

Science fraud: from patchwork mouse to patchwork data

Summerlin pulled two white mice from the container. While they wriggled and squeaked in protest, he inspected the sites of the black skin grafts. Impulsively, Summerlin took his felt-tipped pen out of the breast pocket of his white coat and applied it briefly to the grafted patches on the two white animals. The ink made them look darker. Then he replaced the mice in the bin and strode out . . .

From *The Patchwork Mouse*, an account of William T. Summerlin's 1974 false claim of skin transplantation without immunosuppression (1).

Fraud was so much simpler a generation ago. All one had to do was to take a felt-tipped pen and color a square patch of mouse skin. The incriminating patchwork was also easy to detect. Summerlin's faked "transplants" were discovered by a laboratory assistant who washed off the black ink with a ball of cotton soaked in a little alcohol. Yet the scandal and its upshot in 1974 were just as great as those aroused by the more complex frauds of today. The patchwork incident was described by Jane Brody in *The New York Times* as "a medical Watergate" that reflected "dangerous trends in current efforts to gain scientific acclaim and funds for research." Indeed, Robert A. Good, Summerlin's chief and co-author, was accused of "manipulating national attention and attracting an enormous amount of money for the institute." (2) Soon afterward, Good stepped down as director of Sloan-Kettering, and that was the end of transplantation without immunosuppression. It sank without a trace in the literature: Summerlin's fraudulent papers have been cited only 3 times in the past 25 years; each a refutation (3, 4).

Korean stem cells

Nowadays it takes more than a lab assistant with a cotton swab to detect fraud. In 2005, Seoul National University appointed a broad committee to investigate Professor Hwang Woo-Suk's claim that he had established 11 human embryonic stem cell lines by transfer of somatic cell nuclei (5). The team reported that "The data in the 2005 article including test results from DNA fingerprinting, photographs of teratoma, embryoid bodies, MHC-HLA isotype matches, and karyotyping have all been fabricated . . . the research team of Professor Hwang does not possess



Patchwork Quilt (Courtesy of Michele Fox <http://www.yardgoods.net/>)

patient-specific stem cell lines or any scientific bases for claiming having created one." (6) To reach this conclusion, the committee collected cytogenetic samples, checked hundreds of DNA fingerprint samples, examined mitochondrial DNAs and compared dozens of polymorphic loci in the genes of alleged donors. Like Summerlin's patchwork fraud, Dr. Hwang's fabrication was attributed to scientific pride and overreach. Richard Doerflinger, of the United States Conference of Catholic Bishops, told *The New York Times* that "Hype and ambition have gotten ahead of the science." (7) Soon afterward, Dr. Hwang stepped down from directorship of his unit and that was the end of patient-specific stem cell lines in Seoul.

Remedies for fraud

The worldwide response to Dr. Hwang's fraud was as predictable as that to the patchwork mouse a generation ago: pious hand wringing and angry finger pointing. Now, as then, critics of science blamed the messen-

ger (the journal) rather than the message (the fabrication). Bold changes were demanded in the way science gets written, reviewed, and published; and scientific editors scrambled to get out of the line of fire. But one might say that science journals already have a Sarbanes-Oxley code in place. Most journals already insist that all co-authors sign off on the final manuscript, some oblige each author to spell out his exact role, and others require each author to affirm the accuracy of every stage of the manuscript. Nevertheless, the editor of *Cell* suggests that it is time for the National Academy of Sciences to set strict new standards that apply to all (8). My colleague, Donald Kennedy of *Science*, observed that: "A journal cannot go into authors' laboratories in search of fraud," but hedged his bet: "More actively, we are committed to examining our processes and ourselves in an effort to extract lessons for the future (9)." The *Journal of Cell Biology*, which already has an elaborate digital process in operation to detecting image-fraud, now plans to erect a screen of algorithms designed to spot specific types of image manipulation. The software was developed under a grant from the FBI (9).

Patchwork data

To determine whether *The FASEB Journal* should turn to image scanning, algorithms for detecting statistical swindles, etc., I've looked at recent cases of fraud and come up with some tentative conclusions:

1) Some scientists will cheat and we'll probably never know how often this happens. Young or old, MD or PhD, average or distinguished, male or female, black or white or khaki, some scientists will try to pull wool over the eyes of their colleagues, their reviewers, and their editors.

2) The culture of science is based on trust, not suspicion. Great scientists have had fraud committed under their noses, and good editors have published fabrication. Reviewers and editors must have a keen nose for swindle, but cannot engage in criminal investigation. As in political life, where I tend to side with liberty over security, in science, I'd go for trust over suspicion every time.

3) Therefore, we ought not to rely on machines or algorithms of image or text analysis, but rely on the judgment of our editors, our editorial boards, and our reviewers as to whether a manuscript looks as if the data had been cooked.

4) No measure of "quality assurance", no affidavit of authorship, no oath of responsibility or percent effort can stop a soul hell-bent on self-destruction. And fraud in science, if not in politics, is always self-destructive. Since the name of the game is confirmation, science is self-cleansing: flawed work is soon forgotten and remains uncited.

Those conclusions are based in part on three recent illustrations of the swindler's art.

Cancer of the mouth

A study published by the Norwegian oncologist, Jon Sudbø, in *The Lancet* of October 15, 2005, concluded that long-term use of nonsteroidal antiinflammatory drugs could reduce the risk of oral cancer while exposing patients to higher risks of death from heart disease (10). Sudbø's fraud was exposed when Camilla Stoltenberg of the Norwegian Institute of Public Health, who had access to the primary data, discovered that of the 908 people in the study, 250 shared the same birthday! After Sudbø confessed to his action, an embarrassed spokesman for the hospital admitted that the data were "totally false, actually totally fabricated. His database had been completely fabricated on his computer" (11). The fraud led editors at *The New England Journal of Medicine* to look into two earlier papers by Sudbø and sure enough, the journal issued an "expression of concern" because two photomicrographs in a 2001 paper which purported to represent two different patients and stages of disease were in fact different magnifications of the same photomicrograph. Sudbø had patched histograms of ploidy to overlay his photomicrographs so that the ruse was not immediately evident (12, 13). Keeping with *The Lancet's* antifraud policy, Sudbø's paper not only affirmed that "JS, JLL, SML, and AJD (Sudbø and collaborators) contributed equally to this paper" but also detailed the part each author played in statistical analysis, cutting the sections, writing the paper, etc. Ironically, as required, the paper affirmed that "All authors approved the final report." Conclusion: So much for quality assurance forms. And as to image fraud, Michael Rossner of *The Journal of Cell Biology*, while arguing that "The goal of a journal editor should be to catch these things before publication if at all possible," admitted that his methods are not yet up to catching tricks of magnification like Sudbø's (13).

Immunologic tolerance

Luk van Parijs, a 35 year old "rising star" in the field of RNA interference (RNAi), was dismissed from MIT in November of 2005. After the whistle was blown by co-workers in his lab, Van Parijs confessed that he had fabricated data in grant applications, published papers, and in submitted manuscripts. He'd been hired by MIT on the basis of strong publications as a graduate student at the Harvard Medical School and a productive postdoc stint with David Baltimore at Cal Tech. Now much of his work is under scrutiny. David Baltimore, Cal Tech president, and no stranger to such matters, wired *Science* magazine: "I thought Luk was an excellent scientist and truly cannot understand why he would fake anything" (14). *The New Scientist* engaged experts to scrutinize two of van Parijs's papers, one from Harvard, the other from Cal Tech. The issue remains contested by van Parijs (15). A 1998 paper in *Immunity* describes how *Fas/FasL* and *Bcl-2*, factors

relevant to apoptosis, affect T cell responses to self- and non-self antigens. *The New Scientist* review concluded that "Fig. 1 of the paper contains 8 graphs . . . Three graphs in the top row of the figure look very similar. Yet they are captioned as if they show data from three different mice . . . In the bottom row, three graphs again look very similar. Yet they are again captioned as if they show data from three different mice." Worse yet was found in the Cal Tech paper: "two graphs in Fig. 1C look very similar, especially if the graphs are printed out on transparent paper and superimposed. Yet one is captioned as if it comes from mouse cells infected with a human mutant gene, while the other is captioned as if it comes from mouse cells infected with a normal "wild type" human protein." (15). Conclusion: Even the best of senior scientists at Harvard and Cal Tech can have the wool pulled over their eyes, repeatedly.

Patching genes

In August of 1996, a reviewer for the British journal *Oncogene* found something strange on a submitted Western blot. The image accompanied a paper on cell transformation caused by a fusion protein coded by an abnormal chromosome associated with acute myeloid leukemia. Co-authors of the paper included the recently appointed director of the US National Center for Human Genome Research, Francis Collins, and a young MD-PhD candidate at Michigan, Amitav Hajra. When the anomaly was called to Collin's attention, he immediately confronted the culprit. It was, Collins told *Science* magazine "one of those days you'll never forget." (18) Presented with evidence of a file of fraudulent data that Collins had unearthed, the student confessed. As the US Office of Research Integrity reported, Hajra fabricated data in "five published research papers, two published review articles, in one submitted but unpublished paper, in his doctoral dissertation, and in a submission to the GenBank database." (19) Collins circulated an apology to his colleagues in the field, withdrew the offending publications, and the government eventually exerted sanctions against Hajra. The inquiry had started with that patched Western blot. The reviewer for *Oncogene* noted that two lanes in the Western blot, labeled as two different proteins had the same background artifacts. Collins explained to *Science*: "There is a lane in the upper left, which if you cut it about halfway down, and then took the lower half and turned it 180 degrees so that the bottom is now the top, you end up with something that looks like a lane in the lower right." Not easy to spot, but "absolutely unequivocal once you look," Collins explained. Conclusion: It's hard to see the mote your own eye, and it takes a sharp reviewer to cast it out.

Does fraud matter?

I checked out the citation record for one of the retracted Hajra and Collins papers. As published in

Molecular and Cellular Biology, the experiments would have constituted a dramatic test of the oncogenic potential of the fusion protein (20). According to ISI, it's been cited only 12 times since 1995 (20). As a random control, I looked up the citation record of the publication that immediately followed the Hajra and Collins opus in the same issue of the journal. The paper by Sonenbergs' group at McGill, also describes a protein/protein interaction that controls nucleic acid function (21). That paper has been cited 276 times.

Conclusion

Science is self-cleansing, but check the Western blots. 

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REFERENCES

- Hixson, J. (1976) *The Patchwork Mouse*. Joseph Hixson Anchor Press/Doubleday, Garden City, New York. pp. 4–5
- Brody, J. (1974, April 18) Charge of False Research Data Stirs Cancer Scientists at Sloan-Kettering. *The New York Times*. p. 20
- Summerlin, W. T. (1973) Allogeneic transplantation of organ cultures of adult human skin. *Clin. Immunol. Immunopath.* **1**, 372–384
- Summerlin, W. T., Miller, G. E., and Good, R. A. (1973) Successful tissue and organ transplantation without immunosuppression. *J. Clin. Invest.* **52**, 34a
- Hwang, W. S., Roh, S. I., Lee, B. C., Kang, S. K., Kwon, D. K., Kim, S. J., Park, S. W., Kwon, H. S., Lee, C., K., et al. (2005) Patient-specific embryonic stem cells derived from human SCNT blastocysts. *Science* **308**, 1777–1783
- Seoul National University Investigation Committee. (2006, January 10) Summary of the Final Report on Hwang's Research Allegation. *SNU News*. <http://www.snu.ac.kr/engsnu/>. Accessed January 2006
- Kolata, G. (2005, December 16) Clone Scandal: 'A Tragic Turn' for Science. *The New York Times*. p. A6
- Wade, N. (2006, January 24) It May Look Authentic; Here's How to Tell It Isn't. *The New York Times*. Science section, p. 1
- Kennedy, D. (2006) Good News—and Bad. *Science* **311**, 145
- Sudbø, J., Lee, J. J., Lippman, S. M., Mork, J., Sagen, S., Flatner, N., Ristimaki, A., Sudbo, A., Mao, L., Zhou, X., et al. (2005) Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study. *Lancet* **366**, 1359–1368
- Pincock S. (2006, January 16) Lancet study faked. *The-Scientist.com*; <http://www.the-scientist.com/news/display/22952>. Accessed January 2006
- Curfman, G. D., Morrissey S., and Drazen J. M. (2006) Expression of Concern: Sudbø J et al. DNA Content as a Prognostic Marker in Patients with Oral Leukoplakia. *N Engl J Med* 2001;344:1270-8 and Sudbø J et al. The Influence of Resection and Aneuploidy on Mortality in Oral Leukoplakia. *N Engl J Med* 2004;350:1405-13. *N. Engl. J. Med.* [Epub ahead of print] www.nejm.org (10.1056/NEJMe068020). Accessed January 2006
- Cook, G. (2006, January 21) Medical Journal Says Papers May be Fraudulent. *Boston Globe*, p. A9
- Couzin, J. (2005) Scientific Misconduct: MIT terminates researcher over data fabrication. *Science* **310**, 758

15. Reich, E. S. (2005, October 28) MIT professor sacked for fabricating data. NewScientist.com. <http://www.newscientist.com/article.ns?id=dn8230>. Accessed January 2006
16. Van Parijs, L., Peterson, D. A., and Abbas, A. K. (1998) The Fas/Fas ligand pathway and Bcl-2 regulate T cell responses to model self and foreign antigens. *Immunity* **8**, 265–274
17. Van Parijs, L., Refaeli, Y., Lord, J. D., Nelson, B. H., Abbas, A. K., Baltimore, D., and Uncoupling, I. (1999) L-2 signals that regulate T cell proliferation, survival, and Fas-mediated activation-induced cell death. *Immunity* **11**, 281–288
18. Marshall, E. (1996) Fraud strikes top genome lab. *Science*. **274**, 908–910
19. Office of Research Integrity, Department of Health and Human Services (1997) Office of Research Integrity Newsletter. Case Summaries: Amitav Hajra, University of Michigan. http://ori.dhhs.gov/documents/newsletters/vol5_no4.pdf. Accessed January 2006
20. Hajra, A., Liu, P. P., Speck, N. A., and Collins, F. S. (1995) Overexpression of core-binding factor alpha (CBF alpha) reverses cellular transformation by the CBF beta-smooth muscle myosin heavy chain chimeric oncoprotein. *Mol. Cell. Biol.* **15**, 4980–4989
21. Mader, S., Lee, H., Pause, A., and Sonenberg, N. (1995) The translation initiation factor eIF-4E binds to a common motif shared by the translation factor eIF-4 gamma and the translational repressors 4E-binding proteins. *Mol. Cell. Biol.* **15**, 4990–4997

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