

#### Prof Martin R Tramèr, MD, DPhil

Service d'Anesthésiologie
Département de Médecine Aiguë
Hôpitaux Universitaires & Faculté de Médecine
Genève



Efficacy, Dose–Response, and Safety of Ondansetron in Prevention of Postoperative Nausea and Vomiting

A Quantitative Systematic Review of Randomized Placebo-controlled Trials

Martin R. Tramèr, M.D.,\* D. John M. Reynolds, B.M., B.Ch., D.Phil.,† R. Andrew Moore, D.Sc.,‡ Henry J. McQuay, D.M. §

Anesthesiology 1997; 87:1277-89 A quantitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting

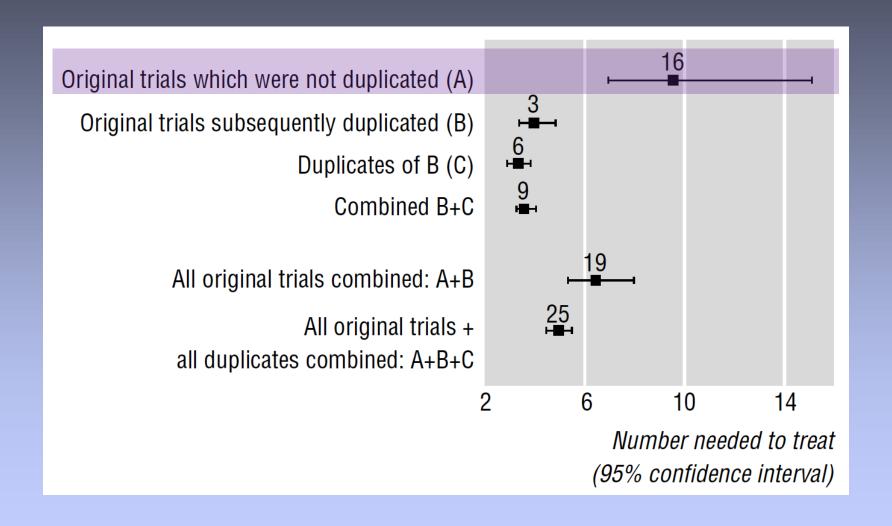
Martin R Tramèr, R Andrew Moore, D John M Reynolds, Henry J McQuay

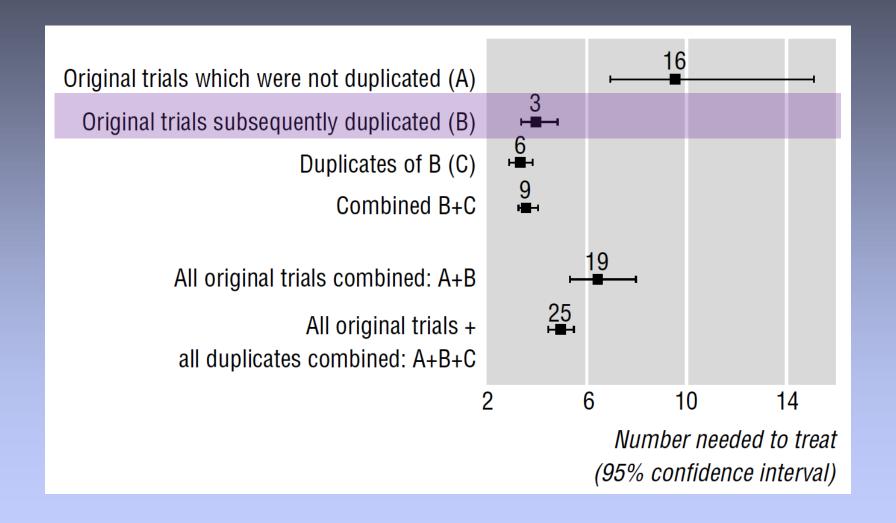
**BMJ** VOLUME 314 12 APRIL 1997

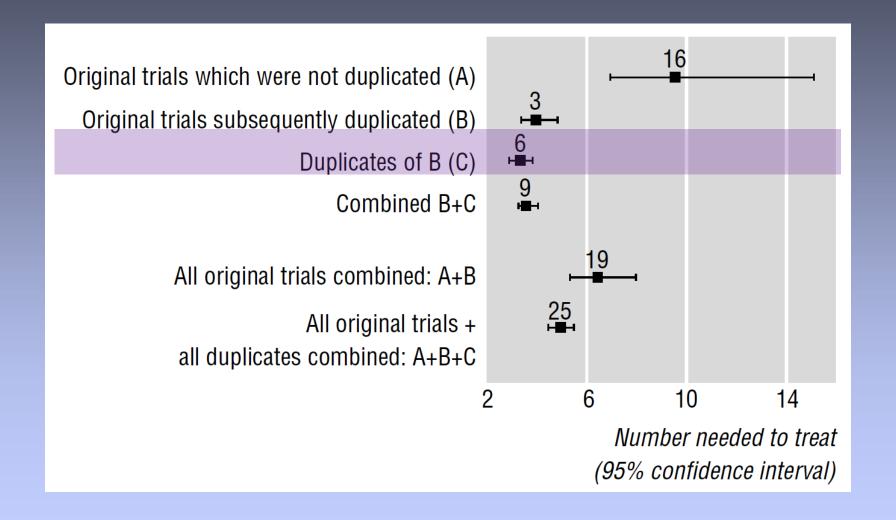
# Impact of covert duplicate publication on meta-analysis: a case study

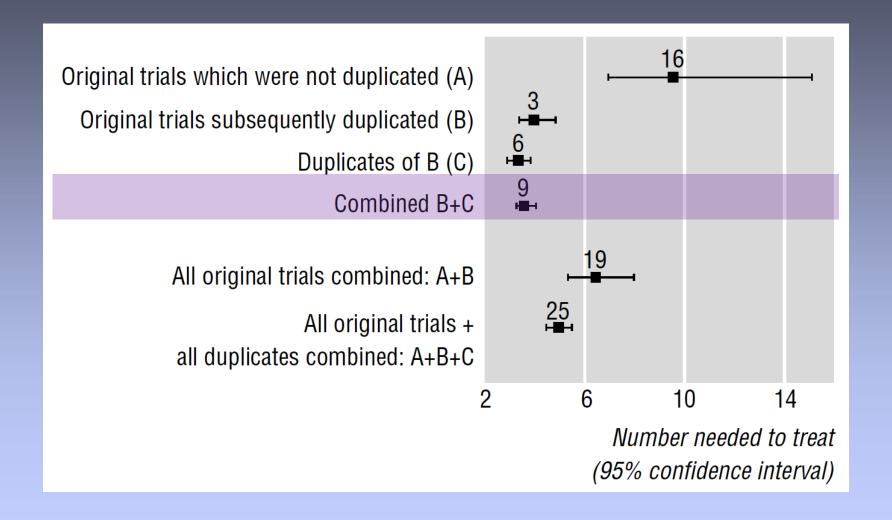
Martin R Tramèr, D John M Reynolds, R Andrew Moore, Henry J McQuay

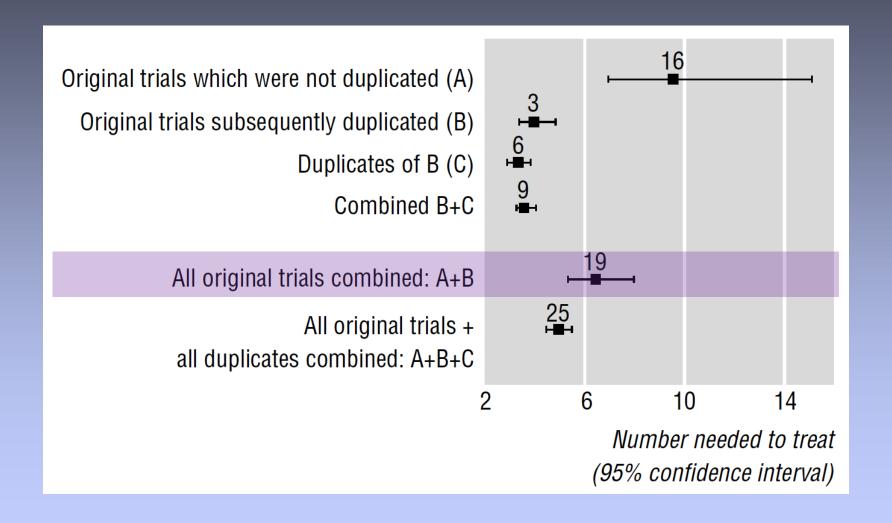
**BMJ** VOLUME 315 13 SEPTEMBER 1997

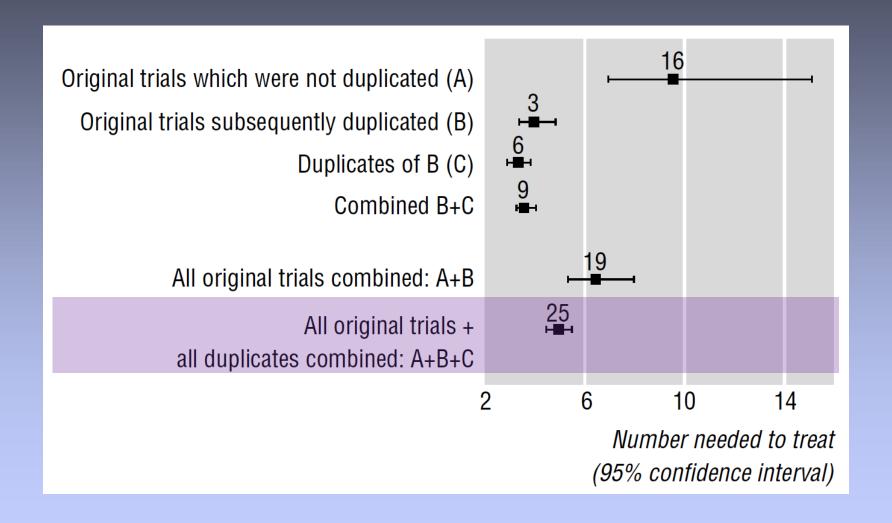














information Determinants of learning to perform uplical anountheela: a pillot shoby (a 11) Rophisconer vi. lenstouphiscones combined with suberlanditor epiducal

## The EICs infinite list of fraud

	Short reference Nationality	Full reference	Populte 14	Decead	Common Title
	Inal et al (submitt Turkey	EJA-D-11-00253	Results Verdi Resubmission of a prev Results		Commet Title  Triage COMPARISON OF FOUR TESTS FOR DIFFICULT LARYNGOSCOPY IN PEDIATRIC PATIENTS
Ì	Borazan et al (sub Turkey	EJA-D-11-00253	54% overlap with oth Plagia		IMAGE COMPARISON OF FOUR TESTS FOR DIFFICULT LARYINGUSCOPT IN PEDIATRIC PAILENTS Possible data fabrication brought to our attention through peer review. Then overlap checked with CrossCheck.
a i	Bedirli et al (subm Turkey	EJA-D-11-00034	47% overlap with oth Plagia		Prosible data abilitation brought to our attention through peer review. Then overlap thetxed with crosscheck.
î	Sitsen et al (subm Netherlands		30% overlap (22% wi Plagia		Through A comparison of the efficacy of levobupivacaine 0,125%, ropivacaine 0,125% and ropivacaine 0,2%, all combined with sufentanil 0.5 mcg/mL, in p
1		EJA-S-11-00107	48% overlap with the Plagia		Through Local anaesthesia efficacy as postoperative analgesia for open anterior-inferior shoulder instability: a prospective randomised controlled study
1		EJA-S-11-00171	59% overlap (10% wi Plagia		Through FENOLDOPAM REDUCES ACUTE KIDNEY INJURY AFTER CARDIAC SURGERY: A META-ANALYSIS OF RANDOMIZED STUDIES
1		EJA-D-11-00223	27% overlap (21% wi Plagia		Through Comparative analysis of desflurane versus sevoflurane on neuroendocrine and inflammatory responses during laparoscopic surgery: a randomized
1		EJA-D-11-00314			Through Association between ABCB1 gene polymorphism and fentanyl's adverse effects in Turkish patients undergoing spinal anaesthesia
1	Abou-Elenain. EJA Egypt	Abou-Elenain Khal	50% overlap with thr Plagia	Retraction	Brought to our attention by an EIC
1	Abou-Elenain et al Egypt		I Plagiate of whole para Plagia		Brought to our attention through peer review
1		EJA-S-11-00198	36% overlap Plagia		Through Whether a Huffing Manoeuvre Immediately before Induction of Anaesthesia can Prevent Sufentanil-induced Coughing?—a randomized trial
1		EJA-D-11-00271	44% overlap Plagia		Through Prognostic value of the intraoperative tissue Doppler-derived index E/e' after non- cardiac surgery
1		EJA-D-11-00334	34% overlap Plagia		Through COMPARISON OF PROSEAL LARYNGEAL MASK AIRWAY AND ENDOTRACHEAL TUBE IN PEDIATRIC STRABISMUS SURGERY- Randomised Clinical Tria
1	Company of the Compan	EJA-S-11-00252	33% overlap Plagia	Rejection	Through The study of the analgesic effect of tramadol in patients undergoing 1aparoscopic cholecystectomy
1	Editabili de di (babi Ital)	EJA-D-11-00371	48% overlap (second : Plagia	Rejection	Through FENOLDOPAM AND ACUTE RENAL FAILURE IN CARDIAC SURGERY, A META-ANALYSIS OF RANDOMIZED PLACEBO CONTROLLED TRIALS.
1	Masaki et al (subn Japan	EJA-D-11-00390 EJA-D-11-00409	30% overlap Plagia	Rejection	Through Perioperative infusion of dexmedetomidine at a high dose reduced postoperative analgesic requirements: A randomized control tria Through Effectiveness of P6 Acustimulation for Postoperative Nausea and Vomiting in Children: A Meta analysis
1	HuangWei et al (sı China Schumacher UK	EJA-D-11-00409	43% overlap Plagia 28% overlap Plagia	Rejection Rejection	
1	Vermeylen Belgium	EJA-D-11-00408	28% overlap Plagia 27% overlap Plagia	Rejection	Through Respiratory protection during simulated emergency paediatric life support Through Supraclavicular brachial plexus blocks: review and current practice
1	Turkoz Turkey	EJA-D-11-00407	19% overlap but 10% Plagia	Rejection	Through Randomized study comparing analgesic effects of bilateral practices and intravenous patient controlled analgesia with morphine in coron.
1	Sun US	EJA-D-11-00410	34% overlap but 10% Plagia	Rejection	Through Does Preoperative Aspirin Reduce Cardiocerebral and Renal Complications in Cardiac Surgery Patients? An Observational and Cohort Study
1	Lin China	EJA-D-11-00417	35% overlap Plagia	Rejection	Through Low tidal volume and high frequency mechanical ventilation increase inflammation and lung injury in streptozotocin-induced diabetes
1	Guigi China	EJA-D-11-00420	40% overlap Plagia	Rejection	Through The feasibility of predicting acute postoperative pain by propofol injection-induced pain
1		EJA-D-11-00434	27% overlap Plagia	Rejection	Through The determination of estimated effect-site concentration of remifentanil for successful tracheal intubation without muscle relaxants in 50% children
1	Abdullah Egypt		43% overlap; discussic Plagia	Rejection	Through Patient Versus Anesthesiologist Controlled Analgesia In Cirrhotic Patients Undergoing Percutaneous Radiofrequency Ablation Of Hepatic Tumors.
1	Zhao China	EJA-D-11-00595	33% overlap (systema Plagia	Rejection	Through Dexmedetomidine premedication on the cardiovascular response induced by laryngoscopy and tracheal intubation: A meta-analysis
1	Salman Turkey	EJA-D-11-00447	51% overlap (discussic Plagia	Rejection	Through PRETREATMENT WITH A VERY LOW DOSE OF INTRAVENOUS ESMOLOL REDUCES PROPOFOL INJECTION PAIN Running Head: Esmolol for propofol i
1	Liu China		37% overlap Plagia	Rejection	Through Delayed Anaesthetic Preconditioning Protects Against Myocardial Ischaemia/reperfusion Injury Via Activation of Nuclear Factor-kB and Upregulation
1	Ozkan Turkey	EJA-D-11-00448	27% overlap Plagia	Rejection	Through The Target Controlled Remifentanii Infusion for Smooth Laryngeal Mask Airway Removal During Emergence from Desflurane -Remifentanii Anesthe
1	Reed UK Almeida et al (sub Portugal	EJA-D-11-00473	22% overlap (21% - 4 Plagia Simultaneous submiss Multip	Rejection sub Rejection	Through Forced Air Warming Design: An Evaluation of Intake Filtration, Internal Microbial Build-Up, and Airborne-Contamination Emissions.  Brought to our attention by an EIC
1			Lack of IRB approval Ethics	Retraction	brought to our attention by an ELC
1			r Lack of IRB approval Ethics	Retraction	
î			Lack of IRB approval Ethics	Retraction	
1			Lack of IRB approval Ethics	Retraction	
1	Röhm et al. EJA 2( Germany		Lack of IRB approval Ethics	Retraction	
1	Röhm et al. EJA 2( Germany	Röhm KD, Schöllh	Lack of IRB approval Ethics	Retraction	
1	Piper et al. EJA 20 Germany		Lack of IRB approval Ethics	Retraction	
1			Lack of IRB approval Ethics	Retraction	
1			Lack of IRB approval Ethics		Peer revi CONSCIOUS SEDATION AND DEEP ANALGESIA FOR ERCP PROCEDURES OUTSIDE THE OPERATING ROOM: a prospective randomized study
1		EJA-D-10-00658 EJA-S-10-00500	Ethical approval one w Ethics		Peer review
1		EJA-S-10-00500	Incomplete ethical req Ethics Incomplete ethical req Ethics	Not resubr	
1		EJA-S-10-00700	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-10-00783	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-10-00789	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-10-00850	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-10-00908	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-10-00935	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-10-00945	Incomplete ethical req Ethics	Not resubr	
1	Total Control of the	EJA-S-10-00986	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-10-01003	Incomplete ethical req Ethics	Not resubr	
1	JOSE I II GOLL I II II Opulli	EJA-S-11-00042	Incomplete ethical req Ethics	Not resubr	
1 1		EJA-S-11-00124	Incomplete ethical reg Ethics	Not resub	
1	SUMIT VASDEV, M India Neritan Myderrizi, Albania	EJA-S-11-00128 EJA-S-11-00154	Incomplete ethical req Ethics Incomplete ethical req Ethics	Not resubr	
1		EJA-S-11-00154 EJA-S-11-00224	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-11-00224	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-11-00298	Incomplete ethical req Ethics	Not resubr	
1			Incomplete ethical req Ethics	Not resubr	
1		EJA-S-11-00324	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-11-00331	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-11-00394	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-11-00252	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-11-00396	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-11-00443	Incomplete ethical req Ethics	Not resubr	
1	/ demical de manuel	EJA-S-11-00481	Incomplete ethical req Ethics	Not resubr	
1		EJA-S-11-00545	Incomplete ethical req Ethics	Not resubr	
1		EJA 2010;27:353- EJA 2010 [PAP]	ESimultaneous submiss Duplic Author has taken full r Duplic		Brought to our attention through peer review  Brought to our attention by an peer reviewer (Martin 18hr) who was preparing a Commentary
1	Cao et al. EJA 201 China	DA ZUIU [PAP]	Author has taken full r Duplic	te Retraction	Brought to our attention by an peer reviewer (Martin Jöhr) who was preparing a Commentary

### Les mauvais exemples de l'anesthésiologie

2009



2011



2012-13



**Dr Scott REUBEN**21 articles retracted

**Dr Joachim BOLDT**88 articles retracted

**Dr Yoshitaka FUJII**183 articles retracted

# Fraude ... Définition

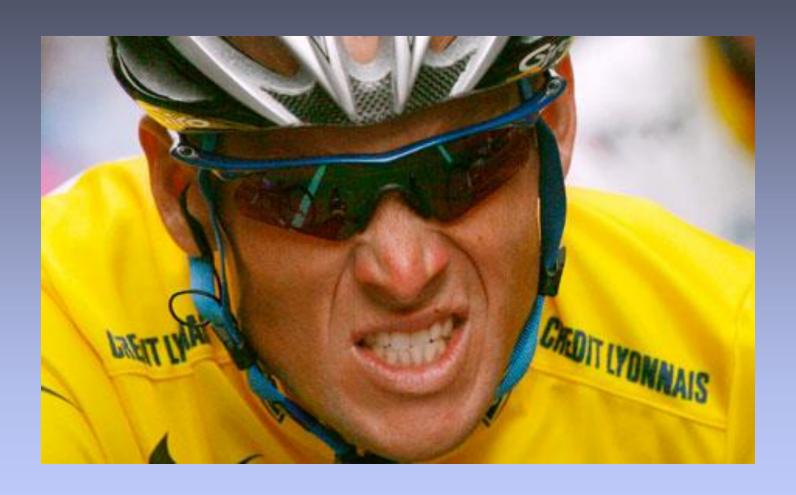
Acte malhonnête fait dans l'intention de tromper en contrevenant à la loi ou aux règlements

#### SYNONYMES:

<u>escroquerie</u> - falsification - resquille (populaire) - <u>tricherie</u>

# La fraude ... Un phénomène commun

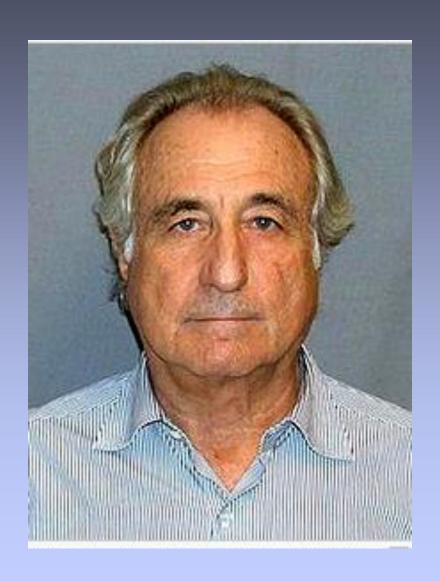
## **Sports**



# **Sports**



## **Finances**



## **Arts (1)**



Wolfgang Beltracchi in court in Cologne last fall. *Inset: Red Picture with Horses*, a painting supposedly by German Expressionist Heinrich Campendonk, forged by Beltracchi; it sold at auction for \$3.6 million in 2006.

#### http://www.vanityfair.com

## **Arts (2)**

#### Struggling Immigrant Artist Tied to \$80 Million New York Fraud

By SARAH MASLIN NIR, PATRICIA COHEN and WILLIAM K. RASHBAUM Published: August 16, 2013 │ ■ 181 Comments

Pei-Shen Qian's neighbors on 95th Street in Woodhaven, Queens, knew he scratched out a living as an artist: he often dried his paintings in the sun, propping them up on the weathered white siding of his modest house.



Pei-Shen Qian

#### Connect With NYTMetro

Follow us on Twitter and like us on Facebook for news and conversation.



Enlarge This Image



Robert Stolarik for The New York Times
Pei-Shen Qian lived and worked in this
house on 95th Street in Woodhaven,
Queens.

₱ Readers' Comments

They were less clear on why he kept his windows covered, or why every so often a man in an expensive car would come to the house carrying paintings to, not from, a painter.

"He would bring a painting in and show it to him, for him to work on or fix up something," Edwin Gardiner, 68, who lives across the street, said before pausing and adding, "I don't know what he did with it."

Parts of the mystery became clearer on Friday as neighbors learned that Mr. Qian, a quiet 73-year-old immigrant from China in a paint-flecked smock, is suspected of having fooled the art world by creating dozens of works that were modeled after America's Modernist masters and were later sold as their handiwork for more than \$80 million.

Mr. Qian, who came here more than four decades ago and struggled to sell his own works in this country, earned just a few thousand dollars for each of his imitations. New York was a center of the art world, but Mr. Qian told friends that he had been disheartened by the difficulties he encountered finding a foothold as an artist.



Edward Hopper (1882–1967) Study for Nighthawks

## Journalism (1)



MEDIA

Tom Kummer, the bad boy of celebrity journalism

🚔 MANDY DE WAAL 📕 MEDIA 21 JUN 2011 09:35 (SOUTH AFRICA) 💟 🚹 🖾 🔡 in



His direct access to stars like Pamela Anderson, Sharon Stone, Courtney Love and Sean Penn was astounding, but even more remarkable was Tom Kummer's talent for getting them to open up and reveal their deepest selves. That was before he crashed and burned because of a trifle called "the truth". By MANDY DE WAAL.



## Journalism (2)

#### Manipulation durch Reporter

#### SPIEGEL legt Betrugsfall im eigenen Haus offen

Ein Reporter des SPIEGEL hat in großem Umfang eigene Geschichten manipuliert. Durch interne Hinweise und Recherchen erhärtete sich in den vergangenen Tagen der Verdacht gegen Claas Relotius - der inzwischen Fälschungen zugegeben und das Haus verlassen hat. Auch andere Medien könnten betroffen sein.

Eine Rekonstruktion in eigener Sache von Ullrich Fichtner



## theguardian





In time, however, discrepancies appeared in the market. Bottles of Clos St Denis from Domaine Ponsot, of vintages between 1945 and 1971, started to turn up. Laurent Ponsot, the head of the house, found this surprising as his family only started making the wine in 1982. He set out to investigate.



Spot the difference: three bottles of wine used as evidence in Rudy Kurniawan's trial. The magnum dates from a time when magnums were not available Photograph: Stan Honda/AFP/Getty Images



## Politics (1)

Karl-Theodor Maria Nikolaus Johann Jacob Philipp Franz Joseph Sylvester Freiherr von und zu **Guttenberg** (born on 5 December 1971)



German politician of the Christian Social Union (CSU)

Member of Parliament from 2002 until March 2011

February 2009: Federal Minister Economics & Technology (1st Merkel cabinet)

October 2009: Minister of Defence (2<sup>nd</sup> Merkel cabinet)

March 2011: Discovery plagiarism in doctoral thesis - Resignation

2011: Member of Center for Strategic and International Studies (CSIS) as a Distinguished Statesman.

Advises European Commission Vice President Neelie Kroes on the promotion of internet freedom regarding questions of foreign affairs.



## Politics (2)

# Le compte suisse du ministre du budget Jérôme Cahuzac

04 DÉCEMBRE 2012 | PAR FABRICE ARFI

« Je n'ai pas de compte en Suisse et n'en ai jamais eu. Il est clair que si vous publiez ça, j'attaquerai »



#### Un haut fonctionnaire fédéral usurpe le titre de docteur depuis 1990

12.11.2014 13:02

Carte de visite, signature, site de l'administration: Urs Staub, chef de section à l'Office fédéral de la culture (OFC), utilise le titre de docteur. Or, il n'a jamais terminé sa thèse. Il reconnaît une erreur.

Urs Staub, chef de la section Musées et collections à l'Office fédéral de la culture (OFC), se prévaut depuis 1990 du titre de docteur en philologie, alors qu'il n'a jamais terminé sa thèse, révèle mercredi le **Bund** et le **Tages-Anzeiger**. Le haut fonctionnaire admet son erreur et la regrette.

L'OFC, de son côté, condamne toute usurpation de titre universitaire, mais précise que le titre de docteur n'était pas déterminant pour occuper le poste de chef de la section Musées et collections. Ses compétences, de plus, sont largement reconnues.

#### **Etonnement à l'OFC**

Contactée mardi soir par les deux quotidiens alémaniques, la directrice de l'OFC Isabelle Chassot tombe des nues. La Fribourgeoise ignorait cette usurpation de titre, a-t-elle indiqué.

Mercredi matin, Isabelle Chassot n'avait toutefois pas encore pu s'entretenir avec le faux docteur, qui doit partir à la retraite dans deux semaines et demie après 30 ans de service.

#### Et dans la science?

# nature

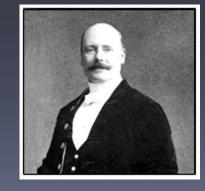
NATURE VOL. 303 2 JUNE 1983

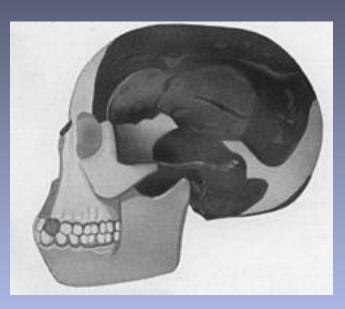
# Is science really a pack of lies?

The past few years have seen a spate of allegations of fraud in science, with the result that the integrity of the research enterprise has been questioned.

# Piltdown Man Eoanthropus dawsoni

**Charles Dawson (1864-1916)** 





"A missing link between apes and humans that would have lived half a million years ago."

"So many people wanted Piltdown Man to be real."

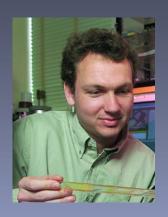
Miles Russel

1907 Otto Schoetensack -> Heidelberg Man 1912 Charles Dawson -> Piltdown Man

Javier Yanes.

The Piltdown Man: The Greatest Scientific Fraud of the 20th Century https://www.bbvaopenmind.com

#### Jan Hendrik Schön: World Class Physics Fraud Gets Last Laugh -A Whole Book About Himself



Jan Hendrik Schön, if you have heard the name, will either fascinate or enrage you. His ability to progress from ridiculous fibs to world-class deception as a 31-year-old physicist working at Bell Labs in New Jersey is certainly impressive.

In 2000 alone, Schön published eight papers in *Science* and *Nature*, publications that claim to be the world standard for quality science, and he became known for his breakthrough of using organic dye molecules to create an electric circuit which when prompted by an electric current behaved as a transistor, leading scientists in a dozen labs to likewise chase some funding, wasting millions of dollars of US government research money. He also garnered the Otto–Klung-Weberbank Prize for Physics in 2001, the Braunschweig Prize in 2001 and the Outstanding Young Investigator Award of the Materials Research Society in 2002.

# What is « scientific fraud »?

# **Scientific fraud**



# **Scientific misconduct**



Fr: Inconduite

- Fabrication
- Falsification
- Plagiarism

TABLE 1 Would various behaviours be judged research misconduct according to seven different definitions of research misconduct?										
Behaviour	RCP 1991 Roy Coll Phys	MRC Med Res Council	US	Denmark 1992	Finland 1994	Norway 1994	Sweden 1997			
Inventing a case	Yes	Yes	Yes	Yes	Yes	Yes	Yes			

TABLE 1
Would various behaviours be judged research misconduct according to seven different definitions of research misconduct?

Behaviour	RCP 1991 Roy Coll Phys	MRC  Med Res Council	US	Denmark 1992	Finland 1994	Norway 1994	Sweden 1997
Inventing a case	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Failing to get consent	No	Yes	Yes	No	Yes	Yes	?

TABLE 1 Would various behaviours be judged research misconduct according to seven different definitions of research misconduct?

Behaviour	RCP 1991 Roy Coll Phys	MRC Med Res Council	US	Denmark 1992	Finland 1994	Norway 1994	Sweden 1997
Inventing a case	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Failing to get consent from an ethics committee	No	Yes	Yes	No	Yes	Yes	?
Publication of <i>post hoc</i> analyses without declaration that they were <i>post hoc</i>	?	Yes	?	?	?	?	;

TABLE 1 Would various behaviours be judged research misconduct according to seven different definitions of research misconduct?

Behaviour	RCP 1991 Roy Coll Phys	MRC Med Res Council	US	Denmark 1992	Finland 1994	Norway 1994	Sweden 1997
Inventing a case	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Failing to get consent from an ethics committee	No	Yes	Yes	No	Yes	Yes	;
Publication of post hoc analyses without declaration that they were post hoc	?	Yes	?	?	;	?	<u>\$</u>
Gift authorship	?	Yes	?	Yes	\$	?	?

TABLE 1 Would various behaviours be judged research misconduct according to seven different definitions of research misconduct?

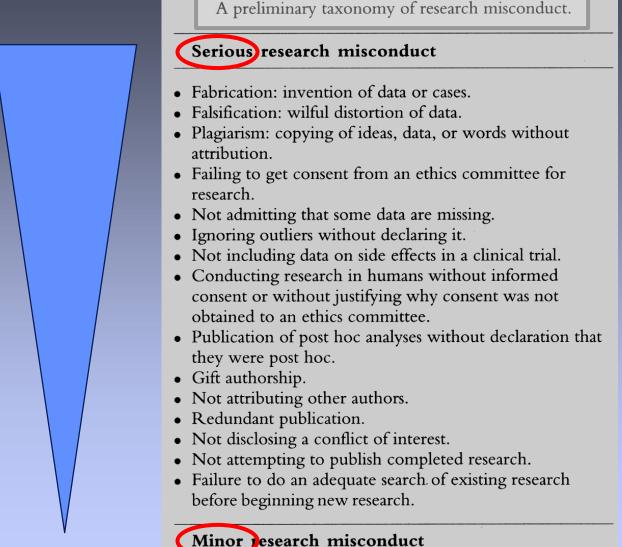
Behaviour	RCP 1991 Roy Coll Phys	MRC Med Res Council	US	Denmark 1992	Finland 1994	Norway 1994	Sweden 1997
Inventing a case	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Failing to get consent from an ethics committee	No	Yes	Yes	No	Yes	Yes	?
Publication of post hoc analyses without declaration that they were post hoc	?	Yes	?	?	?	?	<u>\$</u>
Gift authorship	?	Yes	?	Yes	?	?	?
Not disclosing a conflict of interest	?	<b>,</b>	?	?	?	?	?

#### Smith R. The COPE report 2000 (www.publicationethics.org.uk)

TABLE 1 Would various behaviours be judged research misconduct according to seven different definitions of research misconduct?

Behaviour	RCP 1991 Roy Coll Phys	MRC Med Res Council	US	Denmark 1992	Finland 1994	Norway 1994	Sweden 1997
Inventing a case	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Failing to get consent from an ethics committee	No	Yes	Yes	No	Yes	Yes	?
Publication of post hoc analyses without declaration that they were post hoc	?	Yes	?	?	;	?	<u>\$</u>
Gift authorship	?	Yes	?	Yes	?	?	?
Not disclosing a conflict of interest	?	<b>;</b>	?	\$	\$	?	<b>?</b>
Not publishing completed research	No	?	?	No	No	No	No

#### Smith R. The COPE report 2000 (www.publicationethics.org.uk)



Smith R. The COPE report 2000 (www.publicationethics.org.uk)

# Plagiat ... Définition

1. Acte de quelqu'un qui, dans le domaine artistique ou littéraire, donne pour sien ce qu'il a pris à l'œuvre d'un autre.

#### Synonymes:

<u>calque</u> - <u>compilation</u> - <u>copie</u> - <u>démarquage</u> - <u>imitation</u> - <u>pillage</u> - <u>piraterie</u> (familier)



Study of the systemic and pulmonary oxidative stress status during exposure to propofol and sevoflurane anaesthesia during thoracic surgery

Khaled Abou-Elenain

Eur J Anaesthesiol 2010;27:566-571



### Oxidative Stress Status During Exposure to Propofol, Sevoflurane and Desflurane

Bernard Allaouchiche, MD, PhD\*, Richard Debon, MD\*, Joëlle Goudable, PhD†, Dominique Chassard, MD, PhD\*, and Frédéric Duflo, MD\*

(Anesth Analg 2001;93:981–5)



### Effects of sevoflurane and desflurane on cytokine response during tympanoplasty surgery

G. M. Koksal<sup>1</sup>, C. Sayılgan<sup>1</sup>, G. Gungor<sup>1</sup>, H. Oz<sup>1</sup>, O. Sen<sup>2</sup>, H. Uzun<sup>3</sup> and S. Aydın<sup>3</sup>

Acta Anaesthesiol Scand 2005; **49**: 835–839



### Effects of propofol and desflurane anaesthesia on the alveolar inflammatory response to one-lung ventilation<sup>†</sup>

T. Schilling<sup>1\*</sup>, A. Kozian<sup>1</sup>, M. Kretzschmar<sup>1</sup>, C. Huth<sup>2</sup>, T. Welte<sup>3</sup>, F. Bühling<sup>4</sup>, G. Hedenstierna<sup>5</sup> and T. Hachenberg<sup>1</sup>

*British Journal of Anaesthesia* **99 (3):** 368–75 (2007)

Methods Sixty adult patients undergoing thoracic surgery were randomly allocated to receive propofol (n • 30) or sevoflurane than in the propofol group. (n • 30) anaesthesia. Blood samples and bronchoscopic BAL specimens were evaluated for oxidative activity measurements: Conclusion Sevoflurane seemed to induce a local and systemic oxidative stress, whereas propofol is more likely to have malondialdehyde, glutathione peroxidase and superoxide dismutase. Also BAL specimens were evaluated for numbers of cells, albumin concentrations, proinflammatory cytokines thoracic surgery. (tumour necrosis factor-a, interleukin-8) and proteinases Fur I Anaesthesial 2010-27-566-571 (polymorphonuclear elastase). Results We found a significant decrease for malondialdehyde Keywords: oxidative stress, propofol, sevoflurane, thoracic surgery

and higher values of glutathione peroxidase measurements in the plasma and BAL during propofol anaesthesia. Significantly

### Introduction

Previous experimental and clinical studies on mechanical ventilation<sup>1,2</sup> showed a progressive alteration in pulmonary immune function during anaesthesia and surgery.

Pulmonary infection is a major factor of postoperative morbidity and mortality.3 Although various factors are implicated, the type and duration of anaesthesia can alter the alveolar macrophages that are considered as the first line of pulmonary defence. 4 Previous studies on animals press the cytotoxic or phagocytosis response of alveolar macrophages.<sup>5</sup> Moreover, inhalation of volatile anaes-thetics during mechanical ventilation can augment gene expression of proinflammatory cytokines in the pulmon inflammatory reaction in alveolar macrophages.

release of inflammatory mediators and free radicals has been clearly demonstrated in generalized inflamma ddition, airway inflammation appears to play a central pathophysiological role in patients with asthma, adult

From the Department of Anaesthesiology, Minouliya Faculty of Medicine, Minouliya University, Damanhour, Beheira, Egypt Correspondence to Khaled Abou-Elenain, PhD, Minouflya Faculty of Medicine, Minouflya University, Egypt 8 Fawzy st., via Elmagreezy st., Damanhour, Beheira,

Sevofluran

Sevoflurane group (n · 30)

Egypt Tel: +20 123436409; fax: +20 34277051; e-mail: kh69193@yahoo.com 0265-0215 • 2010 Copyright European Society of Anaesthesiology

CVP, central venous pressure: HR, heart rate: MAP, mean arterial pre paCO<sub>2</sub>, arterial carbon dioxide terraion; paO<sub>2</sub>, arterial oxygen tension; arterial oxygen saturation. Data are expressed as mean • SD with 95% confi

altered statistically over time or between different expo-

centrations as well as IL8. TNF and PMN elastase

Propofol group (n - 30)

0.25 - 0.01 0.07 - 0.02 -0.06 - 0.01 -

226 - 24 280 - 27 -278 - 26

Table 3 Plasma and alveolar concentrations of malondialde glutathione peroxidase and superoxide dismutase in the two

HR (beats per miri)
30 min after induction
End of surgery
2 h after surgery
MAP (invalvig)
30 min after induction
End of surgery
2 h after surgery
(2h) after surgery
2 h after surgery
3000 (mmirical)

zh otter surgery
parO<sub>2</sub> (mmiHg)
30min after induction
End of surgery
2h after surgery
parCO<sub>2</sub> (mmiHg)
30min after induction
End of surgery
2h after surgery
2h after surgery

higher levels of malondialdehyde and lower concentrations of glutathione peroxidase in plasma and BAL were found during offurana anaesthesia. Sunerovide dismutase showed no significant changes during exposure to either anaesthetic.

antioxidant properties. Sevoflurane appears to cause a greater

intrapulmonary proinflammatory response than propofol during

spiratory distress syndrome and chronic obstructive pulmonary disease wherein an increased oxidative stress has been shown in the bronchoalveolar lavage (BAL) fluid

The objective of this prospective, randomized, blinded

clinical study was to evaluate evidence of oxidative stress

in the blood and BAL fluid of patients exposed to either propofol or sevoflurane anaesthesia during thoracic

surgery and to analyse the pulmonary immune function

The present study was carried out in the intensive care unit at Minoufiya University Hospital after written

informed consent was obtained from all patients and institutional review board approval was obtained.

logists (ASA) status II or III and normal lung function

undergoing elective open thoracic surgery using one-lung ventilation (OLV), were included in the study.

Exclusion criteria were persistent tobacco abuse or a

nistory of treatment with immunosuppressant drugs within

elevant obstructive or restrictive lung diseases (vita

capacity or forced expiratory volume in 1s (FEV1) <50% of the predicted values], pulmonary hypertension [mean pulmonary artery pressure (MPAP) >30 mmHg]

DOI:10.1097/FJA.0b013e3283392c1d

Received 15 January 2010 Revised 21 February 2010 Accepted 26 February 2010

In both groups, intraalveolar cell numbers, albumin concentrations as well as interleukin-8, tumour necrosis factor II patients were premedicated with diazepam 0.15 mg kg given orally 2 h before anaesthesia. and polymorphonuclear elastase concentrations increased over time. However, they were significantly higher in the sevoflurane

ence of pulmonary or systemic infections (clinicall

Preoperative screening of all patients was done by obtain-

defined or elevated C-reactive protein levels, leuc

body temperature >37.8C) were also excluded

Refore the operation a thoracic enidural catheter was Before the operation, a thoracic epidural catheter was inserted [T4/5 to T6/7] and the position verified with a test dose consisting of 3ml of bupivacaine 0.5% with adrenaline, 5 mg mi<sup>-1</sup>. Epidural analgesia was started before surgical incision with 1 0ml reprivacaine 0.2% and fentanyl 3 mg mi<sup>-1</sup>, and was maintained for 2–4 days. theter and a central venous catheter in the internal ugular vein (B. Braun, Germany) were inserted in

ntraoperative fluid therapy included crystalloid and olloid infusion, 7 ml kg<sup>-1</sup> h<sup>-1</sup> and 5 ml kg<sup>-1</sup>, respectively.

The patients were randomly allocated to receive propofol (n - 30) or sevoflurane (n - 30) anaesthesia by random numbers (Microsoft EXCEL). Randomization was done centrally by an independent statistician to ensure appro-priate concealment. Allocation of study management was concealed from patients, primary investigators and all coinvestigators until the release of the final statistical analysis

of cls-atracurium 0.1 mg kg<sup>-1</sup>. Anaesthesia was main-tained with a continuous infusion of propofol 6– 8 mg kg<sup>-1</sup> h<sup>-1</sup> and cls-atracurium 2 mg kg<sup>-1</sup> min<sup>-1</sup>. In the sevoflurane group, anaesthesia was induced as above, but maintained with sevoflurane 1 minimum alveolar concentration (MAC) and cls-atracurium 2 mg kg<sup>-1</sup> min<sup>-1</sup>. A left-sided or right-sided double-lumen endobron-chial tube (DLT, Broncho-Cathw 39 or 41 Ch.; Mal-linckrodt Medical Ltd, Athlone, Ireland) was inserted of 0.50 in air, positive end expiratory pressure (PEEP) cmH<sub>2</sub>O and the respiratory rate was adjusted to main-in an end-tidal normocapnia at baseline values (35– 45 mmHg). A tidal volume of 10 ml kg<sup>1</sup> and FIO<sub>2</sub> of 0.8-1.0 was used during OLV to achieve a paO<sub>2</sub> of 80 mmHg. and the respiratory rate was adjusted to maintain a paCO<sub>2</sub> of 35-45 mmHg. PEEP was set to zero during OLV and

nechanisms expressed by larger concentrations of free

ations of GPX, and higher concentrations of GSH

nofal first inhibits GPX activity to augment the pool of

ioxidant defences that protect the tissue against

sible oxidative stress and then enhances GPX activity

mic and alveolar SOD activity was not altered in our

Sova at al 20 studied the antioxidant status and the

It must be emphasized that interpretation of the changes

in local or plasma antioxidant capacity becomes compli-cated by the different methods used in detecting these

changes. The interpretation also depends upon the con-ditions under which the antioxidant capacity is deter-mined because the measurement reflects outcomes in a dynamic system. An increased antioxidant capacity may

not necessarily be a desirable condition if it reflects a esponse to increased oxidative stress. Similarly, a decrease in antioxidant capacity may not necessarily be

an undesirable condition if the measurement reflects

of measurements will be necessary to adequately assess

offects, including the limitation of injury and spread of infection, and the provision of a suitable environment for issue healing and repair.<sup>21</sup> Although acute and massive

tissue heating and repair," Although acute and massive secretion of IL-1 and TNF-a causes respiratory failure, IL-1 and TNF-a potentiate immune resistance in wound healing and bacterial infection when secreted in a con-trolled quantity, <sup>22,29</sup> Massive neutrophil influx induced

Proinflammatory cytokines have local and systematical

ased production of reactive species. Because of these complications, no single measurement of anti-oxidant status is going to be sufficient, but a 'battery' Sevoflurane concentrations, fresh gas flow and air asured at the proximal end of the e

Oxidative stress during exposure to anaesthetics 567

Open thoracic surgical procedures were performed for

ns were performed through a stand

standard single-lumen tubes for postoperative ven

itored for at least 24 h. Fluids and blood transfusions were given as required to maintain central venous pressure (CVP) of at least 4 cmH<sub>2</sub>O, urine output

pressure (MAP), CVP and arterial blood gases] were recorded continuously and evaluated at three stages: 30 min after induction, end of surgery and 2 h after surgery

bronchoscope (Olympus models BF-P40, BF3-C40) through the endobronchial tube. The tip of the bronchoscope was brought into wedge position in a segmental bronchus of the left-sided lower lobe or the right middle took. A directers, randomy crosen segment was lavaged each time. For BAL, 80 ml of 0.9% physiological saline solution was sequentially instilled and suctioned in 20 ml portions, 50.-6%, of which was recovered. The volume of return of lavage fluid did not differ between patient groups. BAL was performed on three occasions; immedi-ately after intubation, at the end of the surgical prosetly acted industries, at the field of the surgical pro-cedures and 2h postoperatively. The fluid was then withdrawn by hand suction into the infusion syringe and filtered through sterile gauze filters. In addition, serial blood samples were taken through the CVP

(1500 rpm, 10 min) and supernatants were immediate red at • 808C until measurements were carried out alondialdehyde (MDA), glutathione peroxidase acti-

570 Abou-Elenair Oxidative stress during exposure to anaesthetics 569

Table 4 Intraalveolar cell numbers, albumin concentral interleukin-8, tumour necrosis factor and polymorphon

roup	elastase concentrations		
_	Variables	Propofol group (n= 30)	Sevoflurane group (n = 30)
		0	į 1.1j
	Calls (- 10 <sup>6</sup> mi <sup>-1</sup> )		
	After induction	0.07 - 0.06	0.08 - 0.07
	End of surgery	0.12- 0.1-	0.17 - 0.06-
	2 h after surgery	0.13 - 0.1 -	0.19 - 0.06°,M
	Alveolar macrophages	rie rie	
	After induction	43.4 - 18.2	42.2 - 19.4
	End of surgery	38.7 - 20.1	36.1 - 18.4
	2 h after surgery	41.1 - 22.4	39.2 - 23.3
	Alveolar granulocytos (		
	After induction	39.4 - 8.7	39.7 - 9.5
	End of surgery	46.2 - 13.1	51.6 - 15.6
	2 h after surgery	54.4 - 14.2	57.8 - 17.1
	Alveolar lymphocytes (	10	
	After induction	17.2 - 7.2	18.1 - 8.0
	End of surgery	15.1 - 7.4	12.3 - 6.8
	2 h after suppery	4.5 - 3.6	3.0 - 6.9
	Albumin (ng mi <sup>-1</sup> )		
	After induction	21.1 - 25	22.0 - 25
	End of surgery	47- 15-M	97.4 - 73 <sup>-M</sup>
	2 h after surpery	67 - 34 · M	116.4 - 83°.H
	IL-8 (ngml <sup>-1</sup> )		
	After induction	0.39 - 0.7	0.40 - 0.7
	End of surgery	0.69 - 0.8 -	1.49 - 0.4° M
	2 h after suppery	0.70 - 0.3 -	3.69 - 0.4° M
	TNF (pant: 1)		
,	After induction	3.2 - 1.3	3.2 - 1.9
	End of surgery	4.9 - 1.8 -	49.8 - 6.1 M
	2 h after suppery	14.8 - 8.1 -	59.5 - 13.8°M
	Elastase (mgmf 1)	140-01	30.5 - 15.0
)	After industrial		

concentrations increased over time. However, the increase was significantly greater in the sevoflurane group

Oxidative stress results from an imbalance between radical-generating and radical-scavenging systems lead-ing to cell membrane impairment or DNA damage.<sup>14</sup>

MDA is a reflection of lipid peroxidation, whereas SOD and GPX are important antioxidant defences that scavenge free radicals such as superoxide  $(O_2^*)$ , hydroxyl  $(OH^*)$  and hydrogen peroxide  $(H_2O_2)$ .<sup>14,15</sup>

The results of the present study show that patients The results of the present subtry show that patients exposed to propofel have lower circulating and alveolar levels of MDA and reduced GPX consumption, whereas patients exposed to sevoflurane have increased MDA concentrations and enhanced GPX consumption in both serum and alveoli.

systemic oxidative stress during exposure to sevoflurane. Moreover, anaesthesia conducted with propofol reduced oxidative stress and enhanced antioxidant defence

European Journal of Anaesthesiology 2010, Vol 27 No 6

naesthesia, mechanical ventilation and surgery all inde-endently initiate the inflammatory response in alveola-acrophages. <sup>1,28</sup> However, there is no general agreement sout the effects of anaesthetics on proinflammatory

tioxidant, mimicking free radical scavenging pro-rties. It resembles the endogenous antioxidant a-toco-erol. <sup>36,17</sup> De La Cruz et al. <sup>18,19</sup> found that propofol numbers, albumin concentrations as well as IL-8. TNF

> opofol. These findings are in agreement with those Takala and Kotani. Takala et al. 26 showed that sevo expression of inflammatory mediators in the opposite direction. Cho et al... 27 reported that sevoflurane attenuates systemic and pulmonary inflammatory responses induced by cardiopulmonary bypass. Suter et al. 28 demonstrates of the control of t strated that sevoflurare pretreatment decreased the production of inflammatory mediators in rat alveolar epithelial cells in lipopolysaccharide-induced injury. Giraud et al. <sup>29</sup> showed that volatile anaesthetics reduce pulmonary epithelial cell secretion of inflammatory cyto-kines in primary culture. A possible explanation of these contradictory results might be the differences in experimental set-ups, the use of several volatile anaesthetics the concentration of the volatile anaesthetic, the time of exposure, and different patient populations and laboratory techniques. In addition, the interpretation of cytokine concentrations in BAL fluids is difficult, because an unknown amount of cytokines remains within the cells.
> Evaluation of secreted cytokine concentrations is limited owing to the lack of established dilution markers and of a reliable method for estimating the volume of the epi-thelial lining fluid. In addition, the integrity of the distal airway may be seriously deranged during BAL. Although volatile anaesthetics are delivered through the lung and may cause airway irritation, there is only limited infor-mation about their effect on different lung cells.

localized ones (as bronchial asthma, chronic obstru

SPX catalyses the oxidation of glutathione (GSH) by cumene hydroperoxide. In the presence of GSH reduc-tage and reduced nicotinamide adenine dinucleotide ate, the oxidized GSH is converted to the re that a concomitant oxidation of reduced ni nide adenine dinucleotide phosphate to nicotinamide

kidation of pyrogallol according to Marklund and Mark lund, <sup>13</sup> One unit of SOD activity is defined as the amou of the enzyme required to inhibit the rate of pyrogali autooxidation by 50%. GPX and SOD activity results a pressed as units per gram of haemoglobin in blood

In the BAL fluid, numbers of cells, albumin concentrations, roinflammatory cytokines [interleukin-8 (IL-8), tumour ecrosis factor-a (TNF-a)] and proteinases [polymorphonuclear (PMN) elastase] were determined.

Numbers of alveolar cells were determined by electronic cell counting using a Coulter Counter D Industrial model (Coulter Electronics, Harpendon, Hertfordshire, UK).

burnin concentrations were estimated by nephe-metry (BN 2000; Dade/Behring, Liederbach, Germany).

Concentrations of II A in the BAI fluids were determined by commercially available quantitative sandwich enzyme immunoassays (Quantikine; R&D Systems Ltd, Abingdon, UK). TNF-a and PMN cell elastase immunoassays were provided by Immunotech, France, and Milenia Biotech, Germany, respectively. Protein concen-trations were measured by an assay for the colorimetric detection and quantification of total protein (Micro BCA Protein Assay Reagent Kit; Pierce, Rockford, Illinois, USA). All samples from one patient were analysed in the same assay run. The samples were measured in

duplicate and the assays were performed according to the manufacturer's instructions. The optical density of the samples was determined by a microplate reader (Saffre; Tecan Ltd, Salzburg, Austria) and analysed using the Safire microplate reader software by interpolation from standard curves. The sensitivities of the test kits were as follows: IL-8, 3.5pgml<sup>-1</sup>; TNF-a, 5pgml<sup>-</sup> PMN elastase, 3 ngml<sup>-1</sup> and protein, 0.5mgml<sup>-1</sup>. Albu min concentrations were estimated by a nephelometer (BN 2000: Dade/Behring).

### Statistical analysis

All data were expressed as the mean with the confidence interval. Demographic and clinical data compared using the Kruskal–Wallis statistic or the F man statistic when appropriate. The blood and the BAL oxidative stress status were evaluated in all groups using two-way repeated-measures analysis of variance. When statistical significance was established (P < 0.05), Bonfer-

The studied groups were comparable regarding patients' characteristics and surgical data (Table 1).

emodynamic and ventilation data did not differ between the groups (Table 2).

Both plasma and alveolar MDA excretion showed a significant decrease during exposure to propofol, though it increased significantly during exposure to sevoflurane

Both blood cell GPX (systemic antioxidant) and alveolar GPX levels showed a significant increase during exposure to propofol, though they were significantly diminished during exposure to sevoflurane (Table 3).

Variables	Propofol group (n = 30)	Sevoflurane group (n - 30
Age (wars)	62 (40-72)	61 (40-69)
Sex (M/F)	17/13	18/12
Weight (kg)	76 (52-112)	76 (63-113)
Height (cm)	171 (152-195)	170 (151-193)
Former smokers	22	20
Preoperative FEV1 (% predicted)	79 (62-92)	78 (60-90)
Preoperative FVC (% predicted)	92 (78-100)	92 (76-100)
Preoperative paO <sub>2</sub> (mmHg)	74.5 (64-86.5)	75.1 (63-87.1)
Preoperative paCO <sub>2</sub> (mmHg)	37.5 (33.7-44.2)	37.9 (32.7-44.4)
Right-sided thoracotomy	14	15
Left-sided thoracotomy	16	16
.obectomy/pneumonectomy	25	26
Atypical pulmonary resection	5	4
Anaesthesia time (min)	144 (79-195)	142 (74-198)
Operative time (min)	134 (65-185)	132 (68-183)
OLV duration (min)	71 (49-112)	72 (45-113)
Fransfused units of blood <sup>a</sup> /patients	14/8	13/7

Data are given as median (range) or numbers. FEV1, forced expiratory volume in 1 s; FVC, for temsion; paO<sub>1</sub>, arterial cryoen tension. \*Leucocrite-depleted entirocrite concentrates.

European Journal of Anaesthesiology 2010, Vol 27 No 6

Oxidative stress during exposure to anaesthetics 571

Richard MJ, Portal B, Meo J, et al. Malondialdehyde kit evaluated for determining plasma and lipoprotein fractions that react with thiobarbitas

American of eythocyte platefriene perodose. J Lab Clin Med 1004 Markhard S. Mathand G. Inschement of the superodo anion radical in the autosidation of pyrogatel and a comministic many for superodo dismutas Eur J Blochem 1974; 47:469 –474.
Herninder-Sawedra D. McCord M. Evolution and five radicals. Importance of adulties stress in human pathology. Rev Med Inst Mex

remittation observed or success and a remaind and new features.

Seques 50: 2007; 6:477–484.

Kozan M. Hashimstot H. Sreafer Dt, et al. Expression of genes for profilamentory cyclokies in advect mercephages desiring propolel an inofficerae annichmie. Amenth Analy 1990; 89:1260–1256.

Margle PC, Myers DC, Darlow ML. et al. The anticolatest potential or propole (2:6-disopropighenool), 8r J. Aneesth 1992; 69:613–618.

Missacchio E, Risalot V, Saucchi M. et al. Arthesisched action of propolel Missacchio E, Risalot V, Saucchi M. et al. Arthesisched action of propole

iver microsomes, mitochondria and brain synaptosomes in the ra Pharmacol Toxicol 1991: 59:75–77.

De La Cruz JP, Sedeno G, Carmona JA, Sanchez de la Cuesta F. The invitre effects of propofol on tissular oxidative stress in the rat. Anesth Analg 1998: 87:1141—1146.

age of sevoflurane over currently available a etics is that its blood-gas partition coefficient is low, giving rapid recovery from general anaesthesia. However, our results showed that sevoflurane produces a systemic and a local oxidative stress in comparison with propofol that might lead to the preferred use of propofol. The

whom cytokine levels are generally higher, the correct choice of anaesthetic may be critical. Acknowledgement The author helped to design the study, conduct the study, analyse the data and write the article.

This author reported no conflicts of interest. This author has seen the original study data, reviewed the analysis of the data, approved the final article, and is the author responsible

Minouflya University is funding the research

Kotarii K, Lin CY. Wang JS, et al. Less of alveolar macrophages during anesthesia and operation in humans. Amesh Analg 1995; 81:1255–1262. Frass CM, Buhling F. Tager M, et al. Antioxidant and arriproteese status in peripheral blood and BAI. Baid offer cardopalmonary bypass. Chest 2001;

120/1509—1608. Half JL, Mander J. A methicative analysis of the risk of pulmonary complications after leperatoray. Chest 1991;99:229–2927. Kötzel NJ, Takahashi S, Sessior DI, et al. Volatile anesthetics augment expression of profifermentary cycloleos in rat allocate maccephages during mechanical ventilation. Anesthesiology 1999;91:187–197. Kötzel NJ, Hallandoo H, Sessior RJ, et al. tessopareties modulation of

Kotarii K. Hushlendo H. Sindari D. H. and a Hestoporstrile modulation of wireder sucception function during in Outname and proposition amendment Amendmentiology 1998; 19:1125–1132. Goods HF, Condelly H. Challate EE, et al. Docussed entications status and increased lpid persolation in potents with spops shock and secondary organ dyslanction. Crit Case Med 1995; 25:4664–651. Blatchis 197, Simon HP, Conn CH, et al. Cubitant activity in expland breath of priestric with organized products syndrome. Lancet 1996; 1:11– of priestric with organized products syndrome. Lancet 1996; 1:11–

14. Van Vyer T, Chanez P, Boonsport J, et al. Safety of bronchoalveoler lavage and bronchial biogoise in pasients with authors of variable sevenity. Am Rev Repair Dis 1902; 464:116–121.
121. Well Add 1916. 122.
122. A Safety and Safety and Safety and Safety and Engineering American productional electrics. Am Rev Repair Dis 1903; 140:146–167.
Doblama AMV, Basiel AHR, Repuil AL Regiod branth hydrogen promide is a marker of acute airway inflammation in podiatic patients with softmax. Am Rev Repair Dis 1903; 148:1656–109.

to use va. ear. If some oil. Current oil. Smelt oil. Current (I his note that 100 current (I his note that 100 current (I his note that 100 current (I his note I have I Kooguchi K, Hashimoto S, Kobayashi A, et al. Role of alveolar macrophage in intiation and regulation of inflammation in Pseudomonas aeruginosa preumonia, Infect Immun 1998: 66:3164—3169.

procursola. Infect Immun 1998; 66:3164—3169. Wrigge H. Zinserfing J. Stabler F. and Effects of mechanical verifiation or release of cytokines into systemic circulation in policets with normal period programs of cytokines in systemic circulation in policets with normal period programs. The period of cytokines in period period in Takala RS, Southa RR, Salo MS, et al. Palmonary inflammatory mediator after seedhams and this period mesenthesis in pigs. Acta Anaesthesis Scand 2004; 48:10–45.

Scand 2004: 48:40–45.

Ohe E. Yoon JH. Hong Si, et al. The effects of sevoltranen on systemic and purincensy inflammatory responses after cardioquinomary typess.
J Cardolnorac Visac Annata 2009; 22:639–645.
State C. Spehn CR, Blamenfeld S. et al. The immunomodalstory effect of sevoltrane in motionis-lies and sevoltrane of the sevoltrane in motionis-lies and sevoltrane of the sevoltrane in sevoltrane sevoltrane disease.

2007; 104:638-645. Giraud O, Mollier S, Rolland C, et al. Halogenated anesthetics reduce interleatin-16-induced cytokine secretion by rat alveolar type II cells in primary culture. Amesthesiology 2000; 98:74-81.

by IL-8 is similarly associated with serious pulmonary dysfunction, though moderate levels of neutrophil infiltrates augment defence against bacterial infection.<sup>24</sup> European Journal of Anaesthesiology 2010, Vol 27 No 6

European Journal of Anaesthesiology 2010, Vol 27 No 6



### "Overlap"

Report	https://crosscheck.ithenticate.com/report/47
	the systemic and pulmonary oxidative s. Similarity Inde By: Khaled Abou-Elenain As of: Aug 16, 2010 10:12:10 AM EDT 5,193 words - 115 matches - 38 sources
Mode:	Similarity Report
sources:	
1	723 words / 14% - Internet from Dec 14, 2009 www.anesthesia-analgesia.org
2	627 words / 12% - CrossCheck T. Hachenberg. "Effects of propofol and desflurane anaesthesia on the alveolar inflammatory response to one-lung ventilation", British Journal of Anaesthesia, 06/07/2007
3	203 words / 4% - CrossCheck G. M. Koksal. "Effects of sevoflurane and desflurane on cytokine response during tympanoplasty surgery", Acta Anaesthesiologica Scandinavica, 7/2005
4	136 words / 3% - CrossCheck Thomas Schilling. "The Pulmonary Immune Effects of Mechanical Ventilation in Patients Undergoing Thoracic Surgery", Anesthesia & Analgesia, 10/2005
5	113 words / 2% - CrossCheck Bernard Allaouchiche. "Oxidative Stress Status During Exposure to Propofol, Sevoflurane and Desflurane", Anesthesia & Analgesia, 10/2001

arity Rep	ort https://crosscheck.ithenticate.com/report/473
	considered as the first line of pulmonary defence. 4 Previous studies on animals suggest that exposure to volatile anaesthetics can suppress the cytotoxic or phagocytosis response of alveolar macrophages. 5 Moreover, inhalation of volatile anaesthetics during mechanical ventilation can augment gene expression of proinflammatory cytokines in the pulmonary lavage.  4 Thus, general
ana	aesthesia can impair the immunological defence
	mechanisms while inducing an inflammatory reaction in alveolar macrophages. The release of inflammatory mediators and free radicals has been clearly demonstrated in generalized inflammatory reactions involving the production of leucocytes. 6 In addition, airway inflammation appears to play a central pathophysiological role in patients with asthma, adult
Fro	om the
	Department of Anaesthesiology, Minoufiya Faculty of Medicine, Minoufiya  University,
Un	manhour, Beheira, Egypt Correspondence to Khaled Abou-Elenain, PhD, Minoufiya Faculty of Medicine, Minoufiy iversity, Egypt 8 Fawzy st., via Elmaqreezy st., Damanhour, Beheira, Egypt Tel: +20 123436409; fax: +20 277051; e-mail: kh69193@yahoo.com
	respiratory distress syndrome and chronic obstructive pulmonary disease wherein an increased oxidative stress has been shown in the bronchoalveolar lavage (BAL) fluid and blood. 7–10 The objective of



### A Unique Content Agency - The Key To Your Success

Tailormade solutions for academic studies, research and career

Looking back on ten years of experience and success as a Unique Content Agency, offering ghostwriting and other creative writing services, ghostwriting and other creative writing services, ACAD WRITE today is among the most important protagonists in this field on the international scene, with offices in Germany, Switzerland, Austria, Great Britain, the USA, Canada and Australia.

The number of our clients has been steadily growing, and likewise the number of our experts and authors who apply their skills and knowledge to our clients' needs by offering them various writing services and coaching. They assist private individuals in writing, offering high-quality academic texts to enterprises and institutes, creating reports for companies, NGOs and foundations, and giving the native speaker's final polishing to English articles to be published in international journals.

The service of our Unique Content Agency will convince you

In an ever-changing globalized world we constantly use our growing expertise and experience to upgrade our quality-standards for the benefit of our clients. Are you looking for a competent partner for your project, or for someone who can turn your idea into a concept? Do you need professional feedback on your work? Are you running out of time with a writing job or research, or is your attention needed elsewhere and you are looking for assistance in writing, or other writing-related services? Do you suffer from Writer's Block?

And do you appreciate steadiness, professionalism, discreet but intensive communication, creativity and transparency – not least where the cost is concerned?

Then look no further, for you will find your personal expert at our Unique Content Agency. **ACAD WRITE** – **WE** are committed to **YOUR** success!



### CHATGPT LISTED AS AUTHOR ON RESEARCH PAPERS

Many scientists disapprove of articles crediting the AI tool as a co-author.

By Chris Stokel-Walker

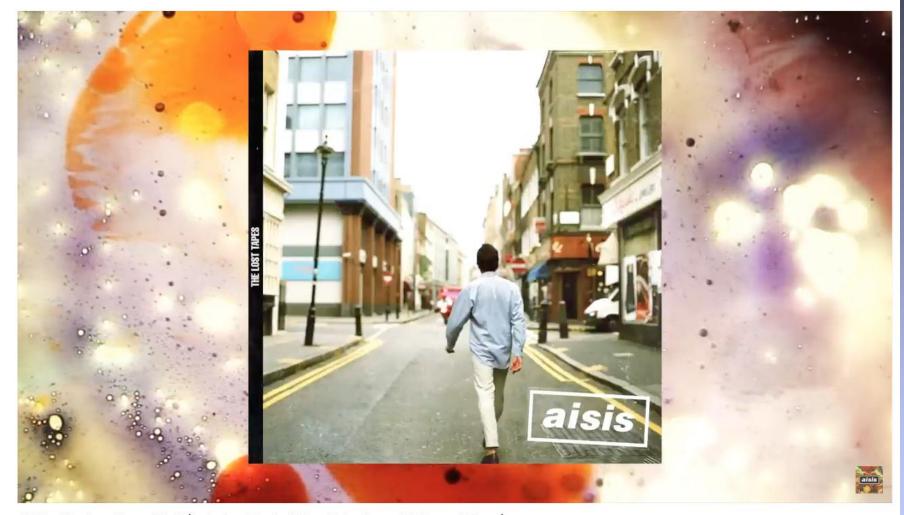
An attribution of authorship carries with it accountability for the work

We would not allow AI to be listed as an author on a paper we published, and use of AI-generated text without proper citation could be considered plagiarism

authors are responsible for the validity and integrity of their work, and should cite any use of LLMs in the acknowledgements section.







AISIS - The Lost Tapes / Vol.1 (In Style of Oasis / Liam Gallagher - AI Mixtape/Album)















### Fabrication ... Définition

- 1. Action de faire, de fabriquer, de confectionner quelque chose : La fabrication de ce gâteau prend du temps.

  Synonymes :
  - confection production
- 2. Action ou manière de fabriquer, de produire quelque chose de ses mains ou de manière industrielle : Défaut de fabrication. Suivre les étapes de la fabrication d'un livre.
- 3. Action de créer, d'inventer quelque chose : La fabrication de fausses nouvelles.
- 4. Action de forger, de modeler une personne pour qu'elle devienne un personnage en vue : Fabrication d'une vedette.



### Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

**BACKGROUND** We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

**METHODS** 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit...

**FINDINGS** Onset of behavioural symptoms was associated, by the parents, with **measles**, **mumps**, **and rubella vaccination**\* in eight of the 12 children, with measles infection in one child, and otitis media in another.

\*MMR = ROR : rougeole, oreillons, rubéole



### Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

**CONCLUSIONS** We have identified a chronic enterocolitis in children that may be related to neuropsychiatric dysfunction. **In most cases, onset of symptoms was after measles, mumps, and rubella immunisation**. Further investigations are needed to examine this syndrome and its possible relation to this vaccine.

Nous avons identifié une entérocolite chronique chez les enfants qui pourrait être liée à un dysfonctionnement neuropsychiatrique. Dans la plupart des cas, les symptômes sont apparus après la vaccination contre la rougeole, les oreillons et la rubéole. Des investigations supplémentaires sont nécessaires pour examiner ce syndrome et sa relation possible avec ce vaccin.

**647 citations (Web of Science®, 21.1.2011)** 



### Retraction—Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Following the judgment of the UK General Medical Council's Fitness to Practise Panel on Jan 28, 2010, it from the published record. has become clear that several elements of the 1998 paper by Wakefield et al1 are incorrect, contrary to the findings of an earlier investigation.2 In particular, the claims in the original paper that children were "consecutively referred" and that investigations were "approved" by the local ethics committee have been

proven to be false. Therefore we fully retract this paper

The Editors of The Lancet The Lancet, London NW1 7BY, UK

- Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998; 351: 637-41.
- Hodgson H. A statement by The Royal Free and University College Medical School and The Royal Free Hampstead NHS Trust. Lancet 2004; 363: 824.

Published Online February 2, 2010

### Early report

### Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

### Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3-10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea Children gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associby the parents, with measles, mumps, and rub vaccination in eight of the 12 children, with meas infection in one child, and otitis media in a children had intestinal abnormalities from lymphoid nodular hyperplasia to a ration. Histology showed patchy chronic inflan in 11 children and reactive ilea perplasia in seven, but no granulomas. Be ioural diso autism (nine), disintegrative focal neurological ab malities and were normal. Abnor al laboratory results the significantly z acid compared with ageraised urinary 03), low haemoglobin in four matched control m IgA in

cation associated gastrointestinal Inter evelopmental regression in a group of which was generally associated possible environmental triggers.

**351**: 637–41 See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell PhD, A P Dhillon MRCPath, S E Davies MRCPath) and the University Departments of Paediatric Gastroenterology

(S H Murch MB, D M Casson MRCP, M Malik MRCP,

M A Thomson FRCP, J A Walker-Smith FRCP,), Child and Adolescent Psychiatry (M Berelowitz FRCPsych), Neurology (P Harvey FRCP), and Radiology (A Valentine FRCR), Royal Free Hospital and School of Medicine, London NW3 2QG, UK

Correspondence to: Dr A J Wakefield

### Introduction

We saw several children who, after a per normality, lost acquired skills, include They all had gastrointestinal abdominal pain, diarrhoea, and eating and, i cases, food intolerance. We cribe clinical fi and gastrointestinal feature of these ch

### Patients and metion

12 children, cons paediatric gastra cerology y of a pervasive developmental abdominal nn, bloating and food symptoms 4 intolerance), were inve ated. All children were admitted to the ed by their parents.

### hical investigations

took histori including details of immunisations and us diseases, and assessed the children. In 11 as obtained by the senior clinician (JW-S). d psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.1 Developmental included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

### Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.2 Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample t test. Urinary creatinine was estimated by routine spectrophotometric

Children were screened for antiendomyseal antibodies and boys were screened for fragile-X if this had not been done



### Wakefield's article linking MMR vaccine and autism was fraudulent

Clear evidence of falsification of data should now close the door on this damaging vaccine scare

Fiona Godlee editor in chief, BMJ, London, UK fgodlee@bmj.com Jane Smith deputy editor, BMJ, London, UK

**Harvey Marcovitch** associate editor, *BMJ*, London, UK

Cite this as: *BMJ* 2011;342:c7452

## HOW THE CASE AGAINST THE MMR VACCINE WAS FIXED

In the first part of a special *BMJ* series, **Brian Deer** exposes the bogus data behind claims that launched a worldwide scare over the measles, mumps, and rubella vaccine, and reveals how the appearance of a link with autism was manufactured at a London medical school

# HOW THE VACCINE CRISIS WAS MEANT TO MAKE MONEY

In the second part of a special *BMJ* series, **Brian Deer** reveals a secret scheme to raise huge sums from a campaign, launched at a London medical school, that claimed links between MMR, autism, and bowel disease

# THE LANCET'S TWO DAYS TO BURY BAD NEWS

In the third part of a special *BMJ* series, **Brian Deer** reveals what happened when he reported misconduct in Andrew Wakefield's MMR research to the medical journal that published it

BMJ | 8 JANUARY 2011 | VOLUME 342

BMJ | 15 JANUARY 2011 | VOLUME 342

BMJ | 22 JANUARY 2011 | VOLUME 342

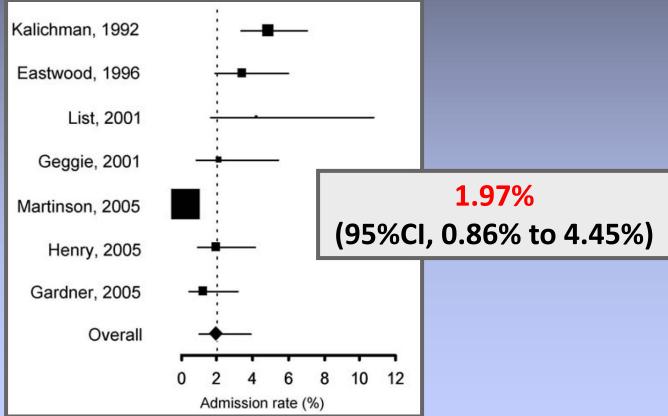
# How common is scientific misconduct?



### How Many Scientists Fabricate and Falsify Research? A Systematic Review and Meta-Analysis of Survey Data

« Have you ever fabricated or falsified research data, or altered or modified results to improve the outcome? »



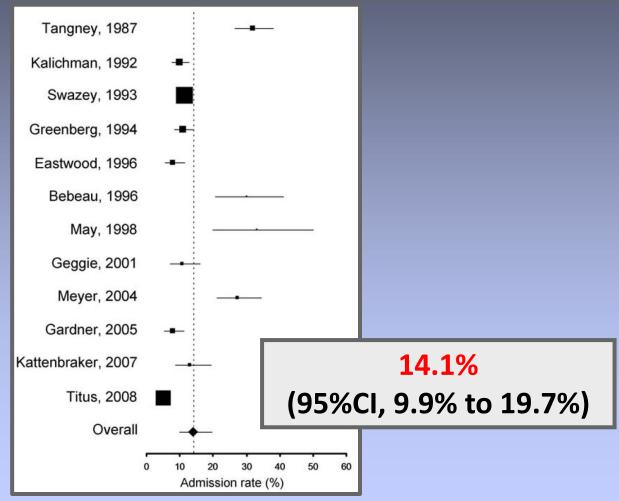


Fanelli D. PLoS One 2009;4:e5738



### « Do you have personal knowledge of a colleague who fabricated or falsified research data, or who altered or modified results to improve the outcome? »





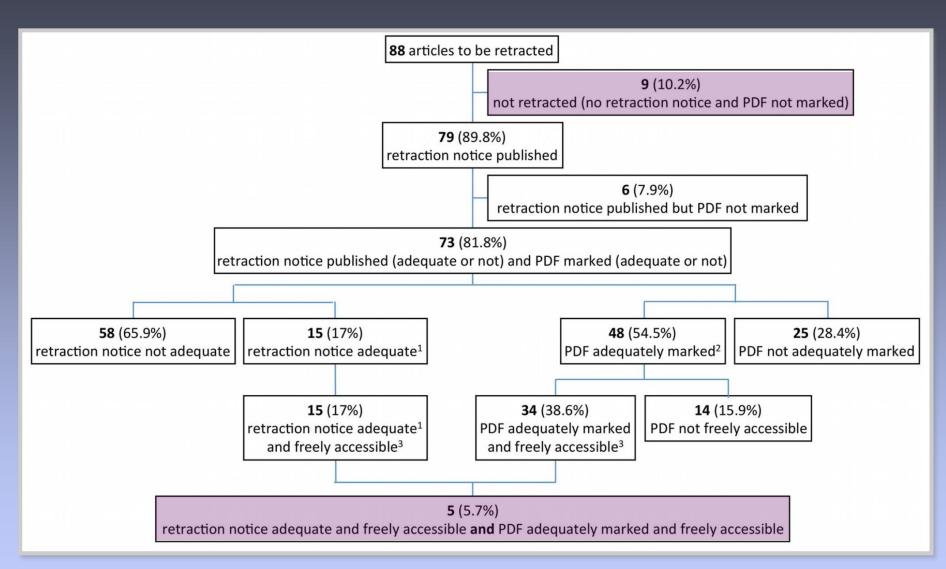
Fanelli D. *PLoS One* 2009;4:e5738

### **How to deal with fraud**

Publication fraud: implications to the individual and to the specialty

- Publication fraud, while not common, transcends the medical literature and is not easily detected.
- Common forms of publication fraud include plagiarism, data fabrication, data falsification and ghostwriting.
- Publication fraud involving even a single article can negatively impact the scientific record.
- Scientific misconduct must be addressed by the relevant institutions, and the scientific record must be corrected.

L'inconduite scientifique doit être traitée par les institutions compétentes et le dossier scientifique doit être corrigé.



Avis de rétractation adéquat et librement accessible, PDF adéquatement marqué et librement accessible

Elia N et al. Plos One 2014; 9: e85846

### Fraud and medical research

(what should be done to prevent it)

### Talk about it

Parlons-en

### Don't trivialize it

Ne pas banaliser

# Le définir - préciser ce qu'il est et ce qu'il n'est pas

Le définir - préciser ce que c'est et ce que ce n'est pas

### PUBLISH OR PERISH — OR BOTH

The liter-

ature of medical science is not unlike the natural environment in which we live. It is a deceptively fragile system that we all need and use. Each of us must take some responsibility for protecting it from abuse, lest it become polluted and unavailable to all.

La littérature médicale n'est pas sans rappeler l'environnement naturel dans lequel nous vivons. Il s'agit d'un système faussement fragile dont nous avons tous besoin et que nous utilisons. Chacun d'entre nous doit prendre la responsabilité de le protéger contre les abus, de peur qu'il ne devienne pollué et inaccessible à tous.