The Tissue Issue

Losing oneself to science?

By EVELYN STRAUSS

Once a physician has removed cells from a person's body, who owns them? Who decides who can use them and for what purposes? Is the person's control over his or her tissue severed along with the cells themselves?

In the late 1950s, pathologist Oscar Auerbach nailed down the link between smoking and lung cancer by examining tissue taken from the airways of several hundred people during autopsies. When he compared his observations with information gathered during interviews with relatives of the deceased, he discovered that lung cells reflect smoking habits: the more cigarettes, the greater the damage (SN: 8/19/61, p. 120). Surgeon General Luther L. Terry cited Auerbach's findings in his first report on the dangers of smoking, and many people credit that research with motivating the warnings that cigarette packages carry to this day.

Auerbach's studies would raise concerns in the 1990s, however. The people whose tissue samples he examined never agreed to participate in the project. Furthermore, researchers these days can look for inherited as well as acquired bases of disease (SN: 11/5/94, p. 298; 12/17/94, p. 408).

Suppose a researcher found a correlation between the presence of a certain gene and lung cancer. Should he or she tell family members who may be at risk? Even if there's no way to prevent or cure the disease? And knowing that their health insurance companies or employers might misuse such information (SN: 10/26/96, p. 262)? What about people who might not want to contribute their tissue, even after death, to some kinds of research projects—such as searches for possible genetic roots of sexual orientation?

"Because of the power of genetics, you can study these materials and find out secrets about a person and his or her relatives," says Arthur L. Caplan, director of the Center for Bioethics at the University of Pennsylvania in Philadelphia. "The old rules for taking tissues aren't cutting it anymore."

The issue comes down to how much control an individual should retain over the use of material from his or her body and the information derived from it. Researchers, ethicists, advocacy groups, legislators, and others are wending their way through the labyrinth of dilemmas surrounding appropriate research on tissue.

Although most participants in the debate seem to agree on the goals—providing protection and respect for individuals while continuing to support research—recipes for success differ. Many ethicists and others proclaim that tighter control is essential to ensure personal privacy and autonomy, while many biomedical investigators envision their research mired in excessive cost and administrative burdens.

"The legal and ethical issues about the use of stored tissue are probably the most profound, complex, and troubling of any ethical issue we have in science today," says Lawrence O. Gostin, a professor of law at Georgetown University in Washington, D.C. "It pits two fundamental values against each other, and there's no easy resolution."

Federally funded research on tissue that can be linked to living persons is tightly regulated. The individuals must give specific consent for the research, or the investigation must meet certain criteria, such as imposing minimal risk upon the subjects. Decisions governing whether projects fulfill these conditions fall to groups called Institutional Review Boards (IRBs), which consist of scientists and other representatives of the local community.

Despite the regulations, plenty of room for controversy remains. Various IRBs interpret the guidelines differently, and people disagree about whether these groups should wield more or less power than they do now. Furthermore, because people who have died are not technically "human subjects," the rules don't apply to many stored samples, says J. Thomas Puglisi of the Office for Protection from Research Risks in Rockville, Md.—even though investigations on such materials may reveal information that could affect surviving relatives.

Policy makers have begun proposing, and in some cases passing, legislation aimed at protecting individuals. Many researchers say that some of the regulations would erect unnecessary barriers between themselves and the tissues they rely on for medical research. "People are in so much of a rush to legislate, they're writing things with language that's so sweeping, it has all kinds of unintended consequences," says David Korn, senior vice president for biomedical research at the Association of American Medical Colleges in Washington, D.C.

Several states have enacted legislation that deals specifically with the use of tissue in research. A 1995 Oregon law, amended last July, grants ownership of tissue, as well as the information derived from it, to the person from whom it was taken. In contrast, the California supreme court ruled that a man whose cells were used to make a valuable commercial product could not claim a share of the proceeds. The court did find that the doctors had violated the man's rights by not informing him of what they were doing with the tissue.

Senator Pete V. Domenici (R–N.M.) has introduced a bill aimed at tightening the rules about use of tissue in genetic research. Even trying to define words such as "genetic" presents problems, says Korn. "You can get genetic information by all different approaches—family history, a variety of lab tests, or directly looking at DNA."

The National Bioethics Advisory Commission (NBAC) will make recommendations regarding the use of human tissue in research in January 1998, says NBAC genetics subcommittee chairman Thomas H. Murray.

Human tissue enters the research domain by two main routes. In one, investigators ask volunteers to provide samples for a research project. In the other, pathologists collect and store material left over from medical procedures.

"Since microscopes began being used to study tissue samples, these tissues have provided the knowledge base on which our current understanding of medicine rests," says Korn.

Current regulations aim to inform patients about what will happen to their samples, at least if investigators use them in federally funded studies. Anyone undergoing a medical procedure must indicate that they understand the possible risks and benefits by signing a form.

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Many institutions incorporate into their consent forms a request for permission to use surplus tissue for research. These documents and the process of requesting such approval have come under close scrutiny in the last several years.

"The forms stink," says Caplan. "People don't read them because they're in language that's too difficult." The general language about research may be too imprecise to provide meaningful—and legally binding—permission, adds Gostin. People can't agree to a use if they don't know exactly what they're agreeing to, he continues.

Most forms do not reveal how researchers intend to handle the information they obtain in terms of confidentiality and privacy, says Robert F. Weir of the University of Iowa College of Medicine in Iowa City. Weir published a study on informed consent in the July-August and September-December 1995 issues of IRB.

How much information should potential tissue donors receive? Covering all of the possibilities may not be realistic. "At the time the tissue is being removed, there's no way to tell the patient what kind of technology may come up in the future," notes Korn.

Furthermore, many people—not just investigators—worry that too much information might overwhelm potential research subjects, thereby interfering with volunteer recruitment or education. "People get freaked out about a five-page consent form," says Iowa's Richard G. Lynch, head of the Federation of American Societies for Experimental Biology committee that's addressing ethical issues in biomedical research. "They say, 'Leave me alone. Just tell me where to sign.'"

At the same time, more informative consent forms may strengthen research projects because "better-informed subjects will probably feel like they're really partners," says Mary Ann Wilson, consumer staff representative at the Alliance of Genetic Support Groups in Chevy Chase, Md. "They're more likely to continue in the project."

The National Action Plan on Breast Cancer (NAPBC) in Washington, D.C., has developed a prototype consent form in which participants make a few general choices. They indicate whether scientists may use their tissue for research on cancer. In a separate question, they can grant permission for use of the tissue in studies of other health problems. The form also asks people to specify whether they want to be invited to take part in future research.

"If it's a preventable disease, a lot of people want to know the results of sample testing," says Abbey S. Meyers, president of the National Organization for Rare Disorders in New Fairfield, Conn., "but most conditions are not treatable—like Alzheimer's, for example."

"When people give samples, they should be able to say, 'Use this to save the world but leave me out of it,'" says Mary Jo Kahn of the Virginia Breast Cancer Foundation in Richmond. She points out that even being offered the choice of knowing can disturb people. "Someone can say, 'I know something about you that you don't know; do you want to know it?' You're either going to freak out and wonder forever or just ask.

"It's wonderful that we have the chance to develop good policy before there is widespread [genetic] testing and before we make a lot of mistakes," Kahn continues. "It just takes one *60 Minutes* show to make it so no one will sign a consent form."

Even if people develop wise guidelines, many dilemmas will remain. What should researchers do with the millions of tissue specimens currently stored in pathology labs around the country? Most of these samples are not accompanied by adequate consent forms because the tissues were collected long before people became as sensitive to the issues as they are today.

Researchers should either go back and get consent or start a new study, says George J. Annas, a medical ethicist at Boston University School of Public Health. Annas has drafted model federal legislation for the use of human tissue in research. "It's not right for you to know more about people than they do without their consent," he says.

The issue should be resolved on a case-by-case basis, argues Elizabeth J. Thomson, program director of clinical genetics research at the National Human Genome Research Institute in Bethesda, Md. "Researchers should ask, 'Do I need to use archival tissue when I know that consent was less than adequate?'" she says.

"If the sample's been there for 50 years, it's absurd to request permission," says Ellen W. Clayton, associate professor of law and pediatrics at Vanderbilt University Medical Center in Nashville. "But if it was last week and you know where the patient is, it would be pretty hard to argue not to ask."

Many scientists contend that demanding consent for every purpose would result in squandering a valuable resource. "Say I want to look at outcomes of different treatment regimens on people who have a particular mutation," says Mark E. Sobel, chief of the molecular pathology section of the National Cancer Institute in Bethesda, Md. "If I can't use old material and I want to look at outcomes, it'll be at least 5 years before I start getting information and another 5 until it's really useful."

Korn suggests setting up a system whereby scientists can tap into follow-up information. "I don't need to know who the patients are, but I need to know what happened to them."

In principle, confidentiality can be achieved if someone strips the samples of names and gives them numbers instead, retaining the key so researchers can obtain information later in order to interpret their findings. IRBs review proposals for such research and decide whether they meet the requirements for waiving consent. Among other criteria, the board requires that it must not be "practicable" to obtain informed consent. "That means almost impossible," says Puglisi. "It's more than just inconvenient."

"Many of us would like to see a broader interpretation that would permit the review board to waive informed consent for coded samples more easily in some cases," says Sobel. Annas disagrees. "The IRB can grant exceptions, and that's a problem," he says. "They're the weak link in the current set of regulations."

Weak link or not, IRBs don't always get the chance to deliberate on research use of stored tissue, says Clayton. "It's really easy to pull up the medical records for everyone admitted to the hospital with condition X," she says. "Then you can go look at those people's tissues. It isn't allowed [without IRB approval], but it's as common as pig tracks."

Coded samples create a fundamental security problem: The person with the key can put everything together. "A lot of these problems have been solved in the banking industry," says Lynch. "I can go to the same ATM as you and get into my account but not yours. I think we should be preventing misuse, not preventing getting at information."

Federal regulations regarding informed consent do not apply to these so-called anonymized samples as long as they were stored before a study began and cannot be linked with the donor—a condition not easily met, says Puglisi. Such research comes at a cost, however: It can deprive participants of medical information that might someday benefit them.

Although participants in the debate over who should control tissue have made great strides in understanding and responding to each others' concerns over the last several years, many issues remain unresolved.

"The problem at the beginning was that people were at different tables, coming up with proposals to deal with the thing they were legitimately concerned about," says Lynch. "Since they didn't know about the other concerns, they created problems. Now we're all sitting at the same table."

Murray suggests that solutions won't necessarily require a strict trade-off between benefits for society and protection for individuals. "This isn't a zero-sum game," he says. "There may well be some creative responses that will maintain what we care about most with respect to both research and privacy." □