Annals of Diagnostic Pathology 61 (2022) 152053

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Letter to the Editors

The key role of the pathologist in both documenting and exonerating accusations of scientific misconduct

General comments

As both a diagnostic surgical pathologist and research pathologist for the last 35 years, I have seen many changes in both fields over this time. Perhaps the most amazing with regards to research is that it used to take several days of library work to read enough papers to get a solid reference list for a publication. Now, using PubMed or similar engines, one can do the same work in a few hours. A downside of the internet and social media is we researchers all are a mouse click away from what I refer to as the "vigilante scientific misconduct" community. These are people and websites that claim to document scientific misconduct to a wide audience. My love of science and research is based a great deal on its objectivity. Most of the great scientists I have known and work with put their focus on discovering the truth and are happy to admit when their idea is wrong, because they saw that the objective data was clearly telling them that another idea was the correct one. This is in sharp contrast to the hysterical finger-pointing and general "bad-mouthing" one sees when someone is accused of misconduct based a claim that a panel in a figure was re-used without having seen the original data or looking at the larger picture of the data set.

What is scientific misconduct?

This would seem to be obvious: it is knowingly lying when reporting research in a publication such that the main points of the paper are based on lies, and not actual data. The Office of Research Integrity (ORI) of the HHS, the standard bearer of such investigations, defines scientific misconduct as 1) having fabricated (completely made up) or falsified (re-use old data and claim it is new and different) data (plagiarism is included in the definition but it is so rare that I included it only in these parentheses), 2) using that data in the publication, 3) the behavior of the scientist must be a significant departure from accepted behavior in the community and 4) it must be done knowingly and intentionally/recklessly. The ORI makes it clear that honest mistakes do not equal scientific misconduct, nor is it misconduct if different investigators disagree on the interpretation of some data. Though the ORI definition is useful, as a scientist, I think we can distill the above points to define scientific misconduct more concisely. It is someone who **knowingly makes up data, uses the data for their main conclusions, and publishes this** (or uses it to apply for a grant). A corollary of this point is that the **main conclusions will be incorrect.**

What about the grey zones?

Another advantage of age (yes, there are a few!) is that one sees that nothing is black and white but rather there are many shades in between. I have seen fellow researchers take good data and enhance it so their points would be more obvious. I have seen colleagues re-use controls because the controls were all acceptable but some were neater and cleaner than others. I am not condoning such behavior. But this is not scientific misconduct because it is not knowingly creating false data and then using it for their main conclusions.

What is known about actual scientific misconduct?

I reviewed each of the cases of documented scientific misconduct listed on the public website of the ORI (HHS) up to 2021. The data surprised me. One question I asked was what is the average number of falsified images in a given paper? The mean number of falsified or fabricated data points (mostly panels) per paper was 62 with a range of 12 to 189. This suggests that when someone is knowingly publishing made up data and using it for their main conclusions they are doing it extensively. This makes sense as it confirms that the primary mindset of the investigator is to deceive for their career advancement. This is also consistent with a report in Science that 500 of >30,000 authors named in the retraction database (which includes co-authors) account for about 25 % of the over 10,000 retractions that were analyzed [1]. The next question I addressed from the ORI database was what was the fate of the articles found to have included falsified/fabricated data? Of the 78 papers recommended to be retracted by the ORI where the journal responded, 6 (8 %) were corrected and 72 were retracted. The 8 % corrected and not retracted impressed me because the authors in 5 of these cases were able to show that the falsified/fabricated data was not essential to the main points of the paper; in the other case the editor noted that only one of the figures was falsified and that too much time had passed to determine if original data could have exonerated the figure. Also, it is easy to find corrections of papers not charged with misconduct where the authors noted mistakes with re-use of panels or incorrect labeling of panels and corrected the mistakes [2-7].

The other obvious but critical point of actual scientific misconduct is that since the main points are based on made up data, they cannot be correct. It is simply not possible for anyone to make up data in complicated biosystems and be accurate. In this regard, I reviewed 10 older manuscripts where investigators were found guilty of falsified data by the ORI (HHS). I took their main findings and searched the literature to compare subsequent studies. In each case, the falsified data was found to be false. I will present some of this data from ET Poehlman since he was from UVMCOM and I heard a lot about it (I am an alumnus). He reported that elderly people who did endurance training had a 35 % increase in norepinephrine levels [8]. This was refuted by many articles. For example, Zouhal et al. showed that such large increases in norepinephrine levels were only found in highly trained athletes and referred

https://doi.org/10.1016/j.anndiagpath.2022.152053

Available online 11 October 2022

to the process as "sports adrenal medulla" [9]. Poehlman et al. also indicated that postmenopausal women showed highly significant increases in insulin levels after menopause in a longitudinal study and no changes in glucose levels [10]. This was refuted by several studies including Kim et al. who showed that glucose levels were significantly increased in a similar population after menopause and that insulin resistance (not levels) were increased but not due to the $p < 0.001$ insulin elevated results reported by Poehlman et al. [11]. In each of these examples ONLY one main point was presented and shown to be wrong. A review of each of the retracted papers from the ORI website showed that most had presented from 5 to 10 original biomedical observations. This explains why over 80 % of these papers were in publications with impact factors >5.

My point is that it is simply statistically impossible for any investigator to report many new findings (again most papers in the verified misconduct category had between 5 and 10 new findings) and be verified by many independent labs if the data were falsified/fabricated. If one assumes that the chance of being correct when falsifying data in a complex biologic system is 1 in 1000 (very conservative) then that to the tenth power is much >1 in a 100 trillion.

What about politics and misconduct?

Any pathologist (or researcher) reading this who has practiced for at least 10 years will agree with this statement: academic institutions commonly use their resources to get rid of staff they don't want, often when a new chair enters the department. This includes committees on credentials, "hostile work environments" and scientific misconduct. The idea is simple: make accusations that are usually untrue to "tell" the person that they need to seek new employment. This is especially common with tenured faculty. Sometimes it will be used against junior investigators if the institution wants to make their senior investigator/mentor leave. When the person leaves the charges are usually either dropped or not pursued, and often not relayed to the new institution. This is just the way things are and to anyone who has experienced it (and most people have after 10 years) it needs no more explanation.

Let's look at two hypothetical cases

1). Dr. John Doe is accused by scientific misconduct by his Academic Center's ORI. The paper claimed that certain microRNAs controlled key oncoproteins. They claim he re-used 32 images in seven papers from Western blots that included some controls but mostly key data for the main points. The paper's main and original point was that three microRNAs regulated four key oncoproteins. John claims that this was an honest error but cannot find the original data due to poor organization skills and that 4 years have passed since the publication. A review of the literature shows that no one has been able to replicate this data.

2) Dr. Jane Doe is accused by scientific misconduct by her Academic Center's ORI. The paper claimed that certain microRNAs controlled key oncoproteins. They claim she re-used 7 images in seven papers from Western blots that included mostly controls not related to her main points. Her paper's main and original point was that three microRNAs regulated four key oncoproteins. Jane claims that this was an honest error and was able to produce the original data, though you wonder if this was done because the original data was not as clear as the replicated data. Jane did agree to repeat the experiments and got equivalent data as reported in the original paper. A review of the literature (the paper was published 4 years ago) shows that 12 independent labs have replicated this data/.

Who is guilty and who is innocent?

The evidence shows that Dr. John Doe knowingly made up a large amount of data that formed the foundation for his main points. As noted above, this is the standard modus operandi for scientific misconduct. The final proof is that no lab could replicate the work.

The evidence shows that Dr. Jane Doe did re-use some panels/data points but it was not data that was the foundation of her main points. She was also able to find the original data and repeat the experiments with the same results. Many independent labs have verified her main points. Even if one assumes that she re-used the data because it was cleaner (which can only be inferred, not proven), this is not scientific misconduct.

What role can the pathologist play in these investigations?

My review of the ORI databank of documented scientific misconduct showed that over 85 % of retracted papers due to misconduct had either pathology/microscopy images or had Western blot/qRTPCR data that could be used to do immunohistochemistry and/or in situ hybridization to either document misconduct or show that the key points of the paper were valid. As someone who does a lot of Western blots/qRTPCR, it has always amazed me that these methods, which involve the obligatory destruction of tissue, are considered more "useful" than in situ hybridization and immunohistochemistry by many investigators. In part this is because the obligatory destruction methods now include more sophisticated techniques such as NGS. But as pathologists we know that in situ hybridization and immunohistochemistry, even when used as it was 20 years ago, still provides the key cell localizing data that can be the essential data in both documenting original scientific findings or proving/disproving scientific misconduct.

Summary and recommendations

In sum, it is important to understand exactly what is scientific misconduct. The essential ingredients of misconduct is that the investigator is intentionally making up data (typically a lot) that all revolves around the main point of the study in order to get published, advance the career, and get funding. The proof of the misconduct is that no other lab can replicate the results. This is why I could document that six papers in which the ORI documented misconduct were NOT retracted because the authors were able to show that the falsified images were not related to the main point of the paper and, in some cases, the experiments were redone. The entire goal of misconduct investigations is to remove conclusions that have no data to support them from the literature.

Again, although plagiarism is included in the ORI definition I will omit this as I can only find one paper in the entire ORI databank where an investigator actually used someone else's data and did not acknowledge the group. Using quotes from papers in the introduction and discussion and not directly referencing the study is not misconduct as it is has nothing to do with the main points of the article. Neither is re-use of controls though we do need to make a system where such behavior is discouraged.

This leads me to my **recommendations** to be able to help resolve issues around misconduct.

1). **Good research practices should be a required course** for anyone doing research in any medical laboratory. I have never had or seen such a course. It could be on-line and teach people about actual misconduct and, just as importantly, discuss and discourage the grey zones of scientific work such as re-using controls and quotes from other papers. One would need a certificate that they finished this on-line course before doing any scientific lab work.

2) **An independent body should investigate all claims of misconduct**. All investigations for misconduct are now done by the institution where the person works. This is an obvious conflict of interest in two ways. The institution may want to hide obvious misconduct because grant money may be at stake but just as likely they may want to find misconduct even if it is not there if the goal is to make the person (or their mentor) leave. It would be straightforward for academia to set up regional committees that investigate misconduct and make certain that no one on the committee is from the institution where the misconduct is

alleged to have occurred. I would also propose that, as the Annals does with peer review papers, the committee members are blinded as to whom the allegations are made against.

3). **Have pathologists play a key role in the investigation in combination with literature review**. As discussed at length, actual misconduct investigations need to document that the investigator knowingly made up data central to their key, original points before misconduct can be asserted. An easy way to document/refute this is to use in situ hybridization and/or immunohistochemistry to see if the original findings can be documented or refuted by a pathologist in combination with a review of the literature to see if independent labs have verified (or not been able to verify) the main points.

4) **Strictly define misconduct**. Finally, although the ORI definition of scientific misconduct is useful, I propose it be made more concise: Scientific misconduct is knowingly making up the key data that is central to the original points of the paper by falsification of fabrication. Anything else would fall out of the range of misconduct and require corrections and training.

References

[1] https://www.science.org/content/article/what-massive-database-retracted-papers-reveals-about-science-publishing-s-death-penalty.

[2] Hollingsworth JW. Correction: hyaluronan fragments contribute to the ozone-primed immune response to lipopolysaccharide. J Immunol 2016;196(5):2426. https://doi.org/10.4049/jimmunol.1600004. Erratum for: J Immunol. 2010 Dec 1; 185(11):6891-8. PMID: 26896484; PMCID: PMC4872703.

[3] Tighe RM, Li Z, Potts EN, Frush S, Liu N, Gunn MD, Foster WM, Noble PW, Hollingsworth JW. Correction: ozone inhalation promotes CX3CR1-dependent maturation of resident lung macrophages that limit oxidative stress and inflammation. J Immunol 2016;196(5):2424. https://doi.org/10.4049/jimmunol.1600002. Erratum for: J Immunol. 2011 Nov 1;187(9):4800-8. PMID: 26896483; PMCID: PMC4874498.

[4] Introne WJ, Westbroek W, Cullinane AR, Groden CA, Bhambhani V, Golas GA, Baker EH, Lehky TJ, Snow J, Ziegler SG, Adams DR, Dorward HM, Hess RA, Huizing M, Gahl WA, Toro C. Neurologic involvement in patients with atypical Chediak-Higashi disease. Neurology 2016;86(14):1320–8. https://doi.org/10.1212/WNL.0000000000002551. Epub 2016 Mar 4. Erratum in: Neurology. 2017 Feb 14;88(7):720. Erratum in: Neurology. 2017 Feb 14;88(7):721. Corrected and republished in: Neurology. 2017 Feb 14;88(7):e57-e65. PMID: 26944273; PMCID: PMC4826336.

[5] Hsia BJ, Ledford JG, Potts-Kant EN, Nikam VS, Lugogo NL, Foster WM, Kraft M, Abraham SN, Wright JR. Correction notice for TNF-R on mast cells regulate airway responses to Mycoplasma pneumoniae. J Allergy Clin Immunol 2016;137(1):336. https://doi.org/10.1016/j.jaci.2015.09.049. Epub 2015 Nov 21. Erratum for: J Allergy Clin Immunol. 2013 Dec;132(6):1420-6. PMID: 26611673; PMCID: PMC5679132.

[6] Wang H, Xu C, Kong X, Li X, Kong X, Wang Y, Ding X, Yang Q. Trail resistance induces epithelial-mesenchymal transition and enhances invasiveness by suppressing PTEN via miR-221 in breast cancer. PLoS One 2014;9(6):e99067. https://doi.org/10.1371/journal.pone.0099067. Erratum in: PLoS One. 2019 Mar 21;14 (3):e0214433. PMID: 24905916; PMCID: PMC4048247.

[7] Li B, Lu Y, Yu L, Han X, Wang H, Mao J, Shen J, Wang B, Tang J, Li C, Song B. miR-221/222 promote cancer stem-like cell properties and tumor growth of breast cancer via targeting PTEN and sustained Akt/NF-κB/COX-2 activation. Chem Biol Interact 2017;277:33–42. https://doi.org/10.1016/j.cbi.2017.08.014. Epub 2017 Aug 24. Erratum in: Chem Biol Interact. 2021 Aug 25;345:109556. PMID: 28844858.

[8] Poehlman ET, Gardner AW, Arciero PJ, Goran MI, Calles-Escandon J. Effects of endurance training on total fat oxidation in elderly persons. J Appl Physiol (1985) 1994;76(6):2281–7. https://doi.org/10.1152/jappl.1994.76.6.2281. Retraction in: Poehlman ET. J Appl Physiol (1985). 2005 Aug;99(2):779. Retraction in: J Appl Physiol (1985). 2005 Aug;99(2):783. PMID: 7928848.

[9] Zouhal H, Jacob C, Delamarche P, Gratas-Delamarche A. Catecholamines and the effects of exercise, training and gender. Sports Med 2008;38(5):401–23. https://doi.org/10.2165/00007256-200838050-00004. PMID: 18416594.

[10] Poehlman ET, Toth MJ, Gardner AW. Changes in energy balance and body composition at menopause: a controlled longitudinal study. Ann Intern Med 1995; 123(9):673–5. https://doi.org/10.7326/0003-4819-123-9-199511010-00005. Retraction in: Sox HC. Ann Intern Med. 2003 Oct 21;139(8):702. PMID: 7574222.

[11] Kim C, Nan B, Kong S, Harlow S. Changes in iron measures over menopause and associations with insulin resistance. J Womens Health (Larchmt) 2012;21(8): 872–7. https://doi.org/10.1089/jwh.2012.3549. Epub 2012 Jun 25. PMID: 22731657; PMCID: PMC3411341.

Gerard J. Nuovo [*,1]

Ohio State University College of Medicine, Columbus, OH, 43210, United States of America

[*] GNOMEDX, 1472 Manning Parkway, Powell, OH 43065, United States of America.

E-mail address: Nuovo.1@osu.edu.

[1] (Retired).