Research ethics and lessons from Hwanggate: what can we learn from the Korean cloning fraud?

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J. Med. Ethics 2008;34;214-221
doi:10.1136/jme.2007.023721

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► An appendix is available online only at http://jme.bmj.com/content/vol34/issue3

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Received 13 November 2007
Accepted 13 November 2007

ABSTRACT

In this review of the Korean cloning scandal involving Woo-Suk Hwang, the nature of the disaster is documented and reasons why it occurred are suggested. The general problems it raises for scientific research are highlighted and six possible ways of improving practice are offered in the light of this case: (1) better education of science students; (2) independent monitoring and validation; (3) guidelines for tissue donation for research; (4) fostering of debate about ethically contentious research in science journals; (5) development of an international code of ethical research practice; (6) fostering of public involvement in ethical review and debate through the web.

Science today is an international enterprise. Large multinational companies and researchers collaborate across the globe. However, it is mostly at the national level that science is regulated and funded. This can result in a confusing patchwork of regulatory policy and ethical guidance that can retard the progress of science and fail to promote ethical behaviour. There are enormous personal and national drives to succeed. The cocktail of pressure to succeed in the presence of patchy national regulation, ethical standards and cultural norms can cause ethical controversy and scientific misconduct. A fine recent example is the Korean cloning scandal.

The Korean scandal starts with Woo-Suk Hwang. Hwang was raised in South Chungcheong Province in a mountain town. He worked on a farm to finance himself through high school. His commitment to study was rewarded when he graduated from Seoul National University as a veterinary scientist. After gaining his PhD, Hwang worked as a veterinary researcher before his desire "to help solve some incurable human diseases"[1] led him to therapeutic cloning using human embryonic stem cells. His early achievements included the creation of transgenic pigs to provide organs for transplant into humans, the cloning of a dairy cow in 1999, and (he claimed in 2003) the development of BSE-resistant cattle. But this, and most of Hwang's early work, was unpublished and unverified.

THE KOREAN CLONING SCANDAL

Between 2001 and 2004, Hwang donated US$250 000 to Ky-Young Park, a biologist at Sunchon National University. She undertook two projects for Hwang, regarding the social impact of BSE-resistant cows (2001) and ethical guidelines and commercial use of bio-organs (2003). From 2002, Ky-Young Park had close connections with the Korean government and often acted as unofficial mediator between Hwang and Roh Moo Hyun's government. Park became more influential in 2003 when she was made presidential advisor on science and technology.[2]

Hwang became a scientific enigma and international celebrity on publication of his 2007 paper "Evidence of a pluripotent human embryonic stem cell line derived from a cloned blastocyst",[3] of which Park was a coauthor. This was the first time anyone had offered proof of a cloned human blastocyst, let alone successfully extracted stem cells from it. However, *Nature* questioned the ethical framework under which Hwang's research was conducted, after an interview indicated that some oocytes used had been donated by junior researchers.[4] Hwang denied the allegation but voluntarily suspended this research until the Biosafety Act of 2003 came into effect in January 2005. Even so, the Korean Bioethics Association (KBA) asked Hwang to answer questions about his funding sources and recruitment of egg donors.[5 6] In response, Hwang and Shin Yong Moon declared that they did not consider the KBA neutral, because it advocated "restricting the pace of biomedical advancements".[7]

Between suspension of his research and the new Korean Biosafety Act becoming law, Hwang collaborated with Gerald Schatten, a researcher studying primates at the University of Pittsburgh. Using techniques for extrusion of oocyte DNA developed by Hwang, Schatten successfully cloned the first monkey embryos. Though a live birth was not achieved, Schatten's group developed embryos to the blastocyst stage, from which it is possible to extract stem cells.[8] The success was seen as a validation of techniques that Hwang had developed for somatic cell nuclear transfer (SCNT).

On 13 January 2005, Hwang's research became the first to be approved under the new Biosafety legislation. Soon after resumption of his research, Hwang told Park and Schatten that four of six stem cell colonies he had created were infected with fungi. Park oversaw implementation of preventive measures but did not officially report the incident.[9] Allegedly, Schatten urged Hwang to publish anyway, since stem cells had "clearly been produced",[10] and just 5 months later Hwang submitted his second ground-breaking paper, "Patient-specific embryonic stem cells derived from human SCNT blastocysts".[11] Schatten was listed as second author.

On 3 August 2005, Hwang and colleagues announced that they had created a cloned Afghan hound, Snuppy.[12] Because canines produce very immature oocytes, many thought that cloning

dogs would be more difficult than human cloning. Once again, the efficacy of Hwang's techniques for cloning using SCNT appeared to be verified. However, the work was overshadowed by Schatten's informing *Science* that Sung-Il Roh, a coauthor on the 2005 human SCNT paper, had illegally traded ova. Schatten assured *Science* that none of the women who donated eggs for their papers had been reimbursed. But just days later Schatten broke links with Hwang, claiming that he had been misinformed about consent issues surrounding the 2004 paper.[13]

Hwang's work and the research ethics underpinning it subsequently came under increasing scrutiny. Pressure for a formal investigation into Hwang's research practices increased after submission of corrected tables for the 2005 paper and Roh's admission that Hwang had unwittingly used 20 eggs that had been paid for.[14] But pressure on Hwang was eased by Moon Il Park, Director and Chair of the Institutional Review Board (IRB) on Human Subjects Research and Ethics Committees at Hanyang University Hospital; the IRB found Hwang's research not to be illegal or in violation of the Declaration of Helsinki. Moon Il Park initially reiterated his belief that none of Hwang's team were oocyte donors,[6] though he was later to correct this belief.

On 22 November, Editor's Notebook, a Korean investigative programme by the Munhwa Broadcasting Corporation (MBC), cast doubt on the claims by Hwang's research team that most Korean people admired Hwang's research and were willing to donate eggs, raising suspicions that there was illegal trade in eggs. The programme resulted in great controversy in Korea. Significantly, the MBC came under fire for reporting against the national interest. A number of companies, concerned about adverse publicity, withdrew commercial support. Subsequently, Hwang conceded that he had used eggs that had been paid for and eggs donated by junior researchers.[13] Moon Il Park concluded that the two junior researchers had donated oocytes voluntarily and without coercion. The payment of approximately US$1445 was for direct expenses and had no impact on the validity of the scientific conclusions.[13]

On 1 December 2005, the MBC turned up the heat on Hwang, openly questioning the credibility of Hwang's research after obtaining samples of five patient-specific cell lines from Hwang's lab. Independent DNA analysis indicated that one cell line did not match its supposed donor.

However, pressure was relaxed on Hwang as reports emerged that the MBC had used threats to coerce incriminating statements about Hwang. The MBC was forced to apologise for unethical journalism practices,[13] having "tricked [Sun Jong] Kim into believing that Korean prosecutors had begun an investigation".[15]

Following accusations regarding the validity of Hwang's research on the Biological Research Information Centre's website, Hwang informed *Science* that the 2005 paper included redundant images.[16] The images were not in the original submission but had been submitted later by Schatten in response to a request for supporting evidence. In response to the weight of mistrust that surrounded Hwang's research, the University of Pittsburgh opened an investigation into Schatten's role in the affair. An investigation by Seoul National University (SNU) quickly followed at Hwang's request.[13]

Scepticism abounded after Schatten expressed doubt about the scientific value of the paper. Asking for his name to be removed from the paper, he stated that new information and re-evaluation of data "casts substantial doubts about the paper's accuracy".[17] This led Dr Ian Wilmut, who is credited with having created Dolly the sheep, to ask for independent verification of Hwang's research.[18] The situation was further muddied on 15 December, when Roh quoted Hwang as saying "there are no cloned embryonic stem cells"![13] Soon after, Hwang and Schatten requested that their paper was retracted because analysis had indicated their data "could not be trusted".[13] Hwang maintained that, though mistakes occurred, patient-matched stem cells were created and he would thaw lines for independent authentication.[19] Hwang declared that patient-specific stem cells were still "the proud technology of our nation".[20]

However, the initial investigations by the SNU concluded that a large proportion of data from the 2005 paper had been fabricated. Results indicated that data came from only two cell lines rather than the eleven stated, and it was soon verified that neither of these two lines had been cloned via SCNT, but that they had been derived from embryos fertilised in vitro.[21] The SNU concluded that both the 2004 and the 2005 papers were based on fraudulent data – the NT-1 cell line described in the 2004 paper appearing to be parthenogenetically derived. Snuppy, however, was a somatic cell clone of a dog named Tie and was not simply highly inbred.[21] *Science* retracted Hwang's 2005 paper on 4 January 2006 and subsequently his 2004 paper. Two papers in which Sun Jong Kim and Sung-Il Roh were involved have also been retracted – one because "upon re-examination of their work, the authors have found that the data in Figure 2A was intentionally fabricated"[22] and the second (*Biology of Reproduction* DOI: 10.1095/biolreprod.105.046870) "was withdrawn after it was shown to contain a photo that is the same as a picture from Hwang's 2005 *Science* paper".[23]

Hwang was fired in March 2006 from his post as a professor at Seoul National University's veterinary department. Prosecutors completed an investigation into the scandal in May 2006. Hwang was indicted on charges of fraud and embezzlement, as well as violation of Korean bioethics laws.

Hwang apologised for his part in the "Hwanggate" scandal but insinuated that other researchers had sabotaged his work, suggesting that scientists at the MizMedi Hospital, where certain procedures were undestaken for Hwang, might have replaced cloned stem cells with other cells.[23] Hwang insisted that his lab was capable of producing patient-specific stem cells and that they could reproduce their result in six months, given a favourable research environment.[13] In support of his claims, the SNU investigation panel stated that Hwang's "team was in possession of technique[s for] creating cloned human blastocyst[s]".[21] However, Hwang saw initial cell colony formation as successful establishment of a cell line. Without further corroborating evidence, the scientific basis for claiming success was "wholly lacking".[21] Subsequently, PD Notebook alleged that the junior researchers had been coerced into donating eggs – an allegation that has since been reiterated by the National Bioethics Committee.[13]

In any episode such as this, especially one occurring in a foreign country, and involving multiple allegations of misconduct, it is very difficult to arrive with certainty at the truth. However, it appears from the evidence available to us that Hwang's team possessed neither patient-specific embryonic stem cell lines nor the NT-1 embryonic stem cell line described in the 2004 paper.[21] Data in both ground-breaking publications was fabricated, as shown by the non-matching DNA profiles. The scenario of a rogue scientist operating to undermine Hwang's research cannot explain the parthenogenetically derived cell line nor the fabrication of DNA profiles. Such acts require scientists to work complicitly to deceive those reviewing and publishing the paper. In March 2006, Hwang admitted ordering researchers to fake data for the 2005 paper.[13] This is difficult to comprehend, given the SNU report suggesting that Hwang was technically able to

produce, and was in possession of, cloned human blastocysts from SCNT. It is likely that this and the parthenogenetically derived embryo were in themselves publishable. It is possible that Hwang submitted the 2005 paper believing that he would soon have the evidence to corroborate it. However, this does not seem to be the explanation for the 2004 paper, which appears to be completely fabricated. And despite this, it does appear that Hwang successfully used SCNT to create Snuppy the dog and that Schatten successfully cloned a monkey.

Hwang rose from global obscurity to *Scientific American*'s "Research Leader of the Year 2005", and exposure of "Korea's Cloning King"[24] as an alleged fraud rocked science. Though the scientific value of Hwang's research is largely discredited, it still raises many important issues with respect to science policy and ethics, "as opponents of research on cloning make political capital from the scandal".[23] Hwang's case highlights that sound transnational ethical oversight is required for reliable science. It appears that Hwang was a good scientist operating in an environment that was conducive to misadventure. Hwang credited his "success" to plentiful funds, abundant oocytes and a supportive (mostly unregulated) political and legal environment.[13] But these, together with ambition, also created an environment for disaster. Hwang met with many pressures but few constraints; the choices he made at each juncture made his decline inevitable. The Machiavellian desire for "community recognition and prestige"[25] in modern science cannot be underestimated or easily mitigated.

How common is research misconduct?

We do not know, but it may be more common than many initially presume, particularly if one includes scientific misbehaviour (see Author responsibility, below) as introduced by the University of Pittsburgh. In fact, there is evidence of systematic scientific misconduct even in heavily regulated research environments. In a survey of researchers at the National Institutes of Health, 1.5% admitted to falsifying or plagiarising data.[26] Luk Van Parijs was recently fired by the Massachusetts Institute of Technology after admitting that he fabricated and altered research papers in order to support grant applications.[26] Such is the pressure to publish that some researchers may start the publication procedure before they have results to support their assertions – believing that they can predict the outcome from their preliminary findings.

The problems of withholding results that are against researchers' or funder's interests, and subsequent publication bias,[27] have long been documented. Such misconduct continues. The authors of a 2000 study of Vioxx failed to inform *The New England Journal of Medicine* that several patients had heart attacks while taking the drug. Additionally, an article on Celebrex in *The Journal of the American Medical Association* has been discredited because the authors submitted only 6 months' worth of the data they collected over 12 months.[28]

No aspect of the research process seems immune to fraud and misconduct. The results can be lethal. Paul Kornak altered patient medical records to facilitate their enrolment in drug trials from which they should have been omitted due to existing conditions. One patient died, and Kornak was recently jailed for criminally negligent homicide.[26]

PRESSURES FACILITATING MISCONDUCT

Funding and publication

Funding directs, if not dictates, science, because without funding, research cannot occur. Publication provides investors with information about the researcher's capabilities, and therefore there is great pressure to publish. An advantage in attracting funding is gained from publishing in the more prestigious journals. The Research Assessment Exercise in the UK implements selective funding for universities – but there is suspicion that the journal in which papers are published is "given greater weight than the papers' content".[29] Groundbreaking papers are more likely to secure a major journal, attract more public and/or commercial interest and be favoured by investors. Researchers are likely to feel pressure to exaggerate their capabilities or the possibilities of their research. There is a fine line between exaggeration and deception.

The majority of funding comes from governments, companies and private investors. Companies have a specific interest in funding research that could improve their profit margins. Pressure from investors does influence research: in a survey by the US National Institutes of Health, 15.5% of respondents admitted to altering their research approach under pressure from funding sources.[26] Barnes investigated whether a scientist's affiliation affected research conclusions. Of 106 review articles about passive smoking published between 1980 and 1995, 37% concluded that passive smoking was not harmful. Of these, 74% were written by tobacco-affiliated authors – and only two tobacco-affiliated researchers concluded that passive smoking was harmful. Barnes found to 95% confidence that conclusions were related to the affiliation of the author.[30] For this reason, many journals require disclosure of conflicts of interest and author affiliations.

Hwang may have felt pressure from the government that funded his research. Since much of Hwang's early research was unpublished, it is interesting that he commanded such a sophisticated lab. Admittedly, his work was better known in South Korea than worldwide; but it is questionable that unsubstantiated claims to have created BSE-resistant cattle should secure some $40 million in government grants. Ky-Young Park was named as a coauthor on Hwang's 2004 paper because of her work on the socioethical concerns involved in cloning;[9] however, the SNU investigation found that she made "no contribution".[2] The KBA has more than 50 listed members and is seen as the principal leader in bioethics policy in South Korea. Why did Hwang fund Park's research (a botanist with no history of ethical study) instead of consulting the KBA? There is suspicion that Hwang "employed" Park to further political support for his own research,[2] in turn increasing his obligations to government funders. Pressure on Hwang to succeed would be immense, because the nationalistic ethos of South Korea would mean Hwang's fame reflected well on the government.[31]

Media and the general public

Hwang "never shied away from the strong appeals to nationalism" that fuelled his rise to stardom. Soon after cloning his first cow, Hwang promised to "spread the Korean people's spirit by cloning the [holy] Mount Paektu tiger".[32] Revered by the public, Hwang was treated like a "rock star".[33] The government issued "Dr Hwang" postage stamps depicting a paralysed person walking again (fig 1), and textbooks were rewritten – one describing Hwang as a potential Nobel Prize winner.[32]

Hwang was a symbol of everything that South Korea stood for and desired, his picture was plastered on public transport and posters were released proclaiming that he would change the world. South Koreans viewed Hwang as holding the hopes of the world[31]; to further Hwang's research was to further South Korea (figs 2,3).

Figure 1 Korean postage stamp celetrating Hwang's supposed achievement. Taken from: http://www.sciencemag.org/cgi/reprint/308/5729/1738a.pdf

At the pinnacle of Hwang's popularity, a survey indicated that 30% of women would donate their ova to research and 45% of men wanted their partners to donate.[34] A website was set up in November 2005 for women to pledge their eggs to research. In seven days, 800 women had signed up and the message board was full of encouragement for Hwang. Kim Yong-Hae, a disabled 27-year-old, wrote "Please don't give up, doctor Hwang. Your research is my only hope. You should take all of my ova if they help".[35] "Worshipped by so many people, Hwang [had] no choice but to accomplish even more as soon as possible so as to live up to the expectation of his fellow country people."[36]

The media were crucial in stoking public reaction, and stories about Hwang's research and its implications for the future of humankind were commonplace. Irresponsible reporting and unfounded speculation by scientists bred misconception and false hope within the general public and probably led to extra pressure on Hwang to deliver results. Unfortunately, some scientists allow misconceptions to occur, as media attention brings fame and funding. Schatten is quoted as having said: "we will be able to make a person to have [sic] immunity against HIV ... his somatic cells can be cloned to produce HIV-resistant cells."[37] After comments like these, scientists and the media were looking for proof; one must either produce results or lose face.

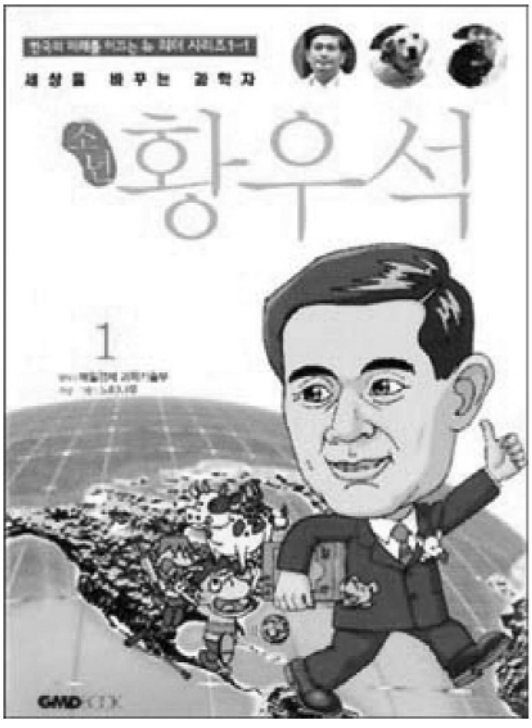

Figure 2 "The scientist that changed the world - Hwang Woo-Suk" — poster appearing on Korean public transport during Hwang's period of popularity.

Lax implementation of weak ethical policy

Investors

The Stem Cell Research Center (SCRC) invested in Hwang's 2004 paper. Hwang's coauthor, Shin Yong Moon, was the SCRC president and sat on its ethics committee, which "prohibits the production of human embryos for stem cell research".[5] Thus, it is questionable whether Moon should have worked on the project and whether the SCRC should have donated money. Similarly, it is problematic that the government department that invested so heavily in Hwang was also his regulator. Ky-Young Park "received the report on the contamination from Hwang in January [2005], but did not report to the president [Roh Moo Hyun] directly"[9] – her failure to do so may have indicated to Hwang that he was politically immune and that the government wanted him to succeed at any cost. Park must have known that Hwang's 2005 paper was compromised because the four infected stem cell lines were included, yet she did not expose or publicly question Hwang. Because Park did not officially report either the infection of Hwang's cell lines or her intervention, it was more difficult to uncover subsequent fabrications.

Research ethics committees

The research ethics committees or IRBs of Hanyang University and the SNU both approved Hwang's research, and his proposal was quickly passed by the National Bioethics Committee. However, it appears that there were numerous oversights. After Hwang's exposure, the Committee determined that Hwang had failed to sufficiently protect donors because he had provided insufficient information on the possible risks of donation and allowed 15 women to donate more than twice.[38] By handing out ova-donation consent forms to junior researchers in his team, Hwang had failed to comply with the Declaration of Helsinki, because he was not acting responsibly with a subject "in a dependent relationship with the physician".[38] Though Hwang is not a physician, the Declaration of Helsinki is seen as the ethical baseline standard for scientific research. Hwang's actions could have been misinterpreted as a request for a donation.

Hwang's somatic cell donors had congenital hypogammaglobulinaemia, spinal cord injury or juvenile diabetes. Magnus and Cho, two ethicists who have provided commentary throughout the Hwang case, find it "easy to understand the value of SCNT experiments using somatic cells donated by individuals suffering from genetic disorders". But they find it "difficult to understand why spinal cord injury patients [were] recruited" because their inclusion increased the likelihood of people inaccurately attributing therapeutic intent to the research (therapeutic misconception).[39] However, because *none* of the donors could feasibly benefit from the research, there was no reason to enrol patients rather than healthy volunteers, especially if one were worried about therapeutic misconception. Somatic cell donors were only required to be unique from oocyte donors. The use of vulnerable groups without reason was also said to be unethical.

Acknowledging Hwang's prominence, Magnus and Cho question how truly independent IRB members were.[39] This is especially worrisome, given allegations that Hwang nominated some IRB members,[40] and the National Bioethics Committee

Figure 3 Poster celebrating Hwang's achievements. Taken from: http://www.occidentalism.org/?cat = 8

head, Yang Sam-Sung, tendered his resignation because of an undeclared conflict of interest.[41] While reviewing Hwang's research for the Committee, Yang Sam-Sung was providing legal advice to Hwang regarding the PD Notebook allegations.[40] Evidence suggests that Hwang was aware of ethical issues following his 2004 paper, and in January 2005 he consulted Dr Jung and together they devised some of the most ethically defensible protocols for research conduct.[42] It now seems that Hwang ignored these protocols, although he, and perhaps IRB members, knowingly gave the impression that they were being adhered to. Insoo Hyun and Jung's concern was first raised by the discrepancy between the timeline for egg and somatic cell donations and the timeline necessary for Hwang to produce data for the March 15 article submission to *Science*. Hyun and Jung reported their "concerns immediately to a member of the Hanyang Hospital IRB and the leadership of the International Society for Stem Cell Research (ISSCR) and its bioethics committee", but no action seems to have been taken as a result. Jung and Hyun had to retract their paper about the ethical integrity of Hwang's research.[43]

Collaborating with Schatten meant that Hwang's research crossed numerous regulatory borders. From information provided by Schatten, the Pittsburgh IRB concluded, using the federal definition, that no human subjects were used[44]; and because samples could not be traced back to the donor, the research was exempt from full IRB review.[45] However, South Korean laws covering organ sharing required that donors benefit preferentially if therapies are developed through research; thus at least one scientist should have been able to link samples to donors. Therefore, while Schatten was involved, Hwang's research should have had full American IRB review. The US National Research Council–Institute of Medicine now recommends that all embryonic stem cell research have full IRB oversight. Part of the problem was that Pittsburgh allows their researchers themselves "to determine if their work constitutes human-subject research, a policy that disregards federal recommendations designed to safeguard people". Miscomprehension or ignorance of South Korean law meant that Schatten's assertion that the research did not involve identifiable people was false. Documented evidence now shows that one of the egg donors later worked in Schatten's Oakland lab.[44]

Problems in science raised by Woo-Suk Hwang's research

Hwang's research raises many general problems relating to scientific research, to do with verification of results, the validity of peer review and authorship. However, here we concentrate on the ethical issues raised by this research.

Journals

Magnus and Cho argue that journals must be satisfied with the ethical conduct of researchers.[45] Whether journals have the resources to evaluate the ethics of a paper is questionable. The Hinxton Group encourages journals to "require a statement from scientists that their research conforms to local laws and policies".[46]

Author responsibility

The ethical issues surrounding Hwang are still contentious, and the number of authors on a single paper makes it unclear where responsibility lies. The link between publications and funding means it is common practice for anyone involved with research, even vaguely, to be a coauthor. Additionally, a lead author may not be the most significant person in the research, as exemplified by the current case surrounding the sheep Dolly, a case with striking similarities to Schatten's being second author on Hwang's 2005 paper. For the past 10 years, Dr Ian Wilmut has been widely credited with the successful creation of Dolly via SCNT-cloning. However, a recent legal hearing forced him to admit that he was the lead author only because of a prior agreement and that Professor Keith Campbell deserved 66% of the credit.[47] Additionally, it appears that much of the work was done by two technicians, Bill Ritchie and Karen Mycock, who because of their positions were not thought worthy of coauthorship, merely being acknowledged at the end of the paper.[48]

There were 15 and 25 authors, respectively, on Hwang's 2004 and 2005 papers. This makes it difficult to assign responsibility for misconduct. Journals are considering making authors detail their involvement in projects[49] so the journals can ascertain whether authorship is valid and assign responsibilities.

It is also ethical misconduct to appear as an author when no significant practical or theoretical contribution has been made. The Pittsburgh investigation panel wrote, "We have no reason to doubt… Schatten's statement to us that his major contribution to the paper was a suggestion that a professional photographer be engaged, so that Snuppy would appear with greater visual appeal. It is less clear that this contribution fully justifies coauthorship".[50] The University of Pittsburgh panel found Schatten guilty of "research misbehaviour"[51] and chided him for his failure to take greater steps to ensure the veracity of Hwang's data.[52] Schatten received US$40 000 from Hwang, including $10 000 for appearing at a press conference.[50] It may be that Hwang used Schatten to give credibility to his research in the West. As Dr Weissmann said, "Everyone wondered how Schatten got to be the senior coauthor, but his vouching for Hwang made it a little more likely".[53]

Failure of education and monitoring of research conduct

Hwang's research highlights the difference between gaining research approval and conducting research ethically. IRB

approval does not ensure ethical practice. Insoo Hyun considers that originally Hwang's team had very little knowledge of ethical standards for human subjects research, since prior to their attempts at human research cloning they had worked only with animal models at Seoul National University's College of Veterinary Medicine. (Insoo Hyun, personal communication, Hinxton UK). A study of over 900 biotechnology researchers in South Korea found that 46% had not heard of the Helsinki Declaration; 39% had heard of it but did not know what it was; and 42% did not know about IRBs.[54] Generally, there is little ethical education in science. Ethics is seen as integral to modern medical training, but degrees in biological sciences do not appear to have kept in touch with the ethical aspects associated with their fast-paced area. As the case of Hwang vividly illustrates, researchers with insufficient education in ethics are a risk to themselves, their colleagues and their institution, and to the scientific community and public in general.

International co-ordination

Hwang's research took place in South Korea with the approval of institutions required by South Korean law. Schatten was working out of America, and no federal funding was used for the research; the creation of human stem cells under these conditions is not prohibited by either South Korean or US law.[45] However, the failure of Schatten and the Pittsburgh IRB to recognise that the Korean law covering organ sharing meant that full IRB review was required demonstrates the difficulty of regulating international collaboration. Regulating stem cell research is a compromise between advancing knowledge and protecting national ethical standards, in which cultural diversity manifests itself as a patchwork of legal environments. Transnational differences in law can leave scientists uncertain about their legal standing when working internationally. Ambiguous use of technical language may discourage scientists from developing legal avenues of research. Alternatively, scientists working within the law may be the target of legal proceedings initiated by people who wish to challenge those ambiguities.[55] The Hinxton Group calls for legal policy to be "clear and explicit" in order to maximise the potential for valid scientific research to be undertaken.[46]

Donation

The South Korean ethos, in promoting altruistic donation, poses new questions for research participation. Excess embryos for in vitro fertilisation (IVF) are seen as the most ethically acceptable source of oocytes, but whether they are suitable for all research is a controversial question. Excess IVF embryos currently have ethical and legal advantages for use in stem cell research, because the woman is a patient, having given clinical consent for the IVF procedure. As a patient, she is able to give research consent for any excess embryos to be used for research. Some results indicate that "fresh" (non-frozen) oocytes are most productive for IVF.[56] The same is probably true for therapeutic cloning. However, it is mostly stored oocytes from older donors that are available to researchers via IVF. To obtain fresh oocytes, Hwang enrolled family members of patients, as in organ donation. Many suggest that oocyte donation and organ donation are equivalent. This may be true when, and if, stem cell therapy becomes clinically viable. However, its clinical viability is unproved, and the argument is invalid and may represent an extension of therapeutic misconception.

The use of altruistic donors raises serious ethical problems and is the subject of a current consultation by the UK Human Fertilisation and Embryology Authority. Women donating eggs purely for research expose themselves to not insignificant risks (studies put the risk of ovarian hyperstimulation syndrome following oocyte procurement at 0.1% up to 8%[57]) only for the presumed future good of others. The BBC reported that by June 2005 five women in the UK had died of ovarian hyperstimulation syndrome.[58] Altruistic donors, especially with regard to organ donation, have their motives severely scrutinised, and there are problems with coercion from family members.

Altruistic donors to research could be treated as research subjects or "research donors",[45] being given full information about the risks of the procedure and realistic estimates of its research value. Information sheets and consent forms (some of which are published online with this paper) used by Hwang dealt little with the risk of procurement, though this is the only significant risk undertaken by participants.

One way to regulate the treatment of donors is through donor databases, as in organ donation. The donor database of the website may be the first step towards such a system, but it is worrying, because the details regarding donation are unclear – at least to us at this time, given that only scant detail is available in English. The website could act as a depository that licensed researchers can use to approach women willing to donate. This would be advantageous in preventing women from donating more than the legal number of times and ensuring that a suitable time is left between procedures. The woman, once contacted, would become a "research donor" and go through the IRB-approved procedures for gaining informed consent. One risk of a publicly accessible database is that it could be used by a private "oocyte procurement" company. Ambiguity surrounding the website highlights the need for regulation of not just research but tissue donation also.

POSSIBLE SOLUTIONS

Education

Hwang's case highlights the numerous threats to ethical integrity faced by scientists today. Good research is dependent on good ethics, and education is the foundation stone to ensure that researchers understand their responsibilities. Education in ethics should be compulsory in biological degrees. It should deal with practical aspects of research: justifying the use of and working with vulnerable groups, informed consent and participants' rights. Researchers working with human subjects should take appropriate courses and satisfactorily demonstrate relevant knowledge. This education should be renewed every few years in light of the constant evolution of science.

Independent monitoring and validation

A scientific and ethical review committee without conflicts of interest should have been able to highlight the ethically questionable aspects of Hwang's research proposal. Thus, ethical assessment independent of, and in an environment separate from, the researcher is essential. However, this assumes that Hwang's proposal detailed the methods he intended to use. Without auditing research to ensure that guidelines are adhered to, scientists have free rein once approved. Hwang was able to ignore the protocols he drew up with Jung – not even asking donors to sign IRB-approved consent forms.[59] Many now suggest that on-site monitoring by IRBs is appropriate.[42] Magnus and Cho suggest that this IRB should be independent of the one approving the research.[39] Additionally, where applicable, suitable agencies could keep patient samples for

independent analysis and ensure that cell lines are submitted to an international depository for validation.[46]

Guidelines on tissue donation

Donors should be carefully and ethically selected; and currently, it would be ethically advantageous to use donors who would not benefit from prospective treatments. It may also be beneficial to set up a donor register to ensure proper regulation of this aspect of research. Healthy donors should be protected by ethical guidelines, just as patients are in clinical research. Science should work towards reducing the misconceptions surrounding stem cell research.

Debate ethically contentious research

The question of whether to publish unethical research has arisen before with reference to Nazi experiments. Many suggest that there should be limits on what is published. Much Nazi "research" had no scientific value and was a simple disregard for human dignity; however, some was important. Dr Epstein used results of his research to help children recover from noma (orofacial gangrene)[60] – the scientific worth of unethical experiments should not be lost. To prevent distribution of scientific credit, unethical research could be published anonymously. If excessive time was spent debating a paper's ethical quality, originality could be lost and this would be disadvantageous to both journal and author.

Hwang's case demonstrates the difficulty in assessing a paper's ethics. Journals could review IRB and consent forms to inform their decisions, and research auditing would support this. However, only with open debate after publication did details of Hwang's research and its ethical questions become apparent. Journals should publish research such as Hwang's, because it would be ethically questionable to withhold valid data. But rather than censoring such research, journals could facilitate debate among lawyers and ethicists by highlighting questionable legal or ethical areas.

Establish an international ethical code of practice

It seems unlikely that global consensus on stem cell research will be reached soon. To facilitate discussion, the Hinxton Group calls for legal clarification with regard to stem cell research(ers). There was consensus that scientists should be free to conduct ethically defensible research in a country where such research is legal. The Group is developing a website where scientific and ethical protocols can be deposited so that collaborating scientists can conform to a common set of protocols appropriate to both jurisdictions and available to public scrutiny.[46] The Group's move towards documenting ethical and scientific policy in its global context is an important step towards establishing global standards of ethical review. What is perhaps urgently needed is a set of "gold standard" ethical procedures that has international credibility. The Declaration of Helsinki and other international guidelines articulate general principles but are poorly placed to address in detail rapidly emerging, complex areas of research, such as egg donation.

Foster public involvement through the web

Much of the detail surrounding Hwanggate was first brought to the fore on online forums. For example, it was a post on the Biological Research Information Centre's website that first addressed image duplication in Hwang's 2005 paper. However, there was also much debate about "whether someone should inform *Science*".[15] Filing charges of scientific misconduct can be a dangerous business, as the press shows that whistle-blowers often pay a high price for their actions. This is largely because we feel that wrongdoing should be reported, and yet we are uneasy with the act of "abusing" another's trust to do so.[61] Although whistle-blowers have done a good deed in removing bad science from the public domain, the knock-on effects of their action damage not only the perpetrator but the organisation with which they are associated. The costs of whistle-blowing can be high.[62 63] It is thus understandable, if not defensible, that companies are less likely to employ someone known to have been a whistle-blower. The exposure of Hwang highlights a way in which this can be done effectively while protecting those acting in good faith: in the anonymous medium of the internet. A website, or "blog", dedicated to discussion of dubious research practices would facilitate the exposure and hopefully reduce research misconduct. The exposure of Hwang took many posts to build momentum and gain credibility, and in this way would prevent the website from being abused by bad-faith bloggers. The web is the new police and conscience.

Another form of novel ethical oversight using the internet and public involvement would be to make research protocols, patient information and consent forms publicly available on the net. Clearly, commercial interests would need to be protected and key parts of the research anonymised, but it is possible in principle for the ethically relevant details to be disclosed without divulging details of novel substances or procedures. It is the risks and benefits that are important for the ethics, not the nature of the intervention or its commercial advantage or value.

CONCLUDING COMMENTS

Evidence suggests that Hwang was originally a pioneering scientist, and nuclear extrusion techniques he developed have furthered cloning research. However, the extreme pressures of his work environment, complemented by lax implementation of ethical policy and his ambition, led Hwang to make grossly unethical decisions that compromised his integrity. Hwang exemplifies the fact that good science requires good ethics.

No amount of education, guidance, review and oversight can stop a determined and talented person who wants to commit fraud. Good rules can detect bad cheaters, but not good cheaters. The vast majority of scientists are men and women of the highest integrity who sacrifice significant parts of their lives for the pursuit of knowledge to benefit others. Perhaps we must also prepare ourselves for the next Hwanggate and protect the science that overall serves us so well.

Acknowledgements: Thanks to Ruth Faden for valuable comments.

Competing interests: None declared.

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