

bmj.com

► News: Exclusion of suspect data raises question mark over safety of common plasma substitute (*BMJ* 2013;346:f1132)

► News: Researcher didn't get ethical approval for 68 studies, investigators say (*BMJ* 2011;342:d833)

Boldt: the great pretender

The withdrawal of almost 90 fraudulent studies by a German anaesthetist is one of the biggest medical research scandals of recent time. **Jacqui Wise** examines what happened and what lessons have been learnt



Faking it: Joachim Boldt

Joachim Boldt was a prominent German anaesthetist with an international research reputation. He was regarded as a leading specialist in intravenous fluid management and was an advocate for the use of colloids, particularly hydroxyethyl starch solutions, to boost blood volume during surgery.

However, a lengthy investigation has led to 88 out of the 102 studies that Boldt has published since 1999 being withdrawn from the medical literature. He has been found guilty of research misconduct, including failure to acquire ethical approval and fabrication of study data, and sacked from his position as professor at Klinikum Ludwigshafen, a large teaching hospital in Ludwigshafen, Germany, where he carried out his research. The retraction of such a

large body of work has had far reaching effects on clinical practice, research oversight, and editorial policies.

Deception unmasked

The story starts in December 2009 when the journal *Anesthesia and Analgesia* published a study comparing the effect of two bypass pump priming solutions, albumin and hydroxyethyl starch colloidal solution, on markers of post-operative inflammation and organ function.¹ On 18 December, two weeks after publication, a reader sent an email to the journal's editor in chief, Steven Shafer, saying he was puzzled by the research. The email said: "The results are all very consistent, all very much statistically significant with very small standard deviation." He

described the results as "extraordinary given the small number of included patients." And "the reported effect on coagulation tests and bleeding is particularly 'magic.'"

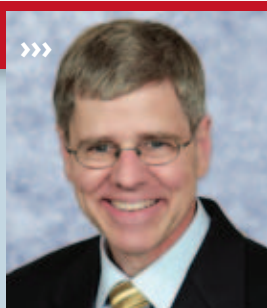
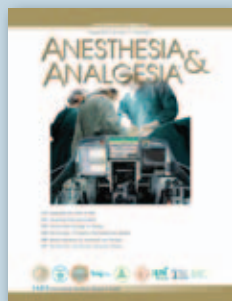
Shafer, who is also professor of anaesthesiology at Columbia University, told the *BMJ*: "Boldt was incredibly prolific. He submitted around one manuscript a month to us and other anaesthesia journals. He tended to publish small studies that you would think were underpowered but often had an interesting finding. All his papers were multiauthored by people with a reputation in anaesthesia. He appeared to have a very effective team."

A second email arrived a day later, also questioning the authenticity of the research. Shafer sent an email to Boldt asking him to discuss the

HOW THE MISCONDUCT UNFOLDED

2009

December 2009
Anesthesia and Analgesia publishes study by Joachim Boldt comparing hydroxyethyl starch versus albumin for cardiopulmonary bypass priming¹



18-19 December 2009
The journal's editor, Stephen Shafer (above), receives two emails questioning the authenticity of the research, one of which describes the effect on coagulation tests and bleeding as "magic"

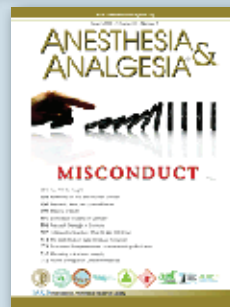
21 December 2009
Shafer tries to contact Boldt by email and phone without success

2010

January 2010
Shafer receives third email questioning the small variability in the paper

May 2010
Shafer contacts Landesärztekammer Rheinland-Pfalz (LAK-RLP), the state medical association, which agrees to carry out investigation

September 2010
Hearing takes place between LAK-RLP and Boldt and his lawyer



October 2010
Anesthesia and Analgesia retracts the study after LAK-RLP finds multiple misrepresentations in the article

November 2010
Klinikum Ludwigshafen hospital convenes an investigating committee, which finds no original patient data or laboratory data and no convincing evidence that the study was performed at all. Boldt's contract with the hospital is terminated

issue. “At this point I just thought there would be a simple explanation, a simple error,” said Shafer.

The paper had been through the journal’s normal peer review process before publication. Shafer went through the research again, but it was only on his third reading that he spotted something else wrong.

“There appeared to be a perfect acid-base balance after surgery. No one has ever seen this in the history of the world. And once I saw that I thought this has to be fake.” He adds ruefully: “Things are very obvious once they are obvious.”

Shafer received a third communication on 5 January 2010 from a senior and well respected investigator in the field, which also questioned the small intersubject variability in Boldt’s research.

Over the next weeks Shafer repeatedly emailed and telephoned Boldt but got no response. “I think he was hoping I would lose interest. He doesn’t know me,” said Shafer.

Shafer kept on doggedly trying to get Boldt to respond to his concerns and also to ascertain which organisation had the authority to look into allegations of research misconduct. Although Klinikum Ludwigshafen is a large academic teaching hospital, it does not have its own research ethics committee—it is covered by one that serves the entire state of Rheinland-Pfalz. Eventually, Shafer contacted the president of the state medical association, Landesärztekammer Rheinland-Pfalz (LAK-RLP). In May 2010 it agreed to investigate.

However, LAK-RLP only had the authority to look into whether Boldt had followed the professional ethical code, not the validity of the research. In October 2010 it concluded that the study was not approved by an ethics committee, there was no evidence of written informed consent, and there was no prospective randomisation. Based on these findings *Anesthesia and Analgesia* retracted the article.

The LAK-RLP and the hospital then formed an investigating committee to determine the integrity of the research. It published its initial findings in November 2010, stating there were no original patient data or laboratory data to support the findings of the study. The head of the perfusionist team told the committee that albumin had not been used as a priming solution since 1999, and according to the pharmacy no albumin had been delivered to the cardiac operating theatres for many years. The committee concluded that there was no convincing evidence that the study was performed at all.

Boldt admitted forging the signatures of the coauthors on the copyright transfer form submitted to *Anesthesia and Analgesia* and was sacked from his position at the hospital. Although Boldt’s coauthors denied participation in the fabrication, they have also since been dismissed for failure to cooperate with the investigation.²

In February 2011, the LAK-RLP said it had reviewed 74 scientific articles and found no evidence of ethical approval for 68 of them.

As a result, the editors of 16 medical journals, including *Anaesthesia* and the *British Journal of Anaesthesia*, posted an open letter retracting 89 articles by Boldt.³

A further, thorough investigation by LAK-RLP and the hospital finally concluded in August 2012.⁴ It found that for most of the 91 publications studied there was no, or incomplete, study documentation. At least 10 of the studies included false statements, such as the number of patients and time points. The committee was able to establish the identities of 455 patients whose data had contributed to Boldt’s research studies. Most of these patients were old and had multiple comorbidities. The investigation committee, however, found no evidence that patients had been harmed.

The investigative report has now been handed to the criminal prosecutor and a criminal investigation is ongoing. Boldt, however, has left Germany and is rumoured to be working as an anaesthetist, possibly in the Czech Republic.

Boldt’s motives for committing the massive fraud remain unclear. Ignaz Wessler, professor of pharmacology and manager of LAK-RLP’s ethics committee, told the *BMJ*: “I don’t think Boldt got financial profit from his actions, but of course he became one of the most distinguished anaesthetists and his motivation was to publish, publish, publish.”

Shafer agrees: “I think his motivation was vanity and self aggrandisement. Boldt was a world

“No one has ever seen this in the history of the world. And once I saw that I thought this has to be fake”

2011

February 2011

LAK-RLP announces that around 90 articles by Boldt may need retraction because the investigator failed to obtain approval from the institutional review board to conduct the research



March 2011

Editors of 18 research journals publish joint statement announcing plans to retract 88 papers dating back to 1999. British consensus guidelines on intravenous fluid therapy for adult surgical patients are withdrawn

2012

August 2012

Independent committee convened by Ludwigshafen hospital produces investigation report which concludes that no patients were harmed as a result of Boldt’s conduct but there were several instances of misconduct



February 2013

JAMA publishes meta-analysis excluding Boldt’s retracted trials which finds that intravenous use of hydroxyethyl starch is associated with a significant increased risk of death and acute kidney injury compared with other resuscitation solutions

2013



“After my experience with Boldt I think the notion that science is built on trust is extremely naive. Journals have to have a high index of suspicion”

expert, flown first class to speak at various meetings around the world. He was wined and dined and considered to be one of the leading experts in his field.”

Better oversight

The affair has prompted research institutions and journals to examine research oversight. Klinikum Ludwigshafen has tightened procedural requirements relating to how it conducts clinical studies. It has also set up a scientific steering committee within the hospital to monitor all clinical studies conducted and to ensure that quality standards are maintained and researchers have access to detailed guidance and support.

Anesthesia and Analgesia has also made some changes to its guidance for authors. For example, all authors on a paper must now sign to say they have seen the original data. Authors must also state the name of the ethics committee or institutional review board that approved the study. Shafer said: “After my experience with Boldt I think the notion that science is built on trust is extremely naive. Journals have to have a high index of suspicion.”

Wessler called on all journals to act in a similar way. “All editors of journals before publishing a piece of research should hold a copy of the statement of approval of the ethics committee. If this was common practice worldwide then such disappointing behaviour would not have occurred.”

So have there been enough changes to stop such a case of research fraud happening again? Wessler said: “Unfortunately not. The proposals for the European Clinical Trial Directive published last July did not mention that ethics committees should be obligatory.⁵ I think this is the wrong signal to give out.”

According to Ian Roberts, director of the clinical trials unit at the London School of Hygiene and Tropical Medicine: “The whole publication system is at fault. There will always be lost, depressed, deluded people in the world. Publication is a game that doctors play and is related to career progression. It is not the way to collate information that can influence the care of hundreds of thousands of patients. It is outdated. Clinical trials should be registered on a website with the protocol there and the data made available. Instead the system relies on hoping that the author is telling the truth.”

Implications for clinical practice

The bulk of Boldt’s work focused on hydroxyethyl starch, a synthetic colloid that has been used for fluid resuscitation since the 1960s. In

Europe, it is used far more widely and for far more conditions than in the United States. There has been longstanding debate over the benefits of hydroxyethyl starch compared with other intravenous fluids such as crystalloids, which are considerably cheaper. The evidence on the benefits and harms of colloids is mixed, with reports of increased risk of bleeding, heart and kidney failure, and anaphylactic shock.

As far back as 1998 a Cochrane systematic review published in the *BMJ* concluded that resuscitation with colloids resulted in four extra deaths for every 100 patients resuscitated. The authors concluded that the evidence does not support the continued use of colloids for volume replacement in critically ill patients.⁶

However, many of Boldt’s studies were included in the evidence used to form clinical guidelines worldwide. Once Boldt’s studies were retracted six medical groups, including the Association of Surgeons and the Intensive Care Society, announced they would withdraw the UK consensus guidelines on intravenous fluid therapy.⁷

Stephen Brett, consultant in intensive care medicine at Imperial College Healthcare Trust and a council member of the Intensive Care Society, said: “Once there were questions over the robustness of research on colloid solutions we immediately got in touch with the manufacturers and we were reassured by them that Boldt’s data had not been included in any regulatory submissions. We were somewhat reassured and continued to use them. However, within intensive care there has been an evolving sense of unease about using starch solutions, particularly in sepsis.”

In June 2012 a Cochrane review found no evidence that resuscitation with colloids reduces the risk of death compared with resuscitation with crystalloids in patients with trauma or burns or after surgery. It concluded that as colloids are not associated with improved survival and are more expensive than crystalloids, their continued use in these patients is hard to justify outside randomised clinical trials. The review’s conclusions, however, were not affected by Boldt’s studies.⁸

Ian Roberts, lead author of the Cochrane review, said: “Boldt’s studies tended to be small trials that focused more on the mechanism of action. They never had a big quantitative effect on mortality. When we did our Cochrane review the endpoint was mortality so when we omitted Boldt’s trials they didn’t make too much difference.”

However, a meta-analysis published in *JAMA* this February did find that excluding Boldt’s studies altered the findings significantly.⁹ It initially found that intravenous use of hydroxyethyl starch was not associated with decreased mortality compared with other resuscitation solutions. But, once seven of Boldt’s discredited trials were excluded from the analysis, the researchers found that hydroxyethyl starch was associated with a significant increased risk of death and acute kidney injury.

In an accompanying editorial, Massimo Antonelli, professor of intensive care medicine at the Università Cattolica del Sacro Cuore, Rome, Italy, said: “With the inclusion of studies by Boldt et al, the medical community might reasonably have concluded that use of hydroxyethyl starch was not inappropriate. Yet the analyses in which these studies were excluded shifts the balance of evidence towards harm.”¹⁰ He added: “This study highlights the serious implications of scientific misconduct on patient safety.”

Another meta-analysis and systematic review that excluded the Boldt studies, published in the *BMJ*, found an increase in adverse events with colloid in patients with sepsis.¹¹

Clinical guidelines are currently being reviewed. In March last year the European Society of Intensive Care Medicine consensus recommendations stated that high molecular weight hydroxyethyl starches should not be used in patients with severe sepsis or risk of acute kidney injury.¹² The European Medicines Agency and the US Food and Drug Administration are both reviewing the safety of hydroxyethyl starch in critically ill patients. And in the UK, the National Institute for Health and Clinical Excellence (NICE) is due to publish new guidelines on intravenous fluid therapy in November.

Ian Roberts has written to the Department of Health calling on it to act now to stop the use of starch solutions in the NHS. “It should be a no brainer—the Department of Health should be able to go into every hospital and say don’t use colloids, but it seems to be a lot harder than it should be. Colloids are more expensive than crystalloids, and are more dangerous, probably killing between 200 and 300 people every year in the UK.”

Jacqui Wise is a freelance journalist, London, UK
jacquiyoung1@gmail.com

Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

References are in the version on bmj.com.

Cite this as: *BMJ* 2013;346:f1738