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Scientific Antlers

Steven Shapin

The Baltimore Case: A Trial of Politics, Science and Character by Daniel Kevles
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It is a contemporary American morality play. The leading roles are played by an alpha male and his junior female colleague; bad behaviour between them is alleged; accusations of lying fly about; charges of cover-up garnish the original accusation; an ad hoc government investigative team runs amok, and due process is trampled underfoot; the credibility of the senior male is tarnished, and he is deemed unsuitable for high office; reputations are damaged; valued institutions are undermined; colleagues turn against each other and the whole affair has a poisonous effect on normal social relations. DNA evidence is crucial to the case, but all finally comes down to questions of intent which material evidence of deeds cannot unambiguously decide. Ultimately, many in the audience to whom the drama played for so long weary of it and wonder whether the chase has been worth the quarry, yet all are agreed that both the alleged bad behaviour and the means of making it accountable are deeply symptomatic of the state into which America has got itself.

The affair is not what it seems, however. It is not Presidential politics but esoteric science. The part of Bill Clinton is here played by the Nobel Prize-winning scientist David Baltimore and the junior female colleague is not Monica Lewinsky but a Japanese-Brazilian-American immunologist named Thereza Imanishi-Kari. Their relations are not sexual but wholly collegial. The out-of-control independent counsel is not Kenneth Starr but a posse partly made up of the self-appointed scientific fraud-busters Walter Stewart and Ned Feder and their patron, the Democratic Congressman John Dingell. For the excellent Linda Tripp with her concealed tape-recorder read Imanishi-Kari's young Irish-American co-worker at MIT, Margot O'Toole, and the 17 pages of laboratory entries she decided to copy from a colleague's notebook – just in case an accusation of criminal wrongdoing should emerge. Both affairs are modern American tragedies (and farces), and both testify eloquently to widespread crises in trust, civility and cultural authority.

In Immuno-gate, as in Monica-gate, public moral and legal mountains rise up from what originally seemed molehills of petty, and usually private, events. The biggest-ever inquiry into alleged scientific fraud lasted almost ten years. It absorbed hundreds of hours of investigative time by Congressional committees and panels of the National Institutes of Health (NIH), and it mobilised some of the most sophisticated forensic lab work of the Secret Service. The cost to the Government must have run into millions of dollars, while the legal bills of the defence team would have been crippling had not much of their work been done on a pro bono basis. The final judgment – delivered by an Appeals Board of the Department of Health and Human Services on 21 June 1996 – was that none of the 19 charges of misconduct was proven 'by a preponderance of the evidence'.

The precipitating occasion for all this was a paper published in the journal *Cell* on 25 April 1986. As is common in much modern Big Science, there were multiple authors, some of them more directly involved in the experimental work than others. The penultimate author was the 1975 Nobel laureate David Baltimore, then director of the Whitehead Institute for Biomedical Research at MIT. By far the most senior of the six authors, Baltimore assumed – and was by others presumed to have – ultimate responsibility for work carried out in his and associated labs at MIT. That is why the affair was eventually called the Baltimore Case even though Baltimore himself was never formally charged with wrongdoing. Most of the research which came to be contested was done by Imanishi-Kari and several assistants. The whistle-blowing Margot O'Toole was a young postdoctoral fellow recently appointed in Imanishi-Kari's lab, hoping for a tenure-track job, but, with a new baby and no dedicated grant support, understandably jittery about her career prospects.

In one of the many mundane miracles of modern life-science you can take a gene coding for a specific antibody from one highly inbred strain of mice (white) and stick it into the fertilised egg of another strain (black). That 'transgene' comes to be carried in each cell of the host mouse's body, and you can easily see why there should be much practical as well as conceptual interest in exactly what the transgene then does. The experimental design here stands proxy for therapeutic interventions – cures for cancer? – years down the medical road.

Is the antibody coded for by the transgene expressed in the host mouse, and, if so, how is it expressed? Antibodies can be characterised by two different parts: a variable part (V) and a constant (C). So the antibody constitution of the donor white mouse is $V_w C_w$ and that of the host black mouse before it receives the transgene $V_b C_b$. But when Baltimore and his colleagues analysed the transgenic mice, one assay revealed what appeared to be $V_w C_b$ molecules. In most biological systems, this result would have been viewed as impossible: V-C is made as a single polypeptide from a single gene. But in immunology there was a popular theory that regarded this odd result as possible, even normal. The assays for V and C markers were not clear-cut and there was a strong temptation to opt for the interpretation that was most exciting to the immunological audience. A lot was at stake here besides scientific fact.

As it happened, much of what was contested about the *Cell* paper concerned the propriety, reliability and sensitivity of the assays used to characterise antibodies, and, of course, the honesty with which the results of these assays were reported. What reagents should be used to detect relevant antibodies? What virtues and vices did different reagents have? What statistical criteria should be employed to establish significance in the resulting data? What molecular techniques should be employed to analyse the antibodies and what cellular entities assayed for the antibodies? Again, like much modern science, that contained in the *Cell* paper was hybrid in nature: people with different kinds of special expertise made common cause and trusted each other. Without such interdependence, the work was impossible.

The *Cell* paper formally thanked Margot O'Toole 'for critical reading of the manuscript', but none of the authors could then have imagined just how critical her reading would become. O'Toole had initially found it 'a beautiful paper, beautiful data, dramatic findings'. Imanishi-Kari gave O'Toole the task of extending the paper's findings, not of replicating the original experiments. But O'Toole didn't find it easy to get the original reagent system to work as it had been reported to do. To Imanishi-Kari, this was a sign that O'Toole might not be a very capable experimentalist; to O'Toole her difficulties eventually suggested another explanation – that the *Cell* paper misrepresented natural reality. Finding a notebook with some of the raw data, O'Toole was shocked (shocked!) to discover a number of discrepancies with published findings, and copied the 17 pages as evidence. Her relations with Imanishi-Kari deteriorating, she raised the matter with two local ad hoc scientific committees. These took the view that one admittedly mistyped mouse and some interpretative differences over the reliability of a reagent were not worth a Federal case. They agreed with Baltimore that if the science was at issue, then future science would sort it out. O'Toole was not content.

The affair now rapidly spiralled out of control. It became technically and legally intricate and emblematic of the state of science in America. Both Congress and the media had recently been sensitised to the problem of scientific fraud. In 1981, then Congressman Albert Gore Jr held hearings on fraud in biomedical research. The Congressman's sensibilities were offended by the very idea: Kevles writes that Gore regarded fraud in the biomedical sciences as 'akin to pederasty among priests'. Two *New York Times* science journalists – William Broad and Nicholas Wade – were outraged at what they saw as bland indifference to the problem on the part of leaders of the scientific community, and in 1982 they published a book – *Betrayers of the Truth* – that alleged widespread fraud and judged science's 'self-policing' mechanisms to be wholly ineffective.

Fired up by the Gore hearings, Stewart and Feder at the NIH substantially gave up their research in favour of becoming full-time ethical policemen. And when a disaffected junior associate convinced O'Toole to involve Stewart and Feder, they sensed a great opportunity. While Imanishi-Kari would carry almost all of the burden of establishing innocuousness, Baltimore had a full rack of scientific antlers and it was his head that would make the most magnificent trophy. The Baltimore Case became 'a perfect object lesson', a 'dramatic example that mom and pop will understand'.

From the fraud-busters' self-help initiative the case bounced over to Dingell's House Subcommittee on Oversight and Investigations, where it was assimilated to existing concern about financial malpractice in Federally-funded universities and waste of taxpayers' money. The idea was to hold the scientific community's 'feet to the fire', to show pampered boffins that scientific fraud is an affront to democratic accountability, and that the people's representatives are serious about how the people's treasure is spent. 'I'm not paid to be a nice guy,' Dingell said. 'I'm paid to look after the public interest.' Congressmen saw O'Toole as a 'post-Watergate saint of science', a heroine in the battle for both public accountability and genuine science: she was congratulated for 'wanting to come forward in the name of scientific truth'. In intermittent hearings on the Baltimore Case from 1988 to 1993, the people's representatives came to sit in judgment on matters of esoteric scientific fact, on competent representation of fact, and on justified inference from fact. They tried to determine what scientific truth is and how the work of making that truth ought to be carried out.

Dingell warned the NIH – which funded Imanishi-Kari's research – to give an earnest of its seriousness in rooting out fraud. The NIH convened a scientific panel which discovered a number of errors in the *Cell* paper, but declined to infer fraudulent intent. But Dingell's committee had already subpoenaed Imanishi-Kari's lab notebooks and other materials. They put them into the hands of the Secret Service for minute forensic investigation, and their findings provided the basis for further inquiries, both in Congress and in the NIH. Baltimore was persuaded to retract the paper. A new Office of Scientific Integrity was established in the NIH, later relocated elsewhere in the Department of Health and Human Services as the Office of Research Integrity.

Another scientific panel, convinced by the forensic work, found Imanishi-Kari guilty of fabricating data. Finally securing access to the work on the basis of which she stood accused, she appealed and, now aided by high-powered legal counsel, won the case. End of story. Happy ending. Several years earlier the NIH had denied Stewart and Feder further Federal funding for freelance fraud-busting. (Stewart, in protest, went on a hunger strike, but is still alive and unrepentant.) Imanishi-Kari, after having her grant support and academic promotion put on hold, won tenure at Tufts University. Baltimore, having been forced, in effect, to resign the presidency of Rockefeller University as a result of the scandal, became President of Caltech, where the weather is much nicer and where a surprised, possibly embarrassed, but presumably not desperately disappointed Daniel Kevles has for many years been employed as a historian of science – for Kevles clearly sets out his own conclusions right at the beginning of his book: it is a 'story of how a great injustice was perpetrated in the name of scientific integrity and the public trust and how it then came to be remedied.' Even Margot O'Toole is not so very badly off: one of Baltimore's powerful scientific enemies at Harvard secured her a job at his Cambridge biotech company, and she presumably gets to keep the

$10,000 Cavallo Award given to courageous individuals 'who take risks for the public interest'.

By the close of this case, far more science had been done in the cause of undoing the *Cell* paper than was done to support its original publication. No paper in the history of modern science has ever been so thoroughly de-constructed, nor have the work-practices involved in making scientific claims ever been so thoroughly opened up to public scrutiny. The de-construction was here done not by academic sociologists or historians wanting a naturalistic picture of how scientific knowledge is made, but by politicians, lawyers, and, crucially, by other scientists, meaning to point a finger of accusation. Kevles is a sure-footed and knowledgeable guide to this work. He leads us through mazes of politics, law and science with a clarity and a high-journalistic virtuosity (veering towards over-kill) which is itself partly a product of the post-Watergate era of American suspicion. But his virtuosity would scarcely have been possible had not so much science been exposed and undone by participants in the Baltimore Case.

Counter-laboratories were mobilised to take apart the immunological knowledge produced at MIT. In the cause of determining exactly when experiments were done, the printer inks on gamma-radiation-counter tapes used to assay antibody were subjected to Secret Service chemical analysis. New statistical procedures were devised to measure suspicious departures from randomness in experimental data, and the reliability of these procedures was itself debated. The significance or triviality of rounded-off figures was argued. The proper methods of sub-cloning hybridomas were contested. Dozens of notebooks from other MIT labs were assembled in an effort to establish canons of normal practice in keeping such records. And, in turn, counter-counter-laboratories were put to work, with ultimate success, to de-construct the de-construction and restore the science to the status quo ante bellum.

The main thrust of Kevles's story is to display the Baltimore Case as a travesty of due process, a warning of what can happen to the liberal institution of science when it is subject to McCarthy-style investigation and interference. Had legal due process been meticulously observed, Kevles implies, all this might not have happened, or might have been resolved more quickly and more virtuously. He is probably right about this, while he leaves almost wholly unexplained the enthusiastic willingness of many eminent scientists to join in the chase, to jump to conclusions, and to spread innuendo. If lasting damage has been done to the American scientific community, then that community itself must assume part of the blame. However, *The Baltimore Case* is too rich to bear only one moral. Here is another.

The scientific community was indeed under attack by outside forces, but those forces came armed with a weapon forged and traditionally circulated by many scientists themselves. That weapon was an idealised picture of scientific knowledge, and, especially, of scientific method. Should you assume that scientific knowledge is an aggregate of intellectually equivalent information-bits, each bit capable of being independently and unambiguously judged true or false, then there is no excuse for including any false bits in any scientific report. And should you assume that scientific inference proceeds by applying to these bits some unambiguous, universal, and effective rational method, there is similarly no excuse for human inferential frailty or even variability. The transit from experimental phenomena to lab notebooks and from notebooks to published papers should be smooth and simple. Uncertainty, disorder and ambiguity can then be reliably taken as evidence of incompetence or dishonesty. And, since Method is so clear and simple, there is no reason to trust expert judgment: scientists who know little or nothing about the area, and for that matter non-scientists, can sit in judgment. It is thought that if you know a textbook version of scientific method, you know enough to have a consequential voice in how science is done.

Congressman Dingell, his henchmen, and, indeed, several of Baltimore's scientist enemies seem to have taken some such textbook story about science as a matter of course. So, in defending himself and his colleague, Baltimore was obliged to show the inadequacies of that account. He had to counter bad philosophy and sociology of science with better. You have no choice but to trust scientific experts, Baltimore implied, just because so much science is a matter of judgment and interpretation. Textbook versions of Method suggesting otherwise are wrong. Some facts are more central than others, and only the relevant experts can discern such significance. Experts know that some findings just have to be disregarded, and there is no rational formula for justifying what to set aside and what to confront as a potentially decisive anomaly. Scientific knowledge is not an aggregate of information-bits, but a fabric which has to be built and assessed as a whole by knowledgeable people. Any piece of science normally contains 'the usual scientific uncertainties'. No contribution to scientific knowledge should be taken as a claim to absolute truth; rather, each paper represents how matters appear to the best judgment of the authors at the time.

Scientific truth or falsity can never be determined statically, since science is an unfolding process in which the only remedy for doubtful science is more science, itself generating more doubt, and so on. The sort of 'data audit' urged by the fraud-busters to cure the disease was in danger of killing the patient. The NIH director, Bernadette Healy – one of the more astute critics of the fraudbusting enterprise – recognised the vexing problems created by attempts at defining scientific misconduct as 'serious deviations' from 'accepted practice'. How, then, could one distinguish error from fraud, unintentional blunders from intentional misrepresentation? The price of policing science in this way was to lump together genuine fraud and 'bold leaps of imagination, clever tinkering and unorthodox methods'. She understood that one might effectively police the appearance of fraud but not its reality. That is because fraud proceeds from an intention to deceive and intentions are not subject to audit.

So rationalist fairy tales about science appear to be very poor tools for defending the integrity and autonomy of the scientific enterprise. And one of the many subplots of Kevles's compelling book is the capacity of such fairy tales to turn into nightmares for a scientific community unwise enough to encourage and endorse them.

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