

Fraud and misconduct in science: the stem cell seduction

Implications for the peer-review process

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Scientific misconduct and fraud occur in science. The (anonymous) peer review process serves as goalkeeper of scientific quality rather than scientific integrity. In this brief paper we describe some limitations of the peer-review process. We describe the catastrophic facts of the ‘Woo-Suk Hwang fraud case’ and raise some ethical concerns about the issue. Finally, we pay attention to plagiarism, autoplagerism and double publications. (*Neth Heart J* 2009;17:25-9.)

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Unfortunately, fraud exists in science and several examples and degrees in terms of severity have been described.¹ Fraud should not be confused with publication bias, which concerns both the tendency to overpublication of studies with a positive outcome and the opposite for studies with a negative outcome, including the unconscious incentives of the researchers involved. The theoretical aspects of the latter have been addressed² and in a more practical analysis it has been demonstrated that of highly cited clinical research studies (i.e. cited more than 1000 times in the period between 1990 and 2003), only 44% were replicated with similar results.³ Incredible as this may sound, this still does not refer to fraud, which is intentional

fabrication of data or manipulation of their analysis or, as we shall see, inappropriate acquisition of data.

Peer review

The Royal Society of London obtained the fiscal responsibility for the *Philosophical Transactions* in 1752 and this may be regarded as the origin of ‘peer review’.^{4,5} Reports on the editorial process of *Radiology*,⁶ *Journal of Clinical Investigation*⁷ and *Cardiovascular Research*⁸ have indicated that there is little concordance between the opinion of different reviewers on identical manuscripts. Editors can – with the help of reviewers – discriminate between low- and high-quality papers in a reasonable way, which follows from the fact that manuscripts rejected by the *Journal of Clinical Investigation*⁹ and by *Cardiovascular Research*¹⁰ were cited at a lower frequency, even when published in journals with a higher impact factor than the journal that had rejected the paper previously.¹⁰ However, in the higher quality range there are many more manuscripts suitable for publication than the number that can be published.¹¹ Reviewers and editors cannot make the distinction between good or excellent papers. Their *a priori* priority ratings have almost no predicative power for future citation.¹⁰ This is even true for *a posteriori* peer ratings when citation data are known.^{12,13} This means that the distinction between good and excellent papers, important for an editor’s decision to publish or not, cannot be made with sufficient trust in objective criteria. It is within this particular context that the problem of recognising scientific fraud has to be appreciated. We will give attention to the recent devastating fraud case in the field of embryonic stem cells under the responsibility of Woo-Suk Hwang in a paper published by the highly esteemed journal *Science*.

The Woo-Suk Hwang fraud case

At the end of 2005, the scientific community was shocked by one of the greatest cases of misconduct in the history of science. Two breakthrough articles about stem cell technology from a Korean laboratory headed by Woo-Suk Hwang, published in *Science*, appeared to be almost completely fabricated and were therefore retracted.¹⁴ The original source papers were published

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Table 1. Timeline of occurrences.

12 February 2004	1st report of human ESC lines derived from cloned blastocysts by Hwang and colleagues in <i>Science</i>
6 May 2004	First publication of doubts about ethical practices in oocytes obtainment
19 May 2005	2nd report in <i>Science</i> about 11 cloned human ESC lines
3 August 2005	Korean team claims to have cloned the first dog in <i>Nature</i>
12 November 2005	Gerald P. Schatten suspends collaboration with Hwang because of doubt about oocyte sources
24 November 2005	Hwang admits unethical behaviour
6 December 2005	Duplicated panels in 2nd <i>Science</i> publication are noticed
12 December 2005	Seoul National University starts the investigation on the Hwang papers
14 December 2005	Schatten asks <i>Science</i> to remove him as author
16 December 2005	Hwang requests retraction of 2nd publication in <i>Science</i>
10 January 2006	Seoul National University releases investigation report
9 February 2006	Seoul National University suspends Hwang as professor
3 March 2006	Hwang submits a manuscript on SCNT as senior author carrying his Seoul National University affiliation ²⁸
20 March 2006	Seoul National University announces dismissal of Hwang
12 May 2006	Hwang submits a manuscript as senior author carrying his Seoul National University affiliation ²⁹
12 May 2006	Hwang is officially charged for fraud by Korean prosecutors
31 July 2006	Hwang submits a manuscript on SCNT as co-author carrying his Seoul National University affiliation ³⁰
30 March 2007	Hwang publishes on SCNT in bovine embryos as senior author in <i>Animal Reproduction Science</i>
6 April 2007	Hwang submits a manuscript on porcine oocyte maturation as co-author carrying his Seoul National University affiliation ³¹

as follows: Hwang W-S, et al. Evidence of a pluripotent human embryonic stem cell line derived from a cloned blastocyst. *Science* 2004;**303**:1669-74 and Hwang W-S, et al. Patient-specific embryonic stem cells derived from human SCNT blastocysts. *Science* 2005;**308**: 1777-83. The reason why we refer to these source items in the text and not in the list of references is that retracted papers tend to be cited even more frequently after retraction than prior to it. Pressing questions arose about the fabrication process itself and whether publication of the two fraudulent articles could have been prevented. By studying this particular case, lessons have to be learned about the status of current review procedures regarding fraud and data manipulation. What can individuals, in their quality as author and reviewer, and editors do to prevent occurrences such as in the stem cell debacle.

The two fraudulent papers concentrated on the concept of therapeutic cloning in humans. In this somatic cell nuclear transfer (SCNT) technology, a nucleus from a patient's somatic cell is transplanted into an enucleated donor oocyte. The resulting blastocyst embryo is used for the isolation of embryonic stem cell (ESC) lines that possess virtually all the patient's characteristics and thus will minimise immune rejection upon transplantation. Until the publication of the fraudulent papers, therapeutic cloning was a cumbersome and inefficient technique and successful therapeutic cloning in humans had not been reported before. In their 2004 paper, Hwang and his associates

claimed to have isolated the first human ESC line derived from SCNT and in their second paper they reported to have improved the efficiency to such an extent that clinical application became within reach.

Two months following the first paper (table 1), criticism arose on the ethics of obtaining the human oocytes used in the study. After initial denial it became clear that egg donors had been paid and two lab members had provided oocytes. This forced Hwang to admit these unethical practices.¹⁵ Subsequently, the scientific content itself raised questions. Duplications of four microscopic photographs in different panels, and designated as different ESC lines, in the publication of 2005 were uncovered,¹⁶ but these were parried as an accidental mistake by Hwang and the *Science* editorial board.¹⁷ Furthermore, DNA fingerprint comparison of presumed donor and derived ESC lines showed no inter-experimental variety and were in fact performed on the same fingerprint profile.¹⁶ Hwang agreed to an independent investigation by Seoul National University.¹⁸ His three most important recent works were investigated: the retracted 2004 and 2005 *Science* papers and a publication in *Nature* about a cloned dog.¹⁹ The conclusions were clear.²⁰ The claim of being the first laboratory to create a pluripotent human ESC line through SCNT was reported to be false. Verification of the DNA fingerprints of cell lines, teratomas and donors showed that the NT-1 cell line was not derived from the designated donor. Second, no evidence was found to verify the conclusions of the

report of the 11 ESC lines in the paper of 2005. The claims were based on material obtained from two ESC cell lines derived by IVF rather than SCNT. Displayed results of DNA fingerprinting, karyotyping, data of MHC-HLA isotyping and photographs of teratoma and embryoid bodies were all fabricated. The publication of the cloned dog was verified as being true, as was confirmed by another independent party, appointed by *Nature*.^{21,22}

Three aspects of this fraud case are curious. First, the restricted availability of the results of the investigations is questionable. A translation in English of the full Korean report exists but, as we found out, is only accessible for Seoul National University, the journal *Science* and the University of Pittsburgh. It is unclear which goal is served by this. Second, our efforts to see the original reviewer's reports (anonymous) were thwarted by *Science*. Our request simply remained unanswered. This suggests that even when a debacle has taken on such dramatic dimensions as in this case, a journal Editor with a big reputation prefers to keep silent. Possibly, the Editor hoped that it was 'only' an incident and that it would involve another journal if it happened again. This seems of little help to solve the problem. Third, although concerns were raised during the review process that proved to be important afterwards, this did not lead to a more critical approach to the paper by the Editors of *Science*. Afterwards, several lament editorials, such as reference 23, were published by Dr Kennedy, Editor-in-Chief of *Science*, but these read as if the case was an accident rather than as a *pars pro toto*.²³

Can fraud be prevented?

How can we expect reviewers to act as policemen if we have to admit that they are not even able to make the distinction between what is good and what is excellent?²⁸⁻¹³ They have no training whatsoever in this, and certainly not in pursuing matters that turn out to be criminal. Still, it might be a good idea to centralise the process of review far more than is usual nowadays. Two reviewers see more than one and three see more than two. By centralising the peer review process it would become possible to significantly increase the number of reviewers per paper. Furthermore, open access to reviewer's comments, also after publication of a paper, may improve the quality of peer review. This can be done with or without abandoning the anonymous state of reviewers. In the past, under the Editorship of David J. Hearse, *Cardiovascular Research* performed a brief survey on the effect of anonymous review.²⁴ It appeared that any journal advocating such a revolutionary policy at that time would lose about 50% of its reviewers.²⁴ Not a single journal can afford that. In addition, when it is considered that many submitted manuscripts will eventually be published somewhere,²⁵ one may ask whether it is not time to make an end to the ineffective way of handling manuscripts. Wouldn't it be a good

idea to centralise this process and give editors the chance to select manuscripts from a centralised system of peer review? We are not the first to suggest attaching reviewers' reports to manuscripts after publication²⁶ and in an electronic era page limitations are no longer an obstacle. None of these suggestions will stop violators of good scientific practice, but the idea of a more open approach to the whole peer-review process will, in our opinion, eventually be unavoidable.

Additional ethical considerations

Hwang resigned from Seoul National University in late December 2005, and was officially dismissed as announced on 20 March 2006.²⁷ But, Woo-Suk Hwang is still active in scientific research and even submitted three manuscripts on behalf of Seoul National University in 2006, which were recently published in *Theriogenology*,²⁸ *Animal Reproduction Science*²⁹ and *Biochemical and Biophysical Research Communications*.³⁰ journals published by Elsevier Science with 2007 impact factors of 1.911, 1.739 and 2.749, respectively. In 2007, he submitted another manuscript on behalf of Seoul National University, which appeared in *Molecular Reproduction and Development*,³¹ published by Wiley InterScience with a 2007 impact factor of 2.538. Currently, he has resumed conducting research in a private research facility in South Korea.³² Although this research does not focus on human stem cell technology,³² his latest publications include optimising SCNT in porcine oocytes.³³

Here we arrive at an interesting ethical issue. Can the scientific community trust one of its members in the future if he or she has committed a serious crime? We have no answer to this ethical question, but feel that ethical issues related to the way data were obtained, as with the collection of oocytes,¹⁵ may be judged in a different way, certainly in different cultures. In our opinion violation of such generally accepted ethical standards is sufficiently handled by rejection of the manuscript, albeit that such crimes may be subject to prosecution afterwards within the legal system of the specific offender. However, when fabrication of data is involved²⁰ one may question whether authors should not be denied the right to submit manuscripts to scientific journals, at least for a considerable period.

On reflection, the consideration that violation of internationally accepted ethical standards is less serious than true fabrication of data, as we started to suggest above, is dangerous. And probably even more dangerous in regimes where freedom of science comes second to political power. There are still important lessons to be learned from the crimes of scientists active during the Nazi regime and from crimes committed by Japanese scientists under the responsibility of Shiro Ishii on Chinese farmers and prisoners of war during the Japanese occupation of China in the Second World War.³⁴ The fact that these crimes were never brought to court in exchange for the availability of the data for

the American biological warfare programme is a scandal and constitutes a crime in itself against the Chinese victims. We would like to underscore that our scepticism about 1) the criminal behaviour of Hwang and associates and 2) about the way this was handled by the responsible authorities should in no way be considered criticism of the type of research (stem cell research). The type of research is not under debate.

Plagiarism, autoplagerism and double publications

Plagiarism and autoplagerism, the latter leading to double publications, are another issue that the scientific community could do without. Plagiarism probably occurs much more often than scientists are aware of and the case of the economist Hans Werner Gottinger is exemplary.³⁵ Also in the social sciences, plagiarism is a problem and there are cases that remain undiscovered for decades.³⁶ In cardiovascular science, we have found several examples of almost identical papers published twice.³⁷⁻⁴⁶ The fact that a paper is published in more than one language, i.e., in Chinese and in English, is not an excuse for double publication. There is nothing wrong with a literal translation with the aim of making data available to a larger audience, provided that it is made clear that it concerns a translation with reference to the original source. However, Wang and Wang published an almost identical paper on the effect of glycine on haemorrhagic shock, first in Chinese in a Chinese journal³⁷ and later with marginal changes in English in another Chinese journal.³⁸ Ma et al. published on the effects of insulin in the ischaemic/reperfused canine heart, first in English in *Cardiovascular Research*³⁹ and later in Chinese in a Chinese journal.⁴⁰ The opposite was done by Yang et al. First they published in Chinese on the effect of arsenic trioxide in the prevention of restenosis within stents in rabbits in a Chinese journal⁴¹ followed later in the same year by an almost identical paper in English in *Cardiovascular Research*.⁴² Two other examples of twin papers with publication first in Chinese in a Chinese journal followed by publication in English in a Western journal concerned the *American Journal of Clinical Pathology*^{43,44} and *Histology and Histopathology*.^{45,46}

This type of misconduct is of all times, but with the expansion of Asian science⁴⁷ with a lot of pressure to publish, it may be that we are seeing just the tip of an iceberg. Programmes that can spot plagiarism and that are routinely used for screening students' papers may become an unavoidable tool for Editors (and reviewers??) and are being optimised for even comparing strings of texts in different languages.^{48,49}

We are well aware that we have addressed several serious issues related to publication of scientific information but that this brief article does not present any clues for a solution. The idea that the work of reviewers who spend so much precious time on manuscripts would be further burdened by checking for fraud and/or

other types of misconduct is not at all appealing. The work on publication of science is based on good faith (see also Reyes⁵⁰). It is questionable whether this is still justified in a modern era in which science has become more and more organised as business. The acquisition of grants and publication of papers as well as their citation have become of paramount importance for the careers of young scientists. Although their attitude to the demands of the 'system' remains their own responsibility, it should be realised that seduction comes with a prize. ■

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