

21^{ème} Journée d'Ethique Médicale Maurice RAPIN

en partenariat avec PFIZER



La fraude dans la recherche clinique

Laurent Brochard



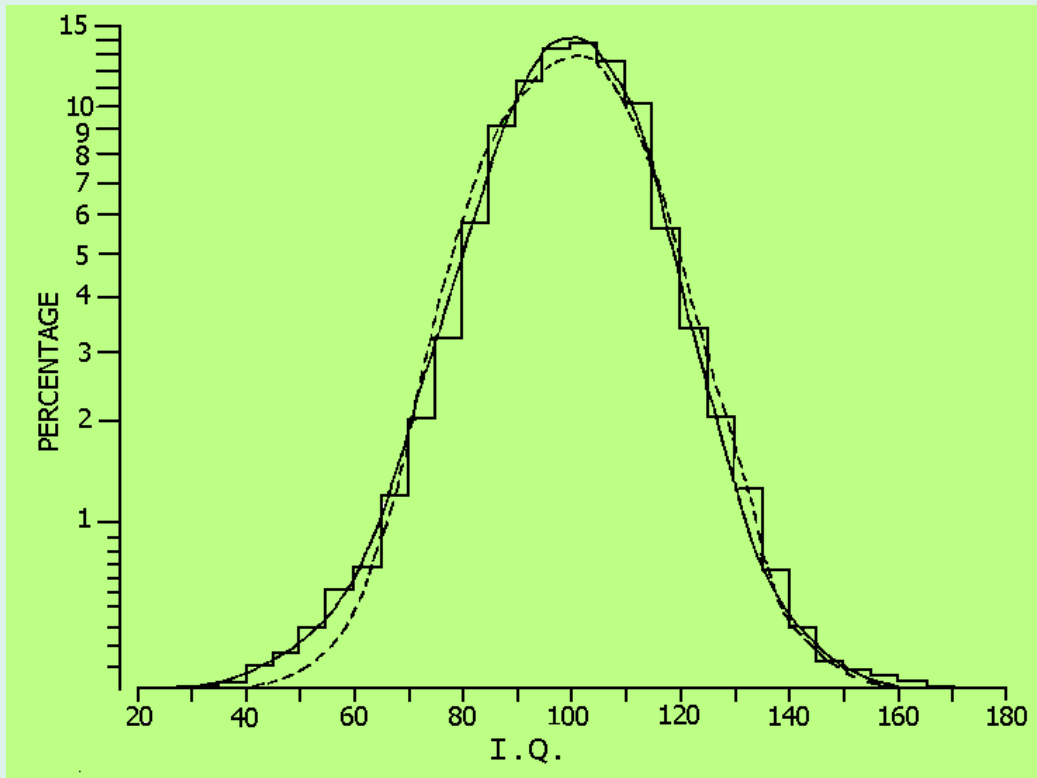
2011

Conflits d'intérêts

- Au cours des 5 dernières années, mon laboratoire de recherche a passé des contrats de recherche avec:
 - Maquet (NAVA)
 - Covidien (PAV+)
 - Dräger (SmartCare)
 - General Electric (FRC)
 - Respirationics (NIV)
 - Fisher Paykel (Optiflow)

Sir Cyril Lodowic Burt

(3 March 1883 – 10 October 1971)



Historians and the Bell Curve Controversies: A Special Symposium

- **Re-reconsidering Burt: Beyond a reasonable doubt**
- William H. Tucker
- **Journal of the History of the Behavioral Sciences**
- Article first published online: 7 Dec1998

DOI: 10.1002/(SICI)1520-6696(199721)33:2<145

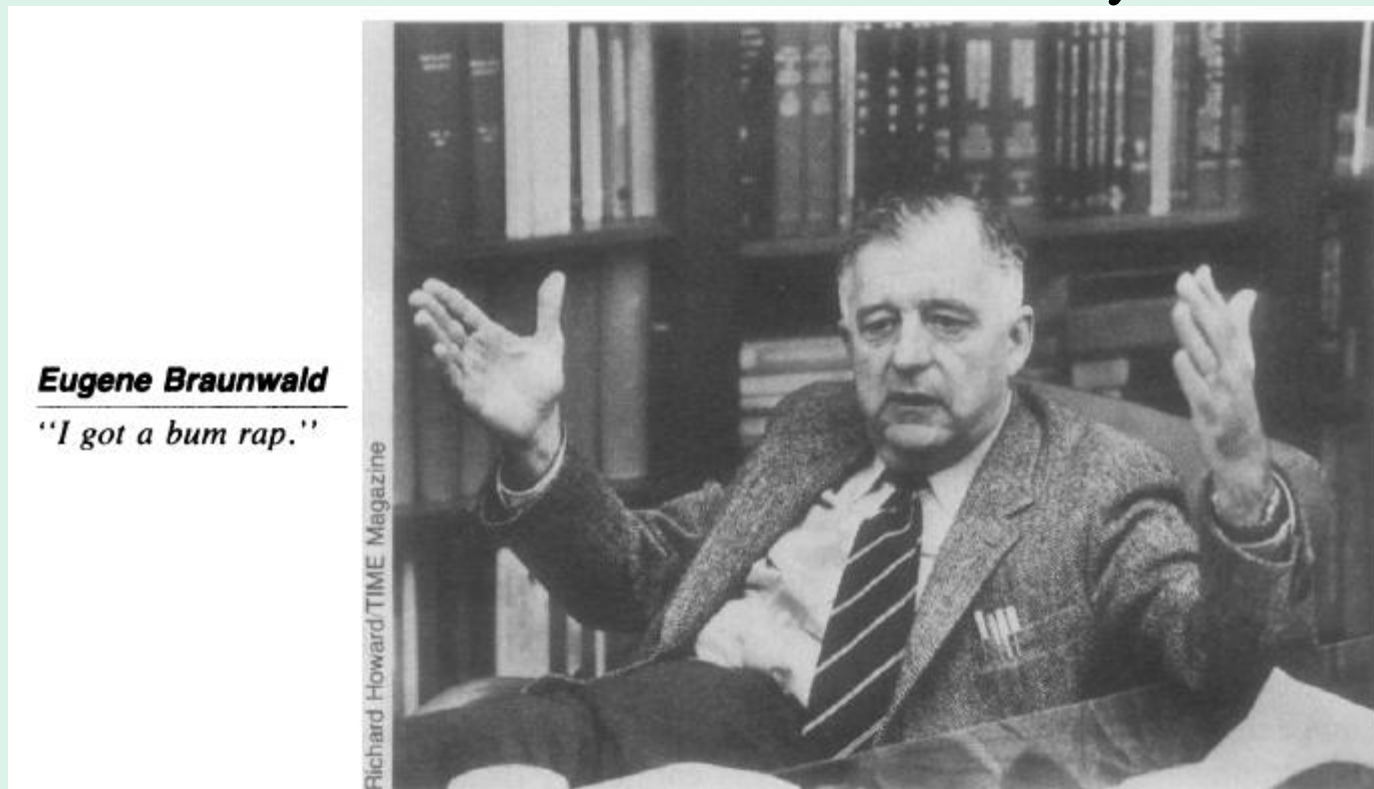


Quand détecter qu'il y a fraude?

Coping with Fraud: The Darsee Case

New evidence suggests that papers published in refereed journals contain fabricated data from Emory as well as Harvard

May 1981



Eugene Braunwald

"I got a bum rap."

Too good to be true...

The Morgan panel did conduct a rigorous statistical analysis of data in Darsee's Harvard publications and uncovered "extensive irregularities" in five papers on which he was first author, with Braunwald and Kloner as coauthors. "The primary responsibility for this situation rests with Dr. Darsee, but must be shared by his coauthors," the panel said. Braunwald and Kloner retracted findings



Howard E. Morgan

Headed inquiry for NIH that criticized most of those involved with the Darsee case.

Recently, evidence has come to light that suggests the trail of Darsee's misconduct goes back to his undergraduate days at Notre Dame, where microbiologist Julian Pleasants heard him give a student seminar in 1969. Prompted by news accounts of the Darsee case, Pleasants looked up two papers Darsee published in the student-run *Notre Dame Science Quarterly*. One paper, on hormones and aging, describes an experiment in which blood was drawn from the tails of 200 rats weekly for the animals' lifetime of 90 weeks or more. In a letter to Braunwald, Pleasants said "By internal evidence these articles are fabrications." Pleasants told *Science* he decided to write because "I felt Braunwald was being blamed unfairly for having changed a person's character when it was already set. It was unfair to Dr. Braunwald and to the general practice of research."

Regular Review

Fraud in science

LARRY ALTMAN, LAURIE MELCHER

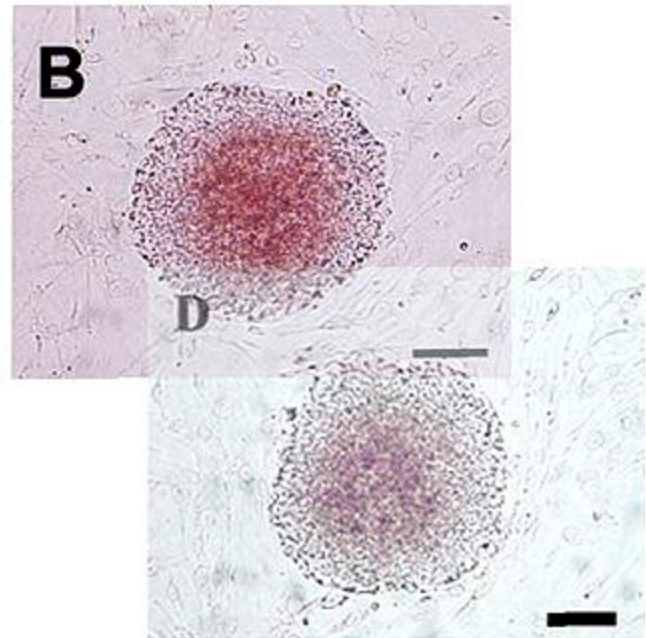
- Plagiarism
- Plagiarism & forgery of data
- Concocting false data
- How big a problem?
- **Publish or perish**
- Society's concern
- Ways of correcting the problem

La fin(?) d'un héros?



Summary of Hwang Woo Suk's Academic Career

He was a national hero in South Korea, his research lab was probably one of the best funded in the world, and he flew first class anywhere he wanted, any time he wanted, for free, courtesy of Korean Air. He was treated like a rock star. His spectacular fall from one of the most envied positions in science plays out like a Greek tragedy.¹



The Legacy of the Hwang Case: Research Misconduct in Biosciences

Péter Kakuk

Abstract This paper focuses on the infamous case of Hwang Woo Suk, the South-Korean national hero and once celebrated pioneer of stem cell research. After briefly discussing the evolution of his publication and research scandal in *Science*, I will attempt to outline the main reactions that emerged within scientific and bioethical discourses on the problem of research misconduct in contemporary biosciences. This case presents a group of problems that might endanger scientific integrity and public trust. Regulatory oversight, ethical requirements and institutional safeguards are often viewed by the scientific community as merely decelerating scientific progress and causing delays in the application of treatments. The Hwang's case represents how unimpeded progress works in contemporary science. Thus, the case might shed light on the often neglected benefits of "the social control of science"

Un nouveau record du monde?

Can J Anesth/J Can Anesth (2011) 58:777–781
DOI 10.1007/s12630-011-9558-7

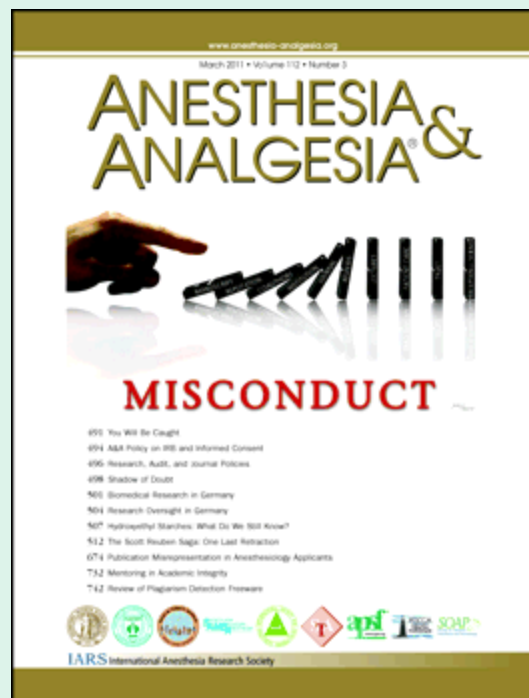
EDITORIALS

Update to readers and authors on ethical and scientific misconduct: retraction of the “Boldt articles”

Donald R. Miller, MD



ATTENTION: The analysis and conclusions of this article are being revised by the authors. This is due to the journal *Anesthesia and Analgesia*'s retraction of a paper by Dr. Joachim Boldt, an author in seven of the studies analyzed in this review. As such, the editors of *Open Medicine* recommend interpreting this review with extreme caution until Zarychanski et al. publish a new analysis and interpretation in *Open Medicine*. For more information, see *Anesthesia and Analgesia*'s press release.



This Article Has Been Retracted

Colloids Versus Crystalloids and Tissue Oxygen Tension in Patients Undergoing Major Abdominal Surgery

Katrin Lang, MD, Joachim Boldt, MD, Stefan Suttner, MD, and Günther Haisch, MD

Department of Anesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Ludwigshafen, Germany

The effects of intravascular volume replacement regimens on tissue oxygen tension (p_{tiO_2}) are not definitely known. Forty-two consecutive patients scheduled for elective major abdominal surgery were prospectively randomized to receive either 8% hydroxyethyl starch (HES) (mean molecular weight 130 kD, degree of substitution 0.4, $n = 21$) or lactated Ringer's solution (RL, $n = 21$) for intravascular volume replacement. Fluids were administered perioperatively and continued for 24 h on the intensive care unit to keep central venous pressure between 8 and 12 mm Hg. The p_{tiO_2} was measured continuously in the left deltoid muscle by using micro-needle implantable partial pressure of oxygen catheters after the induction of anesthesia (baseline, T0), 60 min (T1) and 120 min thereafter (T2), at the end of surgery (T3), and on the morning of the first postoperative day on the intensive care unit (T4). HES 130/0.4, 2029 \pm 360 mL and 11,740 \pm 2,630 mL of RL were given to the

patients within the study period. Systemic hemodynamics and oxygenation (P_{aO_2} , P_{aCO_2}) did not differ significantly between the two volume groups throughout the study. From similar baseline values, p_{tiO_2} increased significantly in the HES-treated patients (a maximum of 59% at T4), whereas it decreased in the RL group (a maximum of -23% at T4, $P < 0.05$). The largest differences of p_{tiO_2} were measured on the morning of the first postoperative day. We conclude that intravascular volume replacement with the HES 130/0.4 improved tissue oxygenation during and after major surgical procedures compared with a crystalloid-based volume replacement strategy. Improved microperfusion and less metabolic wasting may be responsible for the increase in p_{tiO_2} in the HES 130/0.4-treated patients.

(Anesth Analg 2001;93:405-9)

An adequate intravascular volume replacement is essential in the management of patients undergoing major surgery. Hypovolemia may initiate complex pathophysiologic processes that may result in inadequate tissue perfusion and decreased tissue oxygen supply (1). Different intravascular volume replacement regimens have been proposed for providing hemodynamic stability in this situation, including blood and its components (e.g., human albumin), synthetic colloids (dextrans, gelatins, hydroxyethyl starch [HES]), or crystalloids (e.g., lactated Ringer's solution [RL]) (2,3). Various modifications of approved HES have different molecular weights (MWs) (450 kD, 200–260 kD, and 70 kD) and degrees of substitution (DSs) (0.7, 0.62, and 0.5). Recently a new HES with an intermediate MW (130 kD) and a very low DS (0.4) has been developed. This HES specification has

already been approved in several countries for treating hypovolemia. It is supposed to have convincing advantages in pharmacokinetics and pharmacodynamics and may be the safest synthetic colloid. Waitzinger et al. (4) found no clinically relevant plasma accumulation and related side effects after single-dose infusion in healthy volunteers. In an animal study with rats, Bepperling et al. (5) demonstrated a significantly lower or tissue storage with HES 130/0.4 than with conventional HES preparations. Finally, HES 130/0.4 is assumed to have less effect on coagulation compared with HES preparations with higher MWs and higher DSs (6).

The hypovolemic patient is at risk of experiencing tissue hypoperfusion with subsequent development of (multiple) organ failure (7). The effects of different intravascular volume replacement strategies on microcirculation and tissue oxygenation in humans have not been clarified. Monitoring of systemic variables of oxygen metabolism (e.g., oxygen delivery, volume of oxygen consumption) fails to identify which solution is most suitable for avoiding tissue oxygenation deficits. New monitoring devices enable us to measure tissue oxygen tension (p_{tiO_2}) and tension in body

Accepted for publication April 16, 2001.
Address correspondence and reprint requests to Prof. Dr. med. Joachim Boldt, Department of Anesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Brunsenstr. 79, D-67065 Ludwigshafen, Germany. Address e-mail to Boldt.j@klinikum-ludwigshafen.de.

Cardiopulmonary Bypass Priming Using a High Dose of a Balanced Hydroxyethyl Starch Versus an Albumin-Based Priming Strategy

Joachim Boldt, MD

Stephan Suttner, MD

Christian Brosch, MD

Andreas Lehmann, MD

Kerstin Röhm, MD

Andinet Mengistu, MD

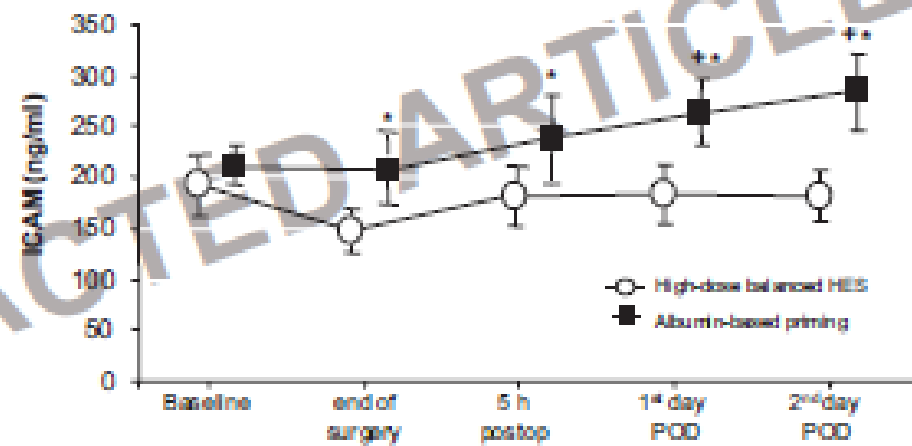
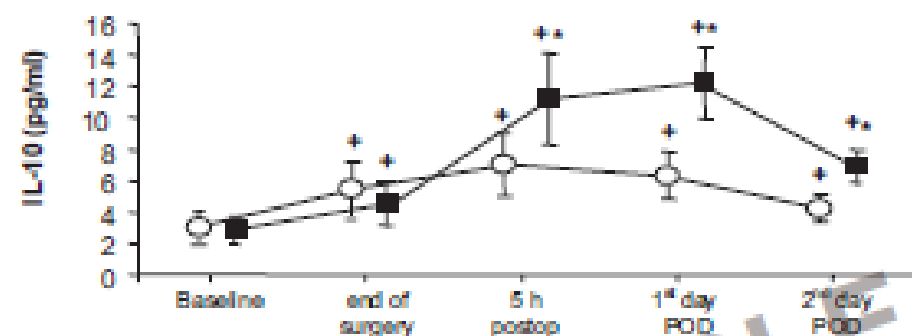
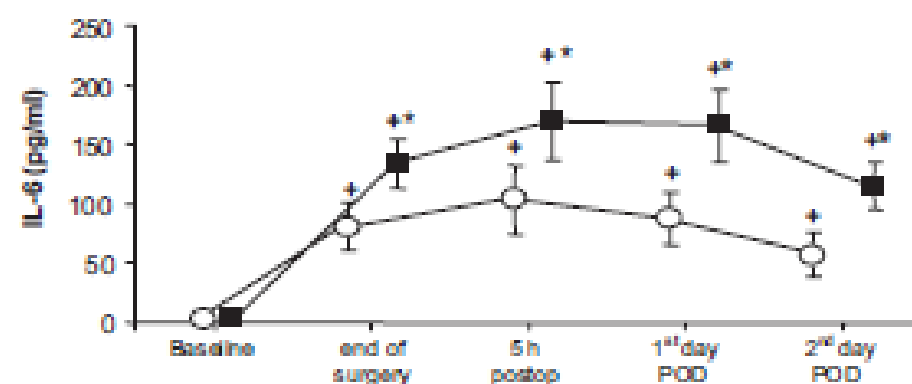
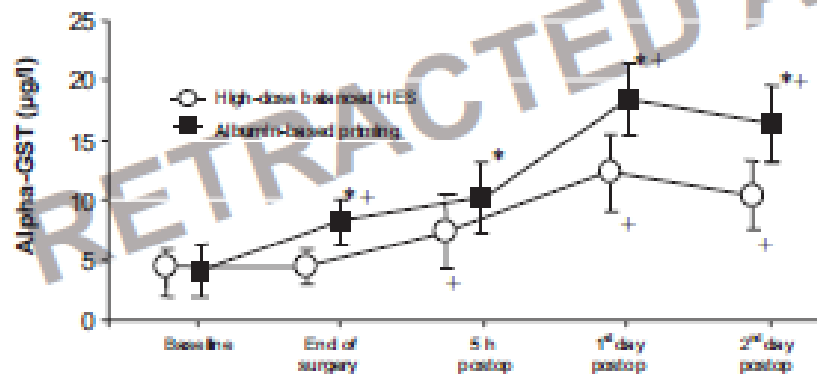
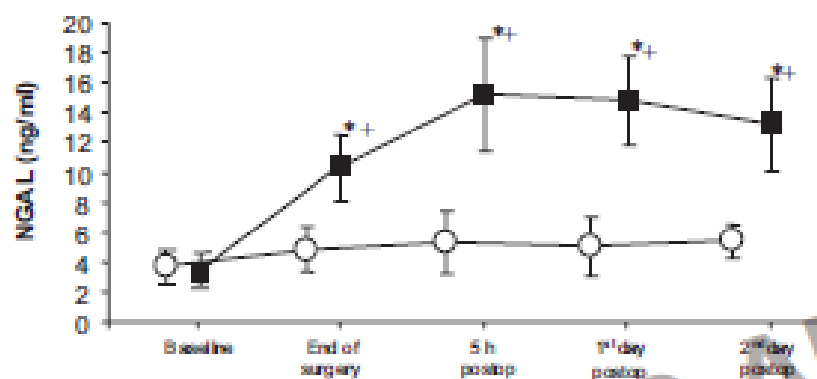
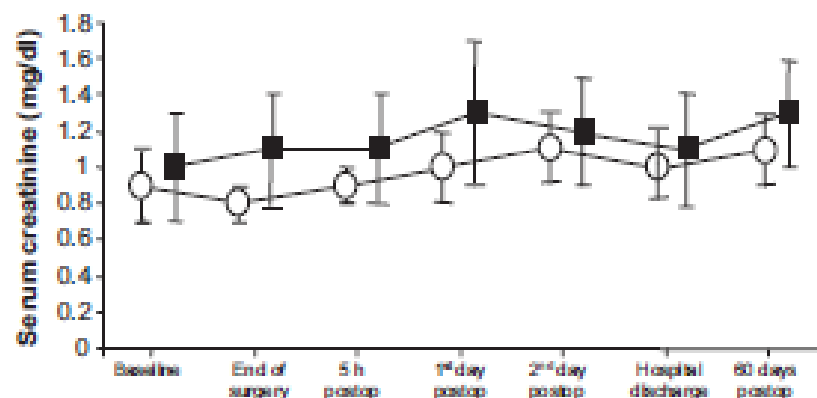
BACKGROUND: The optimal priming solution for cardiopulmonary bypass (CPB) is unclear. In this study, we evaluated the influence of high-volume priming with a modern balanced hydroxyethyl starch (HES) preparation on coagulation, inflammation, and organ function compared with an albumin-based CPB priming regimen.

METHODS: In 50 patients undergoing coronary artery bypass grafting, the CPB circuit was prospectively and randomly primed with either 1500 mL of 6% HES 130/0.42 in a balanced electrolyte solution (Na^+ 140 mmol/L, Cl^- 118 mmol/L, K^+ 4 mmol/L, Ca^{2+} 2.5 mmol/L, Mg^{++} 1 mmol/L, acetate $^-$ 24 mmol/L, malate $^-$ 5 mmol/L) ($n = 25$) or with 500 mL of 5% human albumin plus 1000 mL 0.9% saline solution ($n = 25$). Inflammation (interleukins [IL]-6, -10), endothelial damage (soluble intercellular adhesion molecule-1), kidney function (kidney-specific proteins α -glutathione S-transferase, neutrophil gelatinase-associated lipocalin), coagulation (measured by thrombelastometry [ROTEM $^{\circ}$, Peniapharm, Munich, Germany]), and platelet function (measured by whole blood aggregometry [Multiplate $^{\circ}$ analyzer, Dynabyte Medical, Munich, Germany]) were assessed after induction of anesthesia, immediately after surgery, 5 h after surgery, and on the morning of first and second postoperative days.

RESULTS: Total volume given during and after CPB was 3090 ± 540 mL of balanced HES and 3110 ± 450 mL of albumin. Base excess after surgery was lower in the albumin-based priming group than in the balanced HES priming group (-5.9 ± 1.2 mmol/L vs $+0.2 \pm 0.2$ mmol/L, $P = 0.0003$). Plasma levels of IL-6, IL-10, and intercellular adhesion molecule-1 were higher after CPB in the albumin-based priming group compared with the HES priming group at all time periods ($P = 0.0002$). Urinary concentrations of α -glutathione S-transferase and neutrophil gelatinase-associated lipocalin were higher after CPB through the end of the study in the albumin group compared with the balanced HES group ($P = 0.00004$). After surgery through the first postoperative day, thrombelastometry data (clotting time and clot formation time) revealed more impaired coagulation in the albumin-based priming group compared with the HES priming group ($P = 0.004$). Compared with baseline, platelet function was unchanged in the high-dose balanced HES priming group after CPB and 5 h after surgery, but it was significantly reduced in the albumin-based priming group.

CONCLUSION: High-volume priming of the CPB circuit with a modern balanced HES solution resulted in reduced inflammation, less endothelial damage, and fewer alterations in renal tubular integrity compared with an albumin-based priming. Coagulation including platelet function was better preserved with high-dose balanced HES CPB priming compared with albumin-based CPB priming.

(Anesth Analg 2008;108:1752-62)



Retraction Watch

Tracking retractions as a window into the scientific process

Unglaublich! Boldt investigation may lead to more than 90 retractions



Ludwigshafen Hospital, via Wikimedia

http://commons.wikimedia.org/wiki/File:Klinikum_Ludwigshafen_Nordseite.jpg

Unglaublich is the German word for unbelievable, and it's an apt description for the latest development in the case of [Joachim Boldt](#).

Boldt, a prominent German anesthesiologist, has been at the center of a research and publishing investigation since last October, when the journal *Anesthesia & Analgesia* published a paper by him and his colleagues that was later found to be fraudulent. This investigation has led to the discovery of more than 90 retractions.


Editors-in-Chief Statement Regarding Published Clinical Trials Conducted without IRB Approval by Joachim Boldt


March 4, 2011

To our readers:


Landesärztekammer Rheinland-Pfalz (“LÄK-RLP”), the State Medical Association of Rheinland-Pfalz, Germany serves as the Institutional Review Board (IRB) for clinical research at Klinikum Ludwigshafen, where Dr. Joachim Boldt’s recent research was conducted. On February 25, 2011, LÄK-RLP provided the involved journals with the results of their evaluation of the status of IRB approval for research conducted by Dr. Boldt dating back to 1999. LÄK-RLP determined, to the best of its ability, the status of IRB approval for 102 articles published by Dr. Boldt.

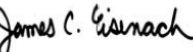
Table 1 lists 88 articles for which LÄK-RLP was unable to verify IRB approval. Table 2 lists 12 articles for which LÄK-RLP was able to verify IRB approval. Table 3 lists 2 articles for which LÄK-RLP determined that IRB approval was not necessary.


Lars S. Rasmussen
Editor-in-Chief, *Acta Anaesthesiologica Scandinavica*

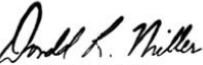

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Editor-in-Chief, *Anaesthesia*

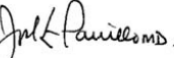

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On behalf of the Editorial Board, *Anästhesiologie Intensivmedizin Notfallmedizin Schmerztherapie*



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Editor-in-Chief, *Anesthesia & Analgesia*


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Editor-in-Chief, *Critical Care Medicine*



Bernd Zwissler
On behalf of the Editorial Board and his CoEditor-in-Chief, Rolf Rossaint, *Der Anästhesist*

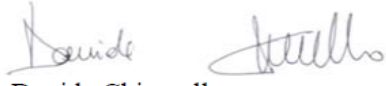

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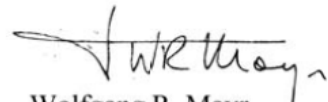

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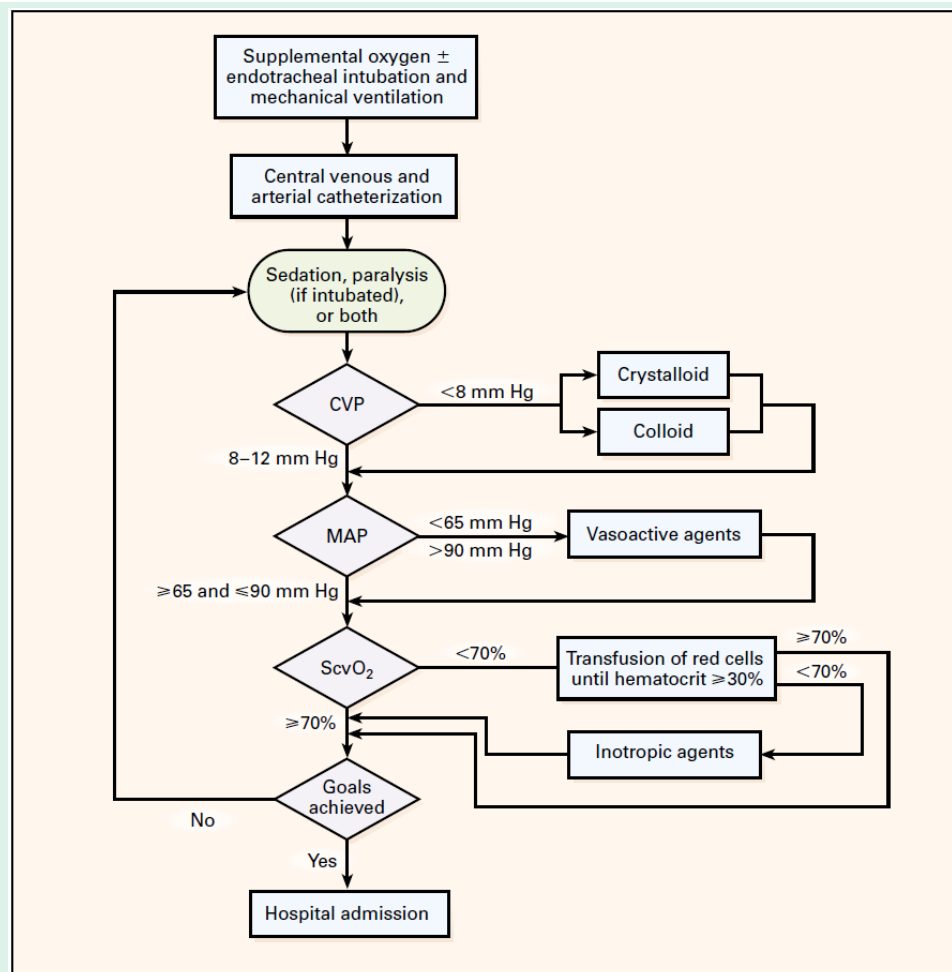

Wolfgang R. Mayr
Editor-in-Chief, *Vox Sanguinis*

La fraude dans la recherche clinique

- Pourquoi?
 - Publish or perish
 - Journal of Negative Results
 - « Cohérence » scientifique
 - Gloire personnelle
 - Pressions institutionnelles, financières
 - Peu d'intérêt académique

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S.,
ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D.,
FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*



New Therapy for Sepsis Infections Raises Hope but Many Questions

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By THOMAS M. BURTON

Seven years ago, doctors got some hopeful news about sepsis, a fast-moving bloodstream infection that kills four million people a year world-wide. A study said an aggressive new therapy cut the death rate by a third. Two medical groups endorsed the new therapy, and scores of U.S. hospitals have adopted it.

But now some doctors are questioning the rigor of the research behind it, which was done at a single hospital. Adding to the concerns: That hospital held patents on a medical device critical to the therapy. And one of the groups that later endorsed the treatment had financial backing from the maker of the device.

"One concern I have is that this hypothesis has been accepted almost without debate by so many people," says Mitchell Fink, a professor of critical-care medicine at the University of Pittsburgh Medical Center. The new therapy typically costs about \$1,100 more per patient, by the estimate of Derek Angus, chief of critical care at the University of Pittsburgh. The U.S. has about 750,000 cases of sepsis each year.

Most Popular Video

TABLE 3. KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

VARIABLE		STANDARD THERAPY (N= 133)	EARLY GOAL-DIRECTED THERAPY (N= 130)	RELATIVE RISK (95% CI)	P VALUE
		no. (%)			
All 263 were included in the intention-to-treat analyses.					
In-hospital mortality†					
All patients	N=127	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	N=124 0.009
Patients with severe sepsis		19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock		40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome		44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	N=124	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	N=120 0.01
60-Day mortality†	N=123	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	N=113 0.03
Causes of in-hospital death‡					
Sudden cardiovascular collapse		25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	N=119	26/119 (21.8)	19/117 (16.2)	—	N=117 0.27

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan–Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

Twenty-seven patients did not complete the initial six-hour study period (14 assigned to standard therapy and 13 assigned to early goal-directed therapy)



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Paris, Mercredi 5 octobre 2011, 09:33:58

Anne Mascret
Ligne directe: 01 53 10 39 32

Plagiat universitaire : Jean-Noël Darde s'inquiète de la présence de plagiaires sur les listes de candidats aux élections du CNU

La « tolérance au plagiat dans le milieu universitaire » : c'est ce que Jean-Noël Darde, maître de conférences à Paris-VIII, dénonce régulièrement dans son blog « [Archéologie du copier-coller](#) », ouvert fin 2009. Il s'inquiète aujourd'hui, mercredi 5 octobre 2011, dans un entretien à AEF, de la présence sur les listes de candidats aux élections du CNU, de personnes dont il a démontré les pratiques de plagiaire, et demande l'intervention des autorités de l'enseignement supérieur, à commencer par l'IGAENR. Comment explique-t-il cette tolérance au plagiat ? « Il y a ceux qui ont peur, ou un peu honte, de s'être laissés abuser par des plagiaires adroits ou parce qu'ils ont lu trop vite un mémoire ou une thèse », suppute l'enseignant. « Enfin, peut-être que certains universitaires ignorent ce qu'est le plagiat. (...) Il ne suffit pas de mettre le titre d'un ouvrage plagié dans la bibliographie ou en note de bas de page pour que ce ne soit plus du plagiat ! », ajoute-t-il. Interrogé sur les solutions à mettre en oeuvre, il explique ne pas croire en la « solution miracle » que représenteraient les logiciels anti-plagiat.

Il pense que « la meilleure prévention » serait « une formation approfondie à l'usage des sources et au référencement, pour les étudiants et les universitaires ». Et il ajoute que l'« une des clés de la lutte anti-plagiat serait d'imposer aux universités d'informer les plagiés de leurs infortunes afin qu'ils puissent exercer leur droit à demander réparation ».



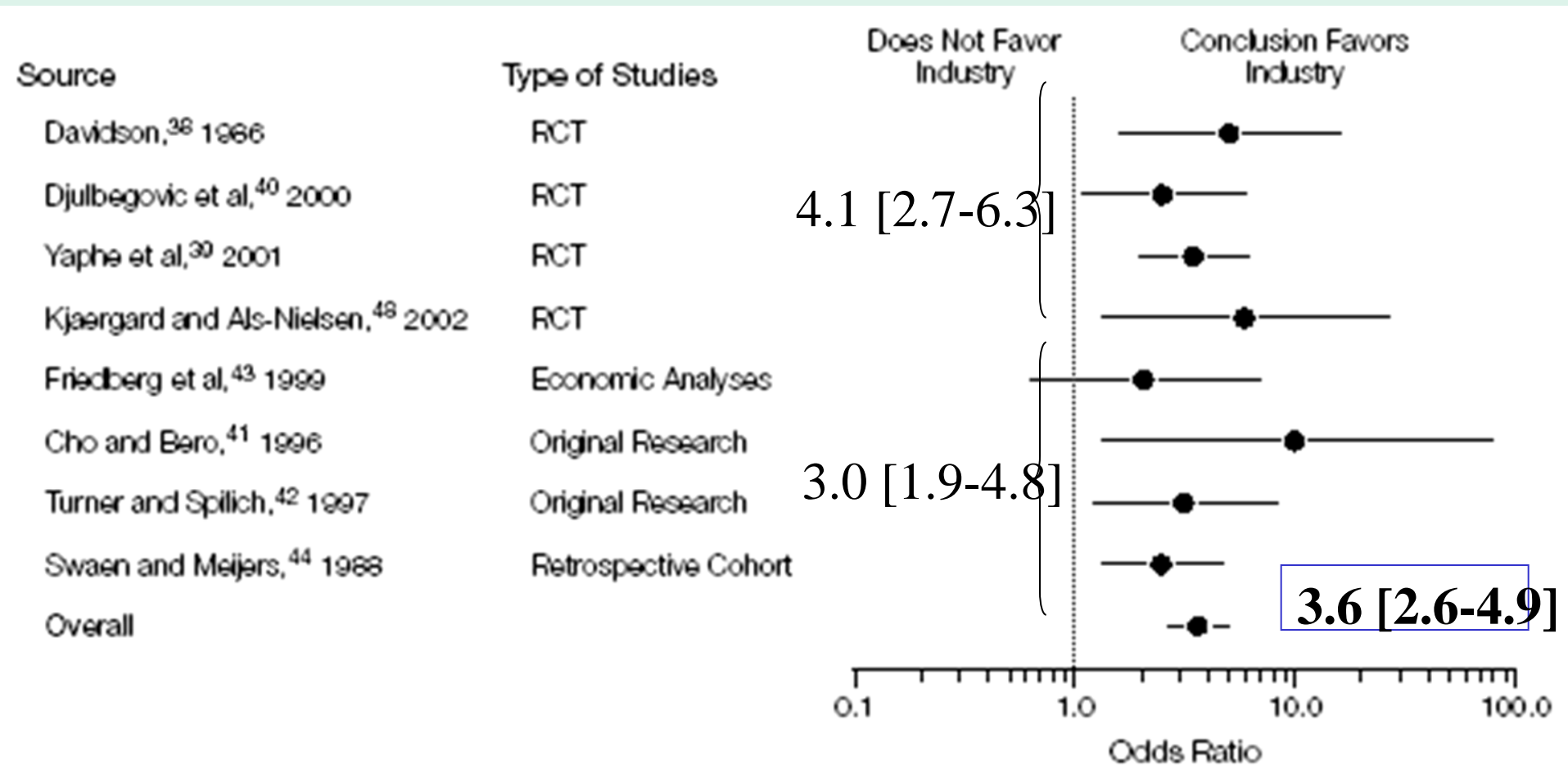
Jean-Noël Darde, maître de conférences à Paris-VIII

© I. Santi

Laurent Brochard

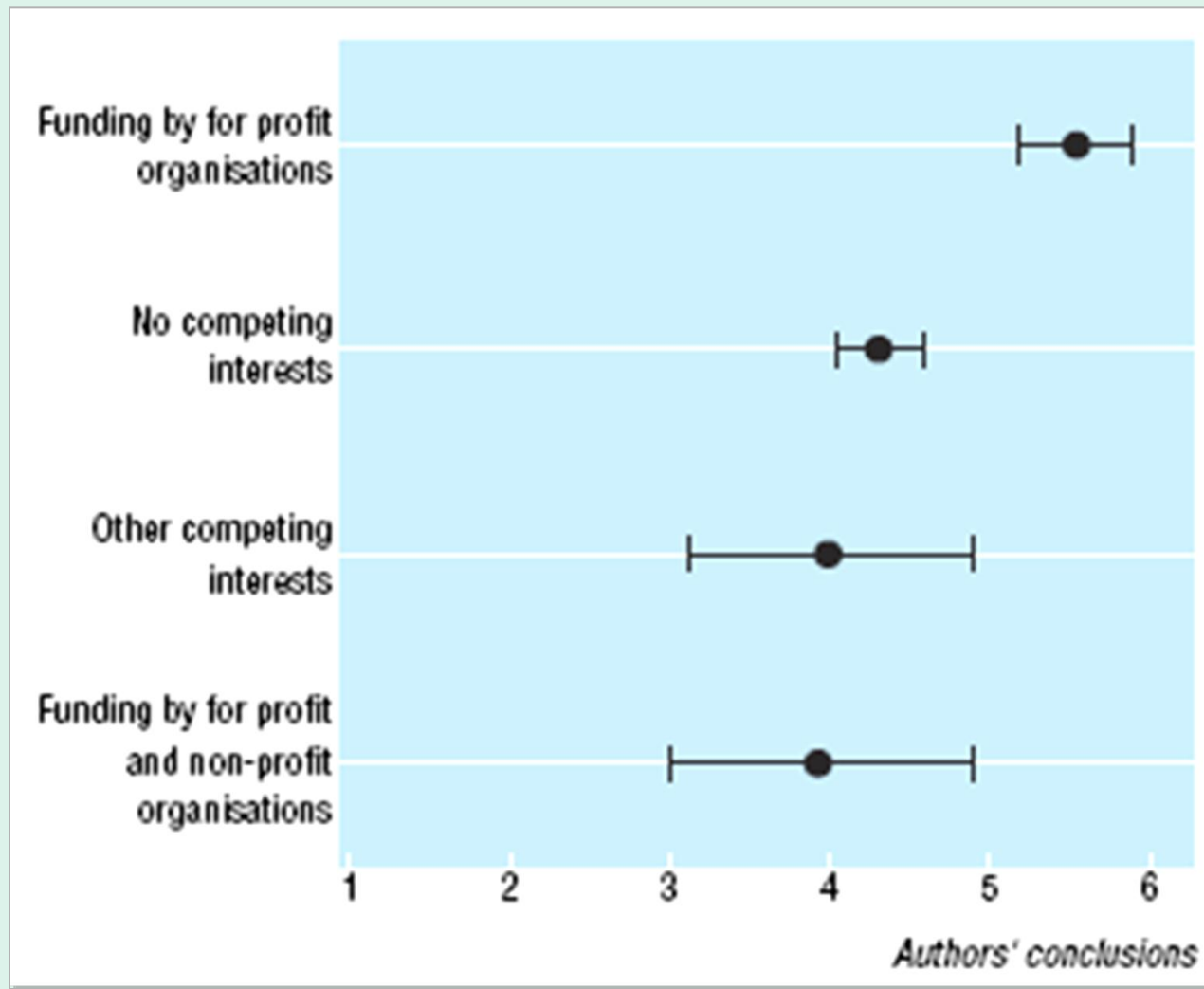
**Redundant publications,
or piling up the medals.
Getting published is *not* the Olympic Games**

Outcomes of Industry-sponsored vs. non-industry-sponsored studies



RCT indicates randomized controlled trial. Error bars indicate 95% confidence intervals.

Source of funding and competing interests



COMMENTARY

Scientists behaving badly

To protect the integrity of science, we must look beyond falsification, fabrication and plagiarism, to a wider range of questionable research practices, argue **Brian C. Martinson**, **Melissa S. Anderson** and **Raymond de Vries**.

‘The modern scientist faces intense competition, and is further burdened by difficult, sometimes unreasonable, regulatory, social, and managerial demands.

This mix of pressures creates many possibilities for the compromise of scientific integrity that extend well beyond FFP.’

Enquête auprès de chercheurs subventionnés par le NIH

Table 1 Percentage of scientists who say that they engaged in the behaviour listed within the previous three years (n = 3,247)			
Top ten behaviours	All	Mid-career	Early-career
1. Falsifying or 'cooking' research data	0.3	0.2	0.5
2. Ignoring major aspects of human-subject requirements	0.3	0.3	0.4
3. Not properly disclosing involvement in firms whose products are based on one's own research	0.3	0.4	0.3
4. Relationships with students, research subjects or clients that may be interpreted as questionable	1.4	1.3	1.4
5. Using another's ideas without obtaining permission or giving due credit	1.4	1.7	1.0
6. Unauthorized use of confidential information in connection with one's own research	1.7	2.4	0.8 ***
7. Failing to present data that contradict one's own previous research	6.0	6.5	5.3
8. Circumventing certain minor aspects of human-subject requirements	7.6	9.0	6.0 **
9. Overlooking others' use of flawed data or questionable interpretation of data	12.5	12.2	12.8
10. Changing the design, methodology or results of a study in response to pressure from a funding source	15.5	20.6	9.5 ***

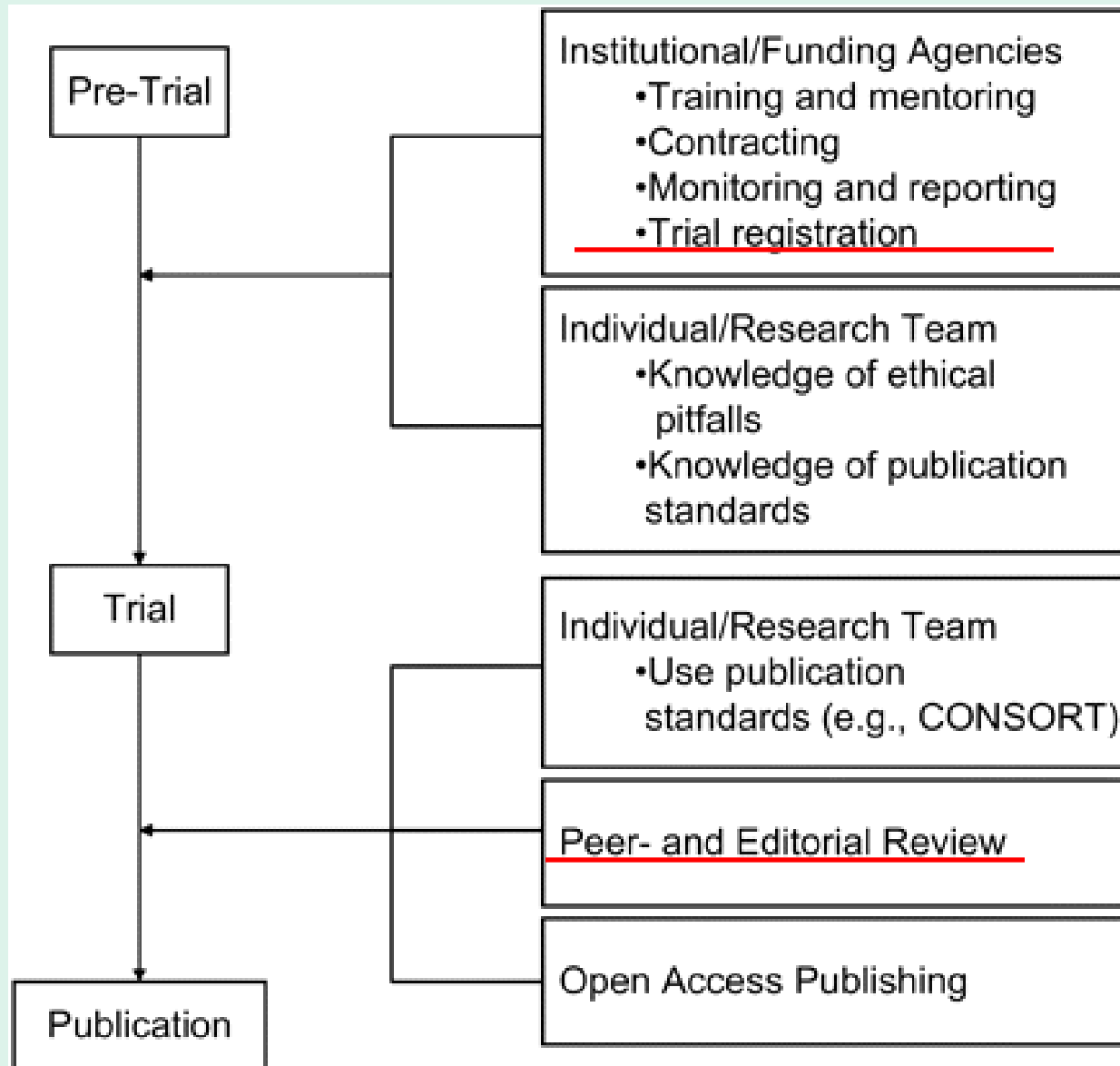
33% des enquêtés ont eu au moins une des 10 attitudes listées dans les 3 ans précédents

Enquête auprès de chercheurs subventionnés par le NIH

Other behaviours	All	Mid-career	Early-career
11. Publishing the same data or results in two or more publications	4.7	5.9	3.4 **
12. Inappropriately assigning authorship credit	10.0	12.3	7.4 ***
13. Withholding details of methodology or results in papers or proposals	10.8	12.4	8.9 **
14. Using inadequate or inappropriate research designs	13.5	14.6	12.2
15. Dropping observations or data points from analyses based on a gut feeling that they were inaccurate	15.3	14.3	16.5
16. Inadequate record keeping related to research projects	27.5	27.7	27.3

Note: significance of χ^2 tests of differences between mid- and early-career scientists are noted by ** ($P < 0.01$) and *** ($P < 0.001$).

Les “entorses” à l’intégrité sont beaucoup plus fréquentes que l’on pourrait croire, et les “fraudes majeures” probablement assez rares.



Research Misconduct, Retraction, and Cleansing the Medical Literature: Lessons from the Poehlman Case

Harold C. Sox, MD, and Drummond Rennie, MD

- The scientific literature is a record of the search for truth. Publication of faked data diverts this search. The scientific community has a duty to warn people to ignore an article containing faked data and must try to prevent inadvertent citation of it.

Conclusion

- Dégâts scientifiques et sociaux importants
- Rapport médecin malade
- Pourquoi un patient accepte de participer à une recherche?
- Parce qu'il/elle a confiance en vous...