

Beyond Fraud — Stem-Cell Research Continues

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The developments in the laboratory of Woo Suk Hwang of Seoul National University in South Korea are profoundly disappointing to all scientists — not solely stem-cell biologists, although we are

the most immediately affected and will be subjected to the greatest scrutiny. It would be an overreaction, however, to attach apocalyptic significance to this incident either for the stem-cell field or for biomedical research in general. Although the events of Hwang's story provide a case study of some of the worst aspects of high-profile, high-stakes global science, they also include some reassuring elements.

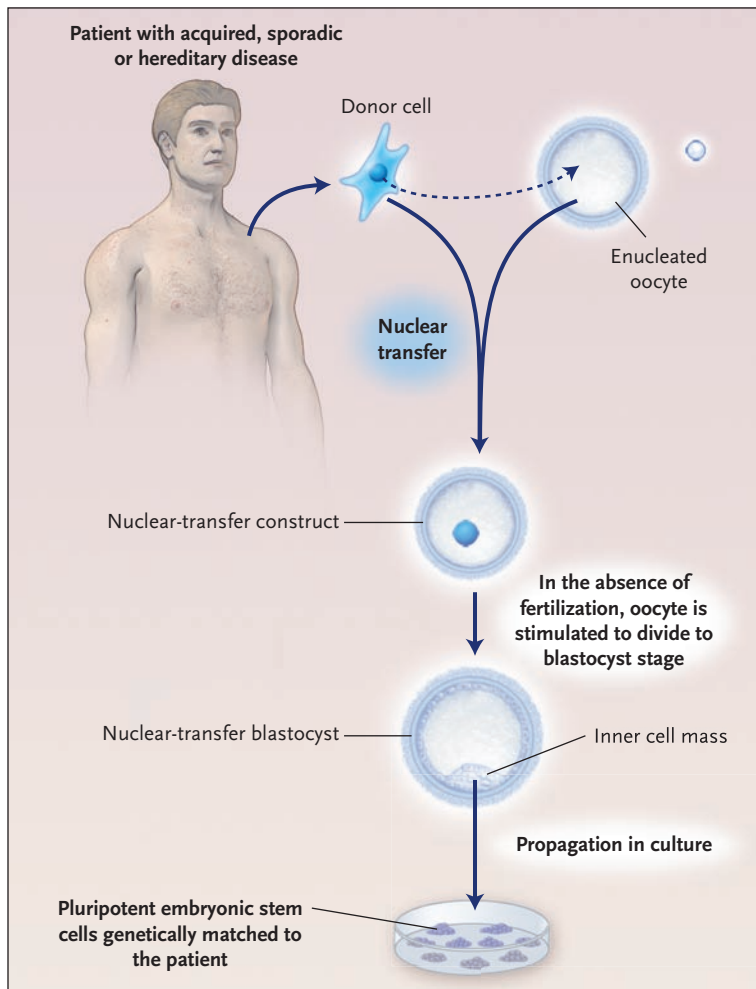
In 2004, Hwang and colleagues¹ reported that it was possible to generate a line of pluripotent human embryonic stem cells by transferring the nucleus of an adult somatic cell into an unfertilized oocyte, which then progressed to the blastocyst stage. Such a stem-cell line would bear a genetic pro-

file identical to that of the donor (see diagram). Although this ability represented more a technological than a biologic advance, the report showed the feasibility of extending insights from lower mammals to humans. Furthermore, it provided a method for developing some tools that stem-cell biologists would like to have at the ready — the capability of generating lines that are immunologically and genetically matched to patients who could then receive stem-cell transplants and of making stem-cell lines for research that faithfully model human diseases.

Though the 2004 report piqued scientists' interest, a second article published by Hwang's group a year later² had greater impact. Where-

as the earlier research had used 242 oocytes to generate a single stem-cell line, by 2005 the research team had reportedly learned to perform the procedures with remarkable efficiency, generating 11 patient-specific stem-cell lines with a success rate of 1 line for approximately every 20 oocytes. The new lines reportedly matched the genetic profiles of patients with a variety of diseases and injuries.

Within six months after the publication of the second article, however, confirmation of ethical lapses in the work began to surface. First, Hwang was alleged to have obtained oocyte donations for the 2004 research from his own research team. Despite the differences between the workplace culture of the United States and that of South Korea, where "coercion" may be perceived differently, the circumstances surrounding the donations involved a serious ethical lapse, since it appeared



The Generation of Embryonic Stem Cells after Somatic-Cell Nuclear Transfer.

The nucleus of a mature (somatic) cell is transferred to an enucleated oocyte *in vitro*. The oocyte is stimulated to progress to the blastocyst stage. Several days later, the inner cell mass is dissected and cultured to produce embryonic stem cells, the genetic makeup of which is identical to that of the patient. The cells can be used as a tissue-culture model for a disease that the patient may have or to generate compatible transplant material.

that Hwang had attempted to cover up the truth — a violation not excused by the honoring of culturally mandated keeping of confidences. The deception was soon discovered to be more profound, in a manner that certainly transcended East–West cultural differences. It is now clear, after independent analysis of the data, that all the results reported in the 2005 publication were fabricated and that the stem cells discussed

in the 2004 report were derived by parthenogenesis, not the cloning of human embryonic stem cells. Since no other scientists have reported the successful generation of human embryonic stem-cell lines by somatic-cell nuclear transfer (SCNT), we do not know whether the procedure works at all, though we still suspect that the hurdles are more technological than biologic.

Hwang's downfall carries two

serious implications for the public's perception of science. First, it reinforces the view that scientists cannot be trusted. Second, it creates the impression that stem-cell biology has been discredited or that progress in this field has been brought to a standstill. Both conclusions would be terribly wrong.

Rogues, though rare, are as much a fact of life in science as in any other endeavor, and often they are drawn to fields that are highly visible. Scientific misconduct is a well-recognized concern and is well policed by the scientific community, as evidenced by the existence of an Office for Research Integrity in the U.S. Department of Health and Human Services and the training in the ethical conduct of science that is required of recipients of U.S. federal research dollars. Editors and referees at peer-reviewed scientific journals conduct routine surveillance to ensure that data are not plagiarized, that no conflicts of interest exist, that human and animal subjects are protected, that patients' confidentiality is intact, and that findings flow plausibly from the stated methods. Indeed, the irregularities in Hwang's reports were unveiled by the scientific community itself (including collaborators and disinterested but critical investigators in South Korea), indicating that this system of peer scrutiny works.

More important, the scientific method provides critical safeguards, and one does not accept a scientific finding as the truth until it has been replicated independently. When the scientific method is pursued (with proper controls), one can determine when truth has not been revealed — whether because of innocent errors in interpretation or methods

or owing to malicious acts of fabrication. Thus, given sufficient time, science — as embodied by review by disinterested yet knowledgeable peers and the establishment of codes of conduct³ — will correct its own mistakes.

It is critically important, in our view, that the response to the Hwang scandal not include the imposition of levels of untutored government regulation, draconian legislation, or criminalization. Indeed, one could argue that governmental intervention in the scientific process actually contributed to some of the problems: in South Korea, government officials may have been complicit in motivating Hwang to publish prematurely. And in the United States and elsewhere, governmental restrictions on funding for stem-cell research have enabled a few well-funded investigators, such as Hwang, to fill the void, establish a monopoly on certain procedures or knowledge, and deprive science of what it needs most — an opportunity for the rapid, independent validation of data.

Should the referees and editors have caught the fabrication and incongruities earlier in the review process? With stories as seemingly groundbreaking as Hwang's, the review system faces a challenge. Novel results are a prerequisite for publication in a prestigious journal, but the essence of innovation is that the results are not simply a replication of, or derivative from, work by other researchers. Reviewers must examine the validity of conclusions on the basis of the data they are given, their fundamental knowledge of the system, and the controls a skeptic might demand, but they have no mechanism for judging whether the data are genuine. Novelty thus allows prevaricators to exploit the system

for a while, but if their results are not reproducible, they will not succeed for long, for truth in science is minted only after many investigators have replicated a finding. Nevertheless, flagrant duplication of photomicrographs in the absence of key control conditions (e.g., analysis of mitochondrial DNA) should have been caught before publication.

We hope that this unfortunate event will serve as an antidote to the "tabloidization" of stem-cell research and will make the public conscious of the fact that the science is difficult. The public needs to be aware that the field must remain grounded within the tradition of all biomedical research endeavors, with the cautious, ponderous accumulation of verifiable data that very rarely garner headlines.

What does the Hwang deception mean for the science itself? It certainly would have been encouraging to know that a desirable technical advance, the ability to generate cell lines efficiently after SCNT, had been achieved. The theoretical usefulness of SCNT is threefold: to make graft material that is genetically and immunologically matched to prospective transplant recipients, to make more representative *in vitro* models of poorly understood human diseases (for testing drugs or unraveling pathophysiological mechanisms), and to provide an alternative method for making stem-cell lines that does not involve the use of fertilized oocytes.⁴ Hwang's team ostensibly surmounted some technological hurdles, bringing us closer to these goals. Now we know that these challenges remain to be overcome.

But although scientists like to know that their arsenal is stocked

with every possible weapon, the specific indications for SCNT in our work remain uncertain. In fact, concern about the need for patient-specific cell lines is now being tempered by the recognition that stem-like cells may actually be less immunogenic than was initially presumed.⁵ There may also be simpler ways to make models of disease — for example, from blastocysts with diseases identified through preimplantation genetic diagnosis. And there may be other ways of circumventing the moral concern about the destruction of embryos in the creation of stem-cell lines (e.g., the dedifferentiation of somatic cells).

SCNT, in other words, plays only a minor role in the wider discipline of stem-cell biology — a branch of developmental biology that has no lack of other challenges to occupy its practitioners' time. The focus of most investigators will continue to be developing an understanding of important core issues concerning the molecular basis of stem-cell growth and differentiation, how a cell acquires its mature identity, and the therapeutic needs of potential target diseases. Indeed, it was to acquire expertise in these more basic, critical, and enabling areas that Hwang sought to collaborate with Western scientists who had made relevant advances. SCNT will continue to be one of the avenues we pursue — though in its proper context, and along with other techniques.

At one point, the research community thought that we might have, in Hwang, a technical virtuoso. Now we recognize that we all remain on an equal footing. The stem-cell field will not only survive this appalling and ultimately cynical act but also flourish so long as the science

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.

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Egg Donation and Human Embryonic Stem-Cell Research

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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 transfer¹ 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.² 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.”²

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,