Scientific Integrity: Performing Pre-Clinical Research the Right Way

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Scientific research is one of humanity's most powerful tools. When used correctly, novel pre-clinical findings may lead to the development of life-saving therapies. This includes transformational therapies such as the COVID-19 vaccine and developing technologies such as focused ultrasound or nanoparticle mediated drug delivery. Unfortunately, some researchers have misused this "scientific power" to reap short-term social and economic benefits through publication of research which is fabricated, falsified, or plagiarized. As of the year 2022, more than 32,000 publications have been removed from journals due to this detrimental practice of research misconduct (Oransky, 2021). This propagation of misinformation causes public distrust of scientific research while delaying the clinical progress of patient-saving therapies. These threats to quality and credible research do not persist without innovative solutions. Organizations have encouraged research responsibility through scrutinization and retraction of decades of published research while others offer programs meant to rid of intrinsic biases at earlier stages of scientific writing. These initiatives continue to sponsor responsibility among scientists and the long-term preservation of scientific integrity.

"One thing I have learned in a long life: that all our science, measured against reality, is primitive and childlike—and yet it is the most precious thing we have."

- Albert Einstein (Quoted in Albert Einstein: Creator and Rebel, by Banesh Hoffmann (New York: Viking, 1972), v; Expanded, p. 261)

Path to Retraction

A team of scientists writes a scientific paper following the completion of a scientific study and submits this manuscript to a certain journal. Every scientific paper is reviewed by a

journal selected panel of reviewers (usually experts within the same field as the topic of the paper) prior to being published in an academic journal. This process, though not rid of its own internal biases, examines the "validity, significance, and originality" of a proposed manuscript while also offering possible revisions (Kelly et al., 2014). After passing through a review board, the manuscript is accepted and published within the pre-specified journal. However, the credibility of a publication may be contested at any time by a journal editor or a publication author and lead to its removal from a journal – a retraction. Depending on the severity of the misconduct, authors may lose their positions or face legal repercussions. Perpetrators are reportedly punished in future endeavors within their own field. Authors with record of a retraction incur a 10%+ decrease in citation rate for any future, legitimized work, suggesting irreversible impacts to a scientist's reputation (Azoulay et al., 2017). The instance of a scientific retraction suggests an additional form of misconduct inherent to the process: peer reviewers. These review teams may indirectly propagate the incidence of research misconduct by neglecting to report illegitimate data. In many cases, more published findings including positive results about a technology, therapy, or biological process yield more readers and encourage more grant support. Journals then provide financial compensation to these reviewers, further perpetuating the occurrence of retractions.

Methods of Research Misconduct: Conscious and Unconscious Actions

Research misconduct may occur through several means including both conscious and unconscious actions. Most retractions result from conscious decisions such as data falsification/fraud, plagiarism, or unethical experimental design (Coudert, 2019; Fang et al., 2012). Fraudulent experimentation is often conducted to embellish or replace undesirable data to

construe a more intriguing scientific conclusion. In many instances, this practice of misconduct is propagated by confirmation bias. Peer reviewers, who are most often involved in the same field of research, may be inherently inclined to embrace findings which benefit their own projects. These benefits are sometimes advantageous in application to specific hypotheses (e.g. proposing a brand new therapeutic application for a drug which is heavily studied in a different researcher's lab) or come in the form of financial gains for the field as a whole. Plagiarism and the recapitulation of previous findings under another's name, duplicate publications, are also considered conscious examples of research misconduct. Unethical research practices underline a less talked about issue. This includes unjustifiable harm projected onto research participants or animals, the negligence to establish data protection, or unacceptable sources of grant funding for scientific projects (Bülow et al., 2021). The retraction of these and related transgressions is important in establishing a baseline of merit for scientists, both current and future, as professionals responsible to the public.

Though obvious perpetrations are undoubtedly detrimental to the integrity of science, seemingly invisible misconducts hidden by human biases may be argued to be even more dangerous. Graduate students, post-doctoral researchers, industry researchers, and countless other groups engaged in medicinal research are burdened by the career pressure of requiring publications for professional success. This concept is often referred to as "Publish or perish" (Enago Academy, 2015). Researchers are increasingly drawn towards unconscious practices including p value hacking where samples are cherry picked, outliers excluded, and controls are ignored in the interest of finding a "significant" event (Head et al., 2015). Similarly, researchers may succumb to hindsight bias, a more inconspicuous version of confirmation bias, where conclusions become more noticeable following data collection compared to hypotheses formed

at the initiation of an experiment (Nosek et al., 2018). Both practices of unconscious bias may be remedied by a replacement test statistic called an effect size which determines the statistical power between two factors based on the sample sizes used for analysis (Charles Lambdin, 2012). Even with the potential of a new reporting value such as the effect size, in the age of the Internet and increased presence of publicity in science, researchers will need to be increasingly aware of any implicit biases when interacting with their data.

The History of Retractions

According to an investigation by Coudert, roughly 3 papers are retracted for every 10,000 publications. Most of these research misconducts are attributed to varying degrees of plagiarism or falsification in data presentation. Moreover, the actual retraction process takes a median time of 2 years following original publication with some papers being retracted after 18 years (Coudert, 2019). The incidence of retractions has reportedly increased in the 21st century though it is unclear whether this may be attributed to more accounts of misconduct or if policing of research has improved (Steen, 2011). Recently, the coronavirus-19 pandemic instigated the research of several diagnostic and therapeutic medicines. However, with this fervor of new research came a "Retraction Tsunami." The high influx of COVID-19 related publications led to 109 retractions and counting (Heidary & Gharebaghi, 2021). The influx of publications was fed with financial and global attention, causing falsified papers to be acutely rewarded with commendable, field attention. In one instance, a paper reporting the supposed effects of Hydroxychloroquine as a treatment for COVID-19 was mistakenly published within the highly publicized journal, *The Lancet* (Group, 2020). Retraction numbers continue to rise in wake of the pandemic along with the breakthrough of potentially revolutionizing medicines.

Nobel Prize Worthy?

Dr. Gregg Semenza, winner of the 2019 Nobel Prize, has received criticism for his controversial research findings. His research supposedly elucidated hypoxia induced factor 1 (HIF-1), a protein critical to the growth of tumors through the development of nutrient rich blood vessels in low oxygen microenvironments. Pancreatic cancers have been specifically targeted due to characteristically lower oxygen concentrations. However, further analysis into Semenza's work spanning more than 15 years has proposed many of these findings (western blots and histology reports) to be falsified (Schneider, 2020). Though at least one paper authored by Semenza has been retracted due to these perpetrations, research investigating HIF-1 continues in wake of the Nobel laureate's supposed success (Oransky, 2021).

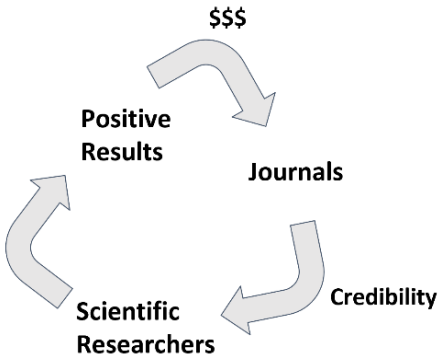

Figure 1: The dangerous cycle between actors involved in research misconduct. Scientific Researchers generate positive results, both accurate and falsified, which are funneled into top journals. These journals generate profits by enforcing reader paywalls. Publication into any journal fuels credibility for scientific researchers leading to increased funding via institutions and other grant organizations for future experiments.

As alluded to before, falsified positive results are promoted in scientific fields mostly due to the detrimental feedback loop between researchers, reviewers, and journals seen in Figure 1. In this scenario, falsified positive results are not only rewarded with publication but also one of the highest honors in science. Boosted by the credibility associated with being a Nobel laureate,

Semenza's publications may not be subjected to the same level of review scrutiny as other attempts at publication. In addition, reviewers who become whistleblowers against a Nobel Prize winner within their same field are certain to face severe backlash. The job of a reviewer is therefore complicated by competing ethical interests of what is right and what is easy.

Nature Controversies

Nature is considered one of the most prestigious journals in Biomedical Sciences through evaluation of its H index. The H-index is a metric corresponding to the number of articles, *n*, within a journal which have *n* number of citations. *Nature* boasts the highest H-index of all journals at 1226 (*Scientific Journal Rankings*, 2021). As *Nature* exists as a beacon for supposedly high-achieving scientific findings, a few notable *Nature* retractions are worth review. Truthfully, this prestige invites several attempts at publication: both legitimate and illegitimate.

In one of the most publicized retractions in the 21st century, *Nature* published work by Haruko Obokata in 2014 claiming a novel method of converting ordinary cells into pluripotent stem cells. Pluripotent stem cells have the unique ability to develop into many different types of cells or tissues in the body. This process of stimulus-triggered acquisition of pluripotency (STAP) was considered revolutionary for its ability to use physical stresses or exposure to highly acidic conditions for the improbable production of versatile cell sources (Cyranoski, 2014). The findings had implications in the generation of patient-specific stem cells for tailored therapies as well as broader applications to cancer research. In the months following its publication into an esteemed journal, researchers raced to reproduce the phenomenon. All subsequent attempts at the STAP methodology proved unsuccessful, raising considerable opposition to the authenticity of Obokata's design. Eventually, Obokata's institution led an internal investigation and advised her

to retract all associated publications after finding her guilty of scientific misconduct (Cyranoski, 2014). Significant resources, time, and public attention were wasted. The fallacy led to a considerable decrease in personal credibility for Obokata but also reflected poorly on the field of stem cell research and a leading scientific journal. As a form of consolation, *Nature* offered a plan to revise the process specifically encircling image manipulation for future review boards.

Most retractions do not receive the media attention of the 2014 STAP investigation but share in the possibility of longer-term ramifications for scientific fields and researchers. For example, Bialas and Stevens were published in *Nature* in 2013 for their work with brain cell synapse development. However, the authors retracted their work in 2022 citing the inability to replicate key results (Bialas & Stevens, 2022). The retraction had consequences beyond the implicated Harvard lab. An article published by Derecki and Kipnis of the University of Virginia in 2022 was retracted shortly after "because it relied on the validity of the data presented therein" (Derecki & Kipnis, 2022).

This incident raises many concerns about the practice of research misconduct. Firstly, citing truthful research is paramount when writing scientific literature. When researchers cite others in their work, these individuals are endorsing the authenticity of this consulted data. This leads to fault on both researchers as the reference to a falsified source to support an argument without evidence of alternate acceptance, or corroborated findings, may be considered fabrication. Secondly, small transgressions in scientific research may magnify through a resultant chain reaction. The premise of citations insinuates researchers are constantly reviewing, reproducing, or building off the work of others in their immediate scientific field. Therefore, a fallacy of scientific judgement in one lab may lead to serious consequences in many labs. Thirdly, timing is everything. The near nine-year timespan between publication and retraction

suggests complacency in scientific thought. The results suggested in the preliminary publication were believed and built upon for several years. Shortening this time gap between publication and retraction is vital to the flourishing of true medicinal discoveries for the treatment of serious illnesses.

Remedies for Research Misconduct

There are several more cases of retractions to enumerate which detail different methods of fraudulence at each step of the publication pathway. However, it is worth highlighting the organizations which are addressing these inconsistencies through programs intended to publicize retractions and encourage research responsibility in all phases of experimental design.

In direct response to the timescale of retraction and the heightened attention towards scientific integrity in recent decades, the non-profit, Center for Scientific Integrity organized the formation of Retraction Watch in 2010. Retraction Watch exists as a blog-based non-profit spearheaded by previous science writers Ivan Oransky and Adam Marcus with a mission to "promote transparency and integrity in science and scientific publishing, and to disseminate best practices and increase efficiency in science" ("The Center For Scientific Integrity," 2015). The site includes a free database listing all retractions as well as news articles providing insight into important cases, effectively publicizing past research misconducts which may have been previously unannounced. The extensive database with more than 32,000 retractions includes the work of several controversial authors including Semenza and Obokata. Retraction Watch has also integrated their data with EndNote, Papers, and Zotero software systems to provide users with updated retraction alerts (Oransky, 2021). This feature is essential to the reproducible work of everyday scientists who engage with high volumes of research publications.

It is obvious a more rigorous process of review is required for marked change to occur. One proposed method is the introduction of a review checkpoint at the onset of scientific writing called preregistration. In application to all research, regardless of field or intention, this preregistration process may be conveniently applied through the Center for Open Science. The Center for Open Science is a program founded by University of Virginia Psychology professor Brian Nosek which seeks to "increase the openness, integrity, and reproducibility of scientific research" by offering programs to review experimental tests prior to implementation and offer guidance to avoid data biases or other scientific maladies (COS, 2022). Utilizing these resources will encourage reproducibility in data findings allowing for truly transformative medicines to be better translated to the clinic. This mission was further validated through an announced collaboration between the Center for Open Science and Retraction Watch in 2015 to extend the technical infrastructure of the retraction database onto the Open Science Framework. This effort further intends to integrate research related metadata already found through Center for Open Science services with updated retraction data, creating an all-encompassing SHARE Notify system for facile interaction with past publication data (COS, 2015). The partnership between these two organizations demonstrates the unity in action which is required for systematic change in scientific publishing.

The Future of Scientific Integrity

The Centers for Open Science and Scientific Integrity are leaders in the mobilization against research misconduct. However, these organizations do have limitations in the scope of complete adherence to scientific integrity. Preservation of the future of scientific integrity

requires the redefinition of the systematic relationships between researchers, reviewers, and sources of funding.

Primarily, scientific researchers are human. In relation to subconscious biases discussed before, these organizations are changing the process and the penalties of scientific publication but are unable to catch every incident along the pathway to publication. Continuity of responsible research is always derived from the researcher and their morals. This could be seen through potentially reprehensible actions as miniscule as exposing control and experimental groups to slightly different times of treatment because it is easier or as massive as exchanging control and experimental group results completely because it aligns better with the hypothesis of the experiment. These perpetrations must be discouraged through education, requiring institutional changes at all levels of university (students and faculty alike). Ethical conversations regarding the responsible conduct of research, prevention of p-value hacking, tackling of inherent biases when reading data, and others must begin in the early phases of undergraduate/graduate studies as has been demonstrated before (Jones et al., 2010).

Researchers, many of whom are professors as well, are also often keen to do only what is required for submission of a publication in the interest of saving time for future experiments or other duties. These professionals may not consult a lengthy database or file for pre-registration of their experimental design because it takes time. This pitfall has already started to be addressed. Grant sources, such as the Focused Ultrasound Foundation, have encouraged pre-registration for all funded publications (*Open Science Policy for Funded Research*, 2021). Responsible interaction with early phases of experimental design will be implied once encouragement becomes requirement, turning grant sources into initiators for scientific integrity rather than motivators for research misconduct. This redefinition of roles would be corroborated by

reformational changes for journals including the use of a double-blind peer review. A double-blind peer review would require both reviewer and author identities to be hidden throughout the feedback process. This system has previously demonstrated a significant reduction in review bias when compared to the common method of single-blind review instituted in the majority of journals today (Tomkins et al., 2017). *Nature* and *The Lancet* have made modest modifications to their respective peer review processes following incidences discussed before (Cyranoski, 2014; Group, 2020). Broad institutionalization of potentially curative methods including double-blind peer review remain untouched for now.

The principle of preregistration also invites concern from researchers due to the privacy of intellectual property. Many scientists are researching novel medicines, diagnostics, or methods and want to ensure their intellectual property rights are maintained during a disclosure to the center for open science through preregistration. Firstly, the content of all submissions to the Center for Open Science is up to the discretion of the authors. Authors may receive important feedback to their experimental design or data analysis even with the omission of proprietary names or processes. More importantly, any manuscript submissions are assigned a permanent digital object identifier (DOI) which perpetually connects the literature with the author's name to establish intellectual ownership (Speidel, 2018). The process of preregistration intends to save time for the researchers and extend their lead time by offering guidance to the writing process.

Conclusion

Scientists exist as the public's ambassadors to the unknown. However, with this power comes an extreme responsibility to produce research results which are clear and truthful. Past researchers engaged in scientific malpractice have glorified false discoveries and distracted the

public from truly viable breakthroughs in medicine. However, these transgressors are not met without opposition. Retraction Watch has reinforced the adoption of ethical research practices by policing past perpetrators of research misconduct. Organizations, including the Center for Open Science stemming from the University of Virginia, have given researchers additional opportunities to receive feedback to correct both conscious and unconscious biases in their work. Truthfully, science is not always flashy and rewarding; however, science presents humanities only chance at learning more about the world and each other. We must therefore treat it with the respect it deserves.

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