

# Virtual Mentor

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### Lessons in dermatology research: protecting vulnerable research participants

by T. Howard Stone, JD, LLM

*“The money was good and the money was easy.” He first tried a deodorant test. He chose the one he thought had the least chance of harming him, and says it was funny watching other prisoners smell his armpits and look for signs of irritation. He was a bit uneasy that the underarm lotion was unlabeled, but the \$25 he received each week smothered his concern. He went on to test hand and body lotions and soon realized the program’s full financial potential. “Three or four tests at a time could mean real easy money. Foot powder tests and deodorants would bring you \$100 per month, and hand creams a buck a day. You could be making \$300 to \$400 a month.”*

Prisoner interview, in Allen M. Hornblum’s “Acres of Skin: Human Experimentation at Holmesburg Prison.” New York, NY: Routledge; 1998:6

### Legacy of early dermatology research

Allen Hornblum’s book, “Acres of Skin,” accented by numerous personal interviews of experiments conducted from the 1950s to the 1970s at Philadelphia’s Holmesburg Prison, is one of the few historical accounts of the extensive and dubious use of prisoners as subjects in dermatology studies of agents used in popular skin care products, some of which—such as Retin-A (tretinoin)—are in wide use today. The lessons learned from Hornblum’s account should resonate any time dermatology research involves people who may be deemed vulnerable as research subjects.

In 1976, profound concerns about prisoners taking part in human research studies—including those testing new dermatology agents or products—were expressed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in its report, *Research Involving Prisoners* [1]. Some of the National Commission’s concerns were based upon findings that money appeared to be a strong motivation for prisoners to take part in the studies. As the result of its deliberations and concerns, the National Commission, which had been charged by the U.S. Congress to study and make recommendations about the protection of human subjects not already subject to federal regulation, advised Congress and the Secretary of the U.S. Department of Health, Education and Welfare (predecessor to HHS) that research involving prisoners as subjects should be significantly restricted. These recommendations, adopted in federal regulations and still in effect today, essentially prohibit investigators from using prisoners in the types of dermatology

research that so commonly relied upon them in the past [2]. Other federal, state and local agencies—even some that may not be subject to the federal regulations referred to above—as well as some of the most prominent professional associations with interests in prisoners, also specifically prohibit the use of prisoners as subjects in such research [3]. For example, under federal regulations pertaining to the U.S. Department of Justice Bureau of Prisons, research projects “must not involve medical experimentation, cosmetic research, or pharmaceutical testing” [4]. Laws and standards such as these could reasonably be interpreted to prohibit dermatology research that uses prisoners as research subjects.

The legacy of the early dermatology studies in prisons has important implications for today’s medical student interested in a dermatology research career. For one, any research on prisoners may be subject to intense scrutiny, given the highly regulated environment and historic concern about studies that involve these populations. Second, people who are similarly situated to prisoners may be no less vulnerable as subjects in dermatology research, particularly when it comes to understanding their participation in research and their risk versus reward.

### **Lessons for dermatology research**

Investigators should be aware of the multitude of federal and state regulations as well as professional standards that will be invoked if they choose to include prisoners as subjects of research. The most recognized federal regulation, which includes what is called the Common Rule and Subpart C and applies specifically to prisoners [5], is just the beginning. Investigators should note that Subpart C of the federal regulation is essentially an embodiment of many—although not all—of the ethical issues considered by the National Commission. Other federal regulations, including those promulgated by other federal agencies such as the FDA and the Department of Justice, must also be considered, as should the laws of the states where research may take place. In studies conducted across multiple sites, the laws of two or more states may apply. Investigators may also be required to demonstrate that their research adheres to professional standards or other general ethical guidelines, such as the World Medical Association’s Declaration of Helsinki—a requirement for studies published in the *Journal of Investigative Dermatology* [6]. Ethical guidelines such as the Declaration of Helsinki are particularly sensitive to protecting persons who may consent under duress to taking part in research, a concern which intuitively would have special application to prisoners as research subjects [7].

Dermatology research now spans a vast field of scientific inquiry—from molecular genetic studies of carcinomas to clinical trials involving eczema—that requires increasing numbers of patients with specified medical conditions to serve as research subjects. And like prisoners generally, prospective subjects in dermatology studies may be disadvantaged as the result of their socioeconomic status and may lack the educational or literacy skills sufficient to provide properly informed consent for taking part in research. As the risk or complexity of dermatology research increases, the need to protect such disadvantaged subjects becomes more pronounced.

For example, the lure of obtaining cash or similar pecuniary benefits was considered by the National Commission as the “overriding motivation” among prisoners for taking part as subjects in research [8]. Current federal regulations impose almost no substantive restrictions upon providing nonprisoner subjects with such benefits, other than to require that research review boards insist upon “additional safeguards” if some or all of the subjects are “likely to be vulnerable to...undue influence.” The National Commission defined “undue influence” in its Belmont Report as “an offer of an excessive, unwarranted, inappropriate or improper reward or other overture...” [9]. Often economic disadvantage is viewed as rendering a prospective subject “vulnerable to undue influence.” Payment for taking part in dermatology research is not uncommon and may range from one-time payments of \$25 for a single visit to payments of \$400 or more for repeat visits in research on topical creams for psoriasis, for example, Phase III research on investigational drugs for severe chronic plaque psoriasis, or research on atopic dermatitis [10]. If federal regulatory provisions and the underlying ethical principles pertaining to the protection of economically vulnerable subjects are to have meaning, investigators may want to consider examining the possible influence that such payments may have upon subjects’ motivation for volunteering as research subjects.

Prospective subjects in dermatology research who are educationally disadvantaged may also be vulnerable. Often, as was the case for many prisoners in early dermatology research, economic disadvantage is concurrent with educational disadvantage, which compounds the vulnerability of research subjects. It can diminish a person’s ability to fully understand and appreciate his or her participation in research—particularly research risk—which may in turn undermine informed consent. Educational disadvantage among prospective research subjects also has profound consequences for investigators. It may jeopardize a subject’s ability to adhere to a research protocol, with obvious consequences for effect size, adverse events and study results. Complex or cutting-edge dermatology research raises the stakes even higher. For example, genetic research examining familial or hereditary risk for psoriasis or melanoma is now under way at dermatology research centers across the U.S. The collection of genetic samples for such studies raises a host of ethical and social issues, and an understanding of both the research and the related ethical and social issues may be especially challenging for an educationally disadvantaged person. In studies such as these, ascertaining subjects’ knowledge of basic genetic concepts, including heredity and genetic predisposition, may be one of several prerequisites for informed consent. Other prerequisites may be addressing the possibility that subjects think their own risk for disease, such as melanoma, will be definitively ascertained by taking part in genetic research and establishing whether investigators will share genetic test results or findings with subjects.

As a threshold matter in designing and implementing their research, dermatology investigators should always consider the likelihood that their studies will attract disadvantaged persons, the explanations for that attraction, the impact that the recruitment of disadvantaged persons may have on obtaining effective informed consent, and the steps that might be taken to protect disadvantaged research subjects.

Some useful preliminary steps might include examining whether disadvantaged persons believe that taking part in a study will improve or guarantee access to treatment, whether the studies are actually being confused with treatment and whether recruitment takes place in predominantly disadvantaged communities. Equally important is the effect of payment upon subjects' decision to volunteer. As stated in the 1979 Belmont Report, "the economically disadvantaged" should be protected against the danger of participating in research "because they are easy to manipulate as a result of their illness or socioeconomic condition" [11]. Protecting human subjects should be the primary concern of every investigator. However, in light of the dubious history of dermatology research involving prisoners, special precaution in research involving all vulnerable persons as research subjects is well-advised.

### Notes and references

1. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Research Involving Prisoners: Report and Recommendations*. Washington, DC:US Department of Health, Education and Welfare: Washington, DC. 1976. Publication No. OS 76-131; Available at [http://www.bioethics.gov/reports/past\\_commissions/Research\\_involving\\_prisoners.pdf](http://www.bioethics.gov/reports/past_commissions/Research_involving_prisoners.pdf) Accessed June 29, 2006.
2. 45 *Federal Register* 301-306 (2006) (codified at 45 CFR §46). Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects.
3. See 28 *Federal Register* 512 (2006) (codified at 28 CFR §512). Michigan Administrative Code R791.733 (2006); American Correctional Association. *Standard 1-HC-3A-09. Research. Performance-Based Standards for Correctional Health Care in Adult Correctional Institutions*. Lanham, Md: American Correctional Association; 2002; National Commission on Correctional Health Care. *Standard P-I-07. Medical and Other Research. Standards for Health Services in Prisons*. Chicago, Illinois; National Commission on Correctional Health Care: 2003.
4. 28 *Federal Register* 512.11(a)(3) (2006).
5. 45 *Federal Register* 46.101-409 (2006) includes the Common Rule as well as Subpart C, in addition to other subparts pertaining to children, pregnant women, human fetuses and neonates.
6. *Journal of Investigative Dermatology. Instructions to Authors. 2006*. Available at: [http://www.nature.com/jid/author\\_instructions.html](http://www.nature.com/jid/author_instructions.html). Accessed June 21, 2006.
7. World Medical Association. *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. Available at: <http://www.wma.net/e/policy/b3.htm> Accessed June 23, 2006. Section 23 of the Declaration states that "when obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or *may consent under duress*." (Italics added).
8. National Commission, 35.
9. 45 *Federal Register* 46.111(b) (2006); National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research*.

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10. The Thompson Corporation. *Trial Information Summary: Psoriasis Research Study*. Available at: <http://www.centerwatch.com/patient/studies/stu87119.html>. Accessed June 21, 2006.

11. *The Belmont Report*, 19-20.

*T. Howard Stone, JD, LLM, is associate professor of bioethics in the Center for Biomedical Research at the University of Texas Health Center at Tyler. He serves on the university's institutional ethics committee, is co-director of the Geriatrics Program for Research and principal investigator for the Cardiovascular Disease Research Ethics (CADRE) Program.*

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