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MISCONDUCT IN BIOSCIENCE RESEARCH

a 40-year perspective

JEFFREY S. FLIER

ABSTRACT Fraud in biomedical research, though relatively uncommon, damages the scientific community by diminishing the integrity of the ecosystem and sending other scientists down fruitless paths. When exposed and publicized, fraud also reduces public respect for the research enterprise, which is required for its success. Although the human frailties that contribute to fraud are as old as our species, the response of the research community to allegations of fraud has dramatically changed. This is well illustrated by three prominent cases known to the author over 40 years. In the first, I participated as auditor in an ad hoc process that, lacking institutional definition and oversight, was open to abuse, though it eventually produced an appropriate result. In the second, I was a faculty colleague of a key participant whose case helped shape guidelines for management of future cases. The third transpired during my time overseeing the well-developed if sometimes overly bureaucratized investigatory process for research misconduct at Harvard Medical School, designed in accordance with prevailing regulations. These cases illustrate many of the factors contributing to fraudulent biomedical research in the modern era and the changing institutional responses to it, which should further evolve to be more efficient and transparent.

FRAUD IN SCIENCE HAS BEEN KNOWN for centuries. One hoax in the 19th century reported a woman giving birth to dead rabbits, a fraud that ruined the careers of two respected British physicians who were deceived, quite embarrassingly, by

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their patient. The Piltdown man was a famous case in England, breathlessly reported as the “missing link” between apes and man. Perpetrated as a hoax for four decades, in 1953 the report was shown to be entirely fabricated. More recently, claimed links between vaccines and autism and reports that a simple method could turn skin cells into stem cells were both exposed as fraudulent science (De Los Angeles et al. 2015; Godlee, Smith, and Marcovitch 2011; Obokata et al. 2014; Wakefield et al. 1998).

The frequency of research misconduct, defined as fabrication or falsification of results or plagiarism, is not known with certainty, nor is it clear whether its prevalence has changed in recent decades (Fanelli 2009). Misconduct as formally defined is distinguished from a far more common problem, irreproducibility of research, which has many causes, of which fabrication and falsification are thought to be uncommon (Flier 2017).

When exposed, scientific fraud garners headlines. The stories clash with the carefully nurtured image of science as an endeavor steeped in objectivity and rationality. They provide an opportunity to humble academics who may seem remote and prone to hubris, or bring down eminent scientists at the top of their fields who failed to anticipate the crisis of integrity that would ensnare them in a web of deceit. As in other professions, defensive reactions to accusations of fraud or misconduct are often more destructive than the fraud itself. Revelation of fraudulent research may have practical consequences, requiring the public to change mistaken understandings built on falsified scientific claims. Remarkably, as with the purported link between vaccines and autism, false beliefs often persist far beyond exposure of the fraud.

During 40 years as a biomedical scientist and academic leader, I’ve witnessed more than my share of research fraud, and I’m profoundly disheartened by every new case. While eliminating all scientific fraud is impossible, understanding the initiation, perpetuation, and response to research misconduct may help guide its prevention and early detection.

“On a bright, cold morning in early February 1980, Jeffrey Flier, a tall, mustachioed young physician, boarded a train in Boston on his way to New Haven to carry out a distinctly disagreeable professional task.” So began a *New York Times Magazine* story, dated November 1, 1981, entitled, “A Fraud That Shook the World of Science” (Hunt 1981). Three years following a move to Boston to set up my Harvard lab, this widely read story brought attention of a kind I wasn’t seeking, even though my role in the story was, to paraphrase Agatha Christie, to be detective chief inspector of the data. As the article vividly recounts, it was a tragic case of research fraud at Yale into which I was reluctantly drawn as an impartial expert auditor. My amateur forensic analysis revealed that all was not well in biomedical research, even in its highest echelons.

The story began with Helena Wachslicht-Rodbard, a young Brazilian physician who joined the Diabetes Branch at the National Institutes of Health (NIH) in 1977 as a visiting scientist. Her ambition was to be a physician-scientist in the area of metabolism, and joining the leading lab in the emerging insulin receptor field was a logical choice. We shared a lab on the 8th floor of NIH Building 10, where I was among those helping orient Helena to the techniques required for her work. Her aim was to quantitate insulin receptors on patients' cells to see if their number was affected by clinical states such as diabetes. We collaborated, and published one paper together (Wachslicht-Rodbard et al. 1981).

One project that Helena undertook involved measuring receptors on cells of patients with anorexia nervosa. This disorder, in which young women restrict their food intake for reasons that remain poorly understood, threatens their health and often their lives. Severe starvation causes blood sugar and insulin levels to be very low. Helena's research would test the hypothesis that in response to low blood insulin levels, the number of insulin receptors on their cells would increase. When I left the NIH in July 1978, Helena was well into her study.

In January 1980, I received a phone call from my NIH mentor Jesse Roth. We had had minimal contact over the prior 18 months, so we caught up on my new lab and on family. Then Jesse got to the point of his call. There was "a problem in the lab," and he "knew that I was the perfect person" to help solve it. A tangled tale emerged. Helena had submitted her paper on insulin receptors in anorexia nervosa to the *New England Journal of Medicine*. Several weeks later the editorial decision arrived in the mail: the paper was rejected. One reviewer was positive; the other raised technical issues and thought the paper unsuitable for a general journal like the *NEJM*. Disappointing news for sure, but such rejections are a normal, if frustrating, part of scientific life. Helena and Jesse spent time considering where to resubmit the paper.

Several months later, Jesse was asked to review a manuscript for another journal, the *American Journal of Medicine*. Submitted by a group at Yale, the topic and results of the paper sounded remarkably similar to Helena's rejected anorexia work. The paper arrived as he was leaving for an extended trip, and like many laboratory chiefs heading out on a lecture tour, he left the paper with a mentee to examine—in this case Helena—saying they would discuss it when he returned.

Upon seeing the title, Helena devoured the paper, and within minutes, she was infuriated. The data and conclusions closely paralleled her rejected paper, and it was evident that several paragraphs from her paper had been plagiarized, word for word. She deduced the authors of this paper must have reviewed her paper. Who were they? None other than a highly regarded group at Yale led by Philip Felig, a respected leader in metabolic research. In his mid-40s, Felig was on the fast track to leadership in academic medicine. Unknown to Helena, he

was an acquaintance of Jesse Roth from their boyhood days in Brooklyn. Helena concluded that Felig and colleagues were academic criminals, and that justice should be swift.

Furious and unaware of prevailing academic protocol, Helena didn't wait for Jesse to return from his trip. She phoned Arnold Relman, the powerful editor of the prestigious *NEJM*, and asserted that her paper had been plagiarized through their review process. He told her he would look into it. She also contacted the dean of Yale Medical School, Robert Berliner, a distinguished scientist and former leader of research at the NIH, and asserted that a senior member of his faculty was guilty of research misconduct. In her justifiably distressed state, she expected sympathy and commitment to rapid action. Unfortunately, and perhaps unsurprisingly given the state of misconduct inquiries at that time, she received neither. Berliner communicated that Yale would examine her claims, and he advised her against continuing to press them. The power differential between the Yale dean and an aggrieved young female postdoc was marked.

Helena appeared in Jesse's office the day he returned, expecting sympathy and support from her mentor. Instead, he expressed concern was that she had taken actions without first consulting him, which in the narrow sense of proper academic protocol was understandable. After all, he was the person asked to review the paper; her action without his consultation and agreement was inappropriate. As the lab chief, he too had interests in getting this right. In addition, he had high regard for Dr. Felig and hoped that he would be able to explain what happened, ideally without an unseemly public scandal. He promised to work to find a solution. But Helena wasn't mollified, she was further incensed.

It was 1979. There were no established procedures for handling such issues. When issues arose, responses were entirely ad hoc. It was easy for an old boys' network to stifle the accusation, or appear to be doing so. There were many unhappy exchanges between Jesse and Helena, but she did not desist. Instead, she got everyone's attention by declaring her intent to publicly denounce Felig at an upcoming national meeting, a serious threat. Jesse sought further input from NIH scientific leadership. After numerous discussions, Roth and Felig conferred and arrived at a solution: they would dispatch a mutually acceptable detective inspector to Yale, a role they hoped I would accept.

Jesse called and asked me, on behalf of himself and Dr. Felig, to visit New Haven to examine the primary data of the Felig anorexia study. My assignment was threefold: to confirm that the study had actually been performed; that their study preceded review of Helena's *NEJM* study; and that the data within their manuscript were consistent with "raw data" in their lab notebooks. Jesse said I was the perfect—if not the only—person to carry this off. Why? I understood the relevant science, I lived not far from New Haven, and, he said, I was trusted by all parties. Still, the prospect was very unappealing. This was an ugly dispute between two influential scientists, one of whom was my mentor. I was a recently

minted junior faculty member without an independent reputation. There were no official rules of engagement for my investigation. But Jesse was extremely persistent, and I agreed.

As I boarded the train, I didn't expect to document fraud that day. I expected to confirm that the studies were conducted, though I harbored doubts about the quality of the data. The data in several papers published by the Felig/Soman group were more "beautiful" than any other lab produced, so I wondered about the integrity of their published graphs. But with Phil Felig sitting there it hardly seemed possible I would be shown evidence of previously unidentified data manipulation. And I wasn't expecting to conduct forensic analysis to confirm the integrity of data I'd be shown.

But fate had another plan. I learned on arrival that Dr. Felig would not be present, as his elderly mother had died several days before. Present were only Dr. Vijay Soman, the first author of the Yale study, and me. An assistant professor in his late 30s, Vijay trained in India and had spent several years with Felig. Not fully independent, he had published more than 20 papers with his mentor. I had met Vijay briefly at national meetings, and, ironically, when I visited Yale in 1977 to explore a possible faculty position after leaving the NIH. When I turned down the Yale offer, Vijay, whose research competence involved physiologic studies in patients, was assigned to learn techniques for studying insulin receptors, which would have been my area had I gone to Yale. Felig clearly wanted to enter that field. Strangely, my declining the Yale offer put Vijay in the position to conduct the work in question.

Vijay seemed nervous, but who wouldn't be under such circumstances. He led me through a maze of dingy equipment-filled corridors typical of research buildings, to a room with data books neatly piled on a large table. We agreed I would first examine the clinical records of the patients in the study, and then the raw data for their receptor binding studies. I rapidly confirmed that there appeared to be actual patients, with studies dated well before Helena's paper was submitted. So far so good. But when I examined the raw data—printouts on narrow strips of yellowing paper—problems immediately arose. The printed counts of measured radioactivity were simply not consistent with the data in the submitted paper. I had conducted such studies many times, working with nearly identical printouts, so that conclusion was obvious, first in one study, then two, then three, then four. There was a serious problem.

After an uncomfortable silence during which I tried to devise an appropriate question, I said, "Vijay, this binding curve doesn't look the way they normally do, and it doesn't look like what you had in your recent manuscript. What's going on? Did you fudge the data?" I don't believe I had ever used the word *fudge* before in this context, but it's the word that emerged to capture my thinking.

Vijay produced some very odd, nervous giggles, and then said, "Yes, I guess I did." That remarkable admission was followed by a long silence; he stopped

talking, and I sat there, stunned, trying to imagine how the drama would unfold. When Vijay next spoke, his speech was agitated. He told me that after he was given Helena's *NEJM* manuscript to review by Felig, he felt under tremendous pressure to finalize his own paper. They sent their negative review to the *NEJM* despite the explicit conflict of interest of working on exactly the same question—publications ethics prevailing then and now would say they should have returned the paper without review. Vijay admitted photocopying sections of the methods section from the rejected manuscript, sections of which appeared verbatim in his paper. Finally, he admitted “cutting corners” to make his own messy data look better than it was. He said he was very, very sorry. The human tragedy was painful to witness.

How to proceed? There was no script, and no one to ask for advice. I decided I had to leave. I thanked him and said I was ready to return to the train station. Vijay insisted quite emphatically on driving me, which didn't appeal to me at all. Did I want to be driven by a scientist who likely understood that his career was over as a result of my inquiry? But etiquette conquered fear, and I allowed him to drive me. No further words were spoken, and after an awkward goodbye, I never saw Vijay again.

Once on the train, at this time before portable computers or cell phones, I took a yellow legal pad from my briefcase and wrote out the core elements of my report. A few pages long, its central message was simple: Vijay admitted to data manipulation. I spent most of the trip wondering how the next steps would play out, and how this might impact the careers of Vijay, Phil Felig, Helena, and myself. Once home, I typed the report and put it in the mail, addressed to the two people who commissioned it: Drs. Roth and Felig.

One or two days later, I received a call from Phil Felig. He began by apologizing for having put me through the discomfort of the audit. But his next statement was stunning. After discussing my visit with Vijay, he said they realized that Vijay had shown me the “wrong data”—not the actual data for their paper, but data from preliminary studies. He apologized profusely and said he would send me a package with the “real” data by overnight mail.

It was clear that a cover-up was now unfolding. Fortunately, this early suggestion of a cover-up didn't last long. I told him the report was already in the mail, and both he and Jesse would likely receive it within days. I pointed out that no one would accept a revised report based on “the correct data substituted by mail after the audit.” A long silence followed. When he finally spoke, his voice was notably different: “I'll call you back,” he said.

As promised, he called several hours later. This time, he said he was sitting in the office of his department chair, Dr. Sam Thier, a prominent academic leader who sequentially became the President of the Institute of Medicine, President of Brandeis University, and President of Partners Healthcare, leading Harvard's two biggest hospitals. Felig reported that subsequent to our earlier call, he and Thier

met and confronted Vijay. He said that Vijay admitted that he, and he alone, was responsible for the plagiarism and data manipulation. Steps to deal with his misconduct would be initiated, and he thanked me for my role in figuring this out. I didn't ask him about the "real data" that he offered to send a few hours earlier.

This was not an ordinary period in Phil Felig's professional life. While the "Soman Affair" was playing out he was negotiating a move from Yale to Columbia's "College of Physicians and Surgeons" to become the Bard Professor and chair of its Department of Medicine. While some facts are disputed, Columbia leadership later stated publicly that the problems unfolding at Yale with his contested paper hadn't been clearly disclosed to the Columbia dean or search committee.

Meanwhile, in response to my findings, Dr. Roth and others he consulted at the NIH decided to audit additional papers from the Felig lab involving Soman. I received another call from Jesse, asking me to carry out this assignment. Having "served my time," I steadfastly refused, suggesting Jerry Olefsky, then an associate professor at the University of Colorado and a major contributor to the insulin receptor field. Olefsky agreed to visit Yale, and he soon called to ask about my Yale experience. He had qualms, as I did, about the role of "auditor," but told me he would let me know how it went.

Olefsky's call came several weeks later and produced no surprises. Things were "pretty much what you described to me, Jeff." Most studies were done, but much of the raw data looked terrible, not the neat and definitive figures in the published papers. And some raw data couldn't be found. As I had, Olefsky was writing a report to be sent to the principals. Neither of us knew what would happen after that.

My next interaction with Phil Felig was truly surreal. He had been chosen as the annual visiting professor at the Beth Israel Hospital. Several months had passed since my audit, and I had heard nothing in response to either my or Olefsky's audits. Felig delivered a long-planned lecture to the department on his research on human amino acid metabolism, saying not a word about his questionable insulin receptor work. I sat in the back of the room, trying to be inconspicuous, and left quickly at the end.

At the annual department dinner that evening at the stately Harvard Club, Felig took me aside and awkwardly stated, "Jeff, just wanted you to know that Jerry Olefsky came by recently and examined a group of Vijay's papers on insulin receptors. I thought you'd like to know that he found them all to be just fine. Thanks again for what you did for us. I'm hoping we can put all of this behind us."

I don't recall what I said in response, or how I appeared to those around us. I have no recollection of his after-dinner speech. It seemed that a second attempt at a cover-up was well underway.

Several months passed until a morning in early August 1980, when I received a call from Lawrence Altman, lead medical reporter from the *New York Times*,

whose name I immediately recognized. He asked to interview me about a case of research impropriety on the part of Philip Felig, and his firing as Chair of Medicine at Columbia, a story he was about to report in the *Times*. As part of the story, he wanted to know about my role, and I provided answers. On the morning of August 9, 1980, a front-page article in the *New York Times* reported that Columbia University had fired Professor Philip Felig, recently installed as Medicine Department Chair (Altman 1980). The reason cited was plagiarism and faulty data in several papers from his Yale lab that hadn't been disclosed during the search, creating issues of trust. The article, and several that followed, referenced Felig's inadequate response when the problem was raised through Helena's persistence and, eventually, my audit (Broad 1980a, 1980b). No doubt, as principal investigator he should have performed an immediate data audit himself. The *Times* identified me as the auditor, and quoted me regarding my findings. This scandal ended Felig's high-flying academic career, even without knowledge of the attempted cover-up that hasn't until now been described. Felig returned briefly to Yale, spent several years in the pharmaceutical industry, and for 30 or so years had a private practice of endocrinology on Fifth Avenue in New York City. He passed away in 2020, at the age of 83.

Vijay Soman, whose research misconduct most directly caused the problem, left the country for his native Poona, India, never to be heard from again, despite several reporters having tried unsuccessfully to track him down. I was recently told by a colleague with family in Poona that he became a successful diabetes doctor after returning to his ancestral town. My recent efforts to find him also failed.

Helena Wachslicht-Rodbard left research shortly after these events, deeply disappointed by the ethics of the scientific community. She reentered clinical training, obtained a US license, and became a very successful clinical endocrinologist and co-founder of the American Association for Clinical Endocrinology.

My involvement in this drama of scientific and publishing fraud caused me to think deeply about the honesty of biomedical scientists and about flaws in our scientific culture. The experience stimulated an ongoing interest in the culture of bioscience, its relationship to bioscience publishing, and how together they advance scientific progress, while periodically threatening it.

I wish I could say that was my only experience with scientific fraud, but unfortunately, it would not take very long for another episode to present itself.

Eugene Braunwald, now 92 years old, is a towering figure in American medicine who played a key role in numerous discoveries that improved the care of patients with heart disease. Appointed chair of the Department of Medicine at the Brigham and Women's Hospital in 1972, he was widely acknowledged in subse-

quent years to be the most powerful academic figure at Harvard Medical School (HMS), with influence spanning every aspect of the academic-medical enterprise. In 1980, he was also named chair of medicine at the Beth Israel hospital (BI), an appointment that was more than a little unusual. The Brigham and Women's Hospital was a Harvard teaching hospital across the street from BI, and in typical Harvard fashion the two hospitals were quite competitive. It was remarkable that anyone could be named to simultaneously chair these two medicine departments, but he was.

In early 1981, EB, as he was universally known, called a meeting of the leadership of his department at BI, then a group of about 20 that included division and unit chiefs. After some routine business matters, he made an important announcement regarding a new faculty recruitment. He had already recruited a cadre of terrific young faculty to BI, many from the Brigham.

EB told us that John Darsee, a young cardiologist and researcher in his large Brigham research group, would soon be appointed assistant professor. He described Darsee as brilliant, incredibly hard-working, and unusually productive. This phenom would soon launch his independent career at BI.

But Darsee never made his move across the street. Soon after his announced recruitment, EB received some shocking news. Bob Kloner, then a young faculty member and trusted leader of Braunwald's lab effort, developed doubts about the veracity of Darsee's work when another lab member directly observed him falsifying data, producing an acute crisis.

When EB was informed, he immediately confronted Darsee, who admitted this specific instance of data falsification. He apologized profusely, claiming the experiment had actually been properly performed. But, he claimed, he had misplaced the original data during a lab move. Under pressure of a deadline, he had mistakenly "recreated it" for the record, as he was observed doing. As his mentor, EB wanted to believe him. He was initially willing to consider the possibility that this was an isolated, if serious, mistake by a stellar individual, made under time pressure and stress.

Unlike Felig, however, EB took additional decisive action. He suspended the NIH grant that funded Darsee's salary, terminated the process for his HMS appointment to assistant professor and the planned move to BI, and informed both HMS Dean Daniel Tosteson and the Brigham leadership of these events. Under enhanced scrutiny, he initially permitted Darsee to continue working on other studies, some involving a multi-center trial in an animal model.

Just a few months later, in October 1981, the enhanced oversight by Braunwald and Kloner produced evidence that Darsee's fabrication was far more extensive. When again confronted, he denied any wrongdoing, but couldn't produce much of the primary data for his studies. Requirements for data management stipulate that primary data must be kept for a minimum of three years, and many investigators keep data until they retire. The Darsee house of cards rapidly collapsed.

EB determined it was time to propose two formal and fully independent investigatory panels. One investigation was based at Harvard Medical School, another at the National Heart, Lung, and Blood Institute (NHLBI), which funded Darsee's project and much of the work in Braunwald's lab. Darsee's experiments and results did not stand up to scrutiny. He was fired, and 30 papers and abstracts were formally retracted from the literature (Broad 1983).

How could this have happened? Darsee had generated data and published abstracts and papers at an unusual rate. Apart from the time it takes to perform experiments, it takes weeks and months to analyze data and assemble it for review, and then to write and edit papers and finalize them to the point where manuscripts are suitable for submission to a journal. In retrospect, his "unusual productivity" should have been a warning sign before the fraud was directly uncovered. Sometimes, when things seem too good to be true, they are in fact too good to be true.

As the problems unfolded, it became clear that Darsee's career of deception didn't begin at Harvard: he had been fabricating research for years before joining the Braunwald-Kloner team. Darsee published papers while a student, resident, and cardiology fellow at Emory, and his letters of recommendation from multiple senior faculty members at Emory, where he was chief resident, were "over the top." Stimulated by the events in Boston, this work was also discovered to be totally fraudulent, resulting in many retractions. At Emory, he published abstracts describing patients that never existed. Research that he published in college was also discovered to be fraudulent. Clearly, he was highly skilled—at research deception. His accelerated career in academic medicine was based on fraud, well before exposure to the Braunwald team. The Harvard and the NHLBI panels both concluded the fraud was the work of Darsee, and Darsee alone, a conclusion few found surprising. The NHLBI report did note the hurried pace of work and perhaps excessive emphasis on productivity in the lab. As might be expected, the story garnered major national attention. In several published articles, the Darsee fraud was described alongside the Yale affair, with both portrayed as indicators of broader problems in the conduct and oversight of biomedical research (Broad 1983).

Braunwald remained publicly silent, avoiding the press for several years. It's unlikely this would be possible today. He eventually wrote an article in *Nature* recounting his experience, and most importantly the lessons he had learned (Braunwald 1987). But his career and reputation post-Darsee didn't visibly suffer. Understanding why requires recounting his remarkable accomplishments.

Braunwald was born in Vienna in 1929. His family left Austria to avoid the Holocaust, arriving in Brooklyn in 1939. For an immigrant kid of that era, his professional path was remarkable. He attended college at NYU and then NYU Medical School, graduating first in his class. He did a medical internship at Mount Sinai Hospital, and did research in a leading cardiac research lab at Columbia

whose director later received the Nobel Prize for developing cardiac catheterization. EB next moved to the NIH as Clinical Associate, rapidly rising to head of the Cardiology Branch at what was then the National Heart Institute. He was recruited to UC San Diego as a very young Chair of its Department of Medicine, and then in 1972, to the Brigham and Harvard, as Chair of the Brigham's vaunted Department of Medicine.

Along the way, he wrote and published over a thousand scientific papers, a major textbook of cardiology, known as Braunwald's *Heart Disease*, and was senior editor of the classic Harrison's *Principles of Internal Medicine*. His discoveries using animal models and large-scale human trials changed the standard of care for heart attacks and heart failure. One of very few cardiologists to have been elected into the US National Academy of Sciences, any list of the most influential cardiologists in history would place him at the very top.

Unlike the effect of Soman's misconduct on Felig, the consequences of the Darsee affair for Braunwald were objectively quite modest. It was of course an extremely painful and embarrassing episode in an otherwise brilliant and productive career. In his retrospective analysis published several years later, EB made several key points (Braunwald 1987). First, during the transition from trainee to faculty status, a mentor must be especially attentive to signs of trouble. Second, once a single event of clear dishonesty in research is identified, the burden should shift to proving that the individual's other work is not flawed. While it's natural to consider extending the benefit of the doubt, it's not a good idea. Finally, in response to initial evidence of such problems, investigations should be handled expeditiously by a fully independent panel. Braunwald wrote that "scientific fraud is a crime, and must be investigated like any other crime." He was correct on all these points. The Darsee and Felig affairs stimulated the design and implementation of new procedures routinely employed today—unfortunately, far too frequently.

The third case in this trio of misconduct played out during my time as dean, and revealed the extent to which institutional procedures had changed over the previous 30 years, and how far we still have to go to improve them.

Piero Anversa received an MD from the University of Parma in Italy and pursued a career as an experimental pathologist, with special interest in pathology of the heart. He spent most of his career at New York Medical College, where he became Professor of Pathology. He published extensively, built a large research group, garnered substantial grant funding, and received much recognition for his work, including major awards from the American Heart Association.

About 20 years ago, his research began to question a longstanding belief within cardiology that the adult heart is incapable of regeneration. That is, unlike some other organs, the heart was believed to have an unchanging number of cardiac

muscle cells throughout adult life. If so, damage to the heart, as occurs in a heart attack, cannot be repaired by new cells arising to replace those damaged by disease. Anversa's published work suggested quite the opposite: that normal adult hearts give birth to new cells at a measurable rate (Beltrami et al. 2003). He published other work, even more surprising, claiming that cardiac progenitor cells can enter the heart from the blood and once there transform into functional heart cells (Orlic et al. 2001). Anversa used modern molecular and cell biology techniques, published in leading journals, was well funded, and gave lectures to standing room only crowds at major national meetings. By challenging longstanding paradigms, his work created quite a buzz. But his presentations also provoked controversy. Some attending his talks recall angry interchanges during discussion periods between Anversa and some researchers who went to the microphone to challenge his findings and interpretations.

This research occurred at a time when the field of regenerative biology had become very exciting, and the idea that stem cells would produce therapies for many serious diseases was gaining favor. Harvard had recently launched a Stem Cell Institute and Department of Stem Cell and Regenerative Biology. Other institutions were seeking to increase their scientific profiles in this area.

One such institution was the Brigham and Women's Hospital, which decided to make a substantial investment in cardiac stem cell biology. The Anesthesiology Department, flush with space and money, played the lead role, in alliance with the Department of Medicine, in which its famed cardiology division resided. Many influential Brigham scientists thought Anversa would be a great catch, and he was thought to be willing to move.

HMS has a well-described approach to conducting searches for new faculty, whether to the school itself or to its hospital affiliates, where most of its faculty reside. The goal is threefold: to identify the best faculty, to avoid recruitments through old boys' networks, and to ensure consideration of women and minority candidates. HMS approved a formal request to convene a search committee, mainly populated by Brigham faculty, with participation by school administration. Out of dozens of possible candidates, Anversa emerged as the lead.

HMS requires additional steps beyond the search committee before appointments as professor can be forwarded to the University, the final step in such academic appointments. A so-called "ad hoc committee," comprised of a new group of internal and external experts in the field, is appointed by the Dean. This committee solicits confidential letters from additional experts, and based on the totality of the evidence, recommends whether the appointment should move on to the next step, which involves an additional HMS standing committee of senior professors drawn from many disciplines. Based on the secret ballot and comments of that committee, the dean makes the final decision. Ideally—and here is where it can get sticky—candidates should not have finalized their negotiation and physical move to Harvard or its affiliated institutions until this academic

review process is complete. It would be embarrassing for someone to quit their prior position, move their family and their lab, only to fail in their appointment as HMS professor.

Not long after becoming dean, I was informed that the Anversa case, initiated under my predecessor, had hit a snag. He had been offered and accepted a job offer from the Brigham, and he had moved his grants and a substantial research team from New York. But at the time he did this, the ad hoc committee had not yet met, obtained external letters, nor opined about his Harvard professorial appointment. Several months into the process, I was told by the Faculty Affairs Dean who managed the process that, based on preliminary discussions, that decision might not be positive. One or more external evaluators and committee members expressed doubt that Anversa's work on human heart cell regeneration would ultimately prove to be correct.

I sought out and spoke with several experts, and I discovered what many in the field already knew: that Anversa was disliked by many in the field, and some vocally doubted his data and conclusions. But most experts were truly excited about his work. If his conclusions about cardiac regeneration were substantially right, they said, his discoveries would have enormous implications for understanding and potentially treating heart disease, the nation's biggest killer. What's more, paradigm-changing work is frequently doubted by the scientific community when initially presented. Clinical trials based on his ideas were already being planned.

While Brigham leadership was communicating their extreme unhappiness that the HMS process "was so slow," I asked the committee to solicit an additional round of expert opinions. Once again, opinions were largely, but not unanimously, positive. After additional committee meetings and discussions, and despite concerns that I shared, the appointment was approved by HMS and the University. In retrospect, I view this as the decision as Dean that I most regretted.

Over the next several years, I regularly inquired about Anversa's research but heard of no problems from his Brigham department colleagues. However, that eventually changed. In 2012, an accusation of data manipulation was brought to the school by a coauthor of one of Anversa's published papers. The coauthor, from the Lawrence Livermore Laboratory, had provided key data for the study in question. This accusation triggered the joint HMS and Brigham process for adjudicating such matters, overseen by an HMS dean for academic and research integrity, a process that hadn't existed at the time of Darsee. First came an initial HMS "inquiry," and when that suggested the need, a formal "investigatory panel" was established. These are confidential proceedings, designed to protect the interests of both the accused and the institutions. Accordingly, when asked to comment by the press or by others, Harvard lawyers advise saying nothing. Many details of this case have already been recorded in the press, so I am able to discuss them (Kolata 2018a).

Perhaps not surprisingly, given what was at stake, the investigation provoked internal lab disputes regarding assignment of blame for what was determined to be intentional data manipulation by one or more members of the team. After several years, Anversa and his colleague Annelina Lera accused another longstanding lab member, Jan Kajstura, of duping them, apparently accepting that several papers did indeed contain fraudulent data. The progress of the investigation dragged on, not least because more and more papers were questioned, and at every stage the procedures were contested by legal maneuvers. In 2014, Anversa and Lera brought an unprecedented lawsuit against the Brigham and HMS, alleging unfair investigatory processes and blaming Kajstura for the misconduct (Johnson 2014). The lawsuit was dismissed by a federal district judge, who concluded the plaintiffs first had to air their grievances with the federal Office of Research Integrity (ORI), which had to await completion of the Harvard investigation. Brigham informed the NIH of interim conclusions that submitted grants contained fraudulent data. As a result, Anversa's grants were suspended, his Brigham lab was shut down, and the Brigham paid a \$10 million settlement to the NIH for fraudulent grant proposals (Kowalczyk 2017) (Freyer 2015). Soon thereafter Anversa and Lera left the country. They initially assumed new positions at the University of Zurich, but that didn't last long.

Over the course of several years, the investigation identified problems with many papers, including inappropriate manipulation of images central to the conclusions. One paper was ordered to be retracted in 2014. It was not until October 2018 that the HMS Standing Committee on Faculty Misconduct finally concluded its five-year investigation, making formal recommendations to both the Dean who succeeded me and a Brigham official, who accepted them. HMS and the Brigham drafted a terse one-paragraph joint statement and sent it to several journalists. The key revelation was "we determined that 31 publications included falsified and/or fabricated data, and we have notified all relevant journals." The identity of the specific papers was not included. A story reporting this by Gina Kolata appeared on the front page of the *New York Times* on October 15, 2018 (Kolata 2018a).

In the fall of 2018, Anversa, now age 83, was living in New York City. In an interview obtained by Kolata and published 14 days after her initial report, Anversa maintained his innocence of all charges of research misconduct, and he expressed belief that his now discredited claims about heart cell regeneration would eventually prove to be true (Kolata 2018b). My surmise is that he suffered from several problems. He lacked critical insight in the area of regenerative biology, a field that he entered late in his research life. He appeared to lack the self-awareness required to understand and correct this scientific weakness. This was exacerbated by a personality prone to anger, defensiveness, and what appeared to be an exaggerated sense of self-importance, as described in an account on the site *Retraction Watch* (2014).

'The full extent to which Anversa was personally involved in the proven data manipulation of his research papers, as opposed to permitting it to flourish by others with whom he worked through inattention and mistaken signals, remains unknown.

The Soman/Felig, Darsee/Braunwald, and Anversa affairs together reveal important insights into misconduct in the world of biomedical research. Let's begin with the three lab heads, whose position entails responsibility for work emanating from their labs. Philip Felig's success arose from a series of careful and widely admired studies of human metabolism that appear to have stood the test of time. He was bright, articulate, and ambitious, and destined for positions of leadership in academic medicine. Felig correctly observed that receptor biology—a new and exciting area of research into how insulin worked on a molecular level—was beginning to eclipse his own area of metabolism. In response, he decided to initiate efforts in this area. He might have used his insights and intelligence to make valuable contributions to this second field, as many excellent scientists have done in such situations.

But in his effort, he paid insufficient attention to the underlying science, borrowed freely and sloppily from the work of others, and allowed himself to be misled by a colleague unfit to do this work. Whether he was initially aware of the manipulated data or not remains unknown, but his junior colleague admitted that he had committed scientific misconduct. Felig was in part responsible through his inattention, perhaps attributable to focusing on his career move at the expense of attention to his lab. Most importantly, when accusations of plagiarism and conflict of interest with the Wachslicht-Rodbard manuscript were lodged, at that time entirely through informal mechanisms, he ignored the seriousness of the claims and his absolute responsibility as senior author to investigate them. Instead, even after my findings of data manipulation in his submitted paper, he tried on two occasions to cover up the findings, a desperate ploy. Finally, he failed to be honest and transparent with his future employers. In this case, the junior scientist was guilty of research misconduct, and the senior scientist was guilty of irresponsible and deficient lab leadership and an attempted cover-up of his colleague's misconduct.

The case of Darsee and Braunwald was entirely different. Over a career spanning more than 50 years, Eugene Braunwald became the world's most influential and accomplished cardiologist. He built and led remarkable departments of medicine and biomedical research that owe him a tremendous debt. While leading medicine at the Brigham and for a period of time at BI, writing and editing two major textbooks, and directing a very large and productive lab, he was bamboozled by a highly skilled sociopathic liar, who had done this before. Braunwald's

error of judgment was believing that Darsee was a once-in-a-generation phenomenon, rather than the once-in-a-generation fraud he proved to be. Despite lacking formal institutional mechanisms to handle such situations, Braunwald took quick and appropriate actions, and during several months of heightened observation, exposed the full extent of Darsee's fraud. No doubt Braunwald suffered great pain during this period. In a life of extraordinary accomplishment, he was deceived by the deliberate fraud of a sociopathic junior colleague, and he learned the possible consequences of a lab grown too large to permit ready identification of such bad actors.

The Anversa affair is yet again different. A highly successful pathologist, Piero Anversa was a leader in the field of cardiac pathology. He transitioned from working in an area in which he was fully competent to one where the biology and experimental approaches appeared to be beyond his competence. His claims to have upended prior scientific dogmas were considered well-supported and transformative by some, and sloppily false by others—a kind of disagreement hardly uncommon in science, and one that could have had a different outcome. Anversa built a team in which technical skills were compartmentalized, and he likely lost the ability to critically evaluate important elements of the work. When his work was challenged, both internally and externally, he responded with anger and defensiveness, rather than taking the criticisms seriously. Many in his lab described it as a hostile work environment. When specific and credible accusations about one paper provoked an officially sanctioned school investigation led by faculty peers and supported by highly competent staff, he denied any errors and took no responsibility. Instead, he lawyered up, counterattacked, and went on to suffer defeat. His personal culpability for the intentional data manipulation, as opposed to the culpability of one or more colleagues, remains hidden in confidential school documents and may never be known to the public.

In each of these cases, junior colleagues played key roles in the scientific misconduct. What about them? I believe Vijay Soman was fundamentally well intentioned, but found himself in over his head when asked to enter a new research area in a lab that expected quick results with insufficient oversight. At a key moment, he appears to have abandoned honest research in an attempt to please his demanding mentor. He left science in disgrace, which was appropriate. I would love to interview him, even after 40 years. Felig was surely guilty of poor oversight and hubris, but his greatest crime was failing to react with integrity to evidence of Soman's misconduct, then attempting to cover it up.

John Darsee was possessed by an apparently irresistible drive to carry out scientific fakery—this despite being intelligent and hard-working enough to succeed as a physician and cardiologist in the most demanding academic environments. When he left the Brigham and Harvard, he practiced as an intensive care physician in upstate New York, married, and settled down. When his prior ethical lapses were brought to the attention of the New York State Medical Board,

his medical license was revoked (*Harvard Crimson* 1984). Explanation for behavior like his awaits understanding of the human psyche far beyond our current knowledge.

My speculation about the role of Anversa's colleague Jan Kajstura is far less secure, pending availability of further investigatory data, which may or may not become publicly available.

Forty years elapsed between the Soman/Felig and Anversa affairs; during that period, institutional responses to misconduct allegations went from nonexistent and ad hoc to complex and sometimes excessively bureaucratic. Of course, stakes are high when serious accusations are made, and confidentiality and due process must be protected. Lawyers for both sides become involved. One consequence is that procedures often drag on for many years, usually without interim conclusions—the Anversa case took six years from start to final determination. At HMS, the investigatory panel reports to a standing committee on misconduct, supported by a dean and legal/investigatory staff. After investigation and deliberation, the committee issues a report to the dean for decision, with or without modification. Final reports signed by the dean are then transmitted to the accused and to relevant institutional parties. Notably, the typically voluminous findings, and even the executive summaries, are not made public. The final report is sent to the ORI, which conducts its own review, after which it may post findings on its website.

Many observers view the ORI as understaffed and, in some respects, dysfunctional (Chawla 2020). Three years after HMS sent ORI its Anversa report, they have yet to take public action, and I'm told it may be years before they do—if ever. How does the public get informed? Often these stories emerge when published papers are officially retracted, prompting research misconduct watchdogs who are constantly scanning for these cases to investigate and publicize. Of course, many investigations end without a finding of misconduct by institutional officials who are responsible for the work, or by ORI, which mainly reviews the work conducted by institutions. Prolonged investigations of scientists who have been wrongly accused may be extremely harmful to their health and well-being, as investigation of these false or unproven accusations disrupt ongoing research and cast a pall of suspicion.

Looking back over 40 years, what lessons have I learned about this sordid corner of the research ecosystem? From innumerable interactions with scientists at all levels, I have no doubt that the great majority of scientists have a commitment to truth that is central to their professional lives; most are powerfully motivated by,

even addicted to, the thrill of discovery. Being around such people has been one of the joys of my life as a scientist.

But that a small minority turn away from that commitment really shouldn't be surprising. In every epoch of human history, some people's values and ethics diverge from social norms. This is true of every profession, whether politicians, clergy, police and military, teachers, or businesspeople. So, we shouldn't be surprised by the occasional researchers for whom truth ceases to be the primary goal. In extreme cases of sociopathy, subverting truth *becomes* their goal, the thrill of deceit replacing the joys of discovery.

Fraud and explicit research misconduct are difficult to understand as deviant human behaviors. As I contemplate the three cases in this paper, and many more I haven't discussed, I don't discern a single personality type. Adding to the difficulty, my assessments, and those of most others who have written about on this topic, are based on observations of the perpetrators' actions, rather than close-up or even clinical assessments of their personalities, values, cognitive styles, and other individual attributes. I draw a major distinction between those, often senior, scientists, who are too distracted to clearly discern the worrisome behavior of colleagues, and those who directly engage in deception. Both behaviors require further understanding.

Although some such miscreants have always lurked in the shadows of the research community, and likely always will, our job is to create an ecosystem where misconduct and fraud are less likely. When they do occur—as they inevitably will—such cases must be identified as early as possible to limit their adverse effects on the community of science. Of course, this is difficult, since we don't want to create an unnecessary culture of suspicion and fear that would itself harm innocent people and reduce our capacity for scientific progress. Certainly, all responsible scientists need to be aware that such people and practices do exist, even if they are uncommon. We must all be responsible for considering possible instances, based on behaviors and data that might suggest them, and reporting these concerns to others when appropriate. Many organizations have provided guidance on optimal training and procedures for reducing such events and managing them if they occur (NASEM 2017).

Once potential misconduct comes to the attention of scientists and their institutions, investigations should be as fair and efficient as possible, within the constraints presented by due process. And when, after due diligence, conclusions are rendered, they should in some form enter the public record, within the constraints imposed by good judgment and applicable law.

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