RESEARCH CONDUCT

Lessons of the Stem Cell Scandal

The finding of fraud associated with the Hwang *et al*. stem cell reports raises issues that need careful scrutiny: authorship, ethics, funding, and science education.

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It has been a shock that dramatic breakthroughs in stem cell research using somatic cell nuclear transfer (SCNT) reported by Hwang and his colleagues in South Korea were largely a product of fraud (*1*). In response, there has been a great deal of soul searching within the scientific community. How could this have happened? Why didn't the peer-review process uncover the fabrication? Do we need to make changes in the way that we conduct and publish research? Rather than putting the way we evaluate research under a microscope, the research community in Korea and elsewhere needs to look at broader, institutional factors contributing to the behaviors that have caused so much dismay in the scientific world.

In the 17th century, trust and integrity in science were central to the system of publication that we have inherited (*2–4*). For example, the scientific community had to decide which reports from explorers from distant parts of the globe were reliable. The issue also arose for the emerging experimental sciences, which Boyle and his colleagues at the Royal Society of London argued depended on actually witnessing the experimental events (*3*). Boyle created the precursor to the modern scientific publication to provide sufficient detail so that other scientists could replicate the experiments, thus adding witnesses to the experimental data. In cases where this was impractical, it would serve to produce sufficient information so that the readers were "virtual witnesses" (*3*, *4*).

An important part of 17th-century scientific epistemology concerned establishing how one could tell that the reports were worth believing. This included information about the skill of purported "witnesses," design of the author, internal consistency of the account given, and whether contradictory "testimony" existed in the scientific literature (*5*). Perhaps the most important protection was the integrity of the "informant," Therefore, establishing the rules by which one was trustworthy (a "gentleman") became critical.

We are the heirs of this system. It is not practical or even possible to investigate in detail each submission to each scientific journal, and even investigation after publication can be difficult (*6*). Science must continue to depend on the integrity of its practitioners. It will always remain possible for a skilled practitioner to (at least temporarily) perpetrate fraud. As in the 17th century, replication will remain a key confirmation of purported results. The antiquated notion of the gentleman scientist is no longer applicable or desirable. What is needed is better articulation of the meaning of integrity and how to foster virtue in scientists. It is here that institutional structures in South Korea failed.

In the case of Hwang *et al*.'s research, basic tenets of individual integrity (intellectual honesty and accuracy in representing contributions to research) were violated. Not only were data fabricated (*1*), but there were fundamental misunderstandings among the researchers about their responsibilities as authors. For example, the inclusion of a high-level government official who did not conduct the research (*7*) was inappropriate. Authors provide the authority of a publication and take responsibility for its authenticity. The attempt by the U.S. scientist Gerald Schatten to remove himself as author was also inappropriate, especially because his avowed contribution to the article was to the overall analysis and preparation for publication (*8*).

In complex, interdisciplinary research, coauthors must often rely on each other to vouch for authenticity. The International Committee of Medical Journal Editors guidelines for authorship implicitly acknowledge this in stating that that "Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content" (*9*). Adopting the concept of a "contributor" advanced by Rennie *et al*. (*10*) would clarify and increase the accountability of individual authors. Rennie *et al*. also proposed the concept of a "guarantor" of a publication, an individual who takes full responsibility for the integrity of the entire publication. The guarantor model only works, however, in an environment where colleagues (especially junior scientists and staff) are free to probe and challenge results.

This underscores the importance of other facets of individual integrity—collegiality, communication, and sharing of resources. It has been speculated that a large, compartmentalized laboratory structure could have contributed to the ability to falsify data (*8*). Such structures, while perhaps encouraging efficiency, could inhibit free flow of information and dilute responsibility for the integrity of the work.

The actions of individual researchers do not exist in a vacuum but are affected by institutional factors (*11*). In South Korea, there was awareness of the need for ethical guidelines for research, as evidenced by the recent passage of laws about stem cell research and human subjects (*12*). However, the science may have been moving much more quickly than the ethical standards could be absorbed. For example, it was reported that 85% of over 900 biotechnology researchers surveyed in South Korea did not know what the Declaration of Helsinki was, and that 42% did not know about Institutional Review Boards (*13*). This study was conducted only in Korea, but may be indicative of an international problem. All research institutions need to assess awareness of ethical standards.

The Korean government reportedly provided Hwang's laboratory with upwards of $65 million in a relatively short period of time for research and new facilities, earmarking over ~$25 million in a single year (*14*), and a large research award as a "supreme scientist" (*15*). Concentrated funding of a single laboratory is not likely to foster the growth of a community necessary to build a new research field. Broader, merit-based funding contributes to scientific integrity by encouraging multiple laboratories to develop similar expertise and to better assess each other's results. Large amounts of funding concentrated in a small number of researchers could promote unhealthy competition by the inordinate pressure created by expectations of returns for such large sums.

The alleged fraud in stem cell research sheds light on another area of potential concern. U.S. policies (*16*, *17*) allow, and perhaps even encourage, deidentification of human biological materials when transferred between researchers, to protect privacy and confidentiality of research subjects. However, if identifiers of research materials are irreversibly removed, it could be difficult or even impossible to reevaluate the validity of the results obtained with them. In the Hwang case, for example, if the stem cell lines had been made anonymous, with codes linking patient identities to cell lines destroyed, and if original donor tissues or materials were lost or completely consumed in the course of the research, it would be impossible to conduct an investigation to determine validity.

In addition, researchers who collect tissue samples do not necessarily know what happens to them in downstream research. Researchers who use the donated tissues do not necessarily know how the tissues were collected or whether the collection was done appropriately (*18*). For example, Sung Il Roh, a coauthor of Hwang's, reportedly admitted to paying for eggs, and to doing so without informing Hwang (*19*). Policies intended to protect research subjects might have weakened some of the institutional structures that encourage research integrity by inhibiting communication between scientists

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and a shared sense of responsibility.

According to a newspaper report, Korea's National Board of Bioethics indicated that, in contrast to claims by Hwang's group, information on serious risks of egg donation were not provided to all donors, and that 16 of 100 donors required in-hospital treatment of adverse effects from the procedure (*20*). Even the most stringent regulations also rely on trust.

The responsibilities to mentor students in navigating the pressures of becoming a scientist can pale by comparison to the drumbeat of competition and the expectation to produce. Contemporary research is nested in a plethora of codes, rules, and laws. It is a challenge to inculcate the skills of responsible research let alone the more general set of nontechnical skills and virtues that ennoble science.

Although some research universities now require that doctoral and postdoctoral students complete fairly elaborate courses in ethics, many more treat students to a sandbox morality lesson consisting of the admonition not to lie, cheat, or steal data. The courses may have little effect on future misconduct (*19*). The idea that research training, such as that required in the United States for some federally funded trainees and emphasized by the National Research Council report (*21*), in itself would have prevented fabrication on such a grand scale in South Korea strains credibility.

Teachers must themselves be judged by the authorities in our institutions—not only for their ability to produce science, but also to be scientists of virtue and integrity. The ability to give testimony and to act as a witness can be modeled, and students should be allowed to exercise skills of discernment and skepticism about results that seem unlikely or behaviors that are worrisome without punishment. The lesson to be learned is that we need to do a better job of holding research institutions accountable for setting up systems and mentorship that will produce integrity in its scientists.

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PUBLIC HEALTH

Community Studies for Vaccinating Schoolchildren Against Influenza

A plan to vaccinate schoolchildren against flu presents an opportunity to assess risks and benefits.

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The Advisory Committee on Immunization Practices and several states are considering recommending annual influenza vaccination in groups beyond the currently recommended high-risk groups. This offers an opportunity that should not be missed: to conduct a nationwide study of the effectiveness of vaccinating schoolchildren against influenza as a means of reducing community transmission. Some public health officials speak of universal vaccination against influenza, meaning a recommendation for all age groups, but schoolchildren, aged 5 to 18 years, are a prime target as they are generally considered to be the most important source of community-wide transmission. Researchers also believe that the immune systems of children respond better to influenza vaccination than do those in the elderly at-risk population. To realize maximum benefit from a study of such effects, we must prospectively sort out the crucial features to be evaluated: effectiveness, benefits, risks, and costs.

Highly pathogenic avian influenza A (H5N1) and its potential to unleash a pandemic are recently in the news. Aside from reducing community-wide transmission of seasonal influenza, vaccinating schoolchildren against influenza and putting its evaluation into place would prepare us for an organized response to an influenza pandemic, whenever it occurs. Our predictions suggest that if limited doses of vaccine were available, as might be expected during a pandemic, vaccinating schoolchildren would be the most efficient approach to reducing overall numbers of influenza cases.

A combination of vaccinating schoolchildren and older adults would be most effective for reducing influenza deaths (*1*, *2*) Results from influenza simulations that we have conducted indicate that vaccinating just 20% of the schoolchildren would do more in reducing overall mortality in adults over 65 years old than vaccinating 90% of the adults over 65 years of age (see chart, page 616, top). Even though schoolchildren and young adults have not been considered at high risk of dying of influenza, annual morbidity is still high, with illness attack rates in schoolchildren exceeding 10% most years. Thus, the benefits would not be limited to the older population.

Expanding annual influenza vaccination would give vaccine manufacturers the incentive of a guaranteed market so that they would be willing to increase production capacity and stabilize the influenza vaccine pipeline. This improves our preparedness for a pandemic strain.

Arguments against and hindrances to vaccinating schoolchildren against influenza need to be taken seriously. Despite the benefits, children already receive many vaccinations, and parents and children balk at the idea of yet another, especially if needed annually. However, even if coverage were incomplete, community-wide benefits could be obtained provided that vaccination rates were 50% or higher, not to mention the direct protection of the vaccinated children. Use of a nasally administered live-attenuated influenza vaccine (LAIV) (*3*) might be an alternative to the traditional shots with killed vaccine. Influenza

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