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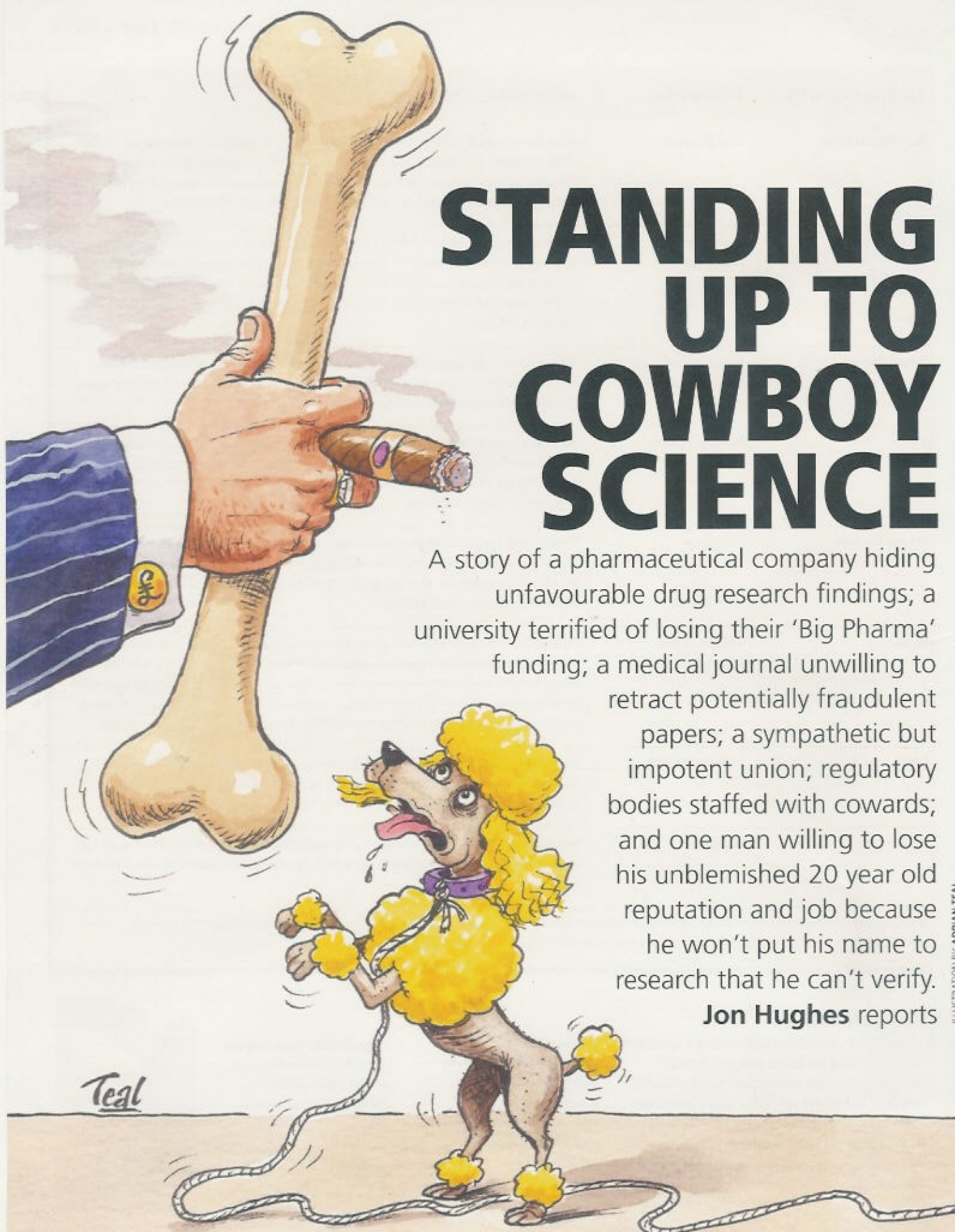


STANDING UP TO COWBOY SCIENCE

A story of a pharmaceutical company hiding unfavourable drug research findings; a university terrified of losing their 'Big Pharma' funding; a medical journal unwilling to retract potentially fraudulent papers; a sympathetic but impotent union; regulatory bodies staffed with cowards; and one man willing to lose his unblemished 20 year old reputation and job because he won't put his name to research that he can't verify. **Jon Hughes** reports

Aubrey Blumsohn is a South African with a lifelong love of science. Give him a proposition and he'll weigh up the evidence. He is precise, inquisitive, methodical. A medical doctor, pathologist and consultant in metabolic bone disease the father of two has a keen interest in statistics and his thorough approach to research is well-regarded by his peers internationally. For most of the past 20 years he has worked at the medical school of Sheffield University, which has a long-standing reputation for research excellence – it has five star government rating – and is among the world's elite institutions in the study of bone. Blumsohn wrote his PhD here before becoming a senior lecturer.

It was in this role that Blumsohn was asked in 2002 to undertake the final and conclusive phase of a study into the treatment of osteoporosis begun by his department head Professor Richard Eastell two years earlier.

Eastell had been working with Proctor and Gamble Pharamceuticals (P&G) to prove that the company's osteoporosis drug Actonel was as good as the market-leading osteoporosis drug Fosamax. While Actonel is already P&G's first billion-dollar drug, it is considered less effective than Fosamax. With the worldwide market for such osteoporosis drugs worth around $6 billion annually, P&G wanted to put itself in pole position before the patents on Fosamax expire in 2008 and the protected brands have to compete with the generics.

In the words of the company the intention was to induce a 'paradigm shift' in the way these drugs are understood to operate and used as part of a marketing strategy to get more doctors to use Actonel. Both Actonel and Fosamax claim to reduce fracture risk by reducing 'bone turnover', the process by which bone continually replenishes itself, gradually losing mineral content, making it brittle.

If the larger study group resulting from Blumsohn's study confirmed Eastell's findings that the benefit of decreased bone turnover 'plateaued' at around 35-40 per cent, then the additional reduction seen with Fosamax would be irrelevant.

WORK BEGINS...

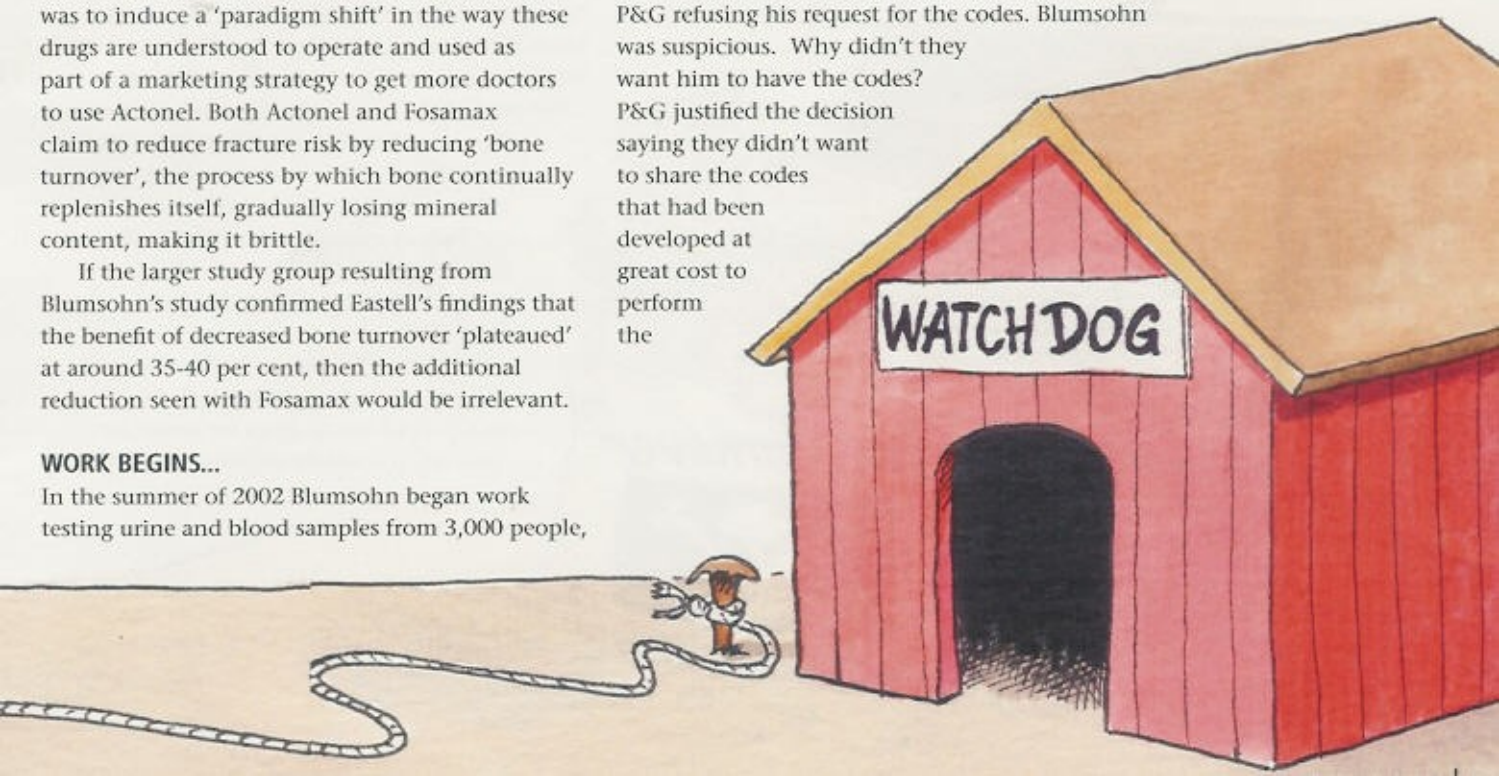
In the summer of 2002 Blumsohn began work testing urine and blood samples from 3,000 people, some on Actonel, and some on a placebo, provided by P&G. At this stage in any drug trial, tests are performed as 'blind studies', to ensure no one can skew the findings. For this reason samples are supplied with randomized codes, to prevent the tester from knowing who was allocated which treatment. Without the codes, the results are just a meaningless list of numbers.

Then Blumsohn started to hear noises off. Apparently, at two international conferences Eastell had been challenged on the results of the preliminary P&G studies. Embarrassingly he was unable to answer in detail and was forced to admit that all the analyses had been done by P&G employees and not by himself. Blumsohn was shocked. He had never encountered a situation where a scientist had validated and presented work on hearsay alone.

> Any trust Blumsohn had in the study evaporated. He was now certain P&G was misreporting the findings for financial gain

Blumsohn sought assurances from Eastell that this was an aberration and that all the data from the study and codes would be made available to him. Eastell duly wrote to P&G's UK statistician, Dr Ian Barton, requesting Blumsohn be allowed to see all the results and have access to the codes, adding that it would protect himself against further challenges about the preliminary results. Meanwhile, Blumsohn returned to his lab to continue measuring bone turnover in the 'blind study'.

In late June 2002 he received an email from P&G refusing his request for the codes. Blumsohn was suspicious. Why didn't they want him to have the codes? P&G justified the decision saying they didn't want to share the codes that had been developed at great cost to perform the



analysis with a third party and that training Blumsohn to use it would delay 'time to result'. Blumsohn was dumbfounded. In that case he was being asked to rubber stamp results without knowing whether the evidence justified them.

That August Blumsohn pressed the issue with Eastell. He told him of his unease and was astonished to be told of the need to be careful because, 'P&G would withdraw their funding from our group'. P&G was not only paying $250,000 for the research Blumsohn was undertaking, the company sponsored the P&G research centre at Sheffield University, believed to be to the tune of £1m annually, and paid the salaries of several staff members. Presuming Eastell to be addressing the realpolitik of the situation, an uneasy compromise was reached. They agreed that the results of Blumsohn's lab tests would be analysed by P&G staff. In return the method of analysis would be given to Blumsohn so he could independently analyse the conclusions arrived at by P&G.

The paper made no mention or declaration of relevant conflicts of interest and yet Blumsohn knew that at least one of the named authors received substantial salary funding from P&G.

However, what turned up from P&G that autumn looked more like a business plan. It mentioned a 'business purpose' and 'brand tactic' which was stated to be 'osteoporosis paradigm shift'. In other words, reducing bone turnover by more than the 35-40 per cent 'plateau' had no beneficial impact on reducing the fracture risk in osteoporosis patients. Ergo: the greater effect of Merck's Fosomax was irrelevant. There was no further explanation or analysis of how the final figures were to be arrived at.

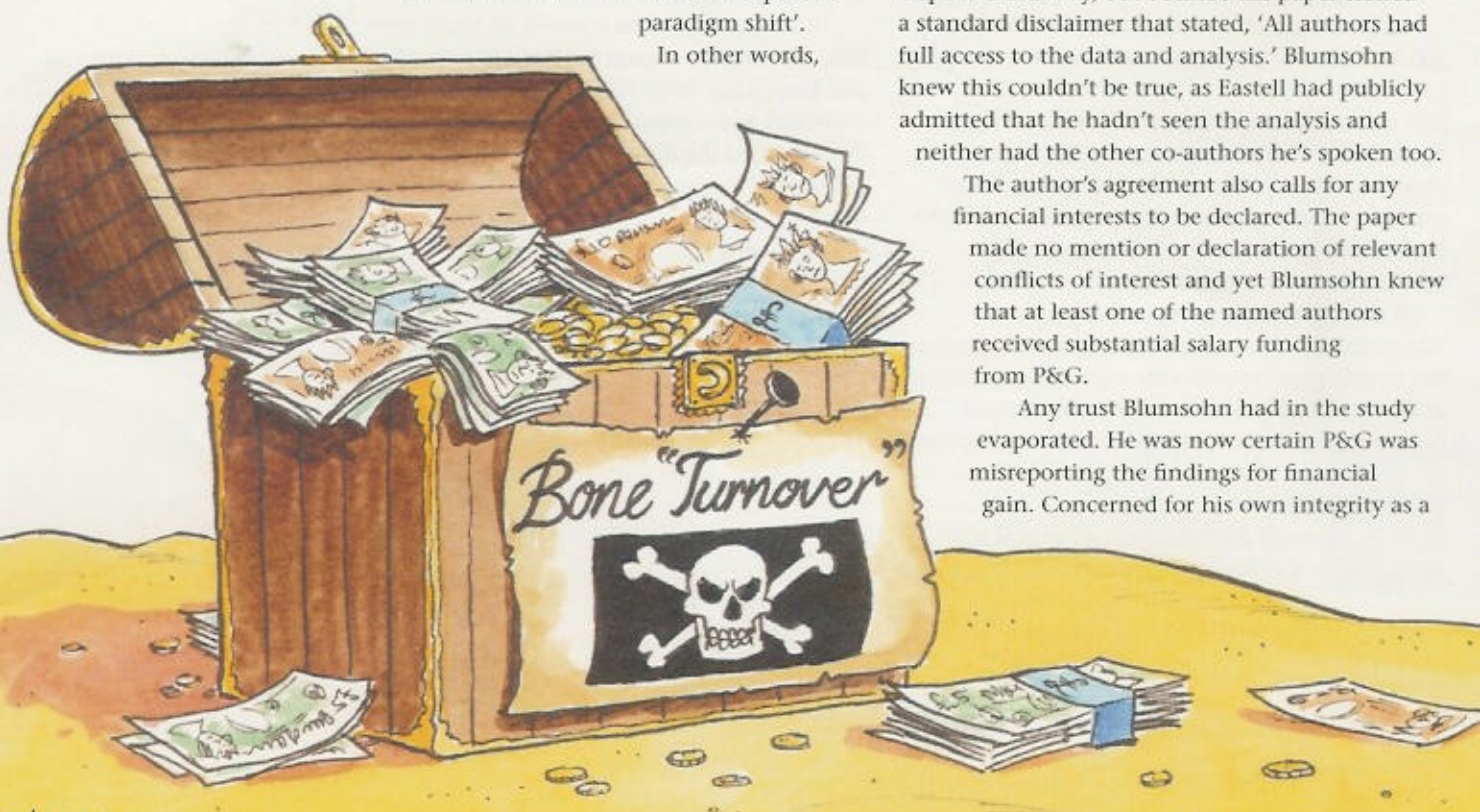
In December 2002, Blumsohn delivered the final results from his laboratory study to P&G and again asked for the codes. None were sent. Instead, in February 2003, Blumsohn received an analysis prepared by John Banner, P&G statistician in America, which made no sense to him. He continued to press for the codes. P&G filibustered. Blumsohn told Eastell that he was concerned by P&G's 'non-transparent' approach.

Meanwhile, Barton sent an email containing the final P&G analysis of Blumsohn's study. It was entitled, 'This is what the medical community has been asking for', and in the body of the text said, 'I truly believe that these data are so important... this fits nicely with our hypothesis.' P&G were eager to start publishing the findings. Blumsohn's lab results were released as headline findings that April to the annual conference of the American Society for Bone and Mineral Research and an intense timetable for publication was drawn up. Blumsohn remained in the dark.

That June the distinguished *Journal of Bone And Mineral Research* published a paper by Eastell, in which he outlined the 'plateau effect'. Blumsohn was stunned, not by the claims, which he couldn't dispute either way, but because the paper carried a standard disclaimer that stated, 'All authors had full access to the data and analysis.' Blumsohn knew this couldn't be true, as Eastell had publicly admitted that he hadn't seen the analysis and neither had the other co-authors he's spoken too.

The author's agreement also calls for any financial interests to be declared. The paper made no mention or declaration of relevant conflicts of interest and yet Blumsohn knew that at least one of the named authors received substantial salary funding from P&G.

Any trust Blumsohn had in the study evaporated. He was now certain P&G was misreporting the findings for financial gain. Concerned for his own integrity as a



scientist and to ensure he wouldn't be personally implicated, he started to covertly record his meetings with Eastell and P&G. Once more he approached Eastell concerned that they would be accused of 'scientific fraud'.

Knowing it would be disastrous to alienate the intended lead author in this critical study, P&G tried to appease Blumsohn and address his concerns. The company still refused to release the codes but they invited him to P&G HQ in Egham, Surrey, to look at the results in more detail in the presence of Dr Ian Barton.

Blumsohn's suspicions about P&G's analysis were confirmed at this July meeting. In the absence of being given the actual data, Blumsohn asked Barton to run some computer-generated data through the statistical computer programme used to analyse the osteoporosis study. The results were, in Blumsohn's view, perverse, showing impossible outcomes, which did not fit with the simulated data. They pressed on.

Blumsohn then asked why the published papers from P&G included graphs with an axis running from -62% to 0%, which he observed meant a substantial proportion of the data would have 'fallen off'. He asked Barton to show him the plots of the figures that had generated these final graphs. He was astonished by what he saw. There was no evidence of a 'plateau effect' in a subset of the data for which P&G had published that there was. In fact, the data appeared to indicate the opposite; the more bone turnover reduced the fewer fractures there appeared to be. In the group of patients with the biggest decrease in bone turnover there were no fractures at all.

Blumsohn was outraged. It could mean only one thing: the published figures had been manipulated and misrepresented. He'd seen enough and left.

He returned to Sheffield and immediately emailed Eastell, alerting him to the fact that the data had been perverted, but he got no response. Feeling increasingly isolated and compromised, Blumsohn sought support elsewhere. He contacted the university's harassment counsellors to alert them to the looming crisis and potential fallout. He also contacted his trade union, the Association of University Teachers (AUT), to find out how he should proceed. While he received good personal support at a local level from the university's AUT rep, the union leaders chose to ignore his appeal to confront the issue of legitimate academic freedom being compromised. Indeed, they suggested if he wanted to raise the issue he should seek support by raising a motion at a local level and take it from there.

In early September Eastell, Barton and Blumsohn met to discuss the 'difficulty'. They all recognised the gravity of the situation and the potential to damage their own reputations and that of the university. The meeting broke up with views aired but little agreed, certainly not to Blumsohn's satisfaction.

The following day Blumsohn met with Eastell to discuss the outcome of the meeting and was astonished that Eastell offered no support. Rather Eastell spelt out his concerns that the relationship with P&G 'would be disturbed' if Blumsohn kept pressing for the codes, adding that 'we need the money', with implicit consequences for Blumsohn's colleagues. Blumsohn was emphatic in response: no codes, no way was he going to put his name to the published research.

P&G's solution? Simple, remove the problematic data from the analysis in the draft publications in order to show P&G's required 'plateau effect'. Blumsohn couldn't believe what was happening.

On May 24 and 26 2004, Blumsohn sent, by email and post, an official letter of complaint to Eastell, who was also responsible for research ethics in his capacity as Research Dean of Sheffield Medical School. Blumsohn said every step must be taken to stop this 'contamination of the science record' and that he couldn't reconcile the current situation with his personal values and statutory responsibilities. Nothing happened for a week.

Rather than setting an example and protecting the public from rogue research the regulators are positively encouraging it through their approach to science

On June 2 Blumsohn received a reply which studiously ignored the concerns he had raised. Blumsohn forwarded his concerns about denial of access to data and his fear that 'fraud' was taking place to the Dean of the Medical School, Professor

Weetman, and University vice chancellor, Professor Bob Boucher. Receipt was acknowledged and the complaint was forwarded to human resources. There the matter seem to be shelved. Blumsohn followed up his initial complaint with several letters to the Weetman and Boucher asking how it were possible that a research dean (Eastell) had not acted upon such a problem were ignored.

In December 2004 P&G lost patience with Blumsohn's perceived intransigence and he was implicitly told in a letter from Eastell that he either got back on side or his name would be removed from the papers being prepared for publication. Eastell also told Blumsohn his demand to see the raw data was unusual and not in line with standard procedure. That spelt the end of the relationship for Blumsohn.

Having had his concerns repeatedly ignored by Eastell, in May 2005 he appointed solicitors to request the data and codes on his behalf from both Eastell and P&G vice president of research and development Larry Games. In general, failure to supply such data would be considered strongly suspicious of fraud. Blumsohn knew Eastell wouldn't be able to supply it. This was confirmed when Eastell's lawyers said Professor Eastell had himself asked for the data and his request had been refused.

Blumsohn alerted John A Eisman, editor in chief of the *Journal of Bone and Mineral Research*, that he had printed a paper under false pretences, that the author's declarations were incorrect, that there were commercial conflicts of interest and that investigators had been deprived of access to all the data. Blumsohn sat back and waited. As far as he could see this was the end game. Either P&G released all the data and codes and allowed him to complete his research or Eisman would have to withdraw the papers he had published exposing P&G to allegations of fraud. But nothing happened. His solicitors received no reply from P&G and Blumshon received no response from Eisman despite numerous attempts to get through to him.

Blumsohn tried to alert the Medicines and Healthcare Regulatory Authority (MHRA), who license drugs in the UK to this potential misrepresentation of research data, but found himself being passed from department to department and was at one point told 'we don't have much experience of dealing in this area.' The MHRA had in the meanwhile itself been subjected to heavy criticism from the Commons Health Select Committee for having severe conflicts of interest, and failing to secure or examine raw data in drug licencing applications. What's more the MHRA declined to accept evidence from Blumsohn and later even threatened to charge him money to review the evidence he did send.

Blumsohn was exasperated. He had done everything in his power to have this matter resolved. He had alerted the university authorities at every turn over three years, his union, the *Journal of Bone and Mineral Research* and the industry watchdogs. Blumsohn despaired. These were all parties that had a vested interest in upholding the integrity of scientific research. If they aren't interested then the implications for science are bleak. Determined not to allow events to end there Blumsohn notified the University authorities of his intention to go public and went ahead, detailing the case to the BBC and the *Lancet*. On September 9 2005 Blumsohn was suspended on full pay for bringing the university into disrepute, something he had been actively trying to prevent.

That same day he received a reply to his solicitor's letter from P&G. It said Blumsohn had had the data and had been given an opportunity to analyse it on his laptop before returning it to the company. It didn't address the 18 explicit requests Blumsohn made for the data, nor the explicit refusals he received.

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For six months Blumsohn remained at home,

NOT AN ISOLATED CASE

Dr Aubrey Blumsohn is just one of many doctors who have found themselves caught up in the murky world of corporate sponsored university research. Not all act as whistle blowers, and those who do often find their reputations attacked, their departments closed and their livelihood threatened.

Other recent and highly public cases include:

1996 Dr Betty Dong, working for the University of California San Francisco (UCSF), had been involved in a study of Synthroid, a drug produced by Boots Co. When she found that the drug was not as effective as the company claimed, Boots stopped her from publishing her results.

1997 David Kern, a professor of Occupational Medicine at Brown University, was hired to look into the illness of two workers at a textile plant. His diagnosis was that they were suffering from a new disease, 'Flock workers lung'. He attempted to publish this information, but was threatened due to a non-disclosure agreement he had signed. He continued to publish and was fired, and his unit disbanded.

1998 Nancy Olivieri, the Toronto-based scientist, broke a confidentiality agreement with the pharmaceutical company Apotex and published research concerning the level of toxicity of its drug Deferiprone for children suffering from thalassaemia. The Hospital for Sick Children, part of Toronto University tried, but failed, to sack her. Olivieri maintains she has been subjected to a continuing series of public criticisms attempting to discredit her – by the hospital and by Apotex.

2000 Dr David Healy is a British psychiatrist who was offered a high-ranking position at the Center for Addiction and Mental Health (CAMH) in Toronto. However, following a speech in which he suggested that Prozac can drive people to suicide – even if they aren't depressed, the job offer was very publicly withdrawn.

his 20 year long career on hold. On 31st March this year he reached a settlement with Sheffield University and left his academic post. An agreed statement read: 'Dr Blumsohn and the University of Sheffield are pleased to announce that they have compromised their differences upon mutually satisfactory terms which they have agreed will remain confidential.' Dr Blumsohn has since declined to comment on his University post.

Blumsohn simply despairs, his belief in science shattered. 'The behaviour of the regulatory bodies mirror all that is worst in the relationship between industry and academia. Rather than help setting an example and protect the public from rogue research the regulators are positively encouraging it through their approach to science,' he told the *Ecologist*. 'The companies jump through the bureaucratic hoops they are asked to provide and then hide behind the process when things go wrong. If companies aren't prepared to put up all their unmanipulated and unfiltered data to be examined then they should be treated with the deserved derision of honest scientists and the public – they should not be protected by government regulators.'

There's little chance of that happening. Tony Blair saw to that when he met with the chief executive officers (CEO) of Astra Zenca, Glaxo Wellcome and Smith Klein Beecham in late 2004. The CEOs told Blair that red tape and regulation had made undertaking research and development in the UK so problematic they were considering moving their final phase trials onto mainland Europe. In the face of this threat Blair sanctioned the creation of four bodies to smooth the way for research and development in the UK.

■ **Jon Hughes** is the Deputy Editor of the *Ecologist*.