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US editor's choice: Someone to watch over me
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Researchers warn of possible risks to children from new epilepsy drugs
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Bush says he will veto stem cell funding, despite vote in favour in Congress
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*10-minute consultation: Chronic kidney disease*
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**Obituaries**

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**Miles Weatherall**
Estlin Waters
BMJ 2007;334:1278, doi:10.1136/bmj.39241.578160.BE
Josephine Alice Coreen Weatherall (née Ogston)
Miranda Mugford, Alison Macfarlane
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Khalid Tariq Al Naib
Saad Shakir
BMJ 2007;334:1279, doi:10.1136/bmj.39234.632002.BE

William Bingham
J S Bingham, E A Barnett
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Stuart Gordon Adam Forsyth
John Ford
BMJ 2007;334:1279, doi:10.1136/bmj.39232.832940.BE

Robert John Jameson
Paul Booth, Angela Jameson, David Jameson
BMJ 2007;334:1279, doi:10.1136/bmj.39234.678438.BE

Geoffrey Laurence Scott
Helena Daly, John Hudson

Anthony Robert ("Bob") Teuten
Richard Teuten
BMJ 2007;334:1279, doi:10.1136/bmj.39218.605984.BE

Minerva

Minerva

BMJ 2007;334:1280, doi:10.1136/bmj.39241.502789.BE1

Minerva
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An event that changed our lives
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Is presumed consent the answer to organ shortages?

BMJ 2007;334, doi:10.1136/bmj.39245.495590.BE

Career focus

Read this week’s articles on
In this week’s BMJ a systematic review by Collins and colleagues compares the diagnostic accuracy of duplex ultrasound, magnetic resonance angiography, and computed tomography angiography for assessing peripheral arterial disease of the lower limb.¹ The review also evaluates the impact of these assessment methods on patient outcomes. It found that contrast enhanced magnetic resonance angiography seemed to be more specific than computed tomography angiography (better at ruling out stenosis of 50% or more in a lower limb vessel) and more sensitive than duplex ultrasound (better at ruling in stenosis of 50% or more). Magnetic resonance angiography was also generally preferred by patients over contrast angiography. So what do these results mean for practising clinicians?

In developed countries up to a fifth of the population over the age of 60 has lower limb peripheral arterial disease, as defined by absent pulses or a reduced ankle brachial pressure index. About a quarter of these people have symptoms—most commonly intermittent claudication. This consists of pain in the leg (usually in the calf) on walking, as a result of atherosclerotic stenosis or occlusion, usually of the superficial femoral artery in the thigh.²

Only a small minority of patients with intermittent claudication undergo imaging with a view to open surgical (bypass, endarterectomy) or endovascular (angioplasty, stenting) intervention. Most claudicants are treated medically in primary³ or secondary care⁴—if they are treated at all.⁵ In contrast, most patients with severe limb ischaemia (rest pain, tissue loss) undergo imaging with a view to interventional treatment, usually by means of bypass surgery or angioplasty.⁶ ⁷

Imaging studies are of little use in peripheral arterial disease unless intervention is being considered and the imaging results are likely to influence the choice and nature of that intervention. In an era of “high tech” medicine we sometimes forget that the purpose of imaging is not just to obtain pleasing pictures but to answer specific clinical questions that have been thoughtfully framed after undertaking a careful history, thorough examination, and non-invasive assessments.⁸ Not surprisingly, Collins and colleagues found that the availability of appropriate clinical data increased the accuracy and quality of imaging interpretation.

The imaging modality should be carefully chosen, in an evidence-based manner, so as to maximise the quality and relevance of information obtained, minimise the risk and inconvenience to the patient, and make the best use of limited resources. But, as Collins and colleagues report, making such a choice can be difficult in people with peripheral arterial disease. They could find few comparative studies and many had serious methodological limitations. Most studies had several potential sources of bias resulting from the nature of the patient population being investigated, the delay between index and reference tests, and the inability to blind observers. Only one study compared patient outcomes. The rest compared diagnostic “accuracy,” which can be hard to define in a clinically meaningful way, especially when data are presented by arterial segment rather than by limb or by patient. Relative sensitivities and specificities, often with wide ranges, for various degrees of arterial stenosis, most commonly 50%—a level of disease with limited biological or clinical relevance—are hard to factor into everyday clinical decision making. In reality, as pointed out by Collins and colleagues, the choice of imaging may be more influenced by patient preference and tolerance as well as the availability of the test.

When a patient with peripheral arterial disease needs diagnostic imaging, it seems sensible to start with the simplest and safest modality, which is undoubtedly duplex ultrasound.¹ ² Only if this proves insufficient should more sophisticated, potentially risky, and costly tests normally be considered. In practice, this is now unusual given the quality of the machines used and the skill of vascular technologists.

Intra-arterial digital subtraction angiography is the reference standard, but magnetic resonance angiography and computed tomographic angiography can provide more information and can be more accurate than ultrasound.¹ ² However, in many cases the extra information and accuracy has little effect on patient management and outcome. The only study in the review by Collins and colleagues that compared patient outcomes found no significant difference between duplex ultrasound and intra-arterial digital subtraction angiography.

In summary, the available data,¹ supported by everyday clinical experience, suggest that duplex ultrasound is the only imaging test needed in most patients. If ultrasound is not sufficient, then most clinicians would probably choose magnetic resonance angiography rather than computed tomographic angiography because it is more versatile, more accurate, is not as affected by arterial calcification,¹ ⁸ and does not involve exposing patients to ionising radiation.⁹ ¹⁰

Diagnostic imaging continues to evolve and improve at an astonishing rate. There is a growing consensus to use the most accurate and cost-effective test available.¹¹ ¹²
that invasive techniques should not be used to visualise the arterial system unless a therapeutic intervention is intended. Thus, diagnostic intra-arterial digital subtraction angiography is likely to become a thing of the past, with open and endovascular treatments for peripheral arterial disease being planned almost exclusively on the basis of duplex ultrasound and, where necessary, magnetic resonance angiography.11 12

2 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). Eur Vasc Endovasc Surg 2007; 33(suppl 1):S1-75.

Provision of primary care in different countries
Priorities of patients should not be overpowered by economic and political incentives

Primary care has an important part to play within healthcare systems.1 The World Health Organization defines the main aim of healthcare systems as the improvement of health, but it notes that financing should be fair and systems of care ought to respond to people's expectations.2 Countries whose healthcare delivery focuses on the role of the specialist tend to fare less well in surveys that take account of these three goals.3 Primary care seems to offer important advantages within healthcare systems in terms of cost containment, health status of the population, and a range of other health related outcomes—the value of a strong primary care base within national healthcare systems is recognised by WHO.4

How can cross national studies provide insight into the optimal organisation of health care?

In this week's BMJ, Bindman and colleagues5 use data from national surveys in Australia, New Zealand, and the United States to compare mix of patients, scope of practice, and duration of visits in primary care. Previous studies have compared patient morbidity and patients' expectations of care between countries.6 7 This study differs in that it examines case mix and exposure to primary care in three countries using rigorous and innovative ways to analyse large nationally representative datasets.

In primary care, length of consultation has been proposed as a marker of quality of care, with longer consultations increasing patients' satisfaction and being more comprehensive and more responsive to patients' needs.8 9 Few studies have reported exposure to primary care in populations or have used such a measure to investigate differences between groups of individuals with regard to the experience or outcome of health care.

In the United Kingdom, a recent national survey of primary care provision10 reported a median consultation length of 13.3 minutes for general practitioners in 2003. UK patients have an average of 4.5 consultations each year, so these figures imply a per capita annual exposure to primary care physicians of around 60 minutes each year—an increase of 28% in just five years.11 Bindman and colleagues highlight a substantial variation in such exposure between the three countries they studied—from 29.7 minutes each year in the US to 83.4 minutes each year in Australia.

Similar methods to those used by Bindman and colleagues to define case mix have been used to investigate the relative contribution of social class and case mix in modelling the use of home visits in primary care settings.12 The methodological approach used in the current study to assess differences in case mix is sophisticated; it draws on a diagnostic coding system developed at Johns Hopkins Hospital, which has been validated for use in primary care. It has the potential to compare case mix in primary care in countries that extensively use morbidity coding systems, such as those of the International Classification of Disease or READ coding system.

A limitation of Bindman and colleagues' study is that only administrative or preventive care codes were recorded in up to 20% of consultations, and these were excluded from the analysis. While the role that doctors play in society varies in different countries, the authors are right to note that such consultations should be included in the overall assessment of case mix. This would enhance the generalisability of the findings and provide a more comprehensive overview of the contribution of primary care to the healthcare system within the country.

It may be surprising to general clinicians providing “comprehensive” first line care that 75% of the workload of US primary care physicians comprises just 46 conditions. Also, this number rose to only 57 conditions
for family doctors in New Zealand, a country that is much more orientated towards primary care than the US, and which has healthcare structures similar to those of the UK National Health Service. Some substantial differences were seen between national populations in primary care case mix—women in the US had lower rates of attending primary care for gynaecological problems, but attendance for endocrine and cardiovascular problems was much higher in the US than in Australia and New Zealand. Such observations may reflect differences between countries in access to care and in the gatekeeping role of family doctors, but they may also result from cultural differences between populations in their interpretation of symptoms and in their use of health services.

Even in Western healthcare systems, inequalities in health status and experience of care exist between individuals. Squandering of resources through failure to provide a strong primary care base within national health systems is likely to reinforce divisions within society, worsen the health status of individuals, and create a healthcare system that is unresponsive to the needs of the population. Cross national comparative studies have the potential to inform the development of services, but they need to take account of the beliefs and values of the people served as well as the ambitions and resources of their health professionals and politicians.


Transition of care in children with chronic disease

Healthcare teams need to adapt to change as much as patients and their families

In this week’s BMJ, a woman with cystic fibrosis describes her experience of living with the disease from childhood to adulthood. Among the many challenges she describes is the “rocky road” of transition from paediatric to adult health care. She says that she would have given anything to attend a transition clinic when she was 16 years old, instead of going straight to an adult clinic at another hospital.

Cystic fibrosis was previously considered a lethal disorder of childhood, but as survival improves, the need for continuous care into adulthood becomes more important. For the past two decades the global cystic fibrosis community has recognised the importance of transferring care from paediatric to adult services, and has set an example for services in other chronic conditions to follow.

Transition to adult care for any child with a chronic life limiting illness should not consist of just transfer to a doctor who treats adults. It should be a clinical and psychosocial process. Adolescence is a time of great change—a normal journey of transition from childhood to adulthood. It is a difficult and exciting time as shifts occur in emotional attachments, autonomy, self identity, sexuality, physical shape, philosophy of life, and vocation. For those with a chronic illness, this developmental stage is complicated further as the teenager takes responsibility for care and faces problems associated with morbidity, mortality, and limitations to life’s options. Coping with these extra problems on top of the normal challenges of adolescence is an immense challenge, which is made worse by being cut off by the paediatric care team that the patient knows and trusts.

Fundamental differences exist between paediatric and adult chronic care. Paediatric care is often multidisciplinary, prescriptive, and family focused. It requires parental direction and consent. Adult care tends to be patient focused, and it encourages autonomy in making decisions about treatment and life choices. Professionals in adult care are familiar with the difficulties associated with sex, pregnancy, work, and raising a family in the context of chronic ill health.

A successful transition process has defined stages. Firstly, the needs and benefits of a move to adult care are explained and discussed with the young adult patient and the parents. A combined clinic is then held where the patient and family meet with the “receiving” team for a multidisciplinary handover. An orientation tour of the adult centre is an important part of the journey. Finally, there is the last goodbye—a visit to ensure that all aspects of transition have been covered.

Surveys show that patients and parents have a positive opinion of such transition clinics. The parents’ biggest concern was whether their child would be able to care for their illness independently, although this concern...
Tamiflu and neuropsychiatric disturbance in adolescents

The case is not proved but caution is advisable

In March 2007 the Japanese authorities advised against prescribing oseltamivir (Tamiflu, Roche) to adolescents aged 10–19 years.1 This unusually severe measure resulted from the separate suicides of two 14 year olds who jumped to their deaths while taking oseltamivir; 9 other deaths (14 in children or adolescents) have been associated with the same drug. So far, similar action has not followed in Europe. When a regulatory authority warns doctors not to prescribe a drug but decides not to retract its marketing authorisation prescribers and patients are entitled to be concerned and a little confused.

Oseltamivir is a sialic acid analogue that inhibits influenza type A and type B neuraminidase, the viral enzyme that allows the release of virus from infected cells. Its main licensed indications are the treatment of flu, short term postexposure prophylaxis after contact with a diagnosed case of flu, and more prolonged (up to six weeks) “seasonal” prophylaxis when flu is circulating in the community. The licence was extended in 2005 to include children aged 1-12 years.

When used to treat otherwise healthy people, oseltamivir reduces the duration of symptoms by 1-1.5 days if started within 48 hours of first symptoms, irrespective of vaccination status, although it may be less effective in those with chronic diseases.2 It also provides a modest reduction in complications such as pneumonia, otitis media in children, and hospital admission.1,4 As postexposure prophylaxis, the protective efficacy of oseltamivir was 80-90% in the family contacts of index cases.3,4,5

As seasonal prophylaxis, the protective efficacy was 74% in healthy people aged 18-65 and even higher in frail elderly people in residential care.8

The National Institute for Health and Clinical Excellence advises that oseltamivir should not be prescribed for otherwise healthy people because the health gain in this group is modest.5,6 However, oseltamivir is recommended for treatment and postexposure prophylaxis in people who are at increased risk of complications because of age or comorbid conditions (box). This restricted recommendation in the United Kingdom has limited prescription of oseltamivir to only a few thousand people.7 In contrast, an estimated 45 million patients have received oseltamivir worldwide.1 This has been partly boosted by encouragement from the World Health Organization, as a way to gain familiarity with antiviral agents before the outbreak of a pandemic.10 Several governments have been stockpiling supplies in preparation for such an event.

So far, oseltamivir has been thought to be well tolerated and safe. The most common adverse effect is dose related nausea, which occurs twice as frequently as with placebo when used as prophylaxis.5 Postlicensing monitoring has revealed very rare reports of raised liver enzymes and hepatitis and of serious skin reactions, including Stevens-Johnson syndrome and erythema multiforme.11 However, the recent events in Japan have prompted a reappraisal.

Before 2007, there had already been more than 100 reports of neuropsychiatric events (including delirium,
Rosiglitazone and implications for pharmacovigilance

Post-surveillance data should be systematically collected and publicly available

On 21 May 2007, the New England Journal of Medicine published a meta-analysis of 42 trials of rosiglitazone (Avandia, GlaxoSmithKline) for treating type 2 diabetes mellitus. It found that the drug was associated with an increased risk of myocardial infarction (odds ratio 1.43; 95% confidence interval 1.03 to 1.98; P=0.03) and death from cardiovascular causes (1.64; 0.98 to 2.74; P=0.06).1

Rosiglitazone, a thiazolidinedione, is an agonist at the peroxisome-proliferator activated receptors in cell nuclei. These receptors modulate the expression of a host of genes, and glycaemic control is achieved primarily through increased insulin sensitivity in peripheral tissues. Rosiglitazone was approved by the US Food and Drug Administration (FDA) in 1999 and by the centralised process of the European Medicines Agency (EMEA) in 2000. Its popularity has increased steadily, with more than one million prescriptions written in the one year period ending March 2006 in England alone—a 22% increase over the previous year.2 However, the recently published meta-analysis raises serious questions about the drug’s safety.

Meta-analyses have unique strengths and weaknesses and this one is no exception.3 Its singular strength is the statistical power generated by data on 15,560 patients from published and unpublished trials. However, it includes clinically heterogeneous trials and criteria used by individual trials to classify adverse events are somewhat unclear. Only summary data are available in the public domain—for example, whether or not a person had a myocardial infarction, not when it occurred—which makes time to event analyses impossible. Also, the total number of adverse events was small, so that misclassification of a few events could alter the conclusions.

In response to the concerns raised by this meta-analysis, an unplanned interim analysis of a large, manufacture sponsored, randomised, open label, non-inferiority trial specifically designed to investigate the cardiovascular...
The case of rosiglitazone.

When these new data are added to the trials in the previous meta-analysis, rosiglitazone is associated with an increased risk of myocardial infarction (odds ratio, 1.3; 1.02 to 1.72). To summarise, the meta-analyses show a significantly increased risk for myocardial infarction, whereas several individual prospective trials do not. More data would certainly help to clarify the matter, but the emerging safety concerns question the prudence of continuing ongoing trials. Notwithstanding the ethical concerns, it may be impossible to prevent an exodus of patients from these trials in light of the ongoing “trial by media” of the drug.

The broader question is how this reflects on regulatory processes used to monitor drug safety. Postmarketing surveillance, or pharmacovigilance, remains the weakest link in the regulatory process on both sides of the Atlantic. The current approach—the FDA’s adverse event reporting system and the European EudraVigilance programme—relies heavily on passive surveillance, and it is based on reports of unusual adverse events from consumers, practitioners, manufacturers, and national regulatory authorities. At best, this creates a case series, one of the weakest forms of epidemiological evidence, that would be insensitive to an increase in common events like myocardial infarcts in diabetics.

Alternatively, the regulatory authorities may require systematic phase IV trials after market authorisation, but these are often not completed in a timely manner. In the United States, completion dropped from 62% in the 1970s to 24% in recent years, and the FDA is ill equipped to act against defaulters. As of September 2006, 930 (74%) of the 1259 postmarket studies were pending or delayed.

This results in a fractured regulatory process, where the preapproval phase is marked by stringent requirements for safety and efficacy data, but performance in postmarketing surveillance falls short of the standards the agencies set for themselves. This is exemplified by the case of rosiglitazone. Rosiglitazone comes from a family of drugs with well documented side effects, and it is associated with increased heart failure, anaemia, and raised low density lipoprotein concentration. However, postmarketing safety data seven years after regulatory approval consist of a patchwork of heterogenous manufacturer sponsored trials, many of which are unpublished. Of note, a similar meta-analysis submitted by the manufacturer to the EMEA and the FDA in August 2006 showed an increased risk in ischaemic events (hazard ratio, 1.31, 1.01 to 1.70). The EMEA updated the product label of the drug, but no specific communication to healthcare professionals was issued. The FDA did neither.

The system needs to be fixed. The Institute of Medicine recommends a life cycle approach to drug evaluation. This would involve a systematic effort to monitor the safety and efficacy of a drug before and after approval using data from well designed clinical trials to inform ongoing risk-benefit analyses. This process could be made more systematic by requiring regulatory authorities to periodically and independently re-evaluate all data gathered after approval for all new molecular entities—particularly drugs with high sales.

In addition, the lack of transparency in the current system needs to be dealt with. There should be a legal requirement for all phase II-IV trials to be registered in a centralised database, such as the National Library of Medicine’s clinicaltrials.gov or an equivalent. Complete datasets from these trials, systematic analyses of the results, and reports of periodic evaluations by the regulatory agencies must be publicly available.

A radical change is needed in the culture of existing regulatory institutions that regard postmarketing surveillance as their secondary mandate. This will require systematic rethinking of the existing regulatory and funding processes, and expediting changes currently in the pipeline. Progress will entail empowering the regulatory agencies with additional authority and resources.

The manufacturer and the FDA will share the spotlight as congressional investigation into the matter starts. In the meantime, what are the implications for patients currently on rosiglitazone? Doctors will need to revisit the indication for the drug on a case by case basis, bearing in mind that several alternatives are cheaper, supported by robust evidence, and now perhaps safer. The decision to switch drugs must be tempered by the fragility of the available evidence and the risks associated with altering patients’ medical regimens. Needless to say, the ongoing use of rosiglitazone merits careful deliberation.

Investing in alcohol is no longer responsible

“Doctors are stalwart drinkers,” says Richards, calling on doctors to do more to tackle alcohol abuse.1 Doctors are also stalwart investors and must begin to use their financial clout as shareholders to remove alcohol from their portfolios.

Last autumn, the multinational drinks industry used its political, business, and financial lobbying muscle to subvert the European Commission’s attempts to bring forward an alcohol strategy based on public health principles.2 In the past, the public health agenda has relied solely on evidence to effect political change. This worked when elected politicians had a stronger influence on society. The business corporations have now become bigger players where the measure of success is profit. Health policy has to accommodate to this change and will have to engage shareholders directly to get them to avoid alcohol at both manufacturing and the sometimes forgotten retailing levels.

Leadership is required from doctors, who are often the first witnesses of alcohol related harm. This can be exercised by refusing to hold shares in alcohol companies and by instructing fund managers to set up and seek non-alcohol based portfolios. It is time to include the manufacture and importantly the sale of alcohol as an unworthy and unethical way of making money for the individual investor. Most doctors would not knowingly invest in tobacco companies, and, although no level of tobacco use is safe, alcohol is no ordinary commodity either1 and even small amounts can cause catastrophic harm.

Advocacy budgets will never come remotely near industry budgets, but doctors interested in the health of the public have to develop expertise on the ways of big business and use this expertise in informing individual shareholders on the wider societal implications of their investments.

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Competing interests: None declared.

1 Richards T. Europe on the rocks. BMJ 2007;334:114.2. (2 June.)

SAFER PLAY IN RUGBY

Time to address safety in the tackle

As an amateur rugby referee who spent the 2005 season refereeing in New Zealand and took part in the RugbySmart campaign I was interested to read the analysis by Quarrie et al of its impact on spinal injuries.1 As they point out, most of the reduction in injuries was accounted for by a reduction in scrum related injuries. Whether a similar campaign would be equally effective in Britain is unclear, given the recent 2006 changes in the scrum engagement procedure; but as pointed out in the accompanying editorial it can certainly do no harm.2

The paper highlighted another area of concern; seven out of eight spinal injuries occurred at the tackle. Over the past 10 years there has been an increase in the high impact, chest high “ball and all” tackle. This area of the game is now associated with the most injuries,3 and this type of tackle puts the tackling player at risk of a head on torso collision and spinal injury.

Instead of further debates over banning the scrum we should concentrate on improving the safety at the tackle area by legislation and educational initiatives similar to those described by Quarrie et al.

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Competing interests: APG is a rugby referee who took part in the RugbySmart campaign.

2 Noakes TD, Draper CE. Preventing spinal cord injuries in rugby union. BMJ 2007;334:1122-3. (2 June.)

PTSD IN NORTHERN IRELAND

Tell us more

Duffy et al provide evidence for the effectiveness of cognitive therapy in post-traumatic stress disorder (PTSD) in the context of terrorism and civil conflict in Northern Ireland.4 More information would have been helpful to interpret the results.

No patients were started on medications during the trial. However, 52% in the immediate therapy group were taking antidepressants already. When were these initiated in relation to the trial? Also, were any changes to the antidepressant dose allowed during the trial? Over 70% in the immediate therapy group had comorbid major depression. The effect of antidepressant initiation just before the trial or dose changes may be partly responsible for the improvement in this group’s symptoms.

The percentages for the overall effectiveness of cognitive therapy are the combined scores of the immediate treatment and waiting list control groups. This makes them uncontrolled scores. The authors are not comparing two groups of patients, one receiving therapy and the other not receiving therapy.

The follow-up mean scores in table 3 have been taken at either four or 12 months. As a clinician, I would be particularly interested in information about the maintenance of gains at 12 months. This is not clear from the table. If gains seen at four months are lost by 12 months, this then raises questions about whether booster sessions are indicated.

Finally, the therapist effect is important. It would be interesting to look at whether
this difference in patient scores is related to the type of qualification in cognitive therapy that the therapists had. Recent research has shown that formal post-qualification training in cognitive therapy is associated with competence.2

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Competing interests: None declared.


SKIN BIOPSY

Watch out for digital nerves

As a hand surgeon, I was concerned about the bottom right picture of figure 3 of the article by Lauria and Lombardi, which seems to show that a skin biopsy had been taken from the radiovolar skin of the left index finger.1 In the summary points box it was suggested that a skin biopsy was easy and almost painless. Furthermore, nowhere was there any indication that potential injuries could be caused by the use of this technique. Skin biopsy as indicated above carries a high risk of causing a digital nerve injury leading to a neuroma causing chronic pain, which may require reconstructive surgery. If volar digital skin biopsies are required then it is much safer to harvest skin biopsy from the index finger.

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Competing interests: None declared.


ROSIGLITAZONE AND HEART DEATHS

Glycaemic control is a myth

Tight control of HbA1c levels has been ensnired in the QOF (quality and outcomes framework) of the new general practitioner contract as being an evidence based proposal. Multiple drugs are licensed on the understanding that they reduce HbA1c levels and that this is a good thing. So should it surprise us that a meta-analysis of trials of rosiglitazone shows a raised risk of myocardial infarction and an increase in cardiovascular deaths?2

The reduction in diabetes related end points, mortality and stroke from using metformin is not explicable on the basis of glycaemic control.2

The data of UKPDS 33, which compared tight glycaemic control with sulphonylureas or insulin with conventional treatment, showed little benefit from tight control.3

The outcomes that did show some clinical benefit were caratuar extractions, retinal photocoagulation, and non-fatal myocardial infarction and all cause mortality—that is, if you can call absolute risk reductions of between 1 and 3 per 1000 patient years as being clinically relevant.

The wonder with drug licensing is that we continue to accept surrogate end points in trials to license new treatments for conditions for which we already have treatments. Show me better data or accept that the control of blood glucose means metformin—anything else is merely for symptom control.

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Competing interests: IRT has coauthored with Adrian Edwards, Glyn Elwin, and Rhys Williams a paper on explaining risk information over the internet to patients with diabetes, which was funded by the BMJ Group.

1 Tanne JH. Study indicates diabetes drug linked to cardiovascular death. BMJ 2007;334:1073. (26 May.)
doi: 10.1136/bmj.39224.364630.DB

HELPING THE WORLD’S POOR

Let’s help doctors work in the third world

Surely it is not beyond the wit of our profession to devise a scheme that will make it easier for UK health professionals to work overseas either as missionaries, volunteers with non-governmental organisations (NGOs), or in other “bona fide” set-ups. Some of the issues Mabey raises also affect UK doctors wanting to take career breaks in the United Kingdom.1

We need to devise a way that UK doctors working overseas can be part of some form of revalidation. We have an oversupply of doctors at the moment trying to get into the Modernising Medical Careers (MMC) process. Allowing some to opt out to work overseas should be encouraged by recognising the experience they will have gained and facilitating their re-entry into the system.

At the moment UK doctors working overseas cost the UK government nothing. The government could recognise this by helping to pay off debts from student loans and help with the General Medical Council’s registration fees, etc. This money could come out of the overseas aid budget.

Some organisations such as the BMA and Medical Protection Society recognise overseas service by offering either free or heavily discounted membership to medical missionaries and NGO volunteers.

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Competing interests: ALP was a medical missionary in Mali, West Africa.

1 Mabey D. Improving health for the world’s poor. BMJ 2007;334:1126. (2 June.)

TRIALS AND ELECTRONIC RECORDS

A frightening industry proposal

The National Care Record Service (CRS), if it is ever deployed, certainly offers amazing potential for pharmaceutical research. The whole COX2/NSAID debacle could have been rapidly resolved by access to the complete prescription records of 55 million people.

But this article sent shudders down my spine about how the Association of the British Pharmaceutical Industry would like to use the service.1 Dr Barker is quoted as saying it would allow drug companies to easily identify patients fitting a trial’s inclusion and exclusion criteria.

Not using anonymised data, it wouldn’t. I suppose it might tell you how many potential candidates there were, but that shouldn’t be too hard to figure out anyway. Anonymised data use for adverse events surveillance is one thing; non-anonymised data to identify potential trial candidates, presumably followed by a direct approach to invite them to join a drug trial, are another matter entirely.

This use is clearly in conflict with current data protection legislation—but Dr Barker should realise this. So why did he propose it?

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Competing interests: None declared.

1 Butcher J. UK will lose clinical trials if electronic records system is delayed, ABPI warns. BMJ 2007;334:1132. (2 June.)
FDA places “black box” warning on antidiabetes drugs

Janice Hopkins Tanne, New York

The US Food and Drug Administration has asked the makers of two antidiabetes drugs—rosiglitazone (marketed as Avandia), made by GlaxoSmithKline, and pioglitazone (Actos), made by Takeda—to place “black box” warnings, the most serious kind, on their labels.

The new labels warn of an increased risk of congestive heart failure. Andrew von Eschenbach, the FDA’s commissioner, announced the warning at a hearing of the US House of Representatives’ Committee on Oversight and Government Reform last week to examine the FDA’s role in evaluating the safety of rosiglitazone.

The new labels do not address the question of whether these drugs pose an increased risk of heart attacks and strokes.

The cardiovascular risk was raised last month by an article and accompanying editorial in the New England Journal of Medicine (doi:10.1056/NEJMo072761).

John Buse, of the University of North Carolina, and the incoming president of the American Diabetes Association, told the hearing that SmithKlineBeecham (now part of GlaxoSmithKline) had tried to intimidate him when he spoke out with his concerns about rosiglitazone’s cardiovascular safety.

Dr Buse said that he had spoken at least twice in June 1999 about “a trend toward increases in serious cardiovascular events and cardiovascular deaths with Avandia as compared to active comparators.”

He said that employees of SmithKlineBeecham had told him in telephone calls that “there were some in the company who felt that my actions were scurrilous enough to attempt to hold me liable for a loss in market capitalisation [share value].” See Editorial, p 1233

Russian clinical research is threatened by ban

Vasilii Vlassov, Moscow

Russia’s Federal Customs Service has blocked the export from Russia of all human biological materials, from hair to tissue and blood samples.

An article in the Russian online newspaper Kommersant says that the decision is thought to have arisen from a report submitted to President Vladimir Putin by the Federal Security Service (formerly the KGB), which warned of the possible development by Western countries of genetic biological weapons against particular nations.

From the end of May the export of materials for clinical research and samples of blood and tissue is forbidden until further notice. Customs officers do not cite any specific document but say that they are carrying out orders.

The decision threatens dozens of clinical trials in Russia, because doctors and scientists need to send many samples abroad to be tested. About two thirds of trials in Russia depend on European laboratory services, and about a half of trials may be stopped because they rely on centralised testing.

The decision also threatens hundreds of patients in Russia who rely on foreign tests for tissue compatibility and such like.

The clinical trials industry is expanding rapidly in Russia and is thought to be worth between $100m (£50m; €75m) and $150m a year. The government’s decision to ban biological exports may have something to do with the struggle to control this growing industry.

Two recent speeches in Russia promoted the idea that Western countries could be developing weapons that would affect specific ethnic groups. In early June Mikhail Zurabov, Russia’s minister of health and social development, said that the development of a genetic weapon against Russia is technically feasible. The next day Andrei Belianinov, head of the Federal Customs Service, was quoted in an interview as saying that the transfer of biomaterials from Russia was equivalent to the “genocide of our nation.” Banning such exports was needed for the “prevention of crime,” he said (Meditsinskaia Gazeta 6 Jun, p 5).
NHS IT system must use unique identifiers to achieve potential

Susan Mayor | LONDON

The new NHS national programme for information technology (IT) must have research built in as a core task, says a report published this week. And it must use unique identifiers for each patient to enable data from different sources to be linked at the level of individual patients if it is to achieve its huge potential for clinical research.

Researchers produced the recommendations after using simulations of clinical studies to test the system.

The programme—the world's largest IT system—is designed to link different computer systems across the NHS, including an NHS care records service that will allow staff from different organisations to access the records of patients anywhere in England.

It has been notorious for its delays and overspends (BMJ 2007;334;815, 21 Apr); but the establishment of connections between different NHS databases, such as those holding primary care records and cancer registry records, could enable researchers to explore a wide range of trends and associations.

To clarify the potential for the use of patients' data from the new IT system, the UK Clinical Research Collaboration, which is the research and development advisory group to Connecting for Health, the agency developing the network, commissioned four simulated research exercises. These exercises were designed to model interventional clinical trials, surveillance, prospective tracking of an identified cohort, and observational epidemiological research.

On the basis of their experience in the simulated exercises, the advisory group recommended that the IT system should make it mandatory to use unique patient identifiers. They proposed that use of the NHS number or its equivalent should be mandatory in all key NHS records and activities, including laboratory records. Currently the use of patient identifiers is recommended but not mandatory.

Ian Diamond, chief executive of the UK Economic and Social Research Council and chairman of the advisory group, said: “To build a complete picture of each patient's health and care, data linkage at an individual patient level will be needed. Pulling information together from different sources for a patient will require a unique identifier for each patient.”

Report of Research Simulations is available at www.ukcrc.org

Gates Foundation funds new institute for global health data

Peter Moszynski | LONDON

The Bill and Melinda Gates Foundation has funded a research centre at the University of Washington in Seattle to help guide international policy making by providing high quality data and analysis of health needs and outcomes. The Institute for Health Metrics and Evaluation, which received a grant of $105m (£53m; €80m) from the foundation, will also assess the performance of health programmes around the world.

“Health policy must be based on evidence, not speculation,” said Tachi Yamada, president of the foundation's global health programme.

“There has been a huge increase in resources for global health in recent years,” Dr Yamada said, “and it's essential to evaluate the impact of these investments.”

The institute's brief is to provide “high quality and timely information on health so that policy makers, researchers, donors, practitioners, local decision makers, and others can better allocate limited resources to achieve optimal results.”

It will be directed by Christopher Murray, who was previously director of the Harvard University Initiative for Global Health and is a former senior official at the World Health Organization.

NICE reviews its guidance against sequential use of anti-TNF

Susan Mayor | LONDON

The National Institute for Health and Clinical Excellence (NICE), the independent body that advises the NHS in England and Wales on use of treatments, has agreed to review its draft guidance against the sequential use of different tumour necrosis factor α (TNF-α) inhibitors in patients with rheumatoid arthritis. It was an adequate response—defined as an improvement in the disease activity score of 1.2 points or more—at six months after treatment started. However, NICE recommended against the use of a second TNF-α inhibitor if a patient had “an inadequate initial response or experienced loss of response later during treatment with a TNF-α inhibitor.”

The institute received six appeals against the appraisal from the
Community care could prevent deaths of thousands of severely malnourished children

John Zarocostas GENEVA
An innovative way of treating severe acute malnutrition, combining timely detection and community based care with traditional hospital treatment for children with medical complications, could help prevent the deaths of hundreds of thousands of children, UN agencies say.

Worldwide about 20 million children under the age of 5 years have severe acute malnutrition, most of whom live in South Asia and sub-Saharan Africa, says the World Health Organization, and about one million die from the condition every year.

The new approach has already greatly improved survival of children with severe acute malnutrition in emergencies in countries such as Ethiopia, Malawi, Niger, and Sudan, the agencies noted.

Evidence shows that about three quarters of children with severe acute malnutrition can be treated at home with highly fortified, ready to use therapeutic foods, says a joint statement issued last week by WHO, the World Food Programme, the United Nations’ standing committee on nutrition, and Unicef.

“Severe acute malnutrition is defined by a very low weight for height, by visible severe wasting, or by the presence of nutritional oedema . . . In children aged 6-59 months, an arm circumference less than 110 mm is also indicative of severe acute malnutrition,” WHO says.

Children with severe acute malnutrition are five to 20 times more likely than well nourished children to die, WHO estimates show.

Margaret Chan, WHO’s director general, said, “It is urgent that this approach, along with preventive action, be added to the list of cost effective interventions being used to improve nutrition and reduce child mortality.”

Ready to use therapeutic foods “have proven very effective in addressing severe acute malnutrition in children,” said Ann Veneman, executive director of Unicef. “So these interventions are an important tool in reducing child mortality.”

Such foods are soft or crushable and can be eaten easily without water by children from the age of 6 months.

Community-Based Management of Severe Acute Malnutrition is available at [www.who.int](http://www.who.int).

NEWS

Severely malnourished children at a Médecins Sans Frontières therapeutic feeding centre in Huambo province, Angola
**Women should be followed for longer after breast cancer**

_Susan Mayor LONDON_

Women who undergo breast conserving surgery for early breast cancer should be followed up for much longer than the three to five years recommended in current guidelines, warns a study published this week. The study shows that relapses can occur at least 10 years after initial treatment.

The study, published in the _British Journal of Cancer_, analysed relapses in 1312 women with early stage breast cancer who underwent breast conserving surgery and postoperative radiotherapy between 1991 and 1998 and who were followed up at two centres in Edinburgh (doi: 10.1038/sj.bjc.6603815). Analysis of the 110 treatable relapses showed that they occurred in 1% to 1.5% of the women in each year of the follow-up period.

But different types of relapse varied in their time scales. The incidence of metastatic relapse peaked at just over 3% a year at two to three years after initial surgery and remained at just over 2% a year for up to five years before decreasing. In contrast, the incidence of locoregional relapse remained constant at 1% to 1.5% over the whole of the follow-up period.

Guidelines in North America and the United Kingdom recommend that follow-up of patients who have been treated for breast cancer concentrate on the first three to five years after initial treatment and that after this follow-up visits should become less frequent or the patient should be discharged.

The Edinburgh study has confirmed previous results showing that the rate of distant relapse peaked in the first five years, but in contrast it found that the incidence of locoregional relapse remained constant, at 1% to 1.5% a year, for at least 10 years.

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**Strike cripples health services in South Africa**

_Pat Sidley JOHANNESBURG_

Some 600 nurses have been fired from South Africa’s public hospitals for taking part in a large civil service strike that has crippled many hospitals, schools, and other government services.

The strike, which is largely about pay and conditions but also signals civil servants’ opposition to the government’s economic policy, has led to many health services effectively shutting down, while others are taking only the most critically ill patients.

The dismissal of the nurses has added new impetus to the strike, which has been running for two weeks and shows no signs of ending.

Nurses, the government maintains, are emergency workers and are not allowed to strike. However, this has not stopped tens of thousands of them, together with other hospital staff across the country, from striking, many of them chanting and dancing angrily outside their hospitals.

Media reports have claimed that patients have died because of the lack of ambulances or because hospitals are providing only limited services. Patients with HIV or AIDS and tuberculosis are also being denied their regular treatment because of clinic closures, they say.

The Chris Hani Baragwanath Hospital, one of the largest hospitals in the southern hemisphere, has been forced to fly premature and sick babies in incubators by helicopters to private facilities. Hundreds of critically ill patients have also been transferred from public to private hospitals, for which the state will have to pay.

The government has sent army personnel...

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**Mortality from 12 top causes in US is still higher among men**

_Roger Dobson ABERGAVENNY_

Mortality is higher among men than women for all the 12 leading causes of death in the United States, a new report shows.

Also, the incidence of most types of cancer is higher among men, who lose 16% more years of potential life before the age of 75 to cancer than women do, the study found.

“Males still experience higher mortality rates than females at all stages of life from conception to old age,” says the report, which was published in the _Journal of Men’s Health & Gender_ (doi: 10.1016/j.jmheg.2007.01.010).

The study, which was based on data from the US Centers for Disease Control and Prevention publication _Health, United States, 2006_, found that the sex difference begins at conception, when 125 boys are conceived for every 100 girls. By birth the ratio has dropped to 105 boys to 100 girls.

By their mid-30s women begin to outnumber men, and by the age of 100 years women outnumber men by a ratio of four to one.

Although the incidence of heart disease and stroke is similar in men and women, men lose many more years of life to these diseases than women do, because they tend to have heart attacks and strokes earlier than women do.

“The years of potential life lost [to stroke] before the age of 75 is 20% higher for men than for women, ie men tend to die of stroke at younger ages than women,” write the authors, from Tufts University School of Medicine in Boston. “A similar phenomenon is seen with acute myocardial infarction, which actually occurs more often in women than in men, but at a later age . . . Men lose approximately 2.3 times more years of potential life before age 75 from coronary heart disease compared to women.”

Their analysis shows that mortality from coronary artery disease, stroke, chronic obstructive pulmonary disease, flu and pneumonia, diabetes, HIV, motor vehicle crashes, homicide, suicide, trauma, liver disease, and cancer are all higher in men. Mortality from all causes is also higher.

In addition, the incidence of lung, colorectal, pharynx, stomach, pancreas, and bladder cancers and non-Hodgkin’s lymphoma and leukaemia are also higher in men. The incidence of cancer in all sites is 46% higher in men than in women.

“These discrepancies between the health of US men and women are striking and call for explanation,” says the report.
US parents take government to court over MMR vaccine claims

Clare Dyer BMJ

The first of three test cases on whether the measles, mumps, and rubella (MMR) vaccine can cause autism opened in the US Court of Federal Claims this week, just days after the hopes of parents in the United Kingdom for a High Court trial of their claims were dealt a final blow.

Last Friday at the High Court in London, Mr Justice Keith disbanded a group action against vaccine manufacturers by 2000 parents who blame MMR for triggering autism in their children.

The UK action ground to a virtual halt in 2004 when the Legal Services Commission withdrew legal aid for the group action, but a few parents soldiered on. Now the few remaining autistic children will have their claims withdrawn or struck out. Only two children, neither of whom has autism, now have public funding to sue manufacturers over the vaccine.

Mr Justice Keith ruled last week, against the parents’ wishes, that three scientific reports commissioned by the manufacturers for the UK litigation may be handed over to the US Department of Health and Human Services, which is fighting claims by 4800 families of children with autism and related disorders under the national vaccine injury compensation programme. The judge ruled that the children’s details must be kept anonymous when the reports are used.

The no fault programme is outside the tort system, but hearings are under the aegis of the Court of Federal Claims. In three test cases, starting with that of 12 year old Michelle Cedillo from Arizona, lawyers for the parents will put forward three theories: that autism, autistic spectrum disorders, and related disorders can be caused by the MMR vaccine, by other childhood vaccines containing the mercury preservative thiomersal (known in the US as thimerosal), or by a combination of thiomersal containing vaccines and MMR.

The case is bound to reignite the controversy that arose when Andrew Wakefield, a gastroenterologist, called for a move to single vaccines at a press conference in 1998 to publicise research indicating possible links between the measles virus, autism, and bowel disease.

UK parents have filed a complaint with the Judicial Complaints Board after discovering that the High Court judge Nigel Davis, who rejected the children’s appeals against the withdrawal of legal aid, failed to disclose that his brother was a main board director of GlaxoSmithKline, the parent company of one of the vaccine manufacturers being sued. A spokesman for the Judicial Communications Office said that the possibility of a conflict of interest arising from his brother’s position “did not occur” to the judge.

Jennifer Horne-Roberts, a barrister whose 18 year old autistic son was one of the would-be claimants, said: “Legal aid has spent £15m (€22m; $30m), not a penny of which came to our children. I think it’s a travesty of justice that we didn’t get a trial in this country.”

Dr Wakefield, who faces disciplinary charges before the General Medical Council, is one of 17 expert witnesses for Michelle Cedillo, whose hearing is expected to last three weeks. If she is successful the US government could be ordered to pay more than $1m in compensation, as well as legal costs.
Hearings highlight mistakes in case of tuberculosis patient

**Janice Hopkins Tanne NEW YORK**

Two hearings last week at the US Congress investigated failings in the case of Andrew Speaker, the 31 year old lawyer from Atlanta who flew to France, Greece, Italy, the Czech Republic, and Canada after being told that he had drug resistant tuberculosis and should not travel on commercial airlines (BMJ 2007;334:1187, 9 Jun).

Health agencies could not prevent him flying, could not locate him on international flights, and were slow to place him on a “no fly” list. The agencies were tardy in notifying the World Health Organization, European countries, and Canada, the hearings found, and a border agent disregarded instructions to stop him.

Congressional representatives called Mr Speaker “a walking biological weapon” and said that if the incident had involved someone with smallpox it could have been disastrous.

The hearings were held by the Senate Appropriations Committee’s subcommittee on labour, health and human services, education, and related agencies and by the House of Representatives’ Homeland Security Committee.

Mr Speaker testified by telephone from the National Jewish Medical and Research Center in Denver. He said that he had been told he was not contagious and that no one forbade him flying.

Mr Speaker’s tuberculosis was detected in January after he underwent radiography for a rib injury. On 10 May his local health department in Fulton County, Georgia, learnt that he had multidrug resistant tuberculosis and advised him not to travel to Europe for his honeymoon.

The department could not forbid him travelling and could act only if he violated an order.

Mr Speaker had planned to travel on 14 May, but on 12 May he flew on a different airline to Paris and then to Greece and Rome. On 12 May, after he had left the United States, the county health department tried to serve him with a written notice advising him not to travel.

Dr Julie Gerberding, director of the Centers for Disease Control and Prevention (CDC), testified that on 18 May the Department of Homeland Security and the CDC began trying to locate him. However, the airline tracking system couldn’t find anyone who had cancelled their original reservations and made entirely new ones.

On 22 May the agencies learnt that he had extensively drug resistant tuberculosis. On 23 May Mr Speaker was contacted in Rome and told to go to an Italian hospital and not to fly.

On 24 May Mr Speaker and his wife flew to Prague and then to Montreal. They drove to the United States that evening and were admitted by a border guard who ignored a computerised alert.

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**IN BRIEF**

**European medicines agency recalls antiretroviral:** Nelfinavir (Viracept), used to treat HIV-1, is being recalled from sale in the European Union after its maker, Roche, revealed that the product had been contaminated with a harmful substance. See www.emea.europa.eu/pdfs/general/direct/pr/25128307en.pdf.

**Virgin sponsors Riders for Health:** To mark the launch on 1 June of its daily flights from Heathrow to Nairobi, Virgin Atlantic has donated 31 motorbikes to help the health outreach charity Riders for Health in rural Kenya. See www.riders.org.

**Coroner warns of needless infant deaths:** Ontario’s deputy chief coroner, Jim Cairns, says that Canadian babies aged under 12 months are dying needlessly because of the increasingly popular practice of letting them sleep with parents or a sibling. Dr Cairns said that a study of 195 investigated deaths between 2004 and 2006 showed that 21 children died in unsafe sleeping environments in 2005, a rise from 16 in 2004.

**Decision making on ending babies’ lives lacks consensus:** The way decisions are made in the Netherlands to end the lives of severely ill and hopelessly suffering newborn babies needs to be clarified through scientific research, says a government advisory committee (www.ceg.m). Despite a new reporting system introduced last year (BMJ 2005;331:1357), no consensus has been achieved over criteria such as the degree of suffering and life expectancy.

**Children of divorced parents are more likely to be taking Ritalin:** The percentage of children taking methylphenidate (Ritalin) is almost twice as high among those whose parents are divorced than among children who continue to live with two biological parents, a study in CMAJ has found (doi: 10.1503/cmaj.061458).

**New toolkit delivers human rights approach to health:** A “Right to Health” toolkit has been launched by the BMA and the Commonwealth Medical Trust to help expose situations where public funds are being used unfairly, such as the construction of more hospitals in large cities or the purchase of expensive equipment that will benefit wealthy or urban populations, while rural populations or vulnerable groups are denied even the minimum standard of health care. See www.bma.org.uk.

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**NHS ends the year £500m in surplus**

**Michael Day LONDON**

The NHS in England has turned the corner on its financial problems, without reducing productivity or harming care, the government said last week.

Unaudited figures indicate that although the NHS finished the financial year 2005-6 in deficit, to the tune of £547m (£810m; $1.1bn), it had finished 2006-7 with a surplus of £500m.

The health secretary, Patricia Hewitt, claimed that the government’s insistence on cost cutting measures had turned things around.

“If we had not taken decisive action then the deficit would have doubled again and would almost certainly have doubled again next year,” she said.

She added that the government had managed to “change the culture in a minority of NHS organisations that expected, year in, year out, to be bailed out” by other parts of the NHS.

“It now means that the NHS is in a very strong position to use the extra £8bn this year on the new drugs and better services that patients rightly expect to get on the NHS,” she said.

David Nicholson, chief executive of the NHS, claimed that services to patients had continued to improve as belts were tightened—despite the fact that hundreds of clinical posts were axed in the past 12 months.

“We have done what we said we would do: we’ve delivered...
New regulations aim to prevent international health crises

Peter Moszynski LONDON

New regulations concerning public health emergencies came into force this week, revising the rules that have been in force since 1969.

The regulations were agreed at the 2005 World Health Assembly and have a far wider scope than the previous ones, including procedures for dealing with new and re-emerging diseases and chemical or radiation events.

The revision broadens the scope of notification to the World Health Organization—from cases of cholera, plague, and yellow fever to “all events which may constitute public health emergencies of international concern and the reporting of other serious international health risks, irrespective of origin or source.”

The regulations were originally intended to help monitor and control six serious infectious diseases—cholera, plague, yellow fever, smallpox, relapsing fever, and typhus—but the last three were dropped in 1969. In the early 1990s the resurgence of epidemics such as cholera in parts of South America and plague in India, and the emergence of new infectious agents, such as Ebola haemorrhagic fever, resulted in a resolution at the 48th World Health Assembly in 1995 to revise the regulations.

The new regulations require automatic notification to WHO of smallpox, wild polio virus, severe acute respiratory syndrome, and new human subtypes of avian flu. The International Health Regulations are available at www.who.int.

Financial performance of primary care trusts in England in 2006-7

Financial stability and improved services for patients,” he said. Critics noted, however, that more than a fifth of NHS trusts in England were still in the red last year (down from a third in 2005-6) and that these trusts had accumulated a deficit of nearly £1bn that still had to be plugged.

Niall Dickson, chief executive of the healthcare think tank the King’s Fund, said, “Today’s figures cannot disguise the fact that the gross financial deficit figure facing the service is £911m, although it is good news that this has improved from the 2005-6 figure of £1.3bn.”

“It is still concerning that more than a fifth of organisations (22%) are responsible for the overall gross deficit now.”

And he added: “The truth is that turning around persistent and underlying deficits can take time and may involve significant changes.”

Gill Morgan, chief executive of the NHS Confederation, which represents most NHS trusts, was more upbeat. She said, “Today’s figures show that because of the hard work and commitment of NHS staff the vast majority of NHS trusts are getting back on track financially.”

However, Universities UK, the vice chancellors’ umbrella body, claimed that the surplus had in part been achieved by raiding education budgets (BMJ 2007;334:388-9). NHS Financial Performance Quarter Four 2006-07 is available at www.dh.gov.uk.

Government says it is consigning waiting lists to history

Michael Day LONDON

The UK government has said that an end to long waiting times for treatment in the NHS in England is finally in sight.

The health minister Andy Burnham said that long delays between referral by GPs and treatment in hospital would be banished for good—with no one waiting more than 18 weeks—by December next year.

New figures show that in March 2007 just under half of all patients in England received their first hospital treatment within 18 weeks of GP referral.

The figures also showed, however, that one patient in eight was still waiting more than a year for treatment.

Nevertheless, Mr Burnham insisted that the latest figures provided firm evidence of progress made towards the December 2008 deadline.

He said, “When it gets there, it will be a huge achievement. And many will be first seen by their GP and then treated in hospital within 10 weeks.

“This is in my view the end of waiting. I think this represents the end of the culmination of our 10 year programme.”

Health unions and NHS managers gave qualified support to Mr Burnham’s claims.

Jonathan Fielden, chairman of the BMA’s consultants’ committee, said, “The fact that almost half of all patients are being treated in 18 weeks is encouraging and is a testament to how hard NHS doctors and other health professionals have been working.”
Exercise and physiotherapy advice help subacute low back pain only in the short term

A four arm multicentre trial recruited 259 people with subacute low back pain. The duration of symptoms at baseline was more than six weeks but less than three months. Patients were randomised to receive a combination of 12 real or sham exercise sessions with a physiotherapist and three real or sham advice sessions over six weeks.

Compared with the sham interventions, real exercise and real advice separately reduced pain (advice: −7 points, 95% CI −1.2 to −0.2, P=0.011; exercise: −0.8 points, −1.3 to −0.3, P=0.004) and improved global perceived effect (advice: 0.8 points, 0.3 to 1.2, P<0.001; exercise: 0.5 points, 0.1 to 1.0; P=0.017) in people with subacute low back pain, but only at six weeks. Compared with sham exercise and sham advice, a combination of real exercise and real advice also improved these outcomes at six weeks (pain: −1.5 points, −2.2 to −0.7, P=0.001; global perceived effect: 1.3 points, 0.7 to 1.9, P<0.001), in addition to function (effect 1.1 points, 0.3 to 1.9, P=0.006).

However, all the effects were smaller at three months, and most were non-significant at 12 months of follow-up. At 12 months, the combination of real exercise and real advice significantly improved function (effect 1.1 points, 0.3 to 1.8, P=0.005) when compared with a combination of sham exercise and sham advice. Although both interventions are widely used for low back pain, this is the first trial to compare the effects of exercise and advice with placebo in people with strictly defined subacute low back pain.

Ann Intern Med 2007;146:787-96

The evidence on gene mutations in hereditary diffuse gastric cancer is accumulating

Hereditary diffuse gastric cancer is an autosomal dominant syndrome of cancer susceptibility. It is caused by germline mutations in the epithelial cadherin (CDH1) gene and is characterised by a high risk for early onset diffuse gastric cancer or lobular breast cancer. The ability to detect CDH1 mutations and thereby identify the syndrome might help prevention in affected people through prophylactic gastrectomy or surveillance for breast cancer. It is still a challenge, however, to tell whether a change in a gene sequence is a benign polymorphism or a pathogenic mutation.

A study published last week, authored by an international group of researchers, reported the clinical and genetic findings in 38 families with hereditary diffuse gastric cancer. In 26 families, at least two people were diagnosed with diffuse gastric cancer, and one case was in a person younger than 50 years. Other included families had either one family member diagnosed with diffuse gastric cancer before 35 years of age, or several people diagnosed after 50 years.

The researchers were able to detect 13 mutations in 15 of the 38 families, which is in accordance with the data on test sensitivity from previous reports. It seems that either we haven’t discovered all of the genes that contribute to this disease, or some mutations are too difficult to identify at the moment. Still, more than a half of the mutations found in the study were recurrent, compared with only 10% reported in previous studies.

Using haplotype analysis, the researchers were also able to demonstrate that some of the mutations were independent in their origin, while others were due to common ancestry.

JAMA 2007;297:2360-72

Lowering homocysteine doesn’t reduce the risk of thromboembolism

Observational studies have found an association between raised total homocysteine concentrations in the serum and venous thromboembolism. Homocysteine is thought to promote thrombosis by enhancing platelet aggregation, increasing thrombin generation, impairing fibrinolysis, and causing endothelial dysfunction.

A placebo controlled trial carried out in 145 centres in 13 countries enrolled more than 5500 people who were over 55 years, had cardiovascular disease or diabetes mellitus, and had at least one other risk factor for atherosclerosis. Patients were randomised to a daily supplement of 2.5 mg of folic acid, 50 mg of vitamin B₁₂, and 1 mg of vitamin B₉, or placebo and were followed up for five years.

As expected, the intervention decreased total plasma homocysteine concentrations, but this wasn’t coupled with a change in the risk for symptomatic deep venous thrombosis or pulmonary embolism. In the intervention group, the mean plasma homocysteine value decreased by 2.2 µmol/l, while it increased by 0.80 µmol/l in the group randomised to placebo. Nonetheless, compared with the group that received placebo, people who received the vitamins had a hazard ratio of 1.01 (95% CI 0.66 to 1.53) for venous thromboembolism, 1.04 (0.63 to 1.72) for deep venous thrombosis, and 1.14 (0.57 to 2.28) for pulmonary embolism.

Thus, decreasing homocysteine concentrations with folic acid and B vitamins did not reduce the risk of symptomatic venous thromboembolism in these patients. Because the lack of efficacy of this treatment was independent...
of plasma concentrations of homocysteine in this trial’s population, measuring plasma homocysteine in older adults with thromboembolism may not be justified. It may still make sense in children and young adults with venous thromboembolism or arterial thrombosis, the authors say.

**Ann Intern Med** 2007;146:761-7

**Preoperative chemotherapy improves outcomes in non-small cell lung carcinoma**

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Eprodisate slows kidney decline in amyloid A amyloidosis

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Amyloid A amyloidosis is a rare complication of chronic inflammatory diseases and chronic infections. In this condition, a proteolytic fragment of serum amyloid A protein—an acute phase reactant produced in the liver—is deposited extracellularly in the tissues as insoluble fibrils. Such deposition causes progressive dysfunction of organs and, eventually, death. A new drug, eprodisate, inhibits polymerisation of amyloid fibrils and their deposition in tissues, and it seems to slow down the decline in kidney function seen in people who have nephropathy associated with amyloid A amyloidosis.

A recent multicentre randomised trial that included 183 people with amyloid A amyloidosis compared eprodisate with placebo. After two years, disease had worsened (concentrations of serum creatinine had at least doubled or creatinine clearance had declined by 50% or more) in 27% of patients randomised to eprodisate, compared with 40% of those who received placebo. The difference, however, did not reach statistical significance (P=0.06). Furthermore, the decline in creatinine clearance was 10.9 ml per minute per 1.73 m² of body surface area in patients randomised to eprodisate, compared with 15.6 ml m² of body surface area in those randomised to placebo (P=0.02). Eprodisate had no effect on progression to end stage kidney disease or the risk of death (hazard ratio 0.54, P=0.29).

Almost all participants in the trial had at least one adverse event, and more than a third had at least one serious adverse event. The incidence of adverse events was similar in the two study groups.

The authors conclude that eprodisate delays the progression of renal disease associated with amyloid A amyloidosis, and they suggest that this drug might be useful in other types of amyloidosis, including familial amyloidosis and Alzheimer’s disease.

**N Engl J Med** 2007;356:2349-60

**Anti-CCP antibodies are more specific than rheumatoid factor for diagnosing rheumatoid arthritis**

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Serum concentrations of antibodies against cyclic citrullinated peptide (anti-CCP) seem to be just as sensitive and more specific than rheumatoid factor for diagnosing rheumatoid arthritis and predicting its progression.

A systematic review and meta-analysis included 37 studies that looked at the diagnostic accuracy of anti-cyclic citrullinated peptide antibodies and 50 studies that assessed the diagnostic accuracy of rheumatoid factor. While the sensitivities were 67% (95% CI 62% to 72%) and 69% (65% to 73%) for anti-cyclic citrullinated peptide antibodies and IgM rheumatoid factor, respectively, the specificity for anti-cyclic citrullinated peptide antibodies was 95% (94% to 97%), compared with 85% (82% to 88%) for IgM rheumatoid factor.

Early diagnosis and treatment of rheumatoid arthritis are crucial to avoid irreversible damage to the joints. Because rheumatoid factor can be present in the plasma of healthy people and people with autoimmune diseases other than rheumatoid arthritis, using anti-cyclic citrullinated peptide antibodies can be of great help in making the diagnosis. The authors propose that these antibodies should be officially recognised as a diagnostic marker, but also acknowledge that publication bias may have played a role in the favourable results.

**Ann Intern Med** 2007;146:797-808
European education ministers have big changes in mind for higher education. Their vision sees students moving between Europe’s universities, taking courses that all count towards comparable qualifications, and, as a result, finding it easier to move around as employees. Governments hope that promoting this agenda will make their universities more attractive around the world and deliver a supply of high quality graduates to the workplace.

They signed up to the idea with a declaration in Bologna in 1999. Since then, despite a low profile in some countries, the wheels of the Bologna process have been turning steadily, bringing closer the goal of a common European higher education area by 2010.

Medicine, however, seems to have been left behind. It is not that medical educators disagree with the Bologna process’s main points, and indeed it would be hard to argue that more exchange within European institutions, more comparable qualifications, and overall higher standards would be a bad thing.

The most obvious problem is that in the Bologna model, harmonisation of the course of study across Europe has meant countries adapting their curriculums to fit a two cycle model, with a three year bachelors degree and a two or three year masters. Ministers agreed to this from the outset, and have reaffirmed it since then, even though it has required considerable upheaval in the many countries where longer study culminating in a masters level degree has been the norm. By the time education ministers met in London in May this year, most declaration signatories were well on the way to making the necessary changes.

**Fitting to the model**
The two cycle model is meant to make it easier for students to move after their bachelors degree either to the job market or to further study in another geographical or subject area. Those who want to continue up to masters level in their original subject can do so, but students who do not are no longer forced to carry on or miss out completely. But this fails to recognise inherent differences between the study of medicine and that of most other subjects, medical educators say.

**MEDINE**
The Thematic Network on Medical Education in Europe (MEDINE) [www.bris.ac.uk/medine](http://www.bris.ac.uk/medine) aims to address educational, institutional, and quality issues in European medical education within the framework of existing European initiatives such as the Bologna process and the European Credit Transfer System. Task forces work on five main activities:

- Agreeing core competencies/learning outcomes for medical education in Europe
- Developing a framework for international recognition of qualifications
- Developing quality assurance standards for the process of medical education for application in Europe
- Enhancing the transparency and public understanding of medical education
- Exploring and developing links between medical education and research.

MEDINE is supported by the European Commission and has more than 100 universities and organisations as partners.

**THE COURSE LEFT OUT IN THE COLD**
Education ministers hope that students and staff will be able to move freely between European universities by 2010. But medicine is being left behind, as Toby Reynolds explains.
The aim would be that you would have people entering into a bachelors programme and at the end of the three years they would have amassed a certain number of credit points. They would then be able to take their credits and go off to do the next two years, the masters, in another European institution,” says Gareth Williams, dean of the faculty of medicine and dentistry at the University of Bristol. Professor Williams is also coordinator of MEDINE, a network set up to look at how European initiatives such as the Bologna process can be best applied to medical education, although he stresses he does not speak for the group:

“It was felt that within Europe there wasn’t enough exchange of ideas and exchange of people, exchange of students. Bologna was also seen as a way of raising the standards in areas of Europe that are bad, by exposing them to best practice elsewhere and by raising students’ expectations. The basic concept is actually quite a good one, and it is applicable to lots of humanities and even the basic sciences. The trouble is that it doesn’t actually lend itself to lots of medical curricula.”

That is largely because medical education in most European countries has moved away from the division between preclinical and clinical study that could have easily fitted into a two cycle course. The curriculum is now more integrated, with clinical and communication skills and contact with patients introduced early in the course.

“Most medical schools are now striving towards complete integration of the basic sciences and the clinical sciences,” says Hans Karle, president of the World Federation for Medical Education. “This will be a problem with this two cycle system, because then you will immediately try to separate the two parts into the basic sciences followed by the clinical sciences.

“Of course that was actually the traditional way of teaching in the past. In all parts of the world we are trying to introduce this integration, and I think it would be harmful to this process if we were not allowed to plan the medical curriculum as a one tier system.”

In addition, medical schools might take on more bachelors candidates than they intended to allow on to the masters programme. As the world federation points out, it is not clear what other employment or course of study would be suitable for bachelor students who did not go on to finish medical studies. And even if courses were split into two, different national quality assurance and certification criteria and language barriers would probably make mobility between different countries’ medical education systems difficult.

Notwithstanding these objections, several countries are adapting their medical education systems to fit the Bologna model. Switzerland has switched to a two cycle system, with theoretical mobility between its medical schools after the bachelor stage. Denmark has introduced a bachelors degree for all medical students after three years of study, although its curriculum is still integrated and no-one is expected to leave at that point. And Spain, France, Austria, Belgium, and the Netherlands have also

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**BOLOGNA PROCESS**

The Bologna process began officially in 1999 when education ministers from 29 European countries signed the Bologna Declaration, pledging to adopt a system of comparable degrees, based on undergraduate and graduate cycles.

They also promised to take steps to increase mobility of students, teachers, and researchers, including the adoption of a system of transferable credits, and to promote European cooperation on issues such as quality assurance and curriculum development.

Subsequent meetings have added the doctoral level as a third stage on top of the bachelors and masters degrees, and have called for the implementation of national qualification frameworks, among other objectives. The ultimate aim is to establish a European higher education area by 2010.

The process has been largely driven by higher education leaders, rather than by the European Commission, and remains a voluntary inter-governmental initiative. By the end of May 2007, 46 countries were signatories to the declaration.

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“The trouble is that [the basic concept of Bologna] doesn’t actually lend itself to lots of medical curricula”
considered ways to introduce the two cycle system.

Concerned by the implications of this trend, the world federation called in 2005 for medical schools to be able to opt out of the two cycle system. But higher education ministers at the London meeting in May did not mention this point. “It doesn’t appear anywhere in the ministerial communiqué. It appears that it is a subject that wasn’t covered,” says David Gordon, president of the Association of Medical Schools in Europe.

Since the Bologna model does not carry the enforceable weight of an international treaty, the realisation of its aims is down to the legislative will of signatory governments. As such, UK medical schools are unlikely to be forced to use the two cycle model, Professor Gordon says. “I don’t think it could creep up on us and happen without warning. I think there is enough understanding that things have to be done sensibly.”

Better standards

Some argue, however, that the Bologna process represents an opportunity for reform. “At a minimal level Bologna could mean that we simply award a bachelor of medicine degree to all of our students after three years of medical school, which in a sense wouldn’t change anything, it would almost be a ghost degree,” says Allan Cumming, director of undergraduate learning and teaching at the University of Edinburgh’s medical school.

“If you take medical students who have been at university for five or six years, they deserve something way beyond an ordinary bachelors degree, so I see it as desirable from that point of view.”

But he adds that such a change could also be an opportunity to modernise curriculums and particularly to start looking at what a student should have learnt on a course. “I think that if you have an appropriate set of learning outcomes for bachelor of medicine, which are clinical enough and medical enough, then it could actually be an aid to integration for those schools that currently just teach science for three years.”

The issue of learning outcomes touches on an important role for the Bologna model in improving medical education. Professor Cumming leads a group in the MEDINE network looking at learning outcomes, using a process called tuning. Tuning was initiated by a group of European universities in 2000 to identify common points of reference for generic and subject specific competencies.

“A lot of the role of Bologna is to tidy things up,” he says. “What medical degrees are called across Europe, how much study is involved, what kind of degree they are, whether or not they entitle the graduate to practise medicine. If you look across Europe there is no uniformity of practice, and in a situation where we are supposed to treat all European medical graduates equally for job applications, that to me is totally unacceptable.

“That’s why we think our tuning project is quite important. We are starting to say these are areas of the curriculum that at least you mustn’t have forgotten about completely. We are not being hugely prescriptive about exactly what the competencies or learning outcomes should be but at least here are the big headings that you have got to have.”

Dr Karle, who leads a MEDINE group looking at quality assurance standards, points out that the Bologna model is not about standardisation, rather about harmonisation and compatibility.

“People might get the feeling that the Bologna process is heading towards a common system of quality assurance, for instance a common European accreditation system of medical schools and their programmes. I don’t think this is feasible in a foreseeable time,” he says. “We think that what is needed is to have approved standards and let medical schools work with these standards in their reform process, and then we could also use these standards in national accreditation systems.”

Many of the changes that will take place under the Bologna model were on the cards for European higher education anyway, Dr Karle says, especially items like transferable credits, enhanced mobility, and promotion of lifelong learning. In addition, he adds, medical education has been slowly moving towards greater harmonisation in Europe since the introduction of European Union directives recognising professional qualifications in 1975.

“The Bologna model may just help that along, or it may prove a catalyst for more radical change, but coming from within the universities, not imposed from outside.

“What really matters is that all medical degrees in Europe are regarded as the same under European employment law when they patently are not,” said Professor Cumming.

“It will take a long time to alter that situation, but at least some sort of start ought to be made in my view. In order to make a start there has to be an acceptance that actually there is a European dimension to medical education, that it is not just a national issue or an institutional issue. That is what a lot of people take issue with, they say it has nothing to do with Europe.”

Toby Reynolds is a medical student and former Reuters journalist, St George’s, University of London, London SW17 ORE. Toby.reynolds@gmail.com

Competing interests: None declared.


Why don’t journalists mention the data?

Have stories about “electrosensitivity” simply been lifted from those promoting this new diagnosis?

 Sometimes, as a doctor who also writes in the newspapers, a dark thought comes across me: wouldn’t it be so refreshing—secretly, wouldn’t it feel so free—to leave the medical thing behind, and just make stuff up, say what I want, spin any story that pleases me, or any story that sells, and gaily ignore the evidence?

For two years now the British news media has been promoting the existence of a new medical condition, called electrosensitivity, or electromagnetic hypersensitivity. The story—or in medical terms the hypothesis—is that a wide range of symptoms are caused by acute exposure to electromagnetic signals, and that these symptoms are ameliorated by this signal being removed.

The features have a lot in common with what might often conventionally be called “medically unexplained symptoms”: tiredness, difficulty concentrating, headaches, nausea, bowel complaints, aches in the limbs, crawling sensations or pain in the skin, and more, for which no explanation is found. Such symptoms have existed since long before the appearance of “electrosensitivity,” and the absence of a clear cause is extremely troubling to both patients and doctors.

If these symptoms were caused by electromagnetic signals, then it should prove possible to study that, ideally in double blind conditions: and yet the media coverage invariably focuses on the scandal of how research into this area has been neglected. But most crucially, there is no mention that this single selected subject in a single unpublished study produced a result that seems to conflict with a literature of 37 studies that have been completed, published, and are overall negative. If this whole Essex study was positive, while it might make an interesting small splash next to the other 37, it would need to be replicated and considered in the context of the negative findings. The alternative is chaos, and being blown in the wind by every Type I error.

So why doesn’t the media ever mention this data? Perhaps they deliberately and mischievously leave it out. Perhaps they never came across it, and are incompetent. Or perhaps they simply lifted their stories verbatim from aggressive and well coordinated lobbyists who promote this new diagnosis (some of whom also sell expensive equipment to sufferers, such as insulating paint at £50 a litre, and insulating beekeeper hats for trips outdoors).

Not only do these lobbyists observe a monastic silence on the issue of the provocation studies, but they also viciously attack anyone who even dares to mention the data, accusing them of insensitivity, of attacking sufferers, and of denying the reality of their symptoms.

The lobbyists viciously attack anyone who even dares to mention the data, accusing them of insensitivity, of attacking sufferers, and of denying the reality of their symptoms.

Their symptoms over time, without knowing if the phone is on or off.

There have now been 37 such double blind “provocation studies” published in the peer reviewed academic literature, and they are almost all negative, although you could argue that the evidence is unanimous. There are, to be clear, seven studies that did find some statistically significant effect for electromagnetic signals: but for two of those, even the original authors have been unable to replicate the results; for the next three, the results seem to be statistical artefacts (one tailed t-tests—presumptuous, you might say—and problems with multiple comparisons); and for the final two, the positive results are mutually inconsistent (one shows worsened mood with provocation, and the other shows improved mood: still sure a one tailed t-test is reasonable?).

These studies test the very hypothesis reported on repeatedly in the media: symptoms are brought on by exposure to a source of electromagnetic signals, and cease when the source is removed. And not only are the studies ignored, but sometimes it feels like the media are actively teasing us. A recent Panorama documentary on BBC 1 covered the possible dangers of Wi-Fi computer networks, and what little evidence the programme did present was flawed in a number of ways.

A large chunk of the programme was devoted to electrosensitivity. It covered the question of testing the phenomenon, in a double blind study. The programme makers even followed someone into a lab at Essex University where they had participated in one provocation study. We are told that this subject did correctly identify when the signal was present or absent two thirds of the time, to a visual backdrop of sciency looking equipment.

But this was anecdote dressed up as data. The study is currently unpublished. We don’t know the protocol, or whether 2/3 for one subject would be statistically significant (there may be only three exposures in total, for example). We don’t know the results of the other subjects. But most crucially, there is no mention that this single selected subject in a single unpublished study produced a result that seems to conflict with a literature of 37 studies that have been completed, published, and are overall negative. If this whole Essex study was positive, while it might make an interesting small splash next to the other 37, it would need to be replicated and considered in the context of the negative findings. The alternative is chaos, and being blown in the wind by every Type I error.

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Symptoms, of course, stand as real, regardless of their cause; and if you were going to offer guilt trips around, you could fairly argue that those who obfuscate on the causes are themselves hindering better understanding and treatment, and so harming patients.

Ben Goldacre is a doctor and writer, London ben@badscience.net
The newspapers love a bogeyman. And big pharma fits the bill perfectly. The image of obscenely well paid executives ripping off the NHS and poisoning the masses for the sake of quick profits has united newspapers of all political persuasions in a deep-held suspicion of the companies’ method and motives.

During my stint as the Sunday Telegraph’s health correspondent, under the impeccably right-wing and laissez-faire reign of Dominic Lawson, bashing drugs companies always guaranteed you space in the paper. And bear in mind this was a publication that considered global warming something invented by Marxists in order to undermine the oil industry. If, however, you tried to move the argument on a little from “drugs companies are evil” to “the regulators are to blame,” news editors’ eyes would glaze over.

The British press has been quick to report concerns about “disease mongering” by the drugs industry as well as safety fears over Vioxx (rofecoxib), Seroxat (paroxetine), Avandia (rosiglitazone), and others. But it has largely been left to campaigners such as Charles Medawar in Social Audit to tackle the failings of the Medicines and Healthcare products Regulatory Agency—and to call for the heat to be turned up on the people who regulate drug companies, rather than simply demonising these profit-making organisations for cutting corners and doing what they do best . . . making profits.

No so in the United States, where thorough newspaper reporting of the Food and Drug Administration’s inadequacies has prompted members of the US Congress to now push for proper post-marketing surveillance of new medicines, and even for the FDA to be split into two separate bodies—one that awards drugs licences, and another that continues to monitor safety and has the power to rescind them.

The real impetus behind these calls for change has been the Vioxx disaster. The agency’s failure to act more quickly on Vioxx, and the behaviour of key figures within the organisation are probably the most alarming aspects of a new investigative documentary on the dark side of the pharmaceutical industry, We’ll Take Care of You by Latanzio Firmian and Alberto Baudo.

The film makers begin with some predictable attacks on big pharma. Drugs company executives are portrayed as Wild West villains and predatory animals. Victims of drug side-effects are nice, ordinary Joes who were just fine until they started taking the tablets—though it’s worth recapping the extent of the Vioxx scandal. Merck’s own paper in the New England Journal of Medicine in June 2000 found that the drug increased users’ risk of stroke or heart attack by four to five times. But despite this risk being in the public domain in June 2000, Merck continued to promote and sell the osteoarthritis treatment until its withdrawal in September 2004. By this time an estimated 60000 people who had been prescribed the drug in the US alone had died from stroke or heart attack.

But it’s when the film focuses on the FDA’s role in the Vioxx affair that things get really interesting. Despite the publication in June 2000 of the pivotal NEJM paper highlighting the cardiovascular risk posed by Vioxx, the FDA took no action.

In September 2001, the FDA said in a
letter to Merck that the company’s assertion that Vioxx was safe for the heart was “simply incomprehensible.” Still it took no action. The following year, the warning label on the Vioxx packets was finally changed to alert patients to cardiovascular risks.

Seen squirming under questioning by Congressional investigators in the documentary, Steven Galson, the director of the FDA’s Center for Drug Evaluation and Research, agreed that even this modest label had taken “longer than it should have.” And his explanation for the delay? “We were trying to work out exactly what was acceptable to both sides.”

Yes, you read that correctly. The issue of a mass-market medicine for a non life-threatening disease raising the risk of heart attack by 500% in millions of people was not a public health emergency in the FDA’s eyes, but simply a source of 18 months’ polite negotiation—with the protection of the manufacturer’s commercial interests evidently high on the agenda.

Almost as bad, the documentary showed how one of the chief whistleblowers at the FDA, David Graham of the FDA’s Office of Drug Safety, needed Congressional protection in order to keep his job after threats and abuse culminated in his sacking from the agency.

Galson has retained his job of head of the Office of New Drugs at the FDA. The FDA’s Commissioner, Lester Crawford, who also came under fire for his role in the Vioxx scandal, quit the agency and has since taken up a job lobbying on behalf of the pharmaceutical industry.

Cynics would say this is why FDA executives make life easy for big pharma—they’re thinking of a cushy six-figure salary there in the not too distant future.

Some of the campaigning elements of the US Congress have the bit between their teeth now—one of the key movers, Democrat Henry Waxman, is leading the attack on the FDA over its handling of rosiglitazone, the GSK diabetes treatment that is also under suspicion for raising patients’ heart attack risk.

And there’s little sign of the press relenting. It would appear that even Washington DC’s mighty pharmaceutical lobbying machine will have its work cut out to prevent some major changes to drug regulation.

Given the depressing similarities between US and European drug regulation—the reliance on industry funding, the dearth of post-marketing surveillance, etc—perhaps it’s time for our policymakers and journalists to start asking a few more questions this side of the Pond.

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WHAT'S ON THE WEB

What’s so precious about originality?

Research aside, the efforts contributors to medical and science journals are forced to go to to avoid self plagiarism are just a waste of time, writes Simon Chapman

The ethics of banning smoking outdoors (I am opposed) is something that I have written on several times, most recently at length in a forthcoming book (Public Health Advocacy and Tobacco Control: Making Smoking History. Oxford: Blackwell, 2007).

This issue has got up some worrying momentum lately and so I find myself being asked to increasingly speak and write about it. I tell those asking me that I have little more to add than I have already written in my previous contributions, yet they insist they want yet another, “different” piece. What is the point, precisely, in me spending hours manicuring, paraphrasing, and in every other way trying to express the same basic arguments that I originally felt I expressed as well as I could? All in the name of not “self plagiarising.”

I can play around with trying to top, tail, and middle things differently, but if the core of what I’m wanting to say is essentially the same, and I’m running into agendas about originality, what is more important here?

Media outlets all over the world daily buy exemplary articles, syndicated columns, features, etc, in recognition that their readerships will not have read a piece that was originally published elsewhere, the web notwithstanding. Why do we in the health and medical specialist journal media feel so precious about originality? When it comes to original research I well understand the point, but many editors on this list are editing journals whose standard fare goes beyond original data into policy analysis and contributions designed to leverage change in some of the world’s most pressing problems (climate change, violence, poverty, obesity, etc).

Anyone who thinks that only data, rather than interpretation and commentary, change the world should get off at the next stop.

Ought we not to differentiate between original data and analysis/commentary? Do we really believe that humanity is best served by the straitjacket of requiring debates, policy advocacy and commentary to always be wholly original? Do we really believe that significant contributors to these debates really only deserve one bite at expressing their best shots, and if the rest of the world happens to miss out on their original contribution in “Calathumpian Journal of Significant Issues,” this is just too bad . . . all in the name of preserving publishing integrity?

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This is an edited version of an article that appeared on the listserve of the World Association of Medical Editorson 30 May 2007.
Delay in fortifying flour with folic acid is unjustified. In many countries this public health measure has increased blood folate levels and reduced neural tube defects. When the effect of folic acid on neural tube defects was shown in 1991, prevention was attempted through diet and supplements. But supplements must be taken before pregnancy is confirmed, and most pregnancies remain unprotected.

Voluntary fortification has proved inadequate. Expert advisory committees considering mandatory fortification with folic acid have concluded that it is necessary, effective, and safe; about 40 countries, including the United States, have adopted this policy.

It is important to reach people who are less well off—they have most to gain from fortification. In Chile, where fortification has achieved a relatively high folic acid intake, neural tube defects were reduced by 43%; in the United States, with a lower fortification level, the reduction was about 20%. With fortification on a global basis, each year about 250,000 children could be saved from spina bifida or anencephaly and the devastating consequences. This public health opportunity should not be lost.

Evidence indicates other benefits from folic acid fortification: a modest but important protection against cardiovascular disease and a suggested reduction in the evidence of a cleft lip and in the rate of cognitive decline with age. We consider the scientific validity of four concerns that are raised against fortification.

### Link with cancer

If judgment were to be made, it would be that folic acid prevented cancer, not that it caused it. The US nurses’ health study followed 88,756 women prospectively, and indicated that long term use of folic acid may substantially reduce the risk of colon cancer. After 15 years, the relative risk was 0.25 (95% confidence interval 0.13 to 0.51), representing 15 instead of 68 new colon cancers per 10,000 women aged 55 to 69.

A meta-analysis of seven cohort and nine case-control studies of colorectal cancer found an overall reduction in risk with folic acid intake. Smaller cohort studies have been cited to show that low folate may protect against colorectal cancer, but this interpretation arises from a data subset analysis, is probably due to chance, and is unsupported by the overall results of the trial.

The aspirin-folate prevention trial concluded that folic acid did not result in a significant decrease in large bowel adenomas, but absence of benefit is not equivalent to the presence of harm. An observed increase of borderline significance was not considered a real effect. Random differences between groups are common in small trials; for example, there were half the number of deaths from all causes in the folic acid group compared with the control group in this trial, which does not mean that folic acid protects against all deaths. A meta-analysis showing a relative risk of 0.99 (0.98 to 1.01) for breast cancer and folate indicates that folic acid neither increases nor decreases the risk of breast cancer. It is important not to overinterpret marginally significant associations from individual studies (such as one on breast cancer); such associations can arise by chance, confounding, or both. The evidence on folic acid and cancer is that there is no harm, and there may be a long term benefit on colorectal cancer.

The case for fortification is sufficiently made on preventing neural tube defects, irrespective of cardiovascular disease prevention. Until recently, the randomised trials of folic acid and cardiovascular disease lacked the statistical power to show that lowering homocysteine by folic acid has a preventive effect, though the HOPE-2 study showed a significant reduction in strokes. A meta-analysis has now confirmed this. The genetic polymorphism studies also indicate that homocysteine is a cause of cardiovascular disease.

The assertion that folic acid exacerbates B-12 deficiency is without scientific foundation. It is based on reports published more than 50 years ago, when patients with B-12 deficiency had unknowingly been incorrectly treated with folic acid instead of B-12, so the neurological consequences of untreated B-12 deficiency progressed while the macrocytic anaemia (indistinguishable from that due to folate deficiency) improved because high dose folic acid can reverse the arrest of DNA synthesis that causes a B-12 macrocytosis deficiency. The doses of folic acid used in fortification are below those which resolve the anaemia associated with B-12 deficiency. Moreover, these concerns are unwarranted, because the clinical consequences of B-12 deficiency can be avoided by awareness of the neurological nature of B-12 deficiency, the application of the appropriate biochemical tests, and treatment with B-12.

Synthetic folic acid is ideal for fortification: it is more bio-available than natural folate and, unlike natural folate, is stable in food, even during cooking. It is readily absorbed into the bloodstream—an advantage, as folic acid must pass from the mother’s blood to the fetus to be effective. Millions of people have consumed folic acid as supplements for decades before fortification and as a result have had free folic acid in their blood with no credible evidence of any adverse health effects.

### Overall assessment

Folic acid fortification shows clear benefit in preventing spina bifida and anencephaly, with substantial evidence on safety, and no valid indication of harm. Public health authorities have a responsibility to take action, recognising that failure to fortify has serious health consequences; withholding a benefit causes harm.

**Competing interests:** GPD is a co-inventor (while at CDC, compensation, if any, will be under the regulations of CDC) of a patent that covers adding folic acid to contraceptive pills and has been a paid consultant to Ortho McNeil on the matter of folate. NJW is a co-inventor of a combination pill for the prevention of cardiovascular disease, which optionally may include folic acid.

**References**

The UK’s Food Standards Agency recently recommended mandatory folic acid fortification of some foods. Nicholas Wald and Godfrey Oakley argue that it’s a safe effective way of preventing spina bifida and anencephaly—but Richard Hubner and colleagues say that more research is needed.

Mandatory fortification with folic acid aims to increase folate intake in women during early pregnancy to reduce neural tube defects in their babies. The case for mandatory fortification is strengthened by the purported association of increased folate intake with reduced incidence of cancer. But new data suggest that folate supplements may promote cancer.

Folate metabolism influences several crucial pathways, including DNA synthesis and methylation, aberrations of which play a role in carcinogenesis. Altered folate metabolism may disrupt these processes, so folate deficiency and supplementation could influence cancer risk. This may be further complicated by using synthetic folic acid: its effects on folate metabolism are not identical to natural folates.1

Epidemiological studies have found that high folate intake is associated with a reduced risk of cancers of the breast, lung, pancreas, oesophagus, stomach, cervix, and the colorectum in particular.2 But recent studies have cast doubt over the epidemiological evidence. A large cohort study found an increased risk of colorectal cancer in people with high plasma concentrations of folate,3 and a meta-analysis of cohort studies investigating folate intake and colorectal cancer risk reported a significant reduction in risk in people with high intake of folate from food—but the association was almost null when folate was from diet and folic acid supplements.4

Potential cancer promoting effects

A neoplastic clone of cells has enhanced growth compared to normal tissue. This attribute is exploited by chemotherapeutic drugs, which inhibit folate metabolism enzymes, interrupting DNA synthesis and inhibiting growth of tumours. Extra folate could promote tumour growth by allowing increased DNA synthesis. Evidence that timing of folic acid supplementation may determine its effects on colorectal carcinogenesis comes from two genetic mouse models of colorectal cancer.5 6 In both models, if intervention was started before lesions developed, moderate folate deficiency enhanced the development of cancer and folic acid supplementation suppressed it—but once a preneoplastic lesion was present, supplementation promoted tumour growth. These studies have led to the hypothesis that in normal epithelial cells folate deficiency promotes neoplastic transformation, which can be avoided by folic acid supplementation, whereas supplementation promotes the growth of existing preneoplastic and neoplastic tissue. Although these studies were in animal models of colorectal cancer, randomised intervention trials in humans support this hypothesis.7 11

The aspirin-folate polyp prevention study recruited 1021 people who had colorectal adenoma removed at colonoscopy, randomised to intervention with folic acid (1 mg/day) or placebo, and it assessed polyp recurrence by colonoscopy at three and six years. The mean number of recurrent colorectal adenomas per patient was increased by folic acid supplementation (rate ratio 1.44; 95% confidence interval 1.03 to 2.02), as was the incidence of advanced colorectal adenoma with high malignant potential (1.31; 0.90 to 1.89). One explanation for this is that folic acid supplementation promoted the growth of pre-existing aberrant crypt foci or small adenomas and these were missed at initial colonoscopy. If this effect of folic acid is genuine it is a public health concern as more than 25% of people aged over 50 have asymptomatic colorectal adenomas.14

New data suggest that folate supplements may promote cancer

Reducing neural tube defects is a worthy aim, but further investigation of the potential cancer promoting effects of exposure to folic acid in susceptible people is desirable before mandatory fortification starts.

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References are in the full version on bmj.com

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How effective are expert patient (lay led) education programmes for chronic disease?

Considerable hyperbole has surrounded the UK expert patient programme, and it has received considerable funding—but will its impact meet expectations?

Chronic conditions now account for 60% of deaths worldwide and are imposing an increasing burden on society and health services. Self management programmes are commonly used to help patients learn the skills to manage their own conditions better. The NHS in the United Kingdom, and countries in Europe (especially Scandinavia), Australasia, and North America have chosen specifically to use courses tutored by trained lay leaders, rather than health professionals such as nurses. Considerable resources have been allocated to support and run such programmes. A major attraction for healthcare planners has been the expectation that such courses will reduce use of health care and will deliver long term cost savings. More debate about the impact of lay led, self management programmes is needed. This article opens up this debate and examines the evidence that “expert patients” consume fewer healthcare resources, with particular reference to data from trials in the UK.

Involving patients in health care

Two main arguments drive the shift towards increasing patients’ involvement in health care. Firstly, it is unethical for patients not to be involved in decisions about their health and, by extension, for the public not to be involved in how care is organised. Secondly, greater patient involvement in the consultation may lead to greater satisfaction, and perhaps more importantly to better health. Patients’ involvement has been championed by organisations like the Picker Institute (www.pickereurope.org), which monitor patients’ experience of care and highlight deficiencies. Systematic reviews show that interventions can promote patients’ involvement and possibly greater satisfaction, but the jury is still out on whether this leads to better health.

Against this background, the UK government has promoted the idea of a patient centred NHS, with initiatives such as patient advisory liaison services, attempts to improve access to care, and “choose and book,” a system that allows patients to choose the hospital to which they are referred by their general practitioner. Another initiative, the expert patient programme, was first announced in Saving Lives: Our Healthier Nation. The programme is based on the work of Halstead Holman and Kate Lorig at Stanford University, who developed the idea of teaching arthritis self care by using lay tutors in 1979. Early, small scale comparisons suggested that trained lay people and professionals could teach self care equally well. Lorig argued that the lay led model was attractive because lay educators were plentiful and relatively cheap and could help other people with the disease by ”modelling” self care more effectively than healthy professionals.

Self care programmes

The success of the Stanford arthritis self management programme (http://med.stanford.edu/patienteducation) spawned a generic programme, the chronic disease self management programme, which was adopted in the UK as the expert patient programme. Both consist of six weekly, lay tutored sessions (box) fostering self care skills through participative techniques such as modelling and action planning.

These programmes are based on Bandura’s social cognitive theory of behaviour, which states that the key predictors of successful behaviour change are confidence (self efficacy) in the ability to carry out an action and expectation that a particular goal will be achieved (outcome expectancy). Self efficacy is seen as an early step in causal pathways of behaviour change in self management programmes; increasing self efficacy (confidence) is a prerequisite for behaviour change which, through improved self management, may influence health and healthcare use. Many health services around the world have adopted this lay led model in the hope that it will deliver cost effective health gains.

Content of standard six week chronic disease self management programme

Session 1—Course overview; acute and chronic conditions compared; cognitive symptom management; better breathing; introduction to action plans
Session 2—Feedback; dealing with anger, fear and frustration; introduction to exercise; making an action plan
Session 3—Feedback; distraction; muscle relaxation; fatigue management; monitoring exercise; making an action plan
Session 4—Feedback; making an action plan; healthy eating; communication skills; problem solving
Session 5—Feedback; making an action plan; use of medication; depression management; self talk; treatment decisions; guided imagery
Session 6—Feedback; informing the healthcare team; working with your healthcare professional; looking forward
Randomised trials of lay led self management programmes in the UK

<table>
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<th>Intervention</th>
<th>Condition</th>
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<th>Self efficacy</th>
<th>Psychological health</th>
<th>Generic health related quality of life</th>
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ASMP= arthritis self management programme, CDSMP=chronic disease self management programme.

**Great expectations**

In 2001 the expert patient task force, led by the chief medical officer, Sir Liam Donaldson, concluded that lay led self management programmes for chronic diseases (or long term conditions) would improve health status, slow the progression of disease, and reduce healthcare use, and that the NHS should invest heavily in the expert patient programme. In 2003 the chief medical officer wrote an editorial for this journal asserting that the expert patient programme ushered in a new era of opportunity for the NHS. He envisaged the programme reducing healthcare use and even mortality when he said: “Such people those with confidence live longer, are healthier, and are an example of how more assertive engagement with the health care system can improve both the length and the quality of people's lives.” To date, the Department of Health has invested £18m (€27m; $36m) in the programme, with an explicit goal of providing the course to 100 000 patients.

**Evidence for change in use of health care**

Recently, a rapid review (commissioned by the National Institute for Health and Clinical Excellence) gave a cautious welcome to lay led self management interventions but pointed out that most evaluations were short term and set in the United States, and some of the data were uncontrolled. A recent paper by Buszewicz and colleagues provides the longest duration of controlled follow-up to date (one year). Of the four evaluations in the UK, two test the arthritis self management programme and two the chronic disease self management programme, including the national evaluation of the expert patient programme carried out by the National Primary Care Research Centre in Manchester. The results of these four studies are similar (table). The good news is that these programmes increase patients' self efficacy—in essence their confidence to change behaviour—and can lead to improved psychological health (although the effect sizes seem small). We found the chronic disease self management programme improved self efficacy in Bangladeshi patients, suggesting that it may be useful for ethnic minorities. However, the changes in self efficacy are generally modest and it is unclear how much patients value improvements in self efficacy compared with, say, a reduction in symptoms or a gain in health related quality of life.

There are also important negative findings: generic measures of self rated health were unaltered in three of four studies, and more importantly, use of health care has remained stubbornly unaltered. The latter is a considerable disappointment because the expert patient programme has been heavily promoted by the UK Department of Health as part of a drive to reduce use of acute health care.

Several factors may explain the failure of lay led programmes in the UK to reduce the use of health care. Firstly, lay led programmes may do as much to promote consultation as they do to reduce it. The chronic disease self management programme teaches techniques to improve communication with clinicians, so patients may be encouraged to consult more. Secondly, any reductions in unscheduled (emergency) care may be obscured by increases in scheduled care. Thirdly, self management programmes may not be as effective at reducing healthcare use in settings such as the UK, which have universal healthcare coverage and well established primary care. It is unlikely that poor delivery of the programme in the UK is a cause since course tutors are assessed and course quality is strictly monitored. Three trials of the chronic disease self management programme in the United States show inconsistent effects on use of health care. The much cited report of a 40% reduction in physician visits in the United States comes from a methodologically weak, retrospective comparison, in which arthritis patients in the community who had volunteered for self care education were compared with a group of arthritis patients with no explicit interest in self management who were under the care of rheumatologists. Trials examining use of health care in the UK are unlikely to have missed an effect of this magnitude.

**Testing questions**

Although improvements in self efficacy and psychological health are welcome, these disappointing results can be compared with the impact of other professionally led self management or rehabilitation interventions in the UK. The six week heart manual programme uses a similar patient empowerment model for rehabilitation after a cardiac event. Over a year, the programme improved psychological adjustment, especially in participants with high anxiety and depression scores at baseline, and it reduced visits to general practitioners and readmission to hospital. Psychological interventions for diabetes improve glycaemic control. Exercise based cardiac rehabilitation reduces mortality.
rehabilitation programmes produce clinically important reductions in breathlessness and fatigue in patients with cardiac obstructive pulmonary disease, yet fewer than 2% of these patients in the UK have access to pulmonary rehabilitation each year. Why have these interventions had more impact than lay led programmes? Firstly, these programmes may be better targeted towards higher risk individuals, who experience greater morbidity. Secondly, key features of successful self management programmes include correcting erroneous health beliefs and teaching specific, clinical, disease management skills—for example, using a written self management plan for asthma. Thirdly, cardiac and pulmonary rehabilitation programmes combine a structured exercise programme with self management advice; lay led programmes in their current form do not provide these additional components.

Questions about impact

Considerable hyperbole has surrounded the UK expert patient programme, and some patients attending courses have given powerful personal accounts of their benefits.

However, these accounts must now be seen in the context of the modest results of four well powered randomised trials in the UK. Although early results suggest that the programme can improve patients’ confidence, questions remain about its impact on health in patients in the UK. How important is self efficacy as an outcome? How long do effects on self efficacy or other outcomes last? Do lay led programmes improve key measures of disease process such as glycaemic control, blood pressure, or weight? Should lay led programmes be targeted at patients with particular illnesses, perhaps with courses specific to these diseases, or at patients with particular psychological profiles? Could the expert patient programme be made more effective, perhaps adding slots for clinicians to teach clinical disease management skills? Our forthcoming Cochrane review should throw light on some of these questions, but more well designed trials are needed to evaluate fully the contribution of lay led education programmes. The government should invest in such a programme of research in the same way it has invested heavily in implementing the expert patient programme.

Although general practice leaders in the UK may be tempted to include referral to the programme in future versions of the quality and outcomes framework, data so far suggest that this would be premature. The expert patient programme is switching from Department of Health funding to becoming a community interest company. As such, primary care trusts or general practice commissioning groups will need to pay for courses; they will need to consider carefully the opportunity costs of investing in this compared with other rehabilitation programmes for chronic disease.
RESEARCH

Duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography for diagnosis and assessment of symptomatic, lower limb peripheral arterial disease: systematic review

Ros Collins, research fellow, Jane Burch, research fellow, Gillian Cranny, research fellow, Raquel Aguiar-Ibáñez, research fellow in health economics, Dawn Craig, research fellow in health economics, Kath Wright, information officer, Elizabeth Berry, senior lecturer, Michael Gough, consultant vascular surgeon, Jos Kleijnen, director, Marie Westwood senior research fellow

ABSTRACT

Objectives To determine the diagnostic accuracy of duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography, alone or in combination, for the assessment of lower limb peripheral arterial disease; to evaluate the impact of these assessment methods on management of patients and outcomes; and to evaluate the evidence regarding attitudes of patients to these technologies and summarise available data on adverse events.

Design Systematic review.

Methods Searches of 11 electronic databases (to April 2005), six journals, and reference lists of included papers for relevant studies. Two reviewers independently selected studies, extracted data, and assessed quality. Diagnostic accuracy studies were assessed for quality with the QUADAS checklist.

Results 107 studies met the inclusion criteria; 58 studies provided data on diagnostic accuracy, one on outcomes in patients, four on attitudes of patients, and 44 on adverse events. Quality assessment highlighted limitations in the methods and quality of reporting. Most of the included studies reported results by arterial segment, rather than by limb or by patient, which does not account for the clustering of segments within patients, so specificities may be overstated. For the detection of stenosis of 50% or more in a lower limb vessel, contrast enhanced magnetic resonance angiography had the highest diagnostic accuracy with a median sensitivity of 95% (range 92-99.5%) and median specificity of 97% (64-99%). The results were 91% (89-99%) and 91% (83-97%) for computed tomography angiography and 88% (80-98%) and 96% (89-99%) for duplex ultrasonography. A controlled trial reported no significant differences in outcomes in patients after treatment plans based on duplex ultrasonography alone or conventional contrast angiography alone, though in 22% of patients supplementary contrast angiography was needed to form a treatment plan. The limited evidence available suggested that patients preferred magnetic resonance angiography (with or without contrast) to contrast angiography, with half expressing no preference between magnetic resonance angiography or duplex ultrasonography (among patients with no contraindications for magnetic resonance angiography, such as claustrophobia). Where data on adverse events were available, magnetic resonance angiography was associated with the highest proportion of adverse events, but these were mild. The most severe adverse events, although rare, were mainly associated with contrast angiography.

Conclusions Contrast enhanced magnetic resonance angiography seems to be more specific than computed tomography angiography (that is, better at ruling out stenosis over 50%) and more sensitive than duplex ultrasonography (that is, better at ruling in stenosis over 50%) and was generally preferred by patients over contrast angiography. Computed tomography angiography was also preferred by patients over contrast angiography; no data on patients’ preference between duplex ultrasonography and contrast angiography were available. Where available, contrast enhanced magnetic resonance angiography might be a viable alternative to contrast angiography.

INTRODUCTION

Lower limb peripheral arterial disease is the atheromatous narrowing or occlusion of an artery or arteries of the leg. If symptoms occur these may include intermittent claudication, ischaemic rest pain, ulceration, and gangrene.1 Risk factors include advanced age, smoking, hypertension, hyperlipidaemia, diabetes, obesity, and family history.2 Management strategies differ for patients with intermittent claudication (often conservative management, with radiological or surgical intervention reserved for patients with reduced quality of life) and patients with limb threatening ischaemia, in whom angioplasty, surgical revascularisation, or amputation are usually required.3 The choice of intervention is governed by the severity of the disease and may involve...
combined treatments. Thus patients with limb threatening ischaemia require a detailed assessment for a suitable treatment plan to be developed.

Intra-arterial contrast angiography is regarded as the reference standard. The drawbacks are those associated with arterial puncture, ionising radiation, and potential nephrotoxicity of iodinated contrast agents. Several alternative imaging techniques are available, including magnetic resonance angiography, computed tomography angiography and duplex ultrasonography. These techniques are less invasive than contrast angiography, although computed tomography angiography carries risks relating to ionising radiation, and both contrast enhanced magnetic resonance angiography and computed tomography angiography carry risks associated with the use of contrast agents.

We carried out a systematic review to examine the evidence regarding the performance of magnetic resonance angiography, computed tomography angiography, and duplex ultrasonography as alternatives to contrast angiography to try to identify a technique that is safer and more acceptable to patients but as effective as contrast angiography for the assessment of symptomatic peripheral arterial disease. Here we present the systematic review of the evidence on effectiveness. The full report with economic evaluation is available elsewhere.

### METHODS

We searched 11 databases (Medline, Embase, BIOSIS Previews, Science Citation Index, NTIS Database, LILACS, SIGLE (system for information on grey literature in Europe), Dissertation Abstracts Online, Inside Conferences, Pascal from 1996 to April 2005, and the Cochrane Database of Systematic Reviews, Issue 3, 2005), six key journals on imaging and vascular disease, and reference lists of included studies for published and unpublished data. No language restrictions were applied. Electronic searches were not limited by study design. Two reviewers conducted each stage of the review process (except in the case of foreign language studies), with disagreements resolved by consensus or referral to a third reviewer. Full details of the review methods, including the search strategies, are described elsewhere. Table 1 presents the inclusion criteria for each section of the review.

We used the QUADAS checklist to assess the quality of diagnostic accuracy studies. The results of diagnostic accuracy studies were analysed according to the imaging tests assessed (magnetic resonance angiography, computed tomography angiography, or duplex ultrasonography). Magnetic resonance angiography technologies were further grouped by specific technique (2D phase contrast, 2D time of flight, or contrast enhanced). We derived the sensitivity and specificity for the detection of stenosis in arterial segments from the 2×2 tables reported in each study. To account for values of zero in the 2×2 tables, we added 0.5 to all cells. Heterogeneity was assessed with the Q statistic.

### Table 1 | Inclusion criteria for each of four sections of review of duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography for assessment of patients with lower limb peripheral arterial disease

<table>
<thead>
<tr>
<th>Study design</th>
<th>Diagnostic accuracy</th>
<th>Impact on patient management/outcome</th>
<th>Acceptability for patients</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td></td>
<td>Randomised controlled trial/controlled clinical trial</td>
<td>Studies of any design, excluding case reports</td>
<td>Studies of any design, excluding case reports</td>
</tr>
<tr>
<td>Index tests/ interventions</td>
<td>Duplex ultrasonography, magnetic resonance angiography, or computed tomography angiography, alone or in combination</td>
<td>Duplex ultrasonography, magnetic resonance angiography, or computed tomography angiography, alone or in combination</td>
<td>Duplex ultrasonography, magnetic resonance angiography, or computed tomography angiography, alone or in combination</td>
<td>Duplex ultrasonography, magnetic resonance angiography, or computed tomography angiography, alone or in combination</td>
</tr>
</tbody>
</table>

Reference standard | Intra-arterial contrast angiography or findings at surgery/follow-up | NA | NA | NA |

Outcome measures | Sufficient information to construct 2×2 tables of test performance | Any treatment decision or long term outcome measure (for example, graft/vessel patency after intervention, morbidity) | Any reported criteria relating to acceptability for patients | Adverse events relating to index test or to currently used contrast agents |
and graphically with forest plots. Most studies provided data for more than one anatomical area (above knee, below knee, foot) or more than one threshold of stenosis (50%, 70%, occlusion). The number of arterial segments assessed per patient and their anatomical distribution varied and was sometimes incompletely reported. Analyses were conducted with Meta-DiSc.7

We have presented a narrative synthesis for studies evaluating the impact of the method of assessment on management and outcome in patients, attitudes of patients, and studies of adverse events.

RESULTS
The search strategy generated 8590 references, of which 650 were considered to be potentially relevant; ultimately 107 met the inclusion criteria. Figure 1 shows the flow of studies through the selection process.

Quality of diagnostic accuracy studies
All included studies were diagnostic cohorts and were conducted in secondary or tertiary care settings. There were several potential sources of bias. Spectrum bias may have been present; over 70% of studies did not include an appropriate range of patients (defined as unselected, prospective adult patients with symptoms indicating lower limb peripheral arterial disease) or failed to provide sufficient details of the population; 48% of magnetic resonance angiography studies, 29% of computed tomography angiography studies, and 57% of duplex ultrasonography studies did not provide adequate details of selection criteria. Spectrum bias may underestimate or overestimate the accuracy of a test by investigating a selected population with regard to the severity of disease, demographics, or comorbidity.5 Bias may occur when the delay between the index test and reference standard are long enough for the disease to have progressed naturally; 20% of magnetic resonance angiography studies, 29% of computed tomography angiography studies, and 36% of duplex ultrasonography studies did not report having less than a one month interval between the index test and reference standard. Bias may also occur when the

Table 2 | Diagnostic accuracy for detection of stenosis 50% or more or occlusion with different assessment methods

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Fontaine stage II/III/IV* (%)</th>
<th>No of segments</th>
<th>Positive result True</th>
<th>False</th>
<th>Negative result False</th>
<th>True</th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast enhanced magnetic resonance angiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cronbergw13</td>
<td>35</td>
<td>9/3/89</td>
<td>418</td>
<td>227</td>
<td>62</td>
<td>20</td>
<td>109</td>
<td>91.9 (87.8 to 95.0)</td>
<td>63.7 (56.1 to 70.9)</td>
</tr>
<tr>
<td>Laissyw16</td>
<td>20</td>
<td>100/0/0</td>
<td>520</td>
<td>104</td>
<td>14</td>
<td>9</td>
<td>393</td>
<td>92.0 (85.4 to 96.3)</td>
<td>96.6 (94.3 to 98.1)</td>
</tr>
<tr>
<td>Lehnartw17</td>
<td>45</td>
<td>NR</td>
<td>220</td>
<td>79</td>
<td>8</td>
<td>4</td>
<td>129</td>
<td>95.2 (88.1 to 98.7)</td>
<td>94.2 (88.8 to 97.4)</td>
</tr>
<tr>
<td>Schaferw19</td>
<td>30</td>
<td>NR</td>
<td>576</td>
<td>138</td>
<td>13</td>
<td>9</td>
<td>416</td>
<td>93.9 (88.7 to 97.2)</td>
<td>97.0 (94.9 to 98.4)</td>
</tr>
<tr>
<td>Steffensw21</td>
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<td>NR</td>
<td>900</td>
<td>185</td>
<td>8</td>
<td>1</td>
<td>706</td>
<td>99.5 (97.0 to 100.0)</td>
<td>98.9 (97.8 to 99.5)</td>
</tr>
<tr>
<td>Sueyoshiw22</td>
<td>23</td>
<td>83/17/0</td>
<td>423</td>
<td>67</td>
<td>3</td>
<td>2</td>
<td>351</td>
<td>97.1 (89.9 to 96.6)</td>
<td>99.2 (97.5 to 99.8)</td>
</tr>
<tr>
<td>Wintererw23</td>
<td>76</td>
<td>87/13/0</td>
<td>1780</td>
<td>362</td>
<td>43</td>
<td>14</td>
<td>1361</td>
<td>96.3 (93.8 to 97.9)</td>
<td>96.9 (95.9 to 97.8)</td>
</tr>
<tr>
<td>2D time of flight magnetic resonance angiography</td>
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<td></td>
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</tr>
<tr>
<td>Baumw2</td>
<td>155</td>
<td>NR</td>
<td>1188</td>
<td>527</td>
<td>101</td>
<td>100</td>
<td>460</td>
<td>84.1 (80.9 to 86.8)</td>
<td>82.0 (78.6 to 85.1)</td>
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<tr>
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<td>NR</td>
<td>544</td>
<td>161</td>
<td>37</td>
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<td>302</td>
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<td>89.1 (85.3 to 92.2)</td>
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<td>18/20/62</td>
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<td>172</td>
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<td>12</td>
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<td>92.3 (87.1 to 95.8)</td>
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<td>NR</td>
<td>378</td>
<td>80</td>
<td>76</td>
<td>7</td>
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<td>92.0 (84.1 to 96.7)</td>
<td>73.9 (68.4 to 78.8)</td>
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<tr>
<td>Yucelw2</td>
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<td>0/84/16</td>
<td>206</td>
<td>65</td>
<td>16</td>
<td>19</td>
<td>119</td>
<td>91.5 (82.5 to 96.8)</td>
<td>88.1 (81.5 to 93.1)</td>
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<tr>
<td>Steffensw1</td>
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<td>100/0/0</td>
<td>253</td>
<td>229</td>
<td>5</td>
<td>5</td>
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<td>97.9 (95.1 to 99.3)</td>
<td>73.7 (48.8 to 90.9)</td>
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<td>Computed tomography angiography</td>
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<td>Heuschmidw27</td>
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<td>78/13/9</td>
<td>568</td>
<td>133</td>
<td>40</td>
<td>16</td>
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<td>90.5 (87.2 to 93.1)</td>
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<td>61</td>
<td>38</td>
<td>886</td>
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<td>93.6 (91.8 to 95.0)</td>
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<td>Pulsw50</td>
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<td>97/3/0</td>
<td>186</td>
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<td>86.2 (78.3 to 91.7)</td>
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<td>74/12/14</td>
<td>327</td>
<td>111</td>
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<td>90.6 (85.9 to 94.2)</td>
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<tr>
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<td>1137</td>
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<td>23</td>
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<td>97.4 (96.1 to 98.3)</td>
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<td>Portugalallw29</td>
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<td>62/4/34</td>
<td>740</td>
<td>240</td>
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<td>83.3 (79.7 to 86.5)</td>
</tr>
<tr>
<td>Duplex ultrasonography</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Aly w73</td>
<td>90</td>
<td>90/9/1</td>
<td>3108</td>
<td>404</td>
<td>27</td>
<td>34</td>
<td>2643</td>
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<td>99.0 (98.5 to 99.3)</td>
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<tr>
<td>Bergamin w55</td>
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<td>404</td>
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<td>95.5 (92.4 to 97.6)</td>
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<td>243</td>
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<td>6</td>
<td>12</td>
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<td>85.9 (76.6 to 92.5)</td>
<td>96.2 (91.9 to 99.0)</td>
</tr>
<tr>
<td>Linke w38</td>
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<td>100/0/0</td>
<td>134</td>
<td>41</td>
<td>4</td>
<td>2</td>
<td>87</td>
<td>95.3 (84.2 to 99.4)</td>
<td>95.6 (89.1 to 98.8)</td>
</tr>
<tr>
<td>Sensierw50</td>
<td>76</td>
<td>88/0/12</td>
<td>469</td>
<td>214</td>
<td>26</td>
<td>28</td>
<td>201</td>
<td>88.4 (83.7 to 92.2)</td>
<td>88.5 (83.7 to 92.4)</td>
</tr>
<tr>
<td>El-Kayali w55</td>
<td>44</td>
<td>NR</td>
<td>357</td>
<td>123</td>
<td>15</td>
<td>3</td>
<td>216</td>
<td>97.6 (93.2 to 99.5)</td>
<td>93.5 (89.5 to 96.3)</td>
</tr>
<tr>
<td>Legemate w58</td>
<td>61</td>
<td>80/16/3</td>
<td>918</td>
<td>179</td>
<td>30</td>
<td>33</td>
<td>676</td>
<td>84.4 (78.8 to 89.0)</td>
<td>95.8 (94.0 to 97.1)</td>
</tr>
</tbody>
</table>

NR=not reported.

*Stage II=intermittent claudication; stage III=ischaemic rest pain; stage IV=tissue loss.
results of the index test are interpreted by someone with prior knowledge of the results of the reference test and vice versa. The index test results were interpreted without knowledge of the reference test results in 84% of magnetic resonance angiography studies and 71% of duplex ultrasonography and computed tomography angiography studies. The reference test results were interpreted without knowledge of the index test results in 84% of magnetic resonance angiography studies, 82% of duplex ultrasonography studies, and 71% of computed tomography angiography studies.

There is evidence that the availability of appropriate clinical data increases the accuracy of interpretation.8 The availability of clinical data was poorly reported, with only one study that evaluated magnetic resonance angiography and duplex ultrasonography reporting that clinical data were available when the imaging results were interpreted. Full details of included studies and quality assessment are on www.york.ac.uk/inst/crd/projects/peripheralarterialdisease.htm.

Assessment of stenosis/occlusion
Fifty eight diagnostic accuracy studies met the inclusion criteria. One evaluated 2D phase contrast sensitivity criteria. One evaluated 2D phase contrast magnetic resonance angiography,11 11 evaluated 2D time of flight magnetic resonance angiography,12 14 evaluated contrast enhanced magnetic resonance angiography,13 13 evaluated computed tomography angiography,14 28 evaluated duplex ultrasonography.15 No studies evaluated 3D time of flight magnetic resonance angiography. Contrast angiography was the reference standard in all studies. As there was significant heterogeneity between individual studies we did not pool data and have presented results as medians (range).

Most of the included studies reported results by arterial segment, rather than by limb or by patient, which does not account for the clustering of segments within patients. Therefore, the increased number of segments assessed is likely to increase the number of true negative test results, and the specificities may be overstated. We report results only for studies where data were reported by arterial segment. Full diagnostic accuracy results are available elsewhere.9

Whole leg
Table 2 shows data for detection of stenosis 50% or more or occlusion. Figures 2 and 3 show sensitivity and specificity data, respectively. Contrast enhanced magnetic resonance angiography had the highest diagnostic accuracy (seven studies13 16 17 19 21–23), with median sensitivity 95% (range 92–99.5%) and median specificity 97% (64–99%). One study had a low specificity (64%) compared with the others; this was the only study to include assessment of foot vessels in the scan.11 2D time of flight magnetic resonance angiography was less accurate (five studies2 6 7 10 12), with median sensitivity 92% (79–94%) and median specificity 88% (74–92%). The use of time of flight magnetic resonance angiography has largely been superseded by contrast enhanced magnetic resonance angiography. Only one study11 evaluated 2D phase contrast magnetic resonance angiography and this reported sensitivity and specificity of 98% and 74%, respectively.

Computed tomography angiography (six studies14 16 18 21 25 26) five of which used multidetector row computed tomography angiography) had median sensitivity 91% (89–99%) and median specificity 93% (83–97%). Duplex ultrasonography (seven studies17 19 21–23) had median sensitivity 88% (80–98%) and median specificity 96% (89–99%). The study with the lowest sensitivity (80%) was the only study in this group with an unacceptable delay (that is, over one month) between the index test and reference standard.14

Table 3 shows data for detection of occlusion. Figures 4 and 5 show sensitivity and specificity data, respectively. Contrast enhanced magnetic resonance angiography (six studies17 19 21–23) had median sensitivity 94% (85–100%) and median specificity 99.2% (97–99.8%). 2D time of flight magnetic resonance angiography (four studies5 6 7 15) had lower sensitivity; median 86% (77–100%) and comparable specificity; median 97% (85–98%). Computed tomography

<table>
<thead>
<tr>
<th>Contrast enhanced magnetic resonance imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cronberg</td>
</tr>
<tr>
<td>0.92 (0.88 to 0.95)</td>
</tr>
<tr>
<td>Laissy</td>
</tr>
<tr>
<td>0.92 (0.85 to 0.96)</td>
</tr>
<tr>
<td>Lenhart</td>
</tr>
<tr>
<td>0.95 (0.88 to 0.99)</td>
</tr>
<tr>
<td>Schafer</td>
</tr>
<tr>
<td>0.94 (0.89 to 0.97)</td>
</tr>
<tr>
<td>Steffens</td>
</tr>
<tr>
<td>0.99 (0.97 to 1.00)</td>
</tr>
<tr>
<td>Sueyoshi</td>
</tr>
<tr>
<td>0.97 (0.90 to 1.00)</td>
</tr>
<tr>
<td>Winterer</td>
</tr>
<tr>
<td>0.96 (0.94 to 0.98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2D time of flight magnetic resonance imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baum</td>
</tr>
<tr>
<td>0.84 (0.81 to 0.87)</td>
</tr>
<tr>
<td>Hoch</td>
</tr>
<tr>
<td>0.79 (0.72 to 0.84)</td>
</tr>
<tr>
<td>Hoch</td>
</tr>
<tr>
<td>0.93 (0.89 to 0.97)</td>
</tr>
<tr>
<td>Snidow</td>
</tr>
<tr>
<td>0.92 (0.84 to 0.97)</td>
</tr>
<tr>
<td>Yucel</td>
</tr>
<tr>
<td>0.92 (0.83 to 0.97)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2D phase contrast magnetic resonance imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steffens</td>
</tr>
<tr>
<td>0.98 (0.95 to 0.99)</td>
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<tr>
<td>Computed tomography angiography</td>
</tr>
<tr>
<td>Heuschmid</td>
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<tr>
<td>0.89 (0.83 to 0.94)</td>
</tr>
<tr>
<td>Martin</td>
</tr>
<tr>
<td>0.90 (0.86 to 0.93)</td>
</tr>
<tr>
<td>Puls</td>
</tr>
<tr>
<td>0.89 (0.78 to 0.95)</td>
</tr>
<tr>
<td>Rieker</td>
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<tr>
<td>0.97 (0.93 to 0.99)</td>
</tr>
<tr>
<td>Catalano</td>
</tr>
<tr>
<td>0.99 (0.97 to 1.00)</td>
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<tr>
<td>Portugaller</td>
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<tr>
<td>0.92 (0.88 to 0.95)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Duplex ultrasonography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aly</td>
</tr>
<tr>
<td>0.92 (0.89 to 0.95)</td>
</tr>
<tr>
<td>Bergamini</td>
</tr>
<tr>
<td>0.80 (0.71 to 0.87)</td>
</tr>
<tr>
<td>Hatsukami</td>
</tr>
<tr>
<td>0.86 (0.77 to 0.92)</td>
</tr>
<tr>
<td>Linke</td>
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<tr>
<td>0.95 (0.84 to 0.99)</td>
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<td>Sensier</td>
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<td>0.88 (0.84 to 0.92)</td>
</tr>
<tr>
<td>El-Kayali</td>
</tr>
<tr>
<td>0.92 (0.93 to 1.00)</td>
</tr>
<tr>
<td>Legemate</td>
</tr>
<tr>
<td>0.84 (0.79 to 0.89)</td>
</tr>
</tbody>
</table>
angiography (five studies, \textsuperscript{26-28,39} \textsuperscript{40} \textsuperscript{53} \textsuperscript{55} \textsuperscript{58} four of which used multidetector row computed tomography angiography) had median sensitivity 97\% (89-100\%) and median specificity 99.6\% (99-100\%).

Duplex ultrasonography (seven studies, \textsuperscript{34} \textsuperscript{35} \textsuperscript{40} \textsuperscript{47} \textsuperscript{55} \textsuperscript{56} \textsuperscript{58}) had median sensitivity 90\% (74-94\%), and median specificity 99\% (96-100\%). One study reported a notably low sensitivity (74\%)\textsuperscript{48}, of the three studies that reported Fontaine classification (a system used to describe the severity of peripheral arterial disease), this was the only study restricted to people with Fontaine stage II (intermittent claudication).

Above and below the knee
Some studies provided separate results on diagnostic accuracy for arterial segments above and below the knee. The accuracy of the different techniques was similar for the detection of stenosis of 50\% or more above the knee: with contrast enhanced magnetic resonance angiography the median sensitivity and specificity were 87\% and 93\%, respectively, above the knee\textsuperscript{18} \textsuperscript{14} \textsuperscript{17} \textsuperscript{20} and 83\% and 92\% below the knee\textsuperscript{18} \textsuperscript{15} \textsuperscript{17} \textsuperscript{24}; with duplex ultrasonography the median sensitivity and specificity were 88\% and 95\% above the knee\textsuperscript{14} \textsuperscript{18} \textsuperscript{17} \textsuperscript{20} \textsuperscript{27} \textsuperscript{52} \textsuperscript{53} \textsuperscript{55} \textsuperscript{56} and 84\% and 93\% below the knee\textsuperscript{14} \textsuperscript{18} \textsuperscript{17} \textsuperscript{20} \textsuperscript{27} \textsuperscript{52} \textsuperscript{53} \textsuperscript{55} \textsuperscript{56}.

Two studies assessed accuracy for the detection of occlusion in the foot: one evaluated 2D time of flight magnetic resonance angiography\textsuperscript{56} and the other contrast enhanced magnetic resonance angiography\textsuperscript{24}. Sensitivities were 86\% and 79\%, respectively, and specificities 27\% and 86\%, respectively. One study assessed the accuracy of duplex ultrasonography for detecting target vessels suitable for surgery in the foot, with sensitivity and specificity of 64\% and 80\% respectively.\textsuperscript{42} Although there was limited evidence, these data suggest that these techniques may be less accurate in the foot.

Impact of method of assessment on management and outcome
Only one controlled trial, a prospective assessment of duplex ultrasonography using a historical control group, met the inclusion criteria for assessing the impact of the assessment method on patients’ management and outcome.\textsuperscript{50} The study included consecutive patients with lower leg ischaemia whose treatment plans were based on the results of either duplex ultrasonography with contrast angiography where indicated (114 patients) or contrast angiography (control group 113 patients).

In 78\% of cases the management plan was based on duplex ultrasonography without the need for contrast angiography. There were no significant differences between the groups in terms of immediate and intermediate outcomes. This trial seems to have been well conducted and the results are likely to be reliable. As it used a historical control group, however, other factors occurring within the timeframe of the trial may have affected the results. Treatment and characteristics of patients were not significantly different between the two groups, although the authors did not comment on some factors that could have influenced outcomes, such as the graft material used, continuation of smoking, and the use of antiplatelet drugs.

Patients’ attitudes
Four studies reported results relating to patients’ attitudes. Two evaluated magnetic resonance angiography and contrast angiography,\textsuperscript{16} \textsuperscript{17} \textsuperscript{27} \textsuperscript{48} and one duplex ultrasonography and magnetic resonance angiography,\textsuperscript{16} \textsuperscript{17} \textsuperscript{27} and one computed tomography angiography, magnetic resonance angiography, and contrast angiography.\textsuperscript{16} \textsuperscript{17} \textsuperscript{27} Significantly more patients (28/30 patients) stated that they would prefer contrast enhanced magnetic resonance angiography over contrast angiography if they had to undergo testing again in the future,\textsuperscript{16} \textsuperscript{17} \textsuperscript{27} and contrast enhanced magnetic resonance angiography scored significantly better on a scale that rated patients’ experience of the test compared with contrast angiography (P=0.0001 and P=0.0002)\textsuperscript{16} \textsuperscript{17} \textsuperscript{27}.

Contrast angiography was reported as the most uncomfortable, followed by contrast enhanced
magnetic resonance angiography, with computed tomography angiography being the least uncomfortable ($P=0.016$). Fifty per cent of patients (who were not claustrophobic and had no metallic implants) had no preference between time of flight magnetic resonance angiography or duplex ultrasonography (49/98 patients). Of those who did express a preference, most preferred time of flight magnetic resonance angiography (40/49 patients).

Within the same population there was no significant difference between time of flight magnetic resonance angiography and duplex ultrasonography on a scale that rated how “bothersome” the tests were. While some of the surveys potentially suffered from recall or sequential bias, they were generally well conducted and the results are probably reliable. As the studies included only patients who were suitable for magnetic resonance angiography, the results cannot be generalised to patients who are not suitable for magnetic resonance angiography, such as those with claustrophobia or metallic implants.

### Adverse events

Nine of the diagnostic accuracy studies, two studies reporting patient attitudes, and 44 additional studies, reported results relating to adverse events. The lack of reporting of data on adverse events cannot be interpreted as no adverse events having occurred. The criteria used in monitoring and recording adverse events varied and were not always reported. These results should therefore be regarded only as a guide to the spectrum of adverse events reported and not as an accurate assessment of their frequency.

The most commonly reported adverse events were minor pain or discomfort during or immediately after the procedure (17% for 2D time of flight magnetic resonance angiography (2/12 patients), 22% for duplex ultrasonography (22/98 patients), and up to 10% for contrast enhanced magnetic resonance angiography (10/98 patients)), acute symptoms in the digestive system associated with contrast enhanced magnetic resonance angiography (up to 10% (2/20) patients), and anxiety associated with 2D time of flight magnetic resonance angiography (10% (4/40) patients), and acute adverse events in the central and peripheral nervous system associated with contrast enhanced magnetic resonance angiography (up to 10% (2/20) patients).

The highest proportion of adverse events was reported for magnetic resonance angiography. Major adverse events (death and severe vascular adverse events), however, were reported in a higher proportion

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Diagnostic accuracy for detection of occlusion with different assessment methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>No of patients</td>
</tr>
<tr>
<td>Contrast enhanced magnetic resonance angiography</td>
<td></td>
</tr>
<tr>
<td>Lenhart$^{17}$</td>
<td>45</td>
</tr>
<tr>
<td>Meaney$^{18}$</td>
<td>20</td>
</tr>
<tr>
<td>Schafer$^{19}$</td>
<td>30</td>
</tr>
<tr>
<td>Steffens$^{21}$</td>
<td>50</td>
</tr>
<tr>
<td>Sueyoshi$^{22}$</td>
<td>23</td>
</tr>
<tr>
<td>Winterer$^{23}$</td>
<td>76</td>
</tr>
<tr>
<td>2D time of flight magnetic resonance angiography</td>
<td></td>
</tr>
<tr>
<td>Baum$^{24}$</td>
<td>155</td>
</tr>
<tr>
<td>Hoch$^{25}$</td>
<td>20</td>
</tr>
<tr>
<td>Hoch$^{26}$</td>
<td>45</td>
</tr>
<tr>
<td>Yucelt$^{27}$</td>
<td>25</td>
</tr>
<tr>
<td>Computed tomography angiography</td>
<td></td>
</tr>
<tr>
<td>Heuschmid$^{28}$</td>
<td>23</td>
</tr>
<tr>
<td>Martin$^{29}$</td>
<td>41</td>
</tr>
<tr>
<td>Puls$^{30}$</td>
<td>31</td>
</tr>
<tr>
<td>Rieker$^{31}$</td>
<td>50</td>
</tr>
<tr>
<td>Catalano$^{32}$</td>
<td>50</td>
</tr>
<tr>
<td>Duplex ultrasonography</td>
<td></td>
</tr>
<tr>
<td>Aly$^{33}$</td>
<td>90</td>
</tr>
<tr>
<td>Bergmania$^{34}$</td>
<td>44</td>
</tr>
<tr>
<td>Hatusaki$^{35}$</td>
<td>29</td>
</tr>
<tr>
<td>Linke$^{36}$</td>
<td>25</td>
</tr>
<tr>
<td>Sensier$^{37}$</td>
<td>76</td>
</tr>
<tr>
<td>Zechner$^{38}$</td>
<td>54</td>
</tr>
<tr>
<td>Legemate$^{39}$</td>
<td>61</td>
</tr>
</tbody>
</table>

NR = not reported.

*Stage II = intermittent claudication; stage III = ischaemic rest pain; stage IV = tissue loss.
of patients who underwent contrast angiography, although the overall proportion who experienced major adverse events was low (severe vascular adverse events: contrast angiography 3% (1/19 patients); contrast enhanced magnetic resonance angiography 0.5% (2/435 patients)). There were two deaths: one with contrast angiography and one with contrast enhanced magnetic resonance angiography.

Studies reported adverse events related to the contrast agent for a small proportion of patients in relation to contrast angiography (acute renal failure in 10% (4/42) of patients with baseline chronic renal insufficiency) and contrast enhanced magnetic resonance angiography (acute renal failure: 1% (3/218) of patients with baseline chronic renal insufficiency; acute change in renal function: 1% (2/136 patients); severe unspecified adverse events related to contrast agent: up to 1% (5/641 patients)). In one study, which was specifically designed to evaluate the dose response and safety of one contrast agent (gadofosveset trisodium),83 a high proportion of patients (25%; 59/238) experienced unspecified adverse events related to the contrast agent after contrast enhanced magnetic resonance angiography.

**DISCUSSION**

**Key findings**

Contrast enhanced magnetic resonance angiography is the most accurate diagnostic technique for the detection of (50% or more) stenosis or occlusion, with most studies reporting sensitivities and specificities of over 90% (based on a “per segment” rather than “per patient” analysis). Magnetic resonance angiography was associated with the highest proportion of adverse events, although these were generally mild, with the most severe events associated with contrast angiography. The results of three surveys on patients’ attitudes showed that patients who had no contraindications for magnetic resonance angiography preferred magnetic resonance angiography to contrast angiography.

The use of computed tomography angiography for the assessment of peripheral arterial disease is a relatively recent development, and its contribution to effective surgical planning remains to be explored. Patients found computed tomography angiography less uncomfortable than contrast angiography or magnetic resonance angiography, and only a few mild adverse events were reported.

The only controlled trial of the effectiveness of imaging procedures, in terms of surgical planning and outcome of patients, found that duplex ultrasonography and contrast angiography were comparable, a result that is seemingly at odds with poor estimates of the diagnostic accuracy for duplex ultrasonography. The sensitivity of duplex ultrasonography seems to be inferior to both contrast enhanced magnetic resonance angiography and computed tomography angiography, which means that duplex ultrasonography may miss some significant stenoses. This may be of particular concern if duplex ultrasonography were to be used to screen patients before surgical planning. Duplex ultrasonography, however, is unlikely to misclassify a whole limb as “normal” and thus inappropriately screen out a patient from further investigation. Fifty per cent of patients expressed no preference between time of flight magnetic resonance angiography or contrast enhanced magnetic resonance angiography, and only a few mild adverse events were reported.

The area of leg assessed probably affects diagnostic performance. Contrast enhanced magnetic resonance angiography and duplex ultrasonography were less accurate for detecting stenoses in the foot. There was insufficient evidence to judge computed tomography angiography. The assessment of potential outflow vessels in the foot is known to be problematic and warrants further research, particularly with respect to newer technologies such as computed tomography angiography. Separate data on calf vessels and foot vessels are required as the inclusion of foot vessels in below knee imaging may lower the accuracy of results.

**Strengths and weaknesses of the review**

We conducted extensive literature searches to locate all relevant studies. The possibility of publication bias

**Fig 4| Sensitivities for the detection of occlusion**
remains a potential problem for all systematic reviews. The extent to which publication bias is an issue for diagnostic studies remains unclear as such studies measure the agreement between the results of the index test and the reference standard, rather than assessing whether there is a significant difference in outcome between an intervention and control group. Studies reporting higher estimates of test performance are more likely to be published, but the extent to which this occurs is unclear. Similarly, tests might not perform as well in the clinical setting as indicated by reports from research studies.

Our review was limited by the lack of high quality, well reported studies. We found only one controlled trial, which used a historical control group that could be subject to bias. Most studies that provided data on diagnostic accuracy had small sample sizes (median 41.5, range 20-183) and reported results on a per segment rather than per patient basis. Our review therefore provides information on the ability of these techniques to detect stenosis within particular arterial segments but not for determining the presence or absence of disease on a per patient or per limb basis. Few included studies reported these data. Analysis by segment also means that the estimates of the 95% confidence intervals for sensitivity and specificity do not account for the clustering of segments within patients. This would also affect statistical testing of heterogeneity, but given the considerable heterogeneity observed, any conclusions are not likely to be affected. The estimates of specificity derived from this type of study may be raised as increasing the number of segments assessed is likely to increase the number of true negatives.

We did not collect data on variability between observers, although we note that the methods used to ascertain degree of stenosis were not generally well reported and few studies directly measured such variability. This is an important issue in the evaluation of tests that require subjective interpretation, and further investigation of its effects on estimates of the accuracy of vascular imaging techniques is needed.

The field of vascular imaging research is evolving rapidly, particularly in relation to the use of computed tomography angiography, which is a relatively recent development in the assessment of peripheral arterial disease. We did not find any study investigating the diagnostic accuracy of the new 64 slice computed tomography angiography as this is a very new development. Our results represent the imaging techniques available at the time the primary studies were undertaken and will become out of date as new techniques emerge.

**Implications for clinical practice**

From data that reported the accuracy of the imaging tests at assessing arterial segments, rather than the whole limb or areas of the limb, contrast enhanced magnetic resonance angiography seemed to have better overall diagnostic accuracy than computed tomography angiography and duplex ultrasonography, and was preferred by patients over conventional angiography. It might therefore be a viable alternative to conventional contrast angiography for assessing patients with peripheral arterial disease before treatment. We could not identify enough data to assess the effectiveness of the imaging tests in terms of surgical planning and postoperative outcomes. In addition, the lack of data on severity of disease and comorbidities reported by the included studies reduces the generalisability of these findings.

**Implications for further research**

Quality assessment highlighted limitations in the quality of methods and reporting of many included studies. Future evaluations of diagnostic tests should follow the STARD guidelines for reporting of diagnostic accuracy studies. They should also consider reporting results by patient or by limb, as well as by segment, if they would be relevant to clinical practice.

Further research should assess the performance and adverse effects of the imaging tests on different subgroups of patients, particularly those who may be at higher risk of certain adverse events, such as those with diabetes and renal insufficiency. Additional separate data are required regarding the performance of the different imaging tests for assessing calf and foot vessels. The use of newer technologies, such as computed tomography angiography, for the assessment of peripheral arterial disease should be assessed.

<table>
<thead>
<tr>
<th>Contrast enhanced magnetic resonance imaging</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenhart</td>
<td>0.99 (0.96 to 1.00)</td>
</tr>
<tr>
<td>Meaney</td>
<td>0.97 (0.95 to 0.98)</td>
</tr>
<tr>
<td>Schafer</td>
<td>1.00 (0.99 to 1.00)</td>
</tr>
<tr>
<td>Steffens</td>
<td>0.99 (0.98 to 1.00)</td>
</tr>
<tr>
<td>Sueyoshi</td>
<td>1.00 (0.99 to 1.00)</td>
</tr>
<tr>
<td>Winterer</td>
<td>0.99 (0.99 to 1.00)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2D time of flight magnetic resonance imaging</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baum</td>
<td>0.85 (0.82 to 0.87)</td>
</tr>
<tr>
<td>Hoch</td>
<td>0.96 (0.93 to 0.98)</td>
</tr>
<tr>
<td>Hoch</td>
<td>0.98 (0.96 to 1.00)</td>
</tr>
<tr>
<td>Yucel</td>
<td>0.98 (0.94 to 0.99)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Computed tomography angiography</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heuschmid</td>
<td>0.99 (0.97 to 1.00)</td>
</tr>
<tr>
<td>Martin</td>
<td>1.00 (0.99 to 1.00)</td>
</tr>
<tr>
<td>Puls</td>
<td>1.00 (0.98 to 1.00)</td>
</tr>
<tr>
<td>Rieker</td>
<td>0.99 (0.99 to 1.00)</td>
</tr>
<tr>
<td>Catalano</td>
<td>0.99 (0.99 to 1.00)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duplex ultrasonography</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aly</td>
<td>0.99 (0.99 to 1.00)</td>
</tr>
<tr>
<td>Bergamini</td>
<td>0.97 (0.94 to 0.98)</td>
</tr>
<tr>
<td>Hatsukami</td>
<td>0.98 (0.95 to 1.00)</td>
</tr>
<tr>
<td>Linke</td>
<td>1.00 (0.97 to 1.00)</td>
</tr>
<tr>
<td>Sensier</td>
<td>0.96 (0.93 to 0.98)</td>
</tr>
<tr>
<td>Zechchner</td>
<td>0.99 (0.97 to 1.00)</td>
</tr>
<tr>
<td>Legemate</td>
<td>0.99 (0.98 to 1.00)</td>
</tr>
</tbody>
</table>

Fig 5 | Specificities for the detection of occlusion
WHAT IS ALREADY KNOWN ON THIS TOPIC

Severity of disease determines the management strategy for symptomatic lower limb peripheral arterial disease, so detailed assessment of patients is needed before a suitable treatment plan can be developed. Intra-arterial contrast angiography is regarded as the reference standard investigation for the assessment of peripheral arterial disease.

WHAT THIS STUDY ADDS

Contrast enhanced magnetic resonance angiography has better overall diagnostic accuracy than computed tomography angiography or duplex ultrasonography and is generally preferred by patients over conventional contrast angiography.

Data on the influence of imaging technologies on the surgical planning and postoperative outcome for patients with peripheral arterial disease are urgently needed. A simple comparison of the accuracy of a technique for defining the degree of stenosis cannot fully assess the ability of a procedure to produce the “vascular road map” as factors such as length and grouping of stenoses are not considered. In addition a comparative diagnostic accuracy study assumes that the result of the reference standard investigation (in this case contrast angiography) is always correct. Therefore, an evaluation with this method can never find that the new technology (index test) gives superior information to that provided by current practice (reference standard).

The most reliable and appropriate method for obtaining comparative data on different testing options would be a randomised controlled trial designed to provide information on the influence of tests on decisions about treatment and outcomes in patients with peripheral arterial disease. Data on health economics could be collected simultaneously. There may be ethical objections to a randomised controlled trial, such as the withholding of an available test, particularly when it is a routine part of assessment of peripheral arterial disease in the institution involved in the study. Such a trial would be difficult because of the refinements in technology over time, the availability of the technologies, and the potentially large sample size required. A large multicentre trial might be necessary.

Contributors: RC (guarantor) was responsible for study selection, data extraction, validity assessment, data analysis, and writing the paper. JB was involved in study selection, data extraction, validity assessment, data analysis, and writing the paper. GC, RA-I, and DC were involved in data extraction, validity assessment, data analysis, and writing the paper. KW devised the search strategy, carried out the literature searches, and wrote the search methods sections of the paper. EB provided advice on technical issues and commented on drafts of the paper. MG provided clinical advice and commented on drafts of the paper. WM provided input at all stages, commented on drafts of the paper, and took overall responsibility for the review.

Funding: Health Technology Assessment Programme (project No 03/07/04). The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Department of Health.

Competing interests: EB is now director of a company that undertakes consulting associated with medical imaging research. Neither she nor JK received payment for their contributions to this review.

Ethical approval: Not required.


Accepted: 10 April 2007
Diagnostic scope of and exposure to primary care physicians in Australia, New Zealand, and the United States: cross sectional analysis of results from three national surveys

Andrew B Bindman, professor; Christopher B Forrest, professor; Helena Britt, associate professor and director; Peter Crampton, professor; Azeem Majeed professor

ABSTRACT

Objectives To compare mix of patients, scope of practice, and duration of visit in primary care physicians in Australia, New Zealand, and the United States.

Design Comparison of three comparable cross sectional surveys performed in 2001-2. Physicians completed a questionnaire on patients’ demographics, diagnoses, and duration of visit.

Setting Primary care practice.

Participants 79 790 office visits in Australia, 10 064 in New Zealand, and 25 838 in the US.

Main outcome measures Diagnostic codes were mapped to the Johns Hopkins expanded diagnostic clusters.

Scope of practice was defined as the number of expanded diagnostic clusters accounting for 75% of all managed problems related to morbidity. Exposure to primary care was calculated from duration of visits recorded by the physician, and reports on rates of visits to primary care for each country.

Results In each country, primary care physicians managed an average of 1.4 morbidity related problems per visit. In the US, 46 expanded diagnostic clusters accounted for 75% of problems managed compared with 52 in Australia, and 57 in New Zealand. Correlations in the frequencies of managed health problems between countries were high (0.87-0.97 for pairwise comparisons). Though primary care visits were longer in the US than in New Zealand and Australia, the per capita annual exposure to primary care physicians in the US (29.7 minutes) was about half of that in New Zealand (55.5 minutes) and about a third of that in Australia (83.4 minutes) because of higher rates of visits to primary care for each country.

Conclusions Despite differences in the supply and financing of primary care across countries, many aspects of the clinical practice of primary care physicians are remarkably similar in Australia, New Zealand, and the US.

INTRODUCTION

Previous studies show that the strength of a country’s primary care infrastructure is positively associated with health outcomes and negatively associated with healthcare costs. In general, these studies have relied on experts to rate the degree to which policies and organisational characteristics of healthcare systems support primary care practice, defined as accessibility, longitudinality, comprehensiveness, coordination, family centredness, and community orientation. Limited research has been done on the clinical content and duration of visits in primary care across countries. We sought to characterise the diagnostic scope of and exposure to primary care in three countries—Australia, New Zealand, and the United States—that vary in the supply of primary care physicians, the accessibility to primary care through health insurance, and the role of primary care physicians as gatekeepers to specialty care.

Of the three countries studied, Australia has the greatest number of primary care physicians per 100 000 population (112) and the largest proportion (56%) of physicians trained in primary care specialties (table 1). In Australia and New Zealand, primary care physicians are trained as general practitioners. In the US, general internists, general paediatricians, and family practitioners all contribute to the pool of primary care physicians.

In the US universal health insurance that covers access to primary care is not available for people under 65 years, as it is in New Zealand and Australia. During the study period about 41 million Americans (15% of the total population) were uninsured and another 16 million adults aged 19-64 were underinsured. These individuals use primary medical care services, but at a lower rate than they would if they had insurance. The national insurance benefits in New Zealand and Australia include cost sharing except for some low income patients. A portion of the population has private insurance to supplement public coverage, but private insurance does not typically cover primary care services.

In Australia and New Zealand, primary care physicians serve as gatekeepers who coordinate and manage access to specialists through their referrals. Some health plans in the US require patients to use primary care physicians to access specialty care, but this practice has been decreasing in recent years, and many patients access specialty care services directly. We hypothesised that there would be substantial overlap in the practice of primary care across the
three countries, but key differences in the US healthcare system would contribute to some observed differences. For example, we expected that the range of problems managed in primary care would be narrower in the US because of the greater proportion of specialist physicians in their healthcare system and more direct access to specialty care for patients. We also expected that differences in the US physician workforce, in combination with a higher proportion of uninsured people, would contribute to a lower per capita exposure time to primary care physicians in the US than in Australia and New Zealand.

**METHODS**

We used three independent nationally representative cross sectional surveys to compare mix of patients, scope of practice, and duration of visit among primary care physicians in Australia, New Zealand, and the US. We used the bettering the evaluation and care of health (BEACH) survey in Australia; the national primary medical care survey (NatMedCa) in New Zealand; and the national ambulatory medical care survey (NAMCS) in the US. The questionnaires include items on whether the encounter is for a new or follow-up patient, patients’ demographics and diagnoses, and duration of visit. The reporting periods are spread evenly throughout the year to reflect seasonal differences.

BEACH is a continuous national survey in which a random sample of about 1000 of Australia’s 17 500 general practitioners participate each year. Participating general practitioners complete (on paper encounter forms) information regarding 100 consecutive encounters with patients. Each general practitioner’s encounters are weighted according to their clinical activity as measured through submitted claims for the previous three month period. For this study, we used data from the 12 month period 2001-2.

The NAMCS is a national annual survey of office based practice in the US. Physicians are sampled with a multistage probability design that involves primary sampling units, practices within those units, and patients’ visits within practices. Depending on the size of their practice, participating physicians contribute anywhere from 20% to 100% of their encounters during the one week study period. For this study, we used the 2001 and 2002 samples and included physicians whose specialties were general internal medicine, general paediatrics, family practice, or general practice.

We calculated national estimates using weights that accounted for the complex survey design.

The NatMedCa survey was performed in New Zealand in 2001-2 among a nationally representative probability sample of general practitioners and patients’ visits. For two periods of one week, each selected general practitioner completed a questionnaire for a 25% systematic sample of patients’ visits. The questionnaire was adapted from the NAMCS administered in the US. To obtain a nationally representative sample, the survey sampled geographic locations and sampled general practitioners from locations stratified by type of organisation and by whether the practice was in a rural or urban setting. General practitioners and visits were weighted to account of different sampling probabilities.

Analysis was limited to office based face to face encounters in which the physician recorded one or more diagnosis codes for morbidities treated during the visit. We excluded visits in which physicians recorded only administrative, process, or preventive care codes. Administrative codes are used in the US to indicate a personal or family history of a disease or an abnormal laboratory or other test result. Process codes are used in Australia and New Zealand to record diagnostic and treatment actions such cardiography or immunisation. We intended to describe preventive care practices for activities such as immunisations, routine health supervision, and cancer screening; however preventive care is not well described by diagnostic codes and differences in how preventive care is recorded in the classification systems used across countries made this problematic. Physicians recorded diagnoses in free text and trained coders converted these into the classification system used in that country. In Australia up to four free text diagnoses were classified according to the International classification of primary care, version 2 (ICPC-2). In New Zealand up to four diagnoses were classified into Read codes. In the US, up to three diagnoses were coded in ICD-9-CM (international classification of disease, 9th revision, clinical modification). To create a common taxonomy for this study, we re-assigned all diagnostic codes to an expanded diagnostic cluster. These clusters are clinically homogeneous groups of diagnostic codes that were developed by Johns Hopkins University. The original grouping algorithm was developed from ICD-9-CM For this project, three of the authors, who are practising primary care physicians, and a separate primary care physician in Australia, assisted in creating

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**Table 1: Characteristics of primary care by country, 2001-2**

<table>
<thead>
<tr>
<th>Characteristics of primary care by country, 2001-2</th>
<th>Australia</th>
<th>New Zealand</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care physicians/100 000 population</td>
<td>112⁵</td>
<td>78⁵</td>
<td>87⁷</td>
</tr>
<tr>
<td>Percentage of primary care physicians</td>
<td>56⁶</td>
<td>42⁵</td>
<td>36⁷</td>
</tr>
<tr>
<td>Percentage of population uninsured for primary care</td>
<td>0</td>
<td>0</td>
<td>15¹⁰</td>
</tr>
<tr>
<td>Percentage with primary care gatekeeping for specialty care</td>
<td>100</td>
<td>100</td>
<td>38¹¹</td>
</tr>
<tr>
<td>Mean No of primary care visits/person/year</td>
<td>5.2⁹</td>
<td>3.2⁸</td>
<td>1.8¹²</td>
</tr>
</tbody>
</table>

*Using methods described by Forrest and Whelan,¹³*
Fig 1 | Age standardised frequency of health problems managed in primary care in Australia, New Zealand, and the US: 2001-2

Table 2 | Demographics of patients as weighted* percentage of primary care visits by country, 2001-2

<table>
<thead>
<tr>
<th></th>
<th>Australia (n=114 402)</th>
<th>New Zealand (n=15 523)</th>
<th>United States (n=42 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded†</td>
<td>13</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Visits by patients who are:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-17 years</td>
<td>17</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>18-64 years</td>
<td>60</td>
<td>52</td>
<td>47</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>23</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Female</td>
<td>57</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>New patients</td>
<td>9</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

*Sampling weights that were specific to each country were applied to account for the complex survey designs to obtain national probability estimates of visits to primary care in each country.
†Visits for administrative, process, or preventive care services only.
condition in Australia (11.3) and New Zealand (9.1). This is also reflected in substantially greater rates of visits per 1000 in the US for diabetes (64.0) and hyperlipidaemia (59.2) than in Australia (31.0 and 32.2, respectively) and New Zealand (25.9 and 11.7, respectively).

The average duration of a visit was about 10% longer in the US than in Australia and New Zealand. They were 16.5 minutes (16.4 to 16.6) in the US compared with 15.0 minutes (14.3 to 15.6) in New Zealand and 14.9 minutes (14.6 to 15.2) in Australia. Visit lengths were longer in the US for all age and sex groups. Because the average number of primary care visits per capita was greater in New Zealand and Australia, however, the per capita annual exposure to primary care physicians was substantially lower in the US. The mean time spent per year in primary care was 29.7 minutes (29.5 to 29.9) in the US, 55.5 minutes (52.8 to 57.8) in New Zealand, and 83.4 minutes (81.9 to 84.8) in Australia (fig 2).

**DISCUSSION**

Despite differences in the supply and financing across countries, many aspects of the clinical practice of primary care physicians are remarkably similar in Australia, New Zealand, and the US. There is a high level of agreement in primary care across countries in the number of problems that are managed per visit, the types of problems that are managed, and the duration of visits.

**Diagnostic scope of practice**

The similarity in the types of problems managed within primary care across countries implies that primary care practice is a definable area of clinical work and not merely the activities that are not performed by specialists. The finding that the range is narrower in the US than in Australia and New Zealand, however, also suggests that the comprehensiveness of primary care is influenced at the margin by the amount of specialisation in the healthcare system. The use of specialists is greater in the US than in either Australia or New Zealand.

The high proportion of specialist physicians in the US in combination with the ability of patients to self refer for specialty services results in some patients seeing only specialists for ambulatory care services. Our results extend these findings to suggest that the availability of specialist physicians might also contribute to defining the range of problems managed in primary care. For example, compared with Australia and New Zealand, the US has lower rates of visits in primary care for the management of reproductive problems in women. The US is also the only country of the three that provides most women with direct access to gynaecologists. The presence of general internists and general paediatricians among US primary care physicians may contribute to a narrower diagnostic scope of practice in the US. Differences in rates of visits for specific problems, such as cardiovascular disease in the US, might also reflect national differences in the prevalence of conditions or health seeking behaviour. Unfortunately, our data do not allow us to determine this.

**Exposure to primary care**

The biggest difference in practice across the three study countries is the substantially shorter time per capita in the US. Annually, the average American receives a little more than half the exposure to primary care physicians than people in New Zealand and just over a third of that in Australia. This difference may have real consequences in terms of preventive care and management of chronic conditions. The provision of prevention services recommended by the US Prevention Services Task Force requires an estimated average of 37 minutes a year for children and 40 minutes for adults. Not only does the time demand for such services exceed the annual time available to the average American in primary care, it does not consider the average additional need of 20-40 minutes a year for each chronic condition a person may have.

More than half of US primary care physicians’ time is spent on the management of acute conditions, and this role further limits their capacity to meet the prevention and chronic care needs of their patients.

Of the three countries we studied, only Australia approaches a per capita exposure to primary care that could reasonably be expected to meet patients’ demands for preventive and acute and chronic care needs. The severe shortfall of available time in primary care for prevention and chronic care management in the US could partially explain why the US does not have health outcomes that correspond to its overall investment in health care.

**Limitations**

Exclusion of visits in which only administrative, process, or preventive care codes were recorded limits our ability to count the amount of preventive care that is actually occurring in primary care. Even with this exclusion, however, we have an accurate estimate of the exposure to primary care by country. This estimate includes all visits, even those in which only preventive, administrative, or process codes would have been recorded.
As with any comparison between countries, our results should be interpreted with caution. Firstly, we looked at only three countries and this limits its generalisability. Secondly, although the data were derived from similar surveys with large samples, there were differences in how some questions were asked and coded. We were careful to consider differences in the surveys and to create common methods of analysis that would limit the introduction of bias, but our results may still include measurement artefact. For example, the US had the highest percentage of visits excluded from analysis because they were coded only with administrative, process, or preventive care codes. These visits may reflect provision of primary medical care services that had they been included would have widened our assessment of the scope of practice in the US relative to Australia and New Zealand. Thirdly, the available cross sectional observational data limit our ability to draw causal inferences and lacked information that would allow us to determine how variation in practice is associated with differences in quality of care. None the less, our study is useful because most previous work has focused on hospital based care and procedures.

Summary

Despite the markedly different approaches countries take towards funding and organising healthcare delivery, a fundamental question remains regarding the role of primary care in a healthcare system. One of the current objectives of the UK government is to shift services from hospital based to primary care settings. This raises questions about the appropriate balance between services supplied by primary care physicians and specialists. Comparisons between countries offer an opportunity to learn from natural experiments and may provide insights into how primary care can best contribute to equitable, efficient, and effective health-care systems.

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Acute coronary syndromes without ST segment elevation

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The diagnosis and management of acute coronary syndromes have been evolving rapidly in recent years. New antithrombotic agents have improved the results of medical treatment, and new methods of estimating a patient’s risk of an adverse outcome help clinicians to decide who may benefit from invasive treatment—that is, coronary angiography and subsequent revascularisation (percutaneous coronary intervention or coronary bypass surgery). As these therapeutic decisions need to be made soon after admission, the classification of acute coronary syndromes is now based on the information that is available on admission.

In the United Kingdom, about 114 000 patients with acute coronary syndromes are admitted to hospital each year.1 More than 5.5 million patients present to a US emergency department with chest pain and other symptoms related to acute coronary syndrome each year.2 Acute coronary syndrome is seen in people of all ages, races, and socioeconomic backgrounds.

Pathology
Acute coronary syndromes generally represent acute complications of chronic atherosclerotic disease of the coronary arteries. The progressive accumulation of inflammatory materials and lipids over the years can ultimately lead to erosions of the intima or rupture of lipid rich plaques. Both events are strongly thrombogenic, and a blood clot often forms. Many of these clots remain clinically undetected but contribute to the progressive thickening of the arterial wall and the narrowing of the vessel. Thrombi may lead to acute reductions in vessel patency, resulting either in sudden onset or worsening of angina; they may also acutely occlude the vessel, causing acute myocardial infarction. Intermediate presentations also occur, with incomplete occlusion leading to myocardial damage or, conversely, with complete occlusion that does not lead to necrosis. The last of these may be the case if adequate collaterals have been formed in the preceding weeks or months as a response to chronic recurrent ischaemia.

How are acute coronary syndromes classified?
Until recently, the two typical clinical presentations were generally referred to as unstable angina and acute myocardial infarction. A diagnosis of acute myocardial infarction requires evidence of myocardial necrosis. Whether myocardial infarction (that is, necrosis of cardiac muscle) is present usually becomes clear at a later stage, on the basis of laboratory tests (elevation of markers such as creatine kinase MB or cardiac troponins) or on the electrocardiogram (loss of QRS voltage or development of pathological Q waves). Because of the therapeutic decisions that need to be made on admission of patients with acute chest pain, before myocardial necrosis may be detected, new terms for the admission diagnosis have been introduced. These are based primarily on the findings on the admission electrocardiogram (table).

If ST segment elevation (suggestive of transmural ischaemia) is present, a diagnosis of ST segment elevation acute coronary syndrome is made. These patients have an indication for urgent reperfusion treatment, either by percutaneous coronary intervention or by administration of a thrombolytic agent. If no ST segment elevations are present (normal or depressed ST segments or T wave inversion), a diagnosis of non-ST segment elevation acute coronary syndrome is made. If myocardial necrosis is documented, as indicated above, a discharge diagnosis of ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction is made. According to current guidelines, any elevation of cardiac markers qualifies as a myocardial infarction.3 Depending on the development of the electrocardiogram after admission, myocardial infarction may be subclassified as Q wave or non-Q wave myocardial infarction. If no evidence of myocardial necrosis exists, a discharge diagnosis of acute coronary syndrome or unstable angina is generally used. In this review, we focus on non-ST segment elevation acute coronary syndrome.

Sources and selection criteria
Acute coronary syndromes represent one of the most intensively studied topics in clinical research. Current guidelines and practice are based on a very large body of evidence, a summary of which is beyond the scope of this review. Our information came from personal archives and searches of Medline with the key words “acute coronary syndrome” and “unstable angina”. We used current guidelines on the management of acute coronary syndromes and searched for relevant Cochrane reviews.
How can we stratify risk in patients with acute coronary syndrome?

The in-hospital management of patients with chest pain is determined by the risk of complications and death. Indicators of high risk include typical complaints, documented coronary artery disease, and advanced age. On physical examination, new mitral regurgitation, hypotension, excessive sweating, pulmonary oedema, and rales are all associated with high risk. On the electrocardiogram, new Q waves, new ST segment deviation, or new T wave inversion with symptoms indicate high risk. Raised cardiac troponin T, troponin I, or creatine kinase MB in the serum indicates myocardial necrosis and a high risk of an adverse outcome. In addition, markers of congestive heart failure, particularly plasma B-type natriuretic peptide, have been shown to be independent predictors of death in patients with non-ST segment elevation acute coronary syndrome.

For patients admitted with this diagnosis, several risk scores have been developed from clinical trials and registries. These can help to identify patients who are most likely to benefit from “invasive” treatment (coronary angiography and revascularisation). As patients included in trials represent a selected group of patients, risk models derived from unselected registries are probably more reliable in clinical practice.

How are patients managed in hospital?

The treatment of patients with non-ST segment elevation acute coronary syndrome, according to current guidelines, consists of two components: to alleviate the patient’s complaints of pain and anxiety and to prevent recurrences of ischaemia and progression to (or to limit) myocardial infarction. This requires intensive antithrombotic treatment, and often an invasive strategy with coronary angiography followed by revascularisation if appropriate.

Drug treatment routinely includes β blockers, which reduce myocardial oxygen demand by reducing heart rate and blood pressure and reduce the risk of arrhythmias and recurrent ischaemia. Sedatives and analgesics may be used with the same goals, by reducing anxiety and pain. Vasodilators, such as nitrates and calcium channel blockers, are used to reduce the dynamic (spastic) component of coronary obstruction, and to lower blood pressure, but none of these drugs has been shown to reduce the risk of myocardial infarction or death.

Predictors of death in patients with acute coronary syndromes, according to the GRACE registry

- Age
- Killip class (heart failure)
- Heart rate
- Blood pressure
- ST deviation on electrocardiogram
- Cardiac arrest
- Raised creatinine
- Raised creatine kinase MB or troponin

How is acute coronary syndrome diagnosed?

The main initial diagnostic challenge is to differentiate acute coronary syndromes from non-cardiac chest pain. The assessment requires a thorough history (including analysis of risk factors), a physical examination, and, often, an electrocardiogram and determination of serum cardiac “markers” (troponin T, troponin I, creatine kinase MB isoenzyme). The most important determinant is the patient’s history. Symptoms of acute coronary syndrome include substernal chest pain, radiating to the arms, the jaw, the neck, the back, or even the abdomen, which may be accompanied by nausea, vomiting, dyspnoea, and diaphoresis. Some patients may present without chest pain, and dyspnoea may be the only complaint. Typical chest pain that occurs suddenly at rest, particularly in a young patient, may suggest acute coronary spasm, which is sometimes associated with the use of cocaine or methamphetamine. Abnormalities on physical examination are usually absent but may include signs of heart failure, such as rales or oedema, hypotension, excessive sweating, or new mitral regurgitation.

Patients suspected of having acute coronary syndrome should be referred to a hospital for observation, electrocardiography, and blood testing (cardiac markers). Importantly, a normal electrocardiogram does not rule out acute coronary syndrome (although it does make it less likely), particularly if documented after relief of symptoms. In addition, normal concentrations of cardiac markers do not rule out acute coronary syndrome, particularly if measured shortly after the onset of complaints. Elevation of these markers takes four to six hours after myocardial necrosis, and six to eight hours are needed before markers of necrosis appear in peripheral blood. If an initial blood test is normal, and the history is highly suggestive, most clinicians do a second test after eight to 12 hours. If this is also normal, and the electrocardiogram is normal or shows little acute evolution, then the patient is at very low risk and may be discharged. However, such patients should have an early stress test to document whether provoked ischaemia is present. If the cardiac biomarkers are raised or the electrocardiogram shows evolutionary changes, admission to hospital is indicated.

Imaging techniques may support the diagnostic process by showing wall motion abnormalities (echo-cardiography, magnetic resonance imaging), ischaemia (nuclear perfusion scanning), or coronary pathology (multislice computed tomography scanning). However, their role has not been firmly established.
Antithrombotic treatment

Antiplatelet agents
Aspirin is the mainstay of treatment. In an authoritative review by collaborating trialists, the use of aspirin was associated with a nearly 50% reduction in relative risk of vascular events compared with placebo. Addition of clopidogrel, a platelet membrane ADP receptor antagonist, was studied in a large clinical trial in patients at high risk. It was associated with an additional 20% relative risk reduction, with a small increase in the risk of bleeding (38% increase in relative risk, 1% in absolute risk). The combination of aspirin and clopidogrel is now recommended in patients admitted to a coronary care unit with non-ST segment elevation acute coronary syndrome. The recommended duration of combined treatment is up to 12 months, depending on several factors, including the level of risk and stent placement.

Inhibitors of the platelet glycoprotein 2b/3a receptor, a third class of antiplatelet agents, have been extensively studied in patients with non-ST segment elevation acute coronary syndrome. In a pooled analysis, the trials show a modest benefit of glycoprotein 2b/3a receptor inhibitors (odds ratio 0.91, 95% confidence interval 0.84 to 0.98; P=0.015), which seems to be limited to patients who have percutaneous coronary intervention. In patients treated non-invasively, the benefit is questionable. These studies were not done in high risk patients scheduled for percutaneous coronary intervention, and they were done before routine administration of clopidogrel was introduced. However, a recent well designed randomised study confirmed that abciximab, a glycoprotein 2b/3a receptor inhibitor, does provide benefit in patients with non-ST segment elevation acute coronary syndrome routinely managed with an invasive strategy when given in addition to aspirin and clopidogrel (relative risk 0.75, 0.58 to 0.97; P=0.03). Bivalirudin is a direct inhibitor of thrombin (that is, independent of antithrombin III) that has recently been compared with combinations of low molecular weight heparins or unfractionated heparin with glycoprotein 2b/3a receptor inhibitors, in patients with acute coronary syndromes having percutaneous coronary intervention. The trial results, which have not yet been published, show that bivalirudin alone was as effective as either type of heparin plus a glycoprotein 2b/3a receptor inhibitor, but with a lower risk of bleeding. However, bivalirudin was not compared with heparin without glycoprotein 2b/3a receptor inhibitors.

Summary of antithrombotic treatment
Taken together, antithrombotic treatment in patients admitted with non-ST segment elevation acute coronary syndrome should routinely include oral aspirin (daily dose 75-150 mg) and clopidogrel (75 mg daily, initial loading dose 300-600 mg). Fondaparinux (at a daily dose of 2.5 mg subcutaneously) is probably the preferred anticoagulant, although this has not yet been adopted in guidelines. Alternatively, unfractionated heparin (initial bolus of 60-70 U/kg (maximum 5000 U) and an initial infusion of 12-15 U/kg/h (maximum 1000 U/h) to a target activated partial thromboplastin time of 1.5-2.5 times control value) or low molecular weight heparins (for example, enoxaparin 1 mg/kg

Anticoagulants
Four classes of anticoagulants have been tested in patients with non-ST segment elevation acute coronary syndrome: unfractionated heparin, low molecular weight heparins, pentasaccharides (inhibitors of factor X), and direct thrombin inhibitors. On top of aspirin, short term treatment (up to seven days) with intravenous unfractionated heparin or subcutaneous low molecular weight heparins halves the risk of myocardial infarction or death according to a recent meta-analysis. No convincing difference in efficacy or safety exists between the two types of heparin, and no clear differences exist between low molecular weight heparins. Their main advantage is the ease of use, with subcutaneous administration and no need for laboratory monitoring. Fondaparinux, a pentasaccharide for subcutaneous use, has recently been compared with enoxaparin, the most widely studied low molecular weight heparin. A large scale randomised comparison found no difference in the occurrence of death or myocardial infarction in the in-hospital phase. However, the risk of bleeding complications was about 50% lower with fondaparinux. In the subsequent six months, this translated into a significantly lower mortality.

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Summary of antithrombotic treatment
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Unanswered research questions
Why do some patients present with unheralded acute myocardial infarction and some with unstable angina, whereas other patients never have acute events in spite of chronic coronary artery disease? How can we identify patients in whom revascularisation procedures will improve prognosis? Does a sex difference exist in the balance between risks and benefits of coronary revascularisation in patients with acute coronary syndromes (as has been suggested by some trial results)? In patients who are selected for revascularisation procedures, is a period of medical stabilisation before the intervention beneficial?
Patients suspected of having an acute coronary syndrome need to be admitted and evaluated by electrocardiography and measurement of cardiac "markers". Acute coronary syndromes are classified on the basis of the presence or absence of ST segment elevation on the admission electrocardiogram. All patients with acute coronary syndromes need intensive medical treatment, including combinations of antithrombotic drugs. In high risk patients, coronary angiography is indicated, with the aim of revascularisation if they have suitable coronary anatomy. Elevation of cardiac markers determines whether a discharge diagnosis of myocardial infarction is made. After discharge, treatment is aimed at preventing recurrences and treating the underlying atherosclerotic disease process.

**SUMMARY POINTS**

The patient’s history is the most important initial diagnostic tool. Patients suspected of having an acute coronary syndrome need to be admitted and evaluated by electrocardiography and measurement of cardiac "markers".

Acute coronary syndromes are classified on the basis of the presence or absence of ST segment elevation on the admission electrocardiogram.

All patients with acute coronary syndromes need intensive medical treatment, including combinations of antithrombotic drugs.

In high risk patients, coronary angiography is indicated, with the aim of revascularisation if they have suitable coronary anatomy.

Elevation of cardiac markers determines whether a discharge diagnosis of myocardial infarction is made.

After discharge, treatment is aimed at preventing recurrences and treating the underlying atherosclerotic disease process.

**Revascularisation**

Debate is ongoing as to whether all patients with non-ST segment elevation acute coronary syndrome should have coronary angiography followed by revascularisation (if indicated and if possible) or whether this should be done selectively in patients at high risk or in those who are refractory to medical treatment. Another question that remains unanswered is whether an initial period of stabilisation ("cooling down") before proceeding to the catheterisation laboratory is beneficial or whether invasive treatment should be done as soon as possible. Although this question has not been studied in randomised trials, several studies have compared an invasive approach to a more “conservative” approach. In a meta-analysis published in 2005, including seven trials and 9212 patients, a routine invasive strategy exceeded a selective invasive strategy in reducing myocardial infarction, severe angina, and readmission to hospital over a mean follow-up of 17 months.

Routine intervention was associated with a higher early mortality hazard and a trend towards a reduction in mortality during longer term follow-up. However, a subsequent randomised study in 1200 high risk patients with non-ST segment elevation acute coronary syndrome who received optimal medical treatment according to current guidelines found no significant difference in the combined end-point of death, myocardial infarction, or readmission to hospital at one year follow-up. This suggests that if medical treatment is optimised, a routine invasive approach may not be necessary. A recent Cochrane review, including all trials published to date, concluded that an invasive strategy in unstable angina/non-ST segment elevation myocardial infarction results in a significant 33% relative risk reduction for both the end points of refractory angina and readmission to hospital at six to 12 months. However, this analysis includes the older trials in which medical treatment was probably less effective.

Current guidelines do recommend an invasive strategy in patients at high risk. If initially a conservative approach is selected—for example, in patients at lower risk—the patient should be closely monitored for recurrent chest pain or signs of ischaemia, using repeat electrocardiograms, monitoring of the ST segment, and serial measurements of the cardiac markers (creatinine kinase MB, troponin). Even in the absence of such signs, the patient may have significant coronary artery disease. Predischarge stress testing is therefore generally done to determine if the patient is stable and whether significant coronary obstructions remain. Alternatively, high risk patients should be considered for angiography and appropriate revascularisation during the initial admission.

**What is appropriate long term treatment?**

After discharge, management of patients with acute coronary syndromes consists of two main components. Firstly, prevention of recurrent ischaemia and death requires continued treatment with aspirin (indestructibly), clopidogrel (at least 9-12 months), and β blockers. Secondly, the underlying atherosclerotic process should be treated by tackling all modifiable risk factors. These include the routine use of a statin to lower plasma low density lipoprotein cholesterol and the use of antihypertensive drugs to lower blood pressure.
density lipoprotein cholesterol concentrations, use of angiotensin converting enzyme inhibitors,3 strict treatment of hypertension and diabetes, cessation of smoking, achieving an optimal body weight, regular physical exercise, and healthy food choices.

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Competing interests: None declared.


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CORRECTIONS AND CLARIFICATIONS

Minerva
We misspelt the second name of one of the authors of the picture item in a recent Minerva (BMJ 2007;334:908, 28 Apr, doi: 10.1136/bmj.39190.509190.BD). Madanagopalan Ethunandan (not Ethunandand) is the correct spelling.

ABC of Clinical Electrocardiography: Conditions not primarily affecting the heart
Here’s a correction referring back to 2002. A caption was wrong in this article by Corey Slovis and Richard Jenkins (BMJ 2002;324:1320-3, doi: 10.1136/bmj.324.7349.1320). In the section “Other non-cardiac conditions” the caption to the first figure should have read: “Short QT interval in patient with hypercalcaemia [not hypocalcaemia] (calcium concentration 4 mmol/l).”

Obituary: Arthur Hamilton Crisp
Professor Arthur Hamilton Crisp died from kidney cancer, and not from stomach cancer as was stated in this obituary by Caroline Richmond (BMJ 2007;334:540, 10 Mar, doi: 10.1136/bmj.39125.617153.FA).

Obituary: John Cosh
In this obituary of John Cosh by Caroline Richmond (BMJ 2005;331:1026, doi: 10.1136/bmj.331.7523.1026) it has emerged two years later that we should not have stated that a manufacturer of herbal medicines, Gerard House, later became Bio-Health Ltd. In fact, we understand that it was David V Smith who founded Bio-Health, in 1981, and then sold shares to new directors in 1996.
A PATIENT’S JOURNEY

Cystic fibrosis

Emma Wicks

As the Good Witch told Dorothy in the *Wizard of Oz* it is always best to start at the beginning. Growing up, I always knew that I had cystic fibrosis, the same way I knew I had blue eyes and my cousins could all run faster than me.

I was lucky enough—though my parents did not think so at the time—to be diagnosed at two days old. The right information at diagnosis is crucial. After being told their daughter had a disease whose name they could not spell, and with no information from the hospital, my parents found out about it for themselves. Parents nowadays might use the internet; mine went to the library. The book they found, printed 15 years earlier, told them to abandon all hope and not become too attached to me.

**Travelling alone**

The road travelled with cystic fibrosis is often deserted, devoid of like minded companions. Growing up, some children picked on me because of my cystic fibrosis, but most of my classmates were too busy learning how to do chest physiotherapy or fighting over the honour of keeping me company when I was too unwell to go out at playtime. I decided that those who were mean were simply jealous of my “special treatment.” If only they had known that I would gladly have swapped with them in an instant.

Today, I welcome and respect the practice of segregation to prevent cross infection. Technology has lessened the impact of infection, but the condition is still not easy to bear. I wish I could sit in a room of people who know what it is to live with it.

I know many people with cystic fibrosis, although none of them are close friends. This is a choice I have made. The close friends with cystic fibrosis that I had previously have all died. Having friends who have cystic fibrosis can become a burden. I know I have this disease and I live with it every day, but to have it staring back at me through the eyes of another can be daunting.

There are the bad days—the ones where I have to ask for a helping hand, when I cannot be independent, when people I love have to clear up vomit and faeces and change their plans around me. Although they probably do not see me as a burden, that is how I feel. It is a bizarre situation, having this disease has made me grow up faster, yet because I am ill I am still heavily dependent on others.

**Companions on the journey**

While still a teenager I told my parents, “I’m old enough to take care of myself.” What rubbish. Nobody, whatever their age or health status, is past needing a bit of help. As I become sicker it will be my loved ones taking care of me once again. I know I will have to rely more on their support in the future. I am not sure who is looking forward to it the least.

Although I do not always want it to be, cystic fibrosis is a huge part of my life and of the lives of those close to me. It is important that healthcare professionals do not forget the people close to me; the relationship professionals have with their patients should extend to the people who care for them every day. My companions resent my illness more than I, because I have control over it while they look on helplessly, and some may need additional support.

It can be hard on my fiancé, as he feels responsible for my wellbeing and compliance with treatment. Moreover, he is still learning, as we all are. He has many questions, some of which seem a bit stupid, but it is important that members of the cystic fibrosis team do not make him feel the questions are unimportant.

**What adults with cystic fibrosis need**

A good relationship with healthcare professionals is essential, as they eventually become part of a patient’s extended family. People with long term conditions need people with whom they can discuss their concerns, beyond the medical ones. I am lucky; I attend a specialist centre where every member of staff is dedicated to looking after people with cystic fibrosis.

It is important that health professionals should see the person with cystic fibrosis as part of the team, their views being as important as professionals’ own. I become frustrated when clinicians seem unable to accept that, having lived with cystic fibrosis for more than 20 years, might know more about my illness than they do. Health professionals may be experts in their field, but patients are experts in their lives. The best doctor-patient relationships are those in which both parties educate each other.

Patients need access to information about cystic fibrosis. If professionals do not provide the right information at the right time, patients will go and look for themselves. Plenty of good quality information is available, but there is just as much incorrect information,
A RESEARCHER’S PERSPECTIVE

Identification of the cystic fibrosis gene in 1989 has led to earlier, more accurate diagnosis, and neonatal screening is being rolled out throughout the UK. Better understanding of the condition has ensured progressively more effective, patient friendly, treatment and care, most of which is carried out at least daily by family members in the home. Many young people around Emma’s age decide against befriending others with cystic fibrosis, and this may result in a feeling of isolation. In 1996, the Cystic Fibrosis Trust began to fund expert patient advisers, contactable through the trust, whose role is to enable all those affected by cystic fibrosis to have a voice in service planning, delivery, and review. Average survival age for those with cystic fibrosis, currently 31 years, is expected to reach 50 years for those born at the turn of the 21st century. For the first time in history, adults with cystic fibrosis in Britain will outnumber children living with the disease. As individuals age and their health declines, many conditions related to cystic fibrosis, such as diabetes, osteoporosis, and liver disease, become more likely.

Living into adulthood also presents those affected with new psychosocial challenges: taking responsibility for their treatment and care; negotiating further education, employment, and finances; gaining greater independence from parents; managing personal relationships; and deciding whether to have families of their own. Transition clinics, staffed by a multidisciplinary team, have been established to enable a smoother journey between paediatric and adult care, although resources are not always sufficient to provide the holistic care that these young adults need. Despite requiring daily, life sustaining treatment, most adults with cystic fibrosis continue to pay prescription charges.

The possibility of a lung or heart-lung transplant is a hope shared by many. End of life care for this population is currently patchy; many young people and families affected by cystic fibrosis that I have worked with are fighting battles with primary care trusts. The bad news

Of course, not everything is as it could be. Everyone with cystic fibrosis in the United Kingdom does not receive safe and appropriate care from a specialist multidisciplinary team. Because adults are not automatically entitled to free prescriptions, I spend a fortune paying for drugs—when I can get them in the first place. My general practitioner is fantastic, but sadly “postcode prescribing” is as prevalent as ever, and across the country, people living with cystic fibrosis are fighting battles with primary care trusts.

Journey’s end

My biggest fear is the future; it is difficult to know what it will bring. It is difficult to plan for the time that my parents were told I would not have. It is hard to think about getting a mortgage, or starting a pension when you’re not sure you’ll live long enough to have a retirement.

But I do not sit worrying about when I’m going to die. I think about it, but do not walk around clutching my funeral arrangements. So, I will worry about the future when it arrives. Until then, there are too many things to live for—my wedding, books to read, and bands I still have to discover.

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too, especially on the internet. Patients need to be able to filter out misleading facts, or have access to people who can guide them.

Losing the path

Having cystic fibrosis is different for everyone. Even with specialist multidisciplinary care it is still possible to lose grip of the steering wheel and veer off course. For example, when I have an acute infection I would love to take my intravenous antibiotics at home. It is much better than sitting in hospital for two weeks, especially when it is too far for anyone to visit. During my childhood my local hospital sent me home, armed with 15 minutes’ worth of training and one nervous mother, because they needed the bed. It was a disaster; we managed only three days, and the experience has stopped me from attempting intravenous treatment at home. I am probably capable, but as I live outside the hospital catchment area for homecare nursing I would have no support. With proper training, sufficient supplies, and adequate support I am sure I would feel differently.

I would have given anything to attend a transition clinic when I was 16. Instead, I received a letter stating that my next appointment would be in an adult clinic at another hospital. Now, people with an up to date atlas of knowledge patrol the rocky roads of Transition. Although this is far from perfect, it is good to know that certain things are improving.

The good news

Mostly, the future is bright. Gene therapy, while not exactly just round the corner, is looking extremely likely and is an incentive to adhere to treatments. The healthier patients’ lungs are, the more likely they will be able to benefit from the therapy. The treatments themselves have become less cumbersome. Carrying out my nebulised treatments used to take an hour of my day; now it takes around 30 minutes, including cleaning the equipment. The new nebulisers are compact enough not to need a separate suitcase for taking them on holidays. The physiotherapists now supply patients with a range of gadgets to clear the chest of mucus. It may not take less time to do, but it is much more pleasant than chest percussion—and I can do it by myself, so nobody has to find time to help me.

The best news is that people with cystic fibrosis are living their lives, and living them longer. We have jobs, families, and children. Most of us are going out and doing things our peers would never dream of doing.
 Established corticosteroid creams should be applied only once daily in patients with atopic eczema

Hywel C Williams

**The clinical problem**

Atopic eczema affects many adults and up to 20% of children, with health costs comparable to diabetes and asthma. One community survey of 1760 young children in the United Kingdom found that 84% had mild eczema, 14% moderate, and 2% severe eczema. Topical corticosteroids are a mainstay of treatment for inflammatory episodes. Most long-established topical corticosteroids such as betamethasone valerate or hydrocortisone are applied at least twice daily, but three newer preparations (mometasone, fluticasone, and methylprednisolone) have been developed for once daily application. Here, I propose that established preparations need be applied only once daily.

**The evidence for change**

Ten randomised controlled trials compared once daily versus more frequent application of topical corticosteroids within the same potency group. The findings are summarised in a UK Health Technology Assessment report and guidance from the National Institute for Health and Clinical Excellence (NICE). Another short term study has been published more recently. None of the studies found clear evidence that applying topical corticosteroids more than once a day produced better overall clinical outcomes in eczema, such as the number of people with a good response. Clear evidence of a faster response with more frequent use or a better response in subgroups such as children was lacking. No data were given on relapse rates.

The main adverse effect of topical corticosteroids is thinning of the skin. The studies included in the technology assessment were too short in duration (three to four weeks) to see if once daily application results in less skin thinning. However, as skin thinning is related to the amount and duration of topical corticosteroid, its strength, and its site of application, reducing the frequency of application could reduce local adverse effects.

It seems logical that applying topical corticosteroids once daily instead of twice daily would reduce costs by up to 50%. However, three newer potent topical corticosteroid preparations have been specifically manufactured and tested for once daily use (mometasone furoate, fluticasone propionate, and methylprednisolone aceponate). Newer once daily preparations may still cost more than twice daily use of older preparations such as betamethasone valerate. No trial has directly compared once daily betamethasone with once daily newer preparations. A blanket recommendation for a switch to once daily application of topical corticosteroids could paradoxically increase costs. This dilemma led to a mixed recommendation in the original NICE guidance to use topical corticosteroids once or twice daily and to use the cheapest alternative. Later papers have been more forthright in supporting once daily application of established corticosteroids.

**The barriers to change**

The case for changing to once daily application of established corticosteroids is strong. It is based on lack of evidence of superior efficacy in 11 randomised controlled trials; cost savings of up to 50% to the state or patient if an established preparation such as betamethasone valerate 0.1% is considered; the convenience to patients of applying preparations just once daily (important as a recent study suggested that mean adherence to twice daily topical corticosteroids was only 23%); and the possibility that side effects such as skin thinning can be reduced. Conflicting written advice in package inserts can be overcome by counselling patients beforehand. A change to once daily topical corticosteroids was suggested 10 years ago. Perhaps the biggest barrier to change is habit.

**How should we change our practice?**

Patients using moderate, potent, or very potent topical corticosteroids more than once a day should switch to once daily use. However, the above evidence on short term use of mostly potent topical corticosteroids in people in secondary care may not be generalisable to those with very mild eczema using mild preparations, such as 1% hydrocortisone, for longer periods.

**KEY POINTS**

- Established topical corticosteroids such as betamethasone valerate have typically been used twice daily or more frequently for treating inflammatory episodes of eczema
- Reducing the frequency of application to once daily does not seem to result in loss of efficacy and could lead to fewer local side effects
- Using topical corticosteroids just once a day may be more convenient for patients and may save costs if established preparations are used

Change Page aims to alert clinicians to the immediate need for a change in practice to make it consistent with current evidence. The change must be implementable and must offer therapeutic or diagnostic advantage for a reasonably common clinical problem. Compelling and robust evidence must underpin the proposal for change.

Series editor: Joe Collier (changepage@bmj.com), professor of medicines policy, St George’s Hospital and Medical School, London. Anyone wishing to propose a change in clinical practice should discuss the proposal with Joe Collier at an early stage.

A full version of this article and the references are on bmj.com
A 68 year old man sees you after you sent him a letter saying that the results of blood tests done over the past year to monitor hypertension show that he has chronic kidney disease (CKD). He is worried, as he thought that high blood pressure was his only medical problem.

What you should do

- Ask about symptoms of cardiovascular diseases (such as breathlessness, pedal oedema, chest pain, claudication), lower urinary tract symptoms, and compliance with antihypertensive treatment.
- Most patients are asymptomatic, but note any symptoms suggestive of underlying systemic diseases such as vasculitis, lupus, or myeloma.
- Ask about cardiovascular risk factors: smoking status, alcohol consumption, diet, and treatment he is taking, including over the counter drugs (especially non-steroidal anti-inflammatory drugs). Ask about family history of diabetes, cardiovascular disease, hypertension, peripheral vascular disease, and polycystic kidney disease.
- Calculate his serial eGFRs.
- Record his blood pressure and weight and analyse his urine (and culture the sample if the results for nitrites and leucocytes are positive). Assess his fluid status and examine his abdomen for enlarged kidneys or bladder.
- Management will vary according to the stage of CKD—see box.
- Offer him a further consultation to discuss any unanswered questions and concerns. Arrange nutritional support if it is needed, and give lifestyle advice. Refer him to a nephrologist if this is indicated by the UK CKD guidelines (see Useful resources box).

What issues you should cover

- Explain the terms CKD and estimated glomerular filtration rate (eGFR). To most patients “kidney disease” means dialysis and shortened life expectancy. Explain that CKD is a spectrum of disease, with mild renal impairment at one end and established renal failure at the other, and that eGFR, a number that is based on the “modification of diet in renal disease” formula, determines the stage of CKD.
- Reassure him that CKD is common (affecting 5-10% of the population, this percentage rising among people aged >70 years). Most people remain well and do not progress to established renal failure but have a higher than normal risk of developing cardiovascular disease. Hypertension is associated with silent development of CKD. Timely identification and optimal management of CKD, including well controlled blood pressure, have been shown to retard its progression. Explain that serial measurement of eGFR will allow you to judge whether his condition is progressing and at what rate.
- Explain that your aims are to ascertain whether there is a correctable cause for the biochemical findings and to limit any damage to his kidneys.

Managing chronic kidney disease

- Stage 1 or 2, and stage 3 with stable function (change in eGFR of <1 ml/min/1.73 m² over six or more months): monitor renal function annually. In cases of progressive stage 3 disease (change in eGFR of >2 ml/min/1.73 m²) monitor six monthly.
- Stage 3: check haemoglobin, potassium, calcium, phosphate, and parathormone concentrations (follow local protocol for parathormone monitoring), and request renal ultrasonography if he has lower urinary tract symptoms, refractory hypertension, or an unexplained progressive fall in his eGFR.
- Stage 4 or 5: refer to secondary care.
- If proteinuria is detected (from an early morning sample), check his urine protein:creatinine ratio and refer him to a nephrologist if the concentration is persistently >100 mg/mmol.
- In the case of a rapidly worsening creatinine concentration (an increase of >50%) or eGFR (a reduction of >25%), ensure that reversible causes have been excluded. A rise of serum creatinine by 20% or fall of eGFR by 15% as an apparent consequence of use of an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) may be due to atherosclerotic renal artery stenosis, requiring immediate discontinuation of the drug and referral to a nephrologist.
- The threshold blood pressure for starting antihypertensive treatment with an ACEI or ARB should be 140/90 mm Hg. Aim for a pressure of <130/80 mm Hg (125/75 mm Hg if proteinuria is present).
- For patients with a 10 year risk of cardiovascular disease of >20% (according to the Joint British Societies’ guidelines on prevention of cardiovascular disease in clinical practice (Heart 2005;91(suppl 5):v1-52)), consider treatment with lipid lowering drugs and aspirin—provided that his blood pressure is <150/90 mm Hg.
- Stop use of any nephrotoxic drug.
Communication: the forgotten palliative care emergency

PERSONAL VIEW Mark Pickering, Rob George

An 67 year old man was transferred to our hospice from the local district general hospital. He had end stage cardiac failure, and an implantable cardioverter defibrillator was in place. The referral was clear: he was coming to die. Just as clear was the fact that he didn’t know his prognosis but was apparently expecting rehabilitation.

By the time I (MP) had admitted him he had turned blue three times, and during one of these cyanotic attacks the defibrillator had discharged. It was clear he was near the end. As I began to explore his understanding of the illness and what the future held for him, I felt a subtle squeeze on my elbow from his wife, as much as to say, “Don’t tell him he’s dying.” It was 4 30 on a Friday afternoon, and this had all the makings of a bad death.

This was obviously a communication emergency. Certain things had to be communicated clearly in a short period of time in order to prevent his death being a complete mess for him and his family. The first priority was to speak with his wife and daughter. Both were fully aware of the prognosis but adamant that he should not be told, as “he couldn’t cope with it.” He had always been the strong one who protected the rest of the family.

I explained that we had an opportunity to speak openly with his wife. As I began to explore his understanding of the illness and what the future held for him, I felt a subtle squeeze on my elbow from his wife, as much as to say, “Don’t tell him he’s dying.” It was 4 30 on a Friday afternoon, and this had all the makings of a bad death.

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A looming bad death had been transformed into a good one

located the nurse consultant, who was known and trusted by the family. The patient’s wife would not consider deactivation without speaking to her, but a brief conversation between the two assured her that this was the appropriate thing to do. It was too near the weekend to undertake the usual full deactivation, but a suitable magnet was sent by courier that evening for use by the nurses in an emergency.

This done, it was time to talk to the patient. As we discussed his prognosis, he turned his eyes up to mine and said, “I thought as much, doc.” He had suspected for a while that he was near the end but needed it confirmed by someone in authority before he would discuss it openly. In a constructive conversation we discussed symptom control, explored some spiritual issues, and agreed on the need to speak openly with his wife and family. By now it was after 5 pm and I was booked on a train to get to a wedding at the other end of the country. I left hoping that the patient and his family would take the opportunity to talk.

On returning the following Tuesday I learnt that he had indeed required sedation with a syringe driver on the Saturday and had died peacefully on Sunday. That lunchtime the family was due to attend for a bereavement meeting and collect the death certificate. I wondered how they would look back on that last Friday evening they had spent with the man they all loved.

Although clearly sad at his death, they were deeply grateful for the frank discussions we had had. After I left on Friday they had spent the evening together saying goodbyes, agreeing funeral arrangements, even enjoying a laugh and a joke together as a family. What a difference from the cloak of secrecy that had prevailed on his arrival! I could not have imagined a better result—a looming bad death had been transformed into a good one by the diagnosis and treatment of a communication emergency. At the end of our meeting his wife presented us with the Christmas present she had bought for her husband before his death—an ornament that now stands in the hospice as a memorial to the short time he spent with us.

Many have written on the importance of recognising and treating emergencies in palliative care and oncology. Likewise, much has been published on the importance of communication in palliative care. But the two concepts have rarely been explicitly linked, with communication identified as a genuine palliative care emergency. Although in practice we often recognise what needs to be done in a particular situation, formally identifying communication emergencies as one of the main emergencies in palliative care would increase awareness and improve their management.

The consequences of misdiagnosing or failing to treat a communication emergency can be important. For patients themselves it could result in a difficult death, where existential distress may simply be labelled as terminal agitation, leading to greater levels of sedation. For relatives it could result in years of avoidable guilt, regret, and sadness. This will most certainly make the normal grieving process more difficult.

Palliative care professionals particularly (but also other healthcare professionals) should be as alert to communication emergencies as to any of the more physical ones. The consequences of missing them can be just as serious.

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Mark Pickering is senior house officer and Rob George is locum consultant, Lions Hospice, Gravesend, Kent.
Fractured: picking up the pieces

An author’s fractured arm led to a book on the intrusive surveillance of doctors, finds Jessica Watson

“Medicine can, and does, save lives and contribute to wellbeing, but much of it is a massive cultural deceit.” This is the controversial conclusion Ann Oakley reaches after being treated for the fracture of her right arm. Increasingly the medical profession is becoming aware of the value of patients’ narratives, yet Ann Oakley is no ordinary patient. As professor of sociology and social policy at the Institute of Education, University of London, she treats her experiences as a “field trip into the land of bodily damage, disability, and personal injury litigation.” In an attempt to make sense of her experiences she launches a huge research project that touches on a myriad themes including limitations of Western medicine, medical litigation, the problem of ageing, disability, and the confusion between bodies and identity.

Oakley portrays doctors as self serving and insular. One recurring theme is a lack of communication and in particular an inability or unwillingness to listen: “It quickly becomes clear that what worries me is not what worries the doctors,” she writes. The doctors in her case were interested in the problems they saw—the state of the scar, the movement of the arm, and the degree of pain. No one took the time to find out what Ann Oakley’s concerns were, largely that her hand felt like “an alien object”: “I don’t feel I have a right arm. It just hangs there at the end of my arm. I hate it.” She is not only right handed but a writer of sociology books and novels, and devotes a whole chapter to exploring the personal, cultural, and psychological significance of the right hand.

The medical model of Western medicine, or “body as machine” approach, “distorts the human experience of living in a body,” Oakley argues. In this model “objective,” quantitative tests are seen as providing the answers, and in the process the patient’s subjective experience is ignored and delegitimised. Nerve conduction studies are an example of “the mechanical model of the body par excellence; the patient doesn’t have to speak, or even, really, be conscious at all.” On the basis of these “objective” tests, doctors discharged Oakley as “cured”—even though “these tests said nothing about sensibility—about what I felt.”

Oakley portrays her physiotherapist in a much lighter fashion than the doctors: “the difference is that Theresa listens when I tell her; she isn’t a machine.” Disappointed by mainstream medicine, Oakley also turns to acupuncture, and its more holistic approach makes her hand “feel a little bit more like part of me again.” A fundamental difference between Western medicine and acupuncture, she argues, is the inseparability of mind and body, and this theme of embodiment is central in the book.

Within this theme Oakley explores several other areas, with some controversial conclusions. Screening “isn’t to prevent disease, but to change identities—to produce patients.” To back this up she says that evidence to support the benefits of screening is minimal, yet screening subjects large numbers of women to unnecessary investigations and anxiety.

She feels that ageing women are excessively medicalised and medicated, with hormone replacement therapy being “the ultimate case study in pharmaceutical marketing, in how to make millions by inventing new conditions that need treatment, playing on people’s susceptibilities, and ignoring the bad news about what drugs do to the body.” Also, one chapter is devoted to a damning criticism of the American system of litigation, blame culture, and lawyers as “ambulance chasers.”

This is a surprisingly readable book, given the complexity of some of the issues discussed. It interweaves the author’s own experiences with other patients’ stories and evidence from research. Some of Ann Oakley’s statements seem to overdramatise the facts to court controversy, but the book has some interesting lessons for doctors.

Although patient centredness, communication skills, and the holistic approach are increasingly being incorporated into medical teaching, this book finds a gap between the theory and practice of these skills. It would be easy to dismiss the concerns raised as the anecdotal experiences of one patient, but many doctors will recognise an uncomfortable reflection of some aspects of medical practice. Whether the doctors did a technically good job in the medical task of fixing broken bones was, to this patient, secondary. Her book reminds us all of the importance of listening to and learning from our patients and encourages reflection on the universal experience of living in a body.

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The doctors in Oakley’s case were interested in the problems they saw—the state of the scar, the movement of the arm, and the degree of pain. No one took the time to find out what her concerns were.
FROM THE FRONTLINE
Des Spence

110%

I am going to give this 110%. Sporting analogies are everywhere, for sport is a microcosm of life itself. Sport incorporates important themes like the team over the individual, obeying rules, the threat of sanctions, persistence, endurance, pride, effort, structure, hierarchy, and—all important—the need to meet defeat and victory with equal measure. Perhaps these crude analogies are legitimate and we should view the NHS as just another big team game.

Let’s work this sporting analogy further. The NHS is at risk of becoming American football: teams within teams, producing reams of meaningless statistics; constantly changing shifts of players; superspecialised players performing one single task; start-stop, clock watching, pointlessly technological; glitzy, covered in layers of padding, pumped up on growth enhancers with unknown long term consequences—even the gleam of the pitch is utterly synthetic. Just expensive and complicated, but worse still: interminable and dull. Our population of health spectators, now obese, gazes on, chomping on foot-long hotdogs as they guzzle down their gallons of fizzy drinks. The announcement system blasts out a deafening and distorted version of “We are the Champions,” drowning out any dissent. All attempts to export this sport, perhaps not unsurprisingly, have failed.

But the traditional model of the NHS is one of a soccer match in a dog fouled city park. The nurses are the defence: solid, dependable, organised, and quietly getting on. The GPs are the midfield: holding the ball, playing it around and holding the possession, helping in defence but sometimes going forward. The consultants are the two fiery glory hunters up front, aggressively seeking to score that all important diagnosis.

So you can stuff staying up half the night for the medical superbowl party. Give me my NHS football world cup, a truly global event with poverty no barrier to success—an event where a truly gifted individual can make a big difference and raise the morale of a whole nation. There is the odd shouting match, but these get “sorted” in the pub afterwards. It is the NHS’s complete simplicity that makes it so beautiful and highly regarded. Had enough? I’ve done my best and you can’t ask more than that.

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Jobs for the boys

PAST CARING
Wendy Moore

Climbing the medical career ladder used to be so much simpler. Before the advent of tedious form-filling, maddening technical hitches, and the rush for too few posts, obtaining a plum job for life was governed by an application system everyone could understand: nepotism.

For centuries, all that was needed for an aspiring trainee physician or surgeon to secure a lucrative countryside practice or a top post at an eminent teaching hospital was the right family connections. In a spirit of continuity only equalled by The Forsyte Saga, medical dynasties ruled supreme. While the Chamberlens kept their midwifery practice in the family for five generations, so the Monros—the unimaginatively named Alexanders I, II, and III—maintained a steely grip on Edinburgh University’s chair of anatomy for 126 years.

Admittedly there were disadvantages. Impatient sons and nephews had to bide their time until dad or uncle retired through ill health or died—although given prevailing medical ignorance this need not be overly long.

And naturally the system proved unpopular with anyone lacking appropriate blood ties. Devoid of illustrious ancestors, surgical apprentice John Flint South gamely accepted the appointments procedure at St Thomas’ when the death of his tutor Henry Cline created a vacancy in 1820. “Several of the other hospital apprentices sent in their humble petitions to the Governors to be chosen their surgeon, I among the number,” he wrote, “but it was a mere matter of form.” Cline’s cousin, Joseph Henry Green, was duly elected to the job.

With no recognition of merit, experience, or competence, the system was similarly unpopular with patients—should they live to voice a complaint. When William Lucas succeeded his father at Guy’s in 1799, his butchery became so notorious that one trainee was put off surgery for good: the young John Keats sought employment elsewhere. After witnessing Lucas amputate a leg from the wrong direction, leaving a generous flap of skin on the discarded limb and a protruding bone on the stump, even the amiable South conceded that his operations were “generally very badly performed, and accompanied with much bungling.”

Ultimately the system became discredited under intense media scrutiny. Lancet editor Thomas Wakley crowned a sustained campaign against nepotism with a dazzling exposé in 1828 of a fatal operation to remove a bladder stone by Bransby Cooper, inept nephew of the esteemed Astley Cooper, at Guy’s. Despite Bransby’s victorious libel suit, the jury’s derisory award of £100 damages made plain that relative values were no longer sufficient recommendation for a medical job. Uncle Astley’s pleading that young Bransby would make a “brilliant operator”—given time—would probably cut little ice even today.

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The casualties of Waugh

My father was not very good at telling jokes. If something was a fact he couldn’t leave it out, and over-inclusiveness is not an aid to mirth. Still, he had a repertoire of old favourites, and one of them, which he told many times, concerned what in those days was still popularly known as the loony bin.

An inmate showed the chairman of the board of visitors around the establishment, and did so with such lucidity that the chairman asked him why he was an inmate at all. He replied that he didn’t know, and asked the chairman to help him secure his release. The chairman promised to do so.

Just as he was leaving the asylum, the chairman felt a blow with a brick on the back of his head.

“Don’t forget now,” said the inmate, waving to him.

This joke is, in essence, identical to the plot of Evelyn Waugh’s short story Mr Loveday’s Little Outing.

Lord Moping is committed to the County Asylum for Mental Defectives (a term still widely in use during my childhood, although educationally sub-normal was taking over) when he tries to hang himself during his wife’s annual garden party.

Lady Moping refuses to countenance a more expensive establishment because she has been so humiliated by his social faux pas; but the richer lunatics have a wing of their own in the asylum, where they are allowed to dress as they please and to have a dinner party every year on the anniversary of their committal.

Mr Loveday, another long term inmate, acts as Lord Moping’s amanuensis during his residence in the asylum. Lord Moping is forever dictating memoranda to the great ones of the earth on such subjects as the fate of major rivers, and his daughter, Angela, is so impressed on a visit to her father by the efficiency of Mr Loveday, who tells her that many years ago he made the slight mistake of knocking a girl off her bicycle and then strangling her, that she vows to secure his release. Mr Loveday tells her that he has only one small ambition, but does not want to say what it is.

This she does, and a meeting is held in the asylum to send Mr Loveday off to his freedom. The doctor assures him that he is so highly esteemed by both staff and patients that there will always be a place for him if he does not like life outside.

Mr Loveday is back within two hours; and all too predictably, he has knocked a young woman off her bicycle and strangled her. He announces with the greatest pleasure that now he will never be released from the asylum again. He had never really wanted to go in the first place.

What exactly is Waugh satirising in his story? Not least, surely, the do-gooding propensities of the well-placed.

BETWEEN THE LINES

Theodore Dalrymple

What exactly is Waugh satirising in his story? Not least, surely, the do-gooding propensities of the well-placed

MEDICAL CLASSICS

Extensible exposure By Arnold K Henry

First published as Exposure of the Long Bones in 1927

Arnold K Henry was a remarkable man. Born in 1886, he graduated from Trinity College Dublin in 1911 and became fellow of the Royal College of Surgeons in Ireland in 1914. In the first world war he served as a surgeon in both the Serbian and the French armies and was decorated by both. He was accompanied by his wife, Dr Dorothy Milne Henry, who was his close collaborator and assistant. He went on to work as a surgeon in Dublin, then as professor of surgery at the University of Cairo and at the Postgraduate Medical School at Hammersmith, and in 1947 returned to Dublin as professor of anatomy. In 1927 Henry published a book entitled Exposure of the Long Bones, which was revised first in 1945 to Extensible Exposure Applied to Limb Surgery and then in 1957 as a second edition entitled simply Extensible Exposure. This volume remains an invaluable reference for surgeons of all persuasions, but particularly those who operate on the limbs.

The book covers a lot of ground; from exposures in the neck, the upper extremity, the thorax, the pelvis, and the lower extremity. As the title suggests, the approaches are extensible. For example, the nerves of the brachial plexus can be followed from the neck into the shoulder and the arm. Where other anatomical texts appear dry and uninteresting, Henry’s descriptions of the practical aspects of surgical exposure are fascinating and are interspersed with anecdotes from his extensive surgical career. He suggests those not following his advice “will only make a mess.” The “striped (and sometimes flashy)” sandwich of supinator containing the posterior interosseous nerve is “thin, so do not nick the nerve.” The vessels on the deep surface of the gluteus maximus sprawl like those of the placenta. Henry is refreshing in his honesty. His description of how his technique for pulmonary embolectomy evolved when operating on three patients is published despite the fact that none survived.

Henry clearly has a sense of humour. He can’t resist a dig at other texts, describing the “huge great sciatic nerve” as the one “oasis of description” Gogarty could find in Cunningham’s anatomy. The whole is written in a style reflecting a classical education; in Henry’s view the hamstring tendons and vastus lateralis are the “Scylla and Charybdis” between which the gluteus maximus may be palpatated. His description of the function of the gluteus maximus is a particular delight.

There is no doubt that Henry was a man of powerful intellect, with an enquiring and analytical mind. This book contains the distilled experience of many years of practice. It is an apt legacy. Fifty years have not diminished its relevance and usefulness.

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Miles Weatherall and Josephine Alice Coreen Weatherall (née Ogston)
Leading pharmacologist in academia and industry, and collator of fetal anomalies

Miles Weatherall occupied prominent positions in both academic life and the research side of the pharmaceutical industry. He did a BSc in pharmacology by thesis in 1941, a year before he studied the subject in the medical course, and immediately after qualifying was asked to prepare a top secret report on mepacrine, which had been invented in Germany before the war and was thought to be useful against malaria. Miles could not believe that the War Office hadn’t thought of this before, musing that the job had perhaps been done five times over, each time so secretly that no one had ever heard the outcome. Thirty years later he came back to mepacrine at the Wellcome, finding his 1943 report quite handy.

After house jobs Miles was classified as unfit for military service owing to a suspected peptic ulcer, which was to inconvenience him for much of his professional life. With a grant from the Medical Research Council he started pharmacological research in Edinburgh under Professor J H Gaddum. This became a lectureship, and in 1949 Miles was encouraged to apply for a similar post at The London Hospital to start a new department.

He established a thriving forward looking department. Academic posts, as opposed to purely research appointments, enabled him to become more broadly involved in general scientific education. His department developed stimulating seminars that were attended by many outside the boundaries of pharmacology.

Miles wrote Statistics for Medical and Other Biological Students jointly with L Bernstein in 1952, a book at least a quarter of a century before its time so far as medical education was concerned. He also wrote the popular (in both senses) Scientific Method and In Search of a Cure: a History of Pharmaceutical Discovery. He became professor of pharmacology in the University of London in 1958.

In 1967 he moved to the Wellcome Research Laboratories at Beckenham, Kent, as head of the therapeutic research division, becoming director of establishment in 1974.

Retirement in 1979 brought a number of new educational activities, including work at Chelsea College and preparing an index for Medical History. Miles wrote several novels and A Weatherall Memoir, all published privately. His interests included railways, gardening, and wine, and he was proud to serve on the committee of the Wine Society. In his last years he was largely housebound devotedly looking after his wife, Jo, during her illnesses; after 62 years of marriage, she predeceased him by a few months (see next obituary). He leaves three daughters and seven grandchildren.

Estlin Waters
Miles Weatherall, professor of pharmacology, London University, and director of establishment, Wellcome Research Laboratories (b 1920; q Oxford 1943; BSc, MA, DM, DSc, FI BIol), died from ischaemic heart disease on 8 March 2007.

Married to Miles Weatherall (see previous obituary), pharmacologist, in 1944, Jo first worked in physiology, including publishing jointly with him on the effect of dithiols on time to death in poisoned rats. Her work on fetal physiology in Oxford during 1957-9 laid the foundation for her later epidemiological work on identifying and preventing fetal anomalies.

Jo conducted health service research studies at Charing Cross Hospital during 1960-2. In November 1963 she reviewed trends in morbidity and mortality attributed to thromboembolic disease as a fellow at the London School of Hygiene and Tropical Medicine. From 1965 she was a medical statistician at the General Register Office (now the Office for National Statistics) working on improvements in reporting and analysing deaths in confidential inquiries into maternal deaths and in multiple cause coding of deaths.

Jo helped to establish a system for routine national reporting of congenital anomalies by birth attendants in England and Wales. In the mid-1960s she was a founder member of the International Clearinghouse for Birth Defect Monitoring Systems. This work culminated in her role from 1978 to 1984 as the founding project leader of the European Register of Congenital Anomalies and Twins (EUROCAT), then based in Leuven, Belgium, and now in Belfast.

Throughout her career Jo was a loving teacher and friend to her children and grandchildren. She and Miles shared their interest in good food and wine with family and friends, offering an open house. Their large garden was an escape from work pressure and a continuing joy in retirement until ill health and disability took hold. They raised funds for the Arthritis Research Campaign by opening it to the public on more than one occasion.

Miranda Mugford, Alison Macfarlane
With help from Alison Robinson, Rosamund Weatherall, Bev Botting, Michel Lechat, Brian Furner, and many others
Jo Weatherall, founding project leader of the European Register of Congenital Anomalies and Twins (EUROCAT) (b 1922; q Edinburgh 1945; BSc, FFCCM), died from respiratory failure on 17 October 2006.
Khalid Tariq Al Naib

Assistant professor of medical microbiology and vice dean for scientific affairs Al Nahrain Medical School, Baghdad (b 1963; BSc Kuwait 1987; MSc, PhD), murdered in Iraq on 30 March 2007.

Khalid Tariq Al Naib was kidnapped and murdered in Iraq on the day he returned from sabbatical at the Peter MacCallum Cancer Centre in Melbourne, Australia; death threats had been sent to his office in Baghdad while he was away. In addition to teaching immunology to undergraduates and conducting his own research in medical microbiology, Khalid also worked with non-governmental organisations, reporting the health status in Iraq, establishing a blood bank in Duhouk as part of a humanitarian programme, and improving Iraqi laboratory services for tuberculosis. One of his objectives on sabbatical was to learn how to improve scientific training and development in Iraq. He leaves a wife, Manal al Musawi, and a baby son, whom he saw once.

Saad Shakir

William Bingham

Former consultant anaesthetist Royal Victoria and Maternity Hospitals, Ulster Hospital, Belfast (b 1916; q Queen’s University, Belfast 1941; MD, FFARCSI, FRCA), died from bronchopneumonia on 21 March 2007.

William (“Bill”) Bingham served on rescue ships in the North Atlantic and subsequently became principal medical officer for the Mediterranean Fleet. Appointed as consultant anaesthetist to Lurgan and Portadown Hospital and later in Belfast, he initiated respiratory intensive care in Ulster, being the first person in Ireland to paralyse and ventilate patients with tetanus (1950). His seminal paper on balanced anaesthesia for caesarean section established the standard of care. He amalgamated the Armagh and Down divisions of the BMA as chairman, and he was chairman of staff of both the Royal Maternity and Ulster Hospitals. Predeceased by a son, he leaves a wife, Nora; three children; and five grandchildren.

J S Bingham, E A Barnett

Stuart Gordon Adam Forsyth

Former general practitioner Tonbridge, Kent (b 1922; q Cambridge/University College Hospital, London, 1945; DCH), d 12 March 2007.

In 1949 Stuart became the fourth partner in the largest practice in Tonbridge. He gained the diploma of child health in mid-career and for many years stood in for the consultant paediatrician at Pembury Hospital in his absence. He also helped in the training of Red Cross and St John Ambulance volunteers. Stuart played the flute in the Tonbridge Philharmonic Orchestra, of which he was later president, and served as chairman of the Tonbridge Musical Society. After his retirement in 1987 he gained the diploma in philosophy of the University of Kent and actively supported the Tonbridge Old People’s Society, later Age Concern, the hall in which they meet being named after him. He leaves a wife, Jean, and five children.

John Ford

Robert John Jameson

Former general practitioner Bath (b 1917; q London 1943), d 18 April 2007.

In 1951 Robert Jameson was appointed to a singlehanded practice in Bath after working in hospital as an obstetric registrar. Obstetrics remained important to him throughout his career. His practice was the first in Bath to have a health visitor and practice nurse. In his practice he observed a large family with “nail patellar” syndrome, and in 1956 published a paper with two coauthors in the Annals of Human Genetics on the linkage of this syndrome to ABO blood grouping. A founder member of the Royal College of General Practitioners, he contributed greatly to patient care and the medical community. His gracious manner endeared him to patients—some still asked about him 22 years after his retirement. He had a deep Christian faith and was active in church life.

Paul Booth, Angela Jameson, David Jameson

Geoffrey Laurence Scott

Former consultant haematologist Bristol and Weston super Mare (b 1936, q Cambridge/St Bartholomew’s Hospital 1961; MA, MD, FRCP), d 3 February 2007.

After qualifying first in his year and working at Barts, Geoffrey Laurence Scott was lecturer and then consultant senior lecturer at St Thomas’ Hospital, where he wrote his MD thesis on the haemolytic effect of dapsone. In 1973 he was a singlehanded consultant haematologist at the Bristol Royal Infirmary and Weston super Mare, a post he held until retirement in 2001. A member of the advisory appointments committee for consultant haematologists in the south west region, Geoffrey also helped to develop the Avon Haematology Unit, now a regional service with six haematologists. Professionally, he was interested in the haematological manifestations of systemic disease. His leisure interests included horse riding, gardening, theatre, and ornithology. He leaves a wife, Jane, and a son.

Helena Daly, John Hudson

Anthony Robert (“Bob”) Teuten

Former general practitioner Brent (b 1925; q St Mary’s Hospital, London, 1949), died from heart failure on 6 January 2007.

After qualifying, Bob Teuten joined the Royal Army Medical Corps, serving partly in Saudi Arabia. He subsequently joined the Territorial Army, becoming a major. He joined his father’s practice in Harlesden in 1952 and took on full responsibility in 1954. He was one of the first doctors to move to the Craven Park Health Centre in Stonebridge Park on its establishment in 1971, where he remained until his retirement in 1995. His many interests included cricket, ornithology, Australian stamps, gardening, and English romantic poetry. He leaves a wife, Margaret, and three children.

Richard Teuten

ADVICE
We will be pleased to receive obituary notices of around 250 words. In most cases we will be able to publish only about 100 words in the printed journal, but we can run a fuller version on our website. We will take responsibility for shortening. We do not send proofs. Please give a contact telephone number and, where possible, supply the obituary by email to obituaries@bmj.com
MINERVA

An Australian doctor has received an email offer from South Africa which suggests he is being considered for an award as a “distinguished contributor to medical knowledge.” Part of the award is said to involve naming a wing in a new oncology centre after him. As much as he’d like to think he was worthy of such recognition, the doctor in question describes himself as a “minor player in radiation oncology” and warns others that this is likely to be another version of the notorious Nigerian money laundering scam and should be ignored.

Patients with newly diagnosed type 2 diabetes are at high risk of stroke in the first five years after diagnosis compared with the general public. Researchers in Canada estimate the risk is more than double the rate for the general population, which confirms the need for aggressive management of cardiovascular risk in these patients right from the start (Stroke 2007;38:1739).

Children born with insufficient numbers of neutrophils are prone to sepsis, but they can be treated successfully with G-CSF (granulocyte colony stimulating factor) to reverse the neutropenia. What’s interesting is that, although G-CSF can improve the cell count, it does not correct the underlying functional deficiency of the neutrophils in defending against microorganisms. Scientists report that the expression of the polypeptides responsible for the antimicrobial machinery of these cells is almost absent in those children who carry the mutant gene even when they are subsequently treated with G-CSF (Blood 2007;109:4716-23).

Toilet trained children who need to provide midstream urine samples should be cleaned around the perineum with soap beforehand to reduce contamination rates (resulting in unnecessary treatment with antibiotics), according to a study in Pediatrics (2007;119:e1288-93). Children randomised to the cleaning group were less likely to have a positive urine sample than those in the non-cleaning group (21% vs 37%).

When medical students present cases they’re often interrupted by their teachers. An observational study carried out in one teaching centre found that the number of interruptions and duration of presentations decreased with the level of the student’s training. But the frequency of interruptions (per minute) did not vary according to the level of the learner. In 40% of trainees’ presentations, the teacher interrupted in order to give an assessment and sometimes a plan before the trainee had done so. Only 8.3% of learners said they found the interruptions disruptive (Academic Emergency Medicine 2007;14:521-5).

An 81 year old woman underwent abdomino-perineal excision of the rectum with the creation of a left iliac fossa colostomy for low rectal cancer. Preoperative colonoscopy had also revealed melanosis coli, a condition associated with the use of laxatives causing mucosal pigmentation. Many staff, both medical and nursing, had never seen melanosis coli, particularly in a stoma, and required reassurance that this stoma was not necrotic but was healthy. This was confirmed by its function and warmth on palpation and the patient’s general state of wellbeing.

A study of more than 12 000 grandparents in the United States concludes that looking after grandchildren is perfectly safe and may even benefit the grandparents’ health (Washington Times, 1 June. www.washingtontimes.com). Whether it’s a full time occupation or just occasional duty, grandparents suffer no ills. Grandmothers, in fact, reported “modest improvements” in their health, tended to exercise more, and had less depression. These findings fly in the face of a media barrage that, over the years, has focused on the alleged problems for grandparents who take care of their grandchildren.