Competing interests and controversy about third generation oral contraceptives. BMJ readers should know whose words they read

Rosendaal, F.R.

ensure that the most fruitful research questions are addressed and the most appropriate outcome measures used, thus maximising the potential for the results to be relevant and beneficial to research consumers. Furthermore, it should lead to a more efficient use of research resources.

We are not Luddites calling for an end to "blue sky" research, and we do not want to see research by committee, but where the research relates directly to patients and their experience of an illness it is essential that their opinions are gathered.

Sufficient evidence is available to show that the involvement of consumers in all aspects of research benefits both researchers and consumers and that such endeavours are achievable.[2,3] We believe that for widespread adoption of consumer involvement to occur, pressure will have to be brought to bear by journal editors and research councils.

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Morphine induced allodynia in child with brain tumour

Signs are more likely to have been due to underlying medical condition

EDITOR—Heger et al remind readers that high doses of morphine may have paradoxical effects.[1] We are surprised, however, at the choice of patient they use to illustrate this lesson.

The diagnosis of pain in an infant depends solely on the observation of his or her behaviour.[2] It is particularly difficult to diagnose pain, let alone characterise it as allodynia, in a 9 month old infant with considerable neurological deficit and raised intracranial pressure. The authors attempt to justify the diagnosis of allodynia in just such a patient. Furthermore, high dose morphine is well reported as a cause of rigidity, catalepsy, akathisia, and myoclonus, which must add to the difficulty of interpreting pain on the basis of observation alone.[3] Two inconsistencies in the case history undermine the speculative diagnosis.

Firstly, the signs of distress provoked by routine nursing that were interpreted as allodynia induced by morphine-3-glucuronide were also recorded before morphine was given. Secondly, when the morphine dose was reduced the patient received methotrimeprazine, dexamethasone, and dypirone, each of which could have eased the signs of distress. The patient's distress had resolved within a week with this new treatment regimen, yet the raised ratio of plasma morphine-3-glucuronide to morphine, which the authors interpret as a cause of her allodynia, remained high for at least 17 days.

We believe that to diagnose allodynia in this patient is to ignore the much greater likelihood that the signs were a consequence of her underlying medical condition. We therefore agree with the authors that "morphine induced hyperalgesia has not been reported in children so far."

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Author's reply

EDITOR—Marples and Murray's comments illustrate how difficult and controversial paediatric palliative care still is. The comments show that treatment guidelines alone are not sufficient for dealing with unexpected complications in terminally ill children with cancer. The guidelines need to be expanded to include a diagnostic work up in patients who do not respond to morphine treatment.

The case we presented was that of a 21 month old patient with an astrocytoma at final stage. This patient received palliative care because the tumour was inoperable. We do not share Marples and Murray's opinion that the diagnosis of pain in infants depends solely on observation of their behaviour. Pain can be quantified even in newborn infants by analysis of three broad areas: behaviour patterns (body movements, facial expression, crying, spectrographic analysis of the quality of the crying); neurochemical secretions (catecholamine, cortisol, renin, vasopressin, β endorphin concentrations); and physiology (heart rate, respiratory rate, blood gas content, palmar sweating). Therefore it is not difficult to diagnose pain in a 21 month old terminally ill child, even one with impaired neurological function.[1]

The impact of a diagnostic procedure has to be weighed against any benefit resulting from it, especially in palliative care. Therefore only qualitative instead of quantitative assessment of pain was performed in this case. There was no question that the treatment of choice was morphine, the dose having to be increased gradually according to the recommendations of the World Health Organisation.[2]

We agree with Marples and Murray that it is difficult to distinguish between "simple" pain and morphine induced pain. When morphine induced allodynia was suspected in our patient the dose of morphine was 700 times higher than the initial dose. A rapid reduction of the dose resolved the symptoms of allodynia. To verify the suspicion that the allodynia was induced by the morphine we determined plasma concentrations of morphine and its metabolites and detected a relatively raised morphine-3-glucuronide to morphine ratio in comparison with normal data in children.[3,4] We regret that no blood sample was taken at the peak morphine dose. We are confident, however, that blood concentrations of morphine-3-glucuronide would have been even higher during maximal dosing.

We believe that to dispute the diagnosis of allodynia in this patient is to continue to ignore the occurrence of morphine induced pain in children.

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Competing interests and controversy about third generation oral contraceptives

BMJ readers should know whose words they read

EDITOR—The influence of competing interests arising from funding by the pharmaceutical industry is worrying in the controversy about third generation oral contraceptives.[1] At the end of 1998 three major studies without sponsoring from the industry found a higher risk of venous thrombosis for third generation contraceptives, unlike three sponsored studies.[2] To date, of nine studies without sponsoring, one study found no difference and the other eight found relative risks from 1.5 to 4.0 (summary relative risk 2.4); four sponsored studies found relative risks between 0.8 and 1.5 (summary relative risk 1.1) (references available on the *BMJ*'s website, www.bmj.com). The sponsored study with a relative risk of 1.5 has been reanalysed several times, yielding lower relative risks; after this failed to convince,[3] a new reanalysis was sponsored by another company.[4]

In 1995 four studies found the same risk. That evidence was sufficient for public health action since equally reliable pills were available. For at least one company the third generation pill secured more than half its revenue. The companies proclaimed that with almost total certainty everything was the result of bias and confounding. Even for a sceptic at the time, that was an unreasonable position: all four studies were reasonably executed and had withstood criticism from the Committee on Safety of Medicines and reviewers of leading journals. Thus, the companies' position ran the high risk of

damaging both their product and their credibility. Their behaviour is reminiscent of that described by Barbara Tuchman in 1984 in *The March of Folly: from Troy to Vietnam*, in which rulers become removed from reality and continuously act against their own best interests despite clear warnings.

Since 1995 three multinational companies have used enormous marketing resources to sow confusion. An avalanche of special symposia and paid supplements convinced outsiders that something had to be wrong with the studies finding the higher risks. Many general practitioners, gynaecologists, and family planners were swayed into accepting methodological arguments that sounded logical because of their legitimate concern with good contraception. However, few are really trained in the intricacies of epidemiological arguments. The companies exerted strong legal pressure on governments. Irresponsible scientists were accused of having caused a pill scare by juxtaposing selected figures without showing longer time trends in unwanted pregnancies. Irrelevant comparisons abounded, as with the risk of thrombosis in pregnancy.

The industry's view on bias and confounding was disproved by the World Health Organisation's scientific committee of leading epidemiologists who were not involved in the controversy.[3] Given the pervasiveness of the competing interest caused by industry funding, *BMJ* readers should know whose words they read.

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Competing interests: Professors Vandenbroucke and Rosendaal have no competing interests except a passion for the integrity of epidemiological reasoning. Dr Helmerhorst has supervised studies sponsored or assigned by various pharmaceutical companies that manufacture oral contraceptives, but none of these companies has funded his research on the comparative merits of second and third generation oral contraceptives.

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Editor's reply

Readers might be interested to look at our website and see further debate over competing interest and third generation contraceptive pills.[1] Ledger suggested that the *BMJ* should not have carried an editorial written by O'Brien, who was advising lawyers acting behalf of women who had developed venous thrombosis while taking third generation contraceptive pills. Lidegaard, who has written for the *BMJ* on this subject previously,[2] disagreed with O'Brien's interpretation of the evidence and argued that professionals who were "consultants in legal processes supporting women suffering venous thromboembolic disease" would be inclined to interpret the evidence one way. Neither Ledger nor Lidegaard declared competing interests, but I asked them to do so. Ledger did not reply, but Lidegaard declared several links with pharmaceutical companies. I defended our decision to ask O'Brien to write the editorial, arguing that disclosure is a better policy than a ban because people who are deeply knowledgeable on a subject and wholly independent are vanishingly rare. I also urged authors: "If in doubt, disclose."

Richard Smith *editor*
BMJ

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2 Lidegaard O. Oral contraceptives and myocardial infarction: reassuring new findings [commentary]. *BMJ* 1999;318:1584. (12 June.)

Science is not a dispassionate activity

EDITOR—The need for transparency in matters of competing interests, highlighted by Smith,[1] is amply illustrated by the recent controversy about third generation oral contraceptives. During this debate considerable sums of money have been spent denigrating well conducted studies with both clear hypotheses at the outset and clear analyses, studies which unexpectedly found that newer pills containing desogestrel and gestodene were associated with higher risks of venous thrombosis than older preparations with other progestogens. Often highly personalised attacks have been made to discredit the work of well respected researchers, regulatory authorities, and the World Health Organisation. At the same time studies with non-validated data, subgroup analyses after the event, controls of different ages recruited for another study, and inappropriate statistical adjustments have been promoted as providing robust evidence of an absence of risk. The proponents of such arguments have often been paid consultants of companies manufacturing oral contraceptives, or people receiving large research grants from these companies. Would such efforts have been made if the first studies had found differences in favour of third generation pills rather than against them?

To this mixture of claim and counterclaim has been added the smokescreen of whether particular oral contraceptives have different risks of myocardial infarction. For most women this issue is irrelevant. Most women stop taking the pill before their mid-30s, well before the age when women experience myocardial infarction. Furthermore, women at low risk—that is, those who do not smoke, who do not have hypertension, and who have their blood pressure measured before taking the pill—are not at risk of myocardial infarction, regardless of the preparation used.

Science is not a dispassionate activity. Money is a powerful motivator, and, as O'Brien points out in his editorial,[2] the stakes are high. A desire for fame, an excessive belief in your own work, and jealousy can also distort personal perspectives. The truth might never be established to the satisfaction of all parties, and even in the age of evidence based medicine opinion guides clinical practice. After much time evaluating the various arguments (including time as a paid consultant to the World Health Organisation's scientific group on cardiovascular disease and steroid hormone contraception[3]), I have concluded, like O'Brien, that all currently available oral contraceptives are safe. I have also concluded that the older formulations have a smaller risk of venous thromboembolism than newer preparations containing desogestrel or gestodene. For this reason, I believe that these older preparations remain the preferred first choice for most women.

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Competing interests: The RCGP Centre for Primary Care Research and Epidemiology (formerly the RCGP Manchester Research Unit) has received funding for its research and education activities from all manufacturers of oral contraceptives. Professor Hannaford has received lecture fees and hospitality from manufacturers of oral contraceptives and has been a paid consultant to the World Health Organisation and solicitors acting for the defence of the manufacturers.

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Italian paediatric association has launched code on competing interests

EDITOR—The *BMJ*'s policy of promoting the declaration of competing interests by authors is praiseworthy and should concern more people than the journal's contributors.[1] Transparency should be requested of lecturers as well as organisers of and delegates to workshops and congresses. Bero's editorial shows how things are changing with publication of the Royal College of Paediatrics and Child Health's report.[2] This idea is also taking hold in Italy.

In 1998 our association, whose main aims are providing continuing medical education, promoting primary care research, and protecting children, launched an initiative to develop a code on competing interests. This was based on the principles of the code of the International Pharmaceuti-