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## A LOOK AT . . . Informed Consent

### A Lot of Rules, Too Many Exceptions

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Outlook

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The highly publicized death in September of an 18-year-old patient in a clinical trial at one of the largest academic gene therapy centers in the world--the University of Pennsylvania's Institute for Human Gene Therapy--has spurred a host of investigations and recriminations. It has also prompted some people to ask a question we shall never be able to answer for sure: If Jesse Gelsinger had known that monkeys had died from the therapy before it was given to humans and that several previous participants had suffered serious toxic reactions to the kind of treatment he was volunteering to undergo, would he have agreed to take part in the trial?

More generally, can we be certain that participants in the proliferating number of experiments being conducted in other centers around the country have been given the information they need before agreeing to participate?

My experience as a former member of the National Institutes of Health advisory committee that oversees gene therapy research suggests that the likely answer to both those questions is no. Gelsinger's untimely death has exposed the shortcomings in the system we have developed to protect patients. Some researchers seem to view the process of informing patients about experiments as a necessary hindrance in their race for scientific glory--and financial reward. Gelsinger's story is viewed by many as an aberration. I believe, however, that it may fit a pattern. Some researchers--not all--don't take seriously enough the need for informed consent, despite the abuses of the past.

Certainly, many of the greatest triumphs of the past 100 years were the accomplishments of medical researchers who tamed rheumatic fever, eradicated smallpox and polio and discovered the magical potency of antibiotics to win countless victories over disease and death.

But for every story of medical success there is a darker one of medical

abuse: the Nazi experiments on defenseless minorities; the Tuskegee experiment in which African American men with syphilis were purposely denied medical treatment for decades by American physicians; and numerous unethical experiments on the mentally retarded and mentally ill who were confined to U.S. institutions. History teaches that we should be cautious about allowing researchers to pursue their investigations without government oversight and regulation to ensure that their research will be meaningful and patients will be adequately protected.

The Nuremberg trials revealed the full horror of medical experiments conducted by Nazi scientists during World War II--and created the political resolve in industrialized countries to establish rules that would protect human subjects in all future clinical experiments. In the United States, this code of conduct for scientific research became known as the "Common Rule," and it was last revised by the federal government in 1981.

The Common Rule requires that all patients--or their legal guardians--who volunteer to participate in clinical trials be fully informed about the details of the experiment. They must have a complete understanding of the risks (even the possibility of unknown dangers) as well as the potential benefits of the experiment. For example, in an early (Phase I) clinical trial, which is conducted solely for the purpose of determining the safety (not the effectiveness) of a treatment, volunteers must be told that they should not expect any personal benefit from the experiment, although the knowledge that scientists will gain from the trial is likely to help other patients in the future. In essence, the motivation for participation must be altruistic--a desire to help humanity, not a desire to help oneself.

The National Research Act of 1974 led to legal protections for all volunteers who participate in medical and psychological research that involve federal funds. The responsibility for ensuring that these rules are obeyed is assigned to an institutional review board (IRB) located at every facility in the United States that conducts research on humans, as long as the institution receives federal money. Privately funded research is not affected. The IRB must ensure that each experiment is scientifically and ethically sound, and must monitor its progress to ensure that patients' rights are adequately protected. Unfortunately, IRBs have been overburdened and underfunded. In recent months, the federal government has stopped all human research at several universities--including Duke University Medical Center, Rush-Presbyterian-St. Luke's Medical Center in Chicago, and West Los Angeles Medical Center--because their IRBs were failing to comply with patient protection rules.

These sorts of shortcomings are particularly troubling in the swiftly moving field of gene therapy. If the example of Gelsinger is anything

to go by--and the closings of these other medical centers suggests it is--patients are not being fully and truthfully informed before being asked to give their consent to participate.

Unlike the infamous experiments that led to the adoption of the Common Rule, modern gene therapy research is primarily funded by private companies, not the government. That's an important distinction. While government-funded academics must share information about their experiments, corporate funding often requires scientists to keep information secret: Companies often insist that releasing research information may provide an advantage to their competitors. If they release news, it is often carefully tailored good news, while the bad news remains hidden in the "trade secret" closet.

The result is that many people have the mistaken impression that gene therapy is already curing people (so far, however, there have been no documented cures), and pin false hopes on the technology. Cancer patients, for example, will often demand admission into a gene therapy trial because it represents their "last chance" to be cured. It is worth noting that the great majority of gene therapy experiments are not conducted on genetic diseases, which are too rare to encourage investment capital, but on cancer, primarily because investors sense that a potential treatment for cancer will be more profitable.

Gene therapy has always been a controversial area of science, because it has the potential to change the essence of the human race. In recognition of this, the government assigned the Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health (NIH) the task of overseeing development of the technology. Composed of volunteer scientists, expert bioethicists, consumer advocates and others who discuss each trial at quarterly public meetings, the RAC created rules called "Points to Consider." Gene therapy researchers must obey these rules if any patients in the trial are treated at a hospital that receives federal funds. But trials sponsored by private companies do not have to obey the rules if patients do not use facilities receiving federal funds.

There have been a number of problems with putting those rules into effect. When members of the RAC have complained that an informed consent document is inaccurate or misleading, they are reminded that only the local IRB has authority to dictate the words in the document. Not even the Food and Drug Administration has any authority over the wording. (The agency focuses solely on science, not ethics, so it cannot demand that a doctor disclose to patients in a trial that he or she owns shares in the sponsoring company and thus stands to benefit financially from the product being tested.) The sole authority for approving informed consent documents--the local IRB--is not required to have any members who are knowledgeable about the technology that they are reviewing.

Members of an IRB (mostly staff of the institution) are usually keenly aware of the need to attract government and industry research grants, and often are unwilling to be too demanding when asked to revise informed consent documents. It sometimes appears that IRBs are more concerned about protecting their institutions' liability concerns than about protecting patients.

In 1994, the RAC's Working Group on Informed Consent strengthened the Points to Consider rules and spelled out exactly what each consent document should address. Of course it is a challenge to make the highly technical work of modern research scientists comprehensible to patients, but the Points to Consider set up some straightforward rules: They require that informed consent documents must be written in understandable language and they state that any adverse effects seen in animal studies and patients who previously participated in the experiment must be disclosed. Nevertheless, researchers and IRBs largely continue to ignore these rules. The FDA, which does not have any bioethicists on its staff, continues to approve new trials with inadequately worded informed consent documents.

In recent years, the RAC's authority over gene therapy research has also lessened. In 1996, Harold Varmus, as director of the NIH, withdrew the RAC's authority to approve gene therapy protocols, which greatly diminished its oversight. Today, the RAC is left with only moral suasion, especially with regard to informed consent documents.

After Jesse Gelsinger died from multiple-organ failure, brought on by the infusion of genetically altered cold viruses into his diseased liver, the FDA found some glaring violations. The informed consent document Gelsinger signed was very different from the documents the RAC had reviewed, and even different from the so-called "final" document that the FDA had seen. Information about the deaths of monkeys in the pre-clinical studies had been deleted, and there was no mention of several serious adverse events experienced by patients who preceded Gelsinger in this trial. As a result, all seven of the University of Pennsylvania's gene therapy studies were recently suspended.

Some of these problems were undoubtedly peculiar to this trial. But the oversight system failed to prevent serious violations of patient protection rules. Gelsinger's death shows that we must take a closer look at these guidelines. After all, gene therapy is only one of many burgeoning biomedical advances. Soon xenotransplantation, stem cells, cloning, in-utero transplants, fetal gene transfers and many as-yet unimaginable giant steps in medicine will be approaching the clinic.

Next week, as a result of the investigations into Gelsinger's death, there will be congressional hearings on gene therapy trials. Now is the time to build the political resolve to fix this problem, before more tragedies occur. We should not allow the Gelsinger case to stop the progress of gene therapy research. The research must move forward with the appropriate patient protections firmly in place to ensure that all clinical trial volunteers are fully informed before they are asked to give their consent.

Abbey Meyers, the founder and president of the National Organization for Rare Disorders, was a member of the National Institute of Health's Recombinant DNA Advisory Committee's (RAC) Gene Therapy Subcommittee from 1989 to 1992, and a member of the full RAC from 1993 to 1996.

#### Even Before Nuremberg

The Nuremberg Code of 1947 is usually referred to as the prototype for regulations regarding informed consent, but debate over medical experimentation goes back to 19th-century Prussia. In 1898, a University of Breslau professor of venereology named Albert Neisser injected serum from syphilitic patients (most of whom were prostitutes) into patients being treated for other conditions. The patients were not informed about the injections nor asked for their consent. When some of them contracted syphilis, Neisser denied his trials were the cause. But news of his experiment prompted a public outcry.

Berlin psychiatrist Albert Moll was one of the few academic physicians who did not side with Neisser at the time. He collected evidence from 600 cases of unethical, non-therapeutic research on humans and called for a new practice: informed consent. Neisser was fined for his actions by the Prussian Royal Disciplinary Court, according to a 1996 account by the British Medical Association.

After the court's action, the Prussian government formed a commission to study the matter further. In 1900, Prussian hospitals and clinics were ordered to perform medical interventions only for diagnosis, healing and immunization-- unless "the human subject was a minor or not competent for other reasons" or if the subject "had not given his or her unambiguous consent" after "proper explanation of the possible negative consequences" of the intervention. Unfortunately, the directive was not legally binding, which could account for its lack of historical impact.

Thirty years later, the Nazi government issued legal guidelines, based on a doctrine of informed consent, that were meant to minimize risk for human subjects. The wording was remarkably similar to informed

consent documents today. The guidelines obviously did not keep Nazi doctors from performing unethical experiments on concentration camp prisoners during World War II. The ethical regulations in human medical research--and the doctrine of informed consent that came about as a result of the Nuremberg trials--were the ones with staying power.

### Cases

Judgment calls about how and when to pursue informed consent are often controversial. Examples in the news during the late 1990s:

\* At a hospital in Philadelphia, doctors treating a 31-year-old man with a particular type of benign brain tumor recommended an untested variation on the usual course of radiation. They did not get the man's consent; he suffered an incapacitating stroke after the treatment. The neurosurgeons had not sought experimental status for the procedure, nor had they submitted their proposal to a hospital review board until they had treated several other patients, more than a year later. A malpractice suit against the doctors and the hospital is set for trial in mid-February.

\* One hundred severely injured trauma victims admitted to emergency rooms across the country were unwitting participants in a drug company's clinical trial for a new blood substitute intended to aid patients in hemorrhagic shock. The product was used to treat 52 patients categorized as having a high expected mortality rate due to their injuries; 24 died, leading the manufacturer to stop the trial. Under government rules, the trial was legal; an FDA waiver allowed the drug company to test its product on trauma victims who are unconscious or otherwise unable to give consent. The hospitals conducting such trials are supposed to notify their communities well in advance. A similar trial using the same blood substitute is ongoing in European hospitals.

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