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Health - Human Research

'Unchecked' Research on People Raises Concern on Medical Ethics

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By SHERYL GAY STOLBERG

WASHINGTON, May 12 — On the outskirts of the nation's capital, tucked away on the sixth floor of a suburban office building, there is a little-known computer data base: a state-by-state accounting of the experiences of every cat, dog, hamster, guinea pig, chimpanzee, rabbit or farm animal used in a laboratory experiment.

Here in the Government's Division of Animal Care, one can discover precisely how many guinea pigs were subjected to biomedical research in 1995 (333,379). Or how many chimpanzees felt pain during research but were comforted with medication (19,712). Civil servants have compiled such numbers for 31 years, ever since Congress passed the Animal Welfare Act.

But there are no comparable figures for people. "We have better information about animal experiments than we do about human experiments," said R. Alto Charo, of the President Clinton's National Bioethics Advisory Commission.

More than two decades after the Federal Government issued regulations to protect human subjects of medical experiments, the research landscape has changed so much that many doctors and scientists are not necessarily covered by the rules. For example, an entire area of study, embryo research, has grown in the private sector over the last 20 years.

The regulations were the direct legacy of the notorious Tuskegee study, which was halted 25 years ago, amid revelations that the Government had withheld treatment for syphilis to black men in Tuskegee, Ala., without their consent.

The Federal regulations were aimed at establishing the twin pillars of ethical research for subjects of federally-financed studies: the assurance that patients would be warned of risks and that an independent panel would evaluate the experiment before it was conducted.

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But as President Clinton prepares to issue a formal apology to the subjects of the Tuskegee study on Friday, there is mounting concern that the Government's protections do not go far enough.

On Capitol Hill, Representative Christopher Shays, Republican of Connecticut, convened a hearing last week to determine the scope of lapses and violations of ethics in experiments. He was startled by the testimony, including accounts of ethics panels, institutional review boards, or I.R.B.'s, set up as profit-making ventures to evaluate proposed experiments for research groups that pay them.

"I found it amazing," Mr. Shays said. "I am struck by the fact that we have I.R.B.'s that can be created by anyone, that we don't even know how many there are. I think the more we get into this the more we are going to realize how casual this process really is."

Moreover, certain privately financed research is not bound by the rules. The loophole means some people — no one knows how many — are participating in studies that are wholly unregulated. When there are complaints, there is nothing the Government can do.

"There is unchecked human experimentation taking place," said Dr. Gary B. Ellis, director of the Federal Office for Protection from Research Risks. How much is impossible to determine. But documents obtained from the research protection agency revealed several examples of possible lapses, though the names of those making the complaints were withheld.

In one instance, the parents of a 3-year-old boy with a rare genetic disease enrolled him in an experimental bone marrow transplant program in 1990, at a state university hospital. The parents said their son emerged from the treatment with profound brain damage, unable to walk, talk or feed himself. There was no way to know if the treatment caused the damage, but in a 1991 letter to the protection agency, his parents said that the consent form they had signed had not fully explained the risks of the procedure.

"Had we been informed of this risk we would not have consented to the transplant," the couple wrote. "We are now faced with the expense and challenge of caring for a brain-damaged child who will now live a much longer life span because they corrected his disease."

In another case, an Oregon breast cancer patient complained that the hospital in which she had received chemotherapy had released information from her medical records to researchers without her consent.

In both cases the research was privately financed, so Dr. Ellis could not investigate. "We have incident after incident where we get to the point where we determine that we don't have the authority," he said. "It's very frustrating."

Senator John Glenn, Democrat of Ohio, has been seeking to close this gap. He introduced a bill, the Human Research Subject Protections Act of 1997, that would require informed consent and board review of all experiments, regardless of who paid for them. The bill also would create criminal penalties for violators — a provision that has drawn criticism from the Pharmaceutical Research and Manufacturers Association of America, which often finances private research.

"We believe in informed consent and our companies bend over backwards when we deal with patients," said Mark Grayson, the group's spokesman. But criminal penalties were unwarranted, he said.

Dr. William E. Gibbons, who directs research on genetic testing of embryos at the Jones Institute for Reproductive Medicine in Norfolk, Va., was also skeptical, saying his scientists already follow Federal guidelines.

"How bad a problem do we actually have?" Dr. Gibbons asked. Replied Senator Glenn: "One violation is too much."

Experts point out that the debate over ethics in human experiments is occurring at a time when medical research is safer than it has ever been. History is dotted with scientific horrors beyond the Tuskegee study, notably the gruesome Nazi experiments of World War II and human radiation experiments financed by the Government during the cold war.

These low points in the annals of medicine gave rise to the current system. The concept of informed consent, that patients must be told in advance about how the experiment might help or hurt them, is rooted in the Nuremberg Code by which the Nazi experiments were judged in postwar trials. But it was not until 1974, two years after the Tuskegee study was disclosed, that the Fedeal Government enacted a set of comprehensive rules designed to protect volunteers for research.

Informed consent was one cornerstone of the new rules. The creation of institutional review boards was the other. Today, these provisions are so universally accepted they are referred to as the Common Rule.

The Common Rule applies to three research categories: studies supported by 17 Federal agencies that adhere to it, including the Department of Defense; experiments to prove the efficacy of a new medicine or device and gain the Food and Drug Administration's approval, and research paid for with private money but conducted by academic researchers whose employers have signed agreements with the Government. About 450 universities now require that their scientists to adhere to the Common Rule.

Although it has been updated six times in the past 23 years (there are now specific provisions for children, prisoners and pregnant women) many ethics experts say the nature of research has changed so dramatically since the Common Rule was drafted that a thorough re-examination is in order.

"The old model presumes that you would do research to find out some important new basic facts about health," said Dr. Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania. "Current research might be for a pharmaceutical company to put a new drug on the market to compete with the five ones that are already there for, say, insomnia or weight loss. The risks and benefits may be different."

In addition, Dr. Caplan said, the boom in research paid for by private industry has created a new phenomenon: commercial review boards that have generated a wave of what Dr. Caplan called "I.R.B. shopping."

At last week's Congressional hearing, Dr. Benmjamin Wilfond, a pediatrician who sits on the review board at the University of Arizona, recalled how one proposal was shopped around.

Not long ago, he said, his board rejected a plan by a university researcher to test a new anti-inflammatory treatment for childhood asthma. The experiment, which was to be paid for by the company seeking approval of the new drug, called for half of the children to receive the new treatment and the other half to receive a placebo. Some of the children given the placebo were to have discontinued their current therapy; the university board thought that was unethical.

Later, Dr. Wilfond said, he learned that the same experiment was being conducted by a private doctor who had submitted the plan to an ethics panel in another state.

What, if anything, Congress can do about lapses is unclear; Government has traditionally been loath to interfere with the private practice of medicine, and no regulatory system is foolproof. "The situation that we have created is generally effective," Dr. Harold Varmus, director of the National Institutes of Health, told Representative Shays last week. "But it's not perfect."

But Ms. Charo, of the bioethics commission, said she believed that expanding the Common Rule to cover all research would be a good first step. At least, she said, regulators might then be able to gather basic statistics for humans as they do for other species. After all, she added wryly: "I'm an animal too."

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