1416

Peter Lurie, MD, MPH
Public Citizen's Health Research Group
&
Center for AIDS Prevention Studies,
University of California, San Francisco

Sidney M. Wolfe, MD
Public Citizen's Health Research Group

Testimony before the

Subcommittee on Human Resources,
Committee on Government
Reform and Oversight,
U.S. House of Representatives

May 8, 1997

Thank you for the opportunity to testify before the Subcommittee on these crucial bioethical issues. Our testimony today will address two subjects: HIV vaccine trials and a National Institutes of Health (NIH)-funded study of needle exchange programs in Alaska. While these two areas may seem disparate, there are several common themes that link them: 1. the difficulty of obtaining informed consent in vulnerable populations; 2. the need to provide research subjects with state-of-the-art medical care; and 3. the conflict of interest between the purported needs of researchers and the clear needs of the research subjects. We will address HIV vaccine trials first.

There is no question that the development and widespread utilization of a vaccine that effectively prevents transmission of HIV would be a public health triumph. With behavioral interventions currently having an important but limited impact upon HIV transmission, an effective vaccine is our best hope for preventing the huge burden of suffering from HIV disease both in the U.S. and abroad. Yet enormous ethical issues complicate potential vaccine efficacy trials. We shall mention just three.

First, because behavioral interventions such as safe sex counseling or the provision of condoms or sterile syringes have the capacity to reduce HIV risk behavior, it is critical to provide research subjects with state-of-the-art behavioral interventions as part of HIV vaccine trials. Yet, to the extent that such interventions are effective, there will be fewer new HIV infections and the ability to demonstrate statistically significant reductions in new HIV infections due to the vaccine will be reduced. This places the researcher in a classic conflict of interest, and creates an incentive to not provide adequate behavioral interventions in conjunction with these vaccine trials. The obvious solution to this dilemma is to employ an independent group of individuals to provide the behavioral interventions, but on several occasions when this has been suggested in the context of HIV vaccine trials it has met with opposition.

The remaining two issues deal with potential HIV vaccine trials in developing countries. Worldwide, an estimated 21.8 million people are presently living with HIV. Over 94% of these individuals live in the developing world; residents of developing countries therefore stand to derive the greatest benefit from such a vaccine. The need for a *vaccine* for a particular country is, however, different from the need for a *vaccine trial* in that country.

The Council for International Organizations of Medical Sciences' ethical guidelines on research in developing countries state unequivocally that "the

ethical standards applied should be no less exacting than they would be in the case of research carried out in [the sponsoring] country." Yet there are already worrisome signs that this fundamental ethical precept will be ignored.

In June 1994, research on two so-called gp120 HIV preventive vaccines was reviewed by the blue-ribbon AIDS Research Advisory Committee (ARAC) of the NIH, and the data were found to be insufficient to support government-funded efficacy trials in the U.S. As far as we know, no data have since been generated that would alter that assessment; indeed reports of a dozen breakthrough infections among subjects fully vaccinated with gp120 have raised further doubts about these vaccines' efficacy. Since 1994, most attention in the HIV vaccine field has now shifted to the so-called ALVAC-HIV vaccine. Yet San Francisco-based Vaxgen is planning, with logistical and statistical help from the Centers for Disease Control and Prevention, to conduct a Phase III trial of its gp120 vaccine in Thailand, even though that vaccine had been rejected for efficacy trials in this country. This seems unethical and exploitative, particularly as there is no guarantee that Thai citizens or those of other developing countries will have access to the vaccine should it be proved effective. Is Vaxgen planning on disclosing to Thai subjects that the vaccine was rejected by U.S. scientists for tests in our country?

Finally, some subjects in vaccine trials will contract HIV infections, either because they are randomized to the placebo group or because the vaccine is not completely effective (or perhaps not effective at all). While such newly infected individuals in industrialized country trials can be referred for care, there is concern that, in the developing countries where HIV vaccine trials are being considered, effective anti-HIV drugs will not be provided to those who become infected during the trial. We believe that it is the researchers' ethical responsibility to ensure that antiviral drugs are provided to all individuals who develop HIV infection during the trial, particularly because participation in such trials may lead some subjects to believe that they are protected from HIV infection and may thus induce them to increase their risk behavior.

We will now turn to the subject of research on needle exchange programs, which again illustrates the need for particular vigilance when conducting research on vulnerable populations.

Since 1991, there have been seven federally funded reviews of the effectiveness of needle exchange programs in preventing the transmission of HIV infection between injection drug users and from the drug users to their

sex partners and children. Every one of those reviews has concluded that needle exchange programs reduce the transmission of HIV infection and that there is no evidence that they lead to increases in community levels of drug use. Even Health and Human Services Secretary Donna Shalala finally conceded in February 1997 that needle exchange programs reduce the number of new HIV infections, although she still failed to remove the ban on federal funding for needle exchange programs.

Despite this unanimity in the research world, including a recent NIH Consensus Development Panel, the NIH has decided to provide $2.8 million for a randomized, controlled trial of the effectiveness of needle exchange to be conducted by Dr. Dennis Fisher of the University of Alaska Anchorage. It is worth noting that, although there is no evidence from a randomized controlled trial that condoms reduce the number of new HIV infections, no-one would consider such a study and effective public health policy has been formulated even in the absence of such evidence.

At least 600 injection drug users will be randomized to either receive sterile syringes for free from a needle exchange program or to receiving information on how to purchase syringes from pharmacies in Anchorage, information all or most will already have. When a subject seeks to obtain syringes at the needle exchange program, the researchers will use the subject's bar-coded identification card to generate the subject's image on a computer screen and thereby establish to which arm of the study the subject has been randomized; those assigned to the pharmacy condition will be turned away and advised how to purchase syringes at pharmacies. Remarkably, the researchers themselves admit in their grant proposal that this "represents the withholding of a potentially life-saving service." Because HIV infection is relatively rare among the drug injectors of Anchorage, the researchers plan to measure the number of new infections with hepatitis B. This will act as a proxy for HIV infection and will allow the researchers to compare the effectiveness of the needle exchange and pharmacy groups in reducing blood-borne infection.

The research is unethical for at least three reasons:

1. If an injection drug user does not enroll in the study, he or she cannot use the needle exchange program at all, thus coercing subjects to enroll;

2. Of injection drug users who enroll in the study, only 50% will be permitted to attend the needle exchange program; the others will be turned away if they seek syringes at the needle exchange program; and

3. The research protocol does not provide adequate assurance that the subjects will receive hepatitis B vaccine. It is highly inappropriate to monitor injecting drug users in both research groups contracting potentially fatal hepatitis B infection when an extremely effective vaccine for hepatitis B exists. It is difficult to imagine an analogous study in which babies were monitored for the occurrence of tetanus, while not being provided with the existing vaccine. But the researchers are faced with a conflict of interest analogous to that regarding behavioral counseling in HIV vaccine trials: if compliance with vaccination is high, there will not be enough new hepatitis B infections to permit statistically meaningful conclusions.

The parallels between the Alaska study and the notorious Tuskegee syphilis study are clear. In Tuskegee, poor rural African American men were denied access to proven treatment for syphilis and went on to develop the disease's complications, including death. In the Alaska study, another group of vulnerable Americans, injection drug users, many of whom are Native American or African American, are being placed at risk for life-threatening infections by being denied adequate access to not one, but two, proven medical interventions: sterile syringes and hepatitis B vaccine.

Indeed, there is an ugly racial dimension to the issue of sterile syringe availability in Anchorage. When we sent casually dressed volunteers to survey pharmacies in Anchorage, only 14% of pharmacies were willing to sell syringes without encumbrance. But an African American woman volunteer was refused syringes at all five pharmacies she visited, including two that had sold syringes to non-African Americans the day before.

When Public Citizen's Health Research Group raised these issues in a series of letters to NIH Director Harold Varmus beginning in October 1996, he immediately put the study on hold and convened a ten-person panel to review our concerns. The panel did not include anyone who could represent the concerns of drug users (such as injection drug users themselves or people who operate needle exchange programs) and instead was comprised primarily of academics, many of whom have obtained research funding from the National Institute of Drug Abuse and may have been reluctant to criticize the Institute. It was no great surprise, therefore, when the panel found no problems with the study design and recommended that it proceed as approved. To his credit, Dr. Varmus went beyond the blanket endorsement of the panel to require expanded efforts to provide hepatitis B vaccine, but still fell short of offering on-site vaccination, which would be the best way of increasing compliance with the three-injection vaccination regimen. Counseling patients about the hepatitis B vaccine and then sending them elsewhere to receive it not only introduces a delay in receiving the vaccine,

but also conveys the impression that the investigators believe that receiving the vaccine is not urgent.

Astonishingly, this blatantly unethical research proposal passed review at multiple levels:

1. The Institutional Review Board at the University of Alaska Anchorage;
2. The NIH's Office for Protection from Research Risks;
3. The National Institute on Drug Abuse's AIDS Review Committee;
4. The panel convened by Dr. Varmus to review the study;
5. The Advisory Committee to the Director of NIH; and
6. Dr. Varmus himself.

The inadequacy of local Institutional Review Board review merits special mention. As a recent General Accounting Office report concluded, some Boards devote only one to two minutes to each study they review and their independence is hampered by "close collegial ties with researchers at their institution." The Cleveland Plain Dealer recently disclosed that of 942 Food and Drug Administration inspections of Institutional Review Boards between 1990 and 1996, 40% revealed poor or missing voting records, 19% showed missing informed consent forms, injury reports or research protocols, and 16% demonstrated that subjects had not been clearly told that the procedures in the study were experimental. In a shocking 13% of inspections, subjects were not offered proven alternative treatments, similar to the situation here.

At no point in these reviews was the adequacy of informed consent called into question, despite an original informed consent form which failed to disclose the following essential pieces of information:

1. The researchers believe that needle exchange is, in their own words, "a potentially life-saving service";
2. The researchers estimate that injection drug users in the pharmacy group are at up to four times increased risk for hepatitis B compared to the needle exchange group;
3. Drug users who don't sign up for the study cannot attend the needle exchange program;
4. Drug users assigned to the pharmacy condition cannot attend the needle exchange program;
5. Drug users assigned to the pharmacy condition who attempt to obtain syringes at the needle exchange program will be turned away;
6. The syringes at the needle exchange program are free;

7. The needle exchange program, unlike the pharmacy, will provide other free services such as condoms, bleach, alcohol wipes, sterile water and HIV prevention literature;
8. The researchers will be monitoring drug users to see if they develop sometimes fatal hepatitis B infection, even though there is a vaccine that could prevent it; and
9. According to the federal government, providing this vaccine to all susceptible drug injectors is the standard of care.

In addition, a readability analysis of the original informed consent form shows that it required a reading level equivalent to 15 years of schooling, even though Dr. Fisher's own research demonstrates that Anchorage injection drug users read at a 9th grade level. As a result of the enhanced scrutiny this grant has generated, the informed consent form has now been modified from its original two to the present five pages and some, although not all, of our objections have been addressed. But the researchers have introduced, and the University of Alaska Institutional Review Board and the NIH have accepted, a new fiction into the informed consent form: that there is no other needle exchange program in Anchorage. Actually, in an effort to reduce the harm from the Alaska experiment, volunteers in Anchorage have set up a needle exchange open to all injection drug users, a fact that was noted by Dr. Fisher himself in a national magazine and which received front page coverage in the Anchorage Daily News on December 23, 1996 and was featured on an Anchorage television station.

As important as informed consent is in this situation, there is one overriding point: not even a perfect informed consent form can make ethical a study that is unethical in design, particularly one that needlessly puts subjects at risk for fatal infectious diseases. The only ethical solution to the situation in Alaska is to cut off funding for the study until it is redesigned so that all drug injectors have access to the needle exchange program and intensive efforts are made to provide hepatitis B vaccination to all drug users in the study.