

## PERSPECTIVE

### The Ethics of Using Human Volunteers for High-Risk Research

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This issue of *JID* contains an article by Vallbracht et al. [1] on the mechanism of liver cell damage in hepatitis A virus (HAV) infection. This study used an in vitro preparation of HAV-infected fibroblasts derived by liver biopsy performed on two research volunteers. The protocol was reviewed and approved by the Ethics Commission of the University of Tübingen. In a letter to the Editor of *JID*, Dr. Vallbracht explained that the two volunteers were "adults (one physician and one student) who, in full possession of their intellectual capacities, agreed to liver biopsies after detailed discussion, clearly aware of the purely scientific aspect of the investigation. . . . these probands came to the hospital of their own free will for this procedure and therefore were not inpatients put under any type of pressure."

The ethics of research with human subjects rest on two essential imperatives: the free and informed consent of the research subject and the evaluation of risks in relation to benefit to subject and to society [2]. In the USA, Institutional Review Boards (IRB) have been established by federal regulation to ensure that these imperatives are heeded [3]. The IRB reviews research protocols and consent forms to ascertain whether full and accurate information is provided to the subjects, whether any coercive features are present, and whether the risks of the research are justified by the potential benefit to the subject or by the importance of the knowledge to be gained. The IRB must also be satisfied that the protocol is scientifically sound, that is, its methods are designed to yield valid information. It is unjustifiable to invite volunteers to accept risks in a poorly designed study.

The IRB system has been in place since the early 1970s. It seems to be working well and to be acceptable to researchers. Very few cases of abuse of the rights and welfare of human subjects have been

reported since the inception of this system [4]. Many other countries have adopted similar review systems. Whatever the process of surveillance, the twin imperatives of consent and risk-benefit ratio are universally acknowledged.

However, these twin imperatives, while clear as abstract principles, are obscure in practice. The degree of competence required for informed consent, the extent of information that must be provided, and the effective absence of coercion in the research setting are often debatable matters. The risk-benefit ratio is often very difficult to evaluate. One reason why the IRB system was chosen was to ensure that these issues are thoroughly debated. These debates have become common events at IRB meetings and often lead to requests that the researcher more clearly elucidate the purposes of the research, modify the procedures, or, most often, state more explicitly the nature of the risks.

The abuses of human rights and welfare that stimulated the creation of research ethics and the establishment of the review process were primarily events in which advantage was taken of ignorant and captive persons. Ignorant of what was to be done to their bodies and of the effects of these actions and bereft of alternatives or of the ability to refuse, these subjects became almost literal "guinea pigs." Their cages were concentration camps or charity wards or, as in the case of the Tuskegee syphilis studies of the 1930s, their own home county. Whatever the source of their coercion, their bodies were forced to yield information that others deemed interesting or useful.

Today, these abuses seem to have been eliminated. The rights and welfare of human subjects have become firmly situated in the world of biomedical research. Researchers and IRBs do, of course, struggle with the interpretation and application of these imperatives in particular cases, but in general the imperatives are acknowledged and appreciated.

The article by Vallbracht et al. raises a quite different issue for the ethics of research than was raised by the historical abuses: Should risks of a certain

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degree of seriousness never be permitted to be offered to a competent and uncoerced volunteer? This question reveals a fundamental obscurity in the ethics of research: It is far from clear what the relation should be between informed consent and the evaluation of the risk-benefit ratio. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which laid the foundations for the ethics and regulation of research in the USA, approached this problem from time to time but never confronted it [5]. The result is an unresolved ambiguity between two basic philosophical positions about research ethics.

If the basic philosophy behind ethical review of research is to protect vulnerable individuals from being exploited, as they were in the historical abuses, it would seem reasonable that the reviewing body might judge a certain risk to be of unacceptable severity in relation to the prospective benefit or information sought. IRBs could, then, rule out certain risks. If, on the other hand, the philosophy of research ethics rests on the free and informed consent of subjects, it would seem that, once individuals are ascertained to be capable of such consent, any risk, regardless of severity, could be offered. Given this philosophy, it is assumed that there are some individuals who are not vulnerable to exploitation. The primary function of the IRB would be to certify such individuals or to permit the researcher to do so. In effect, American IRBs work between these two philosophies and only rarely encounter a case where their incompatibility is manifested.

There is a paradigm for the unexploitable and invulnerable research subject, namely, the researcher himself or herself. Dr. Larry Altman, medical correspondent of *The New York Times*, recently has written the history of those heroes (or fools) of medical research who used themselves as subjects in highly dangerous experiments [6]. John Hunter, infecting himself with gonococcus in 1767, and Walter Forschman, who performed the first heart catheterization on himself in 1929, are certainly the most celebrated of these autoexperimenters, but there have been thousands in the history of medical research. In such cases of autoexperimentation, it might be surmised that there is no vulnerable subject, since the researcher, who presumably fully knows the risks, and the subject, who accepts them, are the same. In no other case is the identity so close. Yet, we might ask whether we can identify persons who are relatively invulnerable, that is, persons who un-

derstand the risks very well and who are free of coercion. We might then ask whether it is ethical to offer very risky research procedures to such relatively invulnerable volunteers.

In the study by Vallbracht et al., the subjects were both adults. One was a physician, the other was identified as a student (a medical student?). Both were, we can presume, competent to understand the nature of the study and, as Dr. Vallbracht reports, "the purely scientific aspect of the study" (i.e., that participation would bring them no benefit except, possibly, satisfaction from their contribution). They were able to comprehend the information provided in the consent form, namely, that in sonographically monitored punch biopsy of the liver "even bleeding complications are not to be expected under normal blood clotting conditions and should be considered rare. At the worst, uncontrollable bleeding would have to be stopped in surgery."

An attentive IRB might have required different wording of these risks. It might have suggested that the risk of complications be stated as <0.05% and even that death be mentioned as a possible outcome. Still, let us suppose that the two subjects were educated enough to know this, even if it were not stated explicitly on paper. Do these two subjects then fulfill our expectations for the relatively invulnerable volunteer? Should we permit them to consider and take this risk for the sake of "pure science?"

An informal telephone survey of five major research institutions in the USA revealed that four had never been asked to approve liver biopsy in normal subjects and that one had been asked (some 10 years ago) and had approved, considering that the risk was low. That institution's IRB did, however, also approve a payment of \$500 per subject "because the procedure is painful." On the basis of this small sample, it appears that researchers are loath to propose this procedure in their protocols. It is not clear how IRBs would respond to the proposal. (The situation is different, of course, if the biopsy is to be used to screen for hepatotoxicity in a phase-2 drug study; in such cases, there is potential benefit to the subject.)

In our culture, we place high value on the autonomy of the individual. Personal autonomy, interpreted in many different ways, has become the lynchpin of our ethics: The actions of a freely consenting and uncoerced person are right, provided those actions do not infringe upon the free actions of another. We revere the words of the philosopher, John Stuart Mill, who wrote in *On Liberty* (1859):

The only purpose for which power can rightfully be exercised over any member of a civilized community, against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant . . . over himself, over his own body and mind, the individual is sovereign. [7]

We respect the liberty of others, even when we judge their use of it imprudent or rash. We will educate, remonstrate, cajole, but rarely restrain or confine those who are inclined to put themselves at risk. We tend to tolerate the Evel Knievels, of greater or lesser notoriety, unless their daredevil activities put others in harm's way. Certainly, we have been reluctant to repeat the Noble Experiment of Prohibition that aimed to protect persons from their own weaknesses. We have a long history of encouraging persons to volunteer for dangerous activities that might "make the world a better place." Why should we prohibit persons from risking their lives in the cause of science?

Yet, there is something about biomedical research that might make us pause before endorsing a thorough-going liberty to volunteer for the highly risky. Autoexperimenters offer themselves as a testing ground for the soundness of their hypotheses: In a sense, they stake their lives on being right. They have put great personal effort into developing their ideas, and their willingness to risk life and health is a clear manifestation of the seriousness of their beliefs. It is in this sense that we can quite properly speak of martyrs of science. Altman [6] quotes Dr. Leo Alexander, who was the architect of the Nuremberg Code, as saying of autoexperimenters, "it is ethically permissible for an experimenter to perform experiments involving significant risks only . . . if he considers the solution of the problem important enough to risk his own life along with those of his non-scientific colleagues."

The volunteer is in quite a different situation. They are being asked to lend their bodies or parts of their bodies to the researcher. They are being asked to trust that the researcher has a worthwhile idea and that the researcher will carefully use what is being willingly donated. The volunteer will appear momentarily in the research and then disappear; he or she will have no place in the subsequent developments or in the history books. Almost always, the volunteer will be a transitory and partial participant in the research endeavor.

It might be reasonable to consider, then, that while the autoexperimenter should be allowed to take any

risks whatsoever, the volunteer should be invited to undertake only risks proportionate to the transitory and partial nature of his participation. The volunteer lends him- or herself, and loans should be made with a high expectation that they will be repaid in full. Major risks should be reserved for major participants, namely, the research team itself.

Even if we are sceptical of this reasoning and incline to accept the argument that an informed and uncoerced volunteer can be invited to undertake significant risks, the question of the "slippery slope" must be raised. This means that while the index case itself is not ethically objectionable, other cases may depart in significant ways, gradually leading to the introduction of abuses. In the matter under discussion the relatively invulnerable volunteer must meet very high standards of comprehension and freedom. Such a volunteer must almost be as informed and uncoerced as the investigator, but given the rarity of such persons and the dynamism of research, the temptation to compromise these standards would be great. It might not be long before an IRB that was willing to approve offerings of high risk to relatively invulnerable volunteers would find itself wrestling with the perplexing "but how relative?"

Of course, in the study by Vallbracht et al., the researchers might have been ineligible to be the subjects of the biopsy, since HAV-infected tissue was needed (perhaps the physician donor was in fact a member of the research team). It may be asked, however, whether the team did consider themselves as first candidates and inquire whether they themselves were suitable. It might also be debatable whether liver biopsy should be considered a high risk. Many other procedures that are commonly permitted in research protocols might be considered as risky. The low risk of death or other serious complications associated with many medical maneuvers might cast doubt on some interventions we may take for granted.

These are all matters of debate. Still, the principle under consideration is whether certain interventions judged to be of high risk ought to be reserved so that not even the competent and uncoerced volunteer should be invited to undergo them. My inclination, based on the reflections stated in this Perspective, is to answer yes.

This judgment does not, however, amount to a condemnation or censure of the study of Vallbracht et al. or of the approval granted by the Ethics Commission of their institution. The issue is not settled; arguments contrary to mine might be persuasive. I

merely propose that if I were asked to debate a policy about offering high-risk, nonbeneficial research to volunteers, I would start with the position I have sketched here.

#### References

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## Errata

In the May 1989 issue of the *Journal*, Inderlied et al. used the wrong symbols in describing figure 2 (Inderlied CB, Kolonoski PT, Wu M, Young S. In vitro and in vivo activity of azithromycin (CP 62,993) against the *Mycobacterium avium* complex. *J Infect Dis* 1989;159:994-997). The symbols designating treatment and no treatment were transposed; the second sentence of the legend should read as follows:

The level of infection at 1 w, but before the start of therapy (▨); after 4 w without treatment (□); and after 4 w treatment with azithromycin (■).

In the June 1989 issue of the *Journal*, Griswold et al. reported a column of data incorrectly (Griswold WR, Lucas AH, Bastian JF, Garcia G. Functional affinity of antibody to the *Haemophilus influenzae* type b polysaccharide. *J Infect Dis* 1989;159:1083-1087). The last column of table 2 should read (change in bold type):

**Table 2.** Avidity of the Bureau of Biologics reference Hib-PS antibody.

Serum dilution	[AB]	P	Avidity
1:160	0.31	0.15	<b>2.74</b>
1:320	0.155	0.33	<b>1.96</b>
1:640	0.078	0.38	<b>3.14</b>
1:1,280	0.039	0.57	<b>2.90</b>
1:2,560	0.02	0.74	<b>2.63</b>
1:5,120	0.01	0.85	<b>2.65</b>
Mean			<b>2.67</b>
Standard deviation			<b>0.396</b>
Coefficient of variation			<b>14.8%</b>

NOTE. Antibody [AB] is shown in  $\mu\text{g/ml}$ ; avidity is in  $\text{nM}^{-1}$ . P is the fraction of unbound antigen.

This alteration does not alter the authors' conclusions regarding the affinity dependence of the Hib-PS antibody assay or the observed avidity increases seen after immunization of adults with Hib-PS. However, two sentences in the second paragraph of Results (page 1085) should read (changes in bold type):

The avidity of the BOB references serum was **2.67  $\text{nM}^{-1}$**  with a coefficient of variation of **14.8%**. This was **higher than 22 of the 25** samples studied.

In the August 1989 issue of the *Journal*, Jonsen (Jonsen AR. Perspective. The ethics of using human volunteers for high-risk research. *J Infect Dis* 1989;160:205-208) incorrectly reported the first physician to perform a heart catheterization on himself. This person was Werner Forssmann (1904-1979), a Nobel laureate in 1956.

In the September 1989 issue of the *Journal*, Hammerschlag et al. inadvertently omitted the name of one author of their article (Hammerschlag MR, Gershon AA, Steinberg SP, Gelb LD. Herpes zoster in an adult recipient of live attenuated varicella vaccine. *J Infect Dis* 1989;160:535-537). Dr. Lorraine Clarke, Department of Pathology (SUNY), should have been included as the fourth author, as she was responsible for the successful isolation of the virus from the patient.

## Ethical Issues Involving Volunteers in AIDS Vaccine Trials

COLLEAGUES—We welcome articles such as Jonsen's thought-provoking perspective in which he addresses ethical issues related to research with volunteers [1]. We wish to expand his comments based on our experiences recruiting and counseling large numbers of volunteers who participate in experimental vaccine trials, especially trials of AIDS vaccine candidates.

Jonsen properly points out the importance of the risk-benefit ratio when the ethical acceptability of clinical research is determined [1]. When obtaining consent from a volunteer for liver biopsy, for example, the risks and often their incidences can be presented to the potential volunteer [2]. In AIDS vaccine testing, however, the half of the equation dealing with risk is virtually unknown. With AIDS vaccines, we cannot provide convincing animal data about the potential for risks such as vaccine-induced immunotoxicity or antibody-induced enhancement of infection. The lack of suitable animal models for human immunodeficiency virus (HIV)-1 vaccine challenge and the lack of knowledge about the components of a protective immune response make counseling difficult [3, 4].

Testing AIDS vaccines also presents a new type of risk not previously experienced by volunteers participating in research studies, that is, the social risk of developing HIV-1 antibody. The consequences of having such antibody are well known to physicians who counsel HIV-infected patients and include discrimination by health and life insurance companies, the military, and blood banks and possibly difficulties with international travel, housing, and employment. AIDS vaccinees in our trials have also been shunned by coworkers and acquaintances who learn of their participation. For these reasons,

lengthy prevaccination counseling and scrupulous maintenance of volunteer confidentiality have been mandatory in AIDS vaccine trials.

When the risks of participation in a study are unknown but potentially serious, the study must be meticulously designed so that the risks are justified by the likelihood of achieving interpretable results. In AIDS vaccine studies, we are convinced that carefully thought-out, prospective, blinded, controlled studies in which investigators adhere exactly to protocol best assures the lowest risk-benefit ratio.

Contrary to Jonsen's view, we discourage self-experimentation because a nonmeasurable bias is sometimes introduced when the volunteer and the observer are the same individual and if the self-experimenter favors a particular outcome. Second, Jonsen states that studies involving "major risks" should be reserved for the investigators only. We maintain that this doctrine does not apply to AIDS vaccine testing in which we must surely rely on Jonsen's "invulnerable" volunteer, that is, the informed, noncoerced volunteer, to assume the major risks.

Finally, we disagree with Jonsen's comment that volunteers are asked "to lend their bodies to the researcher." In fact, the volunteer lends his or her body to society for the potential advancement of the public health. Thus, one should regard the volunteer as fulfilling his responsibility as a citizen and member of the larger community of man in an unusual but powerful way.

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## Absolute Number versus Percentage of T-Helper Lymphocytes in Human Immunodeficiency Virus Infection

COLLEAGUES—Considerable attention has been focused on the use of absolute numbers of CD4<sup>+</sup>/T-helper lymphocytes in the evaluation and management of patients with human immunodeficiency vi-

rus (HIV) infection. Studies have shown that the risk of progression to AIDS can be directly correlated with the absolute T-helper cell number [1]. Calculation of the absolute T-helper cell number is based on the absolute lymphocyte count, which in turn is dependent on the percentage of total lymphocytes in the total white blood cell count [2].

Patients with HIV infection and their health care providers have become intensely focused on the total T-helper lymphocyte count as a measure of the current clinical state of immune function. Unfortunately, the periodic variability of the total lymphocyte count can result in equal variability in the absolute T-helper lymphocyte count [2, 3]. We and others have suggested that for individual patients the percentage of T-helper lymphocytes may be a less variable, more reliable parameter to follow longitudinally [4, 5]. We recently cared for two patients in whom this point was well demonstrated.

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