Letters

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Zanamivir, influenza, and meningococcal disease

Zanamivir may help to fight potential flu epidemic

EDITOR—The zanamivir issue described by Yamey in his news article[1] and the whole subject of treating influenza have ramifications apart from the potential expense to the British taxpayer (who can easily turn into a patient).

I am keen on any development that might help to reduce the burden of disease in hospital wards. If I were asked to state which single condition will fill up my inpatient beds and send healthcare staff home ill most efficiently, I would always choose influenza. Although it is true that influenza is often a mild illness, its association with the development of potentially lethal sequelae is well recognised. It has been described as the best known model of bacterial-viral coinfection.[2] Influenza is a powerful predisposing factor for invasive meningococcal disease[3] one of the few bacterial conditions still regularly killing otherwise normal healthy young people in the United Kingdom. Hubert et al have stated that when an epidemic of influenza-like syndrome is identified, medical practitioners should be informed of the likelihood of an increased incidence and severity of meningococcal disease.[4] We cannot currently vaccinate against *Neisseria meningitidis* type B. Zanamivir has the potential to be useful here. This certainly needs further investigation.

Influenza epidemics result in increased hospital admission rates for bacterial pneumonia,[2] and I have come across many patients who have known the pain and misery of having to have chest drains inserted for the drainage of empyemas as a consequence of having suffered a bout of "not very serious" influenza.

The zanamivir issue merits a broader debate, which should not centre exclusively upon whether or not it will be a helpful agent for groups at high risk. At a recent meeting in Geneva, to mark the 50th anniversary of WHO influenza surveillance, the Director General, Gro Harlem Brundtland, said that, "time to react may be very short—from the first recognition of a new subtype and the onset of a full-blown pandemic, it may be too short to prepare a vaccine and to use it."[5]

We have time to plan now but may not later. Like the little Dutch boy, we may need a finger to stick in the dyke to stop everyone drowning—perhaps zanamivir and similar drugs are that finger.

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Competing interest: STG has received fees for lecturing from GlaxoWellcome.

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NHS regulations are of questionable legality

EDITOR—As Yamey points out in his news article, the National Institute for Clinical Excellence considers that zanamivir (Relenza) is not cost effective and so will very closely monitor its use by doctors in NHS practice.[1] In reality this is a total ban, enforced by threat rather than by legislation. Since general practitioners are not permitted to provide any drug or treatment privately to their NHS patients I wonder what sort of service our patients will receive when this philosophy is taken to its logical conclusion and doctors are required to pay for all the treatments their patients need under the NHS conditions and terms of their service. This is the logical end point of the many recent primary care initiatives.

It may be appropriate to restrict NHS funding for sildenafil (Viagra) as a lifestyle drug, but zanamivir seems to be a potentially lifesaving treatment that might benefit most of the UK's population, particularly when the next influenza epidemic arrives.

All members of our society supposedly have access to free NHS medical care, but this provision is now overtly rationed, and a large number of treatments are simply not available owing to lack of funds. The moderately wealthy, including politicians, can afford medical insurance with instant access to specialist care in sumptuous surroundings. NHS rationing, however, applies to the productive majority of Middle England who are in work but who do not have, or cannot afford, medical insurance or a consultant's private fees. These are the very patients who might wish to pay their doctor a reasonable fee for the many procedures or drugs that the state is no longer prepared to provide for them. They already subsidise the NHS, paying £5.90 per item in prescription charges, and they may wish to purchase zanamivir directly from me if it only meant fewer very costly days off work owing to sickness. This is an option apparently denied to them.[2]

I have not abandoned the medical ethic. I believe a doctor's duty is to treat each of his or her patients to the best of his or her ability, and so he or she can take no part in rationing decisions, including the management of the local NHS primary care group. I also consider the prohibition of effective medical treatments to be morally as unacceptable as the Poor Laws of the nineteenth century. It echoes the ethics of an internment camp.

It may even be illegal.

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Very old people may not use excessive proportion of hospital budgets

EDITOR—The paper by Himsworth and Goldacre showing that time spent in hospital in the final few years of life increases little with

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the advancing age at death[1] reminds me of a study published over 30 years ago.[2] Although Pritchard's paper lacked the benefit of linked records, it showed a striking finding. In a group of 1529 patients who died in Forest Hall Hospital, Glasgow, over five years the proportion who had no previous hospital admissions before their final one rose steeply from about 15% of those aged 60-64 to 50% of men and almost 60% of women aged 90-94.

Although Pritchard's study was much smaller than Himsworth and Goldacre's and open to criticism on several counts, as the author admitted, it nevertheless underlines the contention of Himsworth and Goldacre that we have no grounds for discrimination against very old people on the basis of excessive consumption of hospital resources. In fact, there might be a paradoxical reduction, presumably because highly fit people tend to survive to extreme old age. Furthermore, admissions to hospital of very old people tend to be less costly than those of younger people.[3] Thus, contrary to popular belief, very old people are not necessarily responsible for using an excessive proportion of hospital budgets.

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Managing patients with lung cancer

Effective communication, palliative care, and guidelines are needed

EDITOR—We welcome Simmonds's analysis of the management of patients with lung cancer, the "Cinderella of common solid tumours."[1] We believe, however, that he has created two further Cinderellas. The guidelines he cites represent a big advance over previous guidelines because they include a commitment to patient centred care, underpinned by strong evidence supporting communication.[2] He does not mention communication, but this is the only route to a clear understanding of what an individual patient would choose. A meta-analysis has concluded that chemotherapy can offer prolonged survival of 1.5-3 months. Such evidence does not, however, inform us of the value of such survival to individual patients.

A recent study showed that although 11% of lung cancer patients would not choose a treatment entailing severe toxicity for a possible extra survival of two years, 6% of patients were prepared to do so for a possible survival of only one week.[3] This highlights the importance of providing patients with information of all available options in a manner that is not mediated by the physician's assumption of what should be their preference.

In the case of advanced lung cancer (as in most advanced disease) this must include the option of palliative care, the second Cinderella of Simmonds's editorial.

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Specialist palliative care is needed

EDITOR—The role of specialist palliative care was not mentioned in Simmonds's recent editorial on managing patients with lung cancer.[1] This is of particular concern as one of the main recommendations of the recently published national guidance on improving outcomes in patients with lung cancer is that palliative care should be an integral part of patient management from the outset and that this should be the responsibility of a multiprofessional team that has close links with the lung cancer team.[2]

Patients with lung cancer often have a very poor prognosis, multiple physical symptoms, and psychosocial concerns.[3] In a recent study of 480 patients attending oncology clinics at Guy's and St Thomas's Hospitals, London, those with lung cancer reported the greatest number and severity of problems (V Lidstone, unpublished data). Referral to a hospital specialist palliative care team has been shown to lead to reductions in the severity of several of the symptoms, including pain, experienced by patients with lung cancer.[4]

Studies from France show that pain management in cancer centres is often suboptimal.[5]

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Biomedical literature does not support routine use of laboratory variables as prognostic factors

EDITOR—Simmonds in his editorial on managing patients with lung cancer states that, in addition to the extent of the disease and the performance status, several laboratory variables (for example, serum concentrations of sodium and activity of alkaline phosphatase, aspartate aminotransferase, and lactate dehydrogenase) can be used to guide the treatment of patients with small cell lung cancer.[1]

We have recently reviewed the biomedical literature generated in this field over the past 20 years,[2 3] using the methods recommended by the International Federation of Clinical Chemistry.[4] In the table we have summarised the results of the 52 studies that have evaluated the pretherapeutic prognostic significance (in terms of survival) of serum concentrations of sodium and activities of alkaline phosphatase, aspartate aminotransferase, and lactate dehydrogenase in patients with small cell lung cancer. The column labelled "uncertain significance" corresponds to variables that were found significant by authors who had omitted at least one of the following radioclinical variables from their multivariate statistical analysis: weight loss, age, gender, performance status, and extension of the disease. The situation summarised in the table did not change when we tried to identify the laboratory variables that might have an independent prognostic significance in subgroups of patients with small

Prognostic significance of certain laboratory variables in small cell lung cancer according to 52 different studies published from 1981 to 1998

	No of studies		
	Not significant	Uncertain significance	Significant
Lactate dehydrogenase	17	19	7
Aspartate arninotransferase (+serum glutamic pyruvic transaminase)	10	0	0
Alkaline phosphatase	26	5	3
Sodium concentrations	21	6	6

cell lung cancer who have limited or extensive disease, even if distinguishing such subgroups of patients implies a small number of studies for most of the variables.

Simmonds was right in saying that the extent of the disease and the performance status do not allow a perfect distinction between patients who will benefit from therapy and patients who will not.[5] Doctors should, however, bear in mind that, except perhaps for serum activity of lactate dehydrogenase,[3] the current biomedical literature does not support the routine use of the laboratory variables cited by Simmonds as additional prognostic factors in patients with small cell lung cancer.

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Common international guidelines must be developed

Editor—We agree with Simmonds that evidence based guidelines for clinical practice should help clinicians make better decisions, thereby reducing inappropriate variation and improving patient care.[1] The publication by different organisations of guidelines on the same subject, but with substantial differences in their recommendations, may, however, increase instead of reduce variability in patient care. The guidelines of the clinical oncology information network (COIN) for the non-surgical management of lung cancer, recently published by the Royal College of Radiologists, exemplify this variability.[2] These guidelines for clinical practice are different from others developed in the same field by organisations in different countries. They contain three statements that are difficult to justify on the basis of available scientific evidence.[3–5]

(1) "Patients with good performance status who have locoregionally advanced disease (stage III) should be considered for radical radiotherapy."

A number of prospective randomised studies and a meta-analysis have shown the value of adding chemotherapy to radiation in locally advanced non-small cell lung cancer. Currently, at least three guidelines recommend the use of combined chemoradiation as standard treatment for selected patients.

(2) "In patients with advanced non-small cell lung cancer (stage IIIB and IV) chemotherapy should normally be offered in the context of a clinical trial."

Numerous prospective randomised trials and a meta-analysis have shown a significant survival benefit with platinum based chemotherapy. In addition, recent randomised studies indicate a clear improvement in the quality of life with chemotherapy compared with best supportive care.

Again, contrary to the COIN guidelines, American, Canadian and European guidelines suggest the use of platinum based chemotherapy in selected patients even outside clinical trials.

(3) "Consolidation thoracic radiotherapy increases local control and survival in patients with limited disease who have achieved a complete response to chemotherapy."

The meta-analysis quoted to support this statement shows that the addition of thoracic irradiation to chemotherapy improves survival in patients with limited small cell lung cancer irrespective of the timing of radiation and the type of response to chemotherapy. There is therefore no rationale to limit the use of thoracic irradiation to patients with complete response to chemotherapy. The European state of the art (START) oncology guidelines say that in patients with stage III disease chemotherapy and radiotherapy is standard treatment on a type 1 level of evidence.

Differences between the recommendations of British radiologists and European and North American organisations for the treatment of lung cancer are striking and not justified on the basis of available scientific evidence. The development of common international and multidisciplinary clinical guidelines would be a step forward in further reducing variation and improving patient care.

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Author's reply

Editor—The COIN guidelines focus on the treatment of patients with lung cancer with chemotherapy and radiotherapy and therefore do not address in detail other means of achieving symptom control and palliative care. The need for effective communication with patients is, however, highlighted and it is emphasised that care should be provided by a coordinated multidisciplinary team including specialist palliative care services.[1]

Watine and Ardizzoni et al have highlighted some of the differences between the COIN guidelines and similar American and European guidelines. It is important that guidelines for clinical practice are relevant to the context of those practitioners for whom they are intended. Important differences in evidence based guidelines are, however, a source of concern. The reason may be that they are derived from different evidence bases, there are differences in the interpretation of the outcomes, quality, or generalisability of the primary research, or there is insufficient evidence necessitating development of consensus guidelines. I agree with the suggestion that the development of common international multidisciplinary clinical guidelines would be helpful in further reducing inappropriate variation in treatment and improving patient care.

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Consumer involvement in research is essential

Editor—We agree with Goodare and Lockwood that consumer involvement in the research process is lacking.[1] Our work on osteoarthritis has shown the potential benefit of involving consumers when trying to prioritise the research agenda.

In a survey of 112 people with osteoarthritis of the knee we found that a wider range of treatment options was being used by patients than the research literature would suggest. From a recent systematic review of the available literature on treatments for osteoarthritis of the knee (930 studies) research on physiotherapy, educational, and complementary treatments was relatively uncommon, at 3.5%, 6.5%, and 5.3% of all studies respectively. Altogether 93 (83%) people responded to our questionnaire, not all of whom answered every question. Fifty two (63%) reported that they had tried physiotherapy, 42 (53%) had received educational interventions, and 18 (23%) used complementary therapies. Thus the literature does not reflect the range of treatments used by patients. There are several reasons for this, but certainly one of them is a lack of consumer involvement in research priority setting (J Chard, unpublished findings).

The wholesale inclusion of consumers in the research process may add to the time and cost of individual projects, but consumer involvement will greatly enhance the overall relevance of clinical research. It will

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.[5] 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

1 Electronic responses. The third generation oral contraceptive controversy. *eBMJ* 1999;319 (www.bmj.com/cgi/eletters/319/7213/7950) (Accessed 22 October 1999.)
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.

1 Editor's choice. Interpreting competing interests. *BMJ* 1999;319 (7213). (25 September.)
2 O'Brien PA. The third generation oral contraceptive controversy. *BMJ* 1999;319:795-9. (25 September.)
3 WHO Scientific Group on Cardiovascular Disease and Steroid Hormonal Contraception. Cardiovascular disease and steroid hormone contraception: report of a WHO scientific group. *WHO Tech Rep Ser* 1988;No 877.

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-

cal Manufacturers' Association and the international code for the marketing of breast milk substitutes. The code was intended as a list of recommendations for members without any intention to punish violations. Its main principles are:

- Sponsorship is acceptable if it originates from any industry complying with the international codes
- Sponsorship for individual people and groups must be declared to the local health authority and customers
- Support for participation in congresses and training courses should not include any direct or indirect payments, gifts, or travel expenses for accompanying people
- Research proposals supported by industry must be submitted to an independent ethics committee, with researchers being fully responsible for publishing the results
- Paediatricians should watch over advertising by the industry and reject any claimed benefit of drugs and baby food that contrasts with the codes or current scientific evidence.

A draft of the document was submitted to all 2700 members of the association, who are mainly family paediatricians, and fierce debate ensued. Despite its non-compulsory nature, a few members suggested modifying some sentences to make them more lenient; others opposed the initiative because doctors should respond to their own conscience rather than codes. Most members started to regard sponsorship differently. Some initial outcomes have already been measured.

Although the association has tried to limit costs and consistently reduced registration fees, fewer members have attended some of its more recent events; the same seems to be happening for the next national congress. The Italian Society of Paediatrics was invited to join the code initiative, but more time seems to be needed for a similar code to be adopted formally. The relationship with manufacturers must obviously continue, but it must be based on the ethical principles of transparency and independence, keeping in mind that the most important beneficiary is the patient.

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1 Editor's choice. Interpreting competing interests. *BMJ* 1999;319 (7211). (11 September.)
2 Bero LA. Accepting commercial sponsorship. *BMJ* 1999;319:653-4. (11 September.)

Immunisation does not rule out tetanus

Editor—Shimoni et al illustrate a needed caution to clinicians: do not exclude a diagnosis of tetanus in a patient who has been fully immunised.[1] Their report adds to the list of rare cases of tetanus that have occurred despite complete immunisation. Although the authors state that all reported cases of tetanus in the United States have occurred in people who have not been immunised, this is not altogether true. A catalogue of the 740 tetanus cases reported by the Centers for Disease Control since 1982 discloses that of the minority whose immunisation status was known, 53 cases had completed a primary series, 22 had received their latest booster between five and nine years before, and two had received a booster within five years (table).

In light of their patient's adequate immunisation record, Shimoni et al presume that he should have mounted a protective titre of neutralising antibody. With this I agree. But against what, in particular, does this titre confer protection—clinical infection or fatal infection? The understanding of "protection" was derived from animal studies that correlated serum concentrations of tetanus antibody with symptoms of tetanus.[2] The threshold of 0.01 IU/ml was established because guinea pigs with titres above this level were protected from fatal tetanus, not from clinical tetanus; six of 45 animals with protective levels developed non-fatal tetanus.[3] Similarly, in humans, non-fatal tetanus has been described in 10 out of 64 consecutive patients with antitetanus titres greater than 0.01 IU/ml.[4] More recent cases have borne this out.[5]

A number of rare and exceptional cases of tetanus occur despite adequate immunisation and protective levels of neutralising antibodies. Since tetanus is likely to be fatal if not recognised and treated properly, the caveat from Shimoni et al[1] merits repeating: doctors should entertain the diagnosis of tetanus in the proper clinical setting, regardless of the patient's immunisation record.

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Immunisation status of patients with tetanus in the United States reported by the Centers for Disease Control

Years	No of cases	Immunisation status known	Primary series completed	Latest booster	
				5-9 years	<5 years
1995-97	122	56	16	6	2
1989-90	117	57	12	4	0
1987-88	101	46	5	2	0
1985-86	147	NR	9	5	0
1982-84	253	NR	11	5	0

NR = not reported.

1 Shimoni Z, Dobrousin A, Cohen J, Pitlik S. Tetanus in an immunised patient. *BMJ* 1999;319:1049. (16 October.)
2 McComb JA. The prophylactic dose of homologous tetanus antitoxin. *N Engl J Med* 1964;270:175-8.
3 Sneath PAT, Kerslake EG, Scruby F. Tetanus immunity: the resistance of guinea pigs to lethal spore doses induced by active and passive immunization. *Am J Hygiene* 1937;25:464-76.
4 Goulon M, Girard O, Grosbuis S, Desormeau JP, Capponi MF. Les anticorps antitétaniques: titrage avant séro-anatoxinothérapie chez 64 tétaniques. *Nouv Presse Med* 1972;1:3049-50.
5 Crone NE, Reder AT. Severe tetanus in immunized patients with high anti-tetanus titers. *Neurology* 1992;42:761-4.

Not such distant mirrors

Warm tap water by the bucketful may be useful in flushing body cavities and wounds

Editor—An excerpt from One hundred years ago describes the flushing of the peritoneum introduced by Lawson Tait as being "greatly to the patient's advantage."[1]

In the closing years of the first world war my mother was ward and theatre sister to the celebrated gynaecologist Russell Howard at the London Hospital. She used to tell me how he would empty a bucketful of warm tap water into the abdomen at the end of an operation before sewing up, pelvic peritonitis being then prevalent in Whitechapel.

I found this an excellent way of cleaning up nasty compound fractures before routine debridement.

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1 One hundred years ago: Generalisation of salt infusions. *BMJ* 1999;319:703. (11 September.)

Coffee enemas may be effective shock treatment

Editor—The treatment of shock is described in an excerpt from One hundred years ago.[1] I think that it is worth mentioning that by 1934 the treatment of shock had advanced sufficiently to suggest other methods of management. I have a textbook of the time which states: "Weak hot tea, or coffee, may be given if he [the patient] can swallow, otherwise about a pint of warm coffee can be injected into the rectum, provided this is done with the minimum of disturbance."[2]

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1 One hundred years ago: Treatment of shock. *BMJ* 1999;319:1193. (30 October.)
2 A General Practitioner. *The illustrated family doctor*. Dunstable: Waterlow and Sons, 1934.