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Minerva

Minerva
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Obituary of William Ian McDonald
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Malaria is a major public health problem and is endemic in about 107 countries. The symptoms of uncomplicated malaria are non-specific and similar to many other disease syndromes, including minor viral illnesses. People living in areas where malaria is endemic are often familiar with these symptoms and frequently diagnose themselves, so that over-diagnosis is widespread.1

Prompt and accurate diagnosis of malaria is important for effective case management and if implemented well should reduce mortality from this disease.2 High sensitivity of diagnosis is crucial, and high specificity could reduce unnecessary treatment and improve the diagnosis of other febrile illness.3 In this week’s BMJ, a randomised controlled trial by Reyburn et al assesses the effect of rapid diagnostic tests compared with microscopy for guiding treatment of acute febrile illness in outpatients in Tanzania.4

Light microscopy and rapid diagnostic tests are the two most commonly used methods of confirming a diagnosis of malaria. Microscopy, the gold standard, has several advantages including low cost and high sensitivity and specificity when used by well trained staff. Rapid diagnostic tests (which detect parasite antigens) are easier to perform by staff with basic training, have less waiting time and indirect costs, but are relatively more expensive. A recent decrease in their cost may make it possible to increase their use in sub-Saharan Africa.

Despite the availability of these two methods, presumptive treatment of malaria (without laboratory confirmation) remains common practice.5 Reyburn and colleagues found massive over-diagnosis of malaria.6 Surprisingly, rapid diagnostic tests combined with basic training did not reduce over-treatment for malaria. Of the 1193 and 1204 patients with complete data who were randomised to rapid diagnostic tests and microscopy, respectively, only 52% and 50% had a correct prescription. More than half the prescriptions for antimalarial drugs were given to people who had negative test results (blood smear or rapid diagnostic test).4 Furthermore, children with negative results of rapid diagnostic tests were more likely to be treated for malaria than those with a negative smear.

In the era of artemisinin combination treatments, we urgently need to improve parasitological confirmation of the diagnosis of malaria. Reasons include the relatively high cost of such treatments, which makes unnecessary treatment unsustainable; the need for better care in people who have parasite positive tests; the need to reduce the risk of adverse events and drug use to limit the selection of drug resistant parasites; the need for more robust health information; and the need to identify people with parasite negative tests in whom another diagnosis must be sought.

Reyburn and colleagues found that health workers continue to treat people for malaria even if the diagnostic test is negative,4 emphasising the need to change the behaviour of such workers. However, they also found that this is difficult to do. The practice of treating patients with a negative test may be due to traditional teaching in medical schools, which promotes treatment on the basis of the health worker’s index of suspicion, and also due to ambiguous phrases in some national guidelines.

The World Health Organization’s generic treatment guidelines recommend parasitological confirmation of the diagnosis of malaria where malaria transmission is low, moderate, or unstable.5 In settings where the incidence of malaria is low, WHO recommends that health workers should be trained to identify patients who have been exposed to malaria before they carry out a parasitological test. In stable high transmission settings, where malaria is a common cause of febrile illness in children, WHO recommends that antimalarial drugs should be given to children with fever (≥37.5°C) or a history of fever that has no other obvious cause. In children 5 years old and above, in pregnant women, and in settings with a high prevalence of HIV a diagnosis should have parasitological confirmation.

The WHO guidelines do not state that a patient with a negative test should be treated for malaria. However, some countries, such as Uganda, have adopted phrases like, “Any patient with fever or a history of fever within 24 hours without evidence of other disease should be treated for malaria even with a negative blood smear for malaria parasites.”7 Such recommendations are aimed at increasing antimalarial coverage and potentially reducing the risk of progression to severe disease and death.

However, recent evidence from the field does not support such practices. In Kenya, even with imperfect conditions for microscopy, implementation of revised clinical practice (routine blood test for all febrile adults and restricting treatment to only positive tests) reduced the financial costs for antimalarial drugs, antibiotics,
Microscopy, and errors from over-diagnosing malaria by almost 60%. A study in Uganda among febrile children with a negative smear test for malaria, who were followed up without being given an antimalarial drug, found that less than 1% developed uncomplicated malaria and identified no unfavourable outcomes. Withholding treatment for malaria in people with a negative test was safe and saved treatments for children in more urgent need.

So what can we learn from the study by Reyburn and colleagues? Ideally the findings should “kick start” the process to change the behaviour of health workers. National and international guidelines should be explicit about how to treat patients with negative tests. The choice between rapid diagnostic tests or microscopy will depend on local circumstances, including available skills, the use of microscopy for the diagnosis of other diseases, and whether patients seek treatment from formal health facilities or from community health workers. Innovative approaches beyond basic training will be needed, including regular supervision and team building between laboratory and clinical staff, regular consensus reviews, surveillance and trend analysis for laboratory confirmed malaria and other common febrile illnesses, and interventions to increase public knowledge about the right way to diagnose malaria.

References are on bmj.com

**Oral chemotherapy**

Standardised dosing can improve the safety of prescribing

The use of oral anticancer agents for the treatment of common malignancies has increased over the past few years. Of about 300 new anticancer agents in development, 20-25% are oral products. Many novel “target agents” such as inhibitors of the epidermal growth factor receptor (for example, erlotinib) and the vascular endothelial growth factor receptors (for example, sunitinib and sorafenib) are given orally. Patients prefer oral agents because they are more convenient, allow greater autonomy, and avoid venepuncture and the associated risks of indwelling venous catheters.

Despite the advantages of oral anticancer agents, they do pose challenges such as poor compliance, a small but definite risk of unintentional overdose, and a greater risk of drug-drug and drug-food interactions. In this week’s BMJ, Weingart and colleagues evaluate the safety practices of 62 National Cancer Institute designated centres in the United States with regard to prescribing oral chemotherapy. Such institutions would be expected to have high safety standards, but the survey found that few of the safeguards suggested for parenteral anticancer drugs were used for oral agents given in an ambulatory setting. More than half of the responding centres (23 of 42) had no required element for oral chemotherapy prescriptions; these included the diagnosis, protocol number, cycle number on the prescription, or a double check of the prescription by a second clinician.

Since 1996, most US hospitals have devised programmes for the safe delivery of oral and parenteral chemotherapy. Recommendations emphasise the need for a comprehensive, interdisciplinary approach to reduce the number of errors whereby the accuracy of chemotherapy prescriptions must be verified by a system of double checking. Weingart and colleagues’ survey suggests that these safety recommendations often assume chemotherapy agents will be administered in a monitored, clinical environment, and not in an ambulatory setting. Oral anticancer agents given outside a healthcare centre require the same safeguards as parenteral agents, unless the dosing regimen of oral agents can be simplified.

One source of prescribing error stems from the unique practice in oncology of calculating doses on the basis of the patient’s body surface area (calculated from height and weight). This practice has been repeatedly questioned in recent years, and the evidence to support its use in clinical practice is limited.

The rationale for using body surface area to calculate drug doses is even less clear for oral agents than for parenteral ones, as pharmacokinetic variability between patients is greater for oral agents and less likely to be associated with body size. Thus, calculating the dose of oral anticancer agents on this basis is unlikely to improve safety and may even increase the risk of underdosage or overdosage. Some drug companies have responded to these risks by creating standard starting doses for all patients. However, some widely used oral agents (such as capcetabine) still require dosing on the basis of body surface area.

For doses based on body surface area, safety standards should be the same as for parenteral therapy—the prescription should include the patient’s height, weight, and body surface area; dose per body surface area; final calculated dose; and total number of doses per treatment course. Dosing calculations should be verified by a multidisciplinary system of double checking.

Prescriptions for agents with standardised dosing may not need these elaborate safety measures as the risks of the prescriber making a dosing error or the patient making an error when taking the drug are much lower.

The use of oral anticancer agents will continue to increase as more agents come on to the market. We suggest standardising oral anticancer doses in an effort to improve patient safety.

References are on bmj.com
Coffee and pregnancy
A moderate reduction in caffeine intake in the second half of pregnancy has no effect on birth weight or length of gestation

Some like their coffee black, and some like it white, but whether it is wise to drink coffee in pregnancy is not a black and white issue. Many observational studies have suggested that it is unwise to drink coffee (or indeed any drink containing caffeine) during pregnancy. Some papers report that consumption of more than modest amounts of caffeine during pregnancy may increase the likelihood of infertility, birth defects, miscarriage, stillbirth, premature birth, fetal growth restriction, and cot death. Each such paper has spawned a flurry of further papers reporting a failure to find any such association. One recent review article cited more than 200 papers. The problem is that women who drink more coffee than most nearly always differ from other pregnant women in other ways too. They are more likely to smoke, for one thing, which makes it difficult to decide what is causing what.

In this week’s BMJ, we finally have an interventional study by Bech and colleagues showing that babies born to mothers who drink moderate amounts of coffee do not weigh less than those whose mothers’ drink decaffeinated coffee in the second half of pregnancy (as 12 observational studies had previously suggested).

Caffeine crosses the placenta easily, and the speed with which it is then metabolised declines during pregnancy. Exposure to artificial boluses of caffeine can certainly damage the fetal rat, but only when the amount is 10 times higher than any human would ever ingest, even if they drank nothing but the most potent caffeinated beverage in a dose high enough to render them ill. A widely quoted paper in the Lancet in 1988 suggested that “women who consumed more” caffeine prenatally may be unwise, but the most potent artificial caffeine bolus was only just significant (1.72; 95% confidence interval 1.00 and 2.96). However, we do not know whether continuing high consumption puts the fetus at risk, or whether sustained consumption is simply a marker for a pregnancy that is already doomed, because an increased aversion to coffee is, along with nausea and vomiting, a consistent early feature of a healthy pregnancy. The report of a dose dependent relation between intake of caffeine before pregnancy and the risk of miscarriage suggests that a very high intake of caffeine prenatally may be unwise, but the adjusted odds ratio when the 186 women taking less than 75 mg a day were compared with the 230 taking more than 900 mg a day was only just significant (1.72; 95% confidence interval 1.00 and 2.96). Caffeine consumption does not make preterm birth more likely, and the only report of a link between consumption in late pregnancy and cot death could not be replicated. However, a paper in the BMJ in 2003 did report an excess of fetal death in the second half of pregnancy in Danish women who said at booking that they drank eight or more cups of coffee a day. So too did a subsequent study of women who said they drank four or more cups a day that used data from a national data set. A recent study in Uruguay, which did not fully adjust for smoking status, had similar findings.

Estimating fetal exposure is more difficult than is thought because cup size and the way the drink is prepared vary more than is realised. The caffeine content of different brands of tea and coffee also varies, and these drinks are not the only important dietary sources of caffeine (table).

Common drinks and foods and their typical caffeine content

<table>
<thead>
<tr>
<th>Drink or food</th>
<th>Caffeine content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cola and other “energy” drinks</td>
<td>12–60 mg/300 ml can</td>
</tr>
<tr>
<td>Bottled iced tea</td>
<td>15–25 mg/300 ml bottle</td>
</tr>
<tr>
<td>Brewed tea (non-herbal)*</td>
<td>20–50 mg/cup</td>
</tr>
<tr>
<td>Mate (South American tea)</td>
<td>30–60 mg/cup</td>
</tr>
<tr>
<td>Decaffeinated coffee</td>
<td>4–8 mg/cup</td>
</tr>
<tr>
<td>Instant coffee</td>
<td>40–140 mg/cup</td>
</tr>
<tr>
<td>Brewed coffee</td>
<td>60–200 mg/cup</td>
</tr>
<tr>
<td>Chocolate</td>
<td>5–35 mg/50 g bar</td>
</tr>
</tbody>
</table>

*Twenty per cent more than this for tea brewed for more than 3 minutes. †Taken to be a 300 ml (~10 fl oz) cup.

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1. None declared. Provenance and peer review: commissioned; not externally peer reviewed.

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doi: 10.1136/bmj.39122.395058.80
Managing suspected research misconduct
Authors, editors, and systematic reviewers should protect the public from unsound research data

In this week’s BMJ, Ian Roberts, Richard Smith, and Stephen Evans describe the worrying story of Dr Julio Cruz.¹ Cruz, a previously highly regarded medical researcher and clinician, committed suicide two years ago. Three of his publications about the use of high dose mannitol in head injury have recently been called into question. Furthermore, his coauthors and the editors of the journals in which the three papers were first published have failed to respond adequately to concerns raised about the integrity of the data in these papers.

These events have several important consequences. Many doctors base key treatment decisions on the results of published randomised trials. If some or all of Cruz’s data on high dose mannitol are false, then doctors will be providing their critically ill patients with uncertain and possibly harmful treatment. In doing so, those doctors will also deny their patients other treatments that are based on reliable evidence.

The failure to retract unsound data also has long term consequences as the data become integrated into reviews, meta-analyses, and guidelines. These syntheses of primary research affect the practice of clinicians worldwide, and in turn affect even larger numbers of patients. In addition, unless and until the veracity of Cruz’s data is formally proved or disproved, there is a risk that further research will not be conducted in this area. This again denies practising clinicians the possibility of access to the sound data they need.

Concerns about the authenticity of biomedical research data are increasingly being publicised. Recent high profile examples include publications by Jon Sudbo² and Hwang Woo-suk,¹ both of whom have had their results discredited or retracted. Importantly, however undesirable the publication of unsound data is, the consequences of such publication are made far worse by the subsequent failure of the people involved to react appropriately to valid concerns and correct the scientific record where necessary.

Part of the difficulty in dealing with Cruz’s data relates to his tragic death before the start of any formal investigation. As with at least one other prominent case of alleged misconduct,¹ he belonged to no institution that could be charged with undertaking the necessary investigation. In the wake of Cruz’s death, any reasonable person would assume that the responsibility for the disputed publications rested with the other investigators whose names appeared alongside his on the original papers. These individuals are co-authors of the published papers as defined by the International Committee of Medical Journal Editors,⁵ or at least contributors,⁶ and have themselves denied they were “gift authors.” Where they are unable to verify the findings with which their names are associated, they have a clear obligation, in our view, to take all necessary steps to correct the record. To date they have failed in this duty.

Several groups already provide guidelines on how editors should react if research misconduct, including publication of false data, is suspected. These groups include medical journals,⁷,⁸ the Committee on Publication Ethics,⁹ and the World Association of Medical Editors.¹⁰ In broad terms, editors are advised to discuss the situation with the authors involved. If this discussion does not produce a satisfactory result the situation should be referred to an appropriate higher authority—perhaps the authors’ academic institution or funding body. If, after an appropriate investigation, it is shown that false data have been published, the data should be retracted. Of note, the Committee on Publication Ethics makes particular mention that editors should react promptly to alert readers in situations where inaccuracies or misleading statements may have been published.

It is clear from communications between Roberts and Jane, editor of the Journal of Neurosurgery (which published one of the disputed Cruz papers), that Jane doubted the veracity of the Cruz data. However, an accompanying editorial in that journal by Marshall only alluded to general problems with single centre research studies. Jane did not inform readers that he did not trust the Cruz data and indeed suspected that it was fabricated.¹¹

Despite making considerable efforts, both Roberts and the BMJ Clinical Evidence editorial team have had great difficulty in contacting Michael Apuzzo, editor of Neurosurgery, in connection with the Cruz data. Neurosurgery published the two other disputed Cruz papers, and Apuzzo seems reluctant to address the serious criticisms of his journal’s content. In failing to alert readers promptly to concerns about the Cruz data published in their journals, Jane and Apuzzo have created confusion. The position ought to be made clear in the interests of patients around the world.

It has been left to Roberts, in his capacity as coordinating editor of the Cochrane injuries group, and his colleagues to investigate and attempt to resolve the tangle of claims and counter claims that surround Cruz’s data, and then to bring them out into the open. Their investigation of the three disputed papers should act as a model to which future systematic reviewers could usefully aspire. Systematic reviews, with or without meta-analyses, are appropriately replacing single clinical trials as agents that change and shape clinical practice. Consequently, researchers, such as Roberts, and organisations, such as the Cochrane Collaboration, that produce reviews have a growing responsibility to ensure that the data they summarise are valid. If done consistently, this assessment would become another
Atherothrombosis and ischaemic stroke

Unstable plaque is the main mechanism of stroke in patients with carotid stenosis

Thrombosis due to “unstable” atherosclerotic plaque is the main mechanism underlying acute coronary syndromes, and vascular research has focused mostly on this model. Plaque also causes a substantial proportion of ischaemic stroke, although multiple mechanisms are involved and “stable” plaque is sometimes responsible. For example, in the basilar and proximal middle cerebral arteries, stroke can result from occlusion of a small branch vessel by slow growth of otherwise “stable” plaque in the parent vessel. Slowly growing but stable plaque can also cause cerebral ischaemia due to stenosis and hypoperfusion without thromboembolism. Recent evidence, however, suggests that the predominant mechanism of stroke, at least in patients with carotid stenosis, is similar to the coronary model and involves mainly unstable plaque. This observation has implications for the way we manage and prevent strokes.

Carotid plaques are typically slow growing or quiescent for long periods but may suddenly develop ruptures, fissures, or endothelial erosions, triggering platelet aggregation and formation of thrombus, which leads to local occlusion or embolisation to more distal vessels. Recent studies have correlated histology of the plaque with time since last symptoms in patients with symptomatic stenosis undergoing endarterectomy. Spagnoli and colleagues studied 187 symptomatic plaques and reported that the frequency of thrombocytically active plaque was greater after stroke than after transient ischaemic attack, and that it fell with time from first ischaemic symptoms to surgery.

A similar study of 365 symptomatic carotid plaques found a high frequency of features that mark unstable plaque (for example, rupture of cap in 56.7%, a large lipid core in 59.6%, marked inflammatory infiltrate in 66.9%) and found that many of these features, particularly inflammation, were most frequent in patients with recent cerebral ischaemic events, especially after stroke. Interestingly, cap thickness in ruptured carotid plaques is much greater than that reported in ruptured coronary plaques, which has implications for identifying at risk plaques by imaging. However, rupture is still associated with a relatively thin cap and with pronounced macrophage infiltration.

The finding that coronary-type “unstable” plaque is responsible for a high proportion of transient ischaemic attacks and strokes in patients with carotid stenosis has important implications for prevention. Firstly, it highlights the need for urgency in investigation and treatment. The risk of major stroke distal to symptomatic carotid stenosis is up to 30% during the first month after the presenting event, but this risk falls rapidly with time, as does benefit from endarterectomy. In relevant trials, for patients with 50% or higher stenosis, the number needed to undergo surgery (number needed to treat) to prevent one ipsilateral stroke in five years was five for patients randomised within two weeks after their last ischaemic event versus 125 for patients randomised after 12 weeks. Unfortunately, the current average delay before endarterectomy in the United Kingdom is about 12 weeks, and many patients have a major stroke before investigation or surgery. The rapid fall in risk of stroke with time since presenting event could be due to the development of collateral circulation or the loss of a small subgroup of patients who are particularly susceptible to stroke for some other reason, but this fall is most likely to be due to healing of unstable plaque.

Secondly, the role of unstable plaque in the aetiology of ischaemic stroke indicates that sheer induced platelet aggregation could be involved in thrombus formation and that antiplatelet agents may...
have potential in the prevention of ischaemic stroke. This is consistent with recent data on the potential benefit of a short course of combinations of antiplatelet agents in patients with acutely symptomatic carotid stenosis, and the lack of efficacy of warfarin in patients with intracranial stenosis.

There are also important implications for research. Firstly, unstable carotid plaque can be imaged in vivo, so imaging might have a role in risk stratification. Ulceration of the surface of the plaque on conventional arterial angiography, which is strongly associated with unstable plaque on histology, is a strong independent predictor of stroke, and has been included in risk models for patients with symptomatic carotid stenosis. Carotid ultrasound can identify lipid-rich echolucent plaques, and magnetic resonance imaging can detect both lipid core and intraplaque haemorrhage, although more research is needed to determine whether these assessments predict stroke. Novel imaging techniques using magnetic resonance imaging, positron emission tomography, and molecular radiolabelling also allow quantification of macrophage infiltration, neovascularisation, metabolic activity, and even protease activity and apoptosis.

Secondly, carotid plaques also provide an indirect window on the coronary circulation. Non-invasive measurements of carotid stenosis can predict severe coronary artery disease in patients with suspected ischaemic heart disease and future acute coronary events in patients with coronary artery disease. Importantly, ruptured carotid plaques are more likely than smooth plaques to be associated with future coronary events, which suggests that plaque instability is a systemic phenomenon and that non-invasive assessment of carotid plaque instability might also be a useful index of coronary risk.

Thirdly, the importance of instability of stenosing carotid plaques as a cause of transient ischaemic attack and stroke raises the possibility that, as in the coronary circulation, many acute carotid ischaemic events might be caused by instability in non-stenosing plaque. Although the average risk of stroke in patients without appreciable carotid stenosis is insufficient to merit endarterectomy, recent developments in imaging techniques allow the subgroup of patients with unstable plaques to be better identified and will necessitate further research to determine optimal treatment.

Finally, most of what we know about atherosclerotic plaque and stroke relates to disease at the carotid bifurcation—the only arterial segment routinely imaged after a stroke or transient ischaemic attack in most centres. However, many other points of branching, tortuosity, or confluence of the arterial supply to the brain are also prone to disease. Common sites of extracranial atheroma include the aortic arch, where large plaques are an important risk factor for ischaemic stroke; the proximal subclavian and common carotid arteries; and the origins of the vertebral arteries. The intracranial arteries are prone to atherosclerosis at the carotid siphon, the proximal middle cerebral artery, the intracranial vertebral arteries, and the basilar artery origin. Although intracranial disease does appear to be associated with a high risk of recurrent stroke on medical treatment, the proportion of all strokes caused by plaque at sites other than the carotid bifurcation is unknown and will differ between populations. Carotid and other extracranial atherosclerosis is most common in white men, whereas intracranial disease is most common in black, Hispanic, and oriental populations, in patients with type 1 diabetes, and in younger women. More research is required into imaging and treatment of disease at sites other than the carotid bifurcation, particularly in patients with ischaemic events in the posterior circulation, in whom the early risk of recurrent stroke is probably as high as in patients with carotid stenosis.

References are on bmj.com
increased resources in radiotherapy was made, we have become part of a new cancer network; the five main primary care trusts whose patients we treated no longer exist, and nor does the strategic health authority. To whom, therefore, should we be putting forward our business cases? And what are their funding decisions likely to be in these financially challenged times?

Glasgow is a wake up call, not only for individual departments but for the NHS as a whole: this is a national issue, not a local one.

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Competing interests: None declared.

1 Donaldson L. Reducing harm from radiotherapy. BMJ 2007;334:272. (10 February.)
2 Unintended overexposure of patient Lisa Norris during radiotherapy treatment at the Beatson Oncology Centre, Glasgow in January 2006. Report of an investigation for IR(ME)R.

Culture of secrecy must be tackled

The Royal College of Radiologists welcomes the chief medical officer’s editorial on reducing harm from radiotherapy. In the five years to April 2006, only 211 incidents of a dose greater than intended were reported under the IR(ME) regulations. Many of these were correctable by adjusting subsequent treatment. Patient injury is a rare event; this is as it should be for a non-emergency treatment given routinely to patients with an established diagnosis.

In June 2006 the Royal College of Radiologists set up a multidisciplinary working party to identify measures to prevent and mitigate errors in radiotherapy. One of the main obstacles to this work is the culture of secrecy surrounding radiotherapy incidents. The system for reporting radiotherapy incidents in the United Kingdom is dysfunctional: the results of inquiries are secret; there is no dissemination of learning; errors are repeated; and public confidence is eroded. Most of the incidents reported under the IR(ME) regulations remain confidential and can only be identified under the Freedom of Information Act. The full report of the inquiry into the Leeds incident has still not been published despite the fact that it contains a number of recommendations for practice nationally.

Open publication, as in the Glasgow incident, is the exception but should be the rule. This could be facilitated by establishing a website to host anonymised reports of inquiries. At the very least, a confidential system to disseminate learning on the National Confidential Enquiry into Perioperative Deaths (NCEPOD) model should be established. This would involve collaboration between the National Patient Safety Agency, the Health Protection Agency, and the Healthcare Commission. Change in the UK is essential if we are to improve our learning from errors.

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Competing interests: None declared.

1 Donaldson L. Reducing harm from radiotherapy. BMJ 2007;334:272. (10 February.)
2 Over 200 hurt or killed by botted radiation. Sunday Times 2006 April 30.

RANIBIZUMAB AND BEVACIZUMAB

The cheaper drug, bevacizumab, should be referred to NICE

We think that Chakravarthy and Lim could have said more about the pricing of ranibizumab and bevacizumab. Both drugs are owned by a single company, Roche/Genentech, which has no intention of licensing the cheaper. The US price of ranibizumab is $1950 or roughly £1000 per injection. Monthly injections would cost £12000 per patient. Bevacizumab, which is licensed for cancer treatment, could cost as little as £17 per injection, as the dosages used for eyes are minute compared with cancer. In the US, off-licence bevacizumab is estimated to cost $17-50 (£8-25) including the costs of splitting up the larger cancer doses. By refusing to license bevacizumab for macular degeneration, Roche/Genentech is raising the price by an unprecedented factor of over 50.

Given the lack of data directly comparing these two drugs, we support the call for a head to head trial (indeed we are part of a team bidding to do such a trial). We wish to make three further points.

Firstly, we have modelled how much more effective bevacizumab would have
to be relative to ranibizumab in order to meet the National Institute of Health and Clinical Excellence (NICE) threshold of £30 000/QALY. Using best estimates of current US prices of $1950 and (a high) $50, ranibizumab would need to be 2.5 times more efficacious to meet NICE’s threshold. This seems highly unlikely, given the similarity of the two drugs and the observational data that exist on the effectiveness of avastin. Even if ranibizumab’s price was reduced to $500, it would have to be more than 5% better than bevacizumab to be cost effective.

Secondly, the review by NICE of ranibizumab versus standard care for patients with the predominantly classic form of macular degeneration, due to report by October 2007, could imperil any head to head trial in the UK. Should NICE find in favour of ranibizumab, then those patients may well prefer to be treated with ranibizumab rather than being randomised. Any UK trial must recruit quickly.

Thirdly, bevacizumab has been excluded from the NICE review because it is unlicensed. Exclusion of unlicensed drugs is normally sensible owing to lack of data. However, given that Roche/Genentech, which owns both drugs, has no plans to license the cheaper, an exception should be considered. Even if a trial were to show bevacizumab to be equivalent to ranibizumab, it would require Department of Health authorisation before bevacizumab could be widely used. The department should urgently consider referring bevacizumab for NICE appraisal.

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Competing interests: Both JR and AL are part of a bid for funding of a head to head comparison of bevacizumab and ranibizumab.


MENTAL HEALTH OF OFFENDERS

Young military veterans show similar help seeking behaviour

A study undertaken by the King’s Centre for Military Health Research had similar findings to those reported by Howerton et al.1 The study investigated the help seeking paths of young men (n=74) leaving Colchester Military Corrective Training Centre.2 Young veterans found it difficult to access available resettlement services for a variety of reasons including: previous bad experiences with other services, lack of knowledge of what services were available, and feelings that these services would not be able to help. Additionally, this group had high levels of mental ill health, both before discharge (n=61, 82%) and six months after leaving (n=39, 53%). Only a small minority of those with mental health problems were seeking help for these problems, and most preferred to use informal networks of support, such as friends and family. Six months after leaving, only one participant with a mental health problem reported seeking help for it.

Services need to be better targeted to address the needs of these more vulnerable groups. Further, services based on less formal support networks (such as mentoring) may provide a more successful way to integrate vulnerable groups into resettlement services. In our study population, 82% (n=61) said that they would have found a mentor useful in their transition from military prison into civilian life. This structure could provide “an informal relationship delivered in a formal structure” and so better mimic the chosen support networks of this vulnerable group.

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Competing interests: None declared.


ABORTION

Time to erase the line?

As a longstanding anti-choicer, I commend Gornall on a balanced and informative article on abortion.1 It got me wondering if the abortion debate isn’t all a bit pointless. Pro-choicers and pro-lifers disagree profoundly on whether children can be treated differently depending on whether it’s before or after they’re born. The “right” answer to this seems to depend on what part of the world you’re in. Even within the mainly pro-choice United Kingdom, one nation (Northern Ireland) remains essentially pro-life. This argument will continue for the foreseeable future without a winner.

What if we changed the focus to our main area of agreement: that women and children should be able to lead happy and fulfilling lives?

What if pro-choicers and pro-lifers worked together for a better deal for pregnant women and the parents of young children? Does anyone really want any woman to have an abortion because she can’t afford to have a baby or because her job prospects will be wrecked? As a society, are we really doing enough to give women a real choice? How can a 36 year old medical consultant is able to have children with relatively little detrimental impact on finances or career compared with a 25 year old junior doctor or a 36 year old cleaner? What if maternity pay and leave was funded by the government rather than individual companies so that the cost is evenly distributed? What if …?

The general consensus in Britain is that abortion is a necessary evil. Pro-lifers have spent a lot of time unsuccessfully trying to persuade the public that abortion is too evil to be necessary. It might be time to accept the prevailing view and instead work towards a society where it’s unnecessary to be so evil. And perhaps pro-choicers can join us? Then maybe we can all be truly pro-choice.

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NUTRITIONISTS

Give us food sense, not nonsense

For those uncertain of the quality of nutritionists,1 dietitians have long had an anecdotal way to separate those qualified in nutrition from those not. Avoid the amateur musings of any nutritionist advocating “detox,” “superfood” or multiple food group exclusions at first consultation, or who give “candida overgrowth” as a viable clinical diagnosis. For those considering major dietary exclusions as a blunt tool to correct symptoms, I suggest they recall the quote by Fran Lebowitz, with whom registered dietitians would concur, that “Food is an important part of a balanced diet.”

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Competing interests: None declared.

1 Goldacre B. Tell us the truth about nutritionists. BMJ/2007;334:292. (10 February.)
NHS pays too much for branded drugs

Susan Mayor | LONDON

The UK health services are overpaying by about £500m (€740m; $980m) a year for prescription drugs, says a government report published this week. This is because of the current system for pricing drugs in the United Kingdom, it says, and it calls for the pricing scheme to be changed to reflect the benefit of drugs to patients.

The report, from the Office of Fair Trading, a body that protects consumers’ interests in the UK, found that many alternative products were available in the areas of greatest NHS expenditure, including drugs for raised cholesterol concentrations and high blood pressure.

Several drugs currently prescribed in large volumes were up to 10 times more expensive than alternatives that the researchers considered delivered very similar benefits to patients. They argue that hundreds of millions of pounds are spent on the more expensive products each year, restricting funds available for other drugs.

On the basis of its findings, which included a survey of 1000 GPs on their prescribing habits and a comparison with drug prices in 10 other countries, the Office of Fair Trading argued that the current drug pricing system, the pharmaceutical price regulation scheme, should be reformed, to deliver better value for money to the NHS and to focus business investment on drugs that have the greatest benefits for patients.

The report recommends changing to a patient focused, value based pricing scheme, in which the prices the NHS pays for drugs reflect the therapeutic benefits they bring to patients. It argues that this would enable the NHS to obtain greater value for money from its existing drug budget. The authors estimate that this would release in the region of £500m of expenditure that they say could be used more effectively.

The Pharmaceutical Price Regulation Scheme: An OFT market study can be found at www.oft.gov.uk.
The government suffered three crushing defeats in the House of Lords this week over the controversial Mental Health Bill. The bill would allow people with severe personality disorders who have committed no crime to be detained if they were judged a threat to themselves or others.

As the BMJ went to press on Tuesday, ministers were considering whether to try to reverse the defeats inflicted by peers from all sides during the report stage of the bill.

In the biggest setback for ministers, peers voted by a 71 vote majority to ensure that patients can be detained for treatment only if it is likely to alleviate their condition or prevent it getting worse. The bill simply requires that “appropriate medical treatment” be available for the patient.

The government offered a compromise amendment, defining the purpose of treatment as “to alleviate, or prevent a worsening of, the disorder or one or more of its symptoms or effects.” But the Liberal Democrat peer Lord Carlile successfully pressed his amendment to a vote.

“It is quite wrong that there should be compulsory detention in a hospital where there is no therapeutic benefit,” he said.

A second defeat came because of the definition of mental disorder in the bill. Peers voted by a majority of 88 to make specific exclusions for drug misuse; sexual identity or orientation; cultural, religious, or political beliefs; and disorderly conduct.

In a third defeat for the government, the lords voted by a majority of 39 to ensure that a doctor would take the final decision—rather than merely being consulted by a “clinician” who may not be medically qualified—on whether to renew a patient's detention.

Roche fined over “extravagant” meals for doctors

Bob Burton CANBERRA

Roche has been fined $A75 000 (£30 200; €44 900; $59 100) for breaching provisions of the Australian drug industry’s voluntary marketing code of conduct specifying that hospitality should be “simple and modest.”

In July last year the BMJ (2006;333:169) and the Australian newspaper reported that Roche Products spent more than $A710 000 on three lavish conference dinners for about 330 doctors. Since then the Therapeutic Goods Administration, the Australian government drug regulator, lodged a complaint alleging that Roche may have breached six provisions of the code. Roche is a subsidiary of the Swiss based F Hoffmann-La Roche Group. The meals, associated with a two day long haematology and oncology symposium and another workshop in mid-2005, were provided at leading Sydney restaurants, like the one above.

Roche’s drug rituximab (MabThera), which is used to treat non-Hodgkin’s lymphoma, is the company’s biggest earner and accounted for more than a 10th of the company’s 42bn Swiss francs (£17.4bn; €26bn; $34bn) income in 2006.

The code of conduct committee, which is run by the main lobby group for the drug industry, Medicines Australia, and investigates code complaints, noted that there are “no financial limits on hospitality imposed in the Code,” but nevertheless thought that the code had been breached.

A minority of committee members objected to the suggestion that meals with an average cost of $A215 per attendee were “excessive.” However, most thought that the hospitality was “extravagant” and “brought the industry into disrepute.”

The committee classified the breach of the code as “severe,” which allowed it to impose a maximum fine of $A200 000. Instead it imposed a fine of $A75 000 on the basis that one moderating factor was “the high quality and substance of the education provided.”

Mukesh Haikerwal, national president of the Australian Medical Association, the main doctors’ group, believes the onus is on drug companies not doctors to ensure any hospitality complies with the code.

Peter Mansfield, from the drug marketing watchdog Healthy Skepticism, disagrees. He argues that research on the effect of hospitality on prescribing patterns shows that “the only way to prevent doctors spreading the bias infection is by refusing drug company meals.”

In the year to 30 June 2006, the Australian government spent more than $A145 000 a day on rituximab.

A Roche spokeswoman, Libby Day, said that the company has reviewed its interpretation of the code.

Attorney General to scrutinise Southall’s “special” files

Clare Dyer BMJ

The attorney general, Lord Goldsmith, is to review 4450 “special” files kept on patients and former patients by the paediatrician David Southall amid fears that he may not have disclosed all the material he had when he acted as a prosecution witness in criminal trials.

The review, which is expected to take six months, will also examine all the criminal trials in which Professor Southall acted as a witness for the prosecution in the past 10 years.

A hearing by the General Medical Council into charges that Professor Southall kept “what amounted to secret medical records” on four children ran out of time last December and has been adjourned until November this year.

The consultant paediatrician is thought to have created 4450 “special” files, not placed with hospital medical records, during his time at London’s Royal Brompton Hospital and in his current post at North Staffordshire Royal Infirmary in Stoke-on-Trent.

The attorney general said in a statement to the House of Lords, “It is said that Professor Southall kept so-called ‘special case’ files containing original medical records relating to his patients that were not also kept on the child’s proper hospital file.

“Concerns have been raised that in some of those cases criminal proceedings may have been taken but the existence of the files was not revealed, resulting in their not being disclosed as part of the prosecution process. I share those concerns.

“What is not clear at this stage is the nature and extent of the failure of disclosure, if such it be. I have therefore decided that I will conduct an assessment of the cases where Professor Southall was instructed as a prosecution witness to determine if any ‘special case’ files existed.”

Doctors engaged as prosecution witnesses are obliged to reveal all their material to defence lawyers, including an index of any unused material. The attorney general’s previous review of cases in which parents were convicted of killing their children has already identified a number of cases in which Professor Southall acted as a witness. That review was instigated by concerns about expert evidence after the convictions of Sally Clark and Angela Cannings for murdering their children were quashed.

Professor Southall was found guilty of serious professional misconduct and barred from child protection work for three years in 2004 after accusing Sally Clark’s husband Stephen of murdering one of their sons on the basis of watching a television interview with him.

In the current GMC hearing, the paediatrician is accused of tampering with medical records and keeping secret medical files and making them inaccessible to other people involved in the children’s care. He also faces a new GMC case relating to his research into continuous negative extrathoracic pressure, an experimental system of neonatal ventilation. He denies serious professional misconduct.

Health Bill for England and Wales

Lord Carlile (left), Baroness Meacher and Earl Howe all supported amendments to the Bill

US campaign aims to end industry gifts and speaking fees

Janice Hopkins Tanne New York

A new campaign will urge US doctors, academic medical centres, medical societies, and other healthcare organisations to work together to end the conflicts of interests that result from ties to companies that make drugs and medical devices.

The campaign is funded by a two year, $6m (£3.1m; €4.6m) grant from the Pew Charitable Trusts. It will be organised by The Prescription Project, a new group working with Community Catalyst, a Boston healthcare advocacy group, and the Institute on Medicine as a Profession at Columbia University in New York (www.pewtrusts.org).

The campaign was sparked by an article last year in JAMA (2006;295:429-33), in which leading academics said, “More stringent regulation is necessary, including the elimination or modification of common practices related to small gifts, pharmaceutical samples, continuing medical education, funds for physician travel, speakers’ bureaus, ghostwriting, and consulting and research contracts.

“We propose a policy under which academic medical centers would take the lead in eliminating the conflicts of interest that still characterize the relationship between physicians and the health care industry.”

Robert Restuccia, executive director of The Prescription Project, said, “The prescribing practices of doctors are being influenced by billions of dollars in direct-to-physician marketing. When Americans visit their doctor and get a prescription, they should know he or she is relying only on the best medical information, not the latest marketing campaign.”

The Prescription Project says that US residents received 3.6 billion prescriptions in 2005—about 12.3 a person. National spending on prescription drugs is growing at double the rate of other health services and is approaching $200bn a year. In 2004 consumers paid out of their own pockets for about a quarter of prescribed drugs. Cost effective, evidence based prescribing would benefit many.

The project says it will “document the scope of the problem [industry influence] and its impact on healthcare quality and cost, and collaborate with medical organizations to improve prescribing.”
Prison improves health of female users of illegal drugs

Anne Griffin

The health of female prisoners who are drug users tends to improve during their time in prison, a study from Oxford University funded by the King's Fund has found.

Three quarters of the 505 women studied by researchers from Oxford's public health department had used illegal drugs in the six months before imprisonment. After one and three months' imprisonment, drug users' health had improved, but it remained worse than in the general population.

“The most striking finding was just how poor the women's health was on arrival,” said Emma Plugge, lead author of the study and senior research scientist. “In the case of drug users, [their health was] significantly worse than that of women in … the general population with the poorest health.

“Women described the way in which acquiring drugs and maintaining their addiction had taken precedence in their lives to the detriment of almost everything else, including their health,” said Dr Plugge. “These women led such chaotic lives outside prison that prison life was a respite. Their health improved as a result.”

The study used questionnaires to find out about the women's subjective sense of their own health, as well as about diet, alcohol consumption, and drug use. “Regular meals, consistent shelter and protection from violence by a partner or street violence were all things which many of these women were not getting in the outside world,” said Dr Plugge.

For the study population, some health behaviours had improved in prison: the proportion of smokers remained the same, but the amount smoked decreased; alcohol consumption and drug use decreased; and fewer women were exchanging sex for goods or money.

Twenty seven per cent of women had been paid in money, goods, or drugs for sex at some time before entering prison. After the first month of imprisonment, some women continued to exchange sex for money, goods, or drugs; four women said they had been paid for sex in the past month, and one woman said she had paid for sex.

After three months, women were more likely to be taking drugs for depression or high blood pressure, indicating that health consultations in prison tackle unmet needs. Exercise and diet, however, did not improve, and rates of self harm did not change significantly.

For all the women in the study, poor mental health, mainly depression and anxiety, was a common and significant feature of descriptions of health status. Without drug use and mental illness, the researchers noted, some of the women may not have ended up in prison in the first place: “For many of these women, their prior health status was directly linked to their offending. There was theft to finance chronic addiction and offences directly linked to mental health problems.”

The overall health of women who were not drug users stayed roughly the same during their time in prison. But these women said that they felt their health had declined because of poor hygiene, poor diet and other factors.

The report, The Health of Women in Prison: Study Findings, is available at [www.publichealth.ox.ac.uk/units/prison](http://www.publichealth.ox.ac.uk/units/prison).

German project for drug addicts not extended despite good results

Annette Tuffs

A controversial German project to treat drug addicts, in which severely dependent addicts receive twice daily injections of diamorphine, is not going to be extended by the seven centres in which it now operates, it was announced last week.

The programme, which treats about 300 addicts, has aroused strong opposition from the ranks of the conservative Christian Democrat party, which forms part of Germany's coalition government.

The project started as a controlled trial in 2002, comparing the use of diamorphine and methadone in two groups of drug users, a total of 1120 altogether. The trial ended in June 2006, and the results indicated that the use of diamorphine was more effective in improving the health and lifestyle of addicts than the use of methadone (Current Opinion in Psychiatry 2006;19:631-6).

Opponents of the trial claimed that it made the state a drug dealer and that the €30m (£20m; $39m) spent on the project could have been better spent on preventive measures.

The aim was to treat persistent heroin addicts for whom other treatments had failed and to help them build a relatively normal life.

The addicts had to be at least 23 years old, using intravenous drugs, and addicted to heroin for at least five years.

Results showed that the addicts given heroin fared better than those given methadone. “Those taking heroin did not drop out as much as the methadone group. They had much less illicit drug use of street heroin and cocaine and better health records,” said Christian Haassen, from the Hamburg University Hospital Addiction Centre, who is in charge of the study.

See [www.heroinstudie.de](http://www.heroinstudie.de) for more information, which is also in English.
Tough measures are needed to tackle doping in sport, say MPs

Zosia Kmietowicz LONDON

MPs have called for an independent agency to be established to toughen the United Kingdom’s stance on doping in sport and to set a good example to play “clean” for the 2012 Olympic Games.

In a report the House of Commons Science and Technology Committee says that more needs to be done on every level to combat the use of illegal substances by athletes. School children need to be taught about the risks of doping, and athletes and their attending coaches and doctors need more comprehensive education about which substances are banned and why they appear on the prohibited list, it says.

It also says that more research should be done to develop more sophisticated techniques for detecting banned substances, which should include blood tests as well as urine sampling. And much tougher measures should be introduced for athletes caught doping.

Phil Willis, the committee’s chairman, said: “Sport matters to people, and any scandal associated with British sportsmen or women resonates way beyond the immediate sporting world. It can be a matter of national humiliation.

“The 2012 Olympics have given us the perfect opportunity to showcase the best of British sporting talent. We must not risk turning an occasion for national pride into one of embarrassment and disgrace. That is why the government and the international sporting bodies concerned must do much more to identify and prevent doping scandals now.”

The cross party group of MPs says that athletes caught cheating by using chemicals or biological agents should be banned from sport for four years and ordered to repay any financial gains they have made since their last clean test. Athletes should also have to state where they obtained the banned substances before they are allowed to return to competitive sport.

During its inquiry the committee held four oral sessions taking evidence from athletes, medical officers, sports scientists, and doping experts. The committee concluded that official figures on the incidence of illegal doping may not accurately reflect the problem, and it called for more research into the true scale of the problem.

Figures from the World Anti-Doping Agency show that 2.1% of tests for banned substances resulted in “adverse analytical findings” in 2005; in the UK 1.3% of 7968 tests proved positive in 2005-6.

To make it easier to detect performances improved by illegal substances all UK athletes should be made to compete on the international circuit during the 12 months before the Olympics, says the report. And a new agency that is independent of UK Sport and other national sporting bodies should be set up to test athletes for drug use. The agency should also monitor and evaluate potential new illegal substances and methods as they are developed.

The report also recommends a pilot project to examine the feasibility of a physiological or doping passport to be carried by all athletes. This would record the results of doping tests and natural concentrations of hormones such as erythropoietin during their careers, which would make it easier to detect any substance abuse, the committee says.

The committee also expressed concern at the ease in which banned and potentially dangerous substances can be obtained for use by athletes. It recommended that the government review regulation in this area.

Human Enhancements Technologies in Sport is available at [www.parliament.uk](http://www.parliament.uk)

UK pilot allows pharmacists to supply sildenafil

Susan Mayor LONDON

Doctors are welcoming a pilot study launched in an English city last week in which men with erectile dysfunction can buy sildenafil (Viagra) directly from community pharmacists rather than having to be prescribed the drug by a doctor. But they feel the scheme does not tackle the inequity of the present system, under which some male patients are able to obtain the drug free on the NHS while others are excluded from free treatment. Some experts also object to the fact that the scheme is limited to only one drug.

Three pharmacies—part of the Boots chain—in Manchester are piloting the new service, which involves an initial screening with a pharmacist and long term follow-up for men wanting ongoing provision of sildenafil. The potential for the scheme to be extended across the UK will be assessed later this year.

Geoffrey Hackett, a GP and consultant urologist at Good Hope Hospital in Sutton Coldfield and president of the British Society of Sexual Medicine, argued that more men should be eligible for treatment on the NHS. Drug treatment can be provided only to patients whose erectile dysfunction is due to specified causes, including diabetes, multiple sclerosis, and major pelvic surgery, and where it causes severe distress, as assessed by a specialist.

Dr Hackett said, “Erectile dysfunction should be reclassified as peripheral arterial disease. Treating peripheral vascular disease in the feet and toes in patients with diabetes is an NHS priority. So why is disease affecting another set of peripheral vessels not considered as important?”

He also considered that the Boots programme limits treatment options, “Patients are entering into a consultation where there is only one possible treatment option. But Viagra is only one of the treatment options for erectile dysfunction. Patients should be assessed for the best treatment for them.”

A spokesperson for Boots said, “We make it very clear in our programme that we are only checking if one particular treatment (Viagra 50 mg) works for that patient. We chose Viagra as it has a longer licence than the other treatments available and so more safety data was available.”

“Any scandal associated with British sportsmen or women resonates way beyond the... sporting world”

Dwain Chambers who was banned for using anabolic steroids
Robbing Peter to pay Paul

Junior doctors are seeing cuts in study leave and cancelled courses as trusts and strategic health authorities raid education budgets to balance their books. Lisa Hitchen reports

Lisa Hitchen LONDON

As the end of the financial year looms, UK doctors are worried that strategic health authorities (SHAs) and primary care organisations will use education and training money to reduce their health service deficits.

“There is a commitment for the NHS to balance its books by April. We are very much hoping they won’t take [money] from the education budgets,” said Andrew Rowland, vice chairman of the BMA’s Junior Doctors Committee.

Education and training budgets are vulnerable not only because of deficits in the NHS but also because the money that the Department of Health gives for educating and training doctors is no longer ring fenced.

Until April 2006, the cash given to strategic health authorities for education and training had to be spent on just that—education and training. Last year, however, that protection was removed.

The House of Commons health committee drew attention to the vulnerability of these budgets last December, saying, “There is an immediate danger of funding distributed by the Department of Health for education and training purposes … being used for other purposes by the SHAs” (BMJ 2006;333:1236).

Funding for education and training comes from two levies: the service increment for teaching (SIFT) for undergraduate teaching and the medical and dental education levy (MADEL) for postgraduate teaching. Together with another levy for non-medical staff they make up what is known as the multiprofessional education and training levy (MPET).

Money from SIFT is not payment for teaching as such but is designed to allow for the extra costs to the NHS of having students present when patients are seen by doctors. Consultants in an outpatient clinic, for example, generally see fewer patients if students are present. Money from MADEL, however, pays some salary costs and includes payment for study leave.

With ring fencing gone, NHS money for undergraduate medical training, junior doctors’ study leave, and discretionary posts for academic consultants has all ended up in a central “contingency fund.”

Consequently, medical schools’ SIFT budgets were cut by 5-15% nationally, meaning that some teaching programmes were cancelled, at a time when the number of medical students was rising. These included life support courses, which are needed by doctors working in the acute sector.

One of the medical schools that seemed most at risk was at the University of Leicester, because it gets a massive 67% of its funding for clinical academic posts from the NHS, as opposed to the Higher Education Funding Council. The national average is 38%. Earlier this year it seemed that the school would have to cut some of its medical academic posts, but eventually it managed to make savings without reducing staff. But its 10% cut still means the school has not been able to recruit staff for the next research assessment exercise.

Another organisation affected is Worthing and Southlands Hospitals NHS Trust. Last October the deanery for Kent, Surrey, and Sussex saw a 14% cut in its funding from the South East Coast Strategic Health Authority, with 11.4% of this cut handed on to the Worthing and Southlands Hospitals NHS Trust.

With the hospital getting £340,000 (£505,000; $663,000) less than it was expecting, outgoings, such as for study leave and travel expenses, were stopped.

Junior doctors were extremely demoralised by the situation, said Gordon Caldwell, the director of medical education. Trust in the strategic health authority had been “severely damaged.” Dr Caldwell is adamant that ring fencing should be brought back and is fearful for next year.

Julian Bashforth, chairman of the BMA’s Wessex junior doctors committee, who is about to join a GP vocational training scheme, is equally worried after his dealings with South Central Strategic Health Authority over next year’s funding plans for Southampton University NHS Trust.

A representative from the authority told him earlier this month that the Department of Health was going to restore to it the £38.5m cut from the MPET budget, but the authority’s provisional plan was to pass only £13.5m of this back into training and education. The rest would go into a pot, with £75m from primary care trusts. This £100m would then be divided up after NHS organisations had bid for it.

This year’s cut had already led to freezes in study leave and other budgets and jobs not being replaced, said Dr Bashforth. Money for some essential courses, however, such as paediatric life support, has been found from other budgets.

“We are challenging the SHAs’ right to do this,” he said. “As the PCTs [primary care trusts] are the majority shareholder in the proposed £100m fund, it seems inevitable that they will have the deciding vote when it comes to spending the money. We believe that this would mean losing the majority of the £25m to subsidise clinical services.”

The BMJ contacted South Central Strategic Health Authority, but they did not respond before this article went to press.

Other strategic health authorities are likely to follow the policy of pooling money with PCTs, predicts Michael Rees, chairman of the BMA’s Medical Academic Staff
Committee. “I think what is happening in Southampton will be repeated elsewhere.”

Some GPs who provide undergraduate training with money from SIFT are also worried. Roy Macgregor, a GP partner and lead for undergraduate and postgraduate teaching at a practice in north London, said that the cuts to education budgets were also likely to threaten provision by GPs and that that would have a knock-on effect on “the variety and nature of undergraduate training.”

“The cuts—both from the PCT and the London Deanery—have made attachments to the surgery and study leave more difficult to finance. The deanery has significantly cut the availability of funding to support registrars and the students coming out of medical school,” he said.

But it is not all bad news. Gareth Williams, dean of the faculty of medicine and dentistry at Bristol Medical School, praised his trust for recognising the importance of education and fighting to secure training monies in this financial year.

“Trusts in Bristol have been able to defend teaching, and we are very grateful for that.”

A network of clinical academies set up by the school meant that money used for training could also be more clearly accounted for, unlike arrangements under the traditional SIFT system, which are outdated, he said.

“Because it was negotiated from scratch we know exactly how much money there is, and it is traceable,” he said.

Next year there are plans to run all components of the budget together, he said. With no ring fencing, SIFT money is potentially at risk again, but a big cut is not expected.

Katie Petty-Saphon, executive director of the Council of Heads of Medical Schools, was also “quietly optimistic” for the next financial year—with central budgets for SHAs to pay for education up by 5.3%. “Hopefully that will protect education, and the money will be spent as intended,” she said.

“The situation is plateauing. We are quietly optimistic that it will be much better next year. SHAs have more staff, and they are understanding their roles and responsibilities better. They know they need to be committed to education. This [latest crisis] was a one off, but there still needs to be a real champion for education in the Department of Health.”

The Department of Health remains adamant that it will not reintroduce ring fencing, because it wants to continue to allow SHAs maximum flexibility.

Hospitals get cash for the extra time it takes for doctors to see patients when students are present

IN BRIEF

Inquiry investigates contaminated blood: An independent public inquiry is to examine the provision of contaminated blood by the NHS before 1991, which infected thousands of people with haemophilia with HIV and hepatitis C. The Labour peer Lord Archer of Sandwell, a former solicitor general, will chair the inquiry. Lord Tummb, past president of the Royal College of Physicians, will be medical assessor.

Court says Eli Lilly’s documents must be returned: The US federal court judge Jack Weinstein has said that eight defendants must return Eli Lilly internal documents on the marketing and side effects of olanzapine (Zyprexa) (BMJ 2007;334:59, 171). However, the documents remain available on the internet. His ruling is at www.eff.org/legal/ cases/zyprexa/zyprexa_judgement.pdf

German health reform is finally agreed: The much disputed German healthcare reform passed the final legislative hurdle last Friday. Representatives of Germany’s 16 states approved the bill despite severe reservations in the upper house of parliament. The reform should come into effect on 1 April 2007, but key aspects, such as a new system for collecting and distributing the statutory contributions, were postponed to 2009.

Cruise liners not responsible for ships’ doctors: The Florida Supreme Court has ruled that cruise liners are not responsible for the negligent actions of ships’ doctors, which they successfully argued to be independent contractors. It overturned the decision of a lower court in favour of Elizabeth Carlyle, aged 14 years, whose ruptured appendix was misdiagnosed as flu on a 1997 cruise to Mexico.

German doctors criticise funding of patient group: The German hospital doctors’ union, Marburger Bund, has criticised the health ministry for spending €5.1m (£3.4m; $6.7m) a year until 2010 on the independent patient advisory service corporation, a patient lobby group with a network of 22 offices. The union says doctors and health insurances should be included in the initiative.

UK officials test plans for flu epidemic: Hundreds of health officials from throughout Great Britain took part in a logistical exercise this week to see how a flu pandemic would be dealt with. Officials estimate that a flu pandemic would cause 400 000 deaths in the United Kingdom.
Drug eluting stents may increase long term mortality due to late stent thrombosis

**Drug Eluting Stents**

<table>
<thead>
<tr>
<th>Risk ratio:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug eluting stent</td>
<td>1.03 (0.84 to 1.26)</td>
<td></td>
</tr>
<tr>
<td>Bare metal stent</td>
<td>1.32 (1.11 to 1.57)</td>
<td></td>
</tr>
</tbody>
</table>

Compared with bare metal stents, drug eluting stents seem to have an increased risk of late stent thrombosis, a potentially fatal complication of percutaneous coronary revascularisation. A recent cluster of five research papers and several commentaries shows the complexities of ascertaining which type of stent is better in the long run. The definitive evidence is still a long way off.

There seems to be no doubt that, in the short term, drug eluting stents reduce the need for revascularisation by about a half. In the longer term, however, increased risk of late stent thrombosis might translate into increased risk of death and non-fatal myocardial infarction.

Four recent trials (extensions of the original research that was the basis for getting drug eluting stents approved and which had less than 50% power to detect a doubling of the risk of death in patients for whom treatment with drug eluting stents is approved) failed to show a difference between groups for increased risk of death and non-fatal myocardial infarction. But a large, Swedish non-randomised study found that after six months the risk of death started to increase for people treated with drug eluting stents, compared with those with bare metal stents. At three years, the adjusted risk of death was 1.3-fold higher.

Drug eluting stents are approved only for clinically stable patients without serious comorbidities and with newly diagnosed coronary lesions up to 3 cm long. However, less than 60% of people treated with drug eluting stents today fit this profile. Off-label use in people with more serious disease is common.

Until definitive answers are available on the long term safety of drug eluting stents, it might make sense not to use them off-label, suggests one of the commentaries (http://content.nejm.org/cgi/content/full/NEJMp068304/DC1).

**N Engl J Med** 2007; 356:989-97; 998-1008; 1009-19; 1020-9; 1030-9

**New models predict more accurately women’s cardiovascular risk**

Two new algorithms for predicting women’s cardiovascular risk have been developed and validated in a cohort of nearly 25 000 women (derived from the women’s health study), who were healthy at enrolment and prospectively followed up for a median of 10 years.

The algorithms, which take into account new risk factors as well as the traditional ones, were developed on the basis of recorded cardiovascular events in two thirds of the cohort. The researchers validated the algorithms by comparing predicted and observed outcomes in the remaining third of the cohort.

Compared with the currently used prediction scores based on the US Adult Treatment Panel (ATP) III guidelines, the new algorithms showed marked improvements: they reclassified 40% to 50% of women currently in the intermediate risk category to either a higher risk or a lower risk category, to more accurately predict the observed events.

Model B (the Reynolds risk score), which is somewhat less accurate but easier to use than the more extensive model A, takes into account age, systolic blood pressure, haemoglobin Alc, in women with diabetes, current smoking, total and high density lipoprotein cholesterol levels, high sensitivity C reactive protein, and parental history of myocardial infarction before age 60 years (www.reynoldsriskscore.org).

For women at low risk, neither of the new algorithms showed improvements over the ATP III score. *JAMA* 2007;297:611-9

**Surgery is better than endoscopy for chronic pancreatitis with dilated duct**

A trial randomised 39 people with symptomatic chronic pancreatitis and a distal obstruction of the pancreatic duct to endoscopic transampullary drainage of the pancreatic duct or operative pancreatico-jejunostomy. Most patients had extensive disease with a combination of strictures and stones; people with an inflammatory mass were excluded from the study. The safety committee stopped recruitment early because an interim analysis clearly favoured surgery.

In the two years of follow-up, patients who received surgery had lower pain scores, better physical health, and fewer additional procedures than people who received endoscopy. Three quarters of patients who had surgery had complete or partial pain relief at the end of follow-up, compared with less than a third who had endoscopy. The groups had similar rates of complications, length of stay in hospital, and changes in pancreatic function.

The considerable difference in the pain scores between the groups (25 v 51) at the end of follow-up translates to clinical differences between having no pain and having pain daily, or between taking no sick leave for pain and being permanently unable to work, say the authors. Hope for
We know that treatment with aspirin and high doses of intravenous immunoglobulin improves outcomes for most children with Kawasaki disease—for example, reducing the occurrence of potentially fatal coronary artery aneurysms from 25% (seen in the natural course of the disease) to up to 5% with treatment. Adding corticosteroids early in the treatment doesn’t seem to improve outcomes any further, although previous studies suggested that this strategy might be beneficial for children with this acute vasculitis of unknown cause.

A multicentre double blind trial randomised 199 children with Kawasaki disease to receive (before standard treatment) either 30 mg per kilogram of body weight of intravenous methylprednisolone in a single pulse dose or placebo. At five weeks, the groups had similar coronary dimensions as assessed by two dimensional echocardiography, length of stay in hospital, duration of fever, rates of repeated treatment with immunoglobulin, and rates of adverse events.

A subgroup analysis showed that children with persistent fever had better coronary outcomes with corticosteroids than without. Children at highest risk of resistance to standard treatment may therefore benefit from corticosteroids, but adding corticosteroids to standard treatment in children with Kawasaki disease does not seem to be justified.


**New antenatal blood test for Down’s syndrome looks promising**

Antenatal screening for Down’s syndrome has come a long way since late amniocentesis was an older woman’s only option. But the search continues for a simple blood test that can tell a woman in early pregnancy whether her baby has trisomy 21. Researchers are currently focusing on the fetal DNA found in maternal blood. One emerging technique uses single mutation polymorphisms to distinguish fetal DNA from maternal DNA, and researchers from the US recently used it to count the number of fetal chromosomes in blood samples from 60 women. Eight of the women were tested in the first trimester.

Three women had fetuses with trisomy 21. The new blood test picked up two of them, giving a sensitivity and a positive predictive value of 66.7%. A third woman had a false positive blood test result, and a fourth had a false negative one. The test’s specificity and negative predictive value were both 98.2%. Overall, the test was about as accurate as current serum screening tests, although these results must be considered preliminary. We can be cautiously optimistic that this avenue of inquiry will eventually come up with an accurate and non-invasive test for Down’s syndrome, says an accompanying editorial (pp 440-2). But we are not there yet.

Lancet 2007;369:474-81

**Phlebotomy didn’t improve outcomes in peripheral arterial disease**

The hypothesis that excess iron contributes to cardiovascular disease (iron-heart hypothesis) was postulated in an attempt to explain why the risk of myocardial infarction in women after the menopause increases with age. The hypothesis incriminates excess body iron in the pathophysiology of cardiovascular plaques, through iron catalysed, free radical mediated, oxidative stress.

Much biochemical understanding supports the theory, but most observational studies have failed to show the association between biomarkers of body iron and risk of cardiovascular disease.

A recent trial (part of the US Department of Veterans Affairs Cooperative Studies Program) randomised 1277 people (99% of them men) with symptomatic but stable peripheral arterial disease to usual care or to the phlebotomy regimen designed to reduce iron stores but avoid iron deficiency. During the mean follow-up of four and a half years, the researchers found no difference between the studied groups in all cause mortality or the composite outcome of death, non-fatal myocardial infarction, or stroke.

However, the trial had only 68% power to detect a 30% reduction in mortality. The negative results therefore can’t refute the iron-heart hypothesis. The accompanying editorial (pp 639-41) discusses groups of women after the menopause, in which it still might make sense to study interventions based on the hypothesis. But the author warns that we do have interventions that we know work for preventing atherosclerosis: exercise and weight control.

JAMA 2007;297:603-10
Doubts over head injury studies

Patients are receiving treatment that may be unsound as investigations by Ian Roberts, Richard Smith, and Stephen Evans raise questions about whether influential trials of high dose mannitol ever took place.

Each year, worldwide, many thousands of people are treated in emergency departments for head injuries. Mannitol is an osmotic diuretic that is believed to reduce intracranial pressure after head injury and may improve patient outcome. Between 2001 and 2004, a Brazilian neurosurgeon Julio Cruz and colleagues published three clinical trials comparing high dose and conventional dose mannitol in the treatment of head injury (table).1-3 No other trials had examined this question.

The results showed that high dose mannitol greatly reduced death and disability six months after the head injury. A Cochrane systematic review that included these trials concluded: “high dose mannitol seems to be preferable to conventional dose mannitol in the acute management of comatose patients with severe head injury.”4 However, one of the trials was accompanied by an editorial that questioned the reliability and validity of the results, calling for further multicentre studies.5 A subsequent investigation by the Cochrane Collaboration was unable to confirm that the studies took place.

Doubts over the data

In May 2006, Dr Jorge Mejia, the Colombian national coordinator of the CRASH-2 (clinical randomisation of an antifibrinolytic in significant haemorrhage; [www.crash2.lshtm.ac.uk](http://www.crash2.lshtm.ac.uk)) trial, wrote to IR (who is editor of the Cochrane Injuries Group) after attending a meeting of the Latin American Brain Injury Consortium in Brazil. He was concerned about the inclusion of the Cruz trials in the Cochrane review: “During the discussion some Brazilian physicians expressed some surprise with the inclusion of Julio Cruz’ paper in the meta-analysis (Cruz 2004; J Neurosurgery, 100:376) … Cruz had no patients at his arrival to Brasil, back from USA where he had developed his research career.”

Dr Mejia was clearly shocked by this revelation: “I do not know what to do, but I feel betrayed. I guess that someone should contact the other authors and ask them. I feel that I can not stay passive, but I have no evidence.”

Dr Cruz, the lead author, had killed himself in 2005. However, the reports had

**Table 1 | Details of trials of high dose mannitol**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Intervention</th>
<th>Outcome</th>
<th>High dose</th>
<th>Low dose</th>
<th>Odds ratio (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cruz J, Minoja G, Okuchi K</td>
<td>178 adults with non-missile, traumatic acute subdural haematoma</td>
<td>High dose mannitol v lower dose mannitol</td>
<td>Death at 6 months</td>
<td>13/91</td>
<td>22/87</td>
<td>0.49 (0.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Death severe disability at 6 months</td>
<td>28/91</td>
<td>47/87</td>
<td>0.38 (0.002)</td>
</tr>
<tr>
<td>Cruz J, Minoja G, Okuchi K</td>
<td>141 patients with traumatic, non-missile, acute, intraparenchymal temporal lobe haemorrhages associated with early abnormal pupillary widening</td>
<td>High dose mannitol v lower dose mannitol</td>
<td>Death at 6 months</td>
<td>14/72</td>
<td>25/69</td>
<td>0.42 (0.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Death severe disability at 6 months</td>
<td>28/72</td>
<td>46/69</td>
<td>0.32 (0.001)</td>
</tr>
<tr>
<td>Cruz J, Minoja G, Okuchi K, Facco E</td>
<td>44 adults with traumatic, non-missile, acute, severe, diffuse brain swelling with recent clinical signs of impending brain death</td>
<td>Very early and fast high dose mannitol v lower dose mannitol</td>
<td>Death at 6 months</td>
<td>9/23</td>
<td>14/21</td>
<td>0.32 (0.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Death severe disability at 6 months</td>
<td>13/23</td>
<td>19/21</td>
<td>0.14 (0.01)</td>
</tr>
</tbody>
</table>
coauthors from Italy and Japan, and we contacted them for further information.

Dr Minoja wrote on 15 May 2006:

“It was a pleasure for me to be included along the authors of the papers written by Julio Cruz on the use of high doses of mannitol in head trauma emergencies. My Unit and I did not provide to Dr. Cruz a personal series of randomized patients, but my contribution was discussing with him and sharing his assumption, because occasionally, in emergency situations, I have used and I still use with success aggressive high-dose mannitol approach.”

In a second message, he wrote: “I think that patients were enrolled in USA and more recently in Brazil, but I honestly don’t know the period and in what Institution.”

Dr Okuchi responded:

“Since I did not conduct any study related to the results of Dr Cruz’s high-dose mannitol trials in Japan, I have no data to present you. I did not know any part of the paper before he called me about the acceptance in the journal every time” (18 May 2006).

Dr Facco wrote:

“The paper I am co-author, springs from the clinical experience I shared with Julio Cruz about the potential effectiveness of high doses of mannitol in selected very critical patients. I discussed with him (mainly by phone) about my anecdotal experience I never had the opportunity to check in a prospective study, and he also had the same clinical impression of its effectiveness … Following our discussion, he decided to test high mannitol doses in the emergency setting and involved me as co-author, but my role was ‘philosophical’ rather than clinical: to my knowledge, the study was conducted personally by Julio, probably in Brazil, and I only helped him with discussion and text revision” (22 May 2006).

Since none of the authors could provide any reassurance about the integrity of data, the Cochrane systematic review was withdrawn in 2006 while an investigation was made.

The Cruz papers were published in Neurosurgery and the Journal of Neurosurgery and we wrote to the editors about the concerns. In July 2006, John Jane, the editor of the Journal of Neurosurgery wrote:

“I have tried unsuccessfully to contact you by phone with regard to the Cruz papers. As you can tell by Dr. Marshall’s editorial, we all doubted the data. But to doubt is different from concluding that Dr. Cruz fabricated the data. I thought he did, but hoped as stated in the editorial that publication would encourage repetition of the studies. My Editorial Board thought Dr. Cruz’ work should be published. I wouldn’t trust the data.”

The editorial by Dr Marshall which accompanied the Journal of Neurosurgery report stated:

“These results are clearly of substantial interest, but also raise questions about how reliable and valid are clinical studies that show very dramatic improvements in outcome when they are performed at only one institution. This does not demean the work of Dr Cruz and his colleagues; rather it indicates that multicentre studies, such as those being conducted at present for novel pharmacological therapies, need to be applied to alternative dosing regimens for more traditional methodologies.”

We asked Dr Marshall if he had any concerns about the integrity of the data. He would not respond in writing but he left a phone message saying that he had “serious concerns” about the paper (8 August 2006).

The editorial office of Neurosurgery wrote:

“With a serious charge, the possible fabrication of trials, a case must formally be presented with any and all possible evidence that would indicate the cause for concern and the reviewers must then address the issue. It is not possible or responsible for the Editor of a peer-reviewed journal to act hastily in such a matter without the input of the reviewers who originally accepted the paper, nor would it be responsible to simply pull the papers without presentation of the results of an investigation into the matter. An unsubstantiated claim and verbal recitation of the inquiries made cannot suffice” (8 December 2006).

We have had no further correspondence.
Where did the patients come from?
None of the reports indicated where the patients came from. All of them stated that “institutional review board approval was obtained” but gave no further details. On each report, the Dr Cruz’s affiliation was the “Comprehensive International Centre for Neuroemergencies and Federal University of São Paulo.” Reprint requests were to the centre at a postal box address in São Paulo. We were unable to find any further information about the centre. In October 2006, the Federal University of São Paulo stated in response to our inquiry that it had never employed Dr Cruz.

We also wrote to the Brazilian national committee on ethics in research, which began an investigation. The investigation found that Dr Cruz had given an interview in which he said that the patients in one of the trials were from eight hospitals in Brazil, Italy, and Japan. However, the authors from Italy and Japan had told us that they did not enrol any patients at their hospitals. Dr Minoja had said that he thought that the patients might have been recruited in the US (15 May 2006). We contacted the University of Pennsylvania, where Dr Cruz had worked until March 1995. They searched their records but found no indication that the research was conducted there (Steven Fluharty, personal communication, 8 December 2006).

In September the Committee on Publication Ethics recommended that the living authors seek retraction of the reports on the basis that they were gift authors and could not take responsibility for the results. We wrote to all three coauthors on 21 September asking if they would be willing to seek retraction.

Dr Okuchi replied the next day: “I would like to retract these papers from the journals because I am not able to take responsibility for the content. Could you let me know how to act formally for the purpose.” A few days later (25 September) he wrote again, “On my last e-mail letter, I had mentioned withdrawal of the papers, however I found that I had no right to retract the papers from the journals. It think it depends on whether Dr Cruz will decide or not ... I will contact him in a few days.”

IR wrote again to the coauthors on 10 October explaining that Dr Cruz was dead, stating that “it would be wrong of me not to follow up this matter and so unless you contact the journals in question to seek retraction I will have to write to your institutions to ask for their help. It is an unfortunate business but it will be better for everyone concerned that you take the appropriate steps to resolve this matter.”

Later that month (27 October), Dr Facco wrote on behalf of Dr Minoja and Dr Okuchi. He said that they did not believe that they were gift authors and declined to seek retraction. He argued that the papers were published in an international peer reviewed journal, that the first author had taken responsibility for their content, and that they knew the first author well and believed that “he would never have been able to do something false.”

Wider implications
We are left with serious doubt about important studies but with no way of determining with confidence whether the results are fabricated or real. The main author is dead. There is no institution to investigate. The implications for patients are serious. They are being treated on the basis of potentially unreliable evidence. It is plausible that mannitol in high doses may increase rather than decrease brain swelling. Shortly after the withdrawal of the Cochrane review, the Cochrane Injuries Group was contacted by US researchers preparing guidelines for the management of severe traumatic brain injury and by BMJ Clinical Evidence asking about the outcome of our investigation because the Cruz results were about to be incorporated into guidelines.

There are also implications for the broader scientific community. Earlier this year an investigation by Science of more than a dozen fraud or suspected fraud cases showed “uneven and often chaotic efforts to correct the scientific literature.” If it wants to retain the confidence of the public and politicians, the scientific community needs to do better. Only a minority of countries have an effective national system for responding to scientific misconduct. However, research is a global enterprise and a strong case exists for an international body to respond to the problem of research misconduct.

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Contributors and sources: IR conducted the investigation with advice from RS and SE. All authors contributed to the writing of the manuscript. IR is guarantor.

Competing interests: RS has a longstanding interest in research misconduct and was a founder member of the Committee on Publication Ethics. The only way that he could benefit financially from this article is if more people were to buy his book, which includes a chapter on research misconduct. IR is coordinating editor of the Cochrane Injuries Group and is an author of the mannitol review.

7 Couzin J, Unger K. Cleaning up the paper trail. Science 2006;312:38-43.
BODY POLITIC Nigel Hawkes

Time to face up to “scandal” of funding formula

Sometimes it is the unasked political questions that are the most interesting. If a political party stood up before an election and said: “We intend to give some areas of the country twice as much money to run their health services as others,” questions might well be raised.

The obvious one would be: “How on earth do you justify that?” It would be quickly followed by demanding whether this lopsided generosity produced the desired results. Voters in unfavoured areas where services were being cut, referrals to consultants stymied, or waiting times artificially lengthened would be enraged.

Yet that is what actually happens, largely behind the electorate’s back. In 2004-5, for example, Islington Primary Care Trust received £1566 (£2326; $3054) per head to run its health services, while Wokingham PCT in Berkshire got £752 per head.

It is likely that inner city Islington has greater health needs than leafy Wokingham, but it is difficult to believe that it is more than twice as needy. Both areas need general practitioners, access to hospital services, community care, and all the other services that PCTs are charged with providing.

Can it really cost more than twice as much to deliver these services in Islington as in Wokingham? The cash amounts involved are not simply tinkering at the margin: they are huge. If all PCTs had got as much as Islington, the extra cost to the NHS in 2004-5 would have been more than £20bn.

Deficits have dragged this submerged issue to the surface. At the end of last year the House of Commons Health Select Committee took evidence on the deficits, but its report rather glossed over the effects of the funding formula on the financial performance of PCTs. The official view is, and remains, that there is no correlation between allocations and deficits. It is all down to the competence of the local managers, not to the cash they are given to run their services. This seems barely plausible.

Actually, the hearings did produce a small hole in the dyke of official reassurance, though Professor Barry McCormick, chief economic adviser to the Department of Health, rushed to push his finger into it. In 2004-5, he admitted, the figures did show “a slight tendency” for deficits to cluster in less well funded areas, but he put that down to profligate spending, not lower income.

Why did the relationship appear only in 2004-5? Professor Sheena Asthana of Plymouth University, a critic of the NHS funding formula, has no doubts. She blames the end of brokering, the old system in which cash was shipped around the NHS to resolve local deficits. In effect, she is saying that brokering was how the NHS compensated for a defective funding formula: end brokering and the flaws are revealed.

Her own figures show a strong link between funding and deficits. In 2004-5, only four of the 60 most generously funded PCTs were in deficit, compared with 36 of the 60 least generously funded. The former group got an average of £1166 per head; the latter, only £860 per head. “Poor financial or clinical management is a highly unlikely explanation for the financial difficulties experienced by PCTs,” she said.

The funding formula is designed to secure equal opportunities of access to health care for people at equal risk. That is unexceptionable. The question is whether it works.

The demand for health care is determined by morbidity and demography. Morbidity—the burden of disease—is measured by the existing use of health care, but that is largely determined by its availability. The more doctors, the more illness; the more hospitals, the more admissions. So the formula tends to perpetuate existing patterns by confusing provision with need. Age is taken into account, too, but in a way that underestimates its true impact, critics complain. Rural areas with older populations are disadvantaged.

A government dedicated to reducing health inequalities, and with most of its MPs elected from areas favoured by the formula, has brushed these criticisms aside. It believes that the apparent inequities of funding are justified by the need to narrow gaps in health between rich and poor. But the problem is that greater spending on health care does little to narrow the gaps. They are caused by a multitude of life choices that need to be addressed in other ways—through education, social support, and community action, for example. By the time a patient sees a doctor, the damage is done.

If it were the case that the better funded PCTs ran ambitious local public health and education programmes with their extra money, then the discrepancies in funding might be justified. But they do not. As the chief medical officer has acknowledged, funds intended to address health inequalities have been swallowed up to bail out the acute sector.

What happens is that well funded areas build more capacity, creating more demand, and because this is then taken to demonstrate need, it ensures that they continue to get the lion’s share of resources. Giving evidence to the select committee, Professor Mervyn Stone of University College London said that the present formula was “a national scandal which the Department of Health does not face up to.”

Perhaps it is about to. Despite being in denial over the link between funding and deficits, the department last year announced that it was planning to review the “need formula” for resource allocation, and invited expressions of interest from academics keen to do the work. They have until 8 March to make their bids, and a final decision on who gets the job is due by the end of March.

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Medicine and the Media

Having the last laugh at big pharma

How campaigners are creating humorous videos to hit back at the drug industry

Satire is becoming the latest weapon of campaigners against the influence of drug companies. A series of wickedly clever parodies has been posted in recent months on internet sites such as YouTube (www.youtube.com) and has quickly proved successful in communicating an anti-“big pharma” message to a wide audience.

The most popular spoofs in circulation target direct to consumer drug advertising, which was legalised in the United States in 1997 and is now a mainstay of the country’s television advertising. The object of the lampooning is the way in which drug companies, it is suggested, turn ordinary ailments into medical problems.

The new breed of satirists claim that prescription drug advertisements are now so powerful that they can convince well people that they are sick and need the advertised drug.

The current buzz is around a mock advertising campaign for “Havidol” (as in “Have it all”), a sharply observed parody that promises to treat a mock illness, dysphoric social attention consumption deficit anxiety disorder (DSACDAD).

Feel empty after a full day of shopping? Enjoy new things more than used ones? Does life seem better when you have more than others? Then, claims Havidol’s website (www.havidol.com), you may have the newly identified disorder. Future PHARM, the drug’s manufacturer, claims that more than 50% of people over the age of 18 may have the disorder and that Havidol (slogan: “when more is not enough”) is the “first and only” treatment. You don’t have to stop drinking; in fact, the safety information warns that Havidol is not for you if you have abruptly stopped using alcohol or sedatives. Yet read on and you find that the side effects may include “interspecies communication, dermal gloss, excessive salivation, and terminal smile.”

Look carefully and it’s obvious that Havidol is nothing but a glorious hoax. The fake marketing campaign started life as a New York exhibition by the Australian artist Justine Cooper. The artist has painstakingly recreated the entire drug marketing process—from the invention of a new disorder to creating a magic bullet drug. The drug has a generic name, a brand name, a logo design, a promotional website, and even merchandise.

The campaign is so clever that some people have been duped into believing that the fake drug and illness are for real and have contacted the gallery for prescription information.

Daneyal Mahmood, owner of the gallery exhibiting Cooper’s work, told Reuters: “People didn’t get the fact that this was a parody or satire. The thing that amazes me is that it has been folded into real websites for panic and anxiety disorder. It’s been folded into a website for depression.”

In the first few days after the website went up it had 5000 hits. The number has now reached a quarter of a million. Cooper says that she gave
the campaign an authentic edge to highlight how people could be seduced by advertising into wanting a drug they did not need. “The drug ads themselves are sometimes so comedic. I couldn’t be outrageously spooify, so I really wanted it to be a more subtle kind of parody that draws you in, makes you want this thing, and then makes you wonder why you want it and maybe where you can get it,” she told Reuters.

Other slick parodies lampoon a culture of “disease mongering,” whereby drug companies sponsor diseases and promote them to prescribers and consumers. One YouTube video describes an epidemic called motivational deficiency disorder (first “announced” in the 1 April 2006 edition of the *BMJ* (2006;332:745)). “In its mild form, persons can’t get off the beach,” says the spoof film. Patients become “unmotivated to bread, and die.”

The “sufferer” Roy Moynihan complains, “All my life people have called me lazy. But now I know I was sick.” The disorder’s champion, the neuroscientist Leth Argos, of Hypnos Torpor Medical School, celebrates the success of early clinical trials of the new drug indolebant, made by the drug company HealthTech. Professor Argos tells how a patient’s wife, in tears of joy, telephoned him: “After using indolebant her husband had mowed the lawn, repaired the gutter, and paid an electricity bill—all in one week.”

The *BMJ* columnist Iona Heath makes an appearance to sound a note of caution. Dr Heath said, “I find it truly terrifying how easy it is to create a new disease, and it shows just how very little effort it takes to generate a whole new area of anxiety and possibility for people to convince themselves that they are ill.”

Commentators say they are not surprised by how easy it is to dupe people. Vera Hassner Sharav, who runs Veracare, an email news alert service on medical research ethics and abuses, said: “That people are taken in by these parodies is a testament to how the drug industry has insinuated non-diseases into the culture.”

The power of YouTube, which claims 40 million plays of its videos a day, has not been lost on other campaigners.

For example, several original clips ridicule attention deficit hyperactivity disorder. One video is dedicated to “all those kids who got a prescription instead of understanding.”

A number of videos with a harder campaigning edge concern antidepressants, including a frank interview with an intense former pharmaceutical sales representative caught up in the current furore over the antipsychotic drug olanzapine (Zyprexa). Documents passed to the *New York Times* allegedly suggest that the drug’s manufacturer, Eli Lilly, did not disclose company data showing that 16% of people who took olanzapine for a year gained more than 30 kg (*BMJ* 2007;334:171).

Also shown on YouTube was a series of investigative reports by Nanci Wilson of KeyTV, part of the CBS media group, about the use of selective serotonin reuptake inhibitors in children and adolescents. Sites such as YouTube make it easy to publish and play video clips, and it grants free access to a potential audience of millions. Unless the drug companies fight back successfully the chorus of campaigning voices is only likely to swell.

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WHAT’S ON THE WEB
24/7 surgery to cut NHS waiting lists

“Even in the more efficient trusts, it is rare to find operating theatres in use on Friday afternoons, let alone at the weekends. There are some good, practical reasons for this. Operating theatres require deep cleaning on a regular basis if methicillin resistant *Staphylococcus aureus* is not to become even more prevalent than at present. And staffing up for such round the clock surgery would add enormously to the NHS’s already gargantuan wage bill.”

“On a more prosaic note, who among us would want to undergo a tricky surgical procedure at three in the morning, when even the most skilled surgeons may not be quite up to snuff?”

“Does Mr Blair spell out how this exciting new vision of round-the-clock surgery is to be delivered? Only by invoking his old friends ‘change and innovation’—the same change and innovation that were supposed to accompany the record levels of NHS spending under New Labour, but that have been palpably absent throughout.”

http://aboutsalt.blogspot.com/index.html

“Round-the-clock surgery could be introduced in England to help cut NHS waiting times to a maximum of 18 weeks, Tony Blair is to say. He will suggest the idea of keeping operating theatres open ‘out of hours’ during a visit to a London hospital.”

“Anyone with the remotest knowledge of how to run a business efficiently, someone in private industry for example, would hardly be unaware that exploiting a resource from nine till five that costs in excess of £0.8 million to build and equip is a guarantee of bankruptcy. And after 10 years in government, Tony Blair has finally noticed that the NHS could double the return on one of its biggest capital investments by utilising it round the clock. Wow, if only the New Labour health secretaries since 1997, Frank Dobson, Alan Milburn, John Reid, or Patricia Hewitt had thought of this, then the NHS might be a shining example of efficiency today.”

http://johnchoices.blogspot.com/index.html

“I have to say I was a bit perplexed to read that Tony Blair was promising to get theatres working around the clock to make waiting for procedures a thing of the past.”

“Having watched the BBC programme *Can Gerry Robinson save the NHS?* I had to laugh. After all, why get them working 24 hours a day when you can’t get them working on Friday afternoons. Tony Blair is making a pledge to cut waiting times from a GP deciding to send you off to a consultant to surgery to 18 weeks or less.”

“I have to say I am sceptical. The reason why this does not happen at the moment is not that hospitals can’t cope, though some no doubt can’t, but so many primary care trusts have run out of money to fund the operations so they just don’t get done.”

http://aconservatives.blogspot.com/index.html

Compiled by Rebecca Coombes, journalist
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Should the NHS curb spending on translation services?

**Kate Adams**
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On 12 December 2006, the BBC reported on the high price being paid for the provision of translation services. A conservative estimate for the National Health Service alone was £55m (€82m; $107m), with the true figure likely to be much more, and the cost of providing such services across all public services was said to be rising sharply.1 The report received lots of public feedback, mainly expressing concern. Ruth Kelly, the secretary of state for communities and local government, asked for a review of language services across government departments.

The complex concept of citizenship, with its emphasis on encouraging integration, is high on the government’s agenda and a vital part of this is language competence. People applying for UK citizenship are now required to pass an English test. As a general practitioner in Hackney in inner London I see many patients whose English is either non-existent or so poor that they need translation support. In individual cases, the justification for providing translation services is overwhelming: the provision of care would be substandard without it. But I am concerned that the provision of translation services is inadvertently compounding some of the underlying health and social problems that we are being asked to help with. A significant number of my non-English speaking patients present with either explicit psychological problems or with physical problems that seem to me to have psychological origins and studies support this.2 It strikes me that an important contributory factor to much of this psychological suffering is a sense of being alienated from the mainstream culture.

**Language barrier**
In some of the larger immigrant communities people can shop, move around their communities, and access public services without the need to speak any English. A population survey throughout the United Kingdom in 2006 showed that 5.3% (2.3 million people) speak another language at home.3 Many people who have lived in the UK for more than 20 years speak little English. Can we say that this is in their interests or the interests of the wider community? Less able to pursue self determining activities such as employment and often restricted to smaller communities that may be culturally and politically marginalised, these patients are vulnerable to depression and related psychological responses to alienation. Gender is an important factor here. In some communities, women will often remain at home while the men go out to work. The men are therefore more likely to learn sufficient English to enable them to function in the wider community. Such opportunities are denied to women who remain at home. Where there are relationship problems—a violent husband or partner, for example—the near total dependence that may result from being unable to seek help beyond their community can drive women into depression. What we are seeing is, at least in part, the medicalisation of problems that are actually social or cultural in origin, with some of the costs being borne by the health service.

**Is it really so far fetched to suggest that we should also be prescribing English classes?**
Treating people from an enormous variety of cultures and backgrounds, people who have very different approaches to illness, who present symptoms in unfamiliar ways, and whose cultural beliefs are so varied, is an interesting and rewarding part of inner city medicine. But it is also time consuming and expensive—and in general, not recognised in doctors’ pay systems. Translation services also present some practical problems. Some areas are better served than others and although, in theory, interpreting services by telephone are available around the clock, patients who do not speak English are vulnerable in hospital settings, particularly out of hours, when access to services is difficult. Patients not able to communicate effectively are at risk, and this is a patient safety issue. A US study published in February 2007 showed that hospital patients who have limited English proficiency are more likely to be harmed by adverse events than other patients.4 It is interesting to draw comparisons with British expatriate communities abroad. If you decided to live in a non-English speaking country, would you expect interpreting services to be readily available? This is now an issue in Spain, where there is a large, ageing British expatriot community and many speak little Spanish. Some Spanish doctors are now refusing to treat anyone who cannot speak Spanish unless an interpreter is present.5

**Rights versus duties**
In the UK, the legal right to translation services is unclear. Under international obligations, equality in access to available health services is a guiding principle for the right to health.6 Citizenship must balance rights against duties, and may include a right to a reasonable standard of health care that will, in certain circumstances, entail the use of a translator. But should there not also be a corresponding duty to learn the language of the adopted community which has granted the rights? However we decide to respond to this, health professionals need to encourage their patients to learn English, thereby helping them in the process of integration, otherwise we will be storing up public health problems for the future. Without employment people are more likely to face deprivation, and the links between ill health and deprivation are well known.7 Translation services will always need to be available for elderly people whose English is poor, and for new arrivals, but at a time when the NHS is facing a huge financial crisis, is it in anyone’s interests to see the costs of translation services increasing? High profile campaigns around the UK and from within communities are needed to encourage people to learn English. If doctors can prescribe gym classes for depression, is it really so far fetched to suggest that we should also be prescribing English classes? 

Competing interests: None declared.
Millions of pounds are spent on NHS translation services each year. **Kate Adams** argues that doctors should encourage patients to learn English to avoid future public health problems, whereas **David Jones** believes that current service provision is patchy and more investment is needed.

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**David Jones**, general practitioner, Broadwater Farm Estate, London N17 6BF, david.jones9@nhs.net

**NO**

When the BBC reported the high cost of interpreting services, the conservative estimate was £55m (€82m; $107m).¹ My initial response, as a general practitioner using interpreting services every day, was that this seemed a fairly small sum. I believe that more money should be spent on providing a comprehensive language service and on supporting the doctors and hospitals to use it. This is because there are clinical consequences when interpreters are not available or not used and current practice falls short of General Medical Council expectations.

Full citizenship requires a test of competence in English. Non-English speakers have a responsibility to learn English to contribute to the process of integration and share in British identity and public life and to hold on to unemployment benefit.² The darker side of this idea is that the state’s responsibility to provide adequate language services for those who fail to become competent speakers of English is limited.

Complex factors determine if a migrant to the UK will acquire sufficient English competence to communicate effectively with health professionals. In a 1996 study that explored English language skills in five different ethnic groups, people who were in employment or education performed much better than those at home or retired.³ Cause and effect are difficult to disentangle, and the cultural factors that confine women to the home may not be easy to shift. Longer formal education and younger age on arrival in the UK also seemed to be important factors associated with better English language competence. In this study the length of time in the UK alone had little relation to English language attainment.

In my practice, which is in a deprived inner city area of London with a diverse population of migrants, I often care for three generations of members of my patients’ families who do not speak English are protected from many of the negative features of the wider English speaking culture in ways that have a positive effect on mental health.⁴ It is clearly a disadvantage not to speak the majority language of the country in which you live. Language is a barrier to accessing information. Social and cultural contacts may be limited to those who share the same language. It is not clear that this results in psychological damage. Migration to the UK may have been a difficult experience in many ways, and psychological problems associated with this process are well recognised.⁵ We have no evidence to support the suggestion that being a non-English speaker is an independent cause of mental illness. It may be that people who do not speak English are protected from many of the negative features of the wider English speaking culture in ways that have a positive effect on mental health.⁶

**Influencing language**

Health professionals must not underestimate the importance of cultural, demographic, and technological factors in determining if a patient will acquire English competence. In Carr-Hill et al’s 1996 study, nearly 90% of 1200 people from nine different minority linguistic communities watched television in English.⁷ Ten years later technology has moved on, and the homes of my patients have satellite TV invariably tuned to non-English channels. Even the governments of liberal democracies may be incapable of influencing this area. The United States is often used as an example of a country that has encouraged a strong sense of national identity. It remains a country struggling to manage the language barrier.⁴

It is not clear that this results in psychological damage. Migration to the UK may have been a difficult experience in many ways, and psychological problems associated with this process are well recognised.⁵ We have no evidence to support the suggestion that being a non-English speaker is an independent cause of mental illness. It may be that people who do not speak English are protected from many of the negative features of the wider English speaking culture in ways that have a positive effect on mental health.⁶

**Good medical practice**

The GMC’s 2006 publication, *Good Medical Practice*, clearly states: “To communicate effectively you must: make sure, wherever practical, that arrangements are made to meet patients’ language and communication needs.”⁷ All too often no such arrangements are in place. This is not because such arrangements are impractical but because provision for translation and interpreting in the NHS is patchy and often not adequate or not used. Interpreting services are not audited for quality or uptake, and health professionals do not have training or clinical governance guidelines for the use of interpreters. I have received letters from hospital consultants explaining that a full exploration of a patient’s problem had not been possible because no interpreter was available.

**Current NHS interpreting services may well have negative health and social care consequences because they are so poor**

A recent usage review of telephone and physically present interpreting in two primary care trusts in north London showed that although interpreting services in a range of languages are available, many GPs are choosing not to use them, while a small number of GPs are intensive users.⁸ We should not find this surprising. The use of interpreters, either physically present or available remotely via a telephone link, is time consuming and not supported or rewarded by the GP contract. The use of family members and practice receptionists as informal interpreters as a substitute for professional interpreters is widespread.⁹

What is needed is more, not less, spending on language services. Current NHS interpreting services may well have negative health and social care consequences because they are so poor. A new study from the United States has shown that adverse clinical events are more likely to result in physical harm in patients with limited English proficiency.¹⁰ All doctors working in the NHS, certainly in the inner cities, understand quite clearly that care for non-English speakers regularly falls short of the GMC’s expectation of good communication with patients.¹¹ We must not let the politicians persuade us that it is the patients’ fault.

**Competing interests:** None declared.

References are in the full version on bmj.com
An alternative to the clinical negligence system

Richard Furniss and Sarah Ormond-Walshe analyse the NHS Redress Act and compare it with the current system.

The current system for patients to obtain compensation after medical error has been much criticised. It is seen as complex, slow, and costly, both in terms of legal fees and time of clinical staff. Patients are said to be dissatisfied with the lack of explanation and apologies, and the system is believed to encourage defensiveness and secrecy in the health service. After publishing a consultation document in 2003 that recommended reforming the way in which allegations of clinical negligence in the NHS are handled, the government passed the NHS Redress Act 2006 last November. We examine its likely effects.

**Claims under the new act**

The act introduces a scheme for redress without recourse to the civil law. The scheme will apply to England and Wales and covers only hospital care. It makes provision for investigation, assessment of liability, and remedy for the complainant. This remedy might include an apology, explanation, or award of financial compensation up to a ceiling of £20,000. The scheme is an alternative to (although not a substitution for) proceedings in the civil courts.

The scheme will not be launched before April 2008 and the regulations providing procedural detail will be promulgated in 2007, but the broad process for making a claim is given. The applicant (usually the aggrieved patient, but perhaps a representative of a dead patient) would initially complain to the NHS trust. The NHS Litigation Authority, which currently deals with clinical negligence claims on behalf of NHS trusts, will oversee all trusts. The trust will investigate the claim using methods that seem to be the same as under the existing complaints procedure. As a consequence of the investigation, the patient may get an apology, explanation, or offer of compensation. The same test, and standard, of fault will apply as for clinical negligence claims.

**Current system**

The typical clinical negligence claim does not, of course, begin with the delivery of a writ to an NHS trust. A potential claimant will often have first written a letter of complaint. The trust is likely to have responded to the complaint in detail. Sometimes, the trust provides an acceptable explanation or apology, which brings an end to the matter, as in this example:

A woman who was a practising nurse was in hospital for childbirth. She recognised that she was developing symptoms of pre-eclampsia and told a junior doctor that the baby needed to be delivered as soon as possible. The junior doctor dismissed her concerns. A consultant recognised shortly afterwards that she was correct, and the baby was delivered by emergency caesarean section. There was no lasting harm to mother or baby. A letter of complaint resulted in an investigation, and the junior doctor was spoken to about her future conduct. No further action was taken.

If claimants remain dissatisfied, they will instruct a solicitor, normally an expert in medical claims—classed as expert because of the public funding rules. Claimants whose cases have little merit are unlikely to find a solicitor to continue with the claim. This is because someone has to pay the solicitor’s costs. A case will be publicly funded only if the claimant has limited means and the case has sufficient prospects of success and is proportionate when the likely costs are set against the likely damages.

Other methods of funding include through trade unions or insurers, a “no win, no fee” agreement with solicitors, and the claimant’s private funds. Trade unions and insurers will decline to fund an unmeritorious case, and solicitors are unlikely to take on cases where there is a high risk of not getting a fee. Very few claimants wish to spend their own money on a difficult claim. Consequently, only a minority of prospective claims that are considered by solicitors progress any further.

If a claim is taken up, the next step is usually to obtain a report from an independent medical expert. If the report supports the claimant’s case, a formal letter of claim will be sent to the NHS trust. The trust (or the NHS Litigation Authority, which may take over the conduct of the case) will have three months in which to investigate and respond. This will include an interview with the accused clinicians and perhaps others in the department, and the trust may instruct a separate expert. The trust may admit fault in a formal letter of response or give reasons why it does not consider that the clinician was at fault. If dispute remains, the claimant will issue a claim and start formal legal proceedings.

**Will the redress scheme improve on current system?**

The first criticism of the present situation is that it is complex and slow. But clinical negligence claims are, necessarily, more complex than many other types of case (such as personal injury claims). This is because of, for example, the sophistication of some medical
procedures, the application of the legal test of the standard of care (the Bolam/Bolitho test), and the complexity of medical causation:

A diabetic man attends a hospital podiatrist for treatment of a sloughy and malodorous ulcer on his toe. He is not referred to the diabetic team but discharged into his general practitioner’s care. The lesion becomes gangrenous, and his forefoot needs to be amputated. There is obvious negligence, which is immediately admitted. However, it is unclear whether earlier referral to the diabetic team would have saved the forefoot. Expert evidence is required.

The redress scheme is intended to allow smaller value cases to be settled more quickly. An expert need not be consulted for the claim to be settled.

As the redress scheme is simpler it should also be less costly for claimants. Currently, although claimants may draft an initial complaint without recourse to a lawyer, they are unlikely to be able to instruct an expert or draft a formal letter of claim.

The savings on experts are less clear as the scheme will use them in some circumstances. If the NHS does not offer redress, a medical expert may be instructed to consider the case on behalf of both parties. Many have hoped that, in order to preserve a measure of independence, experts will be commissioned in all but the simplest cases. If, as expected, jointly instructed experts are the norm, the scheme is in danger of being seen as part of the NHS:

A claimant complains that a leading hand surgeon has performed a procedure negligently. Expert opinion is required to determine whether there has been a breach of duty. Obviously, the claimant cannot identify a suitable expert.

The operators of the redress scheme ask another hand surgeon. She is unable to help but recommends a third leading hand surgeon, who provides an opinion unfavourable to the claimant. All three surgeons necessarily know one another fairly well. The claimant suspects a conspiracy.

The scheme will provide free independent legal advice to applicants when there is joint instruction of experts or to assess the acceptability of compensation offers.

Those claimants who are prepared to accept the redress scheme may be satisfied, and indeed receive monetary compensation, with limited lawyers’ fees incurred. However, a claimant who could use the redress scheme is unlikely to be granted public funding for a negligence claim. There is also concern about claimants who reject an offer of £20 000 under the scheme because they believe their case is worth £30 000. The difference between the sum offered and the sum sought may be considered so small that litigation is disproportionate. In such a case, the claimants will be forced to accept less money than they are entitled to.

It is more difficult to see how the redress scheme will avoid clinicians being diverted from their duties. We hope that claims under the scheme will be investigated with the same rigour as current clinical negligence claims. This is essential for the protection of clinicians. Clinicians against whom a claim is made will still be required to meet and discuss it with an investigator.

**Explanations, apologies, and preventive action**

The only remedy provided to the victims of negligence by the legal system is monetary compensation. Undoubtedly, some claimants want an explanation, apology, or a reassurance that steps have been taken to prevent a recurrence. Although these are often given under the current system, they are not a matter of right.

The redress scheme is likely to be more useful to,
and used by, those who have no grounds for monetary compensation because they have suffered no loss:

A clinician negligently fails to diagnose a claimant’s cancer. As a result of the consequent delay in diagnosis, the claimant’s chances of survival are reduced from 42% to 25%. On the balance of probabilities (the legal standard of proof), the claimant would not have survived in any event. Consequently, the claimant has suffered no loss and is entitled to no monetary compensation.

Under the redress scheme, however, the above claimant would (if breach of duty is established) be entitled to an explanation, an apology, and a reassurance about the future. The scheme will therefore fill a gap in the present system. It may therefore produce more, not fewer, complaints.

Defensiveness and secrecy
The government has decided not to make the scheme independent of the NHS. The presumed rationale is that the NHS is better able to own any mistakes if it identifies them itself. The difficulty is that the public is unlikely to perceive the scheme as impartial if the trusts carry out the investigation.

We are aware of no evidence to support the allegation that clinicians and trusts are defensive or secretive or that claimants currently believe that the NHS is defensive or secretive when mistakes have been made. Some claimants may consider that the NHS has something to hide if it does not immediately admit the fault alleged against it. And as a matter of human nature, some clinicians are unable to accept fault even when they have obviously made a mistake. Of course, if a NHS body makes the decisions under the redress scheme these problems will not go away. A claimant who is rebuffed by the redress scheme is as likely to accuse the NHS of secrecy as he or she is under the current system.

More claims
The redress scheme will therefore complement the present system in some cases. It is unusual to obtain public funding for a clinical negligence claim worth less than £20,000 (because it is disproportionate to incur legal fees for such a modest amount) and claims for an apology cannot be made. For this reason, many, if not most, of the claims that are initially brought under the redress scheme will be claims that could not have been brought in the present system. Consider the following case:

A 60 year old man has neurosurgery and a small incision is initially made on the wrong side of his head (because the radiograph was misplaced on the illuminator). He has no third party funder and cannot pay costs himself. There are no special damages (financial loss) and damages for pain, suffering, and loss of amenity will be no more than about £5000. Public funding is unavailable because of the low value of the claim compared with the likely legal costs.

This case would not result in a negligence claim but could be considered under the redress scheme. The redress scheme may, therefore, create more complaints against clinicians that require formal investigation. Overall costs could rise because of the extra cases, and more clinicians will be diverted from their duty as part of the investigations.

If the scheme is widely used it will undoubtedly be extended by raising the limit of financial compensation. If claimants were permitted to recover compensation of up to, say, £50,000, the scheme would deal with many of the claims that are currently brought under the present system. The NHS might then save on the cost of litigation. However, currently the scheme seems likely to give rise to more complaints, many without merit, and the way in which it deals with them may be less satisfactory than at present.

Contributors and sources: The authors are barristers specialising in clinical negligence law, acting for both claimants and hospital trusts. Both have experience in clinical negligence actions in a wide range of medical disciplines.

Competing interests: None declared.


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CORRECTIONS AND CLARIFICATIONS
What is heterogeneity and is it important?
Some technical glitches at final proof stage led to the phrase “χ2 test” being mangled in this article by John Fletcher in the “Clinical epidemiology notes” series (BMJ 2007;334:94-6, 13 Jan, doi: 10.1136/bmj.39057.406644.68). In the caption to figure 1, the part in parentheses should start, “P for χ2 test ….” In figure 2, the chi symbol is also missing at the bottom of the left hand columns (test for heterogeneity) in each of the two sections. These errors occurred in the printed BMJ and in the pdf on bmj.com.

Minerva
We tripped up over a vowel when we miss-spelt neuropaxia as neuropaxia (BMJ 2007;334:162, 20 Jan, doi: 10.1136/bmj.39093.672697.801).

We have already published these corrections on bmj.com.
Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial

Hugh Reyburn, clinical senior lecturer and project leader,1 Hilda Mbakilwa, clinical officer,2 Rose Mwangi, social scientist,1 Ombeni Mwerinde, biostatistician and project data manager,3 Raimos Olomi, professor of paediatrics,4 Chris Drakeley, senior lecturer and project senior scientist,1 Christopher J M Whitty, professor of international health and project coordinator1

ABSTRACT

Objective To compare rapid diagnostic tests (RDTs) for malaria with routine microscopy in guiding treatment decisions for febrile patients.

Design Randomised trial.

Setting Outpatient departments in northeast Tanzania at varying levels of malaria transmission.

Participants 2416 patients for whom a malaria test was requested.

Intervention Staff received training on rapid diagnostic tests; patients sent for malaria tests were randomised to rapid diagnostic test or routine microscopy.

Main outcome measure Proportion of patients with a negative test prescribed an antimalarial drug.

Results Of 7589 outpatient consultations, 2425 (32%) had a malaria test requested. Of 1204 patients randomised to microscopy, 1030 (86%) tested negative for malaria; 540 (54%) of these were treated with an antimalarial drug. Of 1193 patients randomised to rapid diagnostic test, 1005 (84%) tested negative; 540 (54%) of these were treated for malaria (odds ratio 1.13, 95% confidence interval 0.95 to 1.34; P=0.18). Children aged under 5 with negative rapid diagnostic tests were more likely to be prescribed an antimalarial drug than were those with negative slides (P=0.003). Patients with a negative test by any method were more likely to be prescribed an antibiotic (odds ratio 6.42, 4.72 to 8.75; P<0.001). More than 90% of prescriptions for antimalarial drugs were for children in Africa,13 14are treated as malaria cases they do not need them and not given to children who do.

With the growth of resistance to older antimalarial drugs, newer but more expensive drugs need to be used, and artemisinin combination treatment is now being introduced in most African countries.10 11 The cost of these drugs – up to 10 times that of current antimalarial drugs – is their major constraint, and deployment to people who need them is likely to depend on subsidy.12 This may become unsustainable if most antimalarial drugs continue to be given to patients who do not have malaria. If patients with bacterial disease, an important cause of avoidable death in children in Africa,12 14 are treated as malaria cases they may not receive appropriate treatment.8 Improving the diagnosis of acute febrile illness so that antimalarial drugs are targeted to patients who need them and alternative diagnoses sought in others is therefore a public health priority in Africa.

Rapid diagnostic tests have considerable potential as a tool to improve the diagnosis of malaria.15 16 Several commercially available tests are sensitive, specific, and stable under operational conditions.17 Although microscopy remains the gold standard for diagnosis of malaria, its accuracy under operational conditions in Africa is often low, and clinicians are aware of this.4 Results of rapid diagnostic tests are rapidly available, less liable to the theoretical risk of being falsely negative due to parasite sequestration, and visible to both prescriber and patient, and they may result in
greater respect for test results. Initial data indicate that the cost effectiveness of rapid diagnostic tests is reasonable in an era of more expensive drugs such as artemisinin combination treatment, and their use could result in significant savings, especially in areas of low transmission. The national malaria control programmes of several countries, including Tanzania, are therefore considering deploying rapid diagnostic tests in the formal healthcare system as part of the roll out of artemisinin combination treatment. Although studies of the technical performance of rapid diagnostic tests (sensitivity, specificity, and stability) are well advanced, no studies have examined whether their use actually leads to a change in prescribing practice compared with current diagnostic methods, which is fundamental to whether their deployment will be effective and cost effective. We set out to compare rapid diagnostic tests with routine microscopy in guiding treatment decisions for febrile patients in outpatient settings in northeast Tanzania.

**METHODS**

We did the study in three typical government designated public hospitals in northeast Tanzania, one each in areas in which transmission of *Plasmodium falciparum* is very low, low-moderate and high (<1, 1-10, and >10 infected bites/person/year). We phased the study to include the peak malaria transmission season at each site. In low transmission areas malaria is seasonal, peaking in January-March; in high transmission areas it is perennial, peaking in June-August. In common with most hospitals in southern Africa, outpatient care in the study hospitals is largely provided by clinical officers with three years’ clinical training.

We invited clinical staff to participate; all agreed and attended training designed to meet or exceed what would be provided by a national malaria control programme. Training included discussion of rapid diagnostic tests and specifically Paracheck (Orchid Pharmaceuticals), a *P falciparum* specific (histidine rich protein-2) test recommended by the national malaria control programme in Tanzania that meets World Health Organization standards for malaria diagnosis and costs approximately $0.7 (£0.4; €0.5) per test in Tanzania. The trainers discussed studies showing 94-100% sensitivity and 89-100% specificity for Paracheck and outlined the advantages of visible test results less prone to false negatives caused by parasite sequestration. They reviewed Tanzanian national guidelines for diagnosis and treatment of malaria to emphasise that negative malaria tests should lead to alternative diagnoses being considered.

Malaria tests were free for the duration of the study, irrespective of whether patients consented to the study. Before the trial, we did a baseline observational study to determine the pattern of routine diagnosis of malaria. We inspected the prescriptions of all patients leaving an outpatient consultation and asked them whether a malaria test had been requested. For those sent for testing, we recorded the result and subsequent prescription. A reference slide was taken at the same time as the routine slide.

The entry criterion for the main trial was a clinician’s decision to request a malaria test in a patient of any age. The only patients excluded were those for whom the clinician specified microscopy or who were admitted as inpatients for severe disease. Patients with a clinician’s request for a malaria test were invited to take part. If they or their guardians gave informed consent, a standardised history was taken, followed by randomisation to rapid diagnostic test or blood slide by computer generated random numbers in blocks of 10; allocations inserted into opaque envelopes were opened in front of the patient on recruitment. All slips had to be accounted for.

Laboratory staff in the clinic did the rapid diagnostic tests, recorded their result, and gave the test strip to the patient for the clinician to interpret independently and record in the review consultation. We used results recorded by clinicians in the primary analysis of prescribing. Patients randomised to microscopy were tested according to routine hospital practice, and clinicians were given results of the test. We obtained a reference slide for later double reading in both arms. Two experienced microscopists blind to allocation stained reference slides with Giemsa and counted parasites against 200 white blood cells; they examined 100 fields before declaring slides negative. We took a third reading of discordant results as final.

Clinic staff with the test result (rapid diagnostic test or hospital slide) reviewed patients in the study and made clinical decisions that they felt were appropriate. As patients left, study staff inspected their prescriptions and recorded them as an objective record of clinicians’ decisions.

**Sample size calculation**

We designed the study to detect a reduction from an estimated 45% over-prescription to 25% over-prescription in the rapid diagnostic test arm. We needed 128 cases with negative test results in each arm to detect this with 95% confidence and 90% power. Estimating that at high, moderate, and low transmission 40%, 70%, and 90% of cases respectively would be slide negative and allowing for a 25% rate of refusal, we needed a total of 800, 457, and 356 cases at the three transmission bands. To avoid the possible bias between sites of a tendency for practice to change over time as health workers became more familiar and better informed about the rapid diagnostic test, we decided to recruit 800 cases at each site.

**Statistical analysis**

We entered data in Microsoft Access and analysed them with Stata version 9. We finalised the analytical plan before analysis. The primary outcome of the study was the proportion of patients in each arm for whom clinicians requested a malaria test, received a negative result, and prescribed an antimalarial drug anyway. We calculated unadjusted odds ratios and then adjusted them in a logistic regression model with the pre-defined potential confounding factors of age,
Table 1 | Baseline characteristics of patients randomised to blood slide or rapid diagnostic test. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Slide (n=1204)</th>
<th>Rapid test (n=1193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) age (years)</td>
<td>11.4 (2-30)</td>
<td>7.3 (2-29)</td>
</tr>
<tr>
<td>Female</td>
<td>679 (56)</td>
<td>668 (56)</td>
</tr>
<tr>
<td>Fever in previous 48 hours</td>
<td>979 (81)</td>
<td>952 (80)</td>
</tr>
<tr>
<td>Cough in previous 48 hours</td>
<td>493 (41)</td>
<td>499 (42)</td>
</tr>
<tr>
<td>Previous antimalarial drug use in current illness</td>
<td>66 (5.5)</td>
<td>66 (5.5)</td>
</tr>
<tr>
<td>Less than eight years’ education*</td>
<td>888 (74)</td>
<td>876 (73)</td>
</tr>
<tr>
<td>Less than one hour’s travel to clinic</td>
<td>698 (58)</td>
<td>685 (57)</td>
</tr>
<tr>
<td>Median (IQR) reported days ill</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
</tr>
</tbody>
</table>

*Patient or patient’s mother if patient aged under 15.

Table 2 | Patients with negative test result treated with any antimalarial drug by malaria test method and age group, stratified by transmission intensity of *Plasmodium falciparum*

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Slide negative</th>
<th>Rapid diagnostic test negative</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>given antimalarial</td>
<td>No (%)</td>
</tr>
<tr>
<td>Low transmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>185</td>
<td>116 (63)</td>
<td>172</td>
</tr>
<tr>
<td>5-15</td>
<td>38</td>
<td>17 (45)</td>
<td>35</td>
</tr>
<tr>
<td>&gt;15</td>
<td>193</td>
<td>94 (49)</td>
<td>194</td>
</tr>
<tr>
<td>Total</td>
<td>416</td>
<td>227 (55)</td>
<td>401</td>
</tr>
<tr>
<td>Low-moderate transmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>141</td>
<td>88 (62)</td>
<td>171</td>
</tr>
<tr>
<td>5-15</td>
<td>55</td>
<td>39 (71)</td>
<td>59</td>
</tr>
<tr>
<td>&gt;15</td>
<td>171</td>
<td>103 (60)</td>
<td>156</td>
</tr>
<tr>
<td>Total</td>
<td>367</td>
<td>230 (63)</td>
<td>386</td>
</tr>
<tr>
<td>High transmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>88</td>
<td>20 (23)</td>
<td>78</td>
</tr>
<tr>
<td>5-15</td>
<td>29</td>
<td>14 (48)</td>
<td>25</td>
</tr>
<tr>
<td>&gt;15</td>
<td>130</td>
<td>32 (25)</td>
<td>115</td>
</tr>
<tr>
<td>Total</td>
<td>247</td>
<td>66 (27)</td>
<td>218</td>
</tr>
<tr>
<td>All sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>414</td>
<td>224 (54)</td>
<td>421</td>
</tr>
<tr>
<td>5-15</td>
<td>122</td>
<td>70 (57)</td>
<td>119</td>
</tr>
<tr>
<td>&gt;15</td>
<td>494</td>
<td>229 (46)</td>
<td>465</td>
</tr>
<tr>
<td>Total</td>
<td>1030</td>
<td>522 (51)</td>
<td>1005</td>
</tr>
</tbody>
</table>

*Statistical significance of associations in each stratum assessed with fully interacted logistic regression model that included interactions between treatment and indicator variables for each stratum as covariates.

RESULTS

In the one month baseline study, 4081 consultations took place; 70 (1.7%) of these resulted in presumptive treatment for malaria, and 2011 (49.3%) resulted in a request for a malaria slide. For 1813 (90.2%) patients the slide was reported as negative, and 962 (53.1%) of these were treated for malaria.

The intervention ran from January to August 2005. Of 7589 consultations, 63 patients (0.8%) were treated presumptively for malaria and 2425 (32.0%) were sent for a malaria test, of whom 2416 (99.6%) consented to participate and were randomised to rapid diagnostic test or blood slide (fig 1). Data were incomplete in 19 (0.8%) patients, and results are shown for the remaining 2397 cases. Characteristics of patients in each arm were similar (table 1).

In all, 523/1030 (50.8%) patients with a negative hospital slide and 540/1005 (53.7%) patients with a negative rapid diagnostic test were prescribed an antimalarial drug (odds ratio 1.13, 95% confidence interval 0.95 to 1.34; P=0.18). Rapid diagnostic tests showed no advantage in any of the transmission settings (fig 2); the odds ratio was 1.16 (0.88 to 1.52) at the low transmission site, 1.00 (0.76 to 1.35) at low-moderate transmission, and 1.17 (0.78 to 1.75) at high transmission. We found a trend towards an age effect, in that children aged under 5 were more likely to be treated with an antimalarial drug if they tested negative by rapid diagnostic test than if they tested negative by routine slide (table 2). The proportion of test negative patients treated with an antimalarial drug did not vary with the duration of the trial, whether tested by blood slide (odds ratio 0.99 (0.95 to 1.05) per week of trial duration) or by rapid diagnostic test (1.02 (0.97 to 1.07) per week).
We used a logistic model to explore associations between presenting features and prescription of an antimalarial drug for a patient with a negative test result. Adults and patients with a history of fever in the previous 48 hours were more likely to be prescribed an antimalarial drug despite a negative test; we found no significant association with the type of test used (table 3). In 203/1063 (19.1%) of cases in which treatment for malaria was given with a negative test result, the patient did not report a history of fever. Antibiotics were prescribed to 51/362 (14.1%) patients who tested positive for malaria and to 1044/2035 (51.3%) with a negative test (odds ratio 6.42, 4.72 to 8.75; P<0.001); the difference was especially marked in children aged under 5 (16.8, 11.3 to 25.1; P<0.001) (table 4). Prescription of an antibiotic was not influenced by test method: 525/1030 (51.0%) slide negative patients and 519/1005 (51.6%) rapid diagnostic test negative patients were prescribed an antibiotic (P=0.76), and 308/414 (74.4%) slide negative and 310/421 (73.6%) rapid diagnostic test negative children aged under 5 were prescribed an antibiotic (P=0.80).

When we used double read research slide results as a gold standard, 269/1420 (18.9%) patients prescribed an antimalarial drug had \( P \) \textit{falciparum} parasitaemia, and in the low and low-moderate transmission sites this proportion fell to 20/1004 (2.0%). Among children aged under 5, 3/99 (3.0%) tested by rapid diagnostic test had \( >2000 \) parasites/\( \mu l \) on the research slide and did not receive an antimalarial drug, compared with 4/72 (5.6%) in the hospital slide group (P=0.41). If we define a correct prescription of an antimalarial drug as one that is prescribed when parasites are present on research slides and not prescribed when they are not, 616/1193 (51.6%) of patients randomised to the rapid diagnostic test and 606/1204 (50.3%) randomised to a slide test had a correct prescription of an antimalarial drug (odds ratio 1.05, 0.90 to 1.12; P=0.524).

We compared hospital slide and rapid diagnostic test results with the double read research slide (table 5). Rapid diagnostic tests generally performed well (both sensitive and specific) under field conditions. However, in seven cases the rapid diagnostic test result was negative according to both the prescribing health worker and the laboratory assistant but the research slide was positive; in five of these the parasite density was \( >5000 \) \( P \) \textit{falciparum} parasites/\( l \). In two cases, non-\( falciparum \) species were detected. Hospital laboratory slide results were less sensitive than rapid diagnostic tests (71.3% vs 95.4%), and 39 reference slide positive cases were reported as slide negative by the hospital laboratory; in 13 of these the parasite density was \( >5000 \) \( P \) \textit{falciparum} parasites/\( l \). The agreement between the health worker and the laboratory assistant in interpreting the rapid diagnostic test result was high (k=0.913); 4/996 (0.4%) of rapid diagnostic tests were reported as negative by the health worker and positive by the laboratory assistant, and 22/1014 (2.2%) were reported as positive by the health worker and negative by the laboratory assistant.

**DISCUSSION**

Malaria is the single most common diagnosis in most hospitals in Africa and consumes a considerable proportion of available resources. During an era of cheap
and virtually limitless antimalarial drugs, the policy for treating malaria has assumed that it is safer to treat several cases of non-malarial febrile illness with an antimalarial drug than to miss one true case. Our study shows that this policy is associated with high levels of overuse of antimalarial drugs, especially in low-mod-
erate transmission settings where a significant proportion of people in malarial countries of Africa live.22 Clinicians frequently requested tests, but they paid limited attention to negative results, irrespective of intensity of transmission. At the low transmission site, less than 1% of patients treated with an antimalarial drug had malaria parasites in their blood.

Impact of over-diagnosis on cost effectiveness
The potential impact of this level of over-prescription is considerable. Substantial numbers of cases of potentially fatal febrile illness treatable with affordable antibiotics are almost certainly being missed.23 Over-diagnosis of malaria on this scale also threatens the sustainability of deployment of artemisinin combination treatment. These highly effective drugs are essential in east Africa, where alternative treatments are failing, but they are considerably more expensive than current monotherapy and depend on subsidy from the Global Fund and others if they are to reach the current monotherapy and depend on subsidy from the Global Fund and others if they are to reach the current monotherapy and depend on subsidy from the Global Fund and others if they are to reach the current monotherapy and depend on subsidy from the Global Fund and others if they are to reach the
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nosis of malaria on this scale also threatens the susta-
ibility of deployment of artemisinin combination treat-
tment. These highly effective drugs are essential in east Africa, where alternative treatments are fail-
ing, but they are considerably more expensive than
current monotherapy and depend on subsidy from
the Global Fund and others if they are to reach the
poorest groups who are most vulnerable to malaria.24
Sustaining the subsidy for artemisinin combination
treatment, which is essential for malaria in Africa, will
be possible only if this regimen is seen to be cost effec-
tive. These drugs are cost effective if used for malaria in
areas where other drugs have failed, but this depends on
the drug being used for children with true malaria,
as cost effectiveness rapidly falls away at high levels of
parasites.

Table 4 | Prescription of any antibiotic for patients with positive or negative malaria tests by age group

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Positive test</th>
<th>Negative test</th>
<th>Antimalarial drug</th>
<th>No</th>
<th>No (%) given antibiotic</th>
<th>No</th>
<th>No (%) given antibiotic</th>
<th>No</th>
<th>No (%) given antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>⩽5</td>
<td>228</td>
<td>33 (14)</td>
<td>495</td>
<td>365 (74)</td>
<td>340</td>
<td>253 (74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-15</td>
<td>50</td>
<td>7 (14)</td>
<td>141</td>
<td>49 (35)</td>
<td>100</td>
<td>55 (55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>⩾15</td>
<td>84</td>
<td>11 (14)</td>
<td>427</td>
<td>143 (33)</td>
<td>532</td>
<td>179 (34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>362</td>
<td>51 (14)</td>
<td>1063</td>
<td>557 (52)</td>
<td>972</td>
<td>487 (50)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5 | Sensitivity, specificity, and predictive values of rapid diagnostic test or routine blood slide as judged against research slide results

<table>
<thead>
<tr>
<th>Rapid diagnostic test†</th>
<th>Research slide*</th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
<th>Negative predictive value (%)</th>
<th>Positive predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>146</td>
<td>95.4 (94.2 to 96.6)</td>
<td>95.9 (94.8 to 97.0)</td>
<td>99.3</td>
<td>77.7</td>
</tr>
<tr>
<td>Negative</td>
<td>72</td>
<td>985</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital slide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>97</td>
<td>71.3 (68.8 to 73.8)</td>
<td>92.8 (91.3 to 94.3)</td>
<td>96.2</td>
<td>55.8</td>
</tr>
<tr>
<td>Negative</td>
<td>39§</td>
<td>991</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Slide results are positive or negative for any Plasmodium falciparum asexual parasites; in addition, two slides were positive for P malariae asexual parasites.
†Positive by either laboratory technician or prescribing health worker.
‡Parasite densities/l were <1000, 0; 1000-4999, 2; 5000-100 000, 2; >100 000, 3.
§Parasite densities/l were <1000, 15; 1000-4999, 11; 5000-100 000, 8; >100 000, 5.
syndromic, and they have considerable potential to improve diagnosis. In this study, rapid diagnostic tests were more accurate than routine slide testing, and both patients and clinicians reported liking them. Introducing them into routine care, free of charge and after delivering targeted training had, however, no impact on the overuse of antimalarial drugs. Incurring the cost of a test and then prescribing antimalarial drugs for patients with a negative result represents the worst possible outcome economically. Deployment of rapid diagnostic tests or any other diagnostic test to promote the sustainability of artemisinin combination treatment in Africa is likely to fail unless ways can be found to bring about a major change in current prescribing behaviour.

Although rapid diagnostic test and slide results were equally disappointing in guiding antimalarial treatment, the fact that they both seemed to influence the decision to prescribe antibiotics is potentially encouraging given the increasing realisation of the importance of bacterial disease as a cause of infant and childhood mortality. Clinicians with a positive test for malaria were, however, highly unlikely to prescribe anything except an antimalarial drug; this is not always appropriate, as dual infection occurs in all ages.

Potential limitations of rapid diagnostic tests and this study
Current rapid diagnostic tests have limitations. This study showed false negative results in patients with high parasite counts, but we cannot determine whether this was because the test was done incorrectly or because of technical limitations of the test. Possible technical problems include deletion of HRP-2 genes in certain parasites, “flooding” of the antigen capture sites, and defects in the device membrane (Anthony Moody, personal communication, 2006). This supports the legitimate concern that in areas of very high malaria transmission, withholding antimalarial drugs from children under 5 with febrile illness is potentially hazardous even in the face of negative test results, although where clinicians intend to treat for malaria anyway it makes little sense to request a test. In other epidemiological settings and age groups, the negative predictive value of tests will be excellent and the risks of withholding antimalarial drugs from patients with negative tests will be minimal.

Three reasons exist why this trial might not reflect reality in the rest of Africa and may wrongly lead to an impression that deploying rapid diagnostic tests without major additional interventions will have a limited impact. Firstly, prescribers might have altered their normal practice as a result of the study (Hawthorne effect); however, if anything, this is more likely to have encouraged them to follow national policy and take test results into account. Secondly, the levels of over-diagnosis were atypical, but all the available evidence indicates that the findings of over-diagnosis are wholly typical of hospitals throughout the continent; these are well run, government designated hospitals in a stable area, with staff who have received training typical for healthcare providers in Africa. Thirdly, the training provided in the trial was not adequate, but as it was considerably more intensive and tailored to individual settings than would be possible in a national roll out, this seems unlikely to have led to bias against rapid diagnostic tests. The fact that rapid diagnostic tests were a newly introduced technology might have affected their use either positively or negatively, but we found that the tendency to respect negative rapid diagnostic tests did not vary with the duration of the trial.

Deploying more expensive antimalarial drugs may lead to behavioural change, so theoretically the results of this trial will not reflect what will happen if clinicians are prescribing artemisinin combination treatment. The cost of centrally subsidised artemisinin combination treatment to both clinicians and patients will, however, be the same as existing drugs, so it seems unlikely the cost will in itself lead to marked behavioural change. The study reflects behaviour in a hospital setting, and a substantial proportion of febrile illness (often the great majority) is treated outside hospital or not treated at all; a paradox of malaria treatment throughout Africa is that simultaneously with a high proportion of patients given antimalarial drugs not having malaria, a significant proportion (and often the majority) of those who have malaria are not given an antimalarial drug.

Can behaviour be changed?
Rapid diagnostic tests could, if they guided results, have a major impact on the management of malaria in Africa. This trial shows that providing quick and reliable diagnostic tools with basic training may, in itself, have little impact on overuse of antimalarial drugs. The combination of artemisinin combination treatment and rapid diagnostic tests creates an important opportunity to both reduce the burden of mortality from malaria in Africa and improve the treatment of bacterial disease. Understanding the reasons for, and then changing, the habit of over-prescribing antimalarial drugs will need to be a priority if the potential benefits of artemisinin combination treatment are to be realised; simple technical fixes are unlikely. Our findings indicate an urgent need to identify and implement more effective ways to improve the use of antimalarial and antibiotic treatment in Africa.

We thank all the patients and staff at the study sites for their support and participation. Alan Minja, Kenja Mlay, and Rajabu Mlayho were key hospital staff. Anna Mtei, Emmanuel Mwakasungula, Lilian Ngwai, Boniface Njau, Yustina Muchi, Happiness Mwanga, Mary Urio, and Nico Funga collected outpatient data. Kini Chonya and Jan Ostermann assisted with data analysis. Magdalena Massawe, James Kalabashanga, and Habibu Ahamma read research blood films. This study was done as part of the Joint Malaria Programme in northeast Tanzania.

Contributors: HR, CD, and CJMW designed the trial, with help from RO. HR was the project leader, HM, RM, and OM led the trial team, and CD led the laboratory aspects. HR and CJMW drafted the paper, with input from all authors. HR is the guarantor.

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Competing interests: None declared.

Ethical approval: Ethics committees of the National Institute for Medical Research, Tanzania, and the London School of Hygiene and Tropical Medicine.
the over-diagnosis of malaria in febrile patients

Deploying rapid diagnostic tests for malaria, with standard training, made no difference to hospital outpatients and microscopy results are often ignored

In areas of low or moderate malaria transmission, malaria is massively over-diagnosed in

WHAT THIS STUDY ADDS

Rapid diagnostic tests are sensitive and specific for falciparum malaria, and could be cost

effective if their use guided practice

WHAT IS ALREADY KNOWN ON THIS TOPIC

Cases of malaria in the community are often missed, but at the same time over-diagnosis of malaria is widespread in Africa

Rapid diagnostic tests are sensitive and specific for falciparum malaria, and could be cost effective if their use guided practice

Deploying rapid diagnostic tests for malaria, with standard training, made no difference to the over-diagnosis of malaria in febrile patients

REFERENCES


Accepted: 13 December 2006
Oral chemotherapy safety practices at US cancer centres: questionnaire survey

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ABSTRACT

Objective To characterise current safety practices for the use of oral chemotherapy.

Design Written questionnaire survey of pharmacy directors of cancer centres.

Setting Comprehensive cancer centres in the United States.

Results Respondents from 42 (78%) of 54 eligible centres completed the survey, after consulting with 89 colleagues. Clinicians at 29 centres used handwritten prescriptions, two used preprinted paper prescriptions, and six used electronic systems for most oral chemotherapy prescribing. For six commonly used oral chemotherapies, on average 10 centres required a diagnosis on the prescription, 11 required the protocol number, four required the cycle number, nine required double checking by a second clinician, 14 required a calculation of body surface area, and 14 required a calculation of dose per square metre of body surface area. Only a third of centres requested patients’ written informed consent when oral chemotherapy was given off protocol. Nearly a quarter (10) of centres had no formal process for monitoring patients’ adherence. In the past year respondents at 10 centres reported at least one serious adverse drug event related to oral chemotherapy, and respondents at 13 centres reported a serious near miss.

Conclusion Few of the safeguards routinely used for infusion chemotherapy have been adopted for oral chemotherapy at US cancer centres. There is currently no consensus at these centres about safe medication practices for oral chemotherapy.

INTRODUCTION

Common malignancies can be treated with oral chemotherapy.1 This offers patients unprecedented convenience compared with intravenous infusion therapy.2,3 Given the potential toxicities of oral chemotherapy and the importance of adherence for successful treatment, ensuring safe use of these drugs may require special safeguards.4-11 The extent to which such safety practices have been introduced into clinical care is unknown.

To characterise current safety practices for oral chemotherapy we surveyed pharmacy leaders at comprehensive cancer centres in the United States. Given the relatively recent introduction of oral chemotherapies, we expected considerable variation in practice.

METHODS

Sample selection–We used the internet to compile contact information for pharmacy directors at all 62 comprehensive cancer centres designated by the US National Cancer Institute. We excluded eight research centres that do not directly care for patients.

Instrument development–We developed a questionnaire that examined aspects of the use of oral chemotherapy medication. We focused on non-hormonal oral agents with risk of serious toxicity including capcitabine, cyclophosphamide, gefitinib, imatinib, oral methotrexate, and temozolomide. We circulated a draft survey among the quality directors of the Comprehensive Cancer Center Consortium for Quality Improvement and incorporated revisions into the final instrument.

Study protocol–We sent the questionnaire by email and post in September 2005. Non-responders received up to three follow-up telephone calls. If the pharmacy director was misidentified or unable to participate, we encouraged recipients to identify a substitute respondent who was familiar with oral chemotherapy practices.

Data analysis–We deleted respondents’ names and organisations before analysis and tabulated responses using Stata 7.0 (StataCorp, College Station, TX).

RESULTS

Responses We received 42 completed questionnaires from the 54 eligible centres. Table 1 shows the job titles of 33 respondents who reported this information. Thirty one respondents consulted with colleagues about the survey (total 89, median 2, range 0-8).

Prescribing Prescribing practices for oral chemotherapy varied considerably. For most oral chemotherapy prescribing
Clinicians at 29 centres used handwritten prescriptions. At two centres they used preprinted paper prescriptions and at six they used electronic systems (table 2).

Organisations did not have many compulsory requirements on prescriptions. For six commonly used oral chemotherapies (see bmj.com), on average 10 centres required a diagnosis on the prescription, 11 required the protocol number (when appropriate), four required the cycle number, nine required double checking by a second clinician, 14 required a calculation of dose per square metre of body surface area, and 14 required calculation of informed consent. Only a third of centres asked patients to provide written informed consent when oral chemotherapy was given off protocol.

**Coordination and monitoring**

Respondents reported considerable variation in the methods used to coordinate oral and infusion chemotherapy among patients who received both types of treatment. Twenty five centres coordinated care by maintaining a record of oral chemotherapy in the patient’s medication profile. At 26 centres, a nurse or pharmacist reviewed oral chemotherapy during infusion treatment. Seven centres reported no formal coordination.

Clinicians at most centres monitored patients’ adherence to oral chemotherapy among patients who received both types of treatment. Twenty five centres coordinated care by maintaining a record of oral chemotherapy in the patient’s medication profile. At 26 centres, a nurse or pharmacist reviewed oral chemotherapy during infusion treatment. Seven centres reported no formal coordination.

Clinicians at most centres monitored patients’ adherence to oral chemotherapy during office visits. Staff at 10 centres asked patients to bring in logbooks, and staff at nine regularly counted pills. Respondents from nine centres reported no formal process for monitoring adherence.

**Pharmacy services**

Pharmacy services may be underused in the care of patients on oral chemotherapy. Although 33 centres offered patients a formal consultation with a pharmacist, respondents estimated that many (42%) patients declined a consultation.

Thirty four centres had an on-site pharmacy for patients receiving oral chemotherapy who were not on research protocols. Respondents estimated, however, that 38% of eligible patients did not use this facility. Failure to use an on-site pharmacy may be problematic as respondents at 17 centres rated communication between community pharmacies and cancer centres as fair or poor.

**Education of patients**

At most centres physicians shared responsibility with other health professionals for educating patients about oral chemotherapy. Respondents at 25 (60%), 34 (81%), and 40 (95%) organisations indicated that nurse practitioners, nurses, and pharmacists, respectively, were also responsible for educating patients about use and safety. Only a third of organisations provided special training or certification for those who educate patients about these medications.

**Safety assessment**

Respondents at 10 centres reported that a “serious adverse drug event” related to oral chemotherapy had occurred in the past year, and 13 centres reported a “serious near miss.” Respondents at 36 centres indicated that clinicians in their organisations were concerned about the risks of oral chemotherapy.

**DISCUSSION**

Despite the increased use of oral chemotherapy, current practices for prescribing, coordinating and monitoring, and dispensing these medications and educating patients in US cancer centres leave room for improvement. We found that most organisations had no required elements for prescribing oral chemotherapy and few requested patients’ written informed consent for off protocol prescribing. Only about half of cancer centres coordinated oral with intravenous chemotherapy. Most organisations provided little infrastructure to support adherence to treatment. On-site pharmacies and consultation with a pharmacist were widely available to patients, but both were underused. Clinicians from various professions shared responsibility for educating patients about oral chemotherapy, but few centres provided clinicians with relevant formal training.

**Table 1: Details of 42 respondents from US cancer centres who took part in survey of safety practices with oral chemotherapy**

<table>
<thead>
<tr>
<th>Job title given by respondent:</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy director, manager, supervisor</td>
<td>19</td>
</tr>
<tr>
<td>Oncology pharmacist</td>
<td>8</td>
</tr>
<tr>
<td>Quality or clinical outcomes manager</td>
<td>3</td>
</tr>
<tr>
<td>Clinical nurse specialist</td>
<td>2</td>
</tr>
<tr>
<td>Physician director of clinical services</td>
<td>1</td>
</tr>
<tr>
<td>Not specified</td>
<td>9</td>
</tr>
</tbody>
</table>

Colleagues (n=89) with whom respondent discussed survey:

| Pharmacist                                   | 28 |
| Pharmacy director or manager                | 19 |
| Nurse                                       | 13 |
| Nurse manager or administrator              | 10 |
| Nurse practitioner                           | 6  |
| Attending physician                         | 5  |
| Quality, risk, or safety director           | 5  |
| Clinical fellow                             | 2  |
| Medical director or chief medical officer   | 1  |

**Table 2: Prescription writing for oral chemotherapy at 42 US cancer centres. Figures are numbers (percentages) of centres**

<table>
<thead>
<tr>
<th>Proportion of prescriptions generated by method</th>
<th>Majority (&gt;50%)</th>
<th>Minority (≤50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handwritten paper prescriptions</td>
<td>29 (69)</td>
<td>13 (31)</td>
</tr>
<tr>
<td>Preprinted paper prescriptions</td>
<td>2 (5)</td>
<td>40 (95)</td>
</tr>
<tr>
<td>Electronic order entry</td>
<td>6 (14)</td>
<td>36 (86)</td>
</tr>
</tbody>
</table>
Surprisingly few of the safeguards in routine use for infusion chemotherapy at US cancer centres have been adopted for oral chemotherapy. Only one in three organisations required a clinician to note the body surface area or calculation of dose on the prescription for six commonly used oral drugs, and only one in four required the patient’s diagnosis or protocol. One in five organisations required a second clinician to double check the prescription, and fewer than one in 10 required the clinician to enter the treatment cycle. Half of the centres required no safeguards around prescription writing at all.

Study limitations
Medication safety practices at sites that did not respond may differ from those that responded. Our results may overemphasise the perspective of pharmacy directors relative to other oncology clinicians. Similarly, respondents’ characterisation of safety practices reflected their best—but potentially biased—judgments. We asked respondents to consider oral agents with considerable toxicity risks, but they may not have shared a common definition of oral chemotherapy. Finally, it may have been difficult for respondents to characterise medication practices in organisations with practice patterns that varied across clinicians and treatment regimens.

Conclusions
Our data indicate that prescribing, monitoring and coordination, pharmacy practices, and education of patients for oral chemotherapy vary substantially. Despite clinicians’ concern about oral chemotherapies, there is no apparent consensus among oncology professionals about safe practices for these drugs. Safeguards used for infusion chemotherapy cannot be abandoned for oral treatment. The oncology community must define safe medication practices appropriate for oral chemotherapy, develop practice guidelines, and accelerate their adoption.

We thank the Comprehensive Cancer Center Consortium for Quality Improvement (C4QI) for help in completing this project.

Contributors: SNW, JF, AP, SB, LNS, and MC were responsible for conception and design. SNW, JF, DB, LM, and MC collected the data. SNW, AP, LNS, and MC analysed and interpreted data. SNW, JF, DB, LM, AP, SB, LNS, and MC drafted and revised the paper. AP and SNW supervised the study. SNW is guarantor.

Funding: Center for Patient Safety, Dana-Farber Cancer Institute, Boston. SNW was also supported by a K08 Mentored Clinical Scientist Career Development Award (1 K08 HS 11644) from the US Agency for Healthcare Research and Quality.

Competing interests: None declared.

Ethical approval: Dana-Farber Cancer Institute’s institutional review board.


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Effect of reducing caffeine intake on birth weight and length of gestation: randomised controlled trial

Bodil Hammer Bech, assistant professor,1 Carsten Obel, assistant professor,1 Tine Brink Henriksen, consultant,2 Jørn Olsen, professor3

ABSTRACT
Objective To estimate the effect of reducing caffeine intake during pregnancy on birth weight and length of gestation.
Design Randomised double blind controlled trial.
Setting Denmark.
Participants 1207 pregnant women drinking at least three cups of coffee a day, recruited before 20 weeks' gestation.
Interventions Caffeinated instant coffee (568 women) or decaffeinated instant coffee (629 women).
Main outcome measures Birth weight and length of gestation.
Results Data on birth weight were obtained for 1150 liveborn singletons and on length of gestation for 1153 liveborn singletons. No significant differences were found for mean birth weight or mean length of gestation between women in the decaffeinated coffee group (whose mean caffeine intake was 182 mg lower than that of the other group) and women in the caffeinated coffee group. After adjustment for length of gestation, parity, prepregnancy body mass index, and smoking at entry to the study the mean birth weight of babies born to women in the decaffeinated group was 16 g (95% confidence interval +40 to 73) higher than those born to women in the caffeinated group. The adjusted difference (decaffeinated group−caffeinated group) of length of gestation was −1.31 days (−2.87 to 0.25).
Conclusion A moderate reduction in caffeine intake in the second half of pregnancy has no effect on birth weight or length of gestation.

Trial registration Clinical Trials NCT00131690.

INTRODUCTION
Exposure to caffeine in adults is mainly through the consumption of coffee.1 The half life of caffeine is 2.5 to 4.5 hours in non-pregnant women but longer during pregnancy, especially in late pregnancy. Caffeine is rapidly absorbed from the digestive system and passes freely across the placenta.2 In addition, fetuses do not metabolise caffeine well.3 Caffeine increases the levels of circulating catecholamines,4 which may cause uteroplacental vasoconstriction and fetal hypoxia, all of which possibly reduce fetal growth. Caffeine also increases cellular cyclic adenosine monophosphate, which may influence cell development.5

Pregnant women with a high caffeine intake (>300 mg a day) have been shown to give birth to babies with a birth weight 100-200 g lower than those of women with a low caffeine intake,6 although not all studies found this association.7,8 A high daily caffeine intake has also been associated with an increased risk of giving birth to small for gestational age or low birth weight (<2500 g) babies,9-11 but not all studies found this association.12-18 Most studies found no association between caffeine intake and preterm birth.19 Some have shown an association between caffeine intake during pregnancy and miscarriage,20,21 but not all.22,23 These conflicting results have puzzled public health authorities, and in some countries pregnant women are warned against caffeine consumption.

Women with a high caffeine intake during pregnancy differ in many ways from women with a low or no caffeine intake. They smoke more, have a higher alcohol intake, and have attained a lower level of education.12,14 Despite attempts to control for these factors there are limits as to how much can be controlled in non-experimental studies.

We carried out a randomised double blind trial to estimate the effect of reducing caffeine intake on birth weight and length of gestation.

METHODS
We recruited Danish speaking pregnant women who consumed at least three cups of coffee a day and who were less than 20 weeks pregnant. Eligibility criteria included no history of a low birthweight baby (<2500 g), preterm delivery, kidney diseases, epilepsy, diabetes, or metabolic disorders.

From April 1996 to April 1998 we sent a questionnaire to all pregnant women booking for delivery at the Department of Obstetrics, Aarhus University Hospital, to assess coffee intake. At around 16 weeks of pregnancy we contacted those who had stated a daily intake of at least three cups of coffee. Eligible women who agreed to participate received detailed information on the study and a consent form.

From April 1998 to January 2002 we recruited eligible participants through the Danish national birth cohort.24 Participants in the cohort completed a telephone interview around 12 weeks of pregnancy that included information on the inclusion criteria. Eligible participants were randomised to the study after the interview.
women were again informed about the study and recruited if they had signed the consent form.

Randomisation and follow up
The women were randomised to receive caffeinated instant coffee or decaffeinated instant coffee. We bought the coffee from the manufacturer, in identical boxes without labels. The women were allocated to either group by a computer generated randomisation schedule and assigned serial numbers in balanced blocks of six. Staff not in contact with participants and endpoint data applied a label with the serial number to each of the boxes according to the randomisation schedule. After the project coordinator (BHB) had received the consent form (at about 18 weeks’ gestation) she posted six boxes of coffee to each participant, who were registered with the serial number applied to the box. BHB and the participants were blinded to the type of coffee, and the blinding was broken only at the end of the data analyses. The women could request as much coffee as they needed free of charge.

We asked the women to replace their usual coffee with that provided, but we did not advise them on how much to drink or ask them to avoid regular coffee offered by others or intake of other caffeinated beverages such as tea, cocoa, or cola. The women were interviewed throughout pregnancy to obtain data on daily consumption of the study coffee, other caffeinated beverages (coffee, tea, cola, or cocoa), and smoking status. The interviews were scheduled at gestational weeks 20, 25, and 34 and at four weeks after the expected date of delivery. In the final interview we asked the women to guess (or state “don’t know”) which type of coffee they had received.

Outcome measures
The main outcomes were birth weight and length of gestation, which we obtained, along with date of birth, from the Danish national birth register using the mother’s personal identification number. If data were missing (n=29) we used information from the telephone interview four weeks after the expected date of delivery. Gestational age at delivery was estimated by ultrasonography for 94% of the participants and by the date of the last menstrual period for the remaining women. From the national birth register we obtained information on length, head circumference, abdominal circumference, birth length, and ponderal index ([(birth weight (g)/birth length (cm)) x 100]) between the groups. The risk of preterm birth, being small for gestational age, and an Apgar score of less than 7 at five minutes was assessed by logistic regression analyses. Small for gestational age was defined as a birth weight more than two standard deviations below the mean for gestational age on the reference curve as suggested by Marsal et al. Preterm birth was defined as delivery before 37 completed weeks of gestation. In secondary analyses we stratified the main results on smoking status at baseline because an interaction between smoking and coffee consumption has been reported.

To determine if women who received decaffeinated coffee increased their consumption of other caffeinated beverages, we calculated the mean intake of caffeine from study coffee, other caffeinated coffee, tea, cola, and drinking chocolate for women in both arms of the study on the basis of information from the interviews.

All reported P values are two sided, and we defined statistical significance at the 5% level. We used Stata version 8.0 SE for all analyses.

If the standard deviation of birth weight was set to 500 g we calculated that a sample size of 800 women would give 80% power to detect a difference in birth weight of at least 100 g at a 5% two sided significance level.

RESULTS
Overall 1207 pregnant women were randomised. After exclusions, 568 women were randomised to caffeinated instant coffee and 629 to decaffeinated instant coffee (figure). The groups showed only minor differences in baseline characteristics (table 1).

A total of 1,153 women with a liveborn singleton were included in the analysis of birth weight and length of gestation. Of these, 8.6% (54/629) randomised to the decaffeinated group and 4.9% (28/568) randomised to the caffeinated group dropped out of the study before giving birth. The outcomes for these women were included in the main analysis.

Primary analyses
Women randomised to caffeinated coffee had a higher mean caffeine intake during the study period. Based on information from the interviews the mean difference in caffeine intake between the groups was 182 mg a day. Table 2 shows the caffeine intake from other beverages.

The mean birth weight for babies born to women in the caffeinated group was 3539 g (SD 607 g) compared with 3519 g (SD 607 g) for babies born to women in the decaffeinated group (table 3). Using the Wilcoxon rank
sum test no significant difference was found in gestational age between the groups (table 3; \(P=0.48\)).

After adjustment for determinants of birth weight at baseline the mean difference in birth weight between babies of women randomised to decaffeinated minus caffeinated coffee was 16 g (95% confidence interval −40 to 73; \(P=0.57\)).

Secondary analyses

The groups were similar for head and abdominal circumference, ponderal index, and placenta weight (table 3).

The difference in mean birth weight and length of gestation between the groups was not modified by coffee consumption at study entry or by compliance with the protocol (table 4). Women who smoked more than 10 cigarettes a day at study entry, however, had babies with a lower mean birth weight of 263 g (97 to 430; \(P=0.002\)) if they were randomised to decaffeinated coffee compared with babies born to women who were randomised to decaffeinated coffee (table 4, test for interaction \(P<0.001\)). On average these women smoked 15 cigarettes a day in the decaffeinated group (interquartile range 13-15) and 16 a day in the caffeinated group (interquartile range 15-20). For women smoking more than 10 cigarettes a day the mean difference in caffeine intake between the groups was 242 mg/day. For non-smokers the mean difference in caffeine intake between the groups was 154 mg/day. When length of gestation was the dependent variable no statistically significant interaction was found between smoking at study entry and randomisation group (test for interaction \(P=0.25\)).

In the decaffeinated and decaffeinated groups, respectively, 4.2% (23/552) and 5.2% (31/601) of infants were born preterm, 4.5% (25/552) and 4.7% (28/598) were small for gestational age, and 0.8% (4/527) and 1.0% (6/578) had an Apgar score of less than 7 after five minutes. None of these differences was statistically significant.

Compliance

At about 35 weeks’ gestation 53% (295/552) of women in the caffeinated group and 45% (271/601) in the decaffeinated group drank less than one cup of other

### Table 1 | Baseline characteristics of pregnant women randomised to decaffeinated or caffeinated coffee. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Caffeinated coffee group (n=568)</th>
<th>Decaffeinated coffee group (n=629)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>30.7 (4.3)</td>
<td>30.5 (4.3)</td>
</tr>
<tr>
<td>Mean (SD) prepregnancy weight (kg)</td>
<td>66.8 (12.4)</td>
<td>67.8 (13.3)</td>
</tr>
<tr>
<td>Mean (SD) height (cm)</td>
<td>168.6 (6.2)</td>
<td>169.0 (6.1)</td>
</tr>
<tr>
<td>Mean (SD) gestation (days)</td>
<td>122.4 (14.9)</td>
<td>122.9 (14.4)</td>
</tr>
</tbody>
</table>

#### Tobacco consumption (cigarettes/day):

| None                             | 353 (62.2)                      | 387 (61.5)                      |
| 1-10                             | 139 (24.5)                      | 155 (24.6)                      |
| >10                              | 75 (13.2)                       | 84 (13.4)                       |
| Missing data                     | 1 (0.2)                         | 3 (0.5)                         |

#### Parity:

| Nulliparous women                | 166 (29.2)                      | 208 (33.1)                      |
| Multiparous women                | 397 (69.9)                      | 413 (65.7)                      |
| Missing data                     | 5 (0.9)                         | 8 (1.3)                         |

#### Educational level:

| <9 years                         | 5 (0.9)                         | 4 (0.6)                         |
| 9 years                          | 48 (8.5)                        | 61 (9.7)                        |
| 10 years                         | 160 (28.2)                      | 170 (27.0)                      |
| High school                      | 224 (39.4)                      | 225 (35.8)                      |
| Missing data                     | 131 (23.0)                      | 169 (26.9)                      |

#### Secondary analyses

The groups were similar for head and abdominal circumference, ponderal index, and placenta weight (table 3).

The difference in mean birth weight and length of gestation between the groups was not modified by coffee consumption at study entry or by compliance with the protocol (table 4). Women who smoked more than 10 cigarettes a day at study entry, however, had babies with a lower mean birth weight of 263 g (97 to 430; \(P=0.002\)) if they were randomised to decaffeinated coffee compared with babies born to women who were randomised to decaffeinated coffee (table 4, test for interaction \(P<0.001\)). On average these women smoked 15 cigarettes a day in the decaffeinated group (interquartile range 13-15) and 16 a day in the caffeinated group (interquartile range 15-20). For women smoking more than 10 cigarettes a day the mean difference in caffeine intake between the groups was 242 mg/day. For non-smokers the mean difference in caffeine intake between the groups was 154 mg/day. When length of gestation was the dependent variable no statistically significant interaction was found between smoking at study entry and randomisation group (test for interaction \(P=0.25\)).

In the decaffeinated and decaffeinated groups, respectively, 4.2% (23/552) and 5.2% (31/601) of infants were born preterm, 4.5% (25/552) and 4.7% (28/598) were small for gestational age, and 0.8% (4/527) and 1.0% (6/578) had an Apgar score of less than 7 after five minutes. None of these differences was statistically significant.

### Table 2 | Caffeine intake from various beverages in pregnant women.* Values are median (interquartile range) caffeine intake (mg/day)

<table>
<thead>
<tr>
<th>Beverages†</th>
<th>Caffeinated coffee group</th>
<th>Decaffeinated coffee group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study coffee</td>
<td>0 (0-6)</td>
<td>195 (108-260)</td>
</tr>
<tr>
<td>Other coffee</td>
<td>67 (33-175)</td>
<td>50 (33-150)</td>
</tr>
<tr>
<td>Tea</td>
<td>0 (0-50)</td>
<td>0 (0-50)</td>
</tr>
<tr>
<td>Cocoa</td>
<td>0.2 (0-1.1)</td>
<td>0.1 (0-0.7)</td>
</tr>
<tr>
<td>Cola</td>
<td>2.9 (0-8.6)</td>
<td>3.8 (0-8.6)</td>
</tr>
<tr>
<td>Total caffeine intake</td>
<td>117 (56-228)</td>
<td>317 (229-461)</td>
</tr>
</tbody>
</table>

*Based on information from interviews with women of liveborn singletons.
†Amount of caffeine varies with type and amount of coffee used, brewing methods, and cup size. Average estimates of caffeine per cup were: decaffeinated study coffee 65 mg (according to manufacturer), decaffeinated study coffee 0 mg; other coffee 100 mg; tea 50 mg; drinking chocolate and cola per glass (2 dl) 5 mg and 20 mg. Data were not available on size of cups but were available on whether women used regular sized cups or mugs; a mug of coffee was classed as two cups.
Blinding  
In the caffeinated group 35% (191/552) of women guessed the type of coffee they received compared with 49% (296/601) in the decaffeinated group; 20% (123/601) in the decaffeinated group and 22% (121/552) in the caffeinated group could not guess. This difference in guessing was statistically significant. Information was missing for 10% (110/1153) of women; 82 had withdrawn their consent before the final interview, and 28 were unreachable.

Table 3: Differences in anthropometric data for liveborn singletons of mothers randomised to decaffeinated or caffeinated coffee

<table>
<thead>
<tr>
<th>Variable</th>
<th>No of babies</th>
<th>Decaffeinated coffee group</th>
<th>Caffeinated coffee group</th>
<th>Crude difference</th>
<th>Adjusted difference*</th>
<th>No of babies</th>
<th>Adjusted difference† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean birth weight (g)</td>
<td>1150</td>
<td>3519</td>
<td>3539</td>
<td>−19.4</td>
<td>4.6 (−53.5 to 62.7)</td>
<td>1112</td>
<td>16.3 (−40.0 to 72.6)</td>
</tr>
<tr>
<td>Mean length of gestation (days)</td>
<td>1153</td>
<td>279.3</td>
<td>280.2</td>
<td>−0.92</td>
<td>−0.92 (−2.45 to 0.61)</td>
<td>1115</td>
<td>−1.31 (−2.87 to 0.25)</td>
</tr>
<tr>
<td>Mean birth length (cm)</td>
<td>1146</td>
<td>51.9</td>
<td>52.0</td>
<td>−0.14</td>
<td>−0.05 (−0.30 to 0.21)</td>
<td>1108</td>
<td>−0.03 (−0.29 to 0.22)</td>
</tr>
<tr>
<td>Mean ponderal index</td>
<td>1145</td>
<td>2.5</td>
<td>2.5</td>
<td>0.01</td>
<td>0.01 (−0.02 to 0.04)</td>
<td>1107</td>
<td>0.02 (−0.01 to 0.05)</td>
</tr>
<tr>
<td>Mean head circumference (cm)</td>
<td>1006</td>
<td>35.1</td>
<td>35.1</td>
<td>0.03</td>
<td>0.07 (−0.14 to 0.27)</td>
<td>974</td>
<td>0.11 (−0.10 to 0.32)</td>
</tr>
<tr>
<td>Mean abdominal circumference (cm)</td>
<td>979</td>
<td>33.4</td>
<td>33.4</td>
<td>−0.03</td>
<td>−0.001 (−0.27 to 0.27)</td>
<td>949</td>
<td>0.07 (−0.19 to 0.33)</td>
</tr>
<tr>
<td>Mean placenta weight (g)</td>
<td>984</td>
<td>659</td>
<td>673</td>
<td>−14.7</td>
<td>−11.3 (−31.0 to 8.4)</td>
<td>954</td>
<td>−10.6 (−30.5 to 9.3)</td>
</tr>
</tbody>
</table>

Differences are for decaffeinated minus caffeinated groups. Number of babies differs owing to missing data.

*Adjusted for gestational age.
†Adjusted for length of gestation, parity, prepregnancy body mass index, and smoking at entry to study.
‡Adjusted for parity, smoking, and prepregnancy body mass index.
§Adjusted for parity, smoking, prepregnancy body mass index, and length of gestation.

Table 4: Differences in birth weight and length of gestation between mothers, of liveborn singletons, randomised to receive decaffeinated or caffeinated coffee, stratified on coffee consumption at baseline, compliance to study protocol, and smoking at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coffee consumption (cups/day) at baseline:</th>
<th>Birth weight</th>
<th>Length of gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;3</td>
<td>Mean difference† (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>131</td>
<td>−31 (−202 to 240)</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>480</td>
<td>7 (−78 to 92)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>497</td>
<td>57 (−28 to 142)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Missing data</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>283</td>
<td>−9 (−125 to 107)</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>&lt;1</td>
<td>−39 (−150 to 72)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-3</td>
<td>115 (3 to 226)</td>
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<td>92 (−475 to 659)</td>
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<td>Missing data</td>
<td>195</td>
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Differences are for decaffeinated minus caffeinated groups.

*Number with information on all covariates and outcome measure.
†Adjusted for parity, smoking, prepregnancy body mass index, and length of gestation.
‡Test for interaction.
§Adjusted for parity, smoking, prepregnancy body mass index.

caffeinated coffee a day; 24% (132/552) and 24% (147/601) drank one to three cups of other caffeinated coffee a day, whereas 9% (50/552) and 8% (51/601) drank more than three cups of other caffeinated coffee a day. Information on consumption of other caffeinated coffee at 35 weeks’ gestation was missing for 18% (207/1153) of the women (72 gave birth before the third interview and 79 had withdrawn their consent). Data from diaries were available on daily caffeine intake from study coffee, other coffee, tea, cocoa, and cola, but only 51% (293 in each arm) of women returned the diaries (data available on request).
WHAT IS ALREADY KNOWN ON THIS TOPIC
Caffeine intake in pregnancy has been linked to adverse outcome, but evidence from non-experimental studies on impaired fetal growth remains equivocal. Evidence from randomised controlled trials is lacking.

WHAT THIS STUDY ADDS
A moderate decrease in caffeine intake in the second half of pregnancy had no overall effect on birth weight or length of pregnancy.

DISCUSSION
Providing decaffeinated coffee to women who drank three cups of coffee or more a day in early pregnancy had no effect on birth weight or length of gestation.

We found only small differences in potential confounders at baseline between pregnant women allocated to instant caffeinated coffee and those allocated to instant decaffeinated coffee, and we adjusted for these in analyses.

To ensure good compliance we did not impose a strict protocol on the use of caffeinated beverages during the trial. Still, we obtained a difference in caffeine intake of a magnitude that has previously been reported to have an effect on birth weight. The difference in caffeine intake we found (182 mg a day) corresponds to almost three cups of instant coffee a day. We cannot, however, rule out that larger reductions in caffeine may increase birth weight.

Caffeine intake is associated with smoking and alcohol intake, which may influence birth weight. It is possible that a modification of caffeine intake could also influence other lifestyle factors. However, we found no difference between the groups in smoking or alcohol consumption (data not shown).

Women in the decaffeinated group guessed their type of coffee more often than women in the caffeinated group. Women recruited to the study consumed at least three cups of coffee a day, and it is likely that some in the decaffeinated arm had withdrawal symptoms such as headaches.

Slightly more women were randomised to decaffeinated coffee than to caffeinated coffee because of differences between the groups in requesting additional study coffee. When women requested more coffee the first box from the remaining stack of coffee that matched the first supply was chosen. Since women receiving caffeinated coffee requested additional coffee more often we randomised more women to receive decaffeinated coffee. This modification in randomisation probabilities has an effect only on power and not on internal validity of the study.

Comparison with other studies
Our finding of a possible caffeine effect in smokers may be due to chance, but it has some biological plausibility. Smokers metabolise caffeine faster than non-smokers because smoking induces the CYP1A2 pathway for caffeine metabolism. A previous study found that the caffeine metabolite paraxanthine was associated with fetal growth in smokers, whereas serum caffeine was not. A recent study suggested that CYP1A2 activity, and not the absolute levels of metabolites of caffeine, influences fetal growth.

Unanswered questions and future research
Our trial was carried out in the second half of pregnancy when the net increase in fetal weight is highest. If caffeine has an effect on birth weight by mechanisms that only operate early in pregnancy we would not detect it. Furthermore, we cannot rule out that substances other than caffeine in coffee may influence birth weight. Our results emphasise that care should be taken when extrapolating results to smokers.

We thank the women who participated in the study, J. Sonderskov for her support, and M. Vaeth for statistical advice.

Contributors: BHB, CO, TBH, and J.O designed and initiated the trial. BHB, CO, and TBH coordinated the trial, and BHB analysed the data. All authors met regularly and contributed to trial management, all participated in the interpretation of results and in the writing of the paper. BHB is the guarantor.

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Competing interests: None declared.

Ethical approval: This study was approved by regional science ethics committees in Denmark and the Danish Data Protection Agency.

16 Ekenazvi B, Stapleton AL, Kharazi M, Chee WY. Associations between maternal decaffeinated and caffeinated coffee.

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Accepted: 28 November 2006
Dog bites

Marina Morgan,† John Palmer

Bites and maulings by dogs, sometimes fatal, are a worldwide problem and particularly affect children. Every year 250 000 people who have been bitten by dogs attend minor injuries and emergency units in the United Kingdom, and some of them are admitted to hospital for surgical debridement or intravenous antibiotics.

Increasingly, dog bites are the subject of litigation because bite wounds are still being sutured when they should be left open and because of incorrect antimicrobial prophylaxis.

The “hole and tear” effect—whereby canine teeth anchor the person while other teeth bite, shear, and tear the tissues—results in stretch lacerations, easily piercing immature cranial bones. The biting force of canine jaws varies with the breed, from 310 kPa to nearly 31 790 kPa in specially trained attack dogs. Large wounds, significant devitalisation, and high mortality can result, with the highest mortality in neonates (six times that in toddlers), who are usually bitten by household pets.

This review is aimed at clinicians who deal with dog bites. The basic principles of wound management and indications for use of antimicrobials and rabies prophylaxis apply to clinicians in all countries, but the primary focus of this article will be the UK.

Overall, the clinical approach in the UK to management of dog bites is pragmatic and based largely on consensus opinion rather than firm evidence. The major basis for recommending co-amoxiclav is in-vitro sensitivity data of organisms related to dog bites, and most authorities recommend using prophylactic antimicrobials in selected patients at high risk of infection.

**Summary points**

Wound management is as important as use of antimicrobials in preventing infection

Primary closure should be avoided in limb injuries where possible because of increased risk of infection

For patients considered to be at higher risk of infection, the prophylaxis of choice is co-amoxiclav

ERYTHROMYCIN or flucloxacillin should never be used alone prophylactically as Pasteurella infection is usually resistant

Infected wounds presenting within 12 hours of injury are usually due to Pasteurella multocida

Patients at particularly high risk of infection are immunosuppressed patients, particularly those with asplenia or cirrhosis or those who have had a mastectomy

**Sources and selection criteria**

We reviewed the Cochrane Library and performed Medline searches to identify relevant systematic reviews on the management of dog bites, using the keywords “dog-bites”, “reviews”, “prophylaxis”, and “treatment”. We consulted personal archives, Clinical Evidence, and UK national NHS (Prodigy) guidelines.

**How big is the problem?**

Of the estimated 740 people per 100 000 population bitten by dogs annually, a minority seek medical attention. Overall, 2.6/100 000 population need hospital admission. Half of all children are reportedly bitten by dogs at some time, boys more than girls. A recent telephone survey of 1184 families found that the annual incidence of bites in children aged under 15 years was 22/1000.

Accurate mortality figures are poorly documented in the medical literature and difficult to obtain. However, because deaths are newsworthy, the popular press reports are probably reliable indicators of the true number in the UK, and during the past five years, two to three cases a year have made headlines. In the United States annual mortality is 7.1/100 million population, with 57% of deaths occurring in children aged under 10 years.

**Why do dogs bite?**

Most attacks are apparently unprovoked, but dogs are not always to blame. Dogs resent being disturbed while

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**Box 1 | Points to consider during history and examination**

**History**

- For travellers bitten abroad, assess risk of rabies and consider rabies prophylaxis
- Note immunocompromising factors, such as splenectomy, cirrhosis, and steroid therapy
- Note recent antibiotics (infection despite flucloxacillin or erythromycin makes superinfection with resistant organisms such as Pasteurella multocida likely)

**Examination**

- Children with facial or cranial bites need cervical immobilisation until cervical lesions are excluded
- Take careful documentation with diagrams of the wound (photographs may be useful)
- Assess size and depth of the wound, degree of crush injury and devitalised tissue, nerve or tendon damage, and involvement of bones and joints
- Full wound examination and debridement, with local or general anaesthetic if necessary
- Radiography is indicated to exclude embedded teeth or dental fragments, fractures, and bony damage, or in scalp wounds in children
Box 1 | History and examination of the injury

- Inquire about the circumstances of the bite and the dog’s history.
- Ask about the patient’s medical history, including any recent immunisations.
- Assess the extent and type of wound.
- Observe for signs of shock and tetanus.
- Search for any associated injuries.

Box 2 | Procedures for initial wound management

- Irrigate copiously, using tap water or normal saline.
- Remove foreign bodies (teeth).
- Perform a thorough wound toilet and debridement where necessary.
- Delay closure of the wound where possible.
- Raise and immobilise the limb if the injury is associated with (or is likely to cause) swelling.
- Give antibiotics, depending on the risk factors for infection.
- With infected wounds, send pus or a deep wound swab for culture (in clinically uninfected wounds, swabbing is unhelpful).
- Review bites within 24-48 hours, especially if the bites need antimicrobial prophylaxis.
- With infected wounds, send pus or a deep wound swab for culture (in clinically uninfected wounds, swabbing is unhelpful).
- Irrigate copiously, using tap water or normal saline.

Box 3 | Factors that increase risk of infection*

Patient factors
- Alcoholism (increased susceptibility to Pasteurella infection).
- Cirrhosis, asplenia (increased risk of Capnocytophaga).
- Steroid therapy, rheumatoid arthritis, diabetes mellitus, and lymphoedema after radiotherapy (all increase risk of Pasteurella infection). 

Wound factors
- Wounds >6 hours old.
- Devitalised tissue.
- Previously sutured wounds.
- Full thickness wounds involving tendons, ligaments, and joints.
- Bites on limbs, especially hands.

*According to case reports and small reviews.

How should dog bites be managed?

Box 1 suggests how to take a history and do an examination in a patient presenting with a dog bite, and box 2 outlines initial management procedures. Where adequate debridement of deep penetrating wounds is not possible, it is common practice, although unsupported by strong evidence, to irrigate the wound with 250 ml saline, using a 19 or 20 gauge needle or plastic intravenous catheter on a 35 ml syringe.

Irrigation is particularly important if the dog is suspected of being rabid. Gentle debridement after irrigation is essential as irrigation alone may not remove the virus from wound edges; the wound should then be covered with a sterile dressing or a clean dry cloth.

Factors increasing the risk of infection are arbitrarily divided into patient and wound factors (box 3). Many studies involving small numbers of patients have suggested various predisposing factors. A larger observational study—of 769 sequential patients with dog bite wounds presenting to an emergency department—found that the strongest predictors for the development of infection were wound depth, need for surgical debridement, and being female. Box 4 indicates when referral for specialist care is necessary.

Head and neck bites

Unlike adults, in whom only 10% of bites involve the head and neck, most bites in children are to the head or face, with 76% affecting lips, nose, or cheeks.

Exsanguination after carotid trauma is the major cause of death due to bites in children aged under 10 years, so with major trauma, resuscitation is the priority. Penetrating wounds of the neck and thoracic inlet are especially dangerous, and early angiography and exploration may be necessary. Avulsed body parts should be kept cool pending reattachment.

A complete physical examination, followed by intraoral examination to exclude cheek lacerations extending into the oral cavity, is necessary. Children with facial or cranial bites need cervical immobilisation until cervical lesions are excluded. Careful examination and appropriate imaging are necessary; a small scalp puncture wound may overlie intracranial injury and facial fractures.

Facial bites can often be closed primarily. Although rarely necessary, antibiotic prophylaxis decreases the risk of infection to 1%.

Extremity and hand bites

Anatomically, the hand contains many small compartments, and there is a relative lack of soft tissues separating the skin from the bone and joint. Surgical debridement needs to be done by an experienced clinician. Overall, only a fifth of dog bites become infected, compared with 36% of hand bites, and loss of function can result from infection. Hence thorough documentation of the injury and nerves affected is necessary. With a strict protocol of vigorous debridement and irrigation the infection rate can be as low as 0.3%.

Pus needs draining and preferably should be cultured (actual pus rather than a swab). Wounds on extremities should eating and dislike being threatened or feeling that their territory is being invaded, and they can be jealous of attention given to other family members.

There is much debate about which dogs attack humans the most. Most reviewers conclude that the higher risk animals include larger dogs, German shepherd dogs, pit bull terriers, Rottweilers, and chows, but all dogs should be considered dangerous; even smaller dogs such as Jack Russell terriers inflict severe bites.

What are the medicolegal aspects of dog bites?

Litigation associated with dog bites occurs at a steady rate in the UK—initiated by people attacked while walking or delivering mail; compensation claims are also made regularly against clinicians for alleged mismanagement of the original injury. An estimated 5000 postal workers seek medical help for bites annually in the UK.

Police can prosecute owners under the Dangerous Dogs Act 1991 (which makes ownership of certain breeds illegal), and magistrates have the power to have a dog put down. A civil claim against the owner for damages can be made under the Animal Act 1971. Adults have a three year limit in which to begin action, and “no win, no fee” legal firms already exploit this area of litigation. Compensation claims have varied, from a few thousand pounds to tens of thousands of pounds (and even hundreds of thousands for sportsmen whose career is affected by injury).
Dog bite related infections are polymicrobial, predominantly *Pasteurella* and *Bacteroides* spp. Infected bites presenting less than 12 hours after injury are particularly likely to be infected with *Pasteurella* spp, whereas those presenting more than 24 hours after the event are likely to be predominantly infected with staphylococci or anaerobes.

Inform the laboratory of the nature of the wound, as routine laboratory methods may fail to isolate or identify more unusual organisms. Thirteen per cent of infections thought to be penicillin sensitive *Staphylococcus aureus* are actually *S. intermedius*. Culturing aerobically alone or for less than 5-7 days may explain the paucity of pathogens reported in older studies, particularly anaerobes such as *Prevotella*, *Porphyromonas*, and *Fusobacteria* spp. Dog bite organisms often have strange names, the classic example being *Capnocytophaga canimorsus* (dysgonic fermenter type 2 or DF2). With nearly 100 reported cases, DF2 septicemia is often mistaken for fulminating meningococcal disease. Infection usually follows a trivial bite in patients with asplenia or cirrhosis. Typically, Gram negative rods are seen within polymorphs on peripheral blood films. DF2 is sensitive to penicillin and ciprofloxacin. Clinical infection may also result from incorrect management in primary care (figs 1 and 2). Erythromycin or flucloxacillin must never be used alone in prophylaxis. In one small study 70% patients with *Pasteurella multocida* infections (see box 5) had received inadequate or incorrect antibiotics, usually flucloxacillin or erythromycin. There are many reports of clinical failures and several deaths due to failure of erythromycin therapy.

**Box 5 | Characteristics of *Pasteurella multocida***

- Literally “killer of many species”—probably the most virulent pathogen in dog bites and responsible for severe infection
- Present in >50% of dog bites
- The most likely pathogen in infected wounds presenting within 12 hours of the bite
- An aggressive Gram negative pathogen, causing early intense inflammatory response with considerable tissue involvement, and likely to cause metastatic infection with severe sequelae
- Associated with a mortality of 30% in septicemia
- Resistant to erythromycin and flucloxacillin
- Likely to result in tenosynovitis in hand bites especially, and may lead to irreparable damage and amputation

When should prophylactic antibiotics be used?

As only a fifth of all dog bites become infected it is generally accepted that superficial, easily cleaned dog bite wounds do not warrant antibiotics if the patient is otherwise immunocompetent. We found no evidence justifying routine antibiotic prophylaxis for bites at low risk of infection. The consensus of opinion, however, is that antibiotic prophylaxis (co-amoxiclav) should be considered and is probably indicated for all “high risk” dog bites.

A postal survey of 21 UK emergency departments and minor injury units found that prophylaxis was given routinely in 15. Thirteen departments had a protocol, and co-amoxiclav was the antibiotic of first choice.

No strong evidence base supports the routine use of co-amoxiclav. A series of methodologically poor studies, with differing dosages of various antimicrobials and inadequate microbiological methods, has produced a plethora of recommendations for prophylaxis with little valid evidence. The major basis for recommending co-amoxiclav is in-vitro sensitivity data. The NHS guidelines (Prodigy) recommend co-amoxiclav as first choice prophylaxis where indicated, since it covers all commonly expected organisms among the canine oral flora.

Co-amoxiclav covers the penicillin resistant *S. aureus* and anaerobes and *P. multocida*, which is resistant to flucloxacillin and erythromycin.

Some authors advise empirical prophylaxis for all animal bites, while others take a more sensible approach, restricting prophylaxis to injuries or patients deemed at high risk of infection.
Meta-analyses of trials involving prophylactic antibiotics for dog bites

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<tr>
<th>Study</th>
<th>Conclusion</th>
<th>Comments</th>
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<tr>
<td>Cummings, 1994&lt;sup&gt;21&lt;/sup&gt;</td>
<td>In four of the largest studies antibiotics decreased the risk of infection; and to prevent 1 infection, 14 patients needed prophylaxis</td>
<td>Meta-analysis of 8 randomised trials; not a systematic review; 8 trials, 306 patients; different antibiotics compared, only 1 using co-amoxiclav</td>
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<td>Cochrane review, 2001&lt;sup&gt;22&lt;/sup&gt;</td>
<td>No evidence of benefit in dog bites</td>
<td>8 trials, including 6 randomised double blind controlled and 1 randomised controlled trial; different antibiotics compared, only 1 using co-amoxiclav; small numbers of patients; different antibiotic regimens; dog and other animal bites included in trials</td>
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**Meta-analyses**

The conclusion and implications of two meta-analyses relating to antibiotic treatment for animal bites<sup>21,22</sup> are not directly relevant to UK practice (table). Both included trials with no stratification of risk of infection, comparing differing antibiotic regimens and dosages, ranging from penicillinase stable penicillins (such as oxacillin) to co-trimoxazole, cefalexin, and phenoxymethylpenicillin.

Each meta-analysis included eight trials, with six trials common to both. Cummings included one non-randomised controlled trial,<sup>21</sup> and the Cochrane review included one trial of prophylaxis for cat bites and one for human bites.<sup>22</sup> Overall, the patient numbers were small. Only one small trial involving 172 dog bites used co-amoxiclav.<sup>23</sup> In that trial co-amoxiclav (375 mg three times daily for five days) was given to 84 patients, with 88 given placebo. This resulted in a significant difference in infection rates (33% of those receiving co-amoxiclav prophylaxis became infected, compared with 60% receiving placebo).<sup>23</sup>

Most authors agree prophylaxis is of no proved benefit in simple facial dog bites, but the consensus of opinion recommends three to five days of prophylaxis for puncture wounds,<sup>9,11</sup> primary closures,<sup>11,14</sup> high risk patients, and oral-cutaneous (“through and through”) bites,<sup>24</sup> with additional indications suggested by several authors of small reviews of treatment (box 6).

For patients with a true allergy to penicillin, effective alternatives to co-amoxiclav include tetracycline or doxycycline plus metronidazole,<sup>25</sup> a second generation cephalosporin with anti-anaerobic activity such as ceftriaxone, or combination therapy with clindamycin and a fluoroquinolone.

Pregnant women with a history of rash after penicillin should be offered ceftriaxone.

**Treatment of established infection**

Inpatient treatment must cover *Pasteurella*, anaerobes, and staphylococci, and be modified according to culture results. For very severe infections, we use empiric imipenem with cilastatin (500 mg four times daily, intravenously) and clindamycin (900 mg four times daily, intravenously) until Gram stains or cultures are available to guide treatment. For patients with severe allergy to penicillin, ciprofloxacin (400 mg twice daily, intravenously) plus metronidazole (500 mg three times daily, intravenously) replaces imipenem.

**Duration of treatment for established infection**

In practice, treatment is usually 10-14 days for cellulitis, three weeks for tenosynovitis, four weeks for septic arthritis, and six weeks for osteomyelitis. Conversion to oral antibiotics when the C reactive protein concentration falls to <50 mg/l is a pragmatic approach that we find works well in our hospital. If the C reactive protein levels off at a high concentration or continues to rise, then a clinical reappraisal is needed as a second debridement may be advisable, particularly with joint space infections.

**Rabies**

Rabies is transmitted by a transdermal bite or scratch, or salivary contamination of mucosa or skin wounds. It kills 30 000 to 50 000 people a year, mainly in...
developing countries and especially where unvaccinated stray dogs are common. Avoiding exposure to rabies involves education of travellers and advice not to touch animals abroad, especially if they appear unwell and have excessive salivation or paralysis. Prior rabies vaccination may be sensible for travellers to remote areas where rabies is highly endemic.  

Rabies is almost invariably fatal, so even seemingly minor bites in high risk countries should be taken seriously. Local medical advice should be sought on the risks of rabies and prophylaxis after exposure. Thor
cleansing significantly lessens the risk of rabies. Hence flushing the wound under a running tap for several minutes, washing with soapy water or detergent, and particularly using wound disinfectants (such as 40-70% alcohol, tincture, or aqueous solution of povi
dione-iodine) is recommended. Again, primary suturing should be avoided if possible.

**Risk assessment in travellers returning with dog bites**

Rabies vaccine and immunoglobulin should be given if required. Local advice should be sought, as countries differ in the risks of contracting rabies and in the administration and use of vaccine and immunoglobulin. For example, intradermal vaccination may be used in some countries where resources are scarce, and equine rabies immunoglobulin may be the only one available. For travellers returning home to the UK, intramuscular vaccine and human rabies immunoglobulin are obtained by contacting the centres listed in box 7. Information that general practitioners will need to provide when discussing the need for prophylaxis with staff at the centres includes previous vaccination status, country where bitten, site and date of bite, provoked or unprovoked bite, domestic or feral dog, current health of animal, and previous immunisation status of patient.

**Prevention**

An educational intervention, “Prevent a bite” (designed primarily for schoolchildren), was effective in increasing precautionary behaviour among children when confronted with a dog. Generally, children should be taught to treat dogs with respect, avoid direct eye contact, and not tease them. They should be taught not to approach an unfamiliar dog; play with any dog unless under close supervision; run or scream in the presence of a dog; pet a dog without at first letting it sniff you; or disturb a dog that is eating, sleeping, or caring for puppies.

We thank Elizabeth Saunders for valuable comments on the manuscript.

**Contributors:** MM searched the literature on therapeutics and drafted the article. JP added aspects on surgery. Both authors completed and revised the content critically and are joint guarantors.

**Box 7 | Who to contact about risk and management of rabies**

- Health Protection Agency Centre for Infection, 61 Colindale Avenue, London NW9 5EQ ([www.hpa.org.uk/infections/default.html](www.hpa.org.uk/infections/default.html))
- Health Protection Scotland, Clifton House, Clifton Place, Glasgow G3 7LN ([www.hps.scot.nhs.uk](www.hps.scot.nhs.uk))

**Additional educational resources**

- Resources for healthcare professionals

- Resources for patients
  - Dog and cat bites. ([www.prodigy.nhs.uk/patient_information/pls/dog_and_cat_bites.pdf](www.prodigy.nhs.uk/patient_information/pls/dog_and_cat_bites.pdf))—guidance on what to do after a bite

**Competing interests:** None declared.

**Provenance:** Commissioned, peer reviewed.

RATIONAL IMAGING

Investigating suspected pulmonary embolism in pregnancy

Andrew Frederick Scarsbrook, Fergus Vincent Gleeson

A woman in her early 30s presented at 25 weeks’ gestation with shortness of breath and chest pain. Clinical examination was unremarkable. The patient was referred for imaging to exclude suspected pulmonary embolism, as this potentially fatal disorder increases in incidence during pregnancy and is a leading cause of maternal mortality. Physiological changes in pregnancy often cause symptoms that mimic pulmonary embolic disease, such as chest pain and shortness of breath. Objective symptom scoring for assessing the pre-test probability is therefore less reliable in pregnancy and is used only rarely.

What test do I order?

Venous thromboembolism is an important diagnosis to confirm or refute, as the risks of inappropriate use of anticoagulants or missing a pulmonary embolism far outweigh the risks associated with exposing mother and fetus to ionising radiation. In pregnant patients with suspected pulmonary embolism who are acutely and seriously ill, a portable echocardiogram should be the initial test to detect pulmonary embolism if expertise is readily available. In all other pregnant patients, chest radiography should be the first line imaging investigation.

Chest x-ray—This is required to exclude a chest infection or pneumothorax.

Compression ultrasonography of the lower limb—Ultrasoundography is required to exclude deep vein thrombosis. Although this has a low diagnostic yield, it does not expose the mother or fetus to any risk and, if positive, allows appropriate treatment.

If the ultrasound is negative, the chest x-ray is normal, and the patient has no history of lung disease including asthma, a half dose lung perfusion scintigram should be performed. Alternatively, if the patient has lung disease or the chest x-ray is abnormal (and a suspicion of pulmonary embolism remains) a computed tomographic pulmonary angiogram should be performed.

Radionuclide lung scintigraphy—This test has a high negative predictive value and has been carefully evaluated in a prospective case series of pregnant women (n=120) with suspected pulmonary embolism. The incidence of non-diagnostic scans is high in non-pregnant patients, mainly as a result of chronic lung disease. However, pregnant patients are generally younger and less likely to have abnormal lungs. Non-diagnostic scans can be minimised by triaging patients with an abnormal chest radiograph to computed tomographic pulmonary angiography. Fetal radiation exposure is higher with scintigraphy (0.11-0.22 mGy) than with computed tomographic pulmonary angiography (0.01-0.06 mGy), but it is well below the threshold for any specific risks. The only theoretical risk from in utero radiation exposures of less than 50 mGy is induction of malignancy. The estimated incidence of childhood malignancy after in utero exposure is about one in 16 000 per mGy.

To minimise fetal radiation exposure, half dose perfusion scintigraphy is performed as standard practice during pregnancy, with no loss in diagnostic accuracy.

Computed tomographic pulmonary angiography—This is the gold standard diagnostic test in non-pregnant patients with suspected pulmonary embolism, but its use in pregnancy has not been validated. For example, a large multicentre prospective trial (n=824) to assess the efficacy of this test in patients with suspected pulmonary embolism formally excluded pregnant women. Importantly, this test exposes mothers to high doses of radiation. Estimated exposure of maternal breast tissue is up to 35 mGy per breast. The latent carcinogenic effects of radiation exposure are uncertain, but radiosensitive, proliferating, breast tissue is likely to be at increased risk. The lifetime risk of breast carcinoma has been reported to increase after a single 10 mGy dose of radiation to the breast in women under 35 years. The estimated exposure of breast tissue to radiation from half dose perfusion scintigraphy is several magnitudes smaller (0.25 mGy) than that from computed...
Stornoway sausages—the surgical solution at sea

We set sail from North Harris on Friday evening to find a mooring in a bay where we could see a white tailed sea eagle on the nest. It was the epitome of a peaceful and remote Scottish inlet, with not even a mobile (cellphone) signal on any of our available networks.

While watching the nest, I was asked if I could leave my telescope just for a moment to give some medical advice to one of our party. He had started taking warfarin two weeks earlier, before cardioversion from atrial fibrillation a few days before our trip. He was bleeding quite heavily from piles and had been unable to staunch the flow. He didn’t want to cause a disturbance, nor to soil the cabin, but suggested that he lay down to be examined on the “poop” deck.

There was nothing remotely useful in my first aid kit save a rolled up crepe bandage. Pressure seemed to be of little avail. I searched through the ship’s equipment and found some surgical gloves. With advice from the cook, I stuffed a frozen sausage inside a finger of a surgical glove, coated it with corticosteroid cream for someone else’s eczema, and inserted it into the appropriate orifice. Amazingly enough, the bleeding diminished and, after a couple more sausages, stopped.

We reached St Kilda without major incident, though the weather grew progressively more unkind. We returned to the mainland on Sunday morning, 90 years too late for Explorer. What I am glad I am a general practitioner, as the drama of surgical life is really not for me.

Elizabeth A McClure general practitioner, Chester e.a.mcclure@dial.pipex.com

Competing interests: Both patient and doctor were due to have sausages the next morning for breakfast.

is associated with a significantly higher radiation dose than CTPA. For these reasons it has a limited role in evaluating patients with suspected pulmonary embolism, especially those who are pregnant.

**Outcome**

Our patient had no history of lung disease, a normal chest x ray, and negative lower limb ultrasonography. She therefore underwent half dose perfusion scintigraphy, which was normal (figure). Her symptoms resolved spontaneously and the remainder of her pregnancy was uncomplicated.

**Contributors:** FVG had the original idea. AFS selected the patient, searched the literature, and wrote the paper. FVG reviewed and edited the paper and reanalysed the literature. FVG is guarantor.

**Funding:** None.

**Competing interests:** None declared.


Accepted: 12 December 2006
Asymptomatic bicuspid aortic valves diagnosed in childhood need regular monitoring to allow early surgical intervention and prevention of left ventricular failure

Bicuspid aortic valve occurs in 0.8-2% of European and North American populations.\(^1\)\(^2\) It is the most common reason for a predisposition to severe aortic regurgitation or stenosis in middle life, but patients are asymptomatic until late in the disease. Failure to present until clinical symptoms develop—either because the murmur is not detected or is lost to follow-up—can have important consequences. Early detection and continued surveillance are crucial to allow early intervention and preservation of cardiac function. We describe two patients with heart murmurs diagnosed in childhood who were lost to follow-up. Both presented as adults with heart failure and complications of bicuspid aortic valves. One developed aortic stenosis, the other aortic incompetence. Both needed urgent surgery. Many people in the general population with bicuspid aortic valves have never been diagnosed or have been reassured in childhood and are no longer under review.

Case 1
A 48 year old builder presented with shortness of breath at rest and mild icterus. He had been prescribed antibiotics for a presumed chest infection when he visited his general practitioner six months earlier. A heart murmur was noted during that consultation but not followed up. He later recalled that as a child he underwent annual review for a heart murmur. At age 16 he was reassured and discharged from clinic.

On clinical examination the patient had severe aortic stenosis with a slow rising pulse, narrow pulse pressure, and an ejection systolic murmur radiating to the carotids. He had left ventricular failure.

The transthoracic echocardiogram showed a bicuspid aortic valve with severe stenosis (peak pressure gradient 70 mm Hg). The left ventricle was severely dilated and impaired.

Early admission for valve replacement was arranged but he developed hepatorenal failure, which necessitated emergency surgery. The excised bicuspid aortic valve was heavily calcified with a pinhole orifice. It was replaced with a metal prosthesis and the mildly dilated aorta was supported by a pericardial wrap. Renal and liver function improved after the operation. The left ventricle remains dilated and impaired.

Case 2
A 46 year old postman was admitted with increasing shortness of breath on minimal exertion (New York Heart Association functional class III). In early childhood, he had been diagnosed with a heart murmur and followed up in a tertiary centre. At age 10 he was either discharged or stopped attending appointments.

Clinically he had severe aortic regurgitation with a collapsing pulse, positive Corrigan’s sign, a loud early diastolic murmur, and additional diastolic deep rumble (Austin Flint murmur). He had evidence of cardiac failure. Inflammatory markers were normal and blood cultures were sterile.

His electrocardiogram showed left ventricular hypertrophy with widespread fixed T wave inversion (fig 1). The transthoracic echocardiogram confirmed a calcified bicuspid aortic valve with an eccentric jet of severe aortic regurgitation directed along the anterior mitral valve leaflet. The ascending aorta was dilated. He had severe left ventricular dilatation and impairment (fig 2).

He responded to initial treatment with diuretics. Angiography showed normal coronary arteries. He underwent urgent aortic valve replacement during that admission. The ascending aorta measured 5 cm intraoperatively and was therefore also replaced.

Discussion
The normal aortic valve has three almost equally sized leaflets. A bicuspid aortic valve is the result of abnormal aortic cusp formation during valvulogenesis. Although bicuspid aortic valves can function normally, the valve leaflets are subject to increased haemodynamic stress because of their shape and can therefore degenerate.
calcify, and stenose or become incompetent. Bicuspid aortic valves also predispose the patient to endocarditis and are strongly associated with aneurysms and dissection of the aorta. Bicuspid aortic valves have been suggested to be associated with greater mortality and morbidity than all other congenital heart defects combined.

The proposed 0.8-2% prevalence of bicuspid aortic valves in the general UK population would equate to 16-40 patients in an average general practice population of 2000 patients. Bicuspid aortic valves are present in 54% of adults with valvular aortic stenosis who have aortic valve replacement and are the main reason for aortic valve replacement up to the eighth decade of life. As the incidence of rheumatic heart disease falls, a greater proportion of patients who have aortic valve replacement will have bicuspid aortic valves. By their second decade most patients with this condition have evidence of valvular calcification. The pressure gradient across a stenotic bicuspid aortic valve increases by 18 mm Hg each decade and even more rapidly if the cusps are asymmetric in size or in the anteroposterior location.

Bicuspid aortic valves present as aortic regurgitation in 66% of cases. Patients with such regurgitation need surgery at an earlier age than those with aortic stenosis. This may reflect the association with coarctation of the aorta and the complication of infective endocarditis.

Clinical diagnosis of bicuspid aortic valves by auscultation of an aortic ejection click is beyond the skill of most non-specialists, but often an ejection systolic murmur is present and easily heard. Diagnosis is most simply confirmed with cross sectional and Doppler echocardiography. Transesophageal echocardiography has a sensitivity of 78% and specificity of 96% for the identification of a bicuspid aortic valve (though the underlying pathology may be obscured when severe stenosis, cuspal fusion, or a prominent raphe is present). Transoesophageal echocardiography may be better at identifying bicuspid aortic valves, but it is not usually carried out for purely diagnostic purposes.

Because transthoracic echocardiography was not widely available until 15 years ago, and general practitioners have had access only in recent years, many patients have had no definitive diagnosis of their childhood murmur. A further population has defaulted or been lost to follow-up. Women may be more likely than men to be identified as the heart is usually examined at the antenatal clinic.

Once the diagnosis is made, the patient needs follow-up with transthoracic echocardiography three to five yearly because aortic valve disease progresses inexorably. When a gradient of 20 mm Hg or more develops or when greater than mild aortic regurgitation is noted, annual review should be offered until symptoms or the degree of dysfunction indicate the need for surgery.

No drugs have been found to reduce the progression of stenosis, though trials of statins are under way. Antibiotic prophylaxis for dental work is advised by the European and US cardiac societies. Screening of first degree relatives of patients with a bicuspid valve is also advocated because of the high degree of familial association.

Our cases highlight the potential complications of a bicuspid valve, which could have been prevented by regular monitoring and earlier surgery. Avoiding urgent and emergency surgery has advantages in terms of surgical mortality (perioperative mortality for first time aortic valve replacement in the United Kingdom: emergency surgery 12%; urgent 5%; elective 1.9%; personal communication, Bruce Keogh, Society of Cardiothoracic Surgeons and AD Cunningham, Central Cardiac Audit Database) and the longer term effects of ventricular impairment. Bicuspid valves are present in many people who were reassured in early life or lost to follow-up and in many “healthy” middle aged men whose hearts have never been examined. These patients could be identified by auscultation and echocardiography and referred to cardiologists at an early stage. This approach would increase demand for echocardiography, and population screening would have wider implications.

Contributors: SS and RB wrote the initial draft and MH and JRM revised it. JRM is guarantor. The authors all cared for these patients and conceived the idea of the report.

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Competing interests: None declared.

BMJ UPDATES

Hypochondriasis is treatable

Research question
What are the comparative effects of paroxetine and cognitive behaviour therapy in treating severe hypochondriasis?

Answer
Paroxetine probably works as well as cognitive therapy but causes more side effects.

Why did the authors do the study?
Hypochondriasis is a common mental illness with a reputation for being hard to treat. There’s some evidence that cognitive behaviour therapy improves symptoms, but the evidence for antidepressants is much weaker. There are no high quality head to head trials comparing the two.

What did they do?
They recruited 112 Dutch adults to a randomised controlled trial comparing cognitive behaviour therapy, the selective serotonin reuptake inhibitor paroxetine, and a placebo. The comparison between paroxetine (up to 60 mg a day) and the placebo was double blind, and the main analyses were intention to treat. The trial lasted 16 weeks.

All the participants had severe symptoms of hypochondriasis, and three quarters had other mood or anxiety disorders. One in five (21/112) continued to take benzodiazepines during the trial.

The authors assessed participants before and after treatment using the Whiteley index, a standard instrument for measuring the core symptoms of hypochondriasis. They used other standard instruments to measure changes in comorbid mood and anxiety symptoms.

What did they find?
All the groups improved significantly during the trial. There were no significant differences between the cognitive behaviour therapy and the paroxetine group on any outcome measure, including change in the Whiteley index score. In a pooled analysis of data from both treatment groups, active treatment worked better than placebo. The effect sizes on the Whiteley index were 0.44 (modest) for cognitive behaviour therapy versus placebo, and 0.4 (slightly more modest) for paroxetine versus placebo.

Forty five per cent of those treated with cognitive behaviour therapy responded to treatment (a change of ≥1 standard deviation in Whiteley index score), as did 30% of those who took paroxetine and 14% of those who took a placebo. In this analysis, cognitive therapy looked significantly better than placebo (P=0.004), but paroxetine did not (P=0.17). Again, the two active treatments did not differ significantly from each other.

The commonest side effects that were reported more often by the paroxetine group than the placebo group were fatigue (39% v 29%, P=0.02) and sexual dysfunction, including anorgasmia, (32% v 9%, P=0.01).

Thirty of the 112 participants dropped out of their assigned treatment. Participants were equally likely to drop out of all three groups.

What does it mean?
This small trial confirms that up to four months of cognitive behaviour therapy helps people with chronic hypochondriasis, improving their core symptoms as well as comorbid symptoms of depression and anxiety. Paroxetine probably does too, although the results for this treatment were less robust and seemed to depend more on patients completing their treatment. The authors don’t report a power calculation, so it’s hard to know whether they could have missed a clinically important difference between cognitive behaviour therapy and paroxetine. In any event, paroxetine caused more side effects.


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10-MINUTE CONSULTATION

Olfactory loss

E Ofo,1 B O’Reilly,2 A O’Doherty2

A 65 year old man presents with loss of smell and altered taste, affecting his appetite and food intake. He had an upper respiratory tract infection before the onset of symptoms nine months ago. Initially, normal odours were distorted, followed by a constant foul smell for three months, and then complete loss of smell.

What issues you should cover

Olfactory disorder or true taste complaint—Altered olfaction is common and invariably causes flavour loss, which most patients perceive as taste dysfunction. The ability to taste salt, sour, bitter, and sweet remains intact, as it is a function of the chorda tympani nerve with contribution from the glossopharyngeal and vagus nerves.

Degree of olfactory dysfunction—Anosmia is complete loss of the sense of smell. Most patients have hyposmia (decreased sensitivity to some or all odorants). Cacosmia is the detection of normal smell as foul or unpleasant. Dysosmia is distortion of perceived odours.

Quality of life—Do the symptoms affect his quality of life? Weight loss may result from a change in diet. Patients often worry they cannot detect spoilt food or toxic fumes.

Cause—Ascertain a possible cause (see box). In most cases the history, including the nature, timing, onset, duration, and pattern of symptoms, aids diagnosis. Is there altered odorant conduction in the nose or a sensorineural problem? Ask about nasal obstruction, rhinorrhea, and postnasal drip—suggestive of chronic rhinosinusitis. Previous cold or influenza-like symptoms followed by olfactory loss suggests a viral cause. Has he had a recent head injury? Ask about tobacco and cocaine use. Treatments such as calcium channel blockers may alter smell, so take a drug history. Has he been exposed through work to toxic chemicals? Does he have neurological symptoms such as muscle weakness or visual disturbance? Multiple sclerosis, Alzheimer’s disease, and rarely intracranial tumours (meningiomas, frontal gliomas) can present with altered olfaction.

What you should do

Physical examination

Do a routine head and neck examination:

• Assess the nose using an otoscope (or nasendoscope), looking for obstructive and inflammatory causes such as nasal polyps or rhinitis
• Examine the oral cavity to exclude dryness, dental problems, leukoplakia, and infection
• Assess the tympanic membrane for signs of middle ear disease, which may affect the chorda tympani nerve
• Evaluate cranial nerve function (especially cranial nerves V, IX, and X).

POSSIBLE CAUSES OF OLFATORY DYSFUNCTION

- Obstructive—Nasal polyposis,* deviated nasal septum,* intranasal tumour
- Sensory—Viral infection,* chronic sinusitis,* allergic rhinitis,* cigarette smoke,* toxic chemical exposure, drugs
- Neural—Head injury,* Alzheimer’s disease, Parkinson’s disease, hypothyroidism, intracranial tumour
- Most common causes

Diagnosis and treatment

- Sinonasal disease, head injury, and upper respiratory tract infection account for most cases of olfactory dysfunction. Olfaction also reduces with advancing age, and consider “idiopathic” olfactory loss after exclusion of other causes.
- Conductive or inflammatory conditions such as nasal polyps or chronic rhinosinusitis may be treated with a short course of oral steroids (such as 40-60 mg prednisolone for one week) followed by a topical steroid spray for at least one month.
- If a previous (non-acute) upper respiratory tract infection or head injury is suspected, no specific treatment is needed. Olfactory loss may improve with time, and with head trauma, recovery of olfactory function is usual within 12 weeks of injury.
- Patients with sinonasal disease not responding to steroids and those with no obvious cause for altered olfaction should be referred to an ear, nose, and throat specialist.
- When olfaction is potentially irrecoverable, offer advice on managing the disability. Eating can be improved by enhancing flavours using marinades. Smoke alarms should be installed.
- Reassurance and explanation are crucial for patients with olfactory loss as patients often fear a more serious underlying problem

Competing interests: None declared.

USEFUL READING

Parker JN, Parker PM. The official patient’s sourcebook on smell and taste disorders. San Diego: CON Health Publications, 2002

This is part of a series of occasional articles on common problems in primary care. The BMJ welcomes contributions from general practitioners to the series.
STATISTICS NOTES

Missing data

Douglas G Altman1, J Martin Bland2

Almost all studies have some missing observations. Yet textbooks and software commonly assume that data are complete, and the topic of how to handle missing data is not often discussed outside statistics journals.

There are many types of missing data and different reasons for data being missing. Both issues affect the analysis. Some examples are:
1. In a postal questionnaire survey not all the selected individuals respond;
2. In a randomised trial some patients are lost to follow-up before the end of the study;
3. In a multicentre study some centres do not measure a particular variable;
4. In a study in which patients are assessed frequently some data are missing at some time points for unknown reasons;
5. Occasional data values for a variable are missing because some equipment failed;
6. Some laboratory samples are lost in transit or technically unsatisfactory;
7. In a magnetic resonance imaging study some very obese patients are excluded as they are too large for the machine;
8. In a study assessing quality of life some patients die during the follow-up period.

The prime concern is always whether the available data would be biased. If the fact that an observation is missing is unrelated both to the unobserved value (and hence to patient outcome) and the data that are available this is called “missing completely at random.” For cases 5 and 6 above that would be a safe assumption. Sometimes data are missing in a predictable way that does not depend on the missing value itself but which can be predicted from other data—as in case 3. Confusingly, this is known as “missing at random.” In the common cases 1 and 2, however, the missing data probably depend on unobserved values, called “missing not at random,” and hence their lack may lead to bias.

In general, it is important to be able to examine whether missing data may have introduced bias. For example, if we know nothing at all about the non-responders to a survey then we can do little to explore possible bias. Thus a high response rate is necessary for reliable answers. Sometimes, though, some information is available. For example, if the survey sample is chosen from a register that includes age and sex, then the responders and non-responders can be compared on these variables. At the very least this gives some pointers to the representativeness of the sample. Non-responders often (but not always) have a worse medical prognosis than those who respond.

A few missing observations are a minor nuisance, but a large amount of missing data is a major threat to a study’s integrity. Non-response is a particular problem in pair-matched studies, such as some case-control studies, as it is unclear how to analyse data from the unmatched individuals. Loss of patients also reduces the power of the trial. Where losses are expected it is wise to increase the target sample size to allow for losses. This cannot eliminate the potential bias, however.

Missing data are much more common in retrospective studies, in which routinely collected data are subsequently used for a different purpose. When information is sought from patients’ medical notes, the notes often do not say whether or not a patient was a smoker or had a particular procedure carried out. It is tempting to assume that the answer is no when there is no indication that the answer is yes, but this is generally unwise.

No really satisfactory solution exists for missing data, which is why it is important to try to maximise data collection. The main ways of handling missing data in analysis are: (a) omitting variables which have many missing values; (b) omitting individuals who do not have complete data; and (c) estimating (imputing) what the missing values were.

Omitting everyone without complete data is known as complete case (or available case) analysis and is probably the most common approach. When only a very few observations are missing little harm will be done, but when many are missing omitting all patients without full data might result in a large proportion of the data being discarded, with a major loss of statistical power. The results may be biased unless the data are missing completely at random. In general it is advisable not to include in an analysis any variable that is not available for a large proportion of the sample. The main alternative approach to case deletion is imputation, whereby missing values are replaced by some plausible value predicted from that individual’s available data. Imputation has been the topic of much recent methodological work; we will consider some of the simpler methods in a separate Statistics Note.

Competing interests: None declared.


This is part of a series of occasional articles on statistics and handling data in research.
Dog attacks: it’s time for doctors to bite back

PERSONAL VIEW Rachel Besser

This year, like previous years, has seen a spate of coverage in the British media of maulings by dogs. The most recent available data from the Royal Society for the Prevention of Accidents (www.rospa.co.uk) show that 70,000 people attended UK emergency departments in 2002 for injuries caused by dog bites. Many of these were attacks on children by the family pet and take place in the home (European Journal of Pediatrics 2003;162:254-8). Dog bites have become a public health concern and a child protection issue.

As with many public health issues, however, individuals are reluctant to take responsibility and modify their behaviour. The medical profession is left to mop up the mess. Children are particularly vulnerable; one American study found that children under 5 were the age group most likely to have severe head and neck injuries (American Surgeon 1999;65:863-4).

Undoubtedly, few people bitten by dogs die or are left with a profound disability. However, the number of people admitted to UK hospitals after being bitten by a dog is rising, despite a fall in dog ownership. Data collected by the Information Centre for Health and Social Care (www.hesonline.nhs.uk) show that 4,133 patients were admitted to hospital in England in 2006 as a result of injuries from dog bites, almost double the number in 1996, and that 22% of these people were children under 9. Apart from the psychological and physical consequences (including infections) of dog bites, they result in unnecessary expense.

It is clear that the 1991 Dangerous Dogs Act does not work. For a start, it does not cover the majority of bites that occur in the family home, and only 764 people were prosecuted under the act in 2005. Also, all dogs bite, not just the four breeds prohibited under the act (the pit bull terrier, Japanese tosa, Argentine dogo, and fila brasileiro, including cross-breds). Indeed, one study showed that the most common dog bites were from Staffordshire bull terriers, Jack Russell terriers, medium sized mongrels, and Alsatians (BMJ 1991;303:1512-3).

If proposals to license ownership of dogs had succeeded, we would at least have a national canine register to document which dogs show aggression and need closer supervision. But even if the current laws were tightened, dog attacks would continue, because legislation does not get to the root of the problem of why the attacks occur.

Unless we introduce the equivalent of antisocial behaviour orders for dogs—which would probably increase the number of attacks occurring in the family home—there needs to be a change in the way in which we manage dogs in the future.

We must stop placing blame on the dogs themselves and focus attention instead on who holds the other end of the lead—or who isn’t holding the lead, as the case may be. Most dog bites to children at home happen when the child is interacting with the dog in the absence of adult supervision (European Journal of Pediatrics 2003;162:254-8). It is clear that not all dog owners appreciate that children should not be left unsupervised with a dog. Just as some parents are obliged to take parenting classes, I would like to see equivalent mandatory classes for expectant dog owners to teach them about the responsibilities of dog ownership.

Measures targeted at children are also needed. Educational programmes for children, such as the “Prevent-a-bite” scheme in Australia (BMJ 2000;320:1512-3), have shown the potential to instil precautionary behaviour around dogs. Teachers and health visitors are in a position to introduce dog awareness programmes, such as the new Blue Dog project (www.thebluedog.org).

Some people have advocated muzzling all dogs in public places. Although this might prevent some attacks, it would not prevent the large numbers of bites that occur in the family home. Dog-free parks might reduce people’s anxiety about dogs and ensure that children don’t encounter dogs (or their excrement), but again this would not reduce the problem of dog bites on private property. Neutering all dogs would ultimately resolve the problem, but I doubt whether such a move would meet ethical approval.

It is therefore time for medical professionals to act on this issue. Where, for instance, is the medical representative on the Pet Health Council? Doctors, vets, and schools need to work together to research, educate, and advise legislators to prevent dog attacks in the future. I would like to see vets advising all dog owners about bite prevention, and doctors have a part to play in promoting bite prevention when treating patients who have been bitten by dogs.

Ultimately perhaps the only way to stop dog bites will be to ban dogs. In the meantime I suggest a Department of Health campaign for next Christmas: “Just ask for a goldfish.”

Rachel Besser is a trainee within the London Deanery and lifetime dog owner rachelbesser@hotmail.com

From the archive: Is it time to ban dogs as household pets? (see BMJ 2005;331:1278)
**NETLINES**

All health professionals will subscribe to the idea that palliative care matters, so you may be interested in the website Palliative Care Matters [www.pallcare.net](http://www.pallcare.net), which comes from a palliative care specialist who is based in Wales. It is a good, general “one stop shop” with all sorts of information available at the click of a mouse. Links from the home page take you to news, journal articles, and a book. There is a section on syringe drivers and a well stocked links section.

Nephrology Now [www.nephrologynow.com](http://www.nephrologynow.com) gathers together recent relevant articles from the field and associated journals and builds a virtual journal through links to these articles. Subscription to the website, which has an archive of previous editions, is free and painless.

Resuscitation is an important skill for all health professionals, and now you can keep up to date in this field thanks to the UK Resuscitation Council and the super collection of documents at [www.ressus.org.uk/pages/mediMain.html](http://www.ressus.org.uk/pages/mediMain.html).

Top billing goes to the resuscitation guidelines accompanied by algorithms and posters. The remainder of the material is support information, such as frequently asked questions.

“Dr Livingstone, I presume” is a famous quotation about an interesting 19th century medical missionary. If you want to learn more about the man’s life and writings have a look at Livingstone Online [www.livingstoneonline.ucl.ac.uk](http://www.livingstoneonline.ucl.ac.uk). Here you can read his letters and learn about the practice of medicine during his lifetime. This is a bright and breezy site that brings yesteryear alive.

Sending large files attached to emails can sometimes be a problem, but an easy and elegant solution can be found at [www.senduit.com](http://www.senduit.com). From a simple web page you can upload a file from your computer (maximum size 100 MB) on to a web page and then decide how long the uniquely generated link will remain active; the maximum is a week. Press the upload button and an internet address is generated that can then be emailed to your recipient, who can download the file any time before the expiry date.

**Harry Brown general practitioner, Leeds DrHarry@DrHarry.net**

We welcome suggestions for websites to be included in future Netlines. Readers should contact Harry Brown at the above email address

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**PERSONAL VIEW Lesley Morrison**

Treatment not Trident: why nuclear disarmament is a medical issue

The 1983 BMA report *The Medical Effects of Nuclear Weapons* made it clear that preventing the possession and use of nuclear weapons is a matter of concern for doctors. Then over the next 20 years the issue seemed to go away. Except it didn’t: in Britain it’s called Trident and it’s sitting at Faslane naval base in a beautiful loch on the west coast of Scotland.

The proposed replacement of the Trident system of ballistic missiles armed with nuclear warheads will cost British taxpayers about £70bn (£105bn; $140bn). It will cost—and is costing—them a lot more in terms of international credibility and integrity. Under the terms of the Geneva Conventions weapons of indiscriminate use are outlawed. As a one kilotome bomb would kill everyone within a 1 km radius, such a bomb is illegal. It’s also immoral and wrong. The recent Medact report *Britain’s New Nuclear Weapons: Illegal, Indiscriminate and Catastrophic for Health* makes this clear [www.medact.org](http://www.medact.org). The Nobel prize winning organisation International Physicians for the Prevention of Nuclear War, of which Medact is an affiliate, has been speaking out in a similar way for 25 years.

Recently a group of doctors and other health professionals, of whom I was one, participated in “Faslane 365” [www.faslane365.org](http://www.faslane365.org), the year long blockade of Faslane in which community and professional groups of all sorts are drawing attention to what is happening in our name inside the gates. At the gates, under the watchful eye of many senior military strategists, is Trident. If I speak out as a doctor I am doing so to protect the public health. We are, and should be, concerned with social justice.

I have never and would never initiate a conversation in the consultation setting about Trident. If I speak out as a doctor I am doing so away from the consulting room as a member of a growing international movement. Have patients, having heard me on the radio or read my views in the paper, ever said anything to me? Yes. “Well done on taking a stand,” and, “Thanks for doing that for us.” Of course, those who disagree with our stance would be less likely to speak to me again could change their views. The major decision to replace Trident, which would adversely affect the health of millions, has apparently been taken without any opportunity for proper parliamentary or public debate. Our aim in making this public statement was to encourage people to express their concerns, to make their voices heard in the democratic process.

Like any other citizen, tax payer, or patient we have the right to express our views

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Lesley Morrison is a general practitioner, Peebles lesley@ljmorrison.fsnet.co.uk
**REVIEW OF THE WEEK**

**Physician, heal thyself**

Doctors and scientists have been experimenting on themselves for centuries. A new BBC series considers the heroic successes—and spectacular flops, finds **W F Bynum**

When he was about 10 years old, my son once said, in a fit of philosophical insight, “Someone has to sit next to the naughtiest boy in the class.” He was right, of course, and his generalisation also applies to medicine. Someone has to go first, whether it is a new operation, drug, procedure, or experimental finding. For all of our experimental protocols, animal testing, and ethics committees, if it concerns human beings, someone has to be the first.

In these four engaging programmes, Michael Mosley examines the role of self experimentation in medicine during the past two centuries. He divides his programmes by themes; anaesthesia, vaccines, diet and disease, and infections. Mosley, a doctor, has a wonderfully boyish enthusiasm for medicine and is a skilful communicator. He combines a nice mix of history and contemporary themes, interviewing several groups that still practise the traditional craft of using themselves as their experimental subjects. He is keen on experimental participation, subjecting himself to analysis of bodily scrapings and fluids, breathing nitrous oxide, altering his diet, and allowing himself to be bitten by mosquitoes. We see him changing into surgical gear, peering down microscopes, and being subjected to mild discomfort.

He is particularly moving at the graves of his dead heroes and good, too, at seeking out some of their descendants to interview. Thus, we see the son of Fred Prescott, who injected himself with curare to observe its paralysing effects; the widow and son of Victor Herbert, who gave himself megaloblastic anaemia through its paralysing effects; the grandson of Joseph Goldberger, whose work on pellagra was pioneering; and a descendant of Jesse Lazear, who died, aged 34, in the yellow fever experiments in Cuba in 1900.

Mosley presents failures and successes, the mundane and epoch making, in the same excited tone. John Hunter was a great experimentalist and surgeon, but his experiments on syphilis and gonorrhoea were unfortunate, to say the least. He was probably his own subject, but the fact that he acquired both diseases from inoculating his penis with the fluid from a urethral discharge of someone assumed to be suffering only from gonorrhoea set back research on the two diseases for more than half a century. Hunter’s contemporary William Stark literally starved himself to death, subsisting on bread and water, gradually adding other nutrients—but too late, as scurvy (and possibly other conditions) finally killed him. He recorded his diet and symptoms in minute detail, but they had little impact on contemporary thinking. Somewhere, perhaps, Dr Mosley ought to have reflected more fully on the fact that self experiments are often one-off events, without proper control. Their interpretation and reporting can be bound up with the experimenter’s subjective feelings. They are double edged, needing thoughtful design and execution to be top drawer experiments rather than mere acts of bravery, exhibitionism, or flamboyance.

Mosley does show how many modern medical innovations involved self experimentation, although adopting that as his recurrent theme requires the occasional historical sleight of hand. Louis Pasteur’s importance gets him full billing, but his offer to be injected with his new rabies vaccine was not accepted by his colleagues. Robert Koch was never a self experimenter, but he is also part of Mosley’s story. Koch’s main German rival, Max von Pettenkofer, famously drank a phial of cholera germs, to refute Koch’s claims to have discovered the organism causing the disease. Pettenkofer lived to tell the tale, so interpreted his experiment as proof that water sodden soil, not the comma bacillus, causes cholera. He later died by his own hand, not from cholera.

Two of Mosley’s interviews stand out as powerful testimony to the continued importance of this mode of experimental investigation. Hilary Koprowski, born in 1916, is one of the forgotten heroes in the development of polio vaccines, but his eloquent description of his work, and the reasons why he was marginal to the media hype that polio vaccine enjoyed in the 1950s, are wonderful footage. Barry Marshall describes his work on *Helicobacter pylori* as a cause of gastritis and peptic ulcer. His research with pathologist Robin Warren reminds us that simple experiments are often the best, and there are still Nobel Prize winning discoveries to be made with ordinary tools at the bedside and in the laboratory. W F Bynum is professor emeritus, University College London

**Medical Mavericks**

BBC Four, Wednesdays at 9 pm

Rating: ★★★★☆
Brief encounters

It was our parting ritual. The train pulled in, and my father, holding his copy of the Morning Star, was enveloped by the billowing diesel fumes. “Christ,” he said as he rolled his eyes. I had started to cry. Too embarrassed for words at this public display of emotion, he punched me kindly till I stopped. My father may have been fat, balding, and not to everyone’s taste, but he was the only dad I had, and I missed him. Back then I was the only kid in the class to come from a “broken home.”

We British have come bottom of the pile when it comes to making our kids happy, a recent international survey has found, and once again absent fathers are a focus of concern. Although I am wary of surveys (apparently four million Americans report having been abducted by aliens, but I don’t believe even alien technology could produce a tractor beam powerful enough to lift the average American), this is an important point.

You need not spend too long in family practice to come across problem fathers—either as problems to their families or as having problems seeing their family. Men who are still shy of crying in public open the floodgates in the privacy of their general practice. Many fathers express stories of frustrated access, threats from former wives, and an almost universal sense that the courts express naked sexism towards them.

Society still retains a narrow stereotype of fathers. We all share conversations about the inadequacy of a husband’s domestic and parenting skill—“my other kid,” “daddy care,” and the rest. Good humoured it may be, but many a true word is said in jest. People are oily and will twist and turn, but if cornered everyone believes that women are genetically the “better” parent. Here lies the rub: unless society acknowledges that fathers are equal or have the potential to be equal parents—worthy of empathy as well as sympathy—then unfortunately some fathers will feel justified in ducking their responsibilities.

It is not easy being a parent. “What did the baby have for dinner?” my wife asked. “The cat’s food,” I replied. “Again—it’s becoming his favourite,” she said, smiling. Some scars never heal: men and women may be different sorts of parents, but our children need us both. We need to do something to help families stay together; but if we can’t, we can do much more to make sure they stay in contact. I may not like stupid skewed surveys, but I like railway stations even less.

Des Spence is a general practitioner, Glasgow destwo@yahoo.co.uk

Rejection

A senior colleague who had applied for an unpaid non-executive director post received his “no thank you” letter today. It was short, electronically signed by the director “in his absence,” omitted the usual flowery bits praising the candidate, and came as an email attachment called “rejection.” Not the best example of cutting edge management practice. However, if you want to see some even worse rejection letters take a look at [lettersofrejection.com](http://www.lettersofrejection.com), which lists more than 200 US examples.

I like the signage from some surgeries in India, which pronounce that the doctors are MRCP (failed), as at least it shows that they tried. However, my long term favourite story comes from Ireland, where in the chaotic, jobless mid-1980s one friend applied for everything going and then wallpapered his bathroom with the rejection letters, so that his friends could sit in comfort while they contemplated his lack of success.

The organisational landscape of rejection is changing rapidly. With electronic matching of applications for junior jobs in the United Kingdom, computer generated responses are the norm. As the volume of applications by each person goes up, so does the traffic in the anonymous replies that turn applicants down. More and more of us apply for jobs abroad or in international organisations, so we also must navigate new languages and management cultures.

Applicants want the job, but if they do not get it they appreciate feedback. It is difficult to get right; replies should be prompt, written by a senior person, courteous, thank the applicant, and encourage a longer term relation with the organisation. Why alienate someone who took time and trouble to apply and who later may be a client or a colleague? And yet that is what a badly worded rejection letter can do.

We all get more rejections than successes, in jobs and in life; this does not mean that we have failed. Rejection can suggest that we change track or can inspire us to try again. “What will they send me next?” said Edmund Hillary’s gym instructor of the puny schoolboy now known as the man who conquered Mount Everest. “Balding, skinny, can dance a little,” they said of Fred Astaire at his first audition. Beethoven’s music teacher declared him “hopeless” at composing.

Rejection letters should not make us feel like rejects. I encourage readers to send their examples of good, bad, plain funny, and even inspirational rejection letters and stories as rapid responses.

Mary Black is a public health physician, Belgrade, Serbia drmaryblack@gmail.com
Doctors go back to basics

Of what use is literature, especially to doctors? This is a question that has long troubled me and would continue to do so even were my medical and literary accomplishments far greater than they are. As another literary doctor, Somerset Maugham, once put it, by the standards of what eternity is it better to have read a thousand books than to have ploughed a thousand furrows?

This, however, is jumping the gun a little, for just as the existentialists say that existence precedes essence (or is it the other way round; I can never quite remember), so literacy precedes literature, at least now that the age of the epic poem is definitively in the past. And the administrators of at least one NHS trust appear not to be fully convinced that the hospital consultants in their employ can read, at least if one is to take seriously the implications of a little leaflet attached recently to their monthly pay slips.

It was entitled Skills for Life: A Guide for Staff. The trust, in that high-flying, bureaucratic language that derives inspiration equally from the preacher and the secret policeman, declared that it was “fully committed to equipping all employees and teams with the skills, knowledge and attitudes required to improve and deliver services.” I am not certain how one equips people with attitudes, but it all sounds a little reeducation certain how one equips people with attitudes, but it all sounds a little re-education and the secret policeman, declared that the administration camp-ish to me. One could almost have a little leaflet attached recently to their monthly pay slips.

The leaflet informs the consultants that “Following the introduction of the NHS Knowledge and Skills Framework (KSF), the Trust recognises that for all posts, learning and development is crucial for career progression. This means that as an employer our aim is to improve basic skills in the workplace for ‘Workplace Learning Champions’ who should be ‘committed towards the development of basic skills.”

Of course, we all have gaps in our education, or what the leaflet calls “a Spikey Profile.” “Many employees,” it tells the consultants, “have what is considered a Spikey Profile. Some people may have excellent literacy skills, however may not be at the same level when it comes to maths or vice versa.”

Help is at hand, however. “More courses and information is available on request.” All you have to do is contact the Non-Clinical Vocational Training Adviser, or the Vocational Training Manager, or the Clinical Vocational Training Adviser, or the KSF Staff Implementation Lead. If by any chance none of them is in when you call, you could try to contact the Non-Clinical Vocational Training Adviser, or the Vocational Training Manager, or the Clinical Vocational Training Adviser, or the KSF Staff Implementation Lead. If by any chance none of them is in when you call, you could try to contact the Non-Clinical Vocational Training Adviser, or the Vocational Training Manager, or the Clinical Vocational Training Adviser, or the KSF Staff Implementation Lead. If by any chance none of them is in when you call, you could try to contact the National Institute for Adult Continuing Education, or the Adult Basic Skills Strategy Unit.”

Someone in authority in the NHS has obviously read Alice in Wonderland and taken it as an educational blueprint: for the teaching of Reeling and Writhing, Ambition Distraction, Uglification and Derision, as well as Laughing and Grief. Theodore Dalrymple is a writer and retired doctor by developing and providing support to ALL members of staff as part of the ‘Widening Participation’ agenda.”

Among the things to be imparted to consultants by courses of three hours a week for 10 weeks, free of charge and presumably during working hours, were literacy and the ability to read instructions, as well as familiarity with the metric and decimal systems, and addition, subtraction, multiplication, and division. The leaflet asked for “self-nominations” for “Workplace Learning Champions” who should be “committed towards the development of basic skills.”

But Lewin’s most accessible book is Phantastica, in which he describes a wide range of recreational drugs, beginning with pharmacological tolerance. His examples range from adaptation by freshwater amoebae to increasing concentrations of salt in their environment to the adaptability of Everest mountaineers to the adverse effects of altitude. He regales us with the information that hedgehogs can endure large quantities of cantharides, and that opium does not intoxicate ducks, hens, and doves.

Lewin then deals in detail with the major psychoactive drugs, including morphine, heroin, cocaine, cannabis, peyotl, fly agaric, henbane, datura, alcohol, chloral, kava kava, betel, coffee, tea, cocoa, and tobacco, classifying them as euphorics, phantastics, inebriants, hypnotics, and excitants. His descriptions have not, in my view, anywhere been bettered. As the first investigator of Piper methysticum, he details the nature of the plant, how kava kava is prepared and drunk, its effects, and its active ingredients. He then paints the plight of the kavist, “incressantly tormented with the craving for his favourite beverage . . . degenerate through prolonged abuse . . . eyes red, inflamed, bloodshot, dull, bleary, and diminished in their functions . . . extremely emaciated . . .” Not what Western purveyors of kava tell us. Of all the vignettes, that on alcohol is the best, illuminated by a profound historical perspective. Here we learn how alcoholic beverages have been prepared through the ages, around the world, by fermentation and distillation techniques used by Anglo-Saxons and Aymaras, Kalmuks and Quechuas, Tatars and Tungus. And a sober essay on temperance and abstinence gives counterbalance to the intoxicating language and lore of inebriation.

The word Phantastica comes from a Greek word meaning to shine, and that’s what Lewin does here.

Theodore Dalrymple is a writer and retired doctor.

BETWEEN THE LINES

The administrators of at least one NHS trust appear not to be fully convinced that the hospital consultants in their employ can read

Phantastica

By Louis Lewin

Georg Stilke: Berlin, 1924; reprinted by Park Street Press, 1998

Louis Lewin (pronounced Leveen), whom some have called the father of toxicology, died in December 1929, aged 79. He spent a lifetime studying morphine and cocaine, mescaline from Anhalonium Lewini (the peyote plant, named after him by Hennings), the harmala alkaloids, Piper methysticum (kava kava), and Chavica betel. Lewin eventually became a full professor at the Friedrich-Wilhelm Universität in Berlin, although recognition took a long time coming. His most important works were a textbook of toxicology and a compendium of information about the adverse effects of drugs.

But Lewin’s most accessible book is Phantastica, in which he describes a wide range of recreational drugs, beginning with pharmacological tolerance. His examples range from adaptation by freshwater amoebae to increasing concentrations of salt in their environment to the adaptability of Everest mountaineers to the adverse effects of altitude. He regales us with the information that hedgehogs can endure large quantities of cantharides, and that opium does not intoxicate ducks, hens, and doves.

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The word Phantastica comes from a Greek word meaning to shine, and that’s what Lewin does here. One could get drunk on his literary prose, with its historical allusions, without needing recourse to the substances themselves. But don’t rely on my hallucinations: read this classic yourself.

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Jeffrey Aronson
Victor Wynn
Pioneer of metabolic studies of heart disease and founder of an institute

Victor Wynn was one of the first people to specialise in the study of metabolism and established a research laboratory at St Mary’s Hospital, followed by founding and funding the Cavendish Institute, an independent establishment that was later renamed the Wynn Institute. He pioneered electrolyte measurement, now a routine part of post-surgical care and essential to the treatment of kidney failure.

He had strong views—some would say a bee in his bonnet—about the dangers of the contraceptive pill. He was one of the first to recognise the importance of risk factors for cardiovascular disease and their modification. He also undertook the first large studies of the effects of the pill on sugar and fat metabolism, and the changes he observed resembled those seen in men at increased risk of heart disease. He published his findings in the Lancet in 1966, creating a furor. He was interviewed on the Frost Programme, and the resulting scare led the then health secretary, Richard Crossman, to accuse Wynn of making “10 000 women pregnant on a single night.”

He established two charities, the Heart Disease and Diabetes Research Trust and the Atherosclerosis Research Institute, which have jointly raised £15m.

When he arrived in 1950 to work in the surgery department at St Mary’s, the importance of electrolyte measurement was barely recognised and metabolic medicine did not exist as a clinical specialty. Wynn changed all that.

Wynn was born in Melbourne into a well-known wine growing family. From Wesley College, Melbourne, he went to Melbourne University, and did his clinical training and house jobs at the Royal Melbourne Hospital, qualifying in 1944.

He was a medical officer in the Australian air force from 1945 to 1948 and later in his career, from 1963, was a civilian consultant to the Royal Air Force.

He returned to Melbourne as a research fellow researching electrolyte measurement, which in those days was not a normal part of medical practice. He came to St Mary’s in 1950, rising to junior lecturer in 1953; consultant in clinical biochemistry in 1954, and reader in human metabolism in 1960. He was made Britain’s first professor of human metabolism in 1969.

Wynn displayed a can-do Australian spirit in setting up his first laboratory at St Mary’s, commandeering unused hospital space and acquiring the components he needed for his electrolyte measurements from local shops. This entrepreneurial directness, which characterised his approach to research, set him apart from, and at times, at odds with, more conventional colleagues.

He was very good at raising funds from wealthy philanthropists, and often urged his colleagues to emulate him. At his instigation, in 1953 the hospital approved plans to set up a metabolic unit, though it took 16 years to create a 10-bed metabolic ward. The laboratory facilities were insufficient, but, despite a squeeze on medical education and research, the university grants committee approved a small capital grant to buy the former British Railways stables and rebuild them as a metabolic unit. Money was raised from ex-patients and from Dr Leonard Simpson, the hospital’s consultant endocrinologist, whose family owned the department store in Piccadilly (the model for the television comedy series Are You Being Served?). Wynn got the Turriff construction company to construct the building free of charge.

The new laboratories were called the Mint Wing, and by the time it opened Wynn’s interests had turned from electrolytes and renal failure to endocrinology and the long term administration of synthetic steroids. When anabolic steroids were new in the 1960s and were known to prevent muscle wasting and aid recovery from surgery, Wynn showed that they had potent side effects in fat and sugar metabolism, and cautioned against their use. In 1966 he predicted that women taking the pill would be at increased risk of heart attack, and epidemiological studies showed him to be right. In the 1970s he urged cardiologists to pay attention to patients’ cholesterol concentrations, and in the 1980s he called on the food industry to sell “heart friendly” products.

During this time he was a consultant to the Royal Air Force, British Airways, and the Civil Aviation Authority.

On his retirement from St Mary’s, aged 66, he used his energy and fundraising skills to found the Cavendish Institute, located some distance from the hospital and affiliated to the UK National Heart and Lung Institute. It has since been renamed the Wynn Institute and is affiliated to Imperial College.

In 2001 in Melbourne the Wynn Department of Metabolic Cardiology was opened. In 2006 Wynn was made a Fellow of Imperial College. He suffered from heart disease for the last 30 years of his life.

He leaves a wife, Marianne, emeritus professor of German, and a daughter.

Caroline Richmond

Victor Wynn, former professor of human metabolism London University, and chairman Wynn Institute for Metabolic Research (b 1920; q Melbourne 1944; MD, FRCP, FRCPath), d 6 October 2006.
Patrick John Murray Brock

Former consultant anaesthetist Royal Berkshire and Battle Hospitals NHS Trust (b 1941; q Cardiff 1967; FRCA), died from a cerebral haemorrhage on 22 November 2006.

Patrick John Murray Brock took up his anaesthetics post in Reading in 1975, and he remained there for more than 25 years. He was especially interested in obstetric anaesthesia, and he went on to supervise the extensive obstetric anaesthesia service in Reading. He had enjoyed athletics as a student, and throughout his career he continued to compete in marathons and half marathons. Patrick was much loved for his quiet wisdom and matchless sense of humour. He leaves a wife, Margaret; three children; and two grandchildren.

E Young

John Drew Hamer

Former consultant surgeon Queen Elizabeth Hospital, Birmingham (b Nuneaton 1935, q Birmingham 1960; BSc, ChM, FRCS), d 1 September 2005.

After qualifying, John Drew Hamer worked as a general practitioner in Staffordshire. Realising general practice was not for him, he trained as a surgeon and was appointed senior lecturer in 1972 and then consultant surgeon at the Queen Elizabeth Hospital, Birmingham, in 1975. His interest in vascular surgery contributed to the development of the vascular unit. He was secretary of the West Midlands Surgical Society. He maintained his university connections as an honorary clinical senior lecturer. John was a skilled furniture maker, keen sailor, and chorister—he was chairman of the Bromsgrove Choral Society. He leaves a wife, Angela; two children; and five grandchildren.

Andrew J Hamer

John Kenyon (“Titus”) Oates

Former consultant in venerateology Westminster Hospital, Addenbrooke’s Hospital (b 1922; q London Hospital 1946; FRCP, MA), died from ischaemic heart disease complicated by motor neurone disease on 9 August 2006.

John Kenyon (“Titus”) Oates developed his interest in venerateology during the year he spent at Johns Hopkins Hospital, Baltimore as a Fulbright scholar. He aimed to take venerateology out of the dark ages—from hospital basements into mainstream medicine—and put it on a scientific basis. His particular interests were herpes and Reiter’s syndrome. The Facts, written for the general public, was one of the first books to address the myths surrounding this infection. As a teacher and lecturer Titus Oates excelled, and his interviews for radio were well received by producers and public alike. He leaves a wife, Sue; two children; and two grandchildren.

David Rowen

Chris Sonnex

Bruce Henry Davies


After doing a vocational training service scheme, Bruce Henry Davies became a general practitioner in 1986 and then a general practitioner trainer in 1989. Over the next 20 years he became a local legend in a small village practice. Although involved in computerisation from early on, both locally and nationally, he worked for 20 years without an appointment system. He was a trainer and course organiser for the local vocational training service for 12 years and was also a member of the Hambleton and Richmond primary care trust. He was a school governor and loved gardening and cooking; he had a passion for organic food, much of which he grew himself. He leaves a wife and three daughters.

David Hughes

Roger Higson

Sam Wystan Poshela Mhlongo

Professor of family medicine MEDUNSA (b 1940; q Charing Cross, London, 1976; MSc, MRCPGP), died in a car crash on 6 October 2006. Sam Mhlongo opposed apartheid and was imprisoned on Robben Island, where he was close to Nelson Mandela. In exile in London he studied medicine and became a general practitioner. In 1998 he returned to South Africa to a foundation chair at MEDUNSA (Medical University of Southern Africa, now University of Limpopo). President Mbeki appointed him adviser on family health with responsibilities for correcting historic problems and developing services in new communities in the Johannesburg area. One such problem was the different regional and sex related prevalence of HIV/AIDS associated with inaccuracies in serological tests. Sam became known as a well-qualified African opponent of the pessimism of the pandemic of HIV/AIDS, using local wisdom in initiatives to overcome innate inequalities between the sexes, regions, and socioeconomic groups. He leaves a second wife, Maria Giacomin, and their two sons, and a first wife, Anne Morgan, and their daughter and two grandchildren.

Gordon Stewart

Andrew Herxheimer

John Stanley Mornington Zorab

Former consultant anaesthetist and medical director Frenchay Hospital, Bristol (b 1929; q Guy’s Hospital, London, 1957; FFARCS, DHMSA), d 17 July 2006. John Zorab was appointed consultant at Frenchay in 1966. He helped create the intensive care unit and a nationally and internationally renowned anaesthetic department. His other achievements included helping to found the European Academy of Anaesthesia and the European diploma in anaesthesiology and intensive care. He was also on the council of the Association of Anaesthetists and the Board of the Faculty of Anaesthetists of the Royal College of Surgeons. He became president of the European section and later president of the World Federation of Societies of Anaesthesiology. In his latter years he became involved in hospital management at Frenchay, continuing for two years after retirement age. In retirement he studied and qualified in the history of medicine. He leaves a wife, Shirley, and four children.
“Body stuffers” are drug dealers who conceal drugs in their mouths so they can quickly swallow them if they’re approached by the police. This differs from body packers (“mules”), who smuggle packages of drugs in their bowels. In Hamburg, anyone suspected of having swallowed drugs in order to hide them is taken to the Institute of Legal Medicine, where drugs are retrieved by pharmacologically inducing vomiting. Since 2001 this method has successfully recovered drugs in two thirds of suspected cases. Most of the offenders were African men aged 16 to 25 (Journal of Forensic and Legal Medicine 2007;14:96-8).

Despite our hunger for all things digital, especially when they’re free, Minerva was amused to discover that the demand for the printed directory of UK Self Help Groups and Support Organisations at £20 a pop continues to grow (see www.ukselfhelp.info/order). The website (www.ukselfhelp.info), containing the most up to date information, remains free of charge.

Amid the latest rounds of changes to medical postgraduate training in the UK, the quality of our future surgeons is to be determined by a move away from apprentice-style training to one of more ordered education. One surgical specialist registrar observes that “it says much for our island mentality that although we belong to the European Union, we consider European surgical training to be distinct from our own” (Bulletin of the Royal College of Surgeons of England 2007;89:12-4).

A randomised double blind pilot study of long chain omega 3 essential fatty acid supplementation in people who recurrently self harm reports that, at just 12 weeks, the active group had greater improvements in scores for depression, suicidal ideation, and daily stress. Scores for hostility, impulsivity, and aggression remained the same in both groups. The unanswered question is whether insufficient dietary intake of these essential fatty acids is a reversible risk factor for self harm (British Journal of Psychiatry 2007;190:118-22).

Rest alone for osteochondritis dissecans of the knee sometimes fails. To improve blood flow and stability in the articular cartilage and its underlying bone, a recent innovation is to arthroscopically transplant “plugs” of osteochondral cells taken from the non-weight bearing area of the patient’s own knee joint into the unstable fragments. Using magnetic imaging to track 12 knees treated in this way, surgeons found that in all 12 the interface between the avascular fragment and the subchondral bone had disappeared by three months, with no complications arising from the donor site (American Journal of Sports Medicine 2007;35:216-22).

Fewer than 50% of strokes and transient ischaemic attacks were reported as being a probable stroke when reported to the Australian emergency services in a study of stroke and the decision to call for an ambulance. Unprompted recognition of a stroke was associated with facial droop and a previous history of stroke or transient ischaemic attacks, and the factors associated with making the call within an hour of the symptoms starting were speech problems, a family history of stroke, and the event being witnessed by another person (Stroke 2007;38:361-6).

Mothers with drug habits put not just their own parenting skills at risk but they pose problems for their children’s future functioning as parents, according to a longitudinal study in Pediatrics (2007;119:444-51). The results suggest that interventions aimed at reducing drug use in one generation could have knock-on effects on the self esteem of not only the second generation but also the third. Put another way, if the grandchildren’s self esteem is low, multigenerational family therapy may be helpful.

Quite a few adults with epilepsy can actually predict their own seizures before they happen (Neurology 2007;68:262-6). The ones who do this best, according to complex mathematical modelling, are young people with high rates of seizures. The researchers didn’t explore the premonitory symptoms reported to be present in up to half of patients with epilepsy, but it may be these patients who are the successful predictors and therefore the potential candidates for prophylactic treatment for seizures.

Snorting cocaine may cause nasal problems, but ironically it’s still the local anaesthetic of choice for surgeons performing septoplasties, who administer it by inserting drug-dipped sponges into the nostrils. A randomised controlled trial of cocaine 4% solution versus tetracaine 2% solution concludes that tetracaine is significantly better at pain reduction than cocaine, and that the use of cocaine should now be limited (Journal of Laryngology and Otology 2007;121:130-3).

A 65 year old woman was seen in the dermatology clinic with a large friable nodule on her fingertip; it was removed by curettage. Histology confirmed the diagnosis of pyogenic granuloma, a lobulated proliferation of capillary vessels. These common benign tumours occur predominantly on the fingers, lips, face, and gingiva. In most cases no definite cause is found, although minor trauma is often suspected. This lesion may have resulted from a scratch sustained in the garden a week earlier. K J Hunter SpR, T M Finch consultant, department of dermatology, Solihull Hospital, Solihull B91 2JL katie.hunter@nhs.net