



# FOOD, FLATTERY & FRIENDSHIP: WHEN DOCTORS BECOME ENTANGLED WITH DRUG COMPANIES

**Prof Marc Blockman**

Western Cape HIV Symposium  
June 2015

Conflicts of interest:  
lots



# The CAGE Questionnaire for Drug Company Dependence

- Have you ever prescribed **C**elebrex™?
- Do you get **A**nnoyed by people who complain about drug lunches and free gifts?
- Is there a medication lo**G**o on the pen you're using right now?
- Do you drink your morning **E**ye-opener out of a Lipitor™ coffee mug?

If you answered yes to 2 or more of the above, you *may* be drug company dependent.

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*"My fees are quite high, and yet you say you have little money.  
I think I'm seeing a conflict of interest here."*

# Conflict of interest?



“I have never been bought, I cannot be bought. I am an icon, and I have a reputation for honesty and integrity, and let the chips fall where they may.” **“It is true that there are people in my situation who could not receive a million-dollar grant and stay objective. But I do.”**

**“That stuff doesn’t influence me at all. I don’t even know what drug is on my pen. I just go for the food.”**

--Fill in your name here?

# THE VIRTUOUS JUDGE

- Highly-respected judge serves on national board of directors of Red Cross, one of nation's largest NGO's
- Attends 4 meetings/yr; expenses ± R10,000/meeting.
- Red Cross sued by former employee for discriminatory treatment & huge damages sought.
- Judge assigned to decide case. Lawyers for parties believe Judge would be completely impartial & fair.
- Does a COI exist? Should Judge hear/decide the case?

# Definition of COI

‘Conflict of interest’ is:

*A set of conditions (**NOT BEHAVIOUR**)  
in which professional judgment  
concerning a **primary interest**  
tends to be unduly influenced by  
a **secondary interest**.*

*Dual Interests*

# What Interests at Stake?

- What are judge's primary interests as a professional/judge?
  - To carry out mission of law: to render justice fairly/impartially
  - To provide his independent, impartial, unbiased judgements
- What other interests (**secondary**) does Judge have?
  - Decent income, standard of living
  - Status/respect/influence in community & profession
  - Career advancement (to higher level court)



# Are Secondary Interests Bad?

- Secondary interests *not illegitimate* – rather:
  - They are given less relative weight than primary duty/interest.
  - They must not dominate or *appear* to do dominate.
- Goal: not to eliminate secondary interests, but to mitigate risks they will lead to perverse behaviour.
- Does a COI arise in this situation?
  - Judge conceded to be virtuous, high character, fair.
  - Any reason Judge should *not* hear this case?

# Why Regulate COI's..

(1) To maintain integrity/objectivity of professional judgement

- *No assumption professionals dishonest*
- *Rules minimize perverse influences*
- *Hard to know when R influence decisions*
- *Remove factors that cause risky situations*

# Why Regulate COI's..

(2) To maintain public confidence in objectivity of professional judgement:

*Avoid COI even if no actual bias.*

- The virtuous judge must not only do justice but also be seen to do justice.*
- Avoid even the appearance of injustice.*

# What Should Judge Do?

- Several options: most commonly judge would feel compelled to voluntarily step aside from hearing case.
- Alternative: disclose involvement with Red Cross & step aside only if other party objects & shows that he might be biased.
- Which step best resolves problem?



# How About Clinicians & Researchers?

‘Our system would never tolerate judges taking money from those they judge, yet for some reason this doesn’t apply in medicine.’

**Should same rule apply to docs/researchers?**

Lo B, Field MJ. Conflict of interest in medical research, education, and practice. National Academies Press 2009. ISBN 978-0-309-13188-9. [http://www.nap.edu/catalog.php?record\\_id=12598](http://www.nap.edu/catalog.php?record_id=12598).

Moynihan, R. Who pays for pizza? BMJ 326; 31 May 03. 1193-1196.

Norris SL, Holmer HK, Ogden LA, Burda BU, Fu R. Characteristics of physicians receiving large payments from pharmaceutical companies and the accuracy of their disclosures in publications: an observational study. BMC Medical Ethics 2012;13:24. doi:10.1186/1472-6939-13-24.

# Separate, Distinct Missions

**Pharma goal:** develop profitable new products

**Researchers' mission:** research, teach, serve public

When pharma pays researcher, distinction blurs!

Linking of pharma/researchers **raises COI concerns!**

## **A Worrying Tale**

**Scott S. Reuben was Professor of Anesthesiology and Pain Medicine at Tufts University in Boston, Massachusetts and chief of acute pain at Baystate Medical Center in Springfield, Massachusetts before being sentenced to prison for health care fraud.**

**Reuben was considered a prolific and influential researcher in pain management, and his purported findings altered the way millions of patients are treated for pain during and after orthopedic surgeries.**

**Reuben has now admitted that he never conducted any of the clinical trials on which his conclusions were based "in what may be considered the longest-running and widest-ranging cases of academic fraud." Scientific American has called Reuben the medical equivalent of Bernie Madoff, the former NASDAQ chairman who was convicted of orchestrating a \$65-billion Ponzi scheme.**

**On January 7, 2010; Reuben agreed to plead guilty to one count of health care fraud.**

**Prosecutors alleged that Reuben obtained thousands of dollars in grants from pharmaceutical companies for research that he never performed.**

**On May 24, he was sentenced to six months in prison, followed by three years of supervised release.**

**He was ordered to pay a \$5,000 fine, forfeit \$50,000 to the government and make \$360,000 in restitution to pharmaceutical companies.**



# Conflict of Interest in Clinical Practice Guideline Development: A Systematic Review

Susan L. Norris<sup>1\*</sup>, Haley K. Holmer<sup>1</sup>, Lauren A. Ogden<sup>1</sup>, Brittany U. Burda<sup>2</sup>

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## Abstract

**Background:** There is an emerging literature on the existence and effect of industry relationships on physician and researcher behavior. Much less is known, however, about the effects of these relationships and other conflicts of interest (COI) on clinical practice guideline (CPG) development and recommendations. We performed a systematic review of the prevalence of COI and its effect on CPG recommendations.

**Methodology/Principal Findings:** We searched Medline (1980 to March, 2011) for studies that examined the effect of COI on CPG development and/or recommendations. Data synthesis was qualitative. Twelve studies fulfilled inclusion criteria; 9 were conducted in the US. All studies reported on financial relationships of CPG authors with the pharmaceutical industry; 1 study also examined relationships with diagnostic testing and insurance companies. The majority of guidelines had authors with industry affiliations, including consultancies (authors with relationship, range 6–80%); research support (4–78%); equity/stock ownership (2–17%); or any COI (56–87%). Four studies reported multiple types of financial interactions for individual authors (number of types per author: range 2 to 10 or more). Data on the effect of COI on CPG recommendations were confined to case studies wherein authors with specific financial ties appeared to benefit from the related CPG recommendations. In a single study, few authors believed that their relationships influenced their recommendations. No studies reported on intellectual COI in CPGs.

**Conclusions/Significance:** There are limited data describing the high prevalence of COI among CPG authors, and only case studies of the effect of COI on CPG recommendations. Further research is needed to explore this potential source of bias.

# Rent-a KOL

PR Web. What makes a key opinion leader a KOL?  
[http://www.prweb.com/releases/2012/3/prweb9250355](http://www.prweb.com/releases/2012/3/prweb9250355.htm)  
.htm. Accessed 26 March 2014.



*The Key to*  
**Opinion Leader Development™**

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## PRODUCT HIGHLIGHT



### Mobile Friendly Solutions

Our software solutions are now available in a mobile friendly version. You can enter your opinion leader interactions, view your OL profiles and more all from your mobile device (e.g. iPad/iPhone, Android, Blackberry)

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## NEWS & UPDATES

## WELCOME TO KOL, L.L.C.

As our name implies, we are a company devoted to providing Key Opinion Leader software and Key Opinion Leader Management services for pharmaceutical, biotechnology and device companies. We have invented two (2) world-class proprietary web-based applications for managing and developing relationships with KOLs (some have described them as 'knowledge management systems'). More importantly, because we have actual real-world experience from working in the Pharma industry we provide unparalleled service and consulting. We have held positions in medical/scientific affairs, medical science liaisons, medical education, drug information, sales training, strategic marketing, product management and field sales.

The principals in KOL, L.L.C. have deep experience in cardiology, anti-infective, pain management, diabetes, gastroenterology, urology, women's health and central nervous system products. As such, we have developed personal relationships with many KOLs.

We are "The Key to Opinion Leader Development™".

## Comments on the trial in NEJM (2012) 367:13

Robert Wise, M.D.  
University of Cape Town  
Cape Town, South Africa

Cate Fourie, M.D., M.Med.  
University of Stellenbosch  
Stellenbosch, South Africa

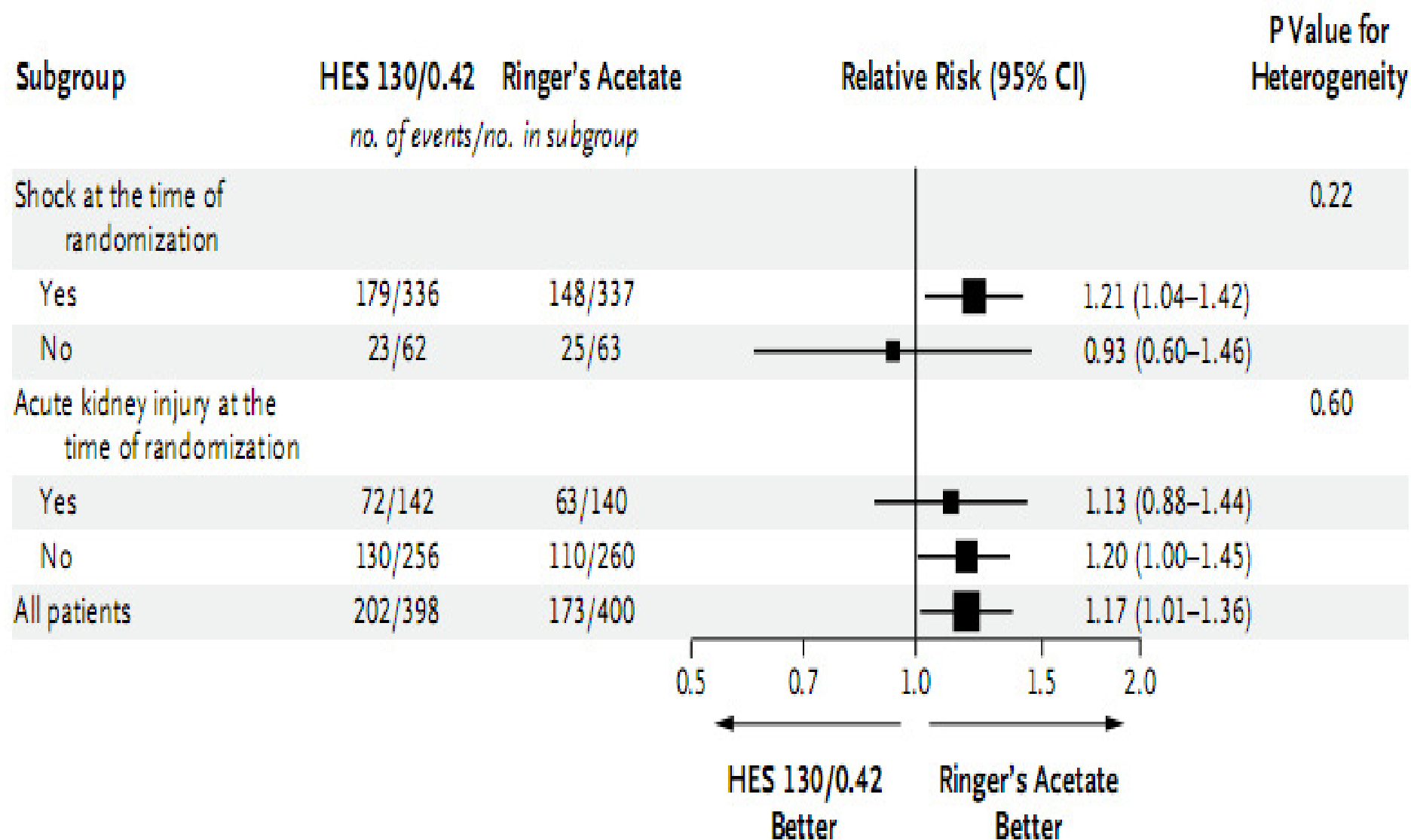
Guy A. Richards, M.D., Ph.D.  
University of the Witwatersrand  
Johannesburg, South Africa  
guy.richards@wits.ac.za

doses administered in previous studies.<sup>2,3</sup> Also, the continued use of large fluid volumes despite renal impairment may have contributed to worse outcomes in the starch group.

At randomization, more patients who received HES than Ringer's acetate had septic shock (179 of 336 patients vs. 148 of 337 patients) and acute kidney injury (72 of 142 patients vs. 63 of 140 patients); this also could have contributed to worse renal outcomes. Of concern, too, is the lack of a protocol for renal-replacement therapy and the use of blood products, although randomization may have lessened the importance of these variables.

Subgroup	HES 130/0.42 no. of events/no. in subgroup	Ringer's Acetate no. of events/no. in subgroup	Relative Risk (95% CI)	P Value for Heterogeneity
Shock at the time of randomization				0.22
Yes	179/336	148/337	1.21 (1.04-1.42)	
No	23/62	25/63	0.93 (0.60-1.46)	
Acute kidney injury at the time of randomization				0.60
Yes	72/142	63/140	1.13 (0.88-1.44)	
No	130/256	110/260	1.20 (1.00-1.45)	
All patients	202/398	173/400	1.17 (1.01-1.36)	

## B Relative Risk of the Primary Outcome



**Figure 2.** Time to Death and Relative Risk of the Primary Outcome.



# Ghostwriting: Dirty Little Secret

*'What is purpose of publications?' ..[The] purpose of data is to support, directly or indirectly, the marketing of our product.'*

- Co publishes paper by unacknowledged medical writer
- Nominally 'authored' by respectable academics
- Profit interests shapes/influences research, writing, & publication
- Study: GW in 75% of publications reviewed
- Estimate: 40% articles (fr specific drugs) ghost managed
- **Respected academics** (e.g. Johns Hopkins) recruited

Sismondo, S. Ghost Management: how much of the medical literature is shaped behind the scenes by the pharmaceutical industry. PLOS Medicine, Sept 2007, vol. 4, issue 9, e286.

MR. Conflict of interest in clinical practice. Chest 2007;132:664-670. DOI: 10.1378/chest.07-0315

Thompson DF. Understanding financial conflicts of interest. N Engl J Med 1993;329:573-6.

# Conflicts in Research 1

60% in USA private funding; 2/3 equity ties

Financial COIs 'pervasive & problematic'

- *1/4 researchers funded by industry*
- *1/3 have financial ties to drug co sponsors*
- *Paid gigs, equity interests for 'thought leaders'*

Evidence: COIs influence research

# Conflicts in Research 2

- Evidence shows pharma tactics inject bias:
  - *Duplicative publications*
  - *Selective publication*
  - *Selective reporting*
- Drug co results more favourable than other (non-sponsored) research:
  - *Inappropriate comparator (e.g., ineffective)*
  - *Study drug dose 'rigged' in its favour*
  - *Unfavourable studies not published*

# Conflicts in Research 3

‘For anyone who relies on published data alone to choose a specific drug, our results should be a cause for concern. Without access to all studies (positive as well as negative, published as well as unpublished . . . Any attempt to recommend a specific drug is **likely to be based on biased evidence.**’

Melander, H et al. Evidence b(l)ased medicine. BMJ 326; 31 May 2003.

Sismondo S. Corporate disguises in medical science: dodging the interest repertoire. Bull Science Technol Soc 2011;31:482-492. doi: 10.1177/0270467611422838 <http://www.thoughtleaderselect.com> Accessed 26 Nov 2014  
<http://www.kolonline.co> Accessed 26 November 2014



# Doctors & Gifts 1

## Extent of gift giving

- *Trinkets, travel, hotel, meals, entertainment*
- *Pharma major funder CME (50% in US)*
- *Fund prof societies, journals, supplements*

## Gift relationship

- ***Triggers obligatory response***
- ***Offer of friendship***

# Doctors & Gifts 2

‘Marketers only ‘doing their job. . . What they do is make people feel entitled – so *it’s not a bribe; it’s their due.*’ (JAMA Editor)

The flip-side of entitlement is indebtedness.

Moynihan, R. Who pays for pizza? BMJ 326; 31 May 03. 1189-1192.

Goldacre B. Bad Pharma: how medicine is broken and how we can fix it. Fourth Estate. 2013. ISBN 978-0007498086  
ProPublica, “Dollars for Docs: How Industry Dollars Reach Your Doctors,” <http://projects.propublica.org/docdollars/>

# Doctors & Gifts 3

Studies show effects of gifts:

- *Prescribing practices changed*
- *Decreased prescribing of generic drugs*
- *Higher drug costs*
- *Erosion of public confidence in medical personnel*

Flodgren G, Parmelli E, Doumit G, Gattellari M, et al. Local opinion leaders: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2011; 8: CD000125 doi:10.1002/14651858.CD000125.pub4

# Doctors & Gifts 4

‘Food, flattery and friendship are all powerful tools of persuasion, particularly when combined.’

Moynihan, R. Who pays for pizza? BMJ 326; 31 May 03. 1189-1192.

Goldacre B. Bad Pharma: how medicine is broken and how we can fix it. Fourth Estate. 2013. ISBN 978-0007498086

ProPublica, “Dollars for Docs: How Industry Dollars Reach Your Doctors,” <http://projects.propublica.org/docdollars/>

## Case

It is a busy day in the office, but you have agreed to speak for a minute to a pharmaceutical representative who has stopped by to drop off some samples of a new quinolone antibiotic, called Ubiquinone. Knowing your interest in golf, he has brought you golf balls emblazoned with the letter “U,” and also invites you to a round of golf at the country club this weekend.

Would you accept the golf balls?

Would you accept the invitation?

(From: “Really difficult Problems in Medical Ethics”)

## **Of principles and pens: attitudes and practices of medicine housestaff toward pharmaceutical promotions**

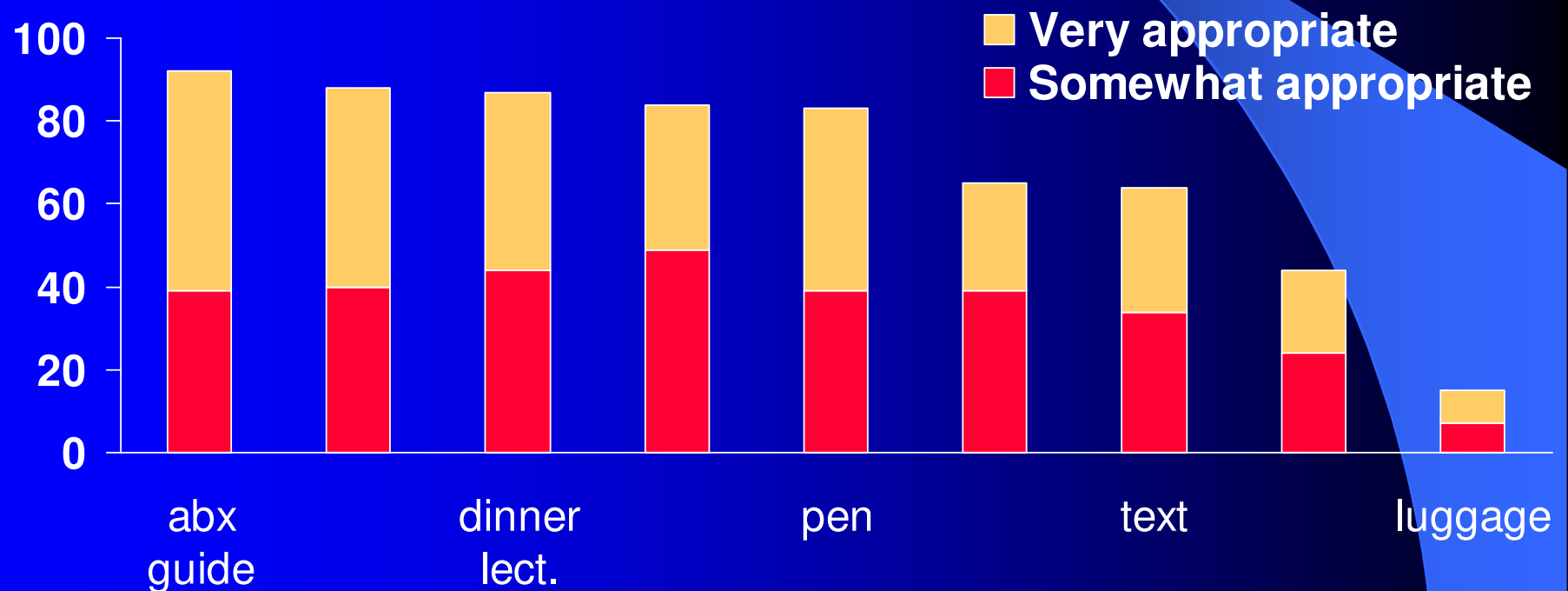
- Survey of 117 1st and 2nd year residents at a university-based IM training program.
- Attitudes towards 9 types of promotion assessed.
- 90% response rate (105/117 residents).

**Am J Med 2001;110:551**



# Of principles and pens: attitudes and practices of medicine housestaff toward pharmaceutical promotions

## Percent Who Consider Appropriate



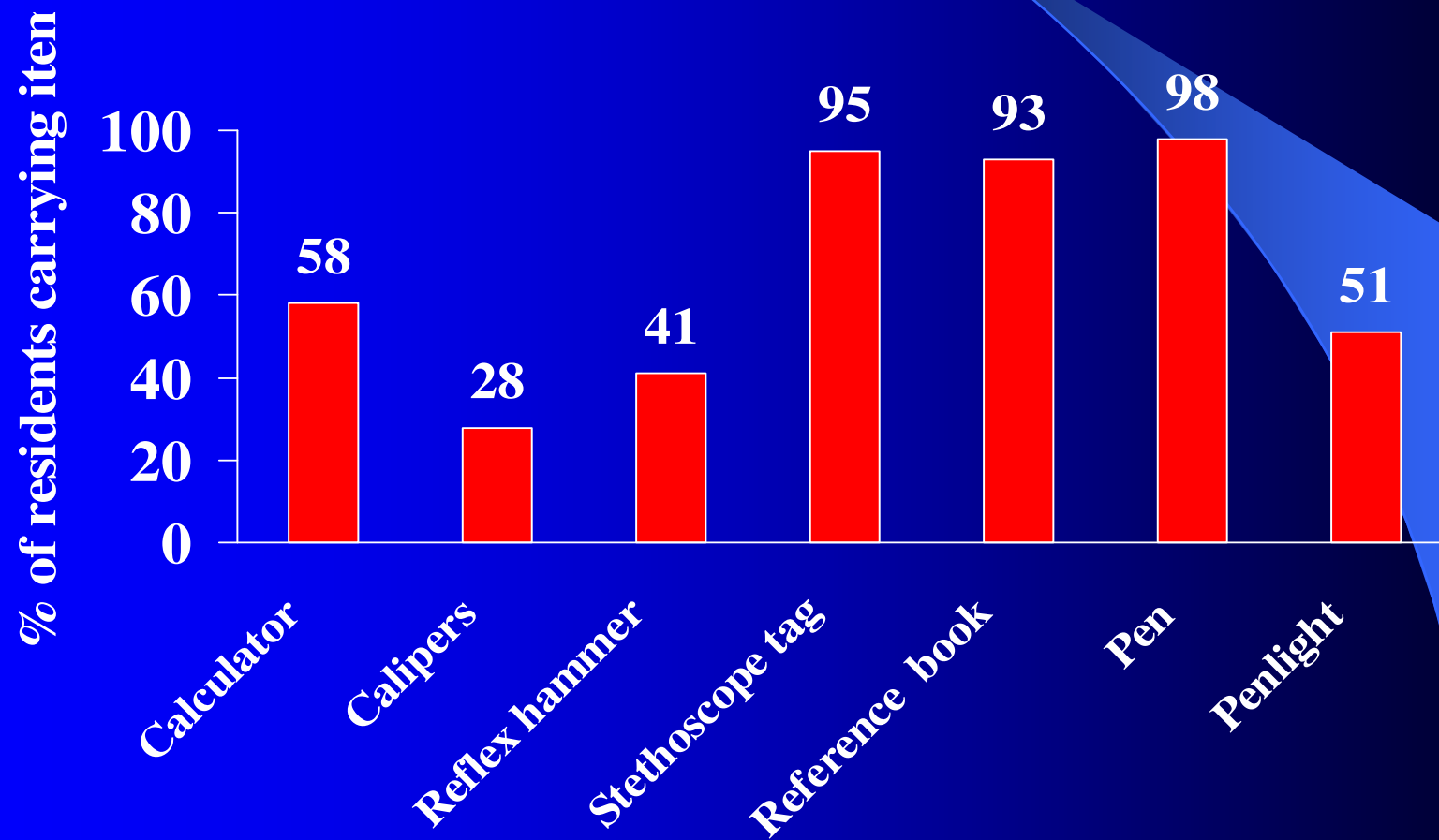
Am J Med 2001;110:551

# Pharmaceutical branding of Resident Physicians

- Survey of 181 primary care residents; 164 (91%) responded.
- First asked to complete survey, then asked to empty pockets of white coats.
- 98% had eaten drug company-sponsored meal within the past year.
- 97% of residents were carrying at least one item with pharmaceutical insignia.

# Pharmaceutical Branding of Resident Physicians

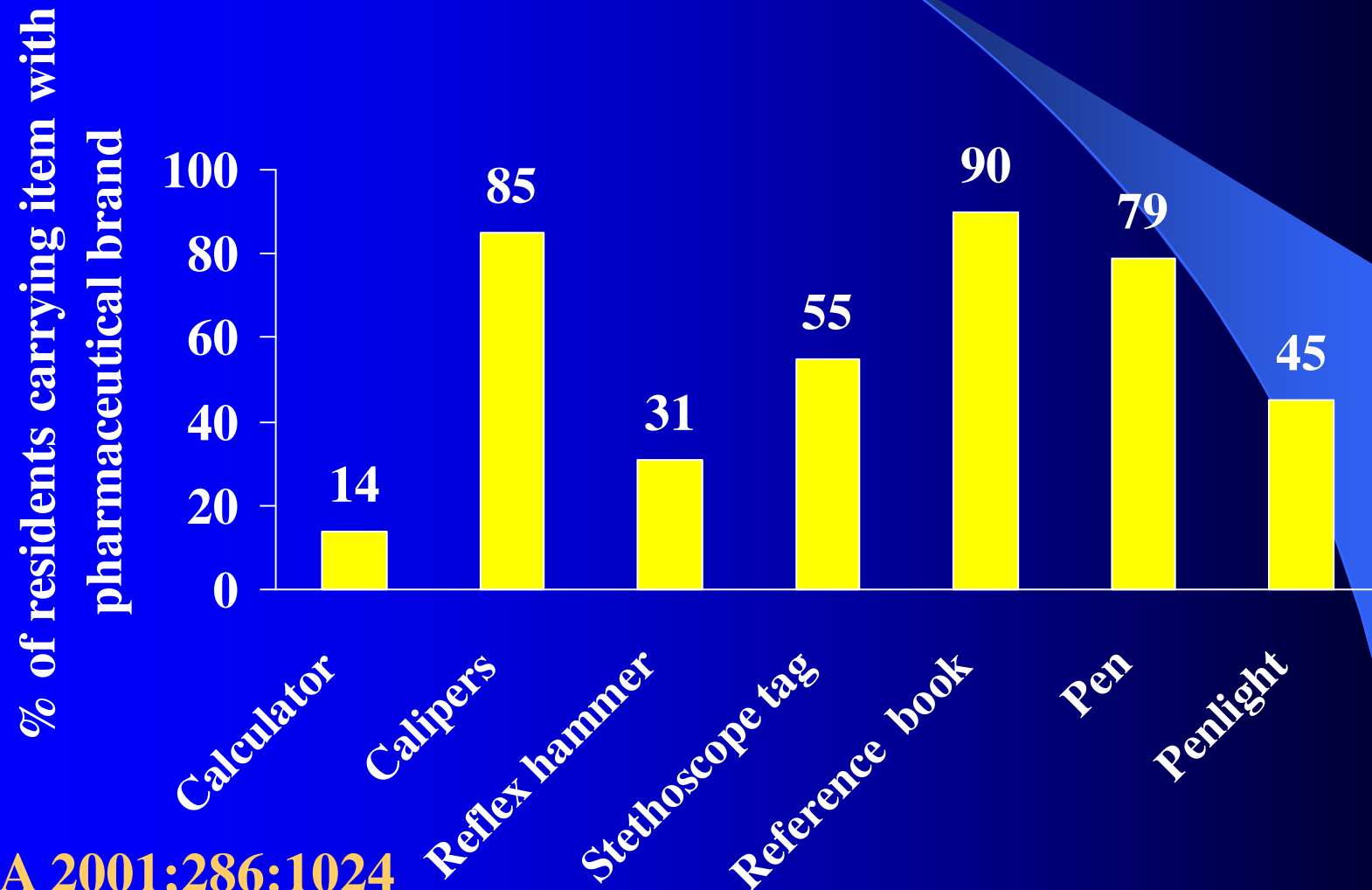
Frequency of items found in residents' white coats



JAMA 2001;286:1024

# Pharmaceutical Branding of Resident Physicians

Frequency of items found in residents' white coats



JAMA 2001;286:1024

## How common are competing interests?

- 75 articles
- 89 authors
- 69 (80%) responded
- 45 (63%) had financial conflicts of interest
- Only 2 of 70 articles disclosed the conflicts of interest

- Stelfox HT, Chua G, O'Rourke K, Detsky AS. Conflict of interest in the debate over calcium channel antagonists. N Engl J Med 1998; 338: 101-105



# Why don't authors declare conflicts of interest?

- Some journals don't require disclosure
- The culture is one of not disclosing
- Authors think that it's somehow "naughty"
- Authors are confident that they are not affected by conflicts of interest

# Does conflict of interest matter?

- **Financial benefit makes doctors more likely to refer patients for tests, operations, or hospital admission, or to ask that drugs be stocked by a hospital pharmacy.**
- **Original papers published in journal supplements sponsored by pharmaceutical companies are inferior to those published in the parent journal.**
- **Reviews that acknowledge sponsorship by the pharmaceutical or tobacco industry are more likely to draw conclusions that are favourable to the industry.**

# Does conflict of interest matter?

- 106 reviews, with 37% concluding that passive smoking was not harmful and the rest that it was.
- Multiple regression analysis controlling for article quality, peer review status, article topic, and year of publication found that the only factor associated with the review's conclusion was whether the author was affiliated with the tobacco industry.
- Only 23% of reviews disclosed the sources of funding for research.
- Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. JAMA 1998; 279: 1566-1570

# Financial Conflicts of Interest and Researcher Interpretation

- Stelfox et al. study: reviewed all studies on the safety of Ca channel blockers in hypertension published in 1995-96
- 70 articles
  - 5 original research papers
  - 32 reviews
  - 33 letters to the editor

# Financial Interests and Researcher Interpretation

	Support of Ca Blockers	Neutral	Critical of Ca Blockers	P Value
Financial Interest in Ca Channel Blockers	96%	60%	37%	<0.001
Financial Interest in Any Manufacturer	100%	67%	43%	<0.001
Honorarium	75%	40%	17%	<0.001
Research Funding	87%	40%	20%	<0.001
Employment or Consultation	25%	33%	17%	0.45



# Conflicts of Interest and Dissemination

- Analysis of 42 placebo-controlled trials of SSRI (selective serotonin reuptake inhibitors) drugs submitted to Swedish drug regulators
  - Results:
    - Experimental drug more effective than placebo: 19/21 published (90.5%)
    - Experimental drug not more effective than placebo: 6/21 published (28.6%)

# Conflicts of Interest and Dissemination

- **Meta-analysis of data from randomized trials that evaluated a 5 SSRI's against placebo in the treatment of depression in children**
  - **Articles reviewed were published in a peer-reviewed journal or unpublished (and reviewed by the Committee on Safety of Medicines)**

# Conflicts of Interest and Dissemination

- **Results:**
  - When published data alone were considered, it appeared that there was a favorable risk-benefit profile for 5/5 drugs studied
  - Addition of unpublished data indicated that the risks outweigh the benefits for 4/5 drugs studied
- Unknown if unpublished articles were not published due to publication bias against negative studies at major journals or the result of industry withholding negative data

# Patients Can Be Harmed

**\$16 billion claim: co knew risk of harm of SSRI**

- Data for approval weak
- Evidence **drug unsafe** for children
- Data manipulated
- **Unfavourable results not published**
- Patients harmed

**Regulatory system failed: biased results used to  
market flawed, profitable drugs**

# Publication of RCT results.

- Studies sponsored by pharmaceutical companies **4x more likely** to have outcomes favouring the sponsors products, than studies funded by other sources. (BMJ 2003;326:1167-70)
- Statistically significant association between industry sponsorship and pro-industry conclusions.
- Industry sponsorship associated with restrictions/delays on publications. (JAMA 2003; 289: 454-65)
- Unfavourable/insignificant findings less likely to be submitted for publication. (The Lancet.2001.358; 1893-1895)

# Words on guidelines and specialist societies

- Most guidelines produced by specialist societies are of poor quality
- Of 431 guidelines produced by specialist societies only one in seven gave information on who produced them, only about a fifth did a search of evidence, and only a quarter graded recommendations
- In specialty guidelines for colon cancer screening radiologists recommend barium enemas while gastroenterologists recommend colonoscopy.

Grilli R, Magrini N, Penna A, Mura G, Liberati A. Practice guidelines developed by specialty societies: the need for critical appraisal. Lancet 2000; 355: 103-6.



# A cautionary tale 1

- Many trials suggest that thrombolytic therapy may be harmful in acute stroke
- Despite that the American Heart Association has recently recommended tPA as a Class I (“definitely recommended”) intervention for stroke in its Guidelines 2000.

# **A cautionary tale 2**

- **The AHA claims that it assembles ‘independent’ panels to make recommendations but will not release conflict of interest statements signed by panellists.**
- **Independent verification reveals that most of the AHA’s expert stroke panellists have had ties to the manufacturers of tPA**

# **A cautionary tale 3**

- **Genentech, the US manufacturer of tPA, contributed over \$11 million to the AHA in the decade prior to the AHA's recommendation.**
- **Is this all a coincidence? Even if it is, it looks bad.**



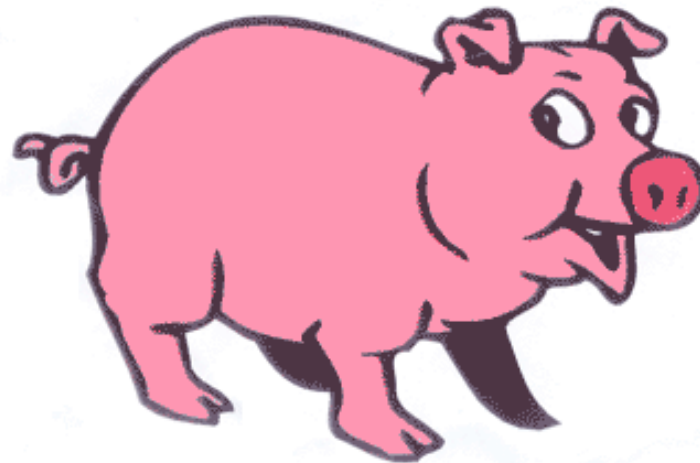
# **Patient Attitudes**

***“What would my patients think about this arrangement?”***

**ASTRAZENECA'S RESPIRATORY TEAM**

would like to invite you to the 1<sup>st</sup> Annual

**HAM - N - SCRAM**



at Heavenly Ham  
212 Green Meadows (next to Johnny's Beanery)  
April 20  
5:00 - 7:30 PM

Come out and get your Easter ham, turkey, or Omaha  
steaks to take home.

Item Number: 442  
Item Type: 19mm  
Physician: Refinader  
Date Received: 3/2/00

## Floral & Dash

*Come and meet your AstraZeneca  
Representatives while placing your order for  
a Valentine's Day Bouquet.*

**Date:** Monday, February 14, 2000  
**Place:** Gethsemane Garden Center  
**Address:** 5739 N. Clark Street  
Chicago, Illinois  
(773) 878-5915  
**Time:** 4:00 p.m. – 7:00 p.m.

*Remember your Valentine this year with  
a beautiful floral bouquet.*

**R.S.V.P. By Friday, February 11 to** [REDACTED]  
**1-800-822-9209 ext.** [REDACTED]

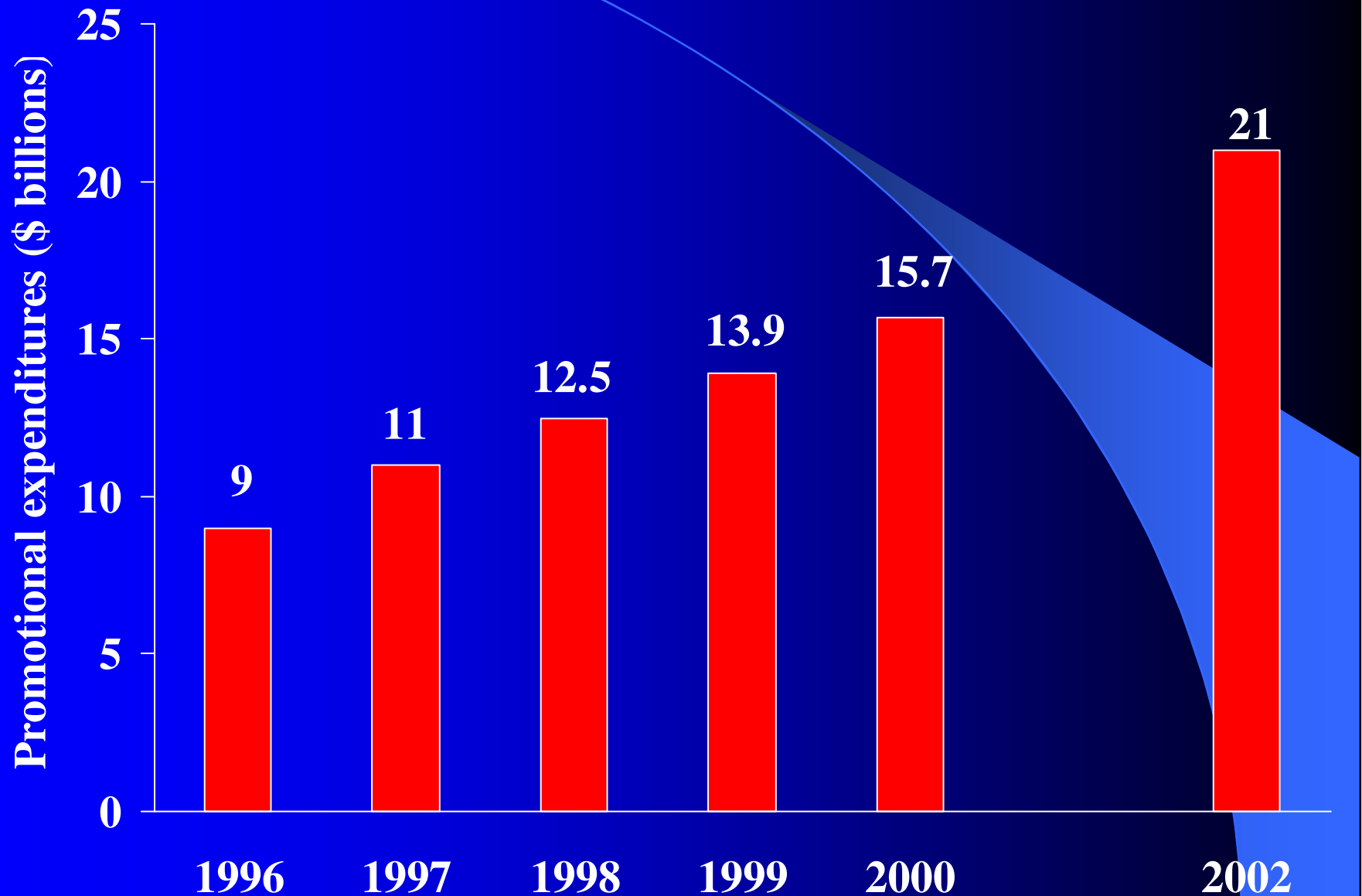


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# Promotional Spending

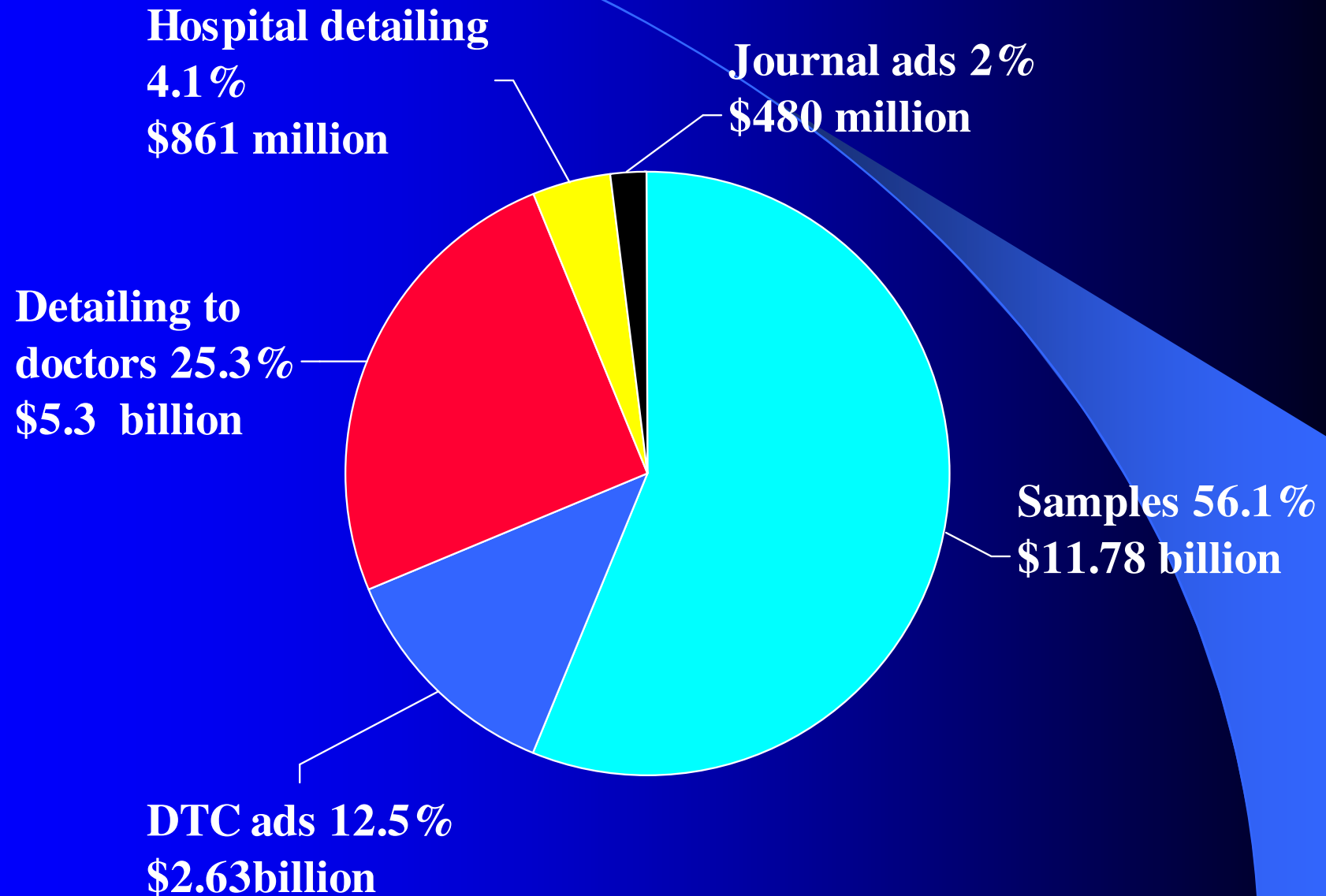


# Promotional spending on prescription drugs, 1996-2002



Source: NIHCM, 2001

# Promotional spending on prescription drugs, 2009



Source: IMS Health

**Total spending: \$21 billion**

# Once-A-Day\* **PRINIVIL** (LISINOPRIL)

PRINIVIL & Cal Ripken, Jr...

**Both  
On the Job.  
Every Day.**

**Hard-at-Work**

Cal Ripken, Jr. — record holder for most consecutive games played†

Cal Ripken, Jr. is not hypertensive and is not taking PRINIVIL.

In many patients....

**PRINIVIL Is  
Hard-at-Work Against Hypertension**

In clinical studies, ACE inhibitors had less effect on blood pressure in black patients than in non-blacks. In addition, black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema than non-blacks.

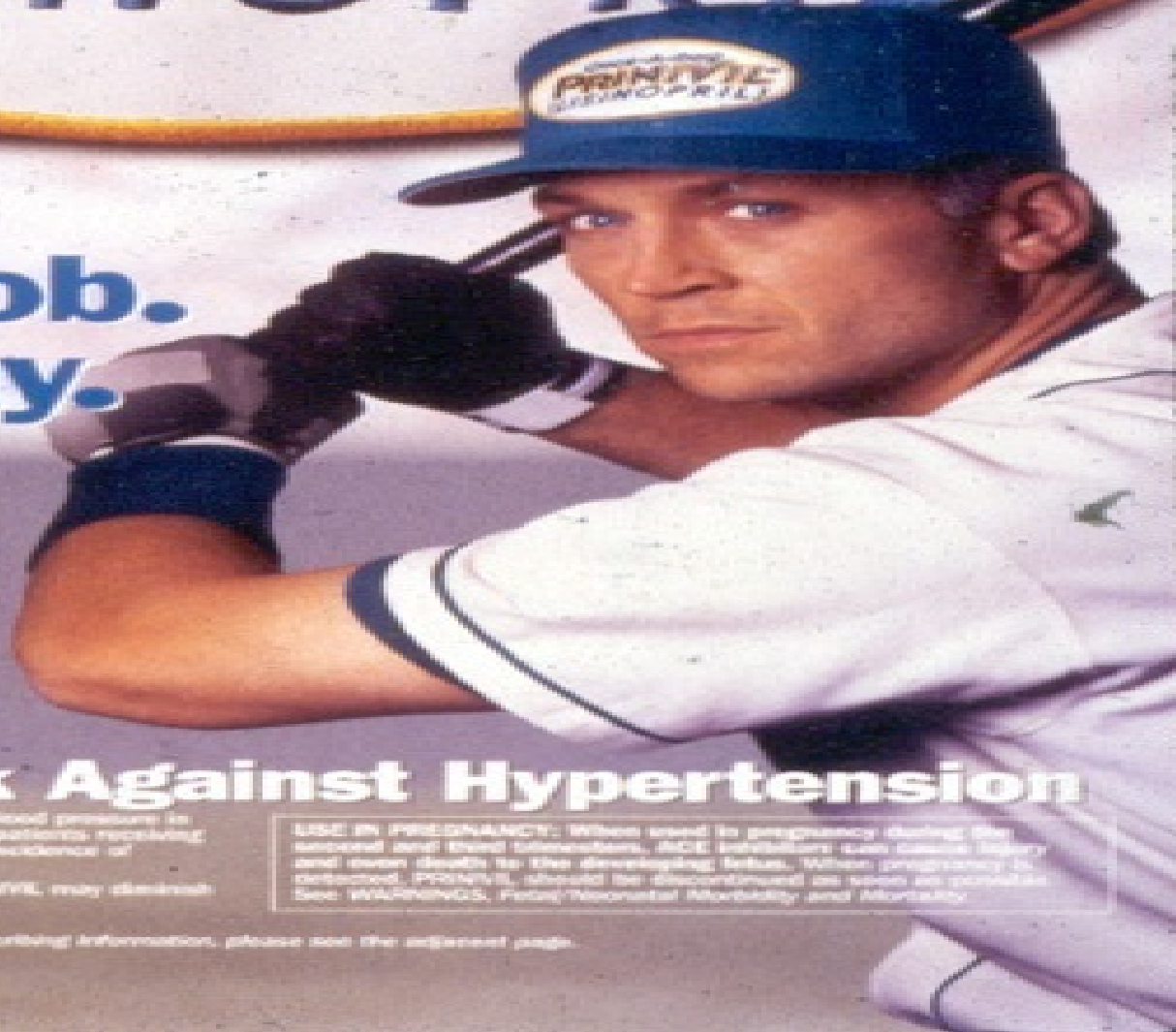
\* In some patients, the antihypertensive effect of PRINIVIL may diminish toward the end of the dosing interval.

**USE IN PREGNANCY:** When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, PRINIVIL should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Mortality and Morbidity.



**MERCK**

For a brief Summary of the Prescribing Information, please see the adjacent page.



# BOTH On the Job. Every Day.

## Hard-at-Work

Cal Ripken, Jr. — record holder for most consecutive games played!

Cal Ripken, Jr. is not hypertensive and is not taking PRINIVIL.

In many patients,...

## PRINIVIL Is Hard-at-Work Against Hype

In clinical studies, ACE inhibitors had less effect on blood pressure in black patients than in nonblacks. In addition, black patients received

USE IN PREGNANCY: When p



# How to respond to conflict of interest?

- “If in doubt, disclose.”
- Sometimes the conflict will be so strong that it will forbid participation
- The danger of trying to eradicate conflict of interest is that it may encourage deception
- “The only person who doesn’t have a vested interest in a subject is somebody who knows nothing about it”
- “The only people who don’t have personality disorders are those who don’t have personalities.”

# How to respond to conflict of interest?

- “Disclosure is almost a panacea.” John Bailar, professor of statistics, University of Chicago
- Disclosure by authors, reviewers, editors, editorial boards, management committees, presidents of societies
- “What isn’t transparent is assumed to be biased, incompetent, or corrupt.”

# Conclusions

- Conflict of interest has an important impact on the information reaching health professionals and the public and on patient care
- Concern about conflict of interest is not just political correctness
- Conflict of interest is very common in medicine



# Conclusions

- **Most conflicts of interest in medicine are not disclosed**
- **Yet disclosure should be the main response to conflict of interest**
- **We in health care need to do a better job of managing conflict of interest**

**Admitting to a conflict  
of interest is not an  
indication of moral  
failure but an honest  
appraisal of the  
potential influence of  
secondary interests on  
one's judgement and  
actions.**

Lesser CS, Lucey CR, Egner B, Braddock CH, Linas SL, Levinson W. A behavioural and systems view of professionalism. JAMA. 2010;304:2732-2737.

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**THANK YOU**