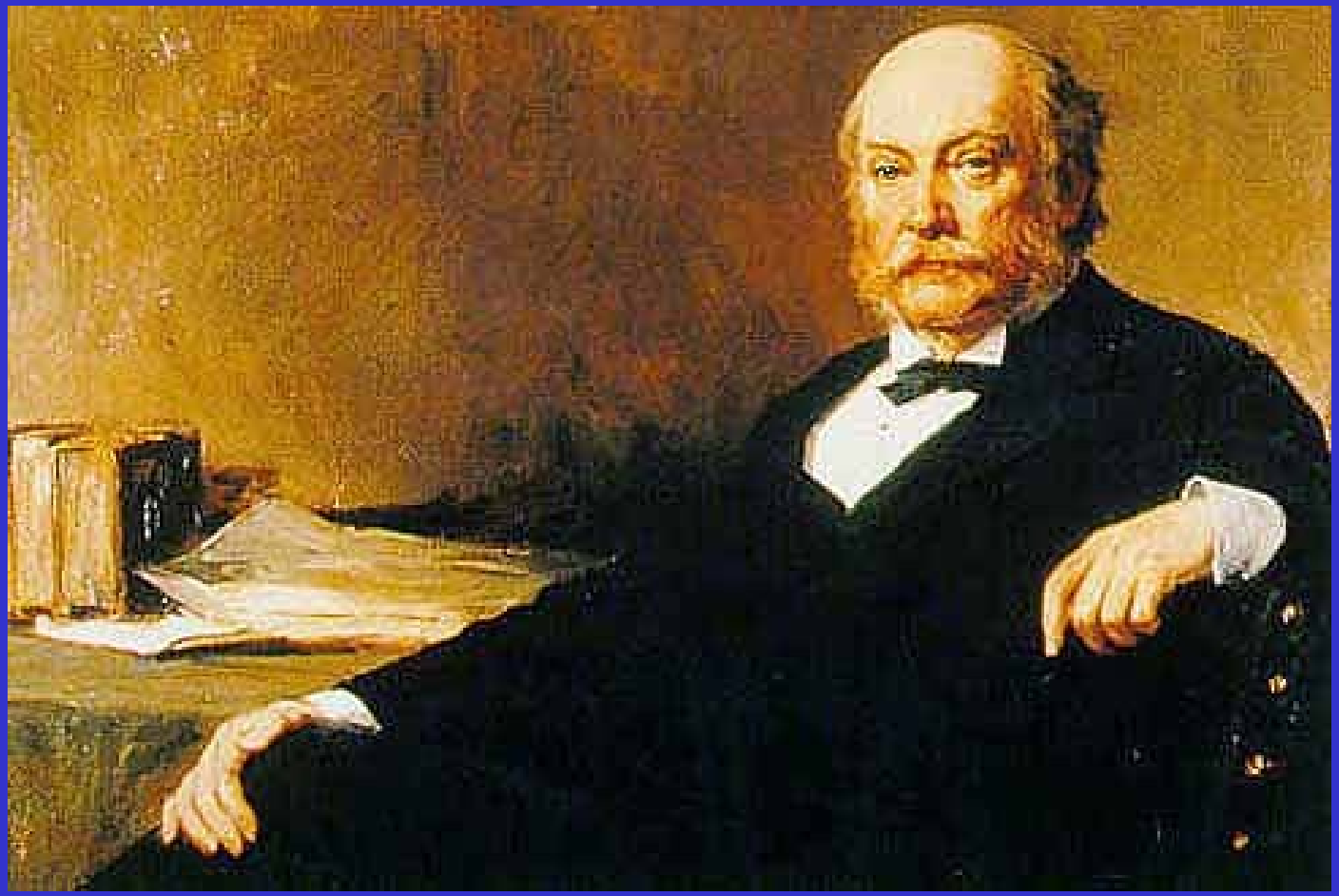
The scandalous failure of scientists to cumulate scientifically

Iain Chalmers

Editor, *James Lind Library*

www.jameslindlibrary.org



Lord Rayleigh, 1842-1919

"One of the very few members of the higher nobility who won fame as an outstanding scientist."

John William Strutt, 3rd Baron Rayleigh

1879-1884
Professor of Experimental Physics, Cambridge

1887-1905
Professor of Natural Philosophy, Royal Institution

1904
Nobel Prize in Physics "for his investigations of the densities of the most important gases and for his discovery of argon in connection with these studies."

REPORT

OF THE

FIFTY-FOURTH MEETING

OF THE

BRITISH ASSOCIATION

FOR THE

ADVANCEMENT OF SCIENCE;

HELD AT

MONTREAL IN AUGUST AND SEPTEMBER 1884.

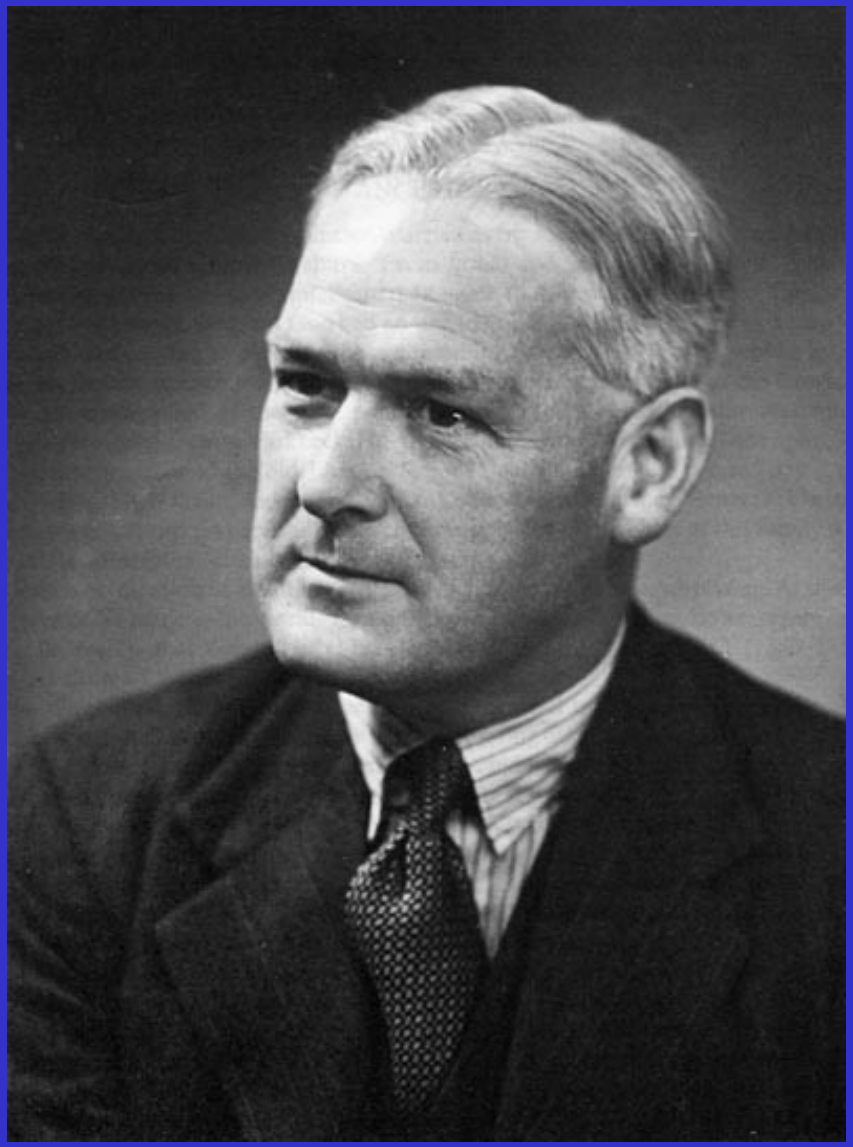
LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1885.

Office of the Association: 22 ALBEMARLE STREET, LONDON, W.

"If, as is sometimes supposed, science consisted in nothing but the laborious accumulation of facts, it would soon come to a standstill, crushed, as it were, under its own weight…

…The work which deserves, but I am afraid does not always receive, the most credit is that in which discovery and explanation go hand in hand, in which not only are new facts presented, but their relation to old ones is pointed out."

Lord Rayleigh, 1884



Austin Bradford Hill
1897-1991

Bradford Hill's 4 questions to ask of researchers when reading their reports of research (1965)

Why did you start?
What did you do?
What answer did you get?
And what does it mean anyway?

Discussion Sections in Reports of Controlled Trials Published in General Medical Journals

Islands in Search of Continents?

Michael Clarke, DPhil; Iain Chalmers, MSc

JAMA. 1998;280:280-282

Classification of Discussion sections in RCT reports published in May issues of *Ann Int Med*, *BMJ*, *JAMA*, *Lancet*, and *N Eng J Med*

	1997 n=26		
First trial addressing the question	1		
Contained an updated systematic review integrating the new results	2		
Discussed a previous review but did not attempt to integrate new results	4		
No apparent systematic attempt to set new results in context of other trials	19		

Discussion Sections in Reports of Controlled Trials Published in General Medical Journals

Mike Clarke, DPhil
Phil Alderson, MBChB
Iain Chalmers, DSc

JAMA. 2002;287:2799-2801

Classification of Discussion sections in RCT reports published in May issues of *Ann Int Med*, *BMJ*, *JAMA*, *Lancet*, and *N Eng J Med*

	1997 n=26	2001 n=33	
First trial addressing the question	1	3	
Contained an updated systematic review integrating the new results	2	0	
Discussed a previous review but did not attempt to integrate new results	4	3	
No apparent systematic attempt to set new results in context of other trials	19	27	

Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report

Mike Clarke, DPhil, UK Cochrane Centre
Sally Hopewell, MSc, UK Cochrane Centre
Iain Chalmers, DSc, James Lind Alliance

Classification of Discussion sections in RCT reports published in May issues of *Ann Int Med*, *BMJ*, *JAMA*, *Lancet*, and *N Eng J Med*

	1997 n=26	2001 n=33	2005 n=18
First trial addressing the question	1	3	3
Contained an updated systematic review integrating the new results	2	0	0
Discussed a previous review but did not attempt to integrate new results	4	3	5
No apparent systematic attempt to set new results in context of other trials	19	27	10

Reports of new research should make clear what contribution the new evidence has made to **the totality of relevant evidence.**

Why should we be expected to subscribe to journals that do not ensure that readers are well served in this respect?

People have suffered and resources have been wasted

because new evidence has not been set in the context of up-to-date, systematic reviews of all other relevant evidence.

The human costs of failing to ensure that new research begins and ends with systematic reviews

"Advice on some life-saving therapies has been delayed for more than a decade, while other treatments have been recommended long after controlled research has shown them to be harmful."

Antman et al. JAMA, 1992

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DR. BENJAMIN SPOCK

BABY AND CHILD CARE

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I think it is preferable to accustom a baby to sleeping on his stomach from the start if he is willing. He may change later when he learns to turn over.

Int. J. Epidemiol. Advance Access published April 20, 2005

Published by Oxford University Press on behalf of the International Epidemiological Association

International Journal of Epidemiology
doi:10.1093/ije/dyi088

Infant sleeping position and the sudden infant death syndrome: systematic review of observational studies and historical review of recommendations from 1940 to 2002

Ruth Gilbert,[1]* Georgia Salanti,[2] Melissa Harden[1] and Sarah See[1,3]

"Advice to put infants to sleep on the front for nearly half a century was contrary to evidence available from 1970 that this was likely to be harmful. Systematic review of preventable risk factors for SIDS from 1970 would have led to earlier recognition of the risks of sleeping on the front and might have prevented over 10 000 infant deaths in the UK and at least 50 000 in Europe, the USA and Australasia."

Ruth Gilbert et al. Int J Epidemiol, 2005

Anti-arrhythmic drugs in myocardial infarction

A 1983 systematic review of 14 randomized controlled trials of anti-arrhythmic drugs in heart attack

"The theoretical potential for a preventive or prophylactic effect of antiarrhythmic drugs …..in the treatment of coronary patients with ventricular arrhythmias has not been realized."

Furberg, 1983

A 1993 systematic review of 51 RCTs of anti-arrhythmic drugs in heart attack involving 23,229 patients

660 deaths in patients allocated drugs
571 deaths in patients allocated to control

89 deaths attributable to drugs

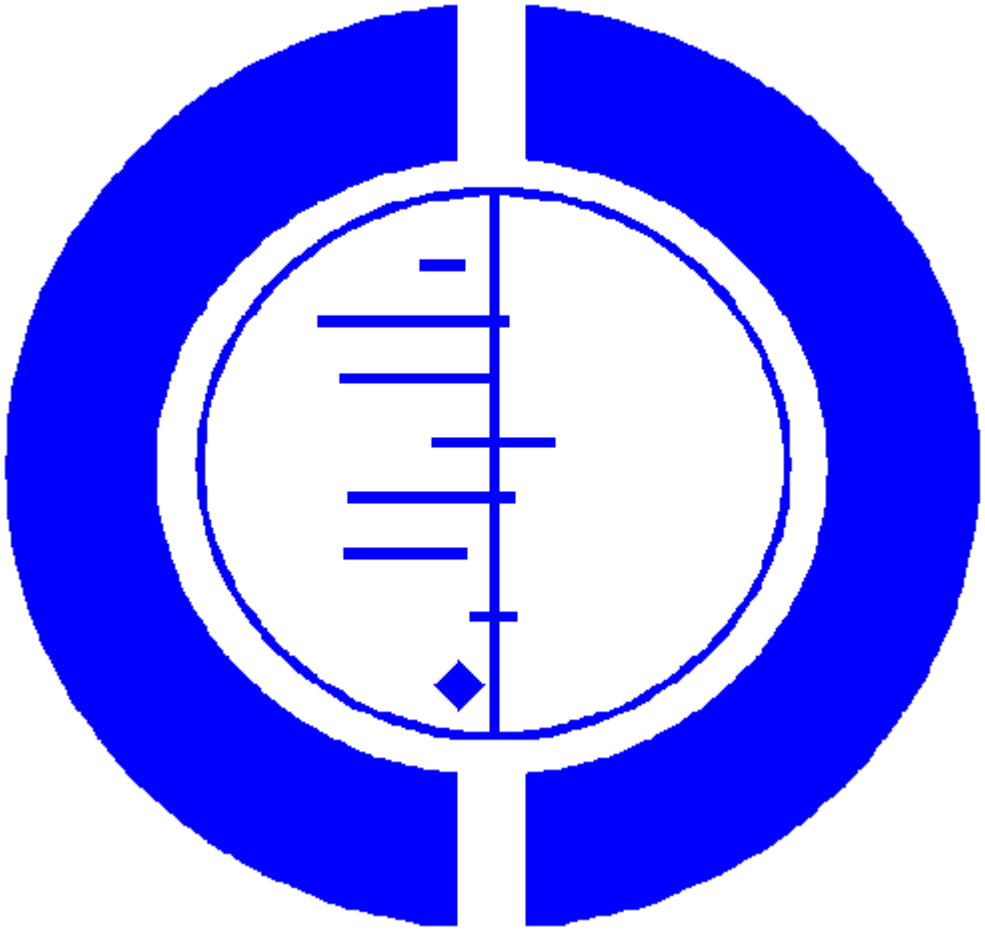
Teo et al. *JAMA* 1993.

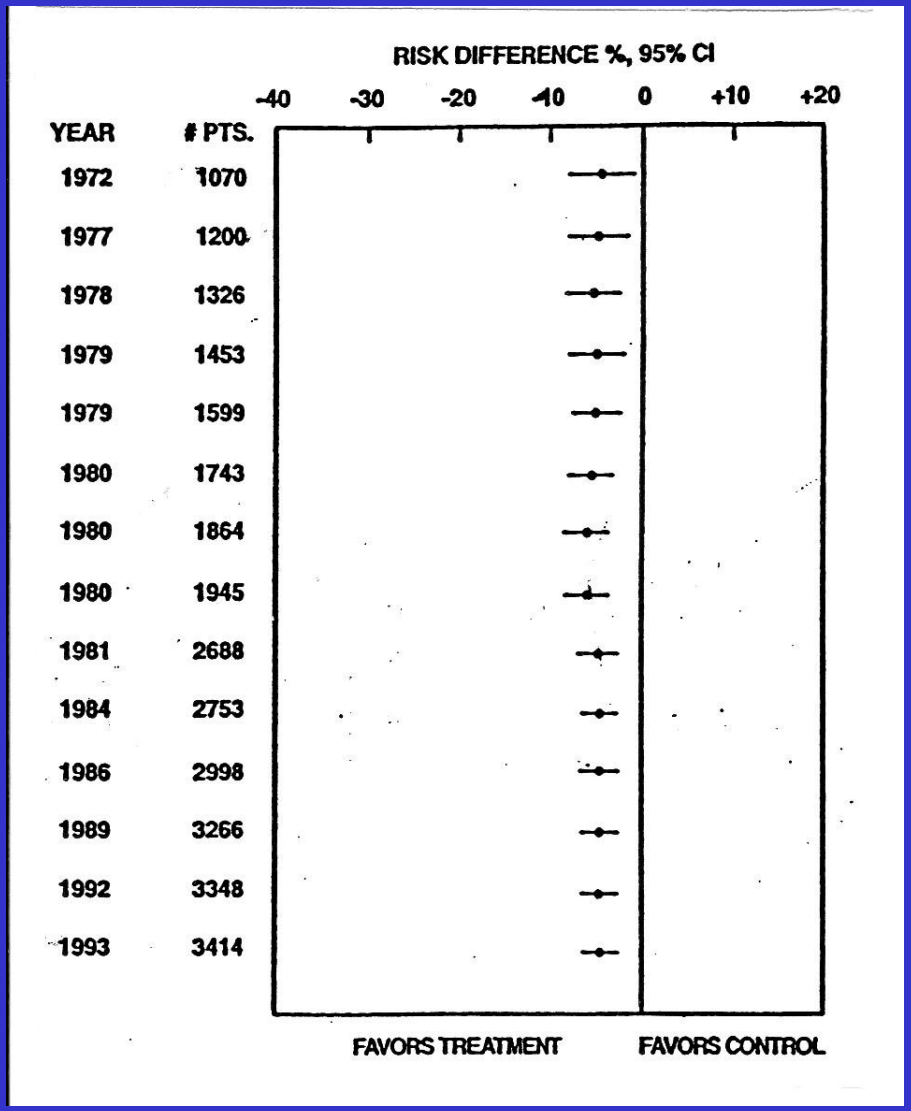
The vast majority of the victims of these drugs were treated outside controlled trials

At the peak of their use in the late 1980s, it has been estimated that these drugs killed as many Americans every year as were killed during the whole of the Vietnam war.

Moore 1995.

If each report of the 51 trials of a class 1 anti-arrhythmic drug had set new results in the context of a systematic review of the results of all previous trials the lethal potential of these drugs could have been recognised a decade earlier.





Preventing complications after premature birth

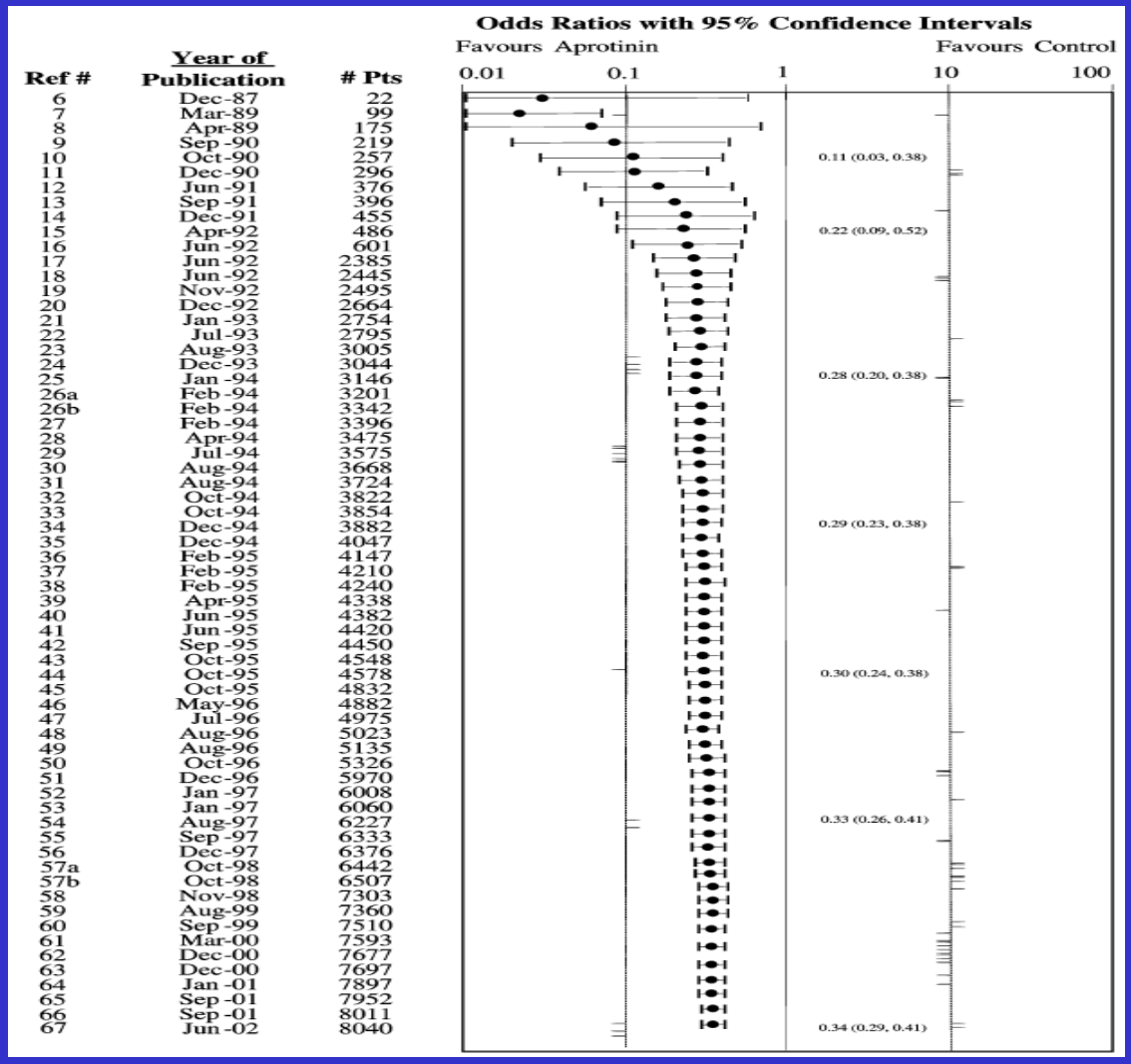
Babies have suffered unnecessarily
and resources have been wasted

Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding?

Dean Fergusson[a,b], *Kathleen Cranley Glass*[b,c], *Brian Hutton*[a] *and Stan Shapiro*[b,c,d]

Clinical Trials 2005; **2**: 218–232

Cumulative estimate of the effect of aprotinin on perioperative blood transfusion, 1987-2002.



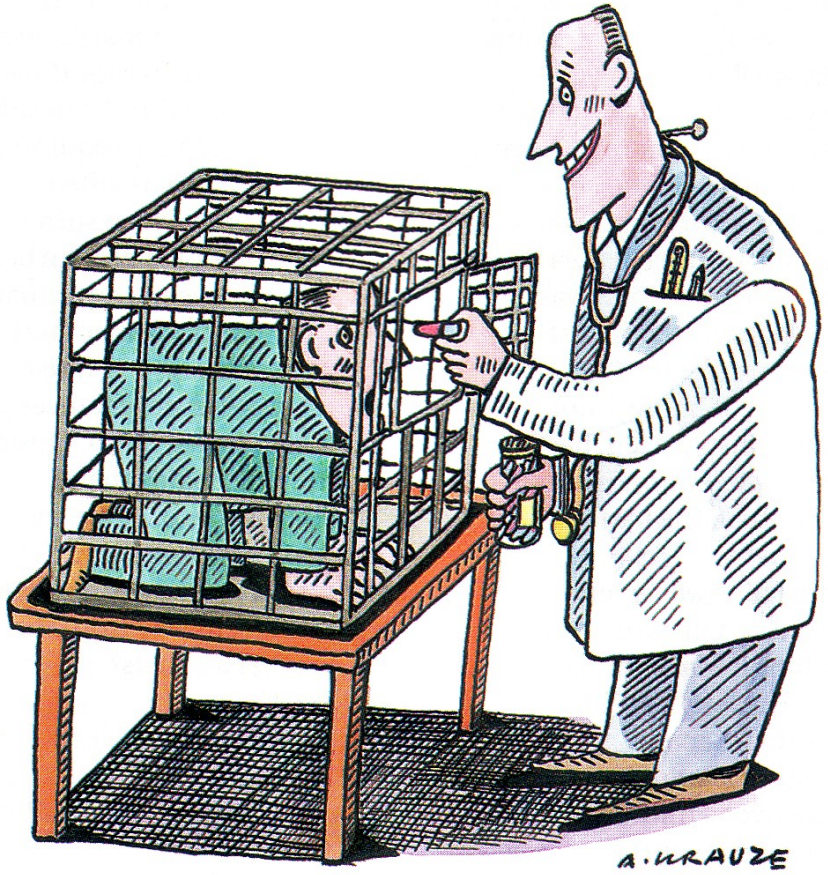
Ref #	Year of Publication	# Pts
6	Dec-87	22
7	Mar-89	99
8	Apr-89	175
9	Sep-90	219
10	Oct-90	257
11	Dec-90	296
12	Jun-91	376
13	Sep-91	396
14	Dec-91	455
15	Apr-92	486
16	Jun-92	601
17	Jun-92	2385
18	Jun-92	2445
19	Nov-92	2495
20	Dec-92	2664
21	Jan-93	2754
22	Jul-93	2795
23	Aug-93	3005
24	Dec-93	3044
25	Jan-94	3146
26a	Feb-94	3201
26b	Feb-94	3342
27	Feb-94	3396
28	Apr-94	3475
29	Jul-94	3575
30	Aug-94	3668
31	Aug-94	3724
32	Oct-94	3822
33	Oct-94	3854
34	Dec-94	3882
35	Dec-94	4047
36	Feb-95	4147
37	Feb-95	4210
38	Feb-95	4240
39	Apr-95	4338
40	Jun-95	4382
41	Jun-95	4420
42	Sep-95	4450
43	Oct-95	4548
44	Oct-95	4578
45	Oct-95	4832
46	May-96	4882
47	Jul-96	4975
48	Aug-96	5023
49	Aug-96	5135
50	Oct-96	5326
51	Dec-96	5970
52	Jan-97	6008
53	Jan-97	6060
54	Aug-97	6227
55	Sep-97	6333
56	Dec-97	6376
57a	Oct-98	6442
57b	Oct-98	6507
58	Nov-98	7303
59	Aug-99	7360
60	Sep-99	7510
61	Mar-00	7593
62	Dec-00	7677
63	Dec-00	7697
64	Jan-01	7897
65	Sep-01	7952
66	Sep-01	8011
67	Jun-02	8040

No way to treat a patient

Tens of thousands of people have been subjected to unnecessary drug trials. **Robert Matthews** says the outrage cannot go on

FEW scandals in science are more chilling than those in which patients have been subjected to risky medical experiments without their knowing it. It's a scenario that seems almost unthinkable in these days of ethics boards, oversight committees and whistle-blowers. Yet new research has lifted the lid on just such a scandal, and one that has been running for decades in many countries. It is now clear that tens of thousands of patients have been subjected to pointless, unethical and potentially lethal medical experiments in hospitals around the world.

The experiments are of the type known as randomised controlled trials (RCTs), which are widely and rightly acknowledged as the acid test of the effectiveness of new therapies. Over the years, RCTs have identified countless life-saving therapies, from new surgical techniques to cancer drugs. Patients who take part are randomly divided



An example of what is needed

A systematic review* revealed uncertainty about whether giving systemic steroids to patients with acute brain injury does more good than harm.

This led to a large, multicentre randomized trial to address the uncertainty, the protocol for which was published.

* Alderson P, Roberts I (1997). Corticosteroids in acute traumatic brain injury: systematic review of randomised controlled trials. *BMJ* 314:1855-9; and *Cochrane Database of Systematic Reviews*.

BMC Emergency Medicine
Volume 1

Research article

The CRASH trial protocol (Corticosteroid randomisation after significant head injury) [ISRCTN74459797]

The CRASH trial management group, on behalf of the CRASH trial collaborators
CRASH Co-ordinating Centre, FREEPOST LON 14211, London, WC1B 3BR, UK

BMC Emergency Medicine 2001 **1:** 1

This article is available from: http://www.biomedcentral.com/1471-227X/1/1

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Accepted	11 Jun 2001
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Outline

Abstract
Background
Study design
Organisation

Abstract

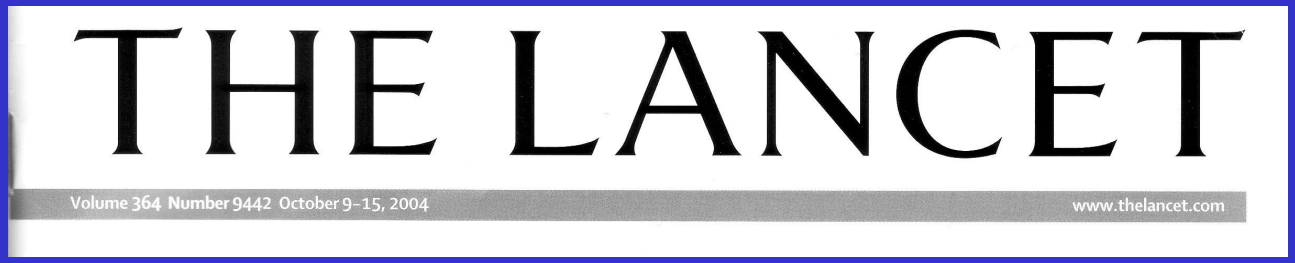
Background

Worldwide, millions of people are treated each year for significant head injury. A substantial proportion die, and many more are disabled. If short term corticosteroid infusion could be reliably shown to reduce these risks by just a few percent then this might affect the treatment of a few hundred thousand patients a year, protecting thousands from death or long term disability.

www.thelancet.com Vol 364 October 9, 2004

A CRASH landing in severe head injury

Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial



"The administration of corticosteroids to brain-injured patients has seemingly caused more than 10 000 deaths during the 1980s and earlier."

The report of the CRASH trial is exemplary because:

- it refers to current uncertainty about the effects of a treatment, manifested in a **systematic review of all the existing evidence,** and in variations in clinical practice
- it refers to **prior publication of the protocol for the study**
- it sets the new results in the context of **an updated systematic review of all the evidence**
- it provides readers with **all the evidence needed for action** to prevent thousands of iatrogenic deaths

Putting clinical trials into context

In recognition that journal editors have a key part to play in ensuring that published research is presented in a way that clearly illustrates why it was necessary and what impact a particular trial has on the existing state of knowledge, *The Lancet* has decided to update its policies in this area. From August, 2005, we will require authors of clinical trials submitted to *The Lancet* to include a clear summary of previous research findings, and to explain how their trial's findings affect this summary. The

Charles Young, Richard Horton
The Lancet, London NW1 7BY, UK

www.thelancet.com Vol 366 July 9, 2005