero fetuses. Prohibits monetary inducement to conceive in order to subject fetus or live-born infant to clinical research activity; prohibits sale of unclaimed bodies.</p>	<p><b>South Carolina</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits purchase and sale of dead bodies.</p>
<p><b>New York</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration but excludes from “valuable consideration” the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue, as well as travel expenses and lost wages of donor (this statute would require regulatory action to cover brain tissue).</p>	<p><b>South Dakota</b> requires consent for research with fetal cadavers, live ex utero fetuses, and live in utero fetuses.</p>
<p><b>North Dakota</b> regulates research with fetal cadavers, live ex utero fetuses, and live in utero fetuses; prohibits research using fetal cadavers obtained through a planned abortion; fetal cadavers not obtained through a planned abortion allowed with maternal consent; bans nontherapeutic research using live ex utero and live in utero fetuses except to preserve mother’s health. Prohibits donation of fetus for experimentation; prohibits the performance of abortions done to obtain material for experimentation; prohibits the sale of live fetuses; prohibits the sale by anyone but the mother of fetal cadavers for research; prohibits the contribution of organs for valuable consideration, but excludes from valuable consideration” the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue; prohibits sales and purchases of an organ or tissue when the organ or tissue is to be removed after death.</p>	<p><b>Tennessee</b> requires mother’s consent for research with fetal cadavers obtained through a planned abortion; maternal consent required for research using live ex utero fetuses. Prohibits sale of tissue from live fetuses for any purpose; prohibits receipt of compensation for an aborted fetus by anyone except the mother.</p>
<p><b>Ohio</b> regulates research with fetal cadavers and live ex utero fetuses; prohibits research with fetal cadavers obtained from abortions except for autopsies and pathological examinations; bans research on live ex utero fetuses. Prohibits the sale of fetal tissue.</p>	<p><b>Texas</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits knowing and intentional transfers of fetal tissue for valuable consideration, but excludes from “valuable consideration” fees to physicians, reimbursement to benefit ultimate receiver, and donor’s travel, housing, and lost wages; prohibits sale of organs for valuable consideration, but excludes from “valuable consideration” costs for removing, transporting, inspecting, preserving, and reimplanting the or an or tissue and for expenses incurred by the donor; prohibits purchase and sale of bodies.</p>
<p><b>Oklahoma</b> regulates research with fetal cadavers, live ex utero fetuses, and live in utero fetuses; prohibits research with fetal cadavers obtained from abortions except for autopsies and pathological examinations; bans nontherapeutic research on live ex utero fetuses and live in utero fetuses. Prohibits the sale of fetal tissue for any purpose.</p>	<p><b>Utah</b> prohibits research using live in utero fetuses. Prohibits sales and purchases of unborn children.</p>
<p><b>Pennsylvania</b> regulates research with fetal cadavers, live ex utero fetuses, and live in utero fetuses; requires mother’s consent for research or human transplantation using fetal cadavers (no payment allowed in return for consent, consent must be obtained after the decision to abort, and the mother may not designate the recipient of any transplanted tissue); bans nontherapeutic research using live ex utero and live in utero fetuses. Prohibits sale of fetal tissue from fetuses obtained through an abortion; prohibits contribution of organs for valuable consideration, but excludes from valuable consideration” the costs of removal and use of organ.</p>	<p><b>Virgin</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from “valuable consideration” the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue.</p>
	<p><b>West Virginia</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from “valuable consideration” the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue, as well as the donor’s travel expenses and lost wages.</p>
	<p><b>Wisconsin</b> has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from “valuable consideration” the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue (this statute would require regulatory action to cover brain tissue).</p>
	<p><b>Wyoming</b> bans experimentation using live ex utero fetuses; prohibits donation of live or viable fetus for experimentation. Prohibits sale of fetal tissue for experimentation from a live or viable fetus obtained through a planned abortion.</p>

SOURCE: Office of Technology Assessment, 1990.

- whether the fetus is dead or alive;
- whether the research involves a fetus prior to, during, or subsequent to an induced abortion;
- whether the pregnant woman consented to the research;
- whether the fetus is in the womb or outside the womb; and
- whether the fetus has reached a point or has acquired characteristics that would warrant treating it as a person, or has acquired some characteristic, such as the capability of experi-

encing pain, that would give it an important claim to protection (this factor is often expressed in terms of the fetus’ viability or nonviability).

Many States’ fetal research laws do not apply to research that is potentially therapeutic to the fetus; this exception is not applicable in the case of neural grafting, since the procedure is not being done for the benefit of the fetus. Nine States underscore their

ban on experimentation on fetuses by prohibiting anyone from donating a fetus for experimentation.

### Research on Fetal Cadavers

Under State law, research involving fetal cadavers and living tissues from fetal cadavers is regulated under the Uniform Anatomical Gift Act (47), which has been adopted by all 50 States and the District of Columbia. However, some States have excluded fetuses from their provisions of the law. Research with fetal cadavers is also regulated in some States by fetal research statutes. According to the provisions of the UAGA, either parent may donate all or any part of a fetus “after or immediately before [its] death,” provided that the other parent does not oppose the gift. Under the UAGA, a “decedent” is defined to include “a stillborn infant or fetus.” The Act covers the donation of all or any portions of the human body for purposes that include both educational and therapeutic benefits. Thus, if abortion and organ donation are both legal, this should also cover tissue donation (55).

Of the 25 States that have more specific laws governing fetal research, 14 have provisions regulating research with fetal cadavers (table 7-2). These laws deviate from the provisions of the UAGA either in their consent requirements or prohibitions they place on the uses of fetal tissue. Eight of these laws require the pregnant woman’s consent for research but make no provision for consent or objection by the father. The California statute that allows research with fetal tissue is silent on the issue of parental consent. The remaining five States diverge from the UAGA, prohibiting any research with fetal cadavers except for pathological examinations or autopsies. The divergences of these 14 laws from the provisions of the UAGA are perhaps attributable to lawmakers’ interests in regulating abortion and related practices. Of the 14, eight apply only to research with abortuses. Of the five statutes that prohibit any research except for pathological examinations, four apply exclusively to abortuses, and one puts more restrictions on research with fetal cadavers resulting from an induced abortion (table 7-2).

### Research on Live Fetuses

There may be instances in which an experimental protocol requires that some action be undertaken on a dying or about-to-be-aborted fetus in order to better prepare the fetus for use as a donor of tissue. There are significant questions about whether such

actions should be permitted. For example, some commentators argue that no research should be permitted on fetuses that are about to be aborted which would not be permissible on fetuses that would be carried to term (46). In addition, there are State statutory constraints on research on live fetuses. Federal regulations provide that, even in cases of federally funded fetal research, the State laws are applicable [46 CFR 46.201(b)].

State laws governing research on live fetuses severely constrain research that is not therapeutic to the fetus itself (thus covering neural grafting research, which is not therapeutic to the fetus). Of the 24 State fetal research laws that regulate research on live ex utero fetuses (see table 7-2),<sup>21</sup> would appear to prohibit research involving neural grafting, either because the procedure is not therapeutic to the fetus or because all experimentation on such fetuses is prohibited. Of these 21 statutes, 5 permit diagnostic and remedial measures to preserve the life or health of the pregnant woman, perhaps leading to the incongruous result that the pregnant woman may donate fetal tissue to herself but to no one else. While it has been argued that an ex utero fetus is not technically a fetus (36), two of the remaining statutes would appear to permit research involving a live ex utero fetus, provided the pregnant woman has consented. The final statute prohibits only the farming of in vitro-fertilized embryos for research purposes and any use of such embryos other than to create a pregnancy.

Of the 14 States regulating research on live in utero fetuses, 13 would appear to prohibit neural grafting research, either because it is not therapeutic to the fetus itself or because all experimentation on such fetuses is prohibited. One State, South Dakota, would apparently permit it, as long as the pregnant woman consented.

### Distinction Based on Whether the Research Is Done in Connection With an Abortion

The most significant factor in regulating research on dead or live fetuses and in determining the extent of restriction imposed appears to be whether the research concerns a fetus that has been or is to be obtained through an induced abortion. Most of the State fetal research statutes were passed as part of abortion legislation. Twelve of the 25 laws apply to research only where it concerns a fetus prior to or subsequent to an induced abortion (see table 7-2). Of the 13 that apply to fetuses more generally, 5 impose

more stringent restrictions on fetal research in conjunction with an abortion.

Another approach that has been used to ensure that fetal research does not encourage abortion is to prohibit the performance of an abortion where some or all of the consideration for the abortion is the donation of fetal remains for experimental use.

In the past, important scientific gains were made through experimentation in the context of an induced abortion. For example, prenatal diagnostic techniques have been developed in pregnant patients about to undergo abortions (27). The most appropriate tissue for neural grafting will probably come from elective, rather than spontaneous, abortions. Tissue from spontaneously aborted fetuses may not be appropriate for neural grafting since a fetal pathology may have led to the miscarriage and since the fetus may have died in utero and deteriorated before being miscarried. Some persons argue that research involving fetuses from induced abortions, whether the fetus be living or dead, is morally impermissible on the grounds that it constitutes cooperation with an immoral practice. The point was made in the following way:

If one objects to most abortions being performed in our society as immoral, is it morally proper to derive experimental profit from the products of such an abortion system? Is the progress achieved through such experimentation not likely to blunt the sensitivities of Americans to the immorality (injustice) of the procedure that made such advance possible, and thereby entrench attitudes injurious and unjust to nascent life? This is, in my judgment, a serious moral objection to experimentation on the products of most induced abortions (whether the fetus be living or dead, prior to abortion or post abortional) (32).

Many State fetal research laws regulate research only where it involves a fetus that is the subject of an abortion, and some impose a stricter standard on research involving fetuses to be aborted than on research involving fetuses to be carried to term. Against this view it is possible to argue that, even if abortion represents a moral wrong in some people's minds, the use of dead abortuses for certain types of research is not only morally legitimate but obligatory. It has been argued that research with fetuses to be aborted is morally justified, provided the research is aimed at deriving information potentially beneficial to other fetuses. This would be unlikely in the case of fetal tissue transplants to Parkinson's patients (7). One neurosurgeon has

argued that there is a moral obligation to do good where possible; since the fetal cadaver is beyond help or hope, to waste its tissues is a moral wrong (50). It has been stated that, by allowing research intended to benefit future fetuses, "what we have done is add a moral good to a morally tragic situation" (28). On the other hand, it has been argued that this practice is comparable to the use of data obtained by Nazi researchers (44).

### *Payment in Connection With Fetal Experimentation*

One of the greatest concerns regarding neural grafting-and the concern that State legislatures are likely to address first-is the possibility that the need for fetal tissue may encourage women to conceive for the sole purpose of donating tissue to relatives or selling it for profit. This could lead to the exploitation of women and intended recipients (33). Currently, 16 State fetal research statutes prohibit the sale of fetal tissue, 7 of them for any purpose and 9 for research purposes (see table 7-2). Some of these statutes apply only to induced abortions and thus would not preclude the sale of a miscarried fetus for tissue transplantation. The penalties attached to some of these laws are very stiff. Selling a viable abortus for experimentation in Wyoming, for example, subjects a person to a fine of not less than \$10,000 and imprisonment of 1 to 14 years [Wyo. Stat. 35-6-115]. Several States have nonuniform UAGA provisions that prohibit transfer of organs or tissues, including fetal organs and tissues, for value. Moreover, some State laws would forbid the sale of fetuses even when they are not being used for research purposes, thus covering payment for neural grafting in the clinical setting.

Biotechnology companies create cell lines from fetal tissue, a fact which raises the possibility that a woman may donate fetal tissue to a company which may then exploit it commercially (57). The issue of commercial exploitation of cell lines was examined in a recent California case (42) (see ch. 8 for discussion). The court held that an individual has a protectable monetary interest in products made from his or her genetic material. The fact that a corporation might profit from fetal tissue whereas the woman who donated it is prevented from receiving consideration for it seems to violate the principle of this case. However, on appeal the California Supreme Court held that the plaintiff did not have a property right to his tissues and cells but did have a

right to informed consent for any use by others of his tissues and cells (43).

It is possible that, because a cell line is new tissue produced from the genetic material of, but not originally apart of, the aborted fetus, laws proscribing the sale of fetal tissue may not apply to cell lines. In fact, a Minnesota law prohibits the sale of living conceptuses or nonrenewable organs but does allow “the buying and selling of a cell culture line or lines taken from a non-living human conceptus . . .” [Minn. Stat. Ann. 145.1627(3)]. In contrast, Nevada’s broadly worded statute making it a crime for anyone to use or “make available. . . the remains of an aborted embryo or fetus for any commercial purpose” could conceivably outlaw the production of cell lines from fetal tissue [Nev. Rev. Stat. Ann. 451.015]. Moreover, it could outlaw cell line transplants.

### *Interstate Transfer of a Fetus*

Some State statutes also contain restrictions on the interstate transfer of fetal tissues. An Indiana law, for example, forbids transporting a fetus from an induced abortion to another State “for experimental purposes” [Ind. Code Ann. 35-1-58.5-6].

In Arkansas, there is a ban on “possession” of the organ, tissue, or material of an aborted fetus [Ark. Stat. Ann. 20-17-802(d)]. However, the Arkansas statute expressly exempts from its provisions physicians and the instructional and research programs of institutions of higher education [Ark. Stat. Ann. 20-17-80 (e)].

## **GOVERNMENT OVERSIGHT**

Issues and questions raised by the introduction and development of neural grafting procedures could make other government regulatory mechanisms relevant. For example, special concerns surrounding neural tissue transplants may require government oversight to protect the interests of the parties involved. Also, fetal rights is a relatively new area of the law, and many of the existing laws designed to protect human subjects in biomedical research do not cover fetal issues. Some of the anticipated problems are discussed below.

### *Potential Constitutional Challenges to Restrictions on Research*

Not all regulations on research are constitutional. Laws restricting research may be struck down as too

vague or as violating the equal protection clause of the Constitution. Those applying to experimentation on fetuses or in the context of abortion may violate the right to privacy (48). In addition, some legal commentators posit that there is a constitutional right to undertake or participate in research. Even if undertaking and participating in research were constitutionally protected, however, certain restrictions to further health and safety would be constitutionally permissible.

Laws governing research must meet certain standards of clarity in order to be constitutional. A Louisiana law prohibiting nontherapeutic experimentation on fetuses was declared unconstitutional by a Federal appeals court, because the term “experimentation” was so vague that it did not give researchers adequate notice about what kind of conduct was banned. The court said that the term “experimentation” was impermissible vague because physicians do not and cannot distinguish clearly between medical experimentation and medical tests. It noted that “even medical treatment can be reasonably described as both a test and an experiment,” for example, “whenever the results of the treatment are observed, recorded, and introduced into the database that one or more physicians use in seeking better therapeutic methods” (37).

Although there is no specifically enumerated right to research in the Constitution, some commentators assert that support for such a right could be derived from the 14th amendment right to personal liberty and the first amendment right to free speech (52). Arguably, the right to participate as a research subject is protected by the 14th amendment’s right to privacy, since an individual’s decision to use his or her body in an experiment designed to further medical knowledge or to be of personal benefit is a private matter (52). This right to research consists of the freedom to pursue knowledge and the freedom to choose the means to achieve that knowledge (52). On the other hand, it has been argued that means have their own morality (44). The Supreme Court has stated that the right to liberty guaranteed by the 14th amendment encompassed freedom to “acquire useful knowledge . . . and generally to enjoy those privileges long recognized at common law as essential to the orderly pursuit of happiness by free men” (41). This language, arguably, applies not only to the researcher’s right to scientific inquiry, but also to an individual’s right to participate as a research subject (52). It could be interpreted as

supporting an individual's right to help acquire knowledge by participating as an experimental subject (52).

Some arguments hinge on the first amendment's protection of free speech, which, it can be argued, includes a right to learn new information. However, one must distinguish the freedom to pursue knowledge from the right to choose the method for achieving that knowledge. Although it is argued that government may not prohibit research in an attempt to prevent the development of new knowledge, it may restrict or prohibit the means used by researchers if the means intrude on interests in which the state has a legitimate concern (52). Therefore, both the Federal and State governments may regulate the researcher's methods in order to protect the rights of research subjects and community safety (52). Research may be restricted, for example, to protect the subject's right to autonomy and welfare by requiring informed, free, and competent consent; however, the state cannot arbitrarily regulate research solely because it deems the knowledge sought to be distasteful or subject to harmful use (52).

### *Fetal Remains Laws*

Every jurisdiction makes some provision for the registration of deaths (usually by death certificate) and the disposition of dead bodies. Most States have a vital statistics statute governing death registration and issuance of permits for transporting or disposing of dead bodies. In most States, dead bodies must be disposed of in an authorized manner within a specified period of time, usually 72 hours after death. Any disposition of a dead body usually requires a permit, which is generally issued only after a death certificate has been filed. Most of these statutes also specify when fetal deaths must be registered and how to dispose of fetal remains. In addition, some States make separate provision for reporting fetal deaths and disposing of fetal remains. These statutes are important, not only because they provide penalties for unauthorized uses of dead bodies, but also because they determine what must be done with fetal remains once their research or clinical value has been exhausted and what reports must be filed.

The two most common sources of authority for conducting research are research statutes and the UAGA. In addition, many States establish an administrative agency to distribute unclaimed dead

bodies for scientific and educational purposes. Since these statutes typically require a lengthy holding period or embalming of the body, they do not provide useful authority for the use of fetal tissue in neural grafts. Moreover, anyone who conducts fetal tissue research that is not authorized by one of these statutes may be charged with corpse abuse or unauthorized dissection. The most common corpse abuse statute follows the Model Penal Code 250.10 and prohibits any use of a corpse that would offend "family sensibilities."

Most jurisdictions exempt fetuses in early stages of development from death certification and registration requirements. These States define "fetal deaths" or "stillbirths" requiring registration in terms of a minimum gestational period, a minimal weight, or both. Eight States apparently require fetal death certificates regardless of the age or weight of the fetus. Of the statutes that require fetal death certificates, at least five exempt deaths resulting from induced abortions. Finally, 13 States do not require death certificates for fetuses of any particular age or weight but do require at least some fetal deaths to be reported. Three of the statutes requiring some report of fetal deaths make special provision for reporting deaths resulting from induced abortions.

Some States require disposition permits regardless of the age or weight of the fetus, while at least six States directly exempt fetuses in early stages of development from permit requirements. Eighteen other States apparently obtain the same result indirectly, by anticipating that disposition permits will be issued only on the filing of a death certificate, but exempting fetuses in early stages of development from death certification requirements. In a few States, whether a permit is required depends on the kind of disposition planned rather than on any characteristic of the fetus.

The most common kinds of dispositions of fetal remains are burial, cremation, and entombment. Kentucky apparently allows only burial of fetal remains [Ky. Rev. Stat. 213.160]. At least 16 statutes anticipate that a health-care institution will dispose of fetal remains and require the institution to report these dispositions. Finally, seven States that provide for fetal death certificates or death reports explicitly exclude fetuses in early stages of development from disposition requirements, make no specific provi-

sion for fetal remains, or authorize an administrative agency to decide what disposition is appropriate.

At least seven of the statutes governing the general disposition of dead bodies make some provision for parental consent to the disposition of fetal remains, while five statutes require parental consent for any disposition of a dead fetus, regardless of gestational age. One of the five statutes requires the pregnant woman's but not the partner's consent when the pregnant woman is unmarried, while the two remaining statutes require consent of a parent only in certain circumstances.

The reamer in which fetal remains are disposed of is also covered under the statutes of some States. The California penal statute clearly does not affect neural grafts; it merely prohibits disposition of fetal remains in sites open to public view [Cal. Penal Code 643]. The California Health and Safety Code requires that fetal remains be incinerated at the conclusion of research, but this provision does not apply to educational institutions [Cal. Health & Safety Code 25957(a)]. The Arkansas statute requires physicians performing abortions to ensure that fetal remains are disposed of in a similar manner to other human tissue [Ark. Stat. Ann. 20-17-802(a)], namely, "incineration, cremation, burial, or other sanitary means prescribed by the State health department" [Ark. Stat. Ann. 20-17-801(a)]. The laws of Florida, Georgia, Minnesota, and North Dakota allow any manner of disposition approved by the State health department. The Florida statute also requires the health department to promulgate rules consistent with the disposition of other human tissues [Fla. Stat. Ann. 390.012(2)]. Whether neural grafts are allowed in these States depends on what regulations are currently in force. Finally, the Massachusetts statute requires fetal remains to be disposed of at the parent's direction, whether by burial, entombment, cremation, or, if the hospital or attending physician is to dispose of the remains, by any method that does not create a public health hazard [Mass. Ann. Laws ch. 11,202]. In addition, the statute requires the hospital or attending physician to inform parents of their right to direct disposition and of any hospital policy governing disposition of fetal remains.

The fetal remains laws in some States have been subject to successful constitutional challenges. A recent Supreme Court case held that an ordinance requiring fetal remains to be disposed of in a humane

## UNIFORM DONOR CARD

of \_\_\_\_\_  
Print or type name of donor

In the hope that I may help others, I hereby make this anatomical gift, if medically acceptable, to take effect upon my death. The words and marks below indicate my desires

I give (a) — any needed organs or parts  
 (b) — only the following organs or parts

\_\_\_\_\_ Specify the organ(s) or part(s)  
 for the purposes of transplantation, therapy, medical research or education,  
 (c) — my body for anatomical study if needed

Limitations or special wishes, if any \_\_\_\_\_

08-21-81 100M/81

**Signed by the donor and the following two witnesses in the presence of each other:**

Signature of Donor	Date of Birth of Donor
Date Signed	City & State
Witness	Witness

This is a legal document under the Uniform Anatomical Gift Act or similar laws

For further information consult your physician or

 **National Kidney Foundation of the National Capital Area, Inc.**  
 2233 Wisconsin Ave., NW, Suite 320  
 Washington, DC 20007

*Photo credit: Office of Technology Assessment*

**An organ donation card.**

and sanitary manner was impermissible vague (16). In addition, laws that specifically required a woman to decide, in advance of an abortion, whether the aborted fetus was to be buried, cremated, or disposed of at the hospital's discretion have been struck down as unconstitutionally interfering with the woman's right to privacy (29).

### *Uniform Anatomical Gift Act*

The Uniform Anatomical Gift Act (47) is the only uniform body of law that might regulate acquisition or donation of fetal tissue implants. Forty-seven States and the District of Columbia presently conform to some form of the 1968 version of the UAGA. California, Connecticut, and Hawaii have adopted a new version of the UAGA, approved by the National Conference of Commissioners on Uniform State Laws in 1987. In fact, in the 25 States that lack fetal tissue research statutes, the UAGA is the primary legislation that would affect this technology (57).

Specifically, the UAGA affects fetal tissue implants by including "a stillborn infant or fetus' in

the definition of “decendent” and by stating that “parts” includes “tissues” (47); however, not all States have included a fetal tissue provision in their version of the UAGA. According to the 1987 version of the Act, either parent may consent to the donation of fetal tissue; in reality, the consent of both parents is necessary because if either objects, a donor who knows of the objection may not accept the gift (47). The UAGA would appear to allow the parents of an aborted or stillborn fetus to designate a recipient, even though this practice would be in direct opposition to the recommendations of the *Report of the Human Fetal Tissue Transplantation Research Panel* (67). The panel expressed concern that such a practice might encourage abortions in order to donate fetal tissue for the treatment of relatives. Furthermore, because of the genetic nature of diseases such as diabetes and Huntington’s disease, the effectiveness of the treatment might actually be jeopardized by implanting fetal cells which possess the same defect that the procedure is supposed to ameliorate (67). The UAGA and the NIH report differ on several points because the UAGA was written before the NIH report and before fetal transplants were thought to have so many possible applications (13).

In adopting the UAGA, many States added sections designed to facilitate and regulate the donation of tissue. The most common nonuniform provisions found in State laws either require hospitals to adopt an organ procurement protocol, which is designed to facilitate the procurement of donor tissue while recognizing the sensitivity of the relatives who must consent to the donation, or simply require hospital personnel to request the relative of a suitable decendent to make the decendent’s organs available for donation (see table 7-2). In either case, physicians wishing to obtain fetal tissue would be required to request parental consent in a professional and sensitive manner. Those laws which require that consent be obtained would require doctors to inform all abortion patients of the possibility of donation for transplants, preferably after the abortion decision had been made. If the consent were sought prior to the decision to abort, it might conceivably influence the decision. For this reason, the Human Fetal Tissue Transplantation Research Panel recommends that the decision to obtain an abortion precede any request to donate tissue for implantation (67). These two procedures probably should be handled by two sepa-

rate advisers, the supervising physician and the researcher (55).

In 1987 the National Conference of Commissioners on Uniform State Laws approved a new model UAGA, which has been adopted by at least seven States. The new version retains provisions allowing the next of kin to designate the fetal tissue recipient and incorporates changes designed to increase the number of organ donations, particularly through required request policies. Organ procurement professionals have traditionally gone to great lengths to assure the public that organ donation will not compromise the patient’s medical care in any way. Accordingly, the family is approached about possible donation only after the patient has been declared dead by the physician. Following these guidelines, parents can be approached about possible donation only after the abortion and after the fetus has been declared dead. Language in the new version of the UAGA, however, suggests it may be permissible to seek consent before the abortion. The new version allows consent to be sought after or immediately before death (14).

The laws of at least eight States would protect recipients of fetal tissue by requiring that all donors be tested for HIV. An additional two States, while not requiring HIV testing of donors, have established standards that decrease the likelihood of AIDS-infected tissues being made available for donation.

Overall, the UAGA and its various manifestations provide some guidelines in the area of fetal tissue transplants. Because this Act was drafted before neural grafting technology became known, it is obviously not designed to address the specific and unique problems that these implants raise.

### *Compensation for Fetal Tissue in a Nonresearch Setting*

There is much concern about the possibility that women will be paid for fetal tissue for transplantations. One commentator points to “the fear that permitting the commercialization of the fetal tissue transplantation system will result in the exploitation of the women who bear tissue for profit and of the critically-ill patients who want to acquire it” (59). The NIH panel recommended that sale of fetal tissue not be allowed, for two reasons:

- . so as not to influence a woman's decision to abort; and
- . so as not to induce an abortion facility to base its choice of abortion procedure on the profitability of the fetal tissue to be retrieved (22).

The prohibition on payment to organ donors generally prohibits payment to women for fetal tissue. In addition, a variety of State statutes also have the same prohibition (table 7-2).

The National Organ Transplant Act, passed under Congress' commerce clause authority, bans the sale of certain listed organs (including certain fetal organs and their subparts) [42 U.S.C. 274(e)] and provides that the Secretary of DHHS list additional organs under the ban. Since the brain is not listed as one of the organs, payment for use of fetal brain tissue for transplantation will not be banned until the Secretary so designates.

In addition to the 16 State fetal research statutes that prohibit the sale of fetal tissues for purposes including research, seven State laws forbid the sale of fetuses or fetal material (see table 7-2). The Florida statute places a flat ban on selling, purchasing, or transferring a human embryo for valuable consideration and on offering or advertising to do so [Fla. Stat. Ann. 837.05(1)]. Nevada prohibits any commercial use of an aborted fetus or fetal material resulting from an abortion [Nev. Stat. Ann. 451.015]. Missouri prohibits knowingly offering or receiving any valuable consideration for the organs or tissues of an abortus, except payments for burial or other final disposition and for pathological examinations [Mo. Ann. Stat. 188.036(5)]. Utah prohibits sales and purchases of, or offers to buy or sell, unborn children [Utah Code Ann. 76-7-311]. The Georgia statute prohibits buying or selling a human fetus or fetal part [Ga. Code Ann. 48-401 *et seq.*], but the prohibition does not apply to donations under the UAGA, reimbursement of a living donor's actual expenses, or payment of costs associated with collecting, storing, and implanting a donated part [Ga. Code Am. 26-9957(b)]. Similarly, the Texas statute prohibits knowing and intentional transfers of fetal tissue for valuable consideration but excludes from "valuable consideration" fees paid to physicians, hospitals, and clinics for services rendered in the usual course of medical practice, reimbursement of legal or medical fees incurred to benefit the ultimate receiver of the tissue, and the donor's travel and housing expenses and lost wages

[Tex. Penal Code 48.02]. Finally, in an unusual provision, Kentucky prohibits selling or purchasing a child for adoption or any other purpose [Ky. Rev. Stat. Ann. 199.590(2)]. Since the statute specifically excludes from its coverage in vitro fertilization in which the genetic donors are a married couple and the fertilized ovum is to be implanted in the wife, the Kentucky legislators seem to have intended "child" to include the human organism from conception and "any purpose" to include medical and scientific procedures. Thus, this statute could be used to prohibit any agreement to pay the pregnant woman for fetal tissue made while the fetus is still alive.

At least 18 jurisdictions have laws forbidding payment to organ donors. Ten of the statutes are nonuniform UAGA provisions. The Delaware UAGA provision clearly does not prohibit payment to the pregnant woman for fetal tissue: it applies only to payments to a donor for disposition of his or her own body [Del. Code Ann. tit. 16, 2713(f)]. Whether the nine remaining UAGA provisions prohibit payment to the pregnant woman depends on two factors—whether any or all of the payment can be considered reasonable costs associated with the use of the tissue, and when the tissue will be removed.

The nonuniform provisions of nine States prohibit the purchase or sale of organs or tissue for valuable consideration but exclude from the definition of "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue. Three States exclude from "valuable consideration" "the expenses of travel, housing, and lost wages" incurred by the "donor." This suggests that the pregnant woman cannot be reimbursed for nonmedical losses and expenses without specific statutory authority. Moreover, under the UAGA, the term "donor" applies only to "an individual who makes a gift of all or part of his body" (47). In the case of fetuses, the pregnant woman is not a donor, but someone authorized to consent to the gift of a decedent's remains. Thus, the pregnant woman may not be paid for agreeing to transfer the fetal remains, even under State laws (47).

Under the nonuniform provisions of four States, California, Hawaii, Idaho, and North Dakota, payment to the pregnant woman may be banned for another reason. These States prohibit sales and purchases of organs and tissues for valuable consideration when the organ or tissue is to be removed

**after the** decedent's death. Unless the fetal **tissue is to be** removed while the fetus is still alive (which may be forbidden under the State's fetal research or **other** statute), payment **to the** pregnant woman is forbidden under these anatomical gift act provisions. The California Anatomical *Gift Act* is supplemented by a penal provision that prohibits a person from knowingly acquiring, receiving, selling, or promoting the transfer or otherwise transferring any organ for transplantation for valuable consideration. It also prohibits the use of an organ known to have been transferred for valuable consideration. The law is directed against brokering organs rather than the direct sale by a donor to a recipient.

Of the eight statutes remaining that prohibit the sale of organs but are not part of the State UAGA, one clearly does not prohibit payments to the pregnant woman. The Tennessee statute prohibits only transfers of organs for valuable consideration that "affect commerce" [Tenn. Code Ann. 68-30-401] and is presumably aimed at brokers. The law of the District of Columbia clearly prohibits such payments, and it excludes nothing of value from the definition of valuable consideration [D.C. Code Ann. 6-260(b)]. The remaining statutes are similar to the nonuniform anatomical gift act provisions previously discussed. Six allow reimbursement of reasonable expenses associated with the removal, preservation, and use of the donated organ, and four make an additional allowance for the donor's losses and expenses.

The Federal and State laws prohibiting payment to organ donors would ban more than just a cash payment to women. They would also cover payment of a woman's abortion expenses in order that she may donate fetal tissue (54). The reach of some State laws may also extend to payment to agencies that retrieve and process the fetal tissue. These agencies would not be able to "sell" tissue to physicians or patients; however, they would be able to recover their costs and overhead for obtaining the tissue. For example, the New York and West Virginia statutes exclude from the definition of "valuable consideration" reimbursement of expenses incurred by non-profit agencies and corporations in offering services related to the location, maintenance, and distribution of the donated organ [N.Y. Public Health Law 4307; W.Va. Code 16-19-7(a)].

Most of the statutes prohibiting transfers of organs for value define organ quite broadly and would cover most types of tissues and organs to be transplanted from fetuses. Other statutes are more limited in the body parts they cover and would require regulatory agency action to cover brain tissue. The Florida statute bans the sale of the kidney, liver, heart, lung, pancreas, bone, skin, or any other organ or tissue specified by rules adopted by the Department of Health and Rehabilitative Services [Fla. Stat. Ann. 873.01(3)(a)]. The New York statute begins with a larger list of items and then provides for regulatory expansion. It defines "human organ" as "the human kidney, liver, heart, lung, bone marrow, and any other human organ or tissue as maybe designated by the commissioner but shall exclude blood" [N.Y. Public Health Law 4307]. To the New York list, Wisconsin adds the pancreas, cornea, eye, bone, skin, and any other organ specified by the department except blood, blood products, and semen [Wisc. Stat. Ann. 146.345]. Michigan has by far the most comprehensive list: "human kidney, liver, heart, lung, pancreas, bone marrow, cornea, eye, bone, skin, cartilage, dura mater, ligaments, tendons, fascia, pituitary gland, and middle ear structures, and any other human organ specified by rule promulgated by the department" [Mich. Comp. Laws Ann. 333. 10204(3)(a)].

Finally, 10 States prohibit "trafficking" in dead bodies—that is, transferring dead bodies for valuable consideration (see table 7-2). These **statutes are** arguably drafted broadly enough to prohibit either payment to or receipt of payment by the pregnant woman for the use of fetal remains. Only one **statute** explicitly covers all bodies and bodily parts [La. Rev. Stat. Ann. 17:2280]. The remaining either cover bodies but do not refer to parts or limit their coverage to unclaimed bodies (those that have not been claimed for burial). The majority of States ban both purchases and sales of dead bodies, but three States prohibit only sales, and one State more broadly proscribes "delivering or receiving for speculation or pecuniary profit." In addition, five statutes prohibit transporting dead bodies out of State.

## SUMMARY AND CONCLUSIONS

The use of neural grafts raises many legal issues, despite the fact that this procedure is showing some promise in the treatment of several disorders. There are grounds for Federal action in this area. To the extent that Federal funds are used to support research involving neural grafting or to pay for the clinical use of such procedures, Federal regulations may establish mandatory policies governing the conduct of such research. Even if Federal funds are not used, the Federal Government has powers under the commerce clause to regulate this activity. This power has served as the basis for the establishment of the FDA, the prohibition on payment to organ donors for transplantation involving interstate commerce, and the regulation of medical laboratories engaged in interstate commerce.

It is difficult to predict how the FDA will choose to regulate the various tissues and products of biotechnology that may be used in neural grafting. Questions of safety and the FDA's current regulation of similar products make it likely that the agency will seek to regulate most neural grafting materials.

Questionable jurisdiction under the Public Health Service Act may limit the ability of the FDA to regulate these materials, since it is unclear whether neural tissue grafts, cell lines, and products of biotechnology to be used as neural grafting materials are analogous to the other articles listed as biologics in the statute. Other legal issues include questions of FDA jurisdiction in relation to when a neural graft is produced and performed intrastate and in relation to the practice of medicine.

Some existing Federal policies governing experimentation and organ transplantation could affect tissue transplants. However, the Federal regulations on fetal research and the Federal law on transplantation were developed before the extensive, recent debate on fetal tissue transplantation. It might be appropriate to amend existing policies to address more directly the concerns raised by neural grafting. In particular, Federal regulations and law might be modified to provide that a woman not be paid valuable consideration for fetal tissue for transplantation and not be allowed to designate a donor. Federal regulations might also be amended to ensure that health-care professionals undertaking counseling and persons involved in abortion procedures are

not also involved in the harvest and transplantation of fetal tissue.

## CHAPTER 7 REFERENCES

1. Anderson, W., and Fletcher, J., "Gene Therapy in Humans: When Is It Ethical to Begin?" *New England Journal of Medicine* 303:1293-1297, 1980.
2. Annas, G., Glantz, L., and Katz, B., *Informed Consent to Human Experimentation: The Subject's Dilemma* (Cambridge, MA: Ballinger, 1977).
3. Areen, J., "Statement on Legal Regulation of Fetal Tissue Transplant," *Report of the Human Fetal Tissue Transplantation Research Panel (Bethesda, MD: National Institutes of Health, 1988)*.
4. Bakay, R., neuroscientist, Emory University, Atlanta, GA, personal communication, December 1989.
5. Barber, B., "The Ethics of Experimentation with Human Subjects," *Scientific American* 234 (February): 25-31, 1976.
6. Barnett, H., Sackett, D., Taylor, D., et al., "Are the Results of the Extracranial-Intracranial Bypass Trial Generalizable?" *New England Journal of Medicine* 316:820-824, 1987.
7. Blank, R., Program for Biosocial Research, Social Science Research Institute, Northern Illinois University, DeKalb, IL, personal communication, Dec. 18, 1989.
8. Bonchek, L., "Are Randomized Trials Appropriate for Evaluating New Operations?" *New England Journal of Medicine* 301:44-45, 1979.
9. Bonchek, L., letter, *New England Journal of Medicine* 301:1181-1183, 1979.
10. Buc, N., Weil, Gotshal & Manges, Washington DC, personal communication, Dec. 18, 1989.
11. Buchanan, A., and Brock, D.W., "Deciding for Others," *Milbank Quarterly* 64:17-94, 1986.
12. Bunker, J., Hinkley, D., and McDermott, W., "Surgical Innovation and Its Evaluation," *Science* 200:937-941, 1978.
13. Carr, S., legislative analyst, Office of Governmental Relations, Association of American Medical Colleges, Washington, DC, personal communication, April 1990.
14. Center for Biomedical Ethics, *The Use of Human Fetal Tissue: Scientific, Ethical, and Policy Concerns* (Minneapolis, MN: University of Minnesota, 1990).
15. Christoffel, T., *Health and the Law: A Handbook for Health Professionals* (New York, NY: Free Press, 1982).
16. *City of Akron v. Akron Center for Reproductive Health, Inc.*, 462 U.S. 416 (1983).
17. Curran, W., "Forward," *Consent to Treatment: A Practical Guide*, F. Rozovsky (cd.) (Boston, MA: Little, Brown, 1984).

18. Fazzini, E., "Neural Transplants in Parkinson's Disease," paper presented at the International Symposium, *Centrol Ramon y Cajal*, Madrid, May 19-20, 1989.
19. Fletcher, J., "Moral Problems and Ethical Issues in Prospective Human Gene Therapy," *University of Virginia Law Review* 69:515-546, 1983.
20. Fletcher, J., Dommel, J., and Cowell, D., "Consent to Research With Impaired Human Subjects," *IRB: A Review of Human Subjects Research* 7 (November-December) :1-6, 1985.
21. Fowler, N., letter, *New England Journal of Medicine*, 301:1181, 1979.
22. Fox, J., "Overview," *Report of the Human Fetal Tissue Transplantation Research Panel (Bethesda, MD: National Institutes of Health, 1988)*.
23. Gill, T., and Lund, R., "Grafting into the Brain," testimony before the Human Fetal Tissue Transplantation Research Panel, National Institutes of Health, Bethesda, MD, Sept. 14, 1988.
24. Greenwald, R., Ryan, M., and Mulvihill, J., *Human Subjects Research: A Handbook for Institutional Review Boards* (New York, NY: Plenum Press, 1982).
25. Gunter, K., Division of Biological Investigational New Drugs, Center for Biologics Evaluation and Research, Food and Drug Administration, personal communication, Feb. 26, 1990.
26. *Halushka v. University of Saskatchewan*, 53 D.L.R. 2d 436 (Sask. 1968).
27. Jackson, L., "Prenatal Genetic Diagnosis by Chorionic Villus Sampling (CVS)," *Seminars in Perinatology* 9:209-218, 1985.
28. Lappe, M., "Balancing Obligations to the Living Human Fetus with the Needs for Experimentation," U.S. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research on the Fetus*, DHEW Pub. No. (OS) 76-127 (Washington, DC: U.S. Government Printing Office, 1975).
29. *Leigh v. Olsen*, 497 F. Supp. 1340 (C.D.N.D. 1980).
30. Levine, R., *Ethics and Regulation of Clinical Research* (Baltimore, MD: Urban & Schwarzenberg, 1981).
31. Loh, L., letter, *New England Journal of Medicine* 301:1182, 1979.
32. McCormick, R., "Experimentation on the Fetus: Policy Proposals," U.S. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research on the Fetus* DHEW Pub. No. (OS) 76-127 (Washington, DC: U.S. Government Printing Office, 1975).
33. *McCoy v. Georgia Baptist Hospital*, 167 Ga. App. 495,306 S.E.2d 746 (1983).
34. Mackler, B., "Regulatory Issues Concerning Organs and Tissues," paper presented at the Annual Educational Conference of the Food and Drug Law Institute, Washington, DC, Dec. 13, 1989.
35. Mahowald, M.B., Areen, J., Hoffer, B.J., et al., "Transplantation of Neural Tissue from Fetuses," *Science* 235:4794, 1987.
36. Mahowald, M.B., Silver, J., and Ratcheson, R.A., "The Ethical Options in Transplanting Fetal Tissue," *Hastings Center Report* 17(February):9-15, 1987.
37. *Margaret S. v. Edwards*, 794 F.2d 994 (5th Cir. 1986).
38. Merchant, B., and Hybritech, X., "Emerging Issues on Product Safety Evaluation," paper presented at the Annual Educational Conference of the Food and Drug Law Institute, Washington, DC, Dec. 13, 1989.
39. Merrill, R.A., and Hutt, P.B., *Food and Drug Law: Cases and Materials* (Mineola, NY: Foundation Press, 1980).
40. Merz, B. "Neurobiologists Join Neurosurgeons in Urging Restraint in Parkinson's Surgery," *Journal of the American Medical Association* 216:2929, 1989.
41. *Meyer v. Nebraska*, 262 U.S. 390 (1923).
42. *Moore v. Regents of the University of California*, 202 Cal. App.3d 1230, 249 Cal. Rptr. 494 (1988), *reh. granted*, 252 Cal. Rptr. 816,763 P.2d 479, 1988.
43. *Moore v. Regents of the University of California*, Supreme Court of the State of California, Case Number S006987, July 9, 1990.
44. Moraczewski, A. S., Regional Director, Pope John XXIII Medical, Moral, Research, and Education Center, Houston, TX, personal communication, Dec. 18, 1989.
45. Mulford, R., "Experimentation on Human Beings," *Stanford Law Review* 20:99-117, 1967.
46. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, U.S. Department of Health, Education, and Welfare, *Research on the Fetus: Report and Recommendations*, DHEW Pub. No. (OS) 76-127 (Washington, DC: U.S. Government Printing Office, 1975).
47. National Conference of Commissioners on Uniform State Laws, *Uniform Anatomical Gift Act*, annual conference, Chicago, IL, 1987.
48. Note, "State Prohibition of Fetal Experimentation and the Fundamental Right to Privacy," *Columbia Law Review* 88:1073-1097, 1988.
49. Ramsey, P., *The Patient as Person: Explorations in Medical Ethics* (New Haven, CT: Yale University Press, 1970), pp. 11-19.
50. Redmond, D. E., neurosurgeon, Neurobehavioral Laboratory, Yale University School of Medicine, New Haven, CT, personal communication, May 1990.
51. Rettig, R. A., "The Politics of Organ Transplantation: A Parable of Our Time," *Organ Transplantation*

- Policy: Issues and Prospects*, J.F. Blumstein and F.A. Sloan (eds.) (Durham, NC: Duke University Press, 1989), pp. 191-227.
52. Robertson, J., "Compensating Injured Research Subjects: II, The Law," *Hastings Center Report* 6(December):29-31, 1976.
  53. Robertson, J., "The Law of Institutional Review Boards," *University of California at Los Angeles Law Review* 26:484-549, 1979.
  54. Robertson, J., "Fetal Tissue Transplants," *Washington University Law Quarterly* 66:443-498, 1988.
  55. Rosner, J., Executive Director, United Parkinson Foundation, Chicago, IL, personal communication, May 1990.
  56. Schwartz, R., "Institutional Review of Medical Research," *Journal of Legal Medicine* 4:143-166, 1983.
  57. Sheehan, A., "Fetal Tissue Implants: An Explosive Technology Needs National Action," *Dickinson Law Review* 92:895-916, 1988.
  58. *State of Louisiana v. Mathews*, 427 F. Supp. 174 (D.C. La. 1977).
  59. Terry, N., "Politics and Privacy: Refining the Ethical and Legal Issues in Fetal Tissue Transplantation," *Washington University Law Quarterly* 66:523-551, 1988.
  60. *United States v. An Article of Drug . . . Bactoidisk*, 394 U.S. 784 (1968), *reh. denied*, 395 U.S. 954 (1969).
  61. *United States v. Calise*, 217 F. Supp. 705 (D. C.N.Y. 1962).
  62. *United States v. Evers*, 453 F. Supp. 1141 (D.C. Ala. 1978).
  63. U.S. Congress, Office of Technology Assessment, *Human Gene Therapy, OTA-BP-BA-32* (Washington, DC: U.S. Government Printing Office, December 1984).
  64. U.S. Congress, Office of Technology Assessment, *Losing a Million Minds: Confronting the Tragedy of Alzheimer's Disease and Other Dementias*, OTA-BA-323 (Washington, DC: U.S. Government Printing Office, April 1987).
  65. U.S. Congress, Office of Technology Assessment, *Life-Sustaining Technologies and the Elderly*, OTA-BA-306 (Washington, DC: U.S. Government Printing Office, July 1987).
  66. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, testimony before the House Committee on Science and Technology, Subcommittee on Investigations and Oversight, Nov. 9, 1983.
  67. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, *Report of the Human Fetal Tissue Transplantation Research Panel* (Bethesda, MD: 1988).
  68. van der Linden, W., "Pitfalls in Randomized Surgical Trials," *Surgery* 87:258-262, 1980.
  69. White, R.M., Associate Professor of Medicine and Oncology, Howard University Cancer Center, Washington, DC, personal communication, June 12, 1990.
  70. Williamson, B., "Gene Therapy," *Nature* 298:416-418, 1982.
  71. Wion, A., Associate Chief Counsel for Drugs and Biologics, Food and Drug Administration, "Legal Issues Concerning Federal Regulation of Tissues," paper presented at the American Association of Tissue Banks-FDA colloquium, Washington, DC, Oct. 1, 1989.
  72. Wion, A., Associate Chief Counsel for Drugs and Biologics, Food and Drug Administration, "Regulatory Issues Concerning Organs and Tissues," paper presented at the Annual Educational Conference of the Food and Drug Law Institute, Washington, DC, Dec. 13, 1989.
  73. Woodcock, J., Director, Division of Biological Investigational New Drugs, Center for Biologics Evaluation and Research, Food and Drug Administration, letter to R. Chin, Office of Technology Assessment, received Oct. 26, 1989.
  74. Woodcock, J., Director, Division of Biological Investigational New Drugs, Center for Biologics Evaluation and Research, Food and Drug Administration, letter to Wendy Pachter, Office of Technology Assessment, received Dec. 14, 1989.
  75. Woodcock, J., Director, Division of Biological Investigational New Drugs, Center for Biologics Evaluation and Research, Food and Drug Administration, personal communication, June 1990.
  76. Woody, K., "Legal and Ethical Concepts Involved in Informed Consent to Human Research," *California Western Law Review* 18:50-79, 1981.