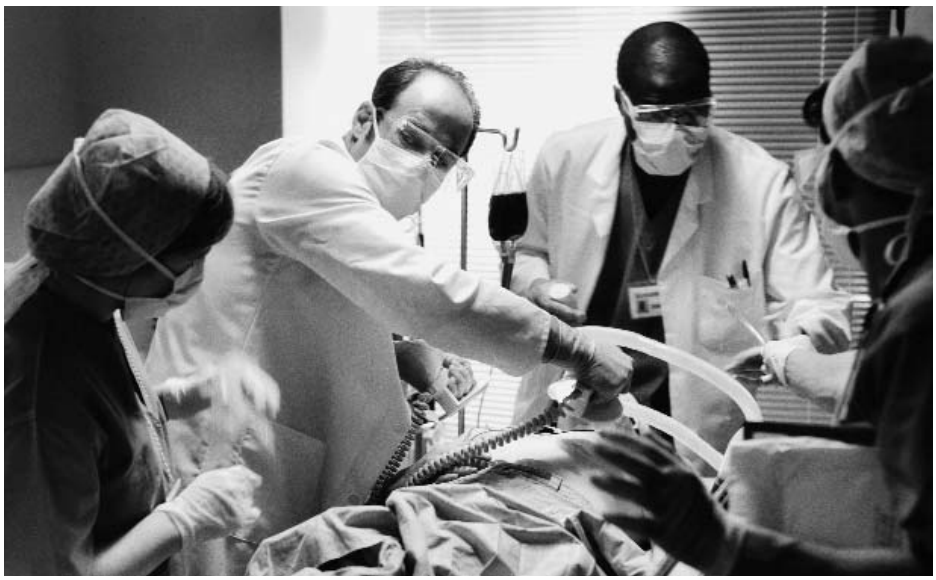
Bioethics in brief
December 2006
UNIVERSITY HOSPITAL OF SUNY UPSTATE MEDICAL UNIVERSITY SYRACUSE, NEW YORK

Informed Consent Unnecessary in Blood Substitute Study



THE CASE

An Emergency Nurse in a teaching hospital with a Level I Trauma Center attends an in-service entitled "Updates in ED Treatment Protocols." At the in-service, she is told that the hospital is participating in a multi-institutional study of PolyHeme, a blood substitute developed to save the lives of patients needing blood but for whom blood is not available.

She asks where she can find the consent forms for the study and is told that, as this is a study of critically ill trauma patients who are generally unable to give consent, a federal law says that consent is not necessary. The ED director explains that the study was approved by both the FDA and the hospital's institutional review board (IRB).

According to the terms of the study, trauma patients will arrive at the ER already assigned to the conventional treatment arm (intravenous fluids in the field, followed by blood transfusions in the hospital as needed) or to the experimental arm (PolyHeme in the field, to be continued for the first 12 hours in the hospital as needed). The nurse is concerned about hanging PolyHeme in the ED for patients who haven't consented, particularly when real blood is easily available and is the standard of care. When she raises the question, she is again assured that the IRB has approved the study.

Do her concerns have merit?

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Visiting the Tissue Issue

Suppose you had given consent for tissues from your body to be used for cancer research. The researcher, also your trusted physician, moves from your local academic medical center to one in another state. What should happen to the research samples? Do they belong to the researcher, to your local institution, or to the researcher's new academic home? Do they belong to you, the patient and research participant? Can you decide what happens to the bodily tissues you have already given?

DOES CONSENT TRUMP OWNERSHIP?

In the first case to address this quandary, *Washington University v. Catalona,* No. 4:03CV1065SNL (E.D. Mo., 2006), a former chief of the urology division at Washington University, St. Louis, accepted a new position at Northwestern University where he sought to continue his prostate cancer research. Several days prior to Dr. Catalona's departure from Washington University, he sent research participants a letter and consent form requesting permission to continue his research with their donated samples at Northwestern. Approximately 6000 participants returned the form giving their consent. Washington University did not release the samples. Instead it filed suit for a declaration of its rights of ownership. The federal court for the Eastern

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Bioethics *in brief*
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Bioethics in Brief is a newsletter of the Center for Bioethics and Humanities, in cooperation with University Hospital's Ethics Committee.

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Have a question about an ethical issue?
We are always happy to talk in confidence about ethical concerns; you may reach us at the Center for Bioethics and Humanities at 464-5404. Ethics consultations are available by calling the hospital operator (464-5540) and asking for the ethics consultant on call, or by contacting any of the ethics consultants at the center (Robert Daly MD; James Dwyer PhD; Kathy Faber-Langendoen MD; Robert S. Olick JD, PhD; and Joel Potash MD).

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The Center for Bioethics and Humanities at SUNY Upstate Medical University, established through the generous support of the Medical Alumni Association, is committed to promoting clinical health care and health policy which is patient-centered, compassionate, and just. We accomplish this through educational initiatives in bioethics and the medical humanities, clinical ethics consultation, and multidisciplinary research and scholarly writing.

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Research Ownership

District of Missouri ruled that the samples were the property of Washington University where the research began.

ROLE OF RESEARCH SUPPORT

The court's decision offers a careful reading of the informed consent documents and of institutional policy and practice regarding establishment and operation of the university's tissue repository. The consent forms characterized research participants as "donors" of their blood, tissues and DNA, and stated that they could not "claim ownership rights" in the products of the research. Pursuant to school policy, intellectual property was owned by the university if (as here) the university provided significant resources to support the research. And a materials transfer agreement (MTA) was required for Dr. Catalona to use research samples elsewhere. An MTA clearly stating that the materials were property of the university had been signed on 7 prior occasions by Dr. Catalona, but not this time. Collectively the consent documents and institutional policies favored Washington University's position. But ultimately the decision required resolution of a narrow and uncharted question: Does the right to withdraw from participation in research encompass the right to return of one's tissue sample and/or the right to transfer one's sample to another researcher or research institution?

INDIVIDUAL RIGHTS DEBATED

Federal regulations governing human subjects research establish a right to withdraw (to discontinue), commonly interpreted to mean the participant may request that his/her samples be destroyed. Adopting this view, the consent forms and explanatory brochure stated that participants could withdraw from the research and request destruction of their samples, but that "results already obtained could not be destroyed or recalled." The question whether the right to withdraw included the right to repossess or transfer one's blood or tissues was not expressly addressed, nor is it resolved by the federal regulations.

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Research Ownership

The court found that no rights of repossession or transfer existed. Research participants had voluntarily donated their samples to the university – not specifically to Dr. Catalona. Moreover, once it had taken possession of the research material the university also assumed all legal responsibility for its storage, use, custody and control. This transfer of ownership rights was complete, except for its reservation to participants of the right to request destruction of their samples consistent with the federal regulations. The decision relies in part on interpretation of Missouri law and of two previous cases (from California and Florida) that severely limited property and ownership rights of individuals who voluntarily give their blood and tissue for research. To the research community this may be a welcome development; to others the case may be a setback for individual rights to control the terms of research participation. Stay tuned for more in this slowly emerging and controversial debate over ownership of tissue samples.

—Robert Olick

World AIDS Day 2006

On December 1, millions of people across the globe marked World AIDS Day. The commemorative day was established by the World Health Organization in 1988 to focus attention on the HIV/AIDS epidemic. Since 1981, more than 25 million people have died of AIDS, and approximately 40 million people worldwide are infected. Health officials in the United States estimate that 1.1 million Americans are HIV-positive, and 25% of them don't know it. Each year, another 40,000 Americans become infected. New York State leads the nation in HIV/AIDS cases, with 7,600 new cases diagnosed in 2004, including 46 in Onondaga County.

FDA Approves HPV Vaccine

Human papilloma virus (HPV), a sexually transmitted disease, may show no symptoms, but it can be deadly; it can cause genital warts and cervical cancer. In June 2006, the Food and Drug Administration marked a public health achievement when it licensed a vaccine against the disease. So far, the vaccine is approved only for females between the ages of 9 and 26.

But some people aren't pleased with the vaccine. Pro-abstinence groups argue it will encourage promiscuous behavior. Others question whether it makes sense to vaccinate adolescents, who are generally sexually inactive, against a sexually transmitted disease. But to vaccine supporters, that's precisely the point. The vaccine is only effective if it's given prior to infection. Once the virus is caught, it cannot be cured, although the body may clear it on its own. State health departments are currently deciding whether the vaccine should be mandatory.

The vaccine, called Gardasil, protects women against the four most virulent strains of HPV: types 6 and 11, which cause 90 percent of genital warts, and types 16 and 18, which cause 70 percent of cervical cancers. According to the CDC and the American Cancer Society, cervical cancer is the No. 2 cancer killer in women, accounting for 3,700 deaths and 9,710 new cases each year. HPV infects 20 million Americans, with 6.2 million cases added annually. More than half of all sexually active men and women will have HPV at some point in their lives.

Some opponents of the vaccine argue that Pap tests, which provide early warnings against cervical cancer, obviate the need for a HPV vaccine. But health departments disagree, noting that the vaccination will reduce abnormal Pap test results as well as the incidence of cervical cancer. Health officials recommend that vaccinated women continue to receive regular Pap tests to protect against HPV strains not covered by the vaccine.

As a recombinant vaccine, Gardasil contains no live virus. Some people have reported local irritation and slight fever after receiving the vaccine. Both private insurance companies and government programs are expected to cover the cost of Gardasil, which stands at $360 for three sequential shots taken over a six-month period. At least one state, New Hampshire, is offering Gardasil free of charge to all girls between the ages of 11 and 18.

—Eli Braun

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Blood Substitute

BACKGROUND ON THE POLYHEME STUDY

In many car accidents, injured drivers and passengers become patients. In the PolyHeme study, they became research subjects too. According to the NIH Clinical Trials website, the PolyHeme study was "designed to assess the survival benefit of administrating PolyHeme to severely injured trauma patients in hemorrhagic shock." The study, which concluded in July 2006, enrolled 720 patients in 18 states. Half received PolyHeme while the other half received saline solution in the ambulance and donor blood at the hospital. University Hospital did not participate.

The blood substitute has several advantages over real blood: it reduces the risk of transmitting hepatitis or HIV, eliminates blood typing, doesn't need to be refrigerated, and lasts a year or more, far longer than the 42-day shelf life of donated blood. Medics could use artificial blood to treat accident victims on the scene, where blood is not available, or injured soldiers on the battlefield who might otherwise die. But artificial blood poses several risks. In a 2001 study, 10 of 81 patients receiving PolyHeme suffered heart attacks, resulting in two deaths, compared to none of the 71 patients receiving blood. In addition, PolyHeme can raise blood pressure to dangerous levels.

The PolyHeme study was approved under a controversial FDA rule that waives the requirement for informed consent in life-threatening situations when informed consent is not feasible and when proven, effective treatments are not available. If potential patients did not want to participate in the study, they had to write to Northfield Laboratories, the developer of PolyHeme, and request a light-blue "exclusion bracelet" to be worn at all times. Ordinarily, patients opt-in to research studies. For the PolyHeme study, they had to opt-out.

INFORMED CONSENT IN EMERGENCY SITUATIONS

As the nurse suspects, the study raises ethical questions concerning informed consent in emergency situations. "If you're in a car accident, of course you want emergency doctors to save your life," said U.S. Senator Chuck Grassley. "But no reasonable person would expect to be treated as an experimental subject without consent." He charged that the trial made "every citizen in the United States a potential 'guinea pig,' without providing a practical, informative warning to the public."

For an accident victim at the scene, artificial blood may prove to be more effective than saline, the current standard of care on ambulances. At the hospital, however, there is an available and effective treatment: real blood. Bioethicists have held that the in-hospital stage of the study failed to meet ethical standards for the protection of human subjects. It mandated an experimental treatment in lieu of a proven one when the patient could not consent. By this view, the study should not have applied the FDA emergency waiver of consent to the in-hospital comparison of PolyHeme and blood.

CAN THE COMMUNITY CONSENT?

There is good reason to question the extent of public disclosure. As part of its approval of the study, the FDA required Northfield Laboratories and hospital IRBs to inform local communities through gatherings at churches, city halls, and other venues. But it remains unclear what community outreach entails. Should it matter that few people attended these meetings? Is there a threshold at which one can say that the "community" consented? In addition, the meetings may not have disclosed the adverse effects of the 2001 study. For example, the materials for community meetings from the Brooke Army Medical Center near San Antonio claimed that "PolyHeme has demonstrated no clinically relevant adverse effects." If study administrators suppressed key information from potential patients, consent cannot possibly be informed.

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Blood Substitute

BALANCING PATIENT CARE AND MEDICAL SCIENCE

The nurse is rightly concerned about her patient. Her primary duty is to provide patients with the standard of care, not to develop a blood substitute. Yet the PolyHeme study complicates her role by putting patient care in the context of a clinical trial. In such cases, how should nurses and physician-researchers navigate their dual and conflicting roles? As caregivers, they are devoted to the care of their individual patients, but as researchers they aspire to improve clinical practice through innovation.

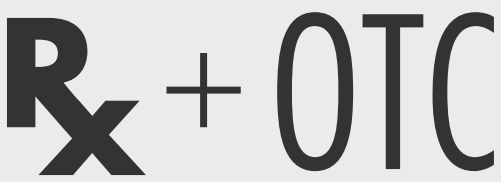
The nurse has been told that both the FDA and the hospital's oversight committee have approved the study. In every hospital, an IRB reviews clinical research protocols for the protection of human subjects. The IRB serves to mediate potential conflicts between the best interests of the individual patient and the scientific interest in developing new therapies. In this study, the IRB was responsible for ensuring that the local community understands that incapacitated trauma victims can be enrolled without their explicit consent and that anyone who objects can wear an exclusion bracelet.

The nurse appropriately raised her concerns with the ED director. She could also contact the IRB itself, which could explain its review process and the FDA regulations. Of interest, at least nine of the 31 participating medical centers dropped out after IRB re-evaluation. She could also call the hospital's ethics consult service, which could help her sort through her obligations.

—Eli Braun and K. Faber-Langendoen

Plan B

In late August, the Food and Drug Administration announced approval for the contraceptive drug known as Plan B to be marketed and sold over the counter (OTC) to women aged eighteen and older. A prescription will still be required for those seventeen and under. The drug has been available with a doctor's prescription since 1999. Because it is a backup method of birth control, an emergency contraceptive that prevents pregnancy, it has been controversial. In particular, certain groups have objected to giving minors easy access to these drugs, bypassing both parental and medical input. The FDA created two joint advisory committees and allowed an extensive period for public comment before issuing its decision. The FDA actually went against its own committees' recommendations in deciding to create the two categories of procurement.



Plan B is a synthetic hormone and comes in the form of two levonorgestrel pills that are taken by mouth after unprotected sex. It stops the release of an egg from the ovary and may prevent the union of sperm and egg. If fertilization has occurred, Plan B may prevent the egg from attaching itself to the womb. Plan B does not work if the fertilized egg has already implanted itself.

Another intriguing aspect of Plan B is that it will be marketed by Duramed for both kinds of consumers, those who can purchase it OTC and those who cannot. The FDA has also said that Duramed is responsible for creating a "rigorous labeling, packaging, education, distribution and monitoring program" to insure that the drug is sold properly.

—Deirdre Neilen

Should Prisoners Be Allowed To Participate In Medical Research?

Until the mid-1970s prisoners in the United States bore more of the burden of research than the general population. In return for their participation in research, prisoners sometimes received payment, special treatment, or special consideration at the time of parole hearings. In the 1700s, for example, prisoners willing to be exposed to smallpox inoculation could avoid hanging. Some prisoners participated in research in hopes of benefiting society.

In the 1950s and 1960s, prisoners at Holmesburg Prison in Philadelphia volunteered to have their skin injected with herpes, chickenpox and wart viruses, yeast, and staphyloccus bacteria; some had their skin tested with cosmetics, radiation, extreme temperatures, and even dioxin (Agent Orange) under the supervision of a University of Pennsylvania dermatologist. Some of the prisoners at Holmesburg developed severe skin disease (chloracne) which lasted for 4-7 months and was not treated. Record-keeping was inadequate so when prisoners later filed complaints they were unable to be verified. Congress began investigating research experiments involving prisoners in the early 1970s, a result of Jessica Mitford's expose, *Kind and Unusual Punishment*. In October 2000, 300 of the Holmesburg prisoners tried to sue in a class action suit, but the statute of limitations had expired.

In 1976, federal regulations established protections for prisoners who take part in research. These protections were further defined by 1981's Common Rule. It was recognized that most prisoners have limited autonomy (they "don't have the key to their own room"), lack privacy, and may not have access to standard health care, so choices to participate in research were subject to coercion, harms that outweighed potential benefits, and might even represent attempts of prisoners just to get access to medical treatments. As a result, research projects involving prisoners were severely curtailed. For the most part research in prisons was stopped or limited to protocols that were considered minimally harmful.

Now, the topic has been raised again for consideration by the Institute of Medicine (IOM) in a 2006 report entitled "Ethical Considerations for Research Involving Prisoners." The IOM report states that research involving prisoners may improve the health of prisoners and the conditions in which they live. The IOM recommends that such research should only be undertaken if it offers a clearly favorable benefit over harm to the prisoner, and not just because prisoners are such a convenient source of subjects. The report (available at http:/www.nap.edu) made five recommendations regarding research involving prisoners:

1) **The definition of prisoners** should include not only the 2.1 million persons in prisons and jails, but also the 4.9 million on parole or probation, because all prisoners have their liberty restricted and need similar protections.

2) **Currently only research funded by 3 federal agencies is regulated.** All human subjects research, regardless of funding source, should follow the same ethical standards, and should be part of a publicly accessible federal register, so that the benefits and burden of research on prisoners could be determined.

3) **A risk-benefit approach should apply. All research should offer potential benefits** to prisoners themselves which outweigh potential harms, and the ratio of prisoners to non-prisoners in the study should not exceed 50 %. Studies with no benefits to the prisoners involved would be precluded, unless there might be benefits to prisoners as a class and low risk of harm.

4) In addition to respect for the prisoners and justice, **there should be collaborative authority,** including input from prisoners, prison staff and administration.

5) **Voluntary informed consent must be obtained and privacy respected.** All research must be monitored by an independent prison research subject advocate familiar with the particular correctional site. There should be consistent monitoring and oversight of all research whether federally or privately funded.

Some people find the IOM's recommendations alarming, a return to past practices which placed vulnerable subjects at the mercy of those in authority. Paul Wright

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Prisoners

who edits *Prison Legal News*, an independent monthly review, was quoted in the *New York Times* as being skeptical of the underlying motives for the IOM's recommendations: "It strikes me as pretty ridiculous to start talking about prisoners getting access to cutting-edge research and medications when they can't even get penicillin and high-blood-pressure pills." Other critics have noted that this report conveniently appeared when the need for more biomedical research subjects has increased. The Alliance for Human Research Protection in Philadelphia reminded readers that problems with Vioxx and Bextra research occurred because early testing did not include large enough numbers of patients. They point out that the prison population has been increasing dramatically, perhaps providing the biomedical industry with what it sees as a good solution to its problem.

Prisoners should not become subjects of medical research merely because of ease of access to them. Perhaps a minimal requirement for medical research in a prison would be the availability of adequate health care to all prisoners in that prison. Next, proposed research should offer the potential of benefit to the prisoner or prisoners as a class. Finally, prisoners should have a way to have any harms resulting from research redressed. Although a prisoner may be truly altruistic or even consider participation in research as a form of penitence, the risks to prisoners are too great to proceed without extreme caution.

—Joel Potash

Nurses Caring for Prisoner Patients in the Acute Care Setting

Across the United States, approximately two million people are being detained in prisons, and the total number is increasing each year. As the population of females rises, so does the demand for women's services. Many people don't realize that prisoners are entitled by law to have access to health care, and indeed, statistics show that an imprisoned individual has an even greater chance than the average citizen of needing health care services that might include hospitalization. Thus, nurses employed in a hospital or any other type of healthcare facility may come into contact with patients who have been either accused or convicted of a crime.

The ethical principle that underlies all nursing practice is respect for the worth and dignity of each patient. During the hospitalization of any patient, the nurse must not only respect that patient, but also maintain confidentiality, respect autonomy, and adhere to other tenets of the professional code of ethics. Nurses may find these standards more difficult to uphold when the patient is also a prisoner. Prisoners have lost their personal freedom; someone else has the final say about their daily activities and schedules. The precept that every patient who has decision-making capacity can choose for him/herself in matters affecting health and well being is difficult to maintain in the case of one who is a prisoner. Similarly, the trust component, so basic to the nursing-patient relationship, is often compromised, because patients are sometimes suspected of malingering or lying about pain or symptoms in order to avoid returning to prison. Furthermore, prisoners are brought to the health care setting by guards who may consciously or unconsciously attempt to influence the nurses' attitudes towards the prisoners.

The goal of health care is to diagnose, comfort, and cure individuals, while the goal of the penal system is to confine and punish individuals who have committed a crime. Because respect for patients and regard for their well being are at the core of nursing ethics, and because trust and advocacy for the best interests of the patient are the cornerstone of nursing care, these values come into conflict with the intentions of those charged with the supervision of prisoners who are also patients.

Nurses caring for prisoners sometimes find their loyalties and ethics questioned as they attempt to fulfill their professional responsibilities. They must strive to remember their focus is on the patient and on being the patient's advocate in all medical matters; they should refuse to engage in any conversations that threaten the patient's right to confidentiality or undermine his/her dignity.

—Barb Fero

A new feature of this newsletter offers excerpts from Upstate's latest issue of *The Healing Muse, a Journal of Literary and Visual Arts* published by the Center for Bioethics and Humanities. These pieces speak to the ongoing and dynamic relationship between medicine and ethics. Below, Veneta Masson, a nurse and poet in Washington, DC, asks us to think about what we offer patients and what they are hoping to receive from us.

Gold Standard

— Veneta Masson

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somewhere. Precious few will reveal
the only thing they know for sure—
that there is no Fort Knox,
only an Oz where wizards
come and go.

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I've proffered through the years—
the abandoned theories,
discredited pills and procedures,
unsubstantiated advice—
all of it gold standard,
I make my confession
and offer this prayer
to the God of Unknowing,
Lord, make me your placebo,
a humble purveyor
of sensible care,
a healer who never fails,
at least, to give a damn.

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