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Office of Research Integrity

NEWSLETTER

The *ORI Newsletter* is published quarterly by the Office of Research Integrity, Office of the Assistant Secretary for Health, Department of Health and Human Services, and distributed to applicant or awardee institutions and PHS agencies to facilitate pursuit of a common interest in handling allegations of misconduct and promoting integrity in PHS-supported research. Please duplicate and circulate this newsletter freely. An electronic copy is available on the ORI home page at http://ORI.HHS.GOV.

IN THIS ISSUE

What Do Retractions Tell Us?

John Krueger, Ph.D., ORI

It is an unwelcome validation of the contemporary public interest in science when news about retractions of research papers appears on the front page of a major national newspaper.[1] Fed by the blogosphere,[2] the fascination with the rise in retractions also mirrors discussion in the scientific weeklies,[3] journal news blogs,[4] and the new social media in science.[5] Subject matter that historically would have appeared in journals devoted to research ethics[6] has appeared in a journal that normally reports results of bench experiments.[7] The problem shows no sign of abating; the latest data from the National Library of Medicine (NLM) for 2012 show that retractions have increased 37 percent-38 percent over 2011.[8]

Retractions have become the public's window into research misconduct, but how valid is this view? On the Office of Research Integrity's (ORI's) 20th anniversary, it is timely to ask: Does the spate of retractions necessarily mean that scientists are more dishonest,[6,7] or are retractions perhaps just a consequence of the way research is now conducted and communicated in the digital age? Are retractions "the new order" or an epidemic that will subside spontaneously? If not, what preventive countermeasures might

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A Research Misconduct Case: 10 Years of Bad Behavior

Susan Garfinkel, Ph.D., ORI

On November 20, 2012, the *Federal Register* published a notice reporting the finding that Dr. Eric J. Smart, a former Professor in the Department of Pediatrics and Physiology at the University of Kentucky (UK), committed research misconduct and agreed to a voluntary settlement for a seven-year period of exclusion from eligibility to apply for, or be supported by, funds from the federal government.

The research misconduct was extensive and occurred over a 10-year period from 1998-2008. In total, Dr. Smart included false claims of images in 10 published papers, one manuscript submitted for publication, seven grant applications, and three progress reports. The false claims in grant applications and progress reports related to experiments conducted with a strain of mice that did not exist at the UK or elsewhere and, thus, could not have been done. In addition, 45 false or fabricated images were included in 10 papers, one submitted

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Retractions *(from page 1)*

work? In looking into the larger issue, we should start with three questions: (1) What is the scope of the problem? (2) What factors contribute to the rise in the retraction trend? and (3) Based on the answer to the first two questions… and beyond "talk" and exhortation…, are there tangible measures that various constituencies can do to combat this trend?

What is the scope of the problem?

NLM tracks the fate of the biomedical research papers that it indexes.[8] Figure 1 shows NLM data for the period from 1996-2011, in which the number of retractions has been normalized by the number of "citations" (i.e., total number of papers) in the same year, to account for the inexorable growth in biomedical research. As pointed out by others, the incidence of retraction has skyrocketed. As dramatic as the rise may appear, however, to date the peak rate is only about 0.04 percent of the annual biomedical literature.[9] This very small number alone does not establish whether the reliability of scientific research has fallen.

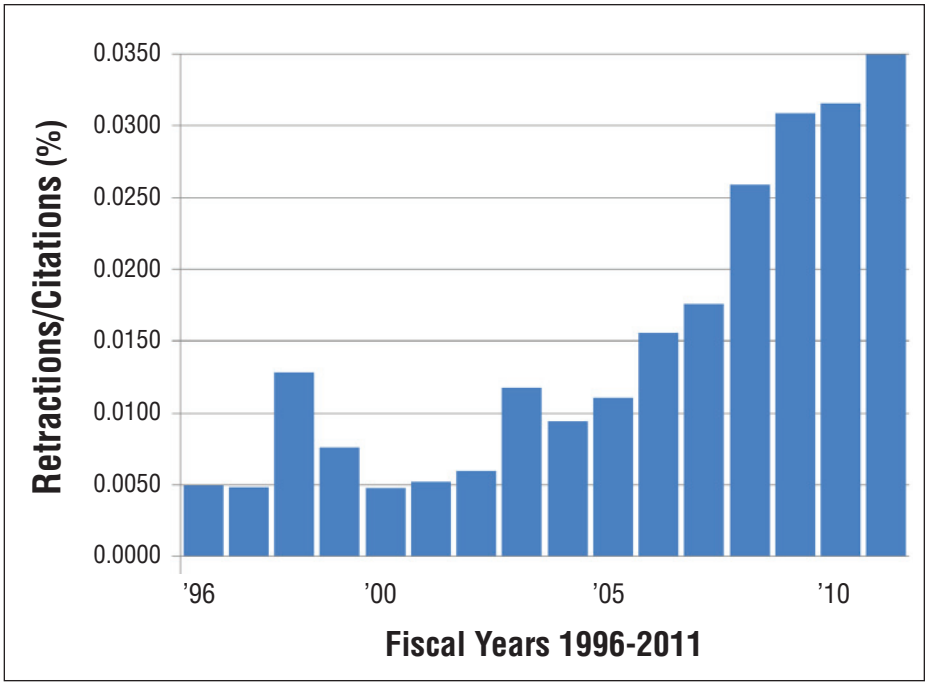

Figure 1. The course of retractions in biomedical literature for the 15-year period from 1996-2011. The annual number of retractions (as notices) has been adjusted by the total number of papers (as citations indexed in MEDLINE) appearing in the same year. The latest data (not shown) are that the 348 retraction notices for 2012 are equivalent to 0.0457%, or a 30.5% increase over 2011.

How can we be sure that changes in what are small numbers represent a significant trend? Figure 2 shows NLM data on retractions that are relative to sources of publishing errors, notably the data for errata published during the same year.[10] When all the data are viewed in this way, a discrete shift now appears, and a quantitative basis for characterizing the trend is suggested. Since 2002, the rate of errata, compared with other sources of errors, has remained relatively constant at about 1 percent (inset), but starting in 2005-2006, the dynamics affecting only retractions changed. The combined effect of the factors causing retraction has suddenly increased tenfold (i.e., from a slope of about 0.009 to about 0.096) (see Figure 2). The existence of a breakpoint in Figure 2 suggests that this rise is not due to random events, as has been asked elsewhere (Steen, 2011[6]). My construct in Figure 2 is possibly artificial, yet the full relation between retractions concerning citations can also be matched well by fitting the data to a single exponential curve. Doing so also shows an approximately tenfold increase in retraction rates over the past 10 years.[11] However demonstrated, the discrete and fairly rapid onset may be easier to reconcile with effects of technological changes rather than a shift in values and attitudes of scientists. (I speculate the latter occurs very slowly.) If this trend persists, the rise in the number of retractions will only accelerate in years to come (as explained later).[12] This means researchers will have to adopt a proactive approach to deal with the consequence.

Timing of Retractions

The research also found the lag between the publication and retraction has lengthened, to a period

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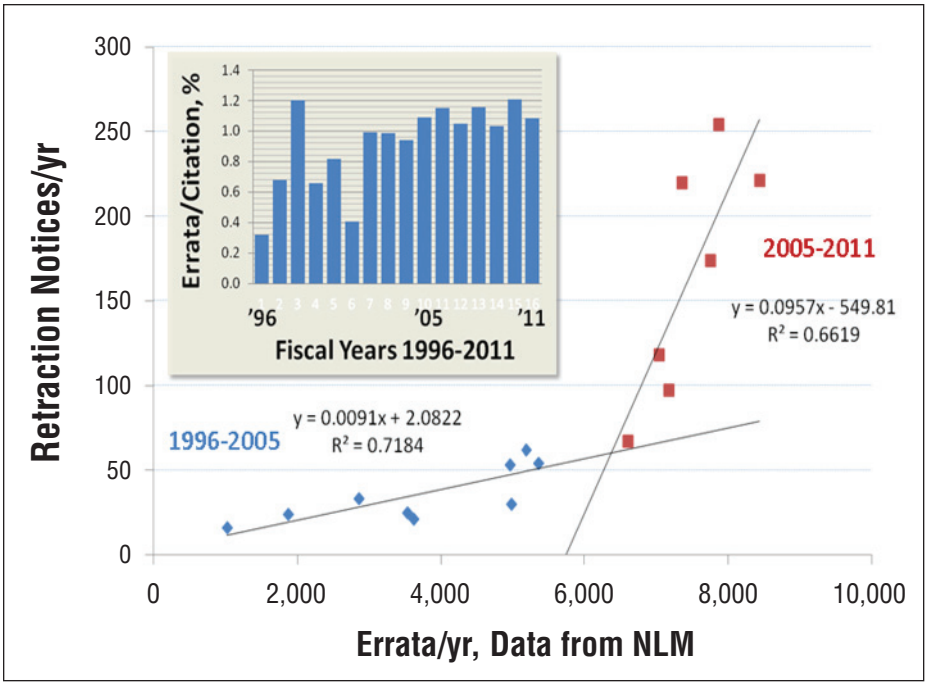

Figure 2. The relation between the number of annual retraction notices and other sources of publishing errors, shown here as errata. A discrete shift in the dynamics favoring retraction is suggested. By this measure, starting in 2005, papers were tenfold more likely to be retracted relative to other forms of publishing errors. No comparable increase occurs in the number of Public Health Service (PHS) findings of research misconduct.

exceeding 35 months (in 2009). (See Figure 3, Steen, 2011[6]; Table 2.[7]) How would a more rapid dissemination of research results via the Internet cause a longer delay in deciding the fate of research results? One explanation is that the accessibility introduced by the Internet facilitates the continuing inspection of papers as never before. This process is more likely to identify a concern if the data are in a more transparent form, such as images. (Plagiarism/reuse of text is also easier to detect.) In fact, the average timing for a retraction is similar to the time it now takes for resolution of most institutional fact-finding processes. They were set up to meet requirements for receipt of the National Institutes of Health (NIH) funding under PHS misconduct regulations.

One concern in these trends is whether decisions about corrections of the literature are being deferred to other authorities. Once a problem is discovered, is the process set up to protect the literature inadvertently impeding its timely correction? Whether the increased delay means that individual papers are taking longer to retract, or whether the transparency and access now place at risk even older papers (due to missing data), is not known.

Retractions Don't "Measure" Misconduct

The ease of fabricating image data means that a few scientists (i.e., "repeat offenders"[9]) can contribute disproportionately to the numbers of retractions, and now their impact will be greater because the baseline of the numbers is quite small. In fact, isolated deviations on the trend support that presumption (Figure 1)[13] and show that retractions are not a measure of misconduct by the community at large. Individual ORI cases have involved an increased number of papers, but that is only a partial explanation, as discussed next.[14]

What factors contribute to the rise in the retraction trend?

"Structural" Factors

Because the rise of retractions has been so rapid, it is worthwhile to examine a combination of structural factors that govern how science is now carried out. Such factors are related to the greater accessibility because of the Internet and "open access." One clear factor has been the ability to detect copying of text using plagiarism software. However, the most noticeable shift in allegations of misconduct over the past decade has been the increase in the number of ORI cases that involve questioned images.[15,16] Thus, another factor may arise through transparency, i.e., access to images with much better detail. Scientific images appear in many forms,[17] but all have intrinsic properties that identify them as being unique and that can occasionally reveal signs of "inauthenticity." Once they are made visible, those signs can be perceived. When that happens, it does not take a lot of specialized

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expertise to determine whether the data are not fully what is claimed.

The risk to retraction is amplified by the convenience conferred by digital technology. Raw data can now be acquired, reduced, placed into a presentation, and submitted for publication in a matter of hours, by one unsupervised individual. Does technology create shortcuts for review by colleagues and for practices that formerly ensured good science but now evolve more slowly? Can traditional "safeguards" keep pace with these changes?

Readers Have Become Reviewers

Open access publication and images make data more transparent to scientists outside of the laboratory.[18] Critical review of details of the results is no longer confined to the peer review process but now lasts "in perpetuity." Detection tools are publicly available,[19] with consequences following the same course as they did with the ability to detect plagiarism. The presence of anonymous accusations over the blogosphere makes it more difficult to not act upon some allegations. Interpretation of the allegations poses a challenge for the community to develop sensible means for reaching a consensus about whether or not an allegation has merit.

Will Questioned Images "Drive" the Retraction Trend?

Since 2005, journals have been reporting their experiences with the prescreening of images in manuscripts that had passed the scrutiny of peer review. Universally, about 1 percent of those accepted papers contained signs of image manipulation that would affect the interpretation of the results and that eventually caused withdrawal of the manuscript.[20] More revealing is the fact that this level of manipulation persisted, *despite the considerable publicity devoted to the problem*.[3] Prescreening obviously prevents many retractions, but not all; more to the point, the majority of accepted manuscripts *are not prescreened*. The uncomfortable truth is that although the rate of retractions has accelerated dramatically, at its current value of about 0.04 percent, retractions are still far less than what might be expected. This finding is based on the experiences of journals and on the incidences of suspected (but unproven) research misconduct, i.e., 1 percent-3 percent.[21]

The dynamic has a yet bigger consequence because the risk for retraction is not confined to the "1 percent-3 percent." Prescreening audits by journals found that 10 percent-20 percent of the manuscripts showed signs of inappropriate image manipulation that are not serious but nonetheless needed correction.[3] These are the so-called presentation issues that, on their face, don't engender an intent to deceive about the results. The difficulty lies in the middle ground between the two behaviors, because in this regime, only the original data can resolve the concern. Thus, more papers are at risk of retraction for reasons other than proven misconduct (as has happened in an ORI case).

Although many retractions can be tied to allegations of misconduct, and the number of papers involved in each case is increasing, their frequency is no measure of the number of scientists who engage in misconduct. There is no reason to think scientists are less honest than society at large. Unlike other endeavors, the conduct of science is transparent, and public correction is the course of normal activity. The fact that retractions represent the strength of science, not its weakness, does not mitigate the negative effect retractions may have upon the public perception.

What can be done to combat the trend?

The above factors suggest that some simple adjustments might help discourage the events leading to retraction. There may be more; below are a few.

Getting Serious about Data Retention Policies

How can journals best protect a paper that is made vulnerable to retraction by a questioned figure? Data retention will become more important as a condition of continued publication in the event of a questioned image. Data retention policies abound, but journals are at the mercy of institutions and funding agencies for their effective implementation.

Development of "Reviewing" Skills

The ability to distance oneself from the "beauty" of the results

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is a useful tactic. The concept has been put into practice by Dr. Julio Turrens, who reported that he and his students found many more examples of inconsistencies when they looked at the image *before reading the paper*.[22] Journals should advise reviewers to look at the images first. Reviews now last in perpetuity and include non-experts and sometimes anonymous critics. Thus, the ability to take a dispassionate look at your lab's data may prove to be a career-saving skill.

Empowering the Peer Reviewers

Do the reviewers get high-resolution images to examine those with the full dynamic range and resolution that would enhance the ability to detect signs of manipulation? Another issue is whether reviewers see supplementary material, or images that are compromised by prepublication portability. Do others besides the reviewers also scrutinize the images?

Channeling the Corresponding Author's Attention

Misconduct cases often reveal a legacy of shortcuts to good practices. To combat this, journals might consider the equivalent of a "prenuptial agreement" with authors (i.e., an understanding of a journal's options), if data cannot be provided to account for a legitimately questioned figure. Any preventive effect may stem less from the need to execute the agreement than from using more aggressive means to get the author's attention, in this case by explicitly asking about data before the paper is published. Can the sponsor institution (or agency) that hosted (or funded) the research exercise a comparable preunderstanding with authors (or grantees) about the fate of questioned papers lacking data?

Conclusions

Even though the numbers of retractions are small, their rise signals a fundamental shift in the conduct of science that revealed itself starting mid-decade. The incidences of retraction—several times greater than the level of findings of PHS research misconduct—is still twentyfold less than the incidences of unreported research misconduct and the likely incidences of image manipulation in science. It is no measure of PHS misconduct, but dealing with perceptions generated by retractions will be a "growth industry" unless better practices can be marshaled toward reducing the problem. Those efforts will span initiatives in data retention, prevention and detection, a transparent process of evaluation, assessment of findings, and management of the public's perceptions through process transparency.

For better or worse, retractions are one of the public windows on science, but they are a bad proxy for understanding the incidence of research misconduct. Retractions pose the risk of a negative perception, so research leaders should extol the transparency of corrections as a unique feature that distinguishes science from other professions. The convenience provided by technology can create shortcuts, detours around other checks and balances in good practice, and enables a small number of individuals who are inclined to engage in misconduct to have a disproportionate effect upon the public's perceptions. Do standard practices need to be "updated" for the digital age? Perceptions about retractions negatively impact all scientists, not just the few responsible; retractions are now everybody's concern.

References and Endnotes

1 See, for example, G. Naik, "Mistakes in scientific studies surge," *The Wall Street Journal*, August 10, 2011, p. A1.

2 Retraction Watch, at *http://retractionwatch.wordpress.com/*

3 R. Van Noorden, "Science publishing: The trouble with retractions," *Nature* 478:26-28, October 6, 2011.

4 See B. Maher, "The new gatekeepers: Reducing research misconduct," *Nature News Blog*, March 21, 2012, *http://blogs.nature.com/news/2012/03/the-new-gatekeepers-reducing-research-misconduct.html?WT.mc_id=TWT_NatureBlogs*

5 "Science Online NYC (SoNYC) 10 – Setting the research record straight," *Of Schemes and Memes Blog*, *http://blogs.nature.com/ofschemesandmemes/2012/03/21/science-online-nyc-sonyc-10-setting-the-research-record-straight*. Event at *http://sonyc9-eorg.eventbrite.com/*; and

Science Policy, Outreach, and Tools Online (SpotOn): London. "SpotOn London 2012: Fixing the fraud: How do we safeguard science from misconduct?" November 12, 2012. Event at

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http://www.nature.com/spoton/event/spoton-london-2012-fixing-the-fraud-how-do-we-safeguard-science-from-misconduct/

6 R.G. Steen, "Retractions in the scientific literature: Is the incidence of research fraud increasing?" *Journal of Medical Ethics* 37:249-253, 2011; and

D.B. Resnik and G.E. Dinse, "Scientific retractions and corrections related to misconduct findings." *Journal of Medical Ethics* 39(1):46-50, January 2013.

7 F.C. Fang, R.G. Steen, and A. Casadevall, "Misconduct accounts for the majority of retracted scientific publications," *http://www.pnas.org/cgi/doi/10.1073/pnas.1212247109*

8 NLM data can be obtained for 2012 to 1995 at *http://www.nlm.nih.gov/bsd/bsd_key.html*

9 A thorough examination of the broader literature (that includes non-biomedical research) has now appeared and comes to the same conclusion. See M.L. Greineisen and M. Zhang, "A comprehensive survey of retraction articles from the scholarly literature." *PLOS ONE* 7(10) | e441181 October 2012 | *http://www.plosone.org*. These researchers concluded that the majority of retractions are not due to misconduct.

10 "**Corrections or corrigenda for previously-published articles are all uniformly considered by NLM to be errata**. NLM does not differentiate between errors that originate in the publication process and those that result from errors of scientific logic or methodology, because journal editors do not make this distinction consistently or clearly." [emphasis mine] From NLM "Errata Data Sheet," *http://www.nlm.nih.gov/pubs/factsheets/errata.html*

11 The relation between retracted papers to citations in any year is $y = 1.22e^{7E-06x}$, $R^2 = 0.8672$, where y is the number of retractions and x is the number of citations in the same year.

12 Extrapolations based on curve fitting these data suggest that if nothing else changes, the rate of retractions/citations will double in approximately six to seven years, reaching perhaps 1,000 per year after 2020.

13 The transient rise in retractions apparent from1998-1999 likely reflects a contribution by two non-U.S. researchers as a result of an initial investigation completed in 1997. (See M. Hagmann, "Panel finds scores of suspect papers in German fraud probe," *Science* 288(5474):2106-2107, 2000.)

14 See, for example, PHS findings for E.J. Smart (2012, 10 papers); J. Thomas (2009, 15 papers) *http://ori.hhs.gov/case_summary*

15 J. Krueger, "Incidence of ORI cases involving falsified images," *ORI Newsletter* 17(4):2-3, September 2009; see also J. Krueger, "Confronting manipulation of digital images in science," *ORI Newsletter* 13(3):8-9, June 2005.

16 Anecdotally, ORI's caseload remains relatively constant. An important question here then is whether the increase in image allegations/cases tracks the ballooning number of images that appear to be published today. That has not been measured, but armed with a suitable definition of an image as the independent variable in principle, it would be fairly direct to compare the number of images per research paper published in 1995, 2000, 2005, and 2010.

17 Scientific images appear in varied forms: continuous-tone autoradiographs and blots (Western, Northern, and Southern), immunolabeled electron micrographs and atomic force micrographs, colored images of cell immunofluorescence, black-and-white images such as physiological traces with characteristic noise, and dot plots of flow cytometry data with characteristic distributions.

18 Even the perfect image forgery is no guarantor against discovery of falsification, since failure to replicate often causes a laboratory to take a fresh (if not the first!) look at the archived original computer images of the raw data.

19 Photoshop-based forensic tools have widely been used in this process. Those which ORI originated in 2005 to examine and compare questioned images have recently been upgraded. Like the forbearers, they are available, along with advice, at ORI's web site. See *http://ori.hhs.gov/advanced-forensic-actions*

20 "Journal 'audits' of image manipulation," *ORI Newlsetter* 17(1):2-3, December 2008.

21 Prescreening is basically an audit conducted within the normal course of research activity. Its result is in remarkable agreement with the independent estimate of the suspected incidence of research misconduct reported in the ORI-sponsored Gallup survey of scientists. This survey also reported the incidence of suspected (but unreported) research misconduct to be from 1 percent-2 percent. (See S.L. Titus, J.A. Wells, and L.J. Rhoades, "Repairing Research Integrity." *Nature* 453:980-982, 2008.) The agreement is better when the non-image-related allegations are factored in and when it is recognized that detections before submission will have filtered out many instances from prescreening.

22 J.F. Turrens, "A reviewer's experience detecting data fabrication in grants and publications: Advice to colleagues." ORI Quest for Research Excellence Conference, Georgetown-Howard Universities. Presentation 55, March 15, 2012.

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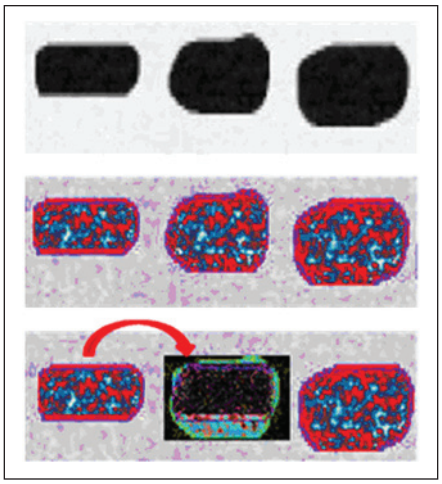
manuscript, and four grant applications. Dr. Smart was the only common author or key personnel member listed on all the affected publications or grant applications.

The research conducted by the Smart laboratory focused on understanding the causes of various cardiovascular diseases, such as atherosclerosis, hypertension, and diabetes. The approach was to study the signals within cells that lead to these disease states—signals that are generated from the surface of the cells and affect how the cells function.

How did he get away with it for so long?

There were two primary ways that the research misconduct remained undetected for so many years. First, the manner in which Dr. Smart ran his laboratory allowed his research misconduct to go undetected because he was directly involved, and in control of, all aspects of preparing figures for manuscripts and grant applications. The UK did an extensive examination of the allegations with two inquiries and two investigations that included interviews of 27 witnesses. The witnesses' testimony led to the conclusion that Dr. Smart relied on a pool of junior technical staff to complete his experiments. He was actively engaged in the design, analysis, and documentation of the research, while the technical staff knew little to nothing about each other's work or the overall project. A small number of postdoctoral fellows or graduate students participated in some of the writing and review of manuscripts, but Dr. Smart finalized all of the image data for presentations in publications or grant submissions, often without knowledge of any other laboratory member.

Second, the manner in which the images were manipulated made the alterations difficult to detect without careful scrutiny. The UK investigations, which included an analysis of the images by a UK expert, by an outside consultant, and DIO's independent oversight review and forensic image analysis, arrived at the same conclusions. The bands in the images were generated by copying and pasting single bands into multiple lanes to generate the figures. The gradient map tool in a forensic analysis program demonstrated common pixilation patterns within the bands that showed they were duplicated, but the outer edges of the bands were cropped and modified to make them appear different. In some cases, entire panels in the figures were fabricated using manipulated bands (see figure below).



When you view these bands in black and white, as most images appear in manuscripts, the bands seem to be different (see top panel). Yet a careful eye might spot that the edges of these bands are abnormally straight and raise some suspicion. Further forensic analysis, by using the gradient map tool to colorize the image (middle panel), demonstrates that the interior of these bands has a common pixilation pattern. When the band in lane one overlays the upper portion of the band in lane two, the resulting black region indicates similarity (see arrow, bottom panel), confirming that these bands are from the same source. Thus, this panel was constructed using one band in which the outer edges were altered to appear as three different bands.

What are the lessons to be learned? First, all laboratory students, and staff, should be on the lookout when one individual is in control of all the data. It doesn't matter whether that individual is the head of the laboratory or a graduate student; more than one set of eyes should review all raw data and research results. This should be the case especially for data included in manuscripts and grant applications. Second, one can never be too careful when reviewing image data. When images for publications are created by the same individuals who obtained the data, this situation allows for easy alterations that can miss detection. Laboratory members and reviewers should remember to examine image data with a discerning eye.

Responsible Conduct in the Global Research Enterprise: New Policy Report Is Released

Diana Arsenieva, Ph.D., Oak Ridge Institute for Science and Education (ORISE) Fellow, ORI

As a followup to the Singapore Statement of 2010, the InterAcademy Council (IAC), and the InterAcademy Panel (IAP), the Global Network of Science Academies published a new policy report on Responsible Conduct in the Global Research Enterprise that was released in September 2012. Although it is not an easy read, this report is relevant to researchers who are starting international or interdisciplinary collaborations.

Growing amounts of research funding in the world, and the increasing number of research scientists who learn, work, and collaborate internationally, lead to unprecedented globalization of the research enterprise. The need to reconcile often varying views on responsible research practices prompted the National Academies of Sciences, represented by IAC and IAP, to call for a highly distinguished international committee to prepare this policy report.

The report focuses on seven fundamental values—honesty, fairness, objectivity, reliability, skepticism, accountability, and openness, which were then applied to specific events in the usual course of research activity. The 45-page document covers challenges commonly encountered by researchers in every stage, from research proposals to research conduct and collaborations, human and animal subjects, authorship issues, peer review, and publication.

The policy report recommends best practices that are appropriate for every stage of research. For example, it is desirable to discuss the order of authors and authorship inclusion guidelines at the beginning of a project. Such discussions may be awkward, but they may be much more uncomfortable at the publication submission stage, especially if there are differences in opinion due to well-established customs of a particular country or discipline. Such differences can ultimately lead to instances in which someone's expectations are not met. An authorship disagreement may also arise if one researcher provided the data and the other provided analysis of the data. Who should be the first and/or corresponding author? Because scientists are increasingly competitive, it's a tough decision. There may be no right or wrong way to answer this particular question, but if there is not a meeting of the minds on the responsible conduct of research issues, and no sincere commitment from each party to focus on the seven fundamental values discussed in the policy report, collaboration may be doomed from the start.

Responsibility to maintain research integrity and to prevent, uncover, and report misconduct falls on all members of the scientific community—from researchers and editors of peer-reviewed journals to academies and institutions that fund research and host research activities. The authors recommend how to distribute these obligations among all the participants of the research process, applied in the international setting.

The policy report also underscores responsibility of the scientific community to maintain public trust. In addition to maintaining research integrity, it requires scientists to accurately communicate results of their research to the public and to be involved with policymaking. This document is another step in international efforts to unify and standardize research principles among countries and among various disciplines of science.

The report is available as a pdf download at *http://interacademycouncil.net/24026/GlobalReport.aspx*

"Whoever is careless with the truth in small matters cannot be trusted with important matters."

Albert Einstein
(1879-1955)

Committee on Responsible Science Discussion with Representatives of Scientific Societies

Raju Tamot, Ph.D., Oak Ridge Institute for Science and Education (ORISE) Fellow, ORI

Members of the scientific community, journal editors, and authorities of regulatory bodies have long argued that they need to work collectively to protect the integrity of science. An exercise to help understand each other's unique observations and suggest ways to enhance the integrity of science was organized at the National Academies' Keck Center, on December 13, 2012.

The Committee on Responsible Science organized a round-table discussion with societies to focus on publication issues associated with the responsible conduct of research (RCR). Representatives of scientific societies, members of the Committee on Responsible Science, study sponsors, editors of various scientific journals, Nancy Wexler (a member of the Academies' Committee on Science, Engineering, and Public Policy), and Richard Bissell (Editor of the Policy on Global Affairs Division) participated in the discussions. An Office of Research Integrity (ORI) representative filed the following report after the conclusion of the round-table discussion.

Robert Nerem, Chair of the Committee on Responsible Science, provided an update on the Responsible Science Study and said that the current study was being undertaken in a changed technological and global environment. He reported that the study would be completed by the first half of 2013 and that the subsequent report would contain chapters on the changed environment, research in science, threats to scientific research, best practices, and recommendations.

The issue of fraud/research misconduct and retractions was the dominant theme during the subsequent discussions. Many noted the high media coverage on cases of research misconduct and retractions, and they voiced concern that these cases would cause the public to lose trust in science and in research. Many, but not all, of the participants felt that research misconduct in science, when viewed by the number of retractions, has been greatly increasing over the past 20 years. Those that were experiencing more retractions in their journals felt that this outcome demonstrated a threat to the integrity of science. They also felt that it was hard to know how to develop best policies to try to prevent publication of falsified, fabricated, or plagiarized work as well as how to report retractions of research misconduct.

Ferric C. Fang, a Professor of Laboratory Medicine and Microbiology at the University of Washington, reported that we need to remember the context of retractions. Retractions are a recent development and represent a very small proportion of the 50-million scientific papers published to date.

His paper reviewed in detail all biomedical and life-sciences research articles indexed by PubMed that had been retracted by May 3, 2012.[1] He found that misconduct accounted for the majority of retracted scientific publications in PubMed. Further, he noted that most of the retracted articles for fraud originated in countries with long-standing research traditions and three-quarters of retractions had their origins in the United States, Germany, Japan, and China. However, he cautioned that retractions do not reflect the true state of misconduct and should not be seen as a measure of science.

Fang also noted that the scientific community has created a lot of pressure which can contribute to the degree of research misconduct. He observed that people are more likely to cheat when they are afraid of losing something. He suggested that people on the "knife-edge," or those Principal Investigators (PIs) who have difficulties keeping their labs, securing funding, and publishing, create a heightened environment for fraud and research misconduct.

His comments sparked other related integrity issues:

- Plagiarism is perceived to be committed by scientists who do not contribute significantly to

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Discussion *(from page 9)*

science and who publish in low-impact journals.

- With global collaboration increasing, it becomes more likely that plagiarism, can become a larger issue—particularly with Asian authors.
- There is a good deal of pressure in science to secure funds and publish. And most medical schools depend on grants for salaries of their staff.
- Pressures are also present in the social science departments; thus, departments are asking their faculty members to secure grants to cover part of their salaries.
- Since there is little funding for replication work, faculty members are under intense pressure to seek funding for new ideas and areas of study.
- PIs are themselves creating an environment that allows misconduct to occur, so our attention should emphasize their role. They either commit misconduct themselves or fail to monitor and be involved with their staff and students.

The second theme of the meeting focused on ethics education and possible ways to develop best practices that would reduce integrity problems. Kate P. Kirby, Executive Officer of the American Physical Society, noted that ethics has earned a bad name in academia. She also noted that faculty members in general loathe annual requirements of ethics education/training. The findings follow:

- It was generally agreed that mandating ethics training for mid-level and established investigators was very hard and would be counterproductive.
- One way to change the system might be to have senior faculty members/investigators teach research ethics.
- Journals should post their ethical guidelines in the front of their journals and possibly also on the submission page for authors and peer reviewers.
- The European Molecular Biology Organization is developing a lab management course and will mandate that PIs take the course with new fellows.
- Individual investigators must take responsibility for their share of work. Thus, anyone who makes an intellectual contribution to any part of the paper could be noted in a separate byline.
- The methods sections in scientific papers need to provide complete details, much like a detailed cooking recipe. This component of reporting research must be improved.
- Journals need to make room for negative findings.
- Journals should require a description of the role of each author, which would add accountability and incentive.
- Institutions should contemplate developing an in-house review system before submission.

Brian C. Martinson, a member of the Committee on Responsible Science, argued that societies, the industry, and scientists had different goals. Although societies are interested in getting new information and therapeutics, the industry is interested in making more profits, and scientists are interested in publishing more papers. He suggested that there is a fundamental need to change the way we align these diverse interests.

Endnote

[1] F.C. Fang, R. Grant Steen, and Arturo Casadevall (2012). "Misconduct accounts for the majority of retracted scientific publications." *PNAS*, October 1, 2012 201212247.

The truth is the only thing worth having, and, in a civilized life, like ours, where so many risks are removed, facing it is almost the only courageous thing left to do.

E.V. Lucas
(1868-1938)

New Interactive Video on Clinical Research

Loc Nguyen-Khoa, M.S., ORI

In February 2011, the Office of Research Integrity (ORI) launched "The Lab," an interactive training video on the handling and prevention of research misconduct in laboratories. Each week, hundreds of learners watch "The Lab," which is available for free on the ORI web site. With the success of this program, ORI has joined forces with the Office of Human Research Protections to pursue the development of a second interactive training video. This time, the focus is on clinical research and social science research.

"A large percentage of allegations of misconduct received by ORI involves clinical research," states John Dahlberg, the Director of ORI's Division of Investigative Oversight. "It makes perfect sense to invest in a product that may help reduce questionable practices in this area."

The new training video delves into the lives of four "playable" characters, including a clinical research coordinator (CRC), an M.D./Ph.D. principal investigator (PI), an Institutional Review Board (IRB) chair, and a research assistant. Each character faces challenges that are typical of their positions, and the learner has the opportunity to make decisions that affect the outcome of the story. This immersive technique has been shown to be an effective and engaging learning method in healthcare, military, and academic settings.

The main story centers on a cancer study that examines the effectiveness of a new drug. Dr. Richard Sowers, the PI, must balance the responsibilities of being a caring oncology doctor, leading a research staff, and following research regulations. The CRC, Jan Klein, is an overworked nurse who is responsible for managing several studies with tasks involving recruiting patients, performing consents, collecting and recording data, and managing technicians. The IRB Chair, Marcy Rosenberg, must make difficult choices handling studies that deviate from protocol. The final character is Megan Boyle, a new Research Assistant who navigates through research protocols for studying quality of life outcomes for cancer patients.

ORI plans to release a beta version that includes the clinical research coordinator scenario in January 2013. The full version is expected to be released in October 2013.

Case Summaries

Eric J. Smart, Ph.D.
University of Kentucky

Based on the report of an investigation conducted by the University of Kentucky (UK) and additional analysis conducted by ORI in its oversight review, ORI found that Dr. Eric J. Smart, former Professor of Pediatrics and Physiology, Department of Pediatrics and Physiology, UK, engaged in research misconduct in research supported by National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), grants R01 HL062844, R01 HL058475, R01 HL064056, R01 HL068059, and R01 HL073693, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, grant R56 DK063025, and National Center for Research Resources (NCRR), NIH, grant P20 RR105592.

ORI found that the Respondent engaged in research misconduct by falsifying and/or fabricating data that were included in ten (10) published papers, one (1) submitted manuscript, seven (7) grant applications, and three (3) progress reports over a period of ten (10) years. Respondent reported experimental data for knockout mice that did not exist in five (5) grant applications and three (3) progress reports and also falsified and/or fabricated images in 45 figures included in the following:

- *J. Biol. Chem*. 277(7):4925-31, 2002
- *Am J. Physiol. Cell Physiol*. 291(6):C1271-8, 2006
- *Am J. Physiol. Cell Physiol*. 294(1):C295-305, 2008
- *J. Lipid Res*. 42:1444-1449, 2001
- *J. Biol. Chem*. 275:25595, 2000
- *J. Biol. Chem*. 277(26):23525-33, 2002
- *Proc. Natl. Acad. Sci. USA* 101(10):3450-5, 2004
- *J. Biol. Chem*. 280(33):29543-50, 2005
- *J. Biol. Chem*. 273:6525-6532, 1998
- *Am J. Physiol. Cell Physiol*. 282:C935-46, 2002
- "Effects of HIV protease and nucleoside reverse transcriptase inhibitors on macrophage cholesterol accumulation in humans," submitted August 6, 2008
- R01 HL078976-01
- R01 HL078979-01A1
- R01 DK063025-01A2
- R01 HL088150-01
- U54 CA116853-01
- R01 HL093155-01
- R01 HL068509-01A1
- Progress reports HL078976-02, -03, and -04.

As a result of its investigation, UK recommended that the publication(s) listed above be retracted or corrected.

Specifically, ORI finds that the Respondent:

- falsely reported in Figure 14 and associated text in NIH grant applications R01 HL07897601 and -01A1 that experiments were performed to determine if endothelial-specific caveolin-1 null mice were protected from saturated fatty acid-induced atherosclerosis, when these mutant mice did not exist in the laboratory at the time; Dr. Smart also falsely reported the use of these mice in related progress reports R01 HL078976-02, -03, and -04 and in three (3) additional NIH grant applications: Figure 11 in R01 HL088150-01, Figure 11 in U54 CA116853, and Figure 9 in DK063025-01A2
- falsified and/or fabricated images in NIH grant application R01 HL078976-01A1 by duplicating and altering bands in 14 Western blot images and one (1) RT-PCR image included in Figures 3, 6, 11, 12, 13, 14, and 15; false Western blots were also included in the earlier version of the grant application R01 HL078976-01, Figures 3, 6, 11, 13, and 14
- falsified and/or fabricated Western blots and one (1) RNase protection assay by duplicating and altering bands in thirty-three (33) figures included in ten (10) published papers, one (1) submitted manuscript, and two (2) NIH grant applications. Specifically, false or fabricated images were included in:
  - Figures 5 and 7, *J. Biol. Chem*. 277(7):4925-31, 2002
  - Figure 4B, *Am J. Physiol. Cell Physiol*. 291(6):C1271-8, 2006
  - Figures 2A, 3A, 6A, and 7A, *Am J. Physiol. Cell Physiol*. 294(1):C295-305, 2008

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- Figures 3, 5, and 6, *J. Lipid Res*. 45:1444-1449, 2001
- Figure 2A, *J. Biol. Chem*. 275(33):25595-99, 2000
- Figures 2A/B/C and 4A/B, *J. Biol. Chem*. 277(26):23525-33, 2002
- Figures 2B/D and 4, *Proc. Natl. Acad. Sci. USA* 101(10):3450-5, 2004
- Figures 1A and 5B, *J. Biol. Chem*. 280(33):29543-50, 2005
- Figures 1A, 2A/B, and 4A, *J. Biol. Chem*. 273:6525-6532, 1998
- Figure 1B, *Am J. Physiol. Cell Physiol*. 282:C935-46, 2002
- Figures 2A, 4, 6B, 7, and 8 in a submitted manuscript
- Figures 7A, 8A, 9A, and 10B in grant application HL093155-01
- Figures 4, 7, and 13 in grant application HL068509-01A1.

Dr. Smart has entered into a Voluntary Exclusion Agreement and has voluntarily agreed for a period of seven (7) years, beginning on October 23, 2012:

(1) to exclude himself from any contracting or subcontracting with any agency of the United States Government and from eligibility or involvement in nonprocurement programs of the United States Government referred to as "covered transactions" pursuant to HHS' Implementation (2 C.F.R. Part 376 *et seq*) of OMB Guidelines to Agencies on Govermentwide Debarment and Suspension, 2 C.F.R. Part 180 (collectively the "Debarment Regulations");

(2) to exclude himself voluntarily from serving in any advisory capacity to PHS including, but not limited to, service on any PHS advisory committee, board, and/or peer review committee, or as a consultant; and

(3) to request that the following publications be retracted or corrected: *J. Biol. Chem*. 277(7):4925-31, 2002; *Am J. Physiol. Cell Physiol*. 291(6):C1271-8, 2006; *Am J. Physiol. Cell Physiol*. 294(1):C295-305, 2008; *J. Lipid Res*. 42:1444-1449, 2001; *J. Biol. Chem*. 275:25595, 2000; *J. Biol. Chem*. 277(26):23525-33, 2002; *Proc. Natl. Acad. Sci. USA* 101(10):3450-5, 2004; *J. Biol. Chem*. 280(33):29543-50, 2005; *J. Biol. Chem*. 273:6525-6532, 1998; *Am J. Physiol. Cell Physiol*. 282:C935-46, 2002.

Terry S. Elton, Ph.D.
The Ohio State University

Based on the reports of two investigations conducted by The Ohio State University (OSU) and additional analysis conducted by ORI in its oversight review, ORI found that Dr. Terry S. Elton, Professor, College of Pharmacy and Davis Heart and Lung Research Institute, OSU, engaged in research misconduct in research supported by National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), grants R01 HL048848, R01 HL084498, and P01 HL70294, National Institute of Child Health and Human Development (NICHD), NIH, grant R21 HD058997, National Institute on Aging (NIA), NIH, grant R01 AG021912, National Institute of Allergy and Infectious Diseases (NIAID), NIH, grant R01 AI39963, and National Eye Institute (NEI), NIH, grant R01 ES012241.

ORI found that the Respondent engaged in research misconduct by falsifying and/or fabricating data that were included in 1 R21 HD058997-01, 1 R21 HD058997-01A1, 1 R21 HD058997-01A2, 1 RC1 HL100298-01, and in:

1. Kuhn, D.E., Nuovo, G.J., Terry, A.V. Jr., Martin, M.M., Malana, G.E., Sansom, S.E., Pleister, A.P., Beck, W.D., Head, E., Feldman, D.S., & Elton, T.S. "Chromosome 21-derived microRNAs provide an etiological basis for aberrant protein expression in human Down syndrome brains." *J Biol Chem* 285(2):1529-43, 2010 Jan 8.
2. Kuhn, D.E., Nuovo, G.J., Martin, M.M., Malana, G.E., Pleister, A.P., Jiang, J., Schmittgen, T.D., Terry, A.V. Jr., Gardiner, K., Head, E., Feldman, D.S., & Elton, T.S. "Human chromosome 21-derived miRNAs are overexpressed in Down syndrome brains and hearts." *Biochem Biophys Res Commun* 370(3):473-7, 2008 Jun 6.
3. Martin, M.M., Buckenberger, J.A., Jiang, J., Malana, G.E., Knoell, D.L., Feldman, D.S., & Elton, T.S. "TGFß1 stimulates human AT1 receptor expression

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in lung fibroblasts by cross talk between the Smad, p38 MAPK, JNK, and PI3K signaling pathways." *Am. J. Physiol. Lung Cell. Mol. Physiol*. 293(3):L790-9, 2007 Sept. (Retracted: *Am. J. Physiol. Lung Cell. Mol. Physiol*. 302(7):L719, 2012 Apr.)

4. Martin, M.M., Buckenberger, J.A., Jiang, J., Malana, G.E., Nuovo, G.J., Chotani, M., Feldman, D.S., Schmittgen, T.D., & Elton, T.S. "The human angiotensin II type 1 receptor +1166 A/C polymorphism attenuates microRNA-155 binding." *J Biol Chem* 282(33):24262-9, 2007, Aug 17.
5. Martin, M.M., Buckenberger, J.A., Knoell, D.L., Strauch, A.R., & Elton, T.S. "TGF-beta(1) regulation of human AT1 receptor mRNA splice variants harboring exon 2." *Mol Cell Endocrinol* 249(1-2):21-31, 2006 Apr 25.
6. Duffy, A.A., Martin, M.M., & Elton, T.S. "Transcriptional regulation of the AT1 receptor gene in immortalized human trophoblast cells." *Biochim. Biophys. Acta*. 1680(3):158-70, 2004 Nov 5.

As a result of its investigation, OSU has recommended that all of the above publications be retracted.

Specifically, ORI finds that the Respondent:

- falsified and/or fabricated Western blots in an NIH grant application in three submissions of the same grant application:
  - Figures 4, 7, 11C: 1 R21 HD058997-01
  - Figures 7B, 7E, 8B: 1 R21 HD058997-01A1
  - Figures 3C, 3F, 6C: 1 R21 HD058997-01A2

  and false Western blots were also included in Figure 6 in grant application 1 RC1 HL100298-01.
- falsified and/or fabricated Western blots in eighteen (18) figures and in six (6) published papers. Specifically false and/or fabricated images were included in:
  - Figures 2C, 2D, 2F, 3C, 3E, 4G, 5C, 5F: *J Biol Chem* 285(2):1529-43, 2010 Jan 8
  - Figures 3B, 3C, 3F, 3H, 3I, 3J: *Biochem Biophys Res Commun* 370(3):473-7, 2008 Jun 6
  - Figures 2, 3, 4B, 5B, 6, 7B, 8A, 9B: *Am. J. Physiol. Lung Cell. Mol. Physiol*. 293(3):L790-9, 2007 Sept
  - Figure 6: *J Biol Chem* 282(33):24262-9, 2007 Aug 17
  - Figure 6: *Mol Cell Endocrinol* 249(1-2):21-31, 2006 Apr 25
  - Figures 5, 6B, 7B, 9B: *Biochim. Biophys. Acta* 1680(3):158-70, 2004 Nov 5.

Dr. Elton has entered into a Voluntary Exclusion Agreement and has voluntarily agreed:

(1) to exclude himself from any contracting or subcontracting with any agency of the United States Government and from eligibility or involvement in nonprocurement programs of the United States Government referred to as "covered transactions" pursuant to HHS' Implementation (2 C.F.R. Part 376 *et seq*) of OMB Guidelines to Agencies on Govermentwide Debarment and Suspension, 2 C.F.R. Part 180 (collectively the "Debarment Regulations") for a period of three (3) years, beginning on November 26, 2012;

(2) to exclude himself voluntarily from serving in any advisory capacity to PHS including, but not limited to, service on any PHS advisory committee, board, and/or peer review committee, or as a consultant for a period of three (3) years, beginning on November 26, 2012; and

(3) to request that the following publications be retracted:

- *J Biol Chem* 285(2):1529-43, 2010 Jan 8
- *Biochem Biophys Res Commun* 370(3):473-7, 2008 Jun 6
- *J Biol Chem* 282(33):24262-9, 2007, Aug 17
- *Mol Cell Endocrinol* 249(1-2):21-31, 2006 Apr 25
- *Biochim. Biophys. Acta*. 1680(3):158-70, 2004 Nov 5.

Shuang-Qing Zhang, Ph.D.
Texas Tech University Health Sciences Center

Based on the report of an investigation conducted by the Texas Tech University Health Sciences Center (TTUHSC) and additional analysis conducted by ORI in its oversight review, ORI found that Dr. Shuang-Qing Zhang, former

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Postdoctoral Researcher, Department of Pharmaceutical Sciences, TTUHSC, engaged in research misconduct in research supported by National Institute of General Medical Sciences (NIGMS), National Institutes of Health (NIH), grant R01 GM069869.

ORI found that Respondent engaged in research misconduct by the falsification and fabrication of plagiarized data that were included in the publication: Zhang, S.Q. & Mehavr, R. "Determination of dextra-methylprednisolone conjugate with glycine linker in rat plasma and liver by high-performance liquid chromatography and its application in pharmacokinetics." *Biomed. Chromatogr*. 24(4):351-357, 2010 (hereafter the "*BC* 2010 article").

Specifically, ORI found that the Respondent:

- falsified Figures 2(c) and 3(c) of the *BC* 2010 article by misrepresenting HPLC data that he had plagiarized, originally generated prior to the Respondent's arrival in the laboratory by a former postdoctoral researcher; in Figure 2(c), the Respondent claimed that the HPLC chromatogram was of a "plasma sample obtained 12 h after intravenous injection of DMP to rats at a single dose of 5 mg/kg," while the actual chromatogram was of a calibration test of 1 μg/ml of DMP added to rat plasma, and similarly in Figure 3(c), the Respondent claimed that the HPLC chromatogram was of a "liver homogenate obtained 3 h after intravenous dose of DMP at a dose of 5 mg/kg," while the actual chromatogram was of a calibration test of 2 μg/ml DMP added to rat liver homogenate .
- falsified and fabricated Figure 4 of the *BC* 2010 article; in the top panel, the Respondent reported the measurement of DMP concentrations in plasma samples of three rats after a single injection of 5 mg/kg DMP while the actual data that he had plagiarized, originally generated prior to the Respondent's arrival in the laboratory by a former postdoctoral researcher, was from a single rat. In the bottom panel, the Respondent reported the measurement of DMP concentrations in liver samples obtained from three rats at 1, 30, 90, 180, 300, and 720 minutes after a single injection of 5 mg/kg DMP, requiring a total of 18 rats, while the actual data that he had plagiarized, originally generated prior to the Respondent's arrival in the laboratory by a former postdoctoral researcher, was from plasma samples from a single rat, and the error bars for both panels were fabricated.

Dr. Zhang has entered into a Voluntary Settlement Agreement and has voluntarily agreed:

(1) to have his research supervised for a period of three (3) years; Respondent voluntarily agrees that within sixty (60) days of the effective date of the Agreement, any institution that submits an application for PHS support for a research project on which the Respondent's participation is proposed or that uses the Respondent in any capacity on PHS supported research, or that submits a report of PHS-funded research in which the Respondent is involved, must concurrently submit a plan for supervision of the Respondent's research to ORI for approval; Respondent agrees that he will not participate in any PHS-supported research after sixty (60) days from the effective date of the Agreement until an appropriate supervision plan is submitted to ORI; the supervision plan must be designed to ensure the scientific integrity of the Respondent's research contribution; and

(2) to exclude himself voluntarily from serving in any advisory capacity to PHS including, but not limited to, service on any PHS advisory committee, board, and/or peer review committee, or as a consultant for a period of three (3) years, beginning on December 4, 2012.

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