

is guided by rigorously obtained, verifiable data.

Dr. Snyder reports having received consulting fees or grant support from Chemicon, Hospira, Genzyme, and GMP and owning equity in RxGen and Saneron. He holds four patents related to engraftable human neural stem cells and for methods, compositions, and kits for promoting recovery from damage to the central nervous system. Dr. Loring reports having received consulting or lecture fees from Cybios, Cell Biosciences, IBC, ABI, CHI, and Lexicon, as well as owning equity in Cybios and Cell Biosciences.

An interview with Dr. Snyder can be heard at [www.nejm.org](http://www.nejm.org).

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## Egg Donation and Human Embryonic Stem-Cell Research

Robert Steinbrook, M.D.

In November 2005, Woo Suk Hwang, the leader of a South Korean team conducting stem-cell research, touched off an international uproar when he admitted that he had used oocytes from junior scientists in his laboratory as well as from paid donors and that he had lied about the circumstances under which the oocytes had been obtained. Subsequent questions about fraud in the underlying science mushroomed into scandal. As of mid-January, the group's 2005 report about the derivation of patient-specific embryonic stem cells from human blastocysts created by somatic-cell nuclear transfer<sup>1</sup> was being retracted, as was its 2004 report in *Science* of the derivation of a stem-cell line from a cloned blastocyst. With the research discredited as fabrication, many of the donated eggs were effectively wasted. This represented a betrayal of the trust between scientists and research subjects. Ongoing inquiries in South Korea suggest that dozens more donors — and hundreds more eggs — were used than were reported. A Seoul National University committee found that between November 2002 and November 2005 Hwang

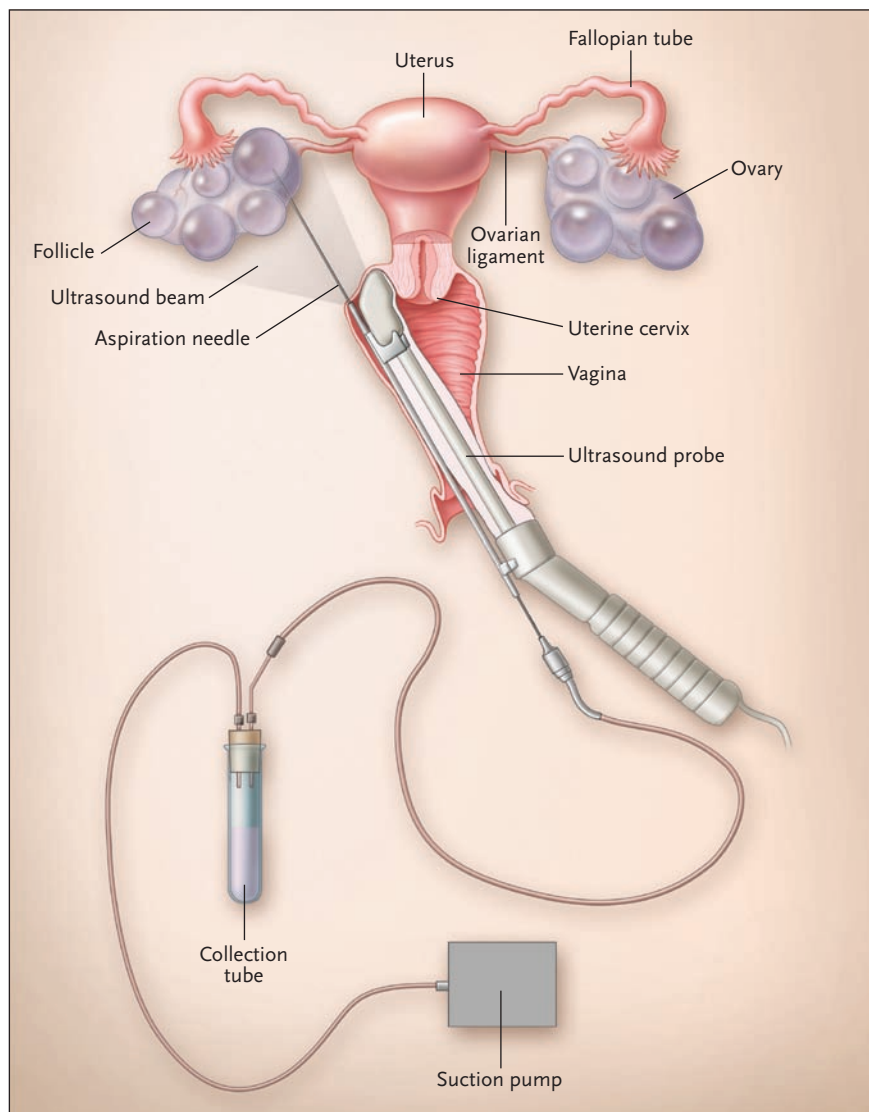
worked with 2061 eggs from 129 women.

Among other things, the debacle in South Korea has focused renewed attention on oocyte donation. Donating eggs is time-consuming, uncomfortable, and potentially risky, but without willing donors, there will be less research on human embryonic stem cells. There is concern that some potential donors are not fully informed about what they are getting into — and fewer might volunteer if they understood the downside. Some observers consider it wrong to pay donors; others consider it the only fair thing to do.

Oocytes are usually donated for reproductive purposes, not for research. According to the Centers for Disease Control and Prevention, donor eggs were used in 13,183 (11.4 percent) of the 115,392 procedures involving assisted reproductive technology that were started in the United States in 2002. Women are routinely paid \$4,000 to \$5,000 per cycle and in some cases considerably more.<sup>2</sup> In other nations, such as Canada and the United Kingdom, such payments are banned (although reasonable expenses can be reimbursed).

Protocols for stimulating the development of multiple ovarian follicles typically involve daily subcutaneous hormone injections over a period of 7 to 10 days. Mature oocytes are retrieved under ultrasound guidance by the insertion of a needle through the vagina in a brief surgical procedure that requires anesthesia (see diagram). The ethics committee of the American Society for Reproductive Medicine cites an estimate that egg donors spend “56 hours in the medical setting, undergoing interviews, counseling, and medical procedures related to the process.”<sup>2</sup>

The injections are uncomfortable and have side effects. The retrieval of oocytes carries risks, such as those of anesthesia and bleeding. Another important risk associated with the procedure is the development of the ovarian hyperstimulation syndrome. This syndrome represents an exaggerated and usually unpredictable response to ovulation-induction therapy, in which capillary permeability is increased and fluid is shifted from the intravascular space to third-space compartments. In severe cases, hospitalization is required, and complications such as ascites,



#### Retrieval of Oocytes.

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pleural and pericardial effusions, and venous thromboembolism may develop.<sup>3</sup> There is some concern that women who undergo multiple cycles of hormonal stimulation may increase their risk of having ovarian cancer later in life. This concern is based on data from research in animals; there have been no conclusive studies in humans.

In the United States, oocytes are infrequently used for basic research in reproductive biology.

However, there is interest in using eggs for somatic-cell nuclear transfer, despite the uncertainty about the technology, as discussed elsewhere in this issue of the *Journal* by Snyder and Loring (pages 321–324). This method of creating embryonic stem-cell lines involves the insertion of the nucleus from a fully differentiated somatic cell into a fresh oocyte from which the nucleus has been removed. Somatic-cell nuclear transfer could lead

to models of disease as well as patient-specific therapies — although both types of application remain hypothetical.<sup>4</sup> Research is also being conducted on parthenogenesis in the hope of creating suitable stem-cell lines from unfertilized eggs.

Research subjects frequently accept risks in order to benefit others, without any chance of benefiting themselves.<sup>4</sup> There is general agreement that laboratory workers should not be egg donors, because their position as subordinates makes it impossible for their donations to be considered fully voluntary. There is also little support for oocyte sharing, in which a woman who is undergoing ovarian stimulation for her own reproductive purposes would be charged a lower fee if she donated some of her eggs to another woman or for use in research. Among the objections are that this approach mixes infertility treatment with research and that it may reduce the donor's chances of becoming pregnant, particularly if few oocytes are produced.

Compensation for egg donation is a particularly contentious issue. In the United States, men are usually compensated for sperm donations, and research subjects are usually compensated when they undergo invasive procedures, such as bronchoscopy or endoscopy. It is inconsistent to compensate subjects for undergoing certain invasive procedures but not others or to allow compensation for egg donation for reproductive purposes but not for research. Moreover, whereas the National Organ Transplant Act of 1984 prohibits the transfer “of any human organ for valuable consideration for use in a human transplantation if the transfer affects interstate commerce,” federal law neither bans nor directly regulates payments

for gametes and embryos. A related issue is that although the commercial potential of stem-cell research is huge, research subjects have no ownership rights in the technology and will not share the financial or other benefits.

Some bioethicists argue that egg donors should be compensated — on the basis of the time and discomfort associated with the process, not the number and quality of the eggs that are produced. According to Bonnie Steinbock, a professor of philosophy at the State University of New York at Albany who has studied egg donation, in the absence of a consensus that no egg donor should be compensated, payment for donations for research is ethically acceptable.<sup>5</sup> In an interview, Steinbock explained: “Any time that we ask people to do things that impose significant burdens and some degree of risk, fairness may require that they be adequately compensated. At the same time, there’s a general consensus that it would be improper to offer enormous sums of money to egg donors that could sway their judgment.”

Despite the reasons for compensating donors, payment for research donations was prohibited in 2005 in Massachusetts and, in 2004, under the stem-cell research initiative in California. Such payments have also been banned in South Korea (although they were legal at the time when some of the donors of eggs used in Hwang’s research were paid). In 2005, the National Academies recommended in its “Guidelines for Human Embryonic Stem Cell Research” that no payments should be provided for donating eggs, sperm, or blastocysts for research. Jonathan Moreno, the cochair of the National Academies committee and a professor of biomedical ethics at the University of Virginia,

said in an interview that the recommendations were justified by the sensitivity of egg donation for stem-cell research and by uncertainties about the actual risk of severe complications in donors. The committee’s recommendation has been criticized — for example, by John Robertson of the University of Texas School of Law at Austin, who has written extensively on stem-cell research. In a commentary on a bioethics Web site, Robertson said the committee “made a political choice to get the field moving, not an ethical one grounded in sound analysis.”

In the aftermath of the South Korean scandal, there is uncertainty about how many research groups will have the requisite approvals and funding for research on somatic-cell nuclear transfer, the number of donors they will seek, and whether enough women will volunteer if their only monetary compensation is reimbursement for expenses. Some have expressed concern that women who choose to donate will primarily be the friends and relatives of persons with diseases or disabilities, who may have overly optimistic notions of the potential for translating the early basic research into therapies.<sup>4</sup> The debacle in South Korea may discourage egg donation. Conversely, the extensive publicity about the need for egg donors could motivate more women to consider volunteering. Given the passions and pressures associated with stem-cell research, there is a continuing potential for secret payments and other problematic practices.

Other unresolved issues are the standards for informed consent and, more broadly, for the ethical derivation of stem cells. For example, the California Institute for Regenerative Medicine — which was established in ear-

ly 2005 with the passage of the California stem-cell initiative — must prohibit “compensation to research donors or participants, while permitting reimbursement of expenses” for human stem cells that are derived with its funding. The institute has interpreted the initiative as prohibiting both payment for a donor’s time and payment for her eggs. It still must decide, however, under what circumstances, if any, it would fund research on stem cells that were derived outside the state from the eggs of paid donors. The California Institute for Regenerative Medicine’s draft standards, which will address this topic as well as informed-consent requirements, are expected to be released in February. They may spur the development of international standards. In May 2006, the institute is planning to hold a conference to examine the risks associated with egg donation. The International Society for Stem Cell Research has also launched a guideline task force; it is expected to present its recommendations at the society’s annual meeting in Toronto in June. Although international consensus is desirable, the inherent complexity of the issues will no doubt make it difficult to achieve.

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Dr. Steinbock is a national correspondent for the *Journal*.

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