How can good publication standards influence research integrity

Sabine Kleinert
Vice-Chair of COPE
Senior Executive Editor *The Lancet*

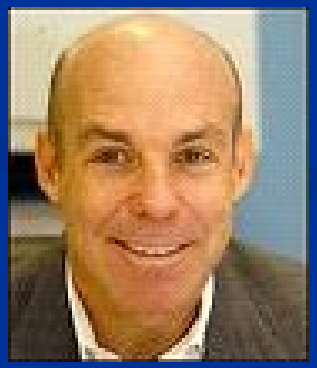
First World Conference on Research Integrity

Lisbon, September 2007

Hwang Woo-Suk,
South Korea, 2005

Hendrik Schön, USA, 2002

Jon Sudbø,
Norway, 2006



Eric T Poehlman,
Canada, 2005

Why does it matter?

- Journal reputation
- Science and medical journals: safeguarding the public record – new research builds on published research
- Medical journals: patients may be harmed or misinformed! (research misconduct = public health issue)

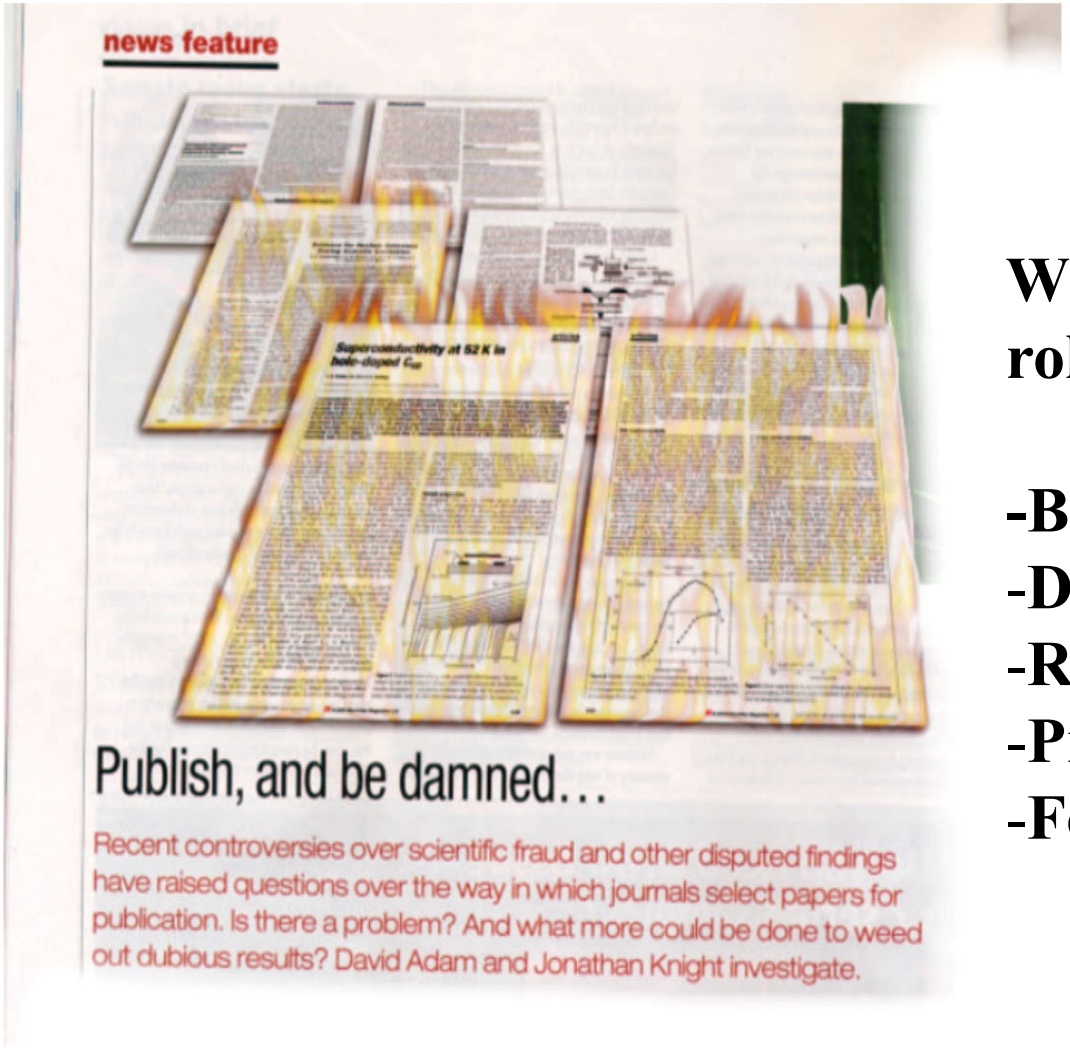
Why does it matter?

Public trust in research

67 retractions in MEDLINE in 2005

97, in 2006

What is worse..... many continue to be cited (or included in systematic reviews) after retraction



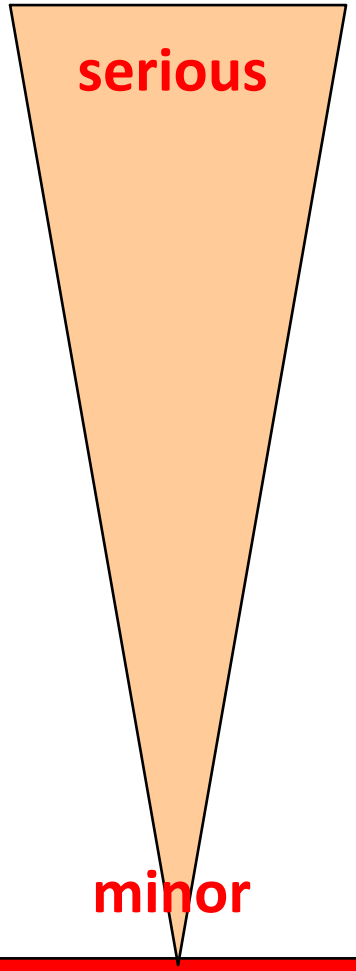
What is journals' and editors' role in:

-Being part of the problem
-Detecting misconduct
-Reacting to misconduct
-Preventing misconduct
-Fostering integrity

- **What is happening to research integrity (pressure to publish)?**
- **Was there anything journals/editors could have done to prevent publication in these high-profile cases?**
- **Should editors have more stringent rules and be less trusting?**
- **Would it actually help?**

Research misconduct - definitions

- **Fabrication of data or cases**
- **Wilful distortion of data (Falsification)**
- **Plagiarism**
- **No ethics approval**
- **Not admitting missing data**
- **Ignoring outliers**
- **No data on side effects**
- **Gift authorship**
- **Redundant publication**
- **Failure to do adequate literature search**



COPE

- started in 1997 as “self-help” group of editors
- 4 meetings a year
- anonymous discussion of suspected misconduct cases
- advice to editors on how to proceed
- cases (and outcomes if available) documented on website
- Guidelines on Good Publication Practice
- annual conferences and reports

Summary of COPE cases 1997- 2006

Year	No of cases	"Evidence of misconduct"	"Probably no misconduct"	Not applicable
1997-2000	108	87	11	10
2001	39	30	9	0
2002	18	14	4	0
2003	22	15	5	2
2004	39	26	8	5
2005	24	21	3	0
2006	35	26	5	4
Total	**285**	**219**	**45**	**21**

Problems/dilemmas discussed (n=285)*

• Duplicate/redundant publication	77
• No ethics approval	34
• Authorship issues	31
• No or inadequate informed consent	30
• Falsification or fabrication	28
• Plagiarism	26
• Unethical research or clinical malpractice	19
• Undeclared conflict of interest	15
• Reviewer misconduct	8
• Editorial misconduct	6
• (miscellaneous	41)

*More than one possible

Of 285 cases,	**172 (60%) pre-publication**
	95 (33%) post-publication

Common difficulties for editors

- **Time consuming!**
- **No reply from authors**
- **No reply from head of institutions**
- **Inadequate investigation by institution**
- **No institution**
- **Managing/analysing raw data**
- **What to do, if alleged misconduct is unproven?**

- since 2001 elected Chair, Vice-Chair, Treasurer, and Council (12 members)
- 2005, Code of Conduct for Editors

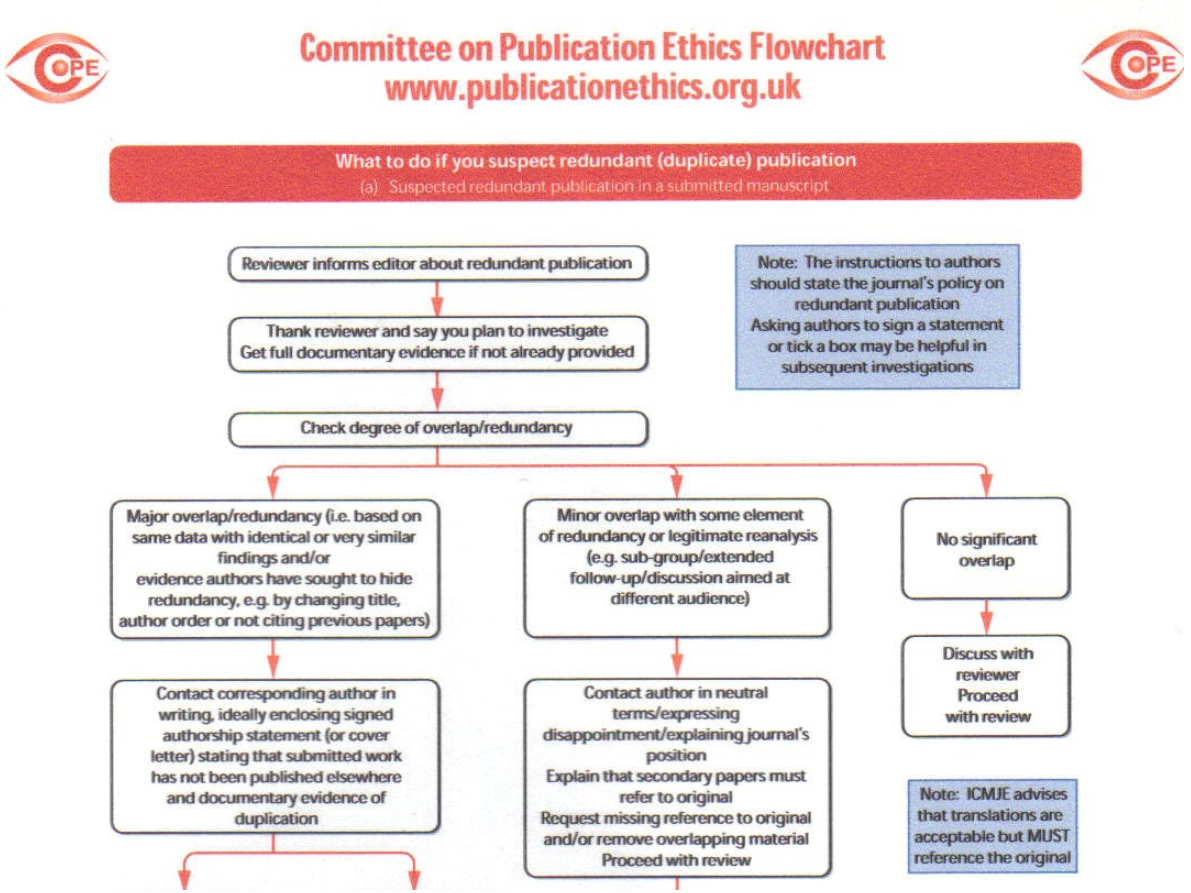
Code of Conduct for Editors

Calls on editors to take seriously their role as guardians of the research record

Sets out minimum standards of good editorial conduct

COPE members must abide by it

2006, COPE flowcharts as practical guides for editors



Committee on Publication Ethics Flowchart
www.publicationethics.org.uk

What to do if you suspect redundant (duplicate) publication
(a) Suspected redundant publication in a submitted manuscript

Reviewer informs editor about redundant publication

Thank reviewer and say you plan to investigate
Get full documentary evidence if not already provided

Check degree of overlap/redundancy

Note: The instructions to authors should state the journal's policy on redundant publication
Asking authors to sign a statement or tick a box may be helpful in subsequent investigations

Major overlap/redundancy (i.e. based on same data with identical or very similar findings and/or evidence authors have sought to hide redundancy, e.g. by changing title, author order or not citing previous papers)

Contact corresponding author in writing, ideally enclosing signed authorship statement (or cover letter) stating that submitted work has not been published elsewhere and documentary evidence of duplication

Minor overlap with some element of redundancy or legitimate reanalysis (e.g. sub-group/extended follow-up/discussion aimed at different audience)

Contact author in neutral terms/expressing disappointment/explaining journal's position
Explain that secondary papers must refer to original
Request missing reference to original and/or remove overlapping material
Proceed with review

No significant overlap

Discuss with reviewer
Proceed with review

Note: ICMJE advises that translations are acceptable but MUST reference the original

COPE future

- Will become a charity (?end of 2007)
- Strengthen role in education
  - Distance-learning for editors (COPE-accredited editors)
  - Workshops for editors
- Improved website
  - Publication ethics blog
  - Letter templates for editors
  - Bulletin/newsletter
- PR strategy

COPE members (August 2007)

282 members (with over 300 journals signed up) from 29 countries:

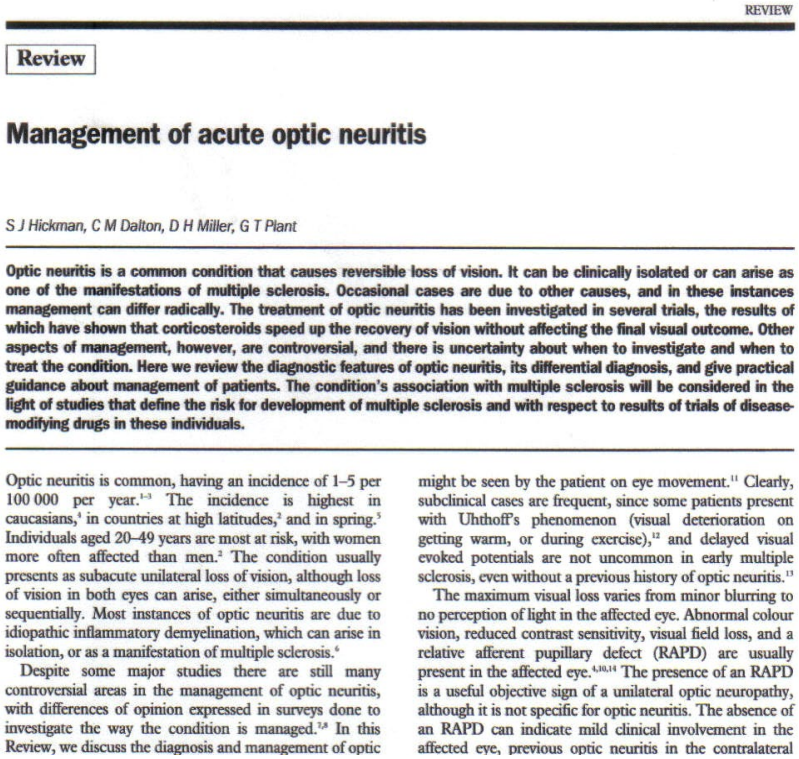
Argentina, Australia, Belgium, Brazil, Canada, China, Croatia, Denmark, Finland, France, Germany, Iceland, India, Iran, Iraq, Ireland, Italy, Japan, New Zealand, Norway, Romania, Serbia, Singapore, Sweden, the Netherlands, Turkey, UK, USA, and Venezuela

Case examples

- **Case 1: Plagiarism in foreign-language journal (+authorship issues)**

- **Case 2: Data fabrication (Jon Sudbø)**

Case 1: plagiarism in foreign language



REVIEW

Review

Management of acute optic neuritis

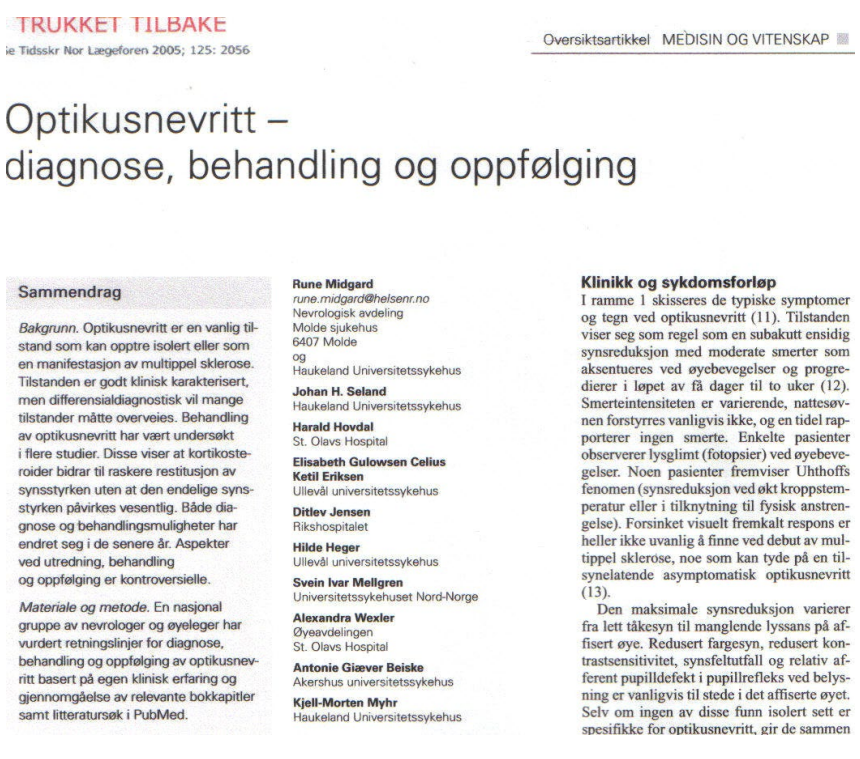
S J Hickman, C M Dalton, D H Miller, G T Plant

Optic neuritis is a common condition that causes reversible loss of vision. It can be clinically isolated or can arise as one of the manifestations of multiple sclerosis. Occasional cases are due to other causes, and in these instances management can differ radically. The treatment of optic neuritis has been investigated in several trials, the results of which have shown that corticosteroids speed up the recovery of vision without affecting the final visual outcome. Other aspects of management, however, are controversial, and there is uncertainty about when to investigate and when to treat the condition. Here we review the diagnostic features of optic neuritis, its differential diagnosis, and give practical guidance about management of patients. The condition's association with multiple sclerosis will be considered in the light of studies that define the risk for development of multiple sclerosis and with respect to results of trials of disease-modifying drugs in these individuals.

Optic neuritis is common, having an incidence of 1–5 per 100 000 per year.[1–3] The incidence is highest in caucasians,[4] in countries at high latitudes,[2] and in spring.[5] Individuals aged 20–49 years are most at risk, with women more often affected than men.[2] The condition usually presents as subacute unilateral loss of vision, although loss of vision in both eyes can arise, either simultaneously or sequentially. Most instances of optic neuritis are due to idiopathic inflammatory demyelination, which can arise in isolation, or as a manifestation of multiple sclerosis.[6]

Despite some major studies there are still many controversial areas in the management of optic neuritis, with differences of opinion expressed in surveys done to investigate the way the condition is managed.[7,8] In this Review, we discuss the diagnosis and management of optic might be seen by the patient on eye movement.[11] Clearly, subclinical cases are frequent, since some patients present with Uhthoff's phenomenon (visual deterioration on getting warm, or during exercise),[12] and delayed visual evoked potentials are not uncommon in early multiple sclerosis, even without a previous history of optic neuritis.[13]

The maximum visual loss varies from minor blurring to no perception of light in the affected eye. Abnormal colour vision, reduced contrast sensitivity, visual field loss, and a relative afferent pupillary defect (RAPD) are usually present in the affected eye.[4,10,14] The presence of an RAPD is a useful objective sign of a unilateral optic neuropathy, although it is not specific for optic neuritis. The absence of an RAPD can indicate mild clinical involvement in the affected eye, previous optic neuritis in the contralateral



TRUKKET TILBAKE

ie Tidsskr Nor Lægeforen 2005; 125: 2056

Oversiktsartikkel MEDISIN OG VITENSKAP

Optikusnevritt – diagnose, behandling og oppfølging

Sammendrag

Bakgrunn. Optikusnevritt er en vanlig tilstand som kan opptre isolert eller som en manifestasjon av multippel sklerose. Tilstanden er godt klinisk karakterisert, men differensialdiagnostisk vil mange tilstander måtte overveies. Behandling av optikusnevritt har vært undersøkt i flere studier. Disse viser at kortikosteroider bidrar til raskere restitusjon av synsstyrken uten at den endelige synsstyrken påvirkes vesentlig. Både diagnose og behandlingsmuligheter har endret seg i de senere år. Aspekter ved utredning, behandling og oppfølging er kontroversielle.

Materiale og metode. En nasjonal gruppe av nevrologer og øyeleger har vurdert retningslinjer for diagnose, behandling og oppfølging av optikusnevritt basert på egen klinisk erfaring og gjennomgåelse av relevante bokkapitler samt litteratursøk i PubMed.

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Haukeland Universitetssykehus

Klinikk og sykdomsforløp

I ramme 1 skisseres de typiske symptomer og tegn ved optikusnevritt (11). Tilstanden viser seg som regel som en subakutt ensidig synsreduksjon med moderate smerter som aksentueres ved øyebevegelser og progredierer i løpet av få dager til to uker (12). Smerteintensiteten er varierende, nattesøvnen forstyrres vanligvis ikke, og en tidel rapporterer ingen smerte. Enkelte pasienter observerer lysglimt (fotopsier) ved øyebevegelser. Noen pasienter fremviser Uhthoffs fenomen (synsreduksjon ved økt kroppstemperatur eller i tilknytning til fysisk anstrengelse). Forsinket visuelt fremkalt respons er heller ikke uvanlig å finne ved debut av multippel sklerose, noe som kan tyde på en tilsynelatende asymptomatisk optikusnevritt (13).

Den maksimale synsreduksjon varierer fra lett tåkesyn til manglende lyssans på affisert øye. Redusert fargesyn, redusert kontrastsensitivitet, synsfeltutfall og relativ afferent pupilldefekt i pupillrefleks ved belysning er vanligvis til stede i det affiserte øyet. Selv om ingen av disse funn isolert sett er spesifikke for optikusnevritt, gir de sammen

Case 1:

- **Paper retracted**
- **Difficulties:**
  - **A number of authors very senior respected Norwegian researchers**
  - **Some on IAB of Norwegian Medical Journal**
  - **Some clearly not very familiar with content of paper (?authorship)**

Case 2: The case of Jon Sudbø

Articles

Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study

J Sudbø, J J Lee, S M Lippman, J Mork, S Sagen, N Flatner, A Ristimäki, A Sudbø, L Mao, X Zhou, W Kildal, J F Evensen, A Reith, A J Dannenberg

Summary

Background Non-steroidal anti-inflammatory drugs (NSAIDs) seem to prevent several types of cancer, but could increase the risk of cardiovascular complications. We investigated whether use of NSAIDs was associated with a change in the incidence of oral cancer or overall or cardiovascular mortality.

Methods We undertook a nested case-control study to analyse data from a population-based database (Cohort of Norway; CONOR), which consisted of prospectively obtained health data from all regions of Norway. People with oral cancer were identified from the 9241 individuals in CONOR who were at increased risk of oral cancer because of heavy smoking (≥15 pack-years), and matched controls were selected from the remaining heavy smokers (who did not have cancer).

Findings We identified and analysed 454 (5%) people with oral cancer (279 men, 175 women, mean [SD] age at diagnosis 63·3 [13·2] years) and 454 matched controls (n=908); 263 (29%) had used NSAIDs, 83 (9%) had used paracetamol (for a minimum of 6 months), and 562 (62%) had used neither drug. NSAID use (but not paracetamol use) was associated with a reduced risk of oral cancer (including in active smokers; hazard ratio 0·47, 95% CI 0·37–0·60, p<0·0001). Smoking cessation also lowered the risk of oral cancer (0·41, 0·32–0·52, p<0·0001). Additionally, long-term use of NSAIDs (but not paracetamol) was associated with an increased risk of cardiovascular-disease-related death (2·06, 1·34–3·18, p=0·001). NSAID use did not significantly reduce overall mortality (p=0·17).

Interpretation Long-term use of NSAIDs is associated with a reduced incidence of oral cancer (including in active smokers), but also with an increased risk of death due to cardiovascular disease. These findings highlight the need for a careful risk-benefit analysis when the long-term use of NSAIDs is considered.

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See http://www.fhi.no

Introduction

Squamous cell carcinoma of the oral cavity is associated with severe disease-related and treatment-related morbidity and a poor prognosis that has not improved greatly over the past three decades.[1,2] Tobacco smoking is the major cause of this disease.[3] Patients who have oral leucoplakia with the genetic instability marker aneuploidy have an 80% risk of developing oral cancer[4] with a high relapse rate and a 70% risk of death in 5 years.[5,6] Complete surgical excision does not reduce the high risk of aggressive, lethal oral cancer associated with aneuploid oral leucoplakia.[4] Smoking cessation could offer some protection in this setting,[3,7] but is often difficult to achieve or sustain.[3,8–10] Therefore, there is an unmet medical need for new treatment strategies, such as chemoprevention with non-steroidal anti-inflammatory drugs (NSAIDs), to reduce the risks of cancer in patients with aneuploid oral leucoplakia.[9–11]

NSAIDs inhibit cyclo-oxygenase (COX) activity and thereby suppress the synthesis of prostaglandin E_2. Raised concentrations of prostaglandin E_2 have been detected in both premalignant and malignant lesions, including squamous cell carcinoma of the oral cavity.[12,13] This increase results from the overexpression of COX-2, the inducible form of COX.[14,15] Several lines of evidence, beyond the finding of raised amounts of prostaglandin E_2 in tumours, suggest that COX enzymes contribute to the development of oral cancer. COX can convert polycyclic aromatic hydrocarbons in tobacco smoke to reactive metabolites, which form mutagenic DNA adducts.[16,17] Prostaglandin E_2 can stimulate cell proliferation and angiogenesis and inhibit apoptosis and immune surveillance.[18,19] NSAIDs protect against the development of oral cancer in animals.[20,21] Observational data have indicated that NSAIDs are associated with the reduced risk of several types of cancers,[22–25] but we know of only two previously published reports of epidemiological studies of NSAIDs with respect to head and neck cancer.[26,27] These reports only included aspirin and showed conflicting results. Before undertaking a trial to investigate NSAIDs in reducing the risk of oral cancer in the very high-risk group of patients with aneuploid leucoplakia, we did a population-based study to examine the potential association between long-term NSAID use and the risk of oral cancer in current and previously heavy smokers. We also examined the potential associations of overall and cardiovascular mortality with NSAID use.

Methods

Risk identification in population-based health-survey database

We did a nested case-control study within the population-based Cohort of Norway (CONOR), which prospectively obtains data for the Norwegian Health Survey from three longitudinal health surveys covering all geographical regions of Norway (Health Surveys of

- Nested case-control study
- 454 cases (oral cancer): 454 controls
- NSAID use: Hazard ratio oral cancer = 0.47 (95% CI 0.37-0.60)
- NSAID use: Hazard ratio CV death = 2.06 (95% CI 1.34-3.18)

6

KREFTBLØFFEN

AVSLØ

av statsministere

– Jeg så med en gang at dette måtte være feil.

Meget godt rykte

Forsker diktet opp data – mottok 70 mill. i støtte

Uforståelig

- January 13, 2006: the story broke
- A chance discovery: how many people truly read the paper?

Aftenposten

JOBB & UTDANNING

- Gi en million pr. gullmedalje

36 sider med råd, tips og inspirasjon for studenter og jobbsøkere.

VIL ANMELDE LAKSESMINKERE

SV KNEBLER SEG SELV OM OLJE

MILD JANUAR-UKE HVERT ÅR

The Lancets sjefredaktør etter forskersvindelen

Krever svar fra alle forskerne

– Vi kan aldri sikre oss helt mot svindel, sier redaktør Richard Horton i «The Lancet».

KREFTBLØFFEN. – Dette er den største svindelen fra en forsker verden noen gang har sett, sier Lancet-redaktør Richard Horton. Han mener det er ubegripelig at medforfatterne av den fabrikkerte kreftstudien ikke har visst noe.

Første kvinne på topp i Afrika

Det lønner seg å starte NÅ.

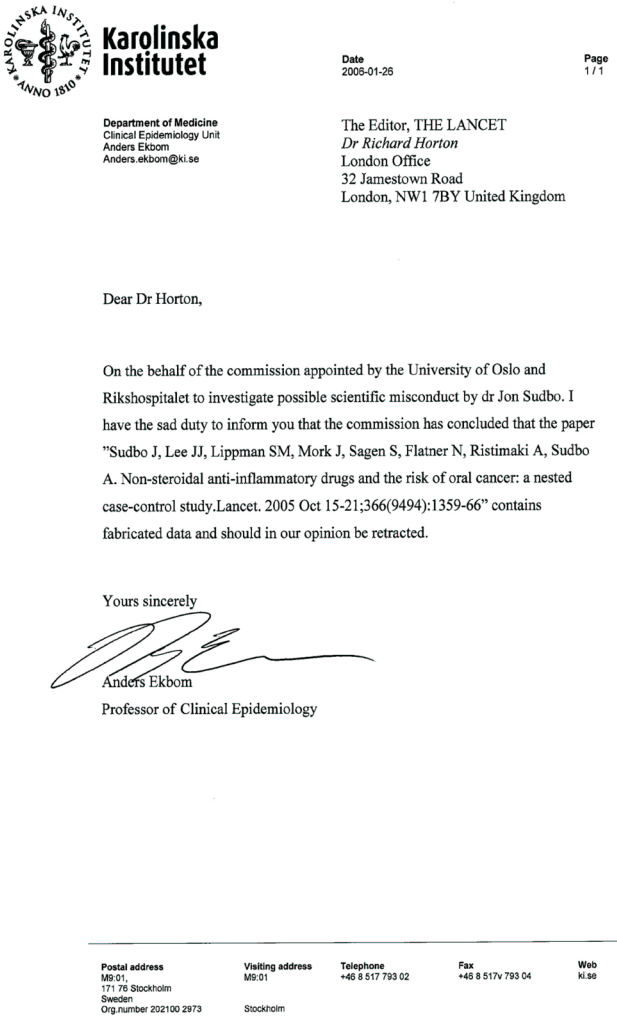
Verdi opptil 800,-

SATS

Tough questions

- Is *The Lancet* more interested in great headlines than correct science?
- How often are you being warned about flawed research?
- Why didn't you listen to your peer reviewers?

The Ekbom Commission



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2006-01-26

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The Editor, THE LANCET
Dr Richard Horton
London Office
32 Jamestown Road
London, NW1 7BY United Kingdom

Dear Dr Horton,

On the behalf of the commission appointed by the University of Oslo and Rikshospitalet to investigate possible scientific misconduct by dr Jon Sudbo. I have the sad duty to inform you that the commission has concluded that the paper "Sudbo J, Lee JJ, Lippman SM, Mork J, Sagen S, Flatner N, Ristimaki A, Sudbo A. Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study.Lancet. 2005 Oct 15-21;366(9494):1359-66" contains fabricated data and should in our opinion be retracted.

Yours sincerely

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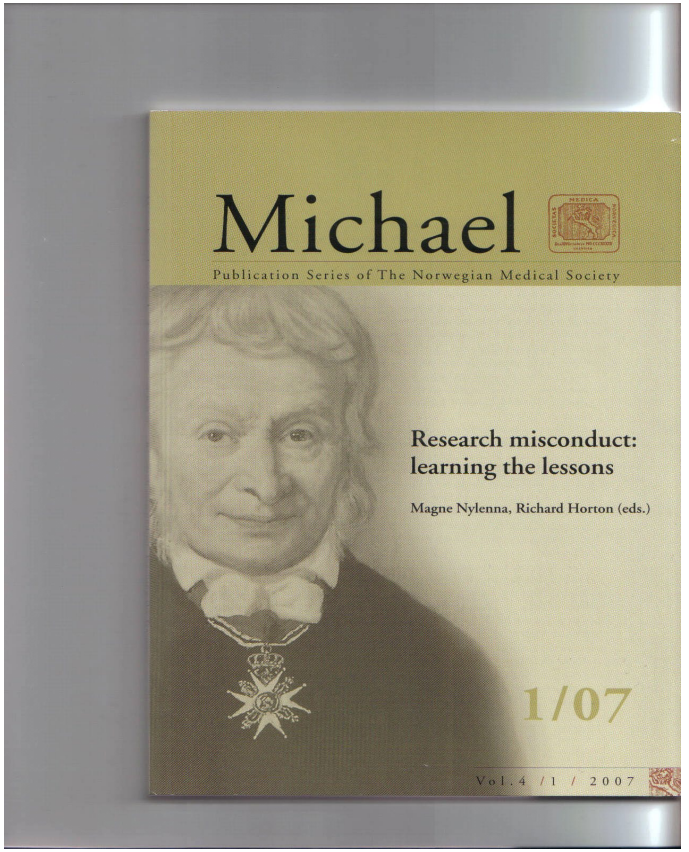
Expression of concern: January 21, 2006

Retraction: February 4, 2006

Summary of Sudbø case

From the left Mr. Sheldon Kotzin, Dr. Richard Horton, Prof. Magne Nylenna, Prof. Anders Ekbom and Dr. Harvey Marcovitch (photo: Kjell Tjensvoll).



What can editors do?

- **COPE – pursue misconduct, adhere to good publication standards**

  COPE support for editors might facilitate response from authors/institutions

- **Heightened vigilance, especially high-risk papers (public impact, collaborations, unexpected results, commercial interest, reviewers' suspicion)**

What can editors do?

- **Insist on prospective trial registration**
- **Check protocol with submission**

What can editors do?

- **Ensure adherence to best reporting standards (CONSORT, STARD, STROBE.....etc) – oddities may be more apparent**

What can editors do?

- **Screening for:**
  - **Plagiarism (CrossCheck or similar)**
  - **Figure manipulation (J Cell Biol)**

BUT: time-consuming and not fool-proof

What can editors do?

- **Declared transparent policies on conflict of interest and role of sponsor (prior to peer review)**

- **Ask questions at submission stage (authors' contributions, involvement of medical writer….etc)**

What can editors do?

- **?? Demand independent data monitoring for all studies**

- **Emphasise responsibility of ALL authors for data integrity!!**

the future: hope or delusion?

If ALL journals, editors, and publishers were to declare openly and insist on good publication policies and standards combining vigilance with swift actions, we would have achieved a large step towards fostering research integrity