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Screening for *Chlamydia trachomatis*

Opportunistic approaches have little evidence to support them

Sexual infections and teenage pregnancies disproportionately affect people living in poverty and social exclusion. In 2004, the government white paper “Choosing health” identified sexual health as a priority area for improvement and service development. The paper followed the publication of the National Strategy for Sexual Health and HIV, which aims to provide “better prevention, better services, and better sexual health.” The strategy described the implementation of a broad National Chlamydia Screening Programme (NCSP) in accordance with the National Health Service plan, which included “a commitment to improving the prevention of ill health and providing screening programmes where they are appropriate.”

In this week’s *BMJ*, an analysis by Low shows how acceptance of the effectiveness of chlamydial screening programmes in Sweden and the United States supported the funding of the National Chlamydia Screening Programme before the balance of benefits and harms was thoroughly understood.

Chlamydia is the most common sexually transmitted disease in England. Its prevalence has increased steadily since the mid-1990s, and rose by 300% from 1995 to 2004. The main burden of infection affects women aged 16-19 and men aged 20-24 years. Although often asymptomatic, associated problems such as pelvic inflammatory disease, infertility, ectopic pregnancy, epididymo-orchitis, ophthalmic complications, and neonatal complications are well described. As with most sexually transmitted infections, *Chlamydia trachomatis* may be a cofactor for HIV transmission.

Chlamydia is the only sexually transmitted infection for which population screening has been implemented. Ideally, a screening programme for infectious disease should identify and treat a sufficient number of infections to reduce transmission in the community, and thus reduce prevalence. There are two main approaches to the design of screening programmes—proactive and opportunistic. Proactive screening—for example, cervical screening in the United Kingdom—uses the population register to identify the target population. People are contacted at intervals defined by the transmission dynamics (which use epidemiological data to estimate the spread or transmission of infection in the absence of intervention within a defined time frame), uptake of screening is monitored, and non-attenders are contacted. Opportunistic screening targets people who attend a healthcare setting. Thus, it reaches only those who attend the service and regular rescreening is unlikely to occur. It also relies upon the health provider remembering to give information and offer the test to those deemed eligible.

The National Chlamydia Screening Programme in England began in 2001. It uses an opportunistic approach and targets sexually active people under 25 years of age within a variety of healthcare settings. It is a dynamic model, which evolves as evidence accumulates. In the third year of the programme, 1777 venues were involved in 26 programme areas, and nearly 100,000 people were screened. Most of these people were women (82%). The incidence of chlamydia infection was 10.1% (95% confidence interval 10.0 to 10.3). Of 8816 positive cases, around 10,000 partners were reported; 49% of partners were tested and 33% were treated. This may seem like a low proportion, but contact tracing is notoriously difficult. In a prior attempt to develop national standards for measuring outcomes of care for gonorrhoea and chlamydia in genitourinary medicine clinics, reports detailing chlamydia outcomes were identified. In large city clinics, 0.43 (0.30 to 0.62) contacts per case were screened compared with 0.64 (0.58 to 0.70) contacts per case in other clinics.

The analysis by Low cites a lack of evidence from randomised controlled trials to support the opportunistic screening method. The opportunistic approach is used in most chlamydia screening programmes in the US, Sweden, and England. Studies showing a reduction in the rates of chlamydia, pelvic inflammatory disease, and ectopic pregnancy over time have been widely cited in support of such screening. A concurrent decrease in the diagnosis of gonorrhoea in Sweden and the UK has occurred, but has been ascribed to extensive safe sex campaigns rather than the chlamydia screening programme. However, rates of chlamydia in Sweden, the rest of Europe, and the US have been steadily increasing since the mid-1990s despite the implementation of opportunistic screening. This increase in rates may reflect the outcomes of targeting more people, the use of more sensitive technology, or a genuine increase in prevalence.

Critics of the National Chlamydia Screening Programme have focused on several issues. These include the use of an opportunistic screening method and its associated fragility; the reduced participation of general practitioners in the programme compared with the pilot schemes, in which doctors were paid for each patient enrolled and participation was mandatory; the low number of men screened; contact tracing failing to reach all partners; and cost effectiveness. In two pilot sites, all general practitioners took part, were paid for each patient enrolled, and generated the highest proportion of tests and cases, achieving an effective screening rate of 50%.

For the full versions of these articles and the references see bmj.com
In the programme itself, participation of general practitioners is optional and largely unremunerated. In 2005–6, the effective screening rate was less than 5% in more than half of programme areas. However, the National Chlamydia Screening Programme is in its third phase of conception and is still expanding, with a large scale implementation due later this year. It has responded with innovative strategies, such as pharmacy based screening programmes, to reach target groups.

A proactive approach to chlamydia screening might be difficult and unacceptable to some people, as screening would start at 16 years of age and not all of those invited would be sexually active. As the aim of the programme is to reduce the prevalence of chlamydia, infected men would need to be identified, and this might have a significant impact on its cost effectiveness. Strategies from the men’s health forum study (supported by the Department of Health), such as depositing test kits and health promotion literature in the workplace, may prove useful. Cost is being questioned by Low in light of conflicting opinions regarding the prevalence of morbidity related to chlamydia, and mathematical modelling relies on high levels of acceptance, uptake, and coverage of screening, in addition to annual repeat testing and partner notification—areas that are continually being developed in the National Chlamydia Screening Programme.

The Department of Health has recruited the National Institute for Health and Clinical Excellence (NICE) to produce public health guidance on interventions, including screening, designed to reduce the transmission of chlamydial infection, together with other sexually transmitted infections and pregnancy in the under 18s. Recommendations include identifying people at risk of infection and providing sexual health counselling. One to one interventions, as well as group and peer based approaches, are highlighted throughout the document. It discusses partner notification and treatment; evidence based methods that have yielded higher contact rates than conventional contact tracing, such as mailing home sampling urine kits and patient delivered partner therapy (this strategy is not legal in the UK). Primary care trust commissioners are asked to ensure that sexual health services are in place to meet local needs.

Sexual health has emerged as a government priority. Despite multiple campaigns in the media, the diagnosis of sexually transmitted infections continues to increase. Most people who are affected are unlikely to seek sexual health testing and may only be assessed via a proactive approach rather than the opportunistic screening programme currently offered.

Coeliac disease in primary care

Is common, underdiagnosed, and can present with non-specific symptoms

Coeliac disease affects around 1% of the general population, but most cases are unrecognised and diagnosis is often delayed considerably. This is surprising, given how common the disease is and how serious its effects can be. Several possible reasons exist for this delay; the most important is that most patients with coeliac disease do not have typical symptoms of malabsorption. Even if these symptoms are present their non-specific nature may not trigger diagnostic suspicion of coeliac disease. Other atypical presentations can occur, especially in older patients, and the disease may even be seen in obese people.

In this week’s BMJ, Hopper and colleagues report a validated clinical prediction rule to determine an effective diagnostic method of detecting all cases of coeliac disease in people referred for gastroscopy. People with positive tissue transglutaminase antibodies and “low risk symptoms,” as well as those with the high risk symptoms of diarrhoea, weight loss, and anaemia, were investigated with duodenal biopsy, while those with a negative antibody result and low risk symptoms were not biopsied. They found that pre-endoscopy serological testing combined with biopsy of people with high risk symptoms had a sensitivity of 100%. They also found that a proportion of high risk patients with positive serology turn out not to have coeliac disease on biopsy, which should prompt reconsideration of the need for a lifelong gluten-free diet. An accompanying commentary in this issue by Graber and Kumar discusses the potential application of the decision rule to clinical practice.

Coeliac disease is characterised by a lifelong intolerance to certain storage proteins contained in wheat, rye, and barley, collectively known as gluten, and it is an unusual combination of food intolerance and autoimmunity. Chronic inflammation of proximal small intestinal mucosa, with atrophy of small intestinal villi, is associated with impaired absorption of nutrients and increased secretion of water and solids because of abnormal intestinal permeability. The disease has been classified into four phenotypes. In classic coeliac disease, patients have intestinal malabsorption and gastrointestinal symptoms, whereas the atypical (most common) form of the disease has few or no gastrointestinal symptoms. Atypical disease has other problems, however, including iron deficiency anaemia, osteoporosis, short stature, infertility, and unfavourable outcomes of pregnancy. In silent coeliac disease, asymptomatic patients are found to have gluten induced villous atrophy, and in latent disease, patients may have normal mucosa or may show villous atrophy, which improves after gluten withdrawal.

The gold standard for the diagnosis of coeliac disease is a proximal small intestinal (duodenal) biopsy, but serum testing for antigliadin and endomysial antibodies is also available and offers reasonable sensitivity and specificity. The American Gastroenterology Association recommends the use, in primary care, of the IgA tissue
transglutaminase antibody test as the single diagnostic serological test. However, coeliac disease may cause IgA deficiency, so that IgG endomyosal antibodies and transglutaminase antibodies should be checked if biopsy is positive but the IgA tests are negative. Furthermore, because the histology of the disease can be patchy, careful quadrantic biopsies from the duodenum are needed. Even then difficulties in the preparation and interpretation of histological material may create diagnostic uncertainty, so that follow-up and reinvestigation may be needed to confirm the diagnosis. 

Coeliac disease is more common in people whose first degree relatives have the condition and in patients with iron deficiency anaemia, low bone mineral density, and other autoimmune disorders, such as type 1 diabetes mellitus and autoimmune thyroid and liver disease. Associations between coeliac disease and several other conditions including Down’s syndrome, Turner’s syndrome, and schizophrenia have been reported. The possible excess of coeliac disease in patients with irritable bowel syndrome and the need to test for the condition in the routine investigation of intermittent abdominal pain and bloating remain controversial. In a recent treatment trial of irritable bowel syndrome in the United Kingdom the prevalence of coeliac disease was 0.7%, similar to the population mean. Coeliac disease is associated with excess mortality, including an increased risk of non-Hodgkin’s lymphoma and other cancers.

A gluten-free diet not only protects against non-Hodgkin’s lymphoma, corrects anaemia, and restores normal nutritional and biochemical status, but it also substantially improves quality of life, particularly if troublesome gastrointestinal symptoms have been present.

What then are the important messages for primary care? Firstly, patients with unexplained diarrhea, anaemia, weight loss, infertility, recurrent miscarriage and low birthweight babies, or low bone mineral density, are at increased risk of coeliac disease and should be investigated in primary care with antibody tests. Secondly, risk of coeliac disease is higher in patients with a first degree relative with the condition and in those with other autoimmune disorders such as type 1 diabetes (with which coeliac disease sometimes shares the HLA markers DQ2 and DQ8) and autoimmune thyroid and liver disease, and serum antibody testing should be considered. Patients with gastrointestinal symptoms strongly suggestive of coeliac disease who test negative should be referred for a specialist opinion. In all patients with positive antibodies the diagnosis of coeliac disease must be confirmed by endoscopic biopsy, for which specialist referral will also usually be required. Thirdly, while a lifelong gluten-free diet can reverse the effects of gluten enteropathy, the diagnosis, once again, must be confirmed by a small intestinal biopsy. Hopper and colleagues’ study offers an attractive algorithmic approach to identifying coeliac disease, and evaluation of this algorithm in a primary care setting is now required.

The 2006 WHO child growth standards

Have implications for nutrition programmes in emergencies

In April 2006, the World Health Organization released its new WHO child growth standards, 16 years after a WHO working group on infant growth recommended that these standards should describe how children should grow rather than how they actually grow. The basis for the new growth standards was six population based studies of infants and children from Ghana, India, Norway, Brazil, Oman, and North America, undertaken between 1997 and 2003. Participants were fed according to accepted international nutritional standards (including breast feeding), and their mothers were adequately nourished and avoided known adverse factors such as tobacco exposure.

The new growth standards show that children born in different regions of the world can and should grow equally well, and they also show that sex and ethnic origin are minor determinants of growth compared with adequate nutrition, environment, and health. However, as expected, important differences in the diagnosis of malnutrition emerge when the standard cut-offs are applied using either the National Center for Health Statistics (NCHS)-WHO reference or the WHO 2006 growth standards.

In this week’s BMJ, Seal and Kerac report the implications of adopting the new WHO child growth standards in emergency and non-emergency child feeding programmes using secondary data analysis from three nutritional surveys in emergency settings. Nutritional status can be expressed using either z scores or percentage of the median values. WHO recommends that weight for height should be expressed as a z score. However, while not recommended by WHO, many agencies working in emergency settings use weight for height expressed as a percentage of the median as the criterion for admission to feeding programmes.

Seal and Kerac tabulated and compared the weight for height z score and percentage of the median cut-offs for moderate and severe acute malnutrition from both the NCHS-WHO growth reference and the new WHO standards. With the new WHO standards, a marked increase (0.5-2.7) in the prevalence of severe wasting was seen if weight for height was expressed as a z score (weight for height ≤3 z scores), confirming a previous report that showed an increase of 1.5-2.5. Paradoxically, however, the new WHO standards showed a significantly lower prevalence of severe wasting when expressed as a percentage of the median (weight for height ≤70% of the median). These findings have serious programmatic and resource implications.

In emergencies, growth standards are used for...
The World Health Organization’s study on domestic violence against women highlights the need for immediate action. The study across 10 countries used robust culturally appropriate methods to assess the extent and effects on health of intimate partner violence and non-partner violence in 240 000 women. The lifetime prevalence of physical or sexual intimate partner violence (or both) in women who had ever had a partner ranged from 15% to 71% (29-62% at most sites), though prevalence varied significantly between and within countries (large cities versus less populated areas).

We know more about the epidemiology of this type of violence than how to identify, prevent, and reduce it. However, recent research has made great strides, including identifying optimal methods for further evaluation of case screening in emergency departments, family medicine practices, and women’s health clinics; examining women’s acceptance of screening; identifying effective interventions; and identifying successful strategies for training and continuing medical education. Further research is still needed, though, especially to evaluate interventions and assess whether universal screening is effective.

We can learn much from WHO’s methodology and data collection methods, which relied, among other things, on partnerships with women’s organisations and with other key stakeholders within each country. Of the 15 recommendations in the WHO report, two concern strengthening the health sector response (box 1) and take a clinical and public policy perspective, as others have done. The recommendations inform the basis for defining the competency of doctors when dealing with intimate partner violence. If the identified competencies reflect the needs of patients, and, as much as possible, broader needs of society, then we are a small step closer to implementing these two WHO recommendations.

The international nutrition community working in emergencies has welcomed the introduction of the new WHO growth standard. Many will agree with Seal and Kerac, however, that a full assessment of the appropriate use of the new WHO standards in the diagnosis of acute malnutrition is urgently needed, and that this should be completed before they are adopted by agencies engaged in running nutritional programmes in emergencies.

Intimate partner violence
Doctors’ roles should be integrated with the needs of patients and society

various reasons, including interpreting the results of nutritional surveys, estimating potential beneficiary figures, and calculating entry and exit criteria for feeding programmes. Increased prevalence of severe wasting varies in different settings when using either the new WHO standards or the NCHS-WHO references. This fact makes the interpretation of nutritional surveys difficult and means that results cannot be converted from one to the other by using a simple algorithm. During the transition period, therefore, both the WHO standards and the NCHS-WHO references should be used until the implications of these differences are better understood.

The choice of using the percentage of the median or the z score for admission of children to feeding centres is more complicated and should be related to functional outcomes. Weight for height expressed as a percentage of the median is used partly because it is a better predictor of mortality than weight for height expressed as a z score when using the NCHS reference. We urgently need to study the functional significance of the weight for height indicators and investigate the suitable z score cut-offs for therapeutic and supplementary feeding in relation to mortality and other functional outcomes.

WHO, the United Nations World Food Programme, and Unicef are in the process of producing a joint statement on community based management of severe acute malnutrition. New evidence using ready to use foods suggests that large numbers of children with severe acute malnutrition can be treated in their communities without being admitted to therapeutic feeding centres or health facilities.

It is difficult and costly for community health workers or volunteers to measure weight for height, and the mid-upper arm circumference is a good predictor of mortality. A mid-upper arm circumference less than 110 mm has therefore been recommended as an indicator of severe acute malnutrition in community based management of malnutrition. It would be useful to investigate whether this measurement can also be used as an indicator for admission to feeding programmes.

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Box 1 | Recommendations from the WHO study1 aimed at strengthening the health sector response to the effects of violence against women

1. Develop a comprehensive health sector response to the effects of violence against women
2. Identify roles for health professionals in advocating for prevention of violence and in providing services to women
3. Coordinate and work with other health professionals and with other sectors that care for abused women (for example, by creating formal referral processes and protocols)
4. Integrate appropriate non-stigmatising, non-blaming, respectful, secure, and confidential responses to violence against women into:
   - All aspects of care (such as emergency services, reproductive health services, mental health services, HIV related services)
   - Sensitising and training of health professionals
5. Use reproductive health services as entry points for identifying and supporting women in abusive relationships, and for delivering referral or support services
6. Sensitise and train reproductive health providers to recognise and respond appropriately to violence by having protocols to deal with it, using referral systems (if such systems are unavailable, providing information about legal and counselling options), ensuring confidentiality, and making women’s safety a priority
7. Add an anti-violence component to antenatal services, parenting classes, and other services that involve men

Box 2 | CanMEDS definitions of doctors’ roles. Reprinted with permission from appendix B of the CanMEDS 2005 physician competency framework2

**Medical expert (the central role)**

As **Medical experts**, physicians integrate all of the CanMEDS roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care

**Communicator**

As **Communicators**, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter

**Collaborator**

As **Collaborators**, physicians effectively work within a healthcare team to achieve optimal patient care

**Manager**

As **Managers**, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system

**Health advocate**

As **Health advocates**, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations

**Scholar**

As **Scholars**, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge

**Professional**

As **Professionals**, physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour

Box 3 | Key features of the health sector WHO recommendations,3 with examples of CanMEDS roles in dealing with intimate partner violence

**Integrating appropriate responses to violence against women into all aspects of clinical care**

**Medical expert**

Apply best practice to identify, intervene, and refer cases of intimate partner violence

**Professional**

Deliver ethical, humane and compassionate care, recognising that blame may be cast, which may cause secondary adverse effects. Recognise limitations in expertise (and seek consultation if necessary)

**Communicator**

Facilitate patient centred therapeutic communication, including active empathic listening to establish trust. Work therapeutically with victims of intimate partner violence and share decision making

**Manager**

Participate in health systems for collaborative decision making and quality improvement. Victims of intimate partner violence need health services; doctors must manage and improve the effectiveness of their Individual provider and overall programme within healthcare systems

**Scholar**

Identify and apply evidence based intimate partner violence screening and interventions, identify knowledge or practice gaps and model these competencies for others

**Advocating for prevention and for services**

**Health advocate and medical expert**

Use medical expertise and influence to improve the overall health of patients and populations, identify and apply health determinants (social, cultural, economic) and strategies to promote health and prevent disease. Doctors must know how to help victims of intimate partner violence in navigating local systems and obtaining appropriate resources

**Working with other health professionals and other sectors**

**Collaborator**

Work effectively and appropriately within health and non-health sectors to facilitate coordinated intimate partner violence responses for individual patients and populations

**Sensitising and training health professionals**

**Scholar**

Educate patients and other providers about intimate partner violence; engage in lifelong learning through critical appraisal of evidence and evidence based practice

**Professional**

Serve as a role model; commit to appropriately dealing with intimate partner violence

purposes, other competency frameworks could also be used. The concept of developing doctors’ competency in intimate partner violence is not new. To be valuable, these frameworks need to share the CanMEDS focus on what distinguishes doctors from other health professionals (medical expert) and on competencies that go beyond doctors’ technical knowledge and skills to the needs and expectations that society places upon them. An open debate about what constitutes such competencies is needed to develop an international perspective and to guide training programmes and continuing medical education. We need to learn from educational leaders about their experiences and evaluations of providing training about intimate partner violence using learning goals matched to competencies. We also need to find effective ways to deal with the resistance that may come from adding this to medical school curriculums.

We must recognise the difference between a doctor knowing and being able to perform a competency and actually implementing that competency in practice. Once we have international consensus on what constitutes such competency, the next step is to assess it in practice, and ultimately to use it to set standards and measure performance.

Finally, we must recognise that efforts to identify what constitutes competency of doctors in dealing with intimate partner violence must be considered in tandem with research, as evidence is still unavailable for many aspects of patient care (for example, universal screening versus diagnostic case-finding methods). All this can only be achieved if doctors and society acknowledge the epidemic of intimate partner violence, recognise it as a global health and human rights issue, and devote resources to dealing with it.
Hospital acquired infection
Control measures for *Clostridium difficile* need to extend into the community

Recent data published by the Health Protection Agency (HPA) show that each year in England around 7000 inpatients have methicillin resistant *Staphylococcus aureus* (MRSA) bacteraemia and more than 50 000 inpatients aged 65 years and over have *Clostridium difficile* infections.1 *C difficile* cases rose by 5.5% in 2006 compared with 2005, whereas MRSA cases fell by 4.3% over a similar period. HPA spokespeople said they thought that the rate of increase of *C difficile* was slowing and MRSA rates had reached a plateau.

My own time series analyses of the reported data failed to detect any significant change in rates of *C difficile* or MRSA, though *C difficile* increases significantly during winter (www.geriatric.med.ed.ac.uk/john_starr.htm). The seasonal variation may be a result of many older people who require antibiotic treatment being admitted to hospital at that time of year. Despite the HPA data, there is a consensus that hospital acquired infection rates remain high and that recent control measures are having only a limited effect, especially on *C difficile*. With more than 2200 deaths attributed to *C difficile* on death certificates in England and Wales in 2004, the mortality rate is fast approaching that for road traffic accidents and is now around half that for suicide.5

Control of *C difficile* is difficult because, unlike MRSA, alcohol hand scrubs are ineffective and its spores are resistant to routine hospital cleaning.3 Moreover, old and frail patients are at highest risk of infection with *C difficile*. Since older people are living longer, hospital admissions of people over 85 years have increased relative to other age groups.5 This continuing change in case mix is likely to increase the absolute number of reported cases.

In December 2006, the Department of Health issued a letter on healthcare associated infections, in particular infection caused by *C difficile*, which called for urgent action.5 In addition to hand hygiene and environmental cleaning, recommendations include prudent antibiotic prescribing, isolation of infected patients, and use of personal protective equipment. Although there is a trend for reduced prescription of antibiotics in the community, it remains high in hospitals and accounts for 59% of prescription costs.6 7 Theoretically, isolation of infected patients should not be difficult. The National Health Service in England still has around 150 000 beds and even if just 20% of these are single rooms that can be used for isolation purposes, there should still be more than adequate capacity. However, the clustering of cases can put a strain on local resources. This is a particular concern with the emergence of hypervirulent strains.8

Another factor that may be driving the incidence of infection with *C difficile* is the community reservoir. Carriage rates in healthy people in the community may be around 5%, perhaps substantially higher in those connected with hospitals, and this may lead to community acquired infection.9 Indeed, the relative increase in community acquired *C difficile* far outstrips that seen in hospital, despite reduced antibiotic use, and may relate to increased use of proton pump inhibitors and other drugs that suppress gastric acid production.10 More than 13 000 cases of community acquired *C difficile* occur each year in the UK, three quarters of which are in people who have not been in hospital during the previous year. In contrast, the HPA identified fewer than 100 community acquired cases of MRSA between 2003 and 2005. This raises the question of whether *C difficile* can still be thought of as purely a hospital acquired infection and, if not, whether other infection control measures are needed, such as screening people in the community before they are admitted electively.

Early accurate diagnosis is fundamental to any infection control programme, whether based in hospital or the community. Laboratory methods to detect *C difficile* have varied considerably in the UK.11 Though variation has been reduced in England, it is still difficult to make comparisons with data from other countries, and thus assess the effects of their infection control policies. Denmark, for example, preferred culture to toxin detection as a diagnostic tool. Denmark also reported two fatal cases of *C difficile* enterocolitis in elephants in 2006, a reminder that animals, including household pets, can be a reservoir for the organism.

A report from the HPA published last year recommended greater international cooperation to tackle *C difficile* by sharing information about the appearance of new strains or changes in the prevalence of known strains.

It also emphasised that infection control guidelines have stayed essentially the same for more than a decade, and were implemented inconsistently across England.12 The recent HPA report presents a mixed message. Although both *C difficile* and MRSA are closely associated with use of antibiotics, in other ways they are quite different. Infection control policies for MRSA have been more successful than for *C difficile*, yet data on hospital acquired infections are often grouped together. In particular, because of the rise in community acquired infection it is important to consider whether a *C difficile* infection control policy solely focused on hospitals remains appropriate.

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### CLOSTRIDIUM DIFFICILE

**Improvement targets for *C difficile* must be valid**

We have identified a potentially distorting factor in the delivery of reductions in *Clostridium difficile* rates. A letter sent to chief executives of trusts, primary care trusts, and strategic health authorities in England in December 2006 stated that the forthcoming NHS operating framework for 2007-8 and the NHS contract require primary care trusts to agree a local target with their acute hospital providers for a significant reduction in *C difficile* infections. The target is expected to be “locally appropriate” and based on “current performance.” A reduction of at least 25% was suggested for trusts with a rate greater than four cases per 1000 bed days (in people over 65), while maintenance of the current rate would be an appropriate target for trusts with a rate of one per 1000 bed days or lower.

The West Midlands Strategic Health Authority initially imposed indicative targets for all acute trusts to negotiate with primary care trusts in the region, based not on the most recent data but on the average of 2004 and 2005 figures. The number of *C difficile* infections has increased by over 25% across the West Midlands during 2006 compared with this figure. Therefore the reductions imposed are in many cases far in excess of the targets suggested in the letter from the Department of Health, or as stated by the strategic health authority (table). Since it was explained to the authority that these targets are inappropriate, it has agreed to recalculate them.

When targets for methicillin resistant *Staphylococcus aureus* (MRSA) bacteraemia were set, they were imposed centrally and have been non-negotiable, despite statistical evidence showing that the methods used were invalid. The MRSA targets will not be met; if *C difficile* rates are to be reduced targets must be potentially attainable.

Although we are in favour of targets that increase the focus on reducing hospital acquired infections, we draw attention to the importance of using contemporaneous baseline data when trying to control a rapidly expanding problem. Infection control teams in trusts should ensure they are aiming at the right target, which should be scientifically valid.

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On behalf of the West Midlands Microbiologists Group

**Competing interests** None declared.


2 Dear colleague letter to chief executives of trusts, PCTs and SHAs dated 7 December 2006. www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcollagueletters/DH_063090


### TRANSPARENCY IN NICE

**Let's open whole process of cost effective modelling**

The National Institute for Health and Clinical Excellence (NICE) needs to go much further than allowing access to its modelling data. The whole cost effectiveness modelling process needs to be opened up to involvement by all stakeholders, and inspection by the public, as it happens. The independent group should be contracted to develop the one and only model that NICE will consider in its appraisal, and it should do so in full and continuous collaboration with all registered stakeholders and interested parties who sign up to the NICE guidelines. The model will be run with any alternative parameters suggested by various parties and the alternative results (along with their evidential basis) submitted to the appraisal committee in a single report. No subsequent questioning of, or submissions regarding, the model structure, the results, or the underlying principles would be accepted in the context of any particular case.

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**Competing interests** None declared.


### GLOBAL PARTNERSHIP

**UK doctors are already put off by changes in training**

We direct collaborative programmes of medical research in low income or middle income countries, with support from UK and local institutions. Each site has a team of local and international doctors, scientists, and support staff. We use high quality research to help understand local health problems and find ways to address these problems. We provide opportunities for local professionals to work with colleagues from the UK and elsewhere, thereby gaining experience to deal with their own problems in their own setting. UK doctors play a crucial part in each of these programmes. They contribute to the work, gain a wider perspective on international health problems, see a large range of disease problems, learn how to be resourceful, and contribute to advances against some of the world’s commonest health problems. Such experience is of great value not only in the host country but for individuals’ development as future NHS professionals. It is also crucial to the international perspective commended in the Crisp report.

Most UK doctors spending time in one of our research programmes wish to return to a career in the United Kingdom. If this re-entry is made difficult or impossible...
they are unlikely to come abroad in the first place. The individual, the NHS, and the international community would all be impoverished as a result.

Modemising Medical Careers (MMC) as currently formulated is likely to make it difficult for a young doctor to spend time working in a developing country. A revised MMC should include mechanisms that not only permit but strongly encourage UK doctors to work in a developing country at some stage during clinical specialist training.

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And Kevin Marsh, Nicholas White, Jeremy Farrar, Neil French, Nick Day, and Sarah Rowland-Jones, representing Kenya Medical Research Institute (KEMRI)-Wellcome Trust Programme, Kenya; Wellcome Trust South-East Asian Tropical Medicine Research Programmes; Hospital for Tropical Diseases Wellcome Trust Major Overseas Programme, Ho Chi Minh City, Vietnam; Karonga Prevention Study, Malawi; Wellcome Trust-Mahidol University-Okhoberd Tropical Medicine Research Programme, Thailand; and MRC Laboratories, the Gambia.

Competing interests: None declared.

NOT EVEN A DOG’S LIFE

It’s not a question of dogs or babies

Veterinary medicine is, for the most part, a form of private medicine. Money that animal owners elect to spend on promoting the health and welfare of their animals does not generally represent funds that would otherwise be used to promote human welfare, at home or abroad. It is money that might otherwise be spent enlarging carbon footprints on foreign holidays, upgrading cars to newer versions, fitting wardrobes or antique shelves, carrying out home improvements. In that sense, choosing to spend money on promoting the health and welfare of other sentient beings is surely not quite so deplorable and shallow as Towey makes out.

Poor countries are denied advanced medical treatment not because of its use in Western pet veterinary medicine but because of macroeconomics and global politics.

Other important questions need to be debated: the ethical boundaries of animal treatment; what is done, and for whom, and when; and when treatment should stop—an animal welfare issue; the ethics of pet keeping itself; and so on. Further, it should not be forgotten that modern medicine has used other animal species to a great extent in terms of research and experimentation. When it is in their interests, animals should also benefit from this. Ghandi said that you could judge a nation by the way it treated its animals.

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Competing interests: AAG is a dog owner, veterinary surgeon, and also concerned with human welfare.

1 Towey R. Not even a dog’s life. BMJ 2007;334:638. (24 March.)

Wish I was a celebrity’s pet

Towey may call the gap in the quality of medical care between the developed and developing worlds obscenity or racism, but most of the Nepalese people who cannot afford the cost of treatment call it fate.1 Medical care in Nepal will, perhaps, continue to be like this for many years to come. Most of us are adapted to this system. We do not attribute it to developed countries but to the inadequacy of our own government.

It is true that many “Western” dogs are more privileged than the human population here in Nepal in terms of medical care. But this disparity does not exist in medical care alone. It is just a part of the total economic gap between the developing and developed world.

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Competing interests: None declared.

1 Towey R. Not even a dog’s life. BMJ 2007;334:638. (24 March.)

HYPERTHYROIDISM

Total thyroidectomy is best operation for thyrotoxicosis

We were concerned by the statement that subtotal thyroidectomy in experienced hands guarantees patients the longest existence without taking drugs.1 This implies that subtotal thyroidectomy is the operation of choice in thyrotoxicosis. We believe that is not the case, firstly, because the operation of subtotal thyroidectomy is not clearly defined: the amount of thyroid tissue left behind varies from centre to centre. Secondly, there is a small but definite occurrence rate of thyroid cancer in both Graves’ disease and toxic multinodular goitre (4% in our series of 100 total thyroidectomies (all pathologies) for thyrotoxicosis). Thirdly, because there is a notable rate of both postoperative hyperthyroidism and hypothyroidism after subtotal thyroidectomy, each outcome effectively defeats the point of the operation type.2 4

Total thyroidectomy is the only appropriate procedure for the surgical management of thyrotoxicosis in the United Kingdom.

It guarantees cure, and, although it also guarantees hypothyroidism, thyroxine replacement treatment is far more predictable as the operation is clearly defined.

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Competing interests: None declared.


IMPACT FACTORS

The dark side

Martyn’s tongue in cheek advice to the new editor of a prestigious—if fictional—journal is to raise the impact factor by various measures including “resisting any sympathy when a paper is submitted on an unfashionable condition such as deafness.” As a psychiatrist working with deaf sign language users I was delighted to see, at last, a mention of deafness in a prestigious—and non-fictional—journal.

My team’s attempts at getting articles published in mainstream journals have been met with responses such as “not of general interest” and “there is a misspelling into mainstream services.” My personal favourite is a reference to a paper on adapting an instrument for culturally deaf sign language users I was delighted to see, at last, a mention of deafness in a prestigious—and non-fictional—journal.

William Tovey may call the gap in the quality of medical care between the developed and developing worlds obscenity or racism, but most of the Nepalese people who cannot afford the cost of treatment call it fate.1 Medical care in Nepal will, perhaps, continue to be like this for many years to come. Most of us are adapted to this system. We do not attribute it to developed countries but to the inadequacy of our own government.

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Competing interests: None declared.

1 Tovey R. Not even a dog’s life. BMJ 2007;334:638. (24 March.)

None declared.

Competing interests: None declared.

Tovey R. Not even a dog’s life. BMJ 2007;334:638. (24 March.)

None declared.
Hewitt says some Muslim GPs breach confidentiality

Michael Day LONDON
Patricia Hewitt, England’s health secretary, has said that some Muslim GPs may be divulging details of the sexual health of female Muslim patients to family members.

Her comments drew an angry response from Muslim GPs, who said that her claims were based only on anecdotal evidence.

However, Mrs Hewitt, who represents a constituency in Leicester with a large ethnic minority community, said, “I have had Muslim women give me chapter and verse on very distressing breaches of confidentiality by Muslim GPs.”

“Some women patients in some Muslim communities are feeling they can’t trust their own GP, who is from the same community and knows their extended family.

“If they go for particular situations, such as a sexual health problem or domestic violence, they fear they will share that information with other members of the family or community.”

Mrs Hewitt made her comments in an interview with the magazine for GPs Pulse (29 Mar, p 2).

Vijoy Singh, chairman of the Leicestershire and Rutland local medical committee, which covers Ms Hewitt’s constituency, said, “No GP would break confidentiality, because if they break it they are liable to be sued. She’s out of touch.”

Mrs Hewitt cited a report published in November last year by the Muslim Women’s Network, which was based on conversations with Muslim women throughout the country, as further evidence of her concerns. The report, She Who Disputes [www.thewnc.org.uk/pubs/shewhodisputesnov06.pdf], noted: “Health services were criticised for being insensitive and there was repeated concern that GPs from within the community could not be trusted to maintain patient confidentiality.”

BMA gives advice on withdrawing treatment

Clare Dyer BMJ
The BMA is advising people in England and Wales to consider appointing a relative or friend to make medical decisions for them if they lose capacity, in the light of legislation coming into force next October.

The advice came as the BMA launched a revised guide for UK doctors on withholding and withdrawing treatment that takes account of new legislation on mental capacity and the results of a series of high profile court cases since the last guidance in 2001.

The court cases include “right to life” cases brought by the parents of the severely handicapped baby Charlotte Wyatt and by Leslie Burke (above), a man with a degenerative condition who wanted a court declaration that artificial feeding and hydration would not be withdrawn from him if he lost capacity and the ability to swallow.

From 1 October, under the Mental Capacity Act 2005, people will be able to draw up a “lasting power of attorney” and appoint a friend or family member to make treatment decisions on their behalf if they become too mentally incapacitated to make such decisions. Treating patients who have appointed an attorney will mean “a significant change to [doctors’] practice,” the guidance says.

Under the new law, which applies to England and Wales, the healthcare team will have to make sure that certain conditions are fulfilled before they rely on an attorney’s consent to or refusal of life prolonging treatment.

Doctors will have to be satisfied that the patient lacks capacity to make the decision and that the scope of the lasting power of attorney is broad enough to cover the particular decision. Attorneys may make decisions on life prolonging treatment only if this is specifically authorised by the power of attorney.

In addition, the lasting power of attorney must be registered with the Public Guardianship Office, and the attorney’s decision must be in the patient’s best interests. Disagreements over the patient’s best interests can be resolved by seeking a declaration from the new Court of Protection. The court will also be able to appoint a deputy to make ongoing health decisions on a patient’s behalf.

For doctors in Scotland the guidance also deals with the similar, but slightly different, regime that applies there. In Northern Ireland the common law will continue to apply.

The Mental Capacity Act also sets up a statutory framework that applies to England and Wales for advance directives or “living wills” refusing life prolonging treatment. These are already binding on doctors under common law if their terms apply to the circumstances of the case.

See [www.bma.org.uk]
Doctors protest about fetal sex tests in early pregnancy

Annette Tuffs HEIDELBERG

Clinical geneticists and gynaecologists in Germany have expressed concerns that a private firm is offering women in the early stages of pregnancy a blood test to determine the sex of their unborn baby. The test is offered from the eighth week of pregnancy, and doctors fear that women who are not happy about the sex of their child may ask for an abortion, which is legal in Germany up to the 12th week of pregnancy and quite easily obtained.

The firm, Plasmagen, offers the test over the internet. It tells women to ask their doctor to take a 2 ml blood sample and send it to the company’s laboratory in Cologne. Test results are available within eight days after the arrival of the sample and are sent back to the woman’s doctor. The test costs €149 (£101; $198); money is refunded if the result proves to be wrong.

Although the firm says that the patient’s doctor should not reveal the test’s result until the 12th week of pregnancy, some doctors believe that patients may be able to access the results earlier—if, for example, they are dishonest about the date of conception.

The German Society for Human Genetics has issued a public statement condemning commercially driven offers of prenatal genetic testing in cases where there is no medical reason for one.

Plasmagen’s test works by searching the mother’s blood for fetal DNA and then looking for Y chromosome material. The firm claims on its website that the test is 99% accurate.

Professor Peter Propping, president of the German Society for Human Genetics, questions the relevance of the sex test. He particularly criticises Plasmagen for saying that the test is useful for cases where the baby may be carrying sex linked disease. This could lead to a number of unnecessary abortions, he says. If a fetus is aborted solely on the basis of its sex, male fetuses that do not carry the gene for the relevant disease will be aborted.

Daniel Inderbiethen, marketing director of Plasmagen, denies that unnecessary abortions will occur when x-linked genetic diseases are suspected. In fact, he says, the availability of the test will result in fewer unnecessary amniocenteses because amniocentesis will not be necessary if the child is known to be a girl.

Electronic prescribing needed to monitor use of antibiotics

Lisa Hitchen LONDON

The lack of electronic prescribing in UK hospitals is hampering effective prescribing of antibiotics, says the Health Protection Agency.

Giving patients the right treatment is fundamental, said Dr Andrew Pearson, deputy director of the agency’s centre for infections, particularly in the case of severe illnesses such as those caused by Clostridium difficile.

“We have got to get some form of computerised monitoring of our prescribing,” Dr Pearson told delegates at a conference on healthcare associated infections in London last week. “The problem is that very few hospitals in the UK have electronic prescribing—just three. It is going to be interesting to see if the Healthcare Commission picks up on that.”

In the United States, computerised monitoring is carried out. Researchers at the University of Maryland used computer software to monitor antibiotic use at different hospitals. Prescribing errors were flagged up as error messages, said Dr Pearson.

“This was a very uncomplicated way of measuring the errors…and will be piloted by one hospital here later in the year.”

On the back of such monitoring, restricting the use of antibiotics can be effective in reducing cases of C difficile infection, said Professor Mark Wilcox, a consultant microbiologist at Leeds Teaching Hospitals NHS Trust.

Dr James Nash, consultant microbiologist at East Kent Hospitals NHS Trust, whose work was referred to at the conference, helped implement a radical restriction of antibiotics to try and reduce the incidence of C difficile infection in three Kent hospitals.

An audit of antibiotic use in 2003 found that 15% of patients who had received ceftriaxone developed C difficile infection. The antibiotic was removed from the wards and used only for treating meningitis. This led to a dramatic fall in cases in 2004.

However, in 2005 cases of C difficile increased again following the arrival of the 025 strain, despite continuing restrictions on the use of ceftriaxone. Emergency policies were introduced, including further restrictions on the availability of broad spectrum antibiotics (notably ciprofloxacin and coamoxiclav) and multiple infection control measures.

The policy changes required considerable negotiation between clinicians and microbiologists, but had positive effects for patients, with C difficile infection rates falling even further in 2006.

Dr Nash added: “It is difficult to know which is the biggest factor—is it changing the antibiotics or all the infection control measures? Changing antibiotic prescribing is the most difficult thing to do and it needs the help of management and the pharmacists.”

WHO recommends circumcision to combat

Peter Moszynski LONDON

The World Health Organization and UNAIDS have published the results of a recent expert symposium on circumcision and AIDS, which insists that “male circumcision now be recognised as an additional important intervention to reduce the risk of heterosexually acquired HIV infection in men”—although with certain caveats on the need to ensure the procedures are done safely and appropriately.

The international consultation, held on 6-8 March, in Montreux, Switzerland, was attended by participants representing a wide range of stakeholders, including governments, civil society, researchers, funding agencies, implementing partners, and advocates for human rights.

The symposium concluded, “There is now strong evidence from three randomised controlled trials undertaken in Kisumu, Kenya, Rakai District, Uganda (funded by the US National Institutes of Health) and Orange Farm, South Africa (funded by the French National Agency for Research on AIDS) that male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 60%.”

It maintains that the evidence examined
The risk of death, myocardial infarction, or other major cardiovascular events in patients with stable coronary artery disease is no lower with percutaneous coronary intervention (PCI) than with the optimal therapy of drug treatment with lifestyle intervention, says a major prospective study that is predicted to change practice.

The trial, published online on 26 March in the *New England Journal of Medicine* (http://content.nejm.org), randomised more than 2000 patients with objective evidence of myocardial ischaemia and significant coronary artery disease to PCI or optimal medical treatment. The results showed no difference in mortality from any cause or in the risk of non-fatal myocardial infarction at a median follow up of 4.6 years.

The findings will change practice, said David Taggart, professor of cardiovascular surgery at Oxford University. “This is a very important trial,” he said. “The results reinforce what some of us have believed for some time: that there is an overuse of PCI in some patients.”

The results illustrate the need for a multidisciplinary approach in which treatment is offered that is in the best interests of patients, rather than individual cardiologists making decisions in isolation, said Professor Taggart. “A significant population of patients can be managed on optimal medical therapy, with no increase in risk of death or MI [myocardial infarction].”

Professor Taggart thought it was surprising how much controversy the results of the trial, known as the COURAGE trial, have generated. “The information was already there from very good trials. COURAGE hasn’t really told us anything new but has backed up, in a definitive way, what we already knew.”

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PCI has traditionally been used less in Europe than in the United States, because there have not been the same financial incentives to carry out some stenting, said Professor Taggart. “Many European health systems are, to some degree, publicly funded, so there has been a slightly more objective view of what is in patients’ best interests.” But use of PCI has been increasing over the past year, he said, and he added that this may now be reviewed.

In an editorial accompanying the study Judith Hochman, professor of cardiology at New York University School of Medicine, and Gabriel Steg, professor of cardiology at Université Paris VII, said, “The COURAGE trial should lead to changes in the treatment of patients with stable coronary artery disease.”

They pointed out that medical therapy had proved its effectiveness in the trial. “Secondary prevention has proved its worth, with lipid-modulating therapy, lifestyle modification and the use of aspirin, beta-blockers and ACE inhibitors.”

Revascularisation should be limited to patients whose condition is clinically unstable, who have left main artery disease, or in whom medical treatment has failed to control symptoms, they advised. See Short Cuts, p 716.

**Drugs are as good as PCI in stable coronary artery disease**

**Susan Mayor** LONDON

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**HIV infections in men in Africa**

“supports the findings of numerous observational studies that have also suggested that the geographical correlation long described between lower HIV prevalence and high rates of male circumcision in some countries in Africa, and more recently elsewhere, is, at least in part, a causal association.”

The latest WHO figures estimate that 66.5 million men—30% of men worldwide—are currently circumcised.

“The recommendations represent a significant step forward in HIV prevention,” said Kevin De Cock, WHO’s director of HIV and AIDS. “Countries with high rates of heterosexual HIV infection and low rates of male circumcision now have an additional intervention which can reduce the risk of HIV infection in heterosexual men.”

The consultation cautioned, “Male circumcision should always be considered as part of a comprehensive HIV prevention package, which includes the provision of HIV testing and counselling services; treatment for sexually transmitted infections; the promotion of safer sex practices; and the provision of male and female condoms and promotion of their correct and consistent use.”

**Kenyan boys hunt at their circumcision ritual**

**Drugs are as good as PCI in stable coronary artery disease**

**Susan Mayor** LONDON

The risk of death, myocardial infarction, or other major cardiovascular events in patients with stable coronary artery disease is no lower with percutaneous coronary intervention (PCI) than with the optimal therapy of drug treatment with lifestyle intervention, says a major prospective study that is predicted to change practice.

The trial, published online on 26 March in the *New England Journal of Medicine* (http://content.nejm.org), randomised more than 2000 patients with objective evidence of myocardial ischaemia and significant coronary artery disease to PCI or optimal medical treatment. The results showed no difference in mortality from any cause or in the risk of non-fatal myocardial infarction at a median follow up of 4.6 years.

The findings will change practice, said David Taggart, professor of cardiovascular surgery at Oxford University. “This is a very important trial,” he said. “The results reinforce what some of us have believed for some time: that there is an overuse of PCI in some patients.”

The results illustrate the need for a multidisciplinary approach in which treatment is offered that is in the best interests of patients, rather than individual cardiologists making decisions in isolation, said Professor Taggart. “A significant population of patients can be managed on optimal medical therapy, with no increase in risk of death or MI [myocardial infarction].”

Professor Taggart thought it was surprising how much controversy the results of the trial, known as the COURAGE trial, have generated. “The information was already there from very good trials. COURAGE hasn’t really told us anything new but has backed up, in a definitive way, what we already knew.”

PCI has traditionally been used less in Europe than in the United States, because there have not been the same financial incentives to carry out some stenting, said Professor Taggart. “Many European health systems are, to some degree, publicly funded, so there has been a slightly more objective view of what is in patients’ best interests.” But use of PCI has been increasing over the past year, he said, and he added that this may now be reviewed.

In an editorial accompanying the study Judith Hochman, professor of cardiology at New York University School of Medicine, and Gabriel Steg, professor of cardiology at Université Paris VII, said, “The COURAGE trial should lead to changes in the treatment of patients with stable coronary artery disease.”

They pointed out that medical therapy had proved its effectiveness in the trial. “Secondary prevention has proved its worth, with lipid-modulating therapy, lifestyle modification and the use of aspirin, beta-blockers and ACE inhibitors.”

Revascularisation should be limited to patients whose condition is clinically unstable, who have left main artery disease, or in whom medical treatment has failed to control symptoms, they advised. See Short Cuts, p 716.
IN BRIEF

Euthanasia in Belgium up by 10%: In 2006 in Belgium 428 people chose to die by euthanasia, an increase of 10% on the 2005 figure. Belgium decriminalised euthanasia in September 2002.

EC to fund registry for stem cell lines: The European Commission has agreed to fund the creation of a registry of human embryonic stem cell lines. It will be a publicly accessible internet site and will contain data on the sources of stem cell lines and clinical trials in the 10 EU countries that allow such research as well as in Australia, Israel, Turkey, Switzerland, and the United States.

A quarter of NHS staff “would not be patients” in their trust: Just over a quarter of health staff told a survey by the Healthcare Commission that they would not be happy to be a patient in their own NHS trust. Two fifth said that they would be happy with the care provided, and about a third were undecided. The commission polled more than 128000 staff. See www.healthcarecommission.org.uk.

British scientists grow part of a human heart: Scientists under the leadership of Magdi Yacoub, professor of cardiac surgery at Imperial College London, have grown part of a human heart from stem cells. Professor Yacoub led a team at Harefield Hospital, Uxbridge, Middlesex, which included physicists, pharmacologists, clinicians, and cellular scientists. Animal trials are scheduled for later this year (Guardian, 2 Apr, p 1).

Patients with haemochromatosis have a higher risk of stroke: People with the genetic mutation for haemochromatosis are more than twice as likely as other people to have a stroke, says a new study of more than 9000 Danish people who were followed for 24 years (Neurology 2007;68:1025–31). The mutation has been linked to brain diseases but not until now to stroke.

UK ban on junk food advertising comes into force: A ban on television advertisements for foods that are high in fat, sugar, and salt during programmes aimed at 4 to 9 year olds came into effect in the United Kingdom this week, although dedicated children’s channels will have until 2009 to phase in the restrictions.

Agency makes better use of anticoagulants its top priority

Lynn Eaton LONDON

Measures to reduce the risk of wrongly administering epidural infusions intravenously and better guidance for patients about anticoagulant drugs are among a series of risk management measures outlined this week to improve patient safety in the NHS.

The guidance from the National Patient Safety Agency comes after a number of avoidable deaths relating to the use of these and other drugs. Keith Ridge, the chief pharmaceutical officer for England, said that awareness of the importance of reducing weaknesses within healthcare systems was increasing.

The highest priority for the agency is the number of deaths associated with the use of anticoagulant drugs, such as warfarin (above), he said. In 2006 alone there were 120 deaths and 480 incidents of serious harm related to warfarin reported to the agency.

“Bupivacaine, when given intravenously, is cardiotoxic,” said David Cousins, head of safe drug practice at the agency, speaking at the launch of the five new safety measures. He said there had been three known deaths as a result of similar errors between 2000 and 2003.

Professor Cousins called for a number of measures to improve patient safety with this and other drugs and procedures. They include better training, better procedures, giving more information to patients, and action by drug manufacturers to reduce risks.

Manufacturers, he says, should develop different systems for linking the infusion bag to the line to prevent a drug intended for intravenous use from being mistakenly attached to an epidural line.

The agency has also introduced guidance on:

- Reducing the risks associated with injectable medicines by being aware which have the highest risk
- Reducing the risk of wrongly giving oral liquid medicines intravenously by using only labelled oral or enteral syringes that cannot be connected to intravenous catheters.

See www.npsa.nhs.uk.
Head of UK scheme to improve junior doctors’ training resigns

Lynn Eaton LONDON

Alan Crockard, the national director of Modernising Medical Careers, the UK government agency set up to redesign the training of junior doctors, announced his resignation last Friday. He resigned because of serious problems with the computerised training application system, known as the medical training application service (MTAS).

The news came as Remedy UK, the organisation that has been leading the protests over the system, announced plans to launch a legal challenge to the proposed single interview process for England. Details of the process were due to be announced as the BMJ went to press.

The solicitors acting for the organisation, Leigh Day and Co, said: “Our client is concerned that the new proposals will involve substantial illegality and unfairness.”

In his resignation statement Professor Crockard called on the chief medical officer for England, Liam Donaldson, to “urgently address” the problems in the current computerised recruitment system.

It is understood that Professor Crockard was frustrated that the application scheme—something he had no direct control over—was jeopardising the reform of training.

Failings in the system had led to an outcry from junior doctors and academics frustrated with the arrangements. Protest marches took place on the streets of London and Glasgow last month (BMJ 2007;334:602, 24 Mar).

“I care passionately about medical education and training,” Professor Crockard said. “The principles of Modernising Medical Careers (MMC) are laudable and I stand by them. More patients should be treated by trained doctors, rather than doctors in training. “The recruitment of doctors into these new training programmes is separate to the development of the educational standards that MMC has been working to deliver. This recruitment process, through the MTAS system, undeniably needs to be reviewed. This process was developed outside my influence.

“I have become increasingly concerned about the well intentioned attempts to keep the recruitment and selection process running. I accept that in many areas and in many specialties, this round of recruitment and selection has been acceptable. But the overriding message coming back from the profession is that it has lost confidence in the current recruitment system.

“In the interest of the most important people in the whole process, the junior doctors, this must urgently be addressed.”

The government’s MTAS review group met on the day that Professor Crockard’s resignation was announced. As the BMJ went to press the group had yet to announce whether it would be standing by its decision to offer applicants for jobs in England only one interview. But Wales, Scotland, and Northern Ireland have decided that they will offer their candidates more than one interview.

Professor Crockard was responsible for developing the two year foundation training programme for medical graduates that was launched in 2005.

For the latest developments see Lynn Eaton’s news updates [http://blogs.bmj.com/category/comment/mtas].

Hewitt predicts 3% NHS growth for three years from 2008

Nicholas Timmins FINANCIAL TIMES

Patricia Hewitt, the health secretary, has said she is confident that the NHS will get a minimum of 3% growth a year in real terms for the three years after 2008.

And the Department of Health has finally agreed to unwind the “double whammy” of the “resource accounting and budgeting” rule—for NHS hospital trusts but not for primary care trusts.

Under the rule, hospitals that overspend, by say £10m (€15m; $20m) on a £100m budget, have not only to pay that off but also lose the same amount from their next year’s budget. In effect the hospital would have to make savings of £20m before the £10m is restored to the following year’s budget.

This plunged 28 NHS hospital trusts into a financial position from which they might not be able to recover. With the NHS set to make a tiny surplus in the financial year just ending, the Department of Health will use part of a £450m contingency reserve created by the strategic health authorities, chiefly by slashing training budgets, to write off the £178m deficit that the trusts, but it is not a complete solution. Four trusts have deficits of between £12m and £21m unrelated to the resource accounting and budgeting rule.

This has to be good news for the affected trusts, but it is not a complete solution. Four trusts have deficits of between £12m and £21m unrelated to the resource accounting and budgeting rule, and the change puts only nine of the 28 trusts back into break even or surplus. Their remaining deficits will have to be handled in the normal way.

Virtual teaching offers new style of radiotherapy training

Zosia Kmietowicz LONDON

A virtual radiotherapy treatment room is allowing practitioners at Hull’s Princess Royal Hospital to develop and refine their skills without setting foot in a real treatment room.

The system, known as the virtual environment for radiotherapy training (VERT), is thought to be the first such facility in the world. Developed by Roger Phillips of the University of Hull’s computer science department, with clinical input from Andy Beavis, honorary senior fellow at Hull University, it projects a life sized treatment room on a screen, allowing trainee and qualified radiographers to practise planning and delivering treatment in a real life situation.

The university is currently developing a consortium with other universities and manufacturers to make VERT more widely available.
**Shortcuts from other journals**

**Hope is fading fast for torcetrapib**

Drugs that increase serum concentrations of high density lipoprotein should theoretically help prevent cardiovascular events such as heart attack. But hope is fading fast for the new drug torcetrapib, which increases concentrations of "good" cholesterol by inhibiting cholesterol ester transfer protein. One clinical trial has already been stopped early because the new drug seemed to cause rather than prevent cardiovascular events, including deaths. Now ultrasound studies show that torceptrapib has none of the expected beneficial effects on coronary or carotid atherosclerosis.

Perhaps torceptrapib produces dysfunctional high density lipoprotein cholesterol. Or perhaps it is a vascular toxin with side effects (such as increased blood pressure) that wipe out any advantage from extra high density lipoprotein cholesterol, says a linked editorial (doi: 10.1056/NEJMe078029). More detailed analysis of the available data may provide the answer.

An equally urgent question is whether the failure of this one agent should halt development of other drugs in the same class. The authors of one study and the linked editorial agree that would be a mistake. Inhibition of cholesterol ester transfer protein was a controversial strategy from the start. But the evidence still supports further cautious exploration of agents that, unlike torceptrapib, don't increase systolic blood pressure.

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BMJ 2007;334:716 (7 April), doi:10.1136/bmj.334.7596.716-a

**Shortcuts from other journals**

**Rosuvastatin halts early atherosclerosis in low risk adults**

Primary prevention of cardiovascular disease is usually based on individual assessments of risk; people who are likely to develop disease are considered for preventive treatments such as statins. But even those assessed as low risk can have subclinical atheromatous disease. In one study, 984 of 5751 middle aged adults at low risk had clear evidence of thickening in the intima-media of the carotid arteries. When the researchers did a placebo controlled trial of rosuvastatin in these people, two years of active treatment stopped early
atherosclerosis from progressing. So should we be screening even low risk adults with carotid ultrasound and treating everyone with early signs of disease?

Probably not, says a linked editorial (pp 1376-8). At least not yet. While it's clear that low risk doesn't mean "no risk," we still don't know enough about the link between carotid intima-media thickness and clinical events to go looking for it in everyone. Changes in surrogate markers for cardiovascular and other diseases don't necessarily translate into better health or longer lives.

This study does remind us, however, of the large burden of potential disease lurking in "the vast person time space of the low risk population," says the editorial. Ambitious and expensive trials that study real clinical events must be done to investigate it properly.

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BMJ 2007;334:716 (7 April), doi:10.1136/bmj.334.7596.716-b

News

Shortcuts from other journals

People with stable coronary artery disease need drugs first, not stents

People with stable coronary heart disease have little if anything to gain from initial treatment with percutaneous coronary intervention (PCI), researchers reported last week. Those treated with the best available drug and lifestyle regimen did just as well in a large randomised trial as those who had the same regimen plus angioplasty and stenting (mostly bare metal). Death rates and other cardiovascular events were closely matched during a median follow-up of 4.6 years. A comparable proportion of patients in each group reached the main composite end point of death or non-fatal myocardial infarction (19% v 18.5%; hazard ratio for the PCI group 1.05, 95% CI 0.87 to 1.27). Angina improved for patients in both groups, but the initial improvement was greater for those who had PCI.

Most Americans who have PCI have stable coronary artery disease. So these findings if widely accepted could signal a substantial change in practice, says a linked editorial (doi: 10.1056/NEJMe078036). Aggressive control of risk factors and serum lipids combined with antiplatelet treatment, blockers, and other recommended drugs is an effective initial strategy that has now been tested in more than 5000 patients. PCI can be deferred safely for most. About a third of the patients in the medical therapy group eventually needed revascularisation in this trial.
News

Shortcuts from other journals

Infected prosthetic heart valves are still dangerous

Infected prosthetic heart valves are a common cause of endocarditis, accounting for about a fifth of all cases recorded in one multinational register. Sixty one medical centres in 28 countries contributed to the register, recording details of all cases of infective endocarditis as they came in. Analysis of entries made over the five years up to 2005 found a higher than expected 21% (556/2670) of cases had an infected prosthetic heart valve. Almost half of these patients (272/556) needed surgery. Just over one fifth (127/556) died while in hospital.

*Staphylococcus aureus* was the leading cause of infected prosthetic valves in this observational study, closely followed by coagulase negative *Staphylococcus*. About a third of all infections on prosthetic valves were linked to contact with healthcare services (203/556). Of these, 43% were thought to be caused by an intravascular device such as an indwelling catheter. Infections picked up during contact with health services were associated with an increased risk of death (adjusted odds ratio, 1.62, 95% CI 1.08 to 2.44). Other predictors of poor outcome were old age; *S aureus* infection; and complications such as heart failure, intracardiac abscess, or stroke.
A bitter dispute over the authorship of a twice published medical paper has pitted a 35 year old Korean doctor against one of the most powerful players in the country’s struggle for biotech supremacy. The battle is threatening to disrupt Korea’s efforts to recover scientific credibility in the wake of the recent scandal over Woo-Sok Hwang’s stem cell research.

On one side is Jeong Hwan Kim, a Korean doctor now working in Singapore. On the other is Kwang Yul Cha, a fertility specialist with important medical business interests in Korea and the United States and an emerging front runner in the race to inherit the disgraced Hwang’s crown as Korea’s foremost stem cell research pioneer.

Dr Kim claims a paper about premature ovarian failure that he originally published in the Korean Journal of Obstetrics and Gynaecology in January 2004 was translated and republished in the American journal Fertility and Sterility under a different title and with different authors in December 2005.

What is indisputable is that Dr Kim’s name was not present in the later version of the paper and that in his place as lead author was Dr Cha, his former employer and the head of CHA Health Systems, a “global healthcare enterprise” whose many interests include the CHA Stem Cell Institute, Pochon CHA University of Health and Medicine, and seven hospitals and clinics in Korea and the CHA Fertility Centre, CHA Regenerative Medicine Institute, and Hollywood Presbyterian Medical Centre in Los Angeles.

Now, as the dispute escalates into a series of allegations and counter allegations, the editor in chief of Fertility and Sterility has been accused of defamation and threatened with legal action by Dr Cha. However, the BMJ has also learnt that following an investigation by the public prosecutor’s office in Korea, Dr Sook Hwan Lee, one of Dr Cha’s coauthors on the disputed paper, has been charged with criminal copyright infringement.

duplicate publication: a bitter dispute

Korea’s scientific community is once again under scrutiny as a row erupts about the origins of a study published in a Korean and a US journal. Jonathan Gornall investigates.

Origins

The story begins a decade ago, when Dr Kim, then a 25 year old graduate from the College of Medicine at Korea University, joined the CHA organisation. After a year as an intern, in March 1998 he began four years of residency in the obstetrics and gynaecology department at CHA General Hospital in Seoul. This was followed by a fellowship at the CHA Infertility Medical Centre and, after a year, promotion to consultant in the same unit. He studied at the graduate school at Korea University while working at CHA General Hospital, achieving a master’s degree in obstetrics and gynaecology in 2001 and completing his PhD in 2003.

Dr Kim told the BMJ that the paper now in dispute had begun life as his PhD thesis and that there were just two names on it when it was published by Korea University in May 2003: his and that of his university supervisor, Jae Sung Kang, head of obstetrics and gynaecology at the university. Dr Kim
The title had changed but comparison of the two papers shows that . . . they are substantially the same

says he submitted his thesis as a paper to the Korean Journal of Obstetrics and Gynaecology in July 2003, one month before he left the CHA group for a post in Singapore.

The paper now carried five additional names. Dr Kim had added Sook Hwan Lee, head of the human genetics laboratory at CHA General Hospital, with whom he says he discussed the study. In addition, he credited as authors three researchers who had carried out DNA extraction from blood samples and Tae Ki Yoon, his superior at the Infertility Medical Centre.

Now in Singapore, Dr Kim says he next saw his paper as a PDF, shortly after it was published in the Korean Journal of Obstetrics and Gynaecology. He was, he says, surprised to see that Dr Lee had become the corresponding author and that an additional three names had been added to the list, which now totalled 10.

He was also surprised to see that the paper now carried a statement that the study had been conducted with the aid of government funding. This was, he says, news to him. “I have never had any penny of it,” Dr Kim told the BMJ. “I paid all my expenditure with my own cash and I have my receipts.”

Duplicate publication
Dr Kim says his surprise turned to shock when he saw the paper had surfaced again—this time in the December 2005 edition of Fertility and Sterility. The title had changed but comparison of the two papers shows that, although sentences have been restructured and they are not word for word identical, they are substantially the same.

He was even more shocked to see that the number of authors had reduced to six and that he was no longer one of them. In fact, only two of the authors credited had also been listed in the Korean Journal of Obstetrics and Gynaecology version of the paper, and one of them was Dr Lee. Dr Kim’s place as lead author had been taken by Dr Cha.

The three other newcomers to the paper included Hyung Min Chung, codirector of the new CHA Stem Cell Institute, and Kyu Bum Kwak, one of the institute’s 36 principal investigators.

Dr Kim says his immediate concern was for his future in Singapore. “They are very strict about these things here. I was the first doctor to have come direct from Korea and work here and I got a very sceptical view from the Singapore Medical Society.

“When my boss, also a fertility specialist, saw the Fertility and Sterility article he very politely asked me, ‘I know KY Cha, and I know he is a big figure, I can’t help but think—did you buy your PhD thesis?’

Shortly after publication of the paper in Fertility and Sterility Dr Kim contacted Dr Alan DeCherney, the journal’s editor in chief. Dr Kim told DeCherney not only that he was the rightful and uncredited author of the paper but also that it had been published before.

Dr DeCherney investigated Dr Kim’s claims and on 21 July 2006 replied to say that while there was “considerable overlap between the article we published and the materials that you submitted . . . the issue of plagiarism cannot be resolved by this journal or its Editorial Board. We suggest that the matter be resolved by your institution. If the matter is resolved in your favor, and there is adequate documentation, please forward the information to us.”

Dr DeCherney told the BMJ: “The way that we sort this out in America is that I would go to the dean or the chairman of the department, but the problem is that this was all done at the CHA [organisation].”

Harvey Marcovitch, chair of the Committee on Publication Ethics, said, “All the appropriate bodies—the International Committee of Medical Journal Editors, the Council of Science Editors—are quite clear that it is wrong to try to publish the same data more than once. Duplicate publication is taken very seriously and COPE deplores it because it can corrupt the record.”

On 9 February this year Dr DeCherney received an email from the editor in chief of the Korean journal, requesting retraction of the article by Fertility and Sterility on the ground of duplicate publication. On 18 February, Dr DeCherney was quoted in an article in the LA Times as saying that he was going to recommend to the April meeting of his editorial board that the paper be withdrawn and the authors banned from publishing in the journal for three years.

On 7 March, Dr DeCherney received a letter from lawyers acting on behalf of Dr Cha. It quoted comments attributed to him in the LA Times on 18 February and in The Scientist on 20 February and accused him of having made “false and defamatory statements” about Dr Cha. It threatened legal action and demanded that Dr DeCherney sign a statement of retraction. The letter, seen by the BMJ, calls for Dr DeCherney to “acknowledge that 1) Dr Cha was entitled to be credited as an author of the F&S [Fertility and Sterility] article; 2) you have no reason to disbelieve Dr Cha’s statement that he was unaware of the prior publication in the KSOG Journal; and 3) Dr Cha did not plagiarise Dr Kim’s work, in that Dr Kim’s name was on the list of authors initially submitted to F&S by Dr Lee, and was only omitted because he could not be located.”

In December last year, Dr Kim filed a lawsuit in Korea against Dr Cha and Dr Lee, alleging breach of copyright. Dr Lee responded by alleging that Dr Kim had defamed her, while the CHA organisation claims that Dr Kim stole the data used in the study. It is Dr Lee, however, who is facing criminal charges in Korea, as a spokesman for the CHA organisation told the BMJ: “Dr Lee confirms that the other authors named in the F&S article were unaware that it had already been published, as is supported by the fact that she is the only defendant named in the public prosecutors office’s charge of copyright infringement, after a full investigation by that body.

“She accepted full responsibility for the dual publication and has apologised to F&S. While she denies most of the charges by Dr Kim, Dr Lee feels that the incident has hurt the reputation of the medical school and the hospital, and as a result has offered to resign her professorship at the medical school and all posts at the hospital and the laboratory.”

The BMJ has been unable to reach Dr Lee to confirm this.

Disputed history
So how was the disputed paper produced and by whom? According to the CHA organisation, Dr Kim’s role in the research was not as important as he would have it. A spokesman for the organisation informed the BMJ that it was Dr Cha who had “originated the idea for the project, and provided guidance and oversight for the collection of the patient samples for the research data upon which the F&S article was based. He is therefore fully entitled under the relevant rules to a credit as a first author.” The spokesman also claimed that Dr Cha had designed the study in 1998 and that he and Dr Lee had been “developing research ideas and plans on premature ovarian failure since 2000 and, accordingly,
began collecting samples among the patients of CHA General Hospital . . . Professors at the Fertility Center of CHA General Hospital worked jointly on research plans . . . they were assigned to collect the blood samples of outpatients . . . who were suffering premature ovarian failure. They passed on their findings to [Dr] Lee, who was the research supervisor.”

As for Dr Kim, he had been “a junior researcher . . . employed by Dr Lee’s laboratory . . . a resident in the CHA General Hospital, to which Dr Lee’s laboratory was attached.” As regards the blood samples which formed the basis of the study, Dr Kim “had collected only two of these samples.” Then, in August 2003 Dr Kim “obtained his doctorate from a third-party institution, and left the hospital shortly afterwards, leaving no forwarding address. Moreover, he took with him without permission the original research data from Dr Lee’s laboratory, and has refused to return it.”

As for the publication of this research, Dr Cha’s lawyers’ letter of 7 March to Dr DeCherney asserts that in 2002 Dr Lee had “offered to let Dr Kim use the data obtained by her laboratory concerning mitochondria DNA to write his thesis,” on the understanding that an article be submitted for publication to a journal in the Science Citation Index. Dr Lee reportedly says she discovered that Dr Kim had submitted his paper to the Korean Journal of Obstetrics and Gynaecology, which is not in the index, when the editors contacted her because they could not locate Dr Kim. Because Dr Lee “had always intended for the data to be published in a SCI [Science Citation Index] publication, and because Dr Kim had taken the original research data, his thesis was the only source left and, consequently, Dr Lee had the KJOG article translated into English and submitted it to F&S.”

There are some obvious problems with this account. If Dr Kim’s role in the study was as minor as the CHA organisation now claims, it is unclear why Dr Lee, the corresponding author for the Korean version of the paper, would have allowed him to be listed as the paper’s lead author. Indeed, given Dr Lee’s supposed intention that the paper be published in a journal in the Science Citation Index, it is strange that she allowed publication in the Korean journal to go ahead at all. Furthermore, given Dr Lee’s role in the Korean paper, why was Dr Cha not included at that stage as an author?

Dr Kim’s version of events is somewhat different. He told the BMJ that it was his study, that he had generated the data for it, and that he had full records, complete with names and time-stamped consent forms, of all the blood samples he had collected from 30 patients he had personally recruited from November 2002. This suggested timeframe is supported by the account in both published versions of the paper, where it is stated that “The study ran from November 2002 to January 2003.”

Moreover, Dr Kim told the BMJ that because the CHA organisation at that time had lacked the necessary equipment to conduct real time polymerase chain reaction analysis of the 30 blood samples, he had paid for the use of another organisation’s facilities and had the receipt. In response to this claim, Dr Cha’s spokesman conceded that Dr Kim had indeed paid some of the costs for the use of such equipment: “Dr Kim paid only 2805 490 won ($2950) [£1500; €2200], related to the marginal variable cost, such as outsourcing to Yonsei [University] and some reagents for that specific experiment. The project cost amounted to 34 378 230 won ($36 400) including the fixed cost of laboratory operation for salary for researchers, equipments, maintaining facilities, etc.”

One matter that is not in dispute is that it was Dr Lee who had the paper translated into English and submitted it to Fertility and Sterility. At this stage, the CHA organisation claims, Dr Kim was included as an author by Dr Lee, but “F&S required all authors to sign certain documents . . . she was unable to find Kim and therefore his name was ultimately left off the list.”

Dr Kim, however, points out that his colleagues at CHA hospital—including Dr Lee—had known for a year before his departure that he was going to work in Singapore, that it would not have been hard to find him there, and that his two email addresses were on the original paper he had submitted to the Korean journal. What is more, after leaving Korea, he remained in direct contact with some of his former colleagues: “A clinician at the infertility centre where S H Lee and I used to work, visited Singapore with his whole family. They stayed at my house for about a week in 2004.” Also, he says, “I sent a New Year message to the vice head of the centre in 2005 and 2006. I don’t think she [Dr Lee] can insist that she couldn’t find my whereabouts.”

Professor Kwang Soo Kim, director of the molecular neurobiology laboratory at Harvard’s Mclean Hospital and the newly recruited codirector of the CHA Stem Cell Institute, now finds himself having to defend his new employer. No fewer than three of his new colleagues at the institute—including his fellow codirector, Hyung Min Chung—are among the disputed authors on the paper. In February he wrote to Dr DeCherney of Fertility and Sterility on behalf of the CHA organisation as “a fellow research scientist with more than 23 years of research experience in the US as well as first-hand knowledge of standards and practices in the scientific community in Korea,” to express regret about the incident.

In his letter, a copy of which the CHA organisation sent to the BMJ, he suggests that “The main issue that appears to be at
“In Korea it has been a customary practice . . . to submit top-quality research outcomes concurrently to internationally recognised journals”

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Competing interests: None declared.

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RESEARCH ETHICS

the center of this controversy is the multiple publication of the paper.” But he then makes a disturbing disclosure: “In Korea, it has been a customary practice and an accepted procedure by the scientific community to submit top-quality research outcomes concurrently (or subsequently) to internationally-recognized journals in an effort to promote and advance the work of Korean scientists, which was also the case when Dr Lee submitted her paper to Fertility and Sterility.

“I personally have very strong objections to this practice and have been trying to convince the scientific leaders in Korea to put a stop to this. It was only recently in 2006 that this guideline was in fact revised in Korea to prohibit this practice.”

Professor Kim’s intervention leaves little doubt about how seriously the CHA group views the potential of the incident to damage its bid to inherit Hwang’s crown: “The reputation and credibility of our university and that of its researchers and scientists are also at stake,” Professor Kim writes. “This is an extremely critical issue in light of the fact that I believe our institution will serve a pivotal role in restoring the severely damaged reputation and credibility of stem cell and life science research in Korea after the Hwang scandal.”

Before his fall from grace, Professor Hwang received the bulk of Korean government funding in stem cell research. In January last year the journal Science retracted two papers by Hwang et al after an investigation committee at Seoul National University concluded that they contained fabricated data. Professor Hwang, who worked at the university and was a national hero in South Korea, had claimed his laboratory had carried out the first cloning of patient specific stem cells, producing no fewer than 11 lines. The inquiry found that the laboratory “does not possess patient-specific stem cell lines or any scientific basis for claiming to have created one.”

The Korean government has responded to the scandal by increasing its commitment to stem cell research, announcing a 10 year investment plan and committing $454m to the CHA organisation. Dr Cha announced the lab had undertaken the lead role in restoring the severely damaged reputation and credibility of stem cell research in Korea after the Hwang scandal.”

Professor Kim’s intervention leaves little doubt about how seriously the CHA group views the potential of the incident to damage its bid to inherit Hwang’s crown: “The reputation and credibility of our university and that of its researchers and scientists are also at stake,” Professor Kim writes. “This is an extremely critical issue in light of the fact that I believe our institution will serve a pivotal role in restoring the severely damaged reputation and credibility of stem cell and life science research in Korea after the Hwang scandal.”

Before his fall from grace, Professor Hwang received the bulk of Korean government funding in stem cell research. In January last year the journal Science retracted two papers by Hwang et al after an investigation committee at Seoul National University concluded that they contained fabricated data. Professor Hwang, who worked at the university and was a national hero in South Korea, had claimed his laboratory had carried out the first cloning of patient specific stem cells, producing no fewer than 11 lines. The inquiry found that the laboratory “does not possess patient-specific stem cell lines or any scientific basis for claiming to have created one.”

The Korean government has responded to the scandal by increasing its commitment to stem cell research, announcing a 10 year investment plan and committing $454m to be distributed more widely. In November last year, CHA Medical Group, which had been untouched by the Hwang debacle, announced its plans to succeed Professor Hwang’s now defunct World Stem Cell Hub by building Korea’s largest stem cell institute on land provided by the Korean government. The BMJ contacted Professor Kim while he was visiting Korea, where he says he now spends 10% of his time, working for the CHA organisation.

“Dr Cha,” he insisted, “was originally involved from the very conception of this idea and he coordinated the overall direction. I still think it’s an issue whether Dr Cha is really deserving first author but what I can say is he was very seriously involved with the design of this paper from the first.”

However, although Professor Kim admitted he had not spoken to his namesake, he appeared to credit Dr Kim with a larger role in the project than had been conceded so far by the CHA group: “As for Dr Kim, Dr Lee also involved his name as coauthor because she thought he deserved at least coauthorship because he analysed and wrote the original paper. He contributed in that manner but other than that in terms of experiments he didn’t do any.”

In America, the dispute over the paper is already causing problems for the CHA group. A research grant of $2.6m, agreed on 15 March by the California Institute for Regenerative Medicine, a state agency established to fund stem cell research in the state’s universities and institutions, has been challenged publicly by a watchdog group, the Foundation for Taxpayers and Consumer Rights. In a letter dated 22 March, the foundation urges the president of the agency to investigate further before handing over the money to the CHA Regenerative Medicine Institute in Los Angeles.

John Simpson, the foundation’s stem cell project director, writes: “It is not clear what the institution’s affiliation is with its corporate parent CHA Medical, CHA Biotech and other corporate for-profit entities . . . Is CHA RMI truly a non-profit institution eligible for funding in this round of grants?”

It is, he says, “imperative that stem cell research funded by the state of California be conducted only by organisations demonstrating the highest ethical standards. Based on what is known so far, a thorough examination of the activities of CHA Regenerative Medicine Institute, its affiliates and leadership is in order before any funds are transferred.”

This is not the first time Dr Cha has been associated with controversy over a published paper. In September 2001 he was listed as the lead of three authors on a report of a study, published in the Journal of Reproductive Medicine, that claimed intercessory prayer had doubled pregnancy rates among women being treated with in vitro fertilisation embryo transfer.

The paper attracted strong criticism that only intensified in May 2004 when Daniel Wirth, an advocate of alternative medicine and one of Dr Cha’s coauthors, pleaded guilty to an unrelated charge of business fraud and was sentenced to five years in prison. In December the same year the third author, Rogerio Lobo, a fertility specialist at Columbia University, withdrew his name from the paper, admitting he had acted only as an adviser on the study. The Journal of Reproductive Medicine has not retracted the prayer paper. It remains in the literature with Dr Cha listed as joint author with Wirth. Professor Lobo, of the department of obstetrics and gynaecology at Columbia University School of Medicine, is now listed as one of the four members of the Advisory Board of the Cha Stem Cell Institute in Korea.
A vaccine that promises protection against a common female cancer—what could possibly be controversial about that? Plenty, if the vaccine in question targets a sexually transmitted infection that causes 70% of cervical cancers and, to be most effective, should be given to girls as young as 10 before they become sexually active.¹

The vaccine is Merck’s Gardasil, which protects against four strains of human papillomavirus: types 16 and 18, responsible for 70% of all cervical cancers, and types 6 and 11, which cause 90% of cases of genital warts.¹ Three injections provide protection for at least five years, but the vaccine is expensive at about $360 (£185; €280) a shot.

The vaccine is undoubtedly set to be a blockbuster product for Merck. Twenty US states are considering bills that would make the immunisation a requirement for school attendance, which could net Merck billions of dollars.² With a rival vaccine (Cervarix) from GlaxoSmithKline due to be approved in the next year, Merck has been engaged in some heavy lobbying of its product (www.gardasil.com). Health freedom organisations, among other critics, have condemned Merck’s “strong arm” marketing methods, claiming the company hopes to use profits from Gardasil to fund the huge litigation costs it has had to pay over rofecoxib (Vioxx).³ And last week the vaccine made front page news in the United Kingdom with a Guardian story questioning Merck’s motives in funding a summit on cervical cancer in Paris for doctors and patient organisations.⁴

Plans for mass vaccination with Gardasil are already well advanced around the world. Approved by the Food and

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Life saving treatment or giant experiment?

Many countries are considering mass vaccination of young girls, but Rebecca Coombes reports that proposals for mandatory immunisation in the US have raised concerns, and not just among religious conservatives.
Drug Administration in June 2006, the vaccination has the green light in Australia, New Zealand, Canada, Mexico, and EU countries.

But in the United States the vaccine has come up against strong opposition. The furore has centred on plans to make the vaccination a mandatory requirement for preteen girls—a move that critics say ignores parental choice, could promote underage sex, and runs counter to policies in some states that encourage young people to abstain from sex until marriage. The row first ignited in Texas, where a surprise edict to make vaccination compulsory for schoolgirls by Texas governor Rick Perry was overturned by the state House of Representatives. It propelled Gardasil on to the front pages and led to editorials in the New York Times and the Washington Post.

Mr Perry insisted that his plan was no different from vaccinating children against polio. “The HPV vaccine provides us with an incredible opportunity to effectively target and prevent cervical cancer,” he said. The governor’s spokeswoman Krista Moody told the New York Times: “The governor believes we should protect as many young women as possible—rich and poor, insured and uninsured—while maintaining parents’ right to opt their daughter out of receiving the vaccine.”

But opponents said that Mr Perry’s order intruded into family life. “Let’s continue to allow only parents and children and doctors to decide if this is right for you,” conservative republican Dennis Bonnen told the Houston Chronicle.

But this wasn’t quite the bruising showdown with America’s religious right wing that some newspapers have billed. Although the conservatives did have concerns, what really inflamed critics was Mr Perry’s links with Merck. Mr Perry, it emerged, had received campaign money from Merck, and his former chief of staff had become a Merck lobbyist.

As a result of the Texan revolt, Merck has backed off pushing for mandatory vaccination, saying it would instead provide vaccine information only if requested by government officials.

In Illinois, a similar bill sponsored by the senate’s majority leader, Debbie Halvorson, also drew flak. An editorial in the Illinois newspaper Register-News pointed out: “Halvorson is also the director of Women in Government, a national cancer-fighting group which has received funding from Merck.” In California, politicians pulled a bill for revision over concerns about parental rights and the lack of a long safety record for the new vaccine.

Some may wonder what all the fuss is about. None of the bills under debate in the US would actually lead to forced vaccination—all include an opt-out clause for concerned parents. Even two of the largest conservative family groups—Focus on the Family and the Family Research Council—say they have no problem with the vaccine, only if there is no parental opt out. No surprise then that a New Mexico bill that will usher in mandatory immunisation is on the verge of being signed by the governor. The Virginia governor has said he would sign a similar bill. Very sensible, said the Washington Post. “Parents will have the final say. They won’t have to cite any reason and no student will be kept out of school because her parents decided against shots. For a virus so widespread and potentially harmful, an opt-out regime, which will lead to higher rates of immunization than one asking parents to opt-in, makes sense.”

Sarah Brown, director of the National Campaign to Prevent Teen Pregnancy, told the Baltimore Sun: “How do we feel about our children being required to receive a vaccine without a lot of long term data on its effects? I understand that . . . But the idea that a vaccine is going to change a woman’s calculus about whether to have sex or not strikes me as intensely unreasonable.”

In a nifty bit of timing, a new study by the Centers for Disease Control and Prevention shows that at least 25 million girls and
Elsewhere, Canada’s latest federal budget includes $C300m (£130m; €190m; $260m) for the vaccine. In the UK, Gardasil is licensed for use in girls as young as 9 and can be bought from private clinics. The NHS has yet to provide the vaccination for free—leading to claims that the government is dragging its feet. Minutes of the Joint Committee on Vaccination and Immunisation show that it is in favour of “vaccination of girls at the age of 11 or 12 years with HPV vaccine.” The minutes also reveal that cost implications are stalling a final decision.

In the developing world—which has much of the burden of cervical cancer disease and practically no screening programmes—there are hopeful signs that the vaccine will be widely introduced. Professor Frazer said: “The offer of vaccine at cost from the two major manufacturers and support from the Bill and Melinda Gates Foundation, together with imminent endorsement by UICC [International Union against Cancer] and WHO for global immunisation should help.” He is involved in plans to introduce the vaccine on the south Pacific island of Vanuatu, to test the feasibility of immunising pre-teens in the developing world.

But there is concern for less poor countries that don’t qualify for funding from the GAVI Alliance, which supports childhood vaccination programmes. Eduardo Franco, director of the division of cancer epidemiology at McGill University, Montreal, told the BMJ: “HPV vaccines will not be subsidised in the ‘middle resource’ countries, such as Brazil, Mexico, Argentina, and India. They do have the required training and screening infrastructures in place. Yet these countries continue to experience high morbidity and mortality because one or more items in the chain of resources needed for effective screening have failed.”

Professor Franco said that the “cruel logic” was that the women who stood to benefit from the vaccine—and pass the message on to their daughters—were those who can afford high quality private health care and already get regular smear tests. “But those women who cannot afford private health care and thus have to depend on the public system (which has low quality, spotty, or non-existent screening) are not being screened adequately or at all. They do not know about HPV vaccines; nor will their daughters be offered vaccination. These are women who, today, develop invasive cervical cancer in these countries.”

Safety concerns

Despite the enthusiasm, there have been inevitable questions over the vaccine’s safety. One Merck funded researcher, Diane Harper, has received publicity for saying that giving the vaccine to 11 year old girls is “a great big public health experiment.” Although praising the vaccine, Dr Harper feared that young women would develop a false sense of security and stop having smear tests.

But Professor Frazer said the vaccine’s safety record was sound, although he acknowledged that ongoing monitoring is required: “The safety record over five years and 250,000 women in controlled trials is pretty impressive, and while the CDC [Centers for Disease Control] report of adverse events possibly vaccine associated had a little press, it was mostly balanced, with commentary that it amounted mostly to fainting and the three cases of Guillain Barré among two million doses over six months was no higher than would be expected by chance in a similar cohort of young women.

“I’ve provided vaccine for my children and don’t see it as an experiment but rather a prudent exercise in risk management.”

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Competing interests: None declared.

Global reach

In Australia, the vaccine has had an easier ride. The first government funded vaccination campaign started there this year, targeting all 12-13 year old girls. For the first two years there is also a free “catch up” programme for women up to 26.

Ian Frazer, the immunologist who created Gardasil and director of the department of medicine at Princess Alexandra Hospital, Brisbane, told the BMJ that objection had been “minimal.”

“Senator Barnaby Joyce implied that the vaccine should not be given to under 18 year olds because it encouraged promiscuity. However, he rapidly changed his mind in the face of public opinion,” he said.

women—or about one in four from age 14 to 59—are infected with at least one type of human papillomavirus.2

“We should protect as many young women as possible—rich and poor, insured and uninsured”
The royal colleges must up their game—or die

The debacle over doctors’ specialist training begs the question of what the royal colleges are for. The onlookers quietly shaking their heads. Maybe, but that hardly seems to justify the wholesale redesign of a system that had produced good doctors, especially as MMC offers plenty of new ways of sidelining those who don’t quite make it.

The question the royal colleges have to answer is how and why they became complicit in a system for postgraduate education that meant they had no influence on MTAS until it was too late. Nobody can say they weren’t warned. Last year’s furore over appointing F1 doctors under MMC went horribly wrong, and produced a lot of injustices. Yet nobody did anything to correct the defects until exactly the same thing happened again, on a much bigger scale and with even greater injustice.

What, exactly, are the royal colleges for? Postgraduate medical education has always been a central role, and examination fees a major source of income. The purpose of MMC, it seems to me, was to wrest control of higher training from the colleges, and shape it in ways designed to suit the employers. The colleges were placated (a cynic might say bought off) by allowing their exams and their income flow to continue, at the price of having little further influence.

Many of those who take the exams hail from overseas. The colleges did not want this source of income to dry up either, but nor did they want foreign graduates to take up too many of the training opportunities. Hence the rage of Professor Allan Templeton, president of the Royal College of Obstetricians and Gynaecologists, who in an email to Dame Carol Black, chairman of the Academy of the Medical Royal Colleges and former president of the Royal College of Physicians of England, complained that the completed forms “fail to identify UK graduates, which we all thought was the major purpose of MMC.” Ouch!

How did the royal colleges allow MMC to become a branch of the Department of Health? This government has been extremely skilful in erecting a Big Tent and inviting all those with influence to step inside. The best example was the NHS Modernisation Board, a classic of inclusion politics. This body was meant to advise the secretary of state, giving those who served on it a tiny taste of power and implicating them subtly in the decisions taken. It produced three reports and then fell silent, its task done. It has since been abolished.

Whatever the reasons, many doctors now feel that their colleges have failed them, and on an issue central to the profession of medicine. “I for one am ashamed to be a member of a royal college which, once so apparently omnipotent, now simply appears impotent and inert,” wrote one doctor to Professor Douglas. It’s unlikely his is a lone voice.

British organisations tend to follow a pattern. Formed to promote shared interests, they enjoy a vigorous and effective youth, a mature but more compliant middle age, and sink finally into a dotage, where they simply exist. Examples of this final stage are the City of London livery companies—the Cordwainers, the Tallowchandlers, the Salters, the Pewterers, and Plaisterers—with their fine halls, excellent dinners, and their charitable donations. There are, astonishingly, still 107 of them, and long may they remain 107 of them, and long may they flourish—they do no harm and provide much innocent enjoyment.

But while the City does not have many (or any) tallowchandlers and cordwainers left, the royal colleges represent a living profession, which has never been more disaffected. Excluding the surgeons and the pathologists, both of whose colleges have displayed some bottle, this disaffection has gone largely unexpressed.

There’s too much happening in the profession these days that is passing the colleges by. They need to raise their game and make clear they are independent bodies with their own ideas and principles—which may from time to time differ from the government’s—unless they want to join the City fossils.

Nigel Hawkes is health editor at the Times nigel.hawkes@thetimes.co.uk
Screening programmes for chlamydial infection: when will we ever learn?

With more countries recommending screening programmes for chlamydial infection, Nicola Low argues that such programmes are not underpinned by sound evidence.

The notion that a programme of widespread screening in Sweden controlled transmission of chlamydial infection and reduced morbidity of the female reproductive tract is commonly cited as fact. Unfortunately, this assertion and similar claims about screening in the United States and Canada are not supported by rigorous research or practice. Here, I will show how misinterpretation of what comprises a screening programme led to uncritical acceptance of the effectiveness of chlamydia screening, and the funding of a National Chlamydia Screening Programme in England, before the benefits and harms were evaluated.

**Screening for chlamydial infection in Sweden**

Swedish researchers were key players in demonstrating the importance of sexually transmitted chlamydial infection in the 1970s and 1980s. They were instrumental in developing diagnostic tests and defining the role of *C trachomatis* in pelvic inflammatory disease and infertility. The first documented “program to identify asymptomatics” started in 1982 and tested women under 30 years seeking contraception, abortion, or antenatal care and male partners of infected women. In 1988, a change in the Swedish infectious diseases law required doctors to provide free testing, treatment, and partner notification for anyone with suspected chlamydia and to report cases. There were educational campaigns, and young people’s clinics were established to make testing easily available.

Rates of chlamydia and its complications decreased up to the mid-1990s, at the same time as widespread testing was introduced (fig 1). Financing services, strong infrastructure, open attitudes to sexual health, and a small population were suggested to contribute to this success. Studies such as these have now been cited as evidence of success of organised chlamydia screening programmes up to 80 times in Web of Science indexed journals and in official reports.

In fact, the fall in rates of chlamydia infection in Sweden coincided with the national campaign to prevent HIV (fig 1). Desire to believe in chlamydia screening seems to have displaced alternative explanations, such as changing sexual behaviour, even though parallel decreases in sexually transmitted infections in countries with no efforts to control chlamydia were attributed to HIV prevention campaigns. Reports of the effectiveness of screening in Sweden persist, despite increasing rates of diagnosed chlamydia since 1995 (fig 1).

**Summary Points**

Lack of an agreed concise definition of a screening programme has contributed to beliefs about the effectiveness of opportunistic screening for chlamydial infection. Opportunistic screening as currently implemented in the National Chlamydia Screening Programme in England has not been evaluated in randomised controlled trials.

Criteria for assessing the appropriateness for introducing a screening programme have not been rigorously applied to chlamydial infection.

Countries implementing or contemplating national chlamydia screening should conduct research to determine if such screening programmes do more good than harm at reasonable cost.

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**Fig 1** Rate of laboratory diagnosed chlamydial infection in Sweden 1985 to 2005

**Screening for chlamydia in the US**

In the US, opportunistic screening was also credited with decreases in rates of chlamydial infection. The Centers for Disease Control and Prevention have supported screening programmes since 1988. A federally funded national Infertility Prevention Program that provides chlamydia screening for women on low incomes attending certain healthcare settings was established by 1995. The most recent report showed that chlamydia positivity in women aged 15-24 years screened in family planning clinics decreased in two of 10 regions from 2003 to 2004, increased in six, and remained the same in two.

**The National Chlamydia Screening Programme in England**

A programme offering opportunistic chlamydia screening (box 1) to all sexually active women and men under 25 years attending a variety of healthcare settings in England is due to be implemented by 2008. One-off screening opportunities in commercial pharmacies, universities, colleges, and other venues are also encouraged. The programme aims to, “control genital chlamydial infection through the early detection and treatment of asymptomatic infections and prevention of sequelae and onward transmission.”

In two pilot sites, all general practitioners took part, were paid for each patient enrolled, and generated the highest proportion of tests and cases, achieving an effective screening rate (box 1) of 50%. In the programme itself, participation of general practitioners...
is optional and largely unremunerated. In 2005-6, the effective screening rate was less than 5% in more than half of programme areas. Performance indicators do not measure key outcomes of repeat screening, prevalence of chlamydial infection, or morbidity.

**What is a screening programme?**

A “screening programme” has no agreed concise definition, although “screening” (box 1) is well defined. Any health service activities that facilitate early disease detection could therefore be called a programme, if certain criteria are fulfilled. I suggest that it should be defined as a continuing organised service that ensures that screening is delivered at sufficiently regular intervals to a high enough proportion of the target population to achieve defined levels of benefit at the population level, while minimising harm (box 1).

In fact, no national chlamydia screening programme exists in Sweden, and “national strategies for the entire area of sexual health and sexuality are presently lacking.” Locally funded activities that promote testing for chlamydial infection for case finding, underpinned by legislation, were widely described and interpreted as screening programmes.

Reliance on the obligations of individual doctors without national coordination, objectives, or outcome standards does not fulfil the suggested definition and is unlikely to achieve the aims of screening.

**Appropriateness of a chlamydia screening programme**

Chlamydia would seem to be an ideal candidate for screening. *Chlamydia trachomatis* is a common, curable, easily diagnosed, sexually transmitted infection that usually causes no symptoms. It can, however, cause devastating complications, including infertility, ectopic pregnancy, neonatal infection, and facilitation of HIV transmission.

Agreed standards should be applied to all diseases for which screening is in place or is being considered. Screening programmes approved by the National Screening Committee require registers that allow proactive invitations (box 1) to be sent to people in the target population to ensure regular uptake. The alternative is opportunistic screening, which reaches people attending health or other services (box 1). A health professional is responsible for offering the test at regular intervals. Cervical cancer screening in the United Kingdom was initially opportunistic, but screening was poorly targeted and consistent reductions in mortality only occurred after a proactive programme increased regular coverage.

Opportunistic screening is widely assumed to be the only acceptable model of service delivery for chlamydia. In England, postal invitations to young people who were not yet sexually active were deemed inefficient and the coverage of opportunistic screening stated to be adequate before alternatives had been investigated. The assumption about coverage was based on high acceptance (box 1) once chlamydia screening had been offered. However, not everyone uses the services that provide testing and not everyone who uses those services is offered a test. Subsequent research has shown that effective screening rates (box 1) are 30-40% for both proactive and opportunistic approaches, and costs per screening invitation are similar.

Gray has suggested another important difference between chlamydial infection and chronic diseases: that a person’s risk of acquiring an infection depends on its prevalence in the population. A chlamydia screening programme must therefore control

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**Box 1 | Definitions of screening programmes**

**Screening**

Members of a defined population, who may not know they are at risk of a disease or its complications, are asked a question or offered a test to identify those who are more likely to be helped than harmed by further tests or treatment (UK National Screening Committee).

**Screening programme**

A continuing public health service that ensures screening is delivered at sufficiently regular intervals to a high enough proportion of the target population to achieve defined levels of benefit at the population level, while minimising harm (my definition, based on previous work).

**Proactive screening**

Population registers are used to invite members of the population at risk for screening at appropriate intervals; also known as population, register based, call-recall, cyclical, active, or systematic screening.

**Opportunistic screening**

A health professional offers a screening test to patients attending health care or other defined settings for unrelated reasons; the onus is on the health professional to repeat the test offer at appropriate intervals; also known as case finding.

**Acceptance rate**

Number of people who accept a screening test as a proportion of those offered the test; measures acceptability of the test in the population receiving the offer.

**Effective screening rate**

Number of people screened as a proportion of those eligible for screening; measure of screening coverage at population level.

**Offer rate**

Number of people offered the screening test as a proportion of those eligible for screening.
transmission through both regular regular screening and partner notification to reduce morbidity. Thus, the model for chlamydia screening might differ from that for a non-communicable disease, but standards for the organisation and appropriateness of screening should be the same. Key criteria of the National Screening Committee, outlined below, have not been stringent applied to chlamydia.18

Natural history should be adequately understood
Increasing evidence shows that the rate of progression of endocervical chlamydia to pelvic inflammatory disease is lower than previously thought.19 Population based studies consistently estimate lower incidence rates of pelvic inflammatory disease than clinic based studies.19 Infections detected by screening asymptomatic people might therefore have a better prognosis than symptomatic infections, because of differences in the burden of the organism. Descriptions of chlamydial infection and its consequences,5 and models of the impact of screening,19 however, nearly always cite the higher estimates.

Evidence from high quality randomised controlled trials
The Department of Health funded pilot studies of opportunistic chlamydia screening,24 even though no randomised controlled trial had shown that this intervention reduced long term morbidity.1 The National Screening Committee accepted that, “In Scandinavia, screening for chlamydia has been found to reduce the risk of infertility and ectopic pregnancy,”22 on the basis of only uncontrolled ecological studies. A systematic review, commissioned after the National Chlamydia Screening Programme was introduced, has confirmed that no randomised controlled trial has evaluated opportunistic chlamydia screening as it is currently practised.25 Evidence from trials of proactive screening cannot be extrapolated to opportunistic screening and is limited by methodological biases that overestimate the benefits.25 No trial evidence about the effects of more than one round of screening for either approach is available.

Value for money
Most studies cited as showing that chlamydia screening is cost effective do not satisfy accepted quality criteria for economic evaluations.18 The need for dynamic mathematical modelling has been largely ignored, in contrast with work on other infections.18 Furthermore, most studies make two assumptions that overestimate the cost effectiveness of chlamydia screening—that the incidence of pelvic inflammatory disease and regular screening rates are higher than are seen in practice.2 Under realistic assumptions, introducing a chlamydia screening programme is likely to be an expensive intervention.18

Lessons to be learnt
Belief in the success of opportunistic screening persists,3 6 despite an absence of evidence of effectiveness17 and increasing rates of chlamydia in countries that are assumed to have such programmes.5 6 24

Increased testing with highly sensitive tests explains only part of the observed rise. In Sweden, rates of chlamydial infection in 15-19 year olds began to increase before nucleic acid amplification tests were available, and rates were also increasing in some laboratories before they changed diagnostic methods.4 Reasons that have been suggested to explain the resurgence of chlamydia include inadequate partner notification,20 and a loss of immunity after widespread early treatment.6 The possibility that the opportunistic screening approach has not achieved regular screening has not been widely discussed.20 Unsubstantiated belief also seems to have allowed the requirements of the National Screening Committee and the experience of other UK screening programmes to be over-ridden. Uncertainty about the status of chlamydia screening is, however, emerging. National Screening Committee policy is that screening should not be offered to pregnant women20 owing to insufficient evidence of effectiveness, whereas the National Chlamydia Screening Programme recommends screening in antenatal clinics.2 Countries currently considering introducing screening policies or programmes include France, Romania and Slovenia, Ireland,21 the Netherlands,22 and Australia.23 Policy makers and researchers in these countries need to learn from the past and move forward by generating the evidence required (Box 2) to determine whether this intervention does more good than harm at reasonable cost.

Box 2 | Research needed to establish benefits and harms of chlamydia screening programmes

<table>
<thead>
<tr>
<th>Validity of screening tests</th>
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<tbody>
<tr>
<td>• Systematic review of diagnostic studies of nucleic acid amplification tests to determine if higher observed yields of Chlamydia trachomatis in vulval or vaginal specimens than in urine specimens is clinically important</td>
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<thead>
<tr>
<th>Epidemiology and natural history of the condition</th>
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<tr>
<td>• Cohort studies to track progression of lower genital tract C trachomatis infection (detected with nucleic acid amplification) to pelvic inflammatory disease and other reproductive tract morbidity. Stored repeated endocervical specimens (such as those from human papillomavirus vaccine trials), with linkage to medical records, could be used</td>
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<tr>
<td>• Cohort studies to estimate the incidence of neonatal complications after perinatal maternal chlamydial infections detected with nucleic acid amplification tests</td>
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<tr>
<td>• Prospective studies of the associations between quantitative measures of chlamydial organism load, symptomatic and asymptomatic lower and upper genital tract disease, and transmission of infection</td>
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<td>• Prospective studies to define appropriate screening intervals more accurately</td>
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<th>Effectiveness of screening for reducing morbidity</th>
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<tr>
<td>• Randomised controlled trials to examine the effectiveness of opportunistic and proactive chlamydia screening, including more than one round of screening and measuring uptake of initial and repeat invitations, and biological outcomes</td>
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<tr>
<td>• Randomised trials to examine ways of increasing the uptake of regular repeat screening</td>
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<th>Value for money</th>
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<tr>
<td>• Cost effectiveness analysis using economic and epidemiological data collected in randomised controlled trials and dynamic mathematical models to examine the impact of interventions on transmission of chlamydia and incidence of complications</td>
</tr>
<tr>
<td>• Prospective studies to determine utility values for quality adjusted life years with pelvic inflammatory disease, ectopic pregnancy, tubal infertility, and epididymo-orchitis</td>
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</table>
Contributors: NL is an epidemiologist and accredited physician in genitourinary medicine and public health with a research interest in screening programmes for sexually transmitted infections. This article uses information that emerged from a longstanding collaboration on Chlamydia in Uppsala, Sweden with Björn Herrmann and Matthias Egger, and is based on plenary talks at the Australasian Sexual Health Conference 2006 and the 22nd IUSTI-Europe Conference on Sexually Transmitted Infections 2006. Discussions and research collaborations with Judith Stephenson, University College London, and Jackie Cassell, Brighton and Sussex Medical School, also informed the present discussion.

Funding: NL is employed by the University of Bern, which received funding from the UK National Institute for Health and Clinical Excellence (NICE). Part of the research referred to in this article was commissioned by NICE to inform the development of its forthcoming guidance on the prevention of sexually transmitted infections; and the full report is available online (www.nice.org.uk/page.aspx?o=37177). This article does not constitute NICE guidance. The Chlamydia Screening Studies (ClAS) project was funded by the NHS Health Technology Assessment programme (project number 97/32/31).

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Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool

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ABSTRACT

Objective To determine an effective diagnostic method of detecting all cases of coeliac disease in patients referred for gastroscopy without performing routine duodenal biopsy.

Design An initial retrospective cohort of patients attending for gastroscopy was analysed to derive a clinical decision tool that could increase the detection of coeliac disease without performing routine duodenal biopsy. The tool incorporated serology (measuring antibodies to tissue transglutaminase) and stratifying patients according to their referral symptoms (patients were classified as having a “high risk” or “low risk” of coeliac disease). The decision tool was then tested on a second cohort of patients attending for gastroscopy. In the second cohort all patients had a routine duodenal biopsy and serology performed.

Setting Teaching hospital in Sheffield.

Participants 2000 consecutive adult patients referred for gastroscopy recruited prospectively.

Main outcome measure Evaluation of a clinical decision tool using patients’ referral symptoms, tissue transglutaminase antibody results, and duodenal biopsy results.

Results No cases of coeliac disease were missed by the pre-endoscopy testing algorithm. The prevalence of coeliac disease in patients attending for endoscopy was 3.9% (77/2000, 95% confidence interval 3.1% to 4.8%). The prevalence in the high risk and low risk groups was 9.6% (71/739, 7.7% to 12.0%) and 0.5% (6/1261, 0.2% to 1.0%). The prevalence of coeliac disease in patients who were negative for tissue transglutaminase antibody was 0.4% (7/2000). The sensitivity, specificity, positive predictive value, and negative predictive value for a positive antibody result to diagnose coeliac disease was 90.9%, 90.9%, 28.6%, and 99.6%, respectively. Evaluation of the clinical decision tool gave a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 60.8%, 9.3%, and 100%, respectively.

Conclusions Pre-endoscopy serological testing in combination with biopsy of high risk cases detected all cases of coeliac disease. The use of this decision tool may enable the endoscopist to target patients who need a duodenal biopsy.

INTRODUCTION

Coeliac disease is a common chronic inflammatory bowel condition encountered by doctors. Serological screening in healthy volunteers around the world has estimated the prevalence at 0.5-1.0%.1,7 A recent meta-analysis indicated that the ratio of known to undiagnosed cases of coeliac disease was 1:7.9 This suggests a failure in case finding for this disease.6,9 The median age for diagnosis of coeliac disease in adults is between the fourth and fifth decade.10-12 The median delay in diagnosis ranges from 4.9 to 11 years.10-12

Patients with adult coeliac disease usually present with diarrhoea, weight loss, or symptoms that suggest malabsorption or anaemia. This type of coeliac disease is known as the classic (typical) form. The disease may not always be recognised however because of the insidious nature of its presentation, and many visits to hospital may be needed before diagnosis.13 Patients can also have the silent or atypical form of disease. These patients may present with non-specific abdominal pain,14 oesophageal reflux,15 16 osteoporosis, crypto- genic hypertransaminasaemia, insulin dependent diabetes mellitus,17 or neurological symptoms.13,18 Untreated coeliac disease is associated with high morbidity and increased mortality.19,20

Although the presentation of patients with coeliac disease may be protean, serological markers are a cheap and non-invasive method for clinicians in primary care and secondary care to identify patients with this disease. The positive and negative predictive value of combining the measurement of IgA antibodies to tissue transglutaminase and IgA endomysial antibodies has been reported to be greater than 96%.21 Current serological testing for coeliac disease involves the use of one or both of these antibodies, depending on local practice.22 However, the internationally accepted “gold standard” diagnostic test for coeliac disease is the demonstration of villous atrophy on a duodenal biopsy.23 24 Such biopsies are graded...
histologically according to the modified Marsh criteria and reflect the pathological progression (histologically) towards coeliac disease. Marsh grade 0 is normal duodenal mucosa, grade 1 is the presence of a raised intraepithelial lymphocyte count, and grade 2 is raised intraepithelial lymphocytes and crypt hyperplasia. Marsh grade 1 and grade 2 lesions are considered to be early changes in patients who are likely to develop coeliac disease. Marsh grade 3 is raised intraepithelial lymphocytes and crypt hyperplasia with progression of the inflammation to villous atrophy. Marsh grade 3 is subdivided into Marsh 3a—partial villous atrophy, 3b—subtotal villous atrophy, and 3c—total villous atrophy.25,26 The presence of a Marsh 3 lesion (villous atrophy) on duodenal biopsy together with a positive antibody profile is currently internationally accepted as coeliac disease, although antibody negative coeliac disease does exist.23,24 This may occur if patients are IgA deficient (and cannot generate IgA tissue transglutaminase antibodies or endomysial antibodies), but it can also happen in patients who have normal total IgA immunoglobulin concentrations. Such patients are classed as having coeliac disease if they have villous atrophy on duodenal biopsy and the appropriate human leucocyte antigen pattern (HLA DQ2 or HLA DQ8). They should also have symptoms suggestive of coeliac disease that respond to a gluten-free diet and show a corresponding improvement in histology.23,24 A previous European multicentre series reported that antibody negative coeliac disease accounted for 6.4% (8 of 126) of all cases of coeliac disease.27

A duodenal biopsy can be taken from any patient referred for gastroscopy. We and others have reported that 13.6% of patients later diagnosed with coeliac disease had had a gastroscopy within the previous five years but no duodenal biopsy had been taken.10 This may be because of sole reliance on endoscopic features for recognising coeliac disease, even though such features are only 50-87.5% sensitive for detecting this disease.28 Higher levels of detection are thought to correlate with endoscopic experience and the severity of villous atrophy. In addition, inter-rater reliability is poor.28 Because of the limitations of endoscopy, antibody negative coeliac disease, and delays in diagnosis, many centres around the world suggest or recommend routine duodenal biopsy. In clinical practice, however, this policy varies greatly, and reported rates of duodenal biopsy range from 30.9% to 74%.29-32 The reported prevalence of coeliac disease when taking a routine duodenal biopsy ranges from 1.0% to 5.2%.33-42 However, prevalence depends greatly on the population studied. Since the advent of tissue transglutaminase and endomysial antibodies, the practice of routine duodenal biopsy has not been fully evaluated in the context of referrals from primary care.

We devised and evaluated a clinical decision tool that used a combination of pre-endoscopy serological testing (for tissue transglutaminase antibodies) and assessment of symptoms to identify patients with coeliac disease. This decision tool might help increase the detection of coeliac disease in patients attending for gastroscopy without the need to perform routine duodenal biopsy.

METHODS
Retrospective analysis and creation of a clinical decision tool
From January 2003 to January 2004 our centre performed 5979 gastroscopies. We analysed the data from 1464 unselected patients who had both a gastroscopy and duodenal biopsy. On the basis of this retrospective data, the prevalence of new cases of coeliac disease identified in patients referred for endoscopy was 4.2% (61 of 1464).

We assessed the indications for referral in these unselected patients and whether the biopsy findings indicated coeliac disease. We categorised patients with indications of weight loss, anaemia, or diarrhoea as having a “high risk” for coeliac disease. In routine clinical practice, such patients should have a duodenal biopsy taken as per British Society of Gastroenterology guidelines.43,44 Anaemia was defined as a haemoglobin concentration of less than 120 g/l in female patients and less than 130 g/l in male patients; diarrhoea was defined as a bowel frequency of more than three times a day (both definitions as suggested by British Society of Gastroenterology guidelines).43,44 Patients were deemed as having lost weight if this was stipulated in the referral letter from their general practitioner and confirmed by the patient at gastroscopy. The remaining patients (whose symptoms were atypical for coeliac disease) were categorised as having a “low risk.” Symptoms classified as low risk include all other indications for gastroscopy, such as abdominal pain, reflux, dyspepsia, vomiting or nausea, and chest pain. Of the 1464 patients analysed who had gastroscopy and a duodenal biopsy, 1085 (74.1%) were high risk and 379 (25.9%) were low risk.

In this retrospective group, tissue transglutaminase antibody titre was part of the antibody profile performed in 109 patients. Eighty-nine of the 109 patients (81.7%) were at high risk and 20 (18.3%) were at low risk of coeliac disease. Tissue transglutaminase antibody testing was performed in these patients because the investigating doctor considered coeliac disease to be a possible cause of their symptoms before gastroscopy. Eighteen of the 109 patients (16.5%) had coeliac disease, two of whom were negative for tissue transglutaminase antibodies. Nineteen of the 109 patients were positive for tissue transglutaminase antibodies—16 had coeliac disease but three had a normal duodenal biopsy. The sensitivity, specificity, positive predictive value, and negative predictive value for tissue transglutaminase antibodies in the detection of coeliac disease were 94.1%, 96.7%, 84.2%, and 97.8%. The two antibody negative patients with coeliac disease both had high risk referral symptoms. When we combined the referral indication of high risk with positive tissue transglutaminase antibody results the sensitivity for diagnosing coeliac disease was 100% (95% confidence interval 82.4% to 100%).
Prospective evaluation of clinical decision tool

We recruited patients from a single endoscopy department at the Royal Hallamshire Hospital, Sheffield. This centre serves a population of around 250,000 and carries out 5000-6000 gastroscopies annually. The patients had been referred by their general practitioner for either gastroscopy or a consultation and gastroscopy. A single endoscopist recruited participants for the evaluation study (second cohort) during a 26 month period (January 2004 to April 2006). The department of medical gastroenterology currently performs duodenal biopsy as part of the endoscopic examination. We classified all patients according to the referral information into high risk and low risk groups. At gastroscopy, we confirmed the symptoms described in the referral letter by questioning the patient directly and obtained patient consent. Quadrantic biopsies were taken from the second part of the duodenum in all patients. We also took a blood sample which was analysed for IgA tissue transglutaminase antibodies. We excluded patients if they had a known diagnosis of coeliac disease, coagulopathy (international normalised ratio $>1.3$ or platelets $<80\times10^9$/litre), or active gastrointestinal bleeding, or if a suspected carcinoma was identified during the examination (n=220).

Duodenal biopsy specimens were fixed in buffered formalin and embedded in paraffin wax. Standard 3 µm thick sections at three levels were stained with haematoxylin and eosin and reported routinely. We graded villous atrophy according to the modified Marsh criteria.

We used a commercially available enzyme linked immunosorbent assay to measure IgA antibodies to tissue transglutaminase. A titre of $>15$ U/ml was taken as positive (as recommended by the manufacturer).

We classed patients with villous atrophy and a negative antibody profile as having antibody negative coeliac disease only if they fulfilled previously described criteria. To support such a diagnosis, we excluded alternative causes of villous atrophy (such as infection with *Giardia* or *Helicobacter pylori* or selective IgA deficiency). In addition, all cases of coeliac disease and any equivocal cases were then reviewed by a gastrointestinal histopathologist who independently assessed the consistency of sampling and reporting.

Data analysis

We used SPSS version 10.0 to analyse the data; 95% confidence intervals were calculated by the Wilson method. We determined the sample size needed for our prospective study in consultation with the Sheffield University statistical services unit at the start of the study. For our prospective study to give a sensitivity of 100% (like our retrospective data), but with a narrower confidence width, our sample size needed to be 2000. This would give a 95% confidence interval of 98.8% to 100% (a width of 1.2%).

RESULTS

We recruited 2000 patients (1167 (58.3%) women, mean age 55.8, range 16-94). No patients refused to participate in the study. We categorised 739 patients into the high risk group and 1261 into the low risk group according to their referral indications (fig 2). In total, 77 patients were newly diagnosed with coeliac disease. The independent gastrointestinal histopathology review confirmed consistency in both sampling and reporting of duodenal biopsies. No diagnoses were changed as a result of this review.

The prevalence of coeliac disease in all patients attending for gastroscopy was 3.9% (77/2000, 95% confidence interval 3.1% to 4.8%). In the high risk group prevalence was 9.6% (71/739, 7.7% to 12.0%).

The prevalence of tissue transglutaminase antibody negative coeliac disease was 0.4% (7/2000, 0.2% to 0.7%). All cases of antibody negative coeliac disease occurred in the high risk group (fig 2). Only one of these seven antibody negative patients had selective IgA deficiency. Antibody negative coeliac disease accounted for 9.1% (7/77, 4.5% to 17.6%) of cases within this cohort.

The prevalence of coeliac disease in the low risk group was 0.5% (6/1261, 0.2% to 1.0%). Symptoms (abdominal pain, reflux, and irritable bowel syndrome) improved in these six patients when they ate a gluten-free diet (duration of follow-up three to 18 months).

Using the tissue transglutaminase antibody test alone to diagnose coeliac disease gave a sensitivity, specificity, positive predictive value, and negative predictive value of 90.9%, 90.9%, 28.6%, and 99.6%.
Evaluating the clinical decision tool

Combining biopsy of the high risk group and those patients with a positive antibody result gave a sensitivity of 100% (77/77, 95.2% to 100%). The specificity was 60.8% (1170/1923, 58.6% to 63.0%), positive predictive value was 9.3% (77/830, 7.5% to 11.4%), and negative predictive value was 100% (1170/1170, 99.7% to 100%) (fig 2). The prevalence of coeliac disease in patients undergoing biopsy as a result of the decision tool was 9.3%.

**DISCUSSION**

Previous investigators have suggested clinical algorithms for diagnosing coeliac disease. We devised and evaluated a strategy of pre-endoscopy serological testing for coeliac disease combined with biopsy of high risk cases. The clinical decision tool had a sensitivity of 100% (95.2% to 100%) in our cohort of patients and no cases of coeliac disease were missed. Although the decision tool was accurate, the confidence interval was around 5%, so this tool may not necessarily detect all cases when applied to other groups.

**Limitations**

We performed the serological testing in secondary care on patients from primary care. We did not test the implementation of this decision tool in primary care. The prevalence of coeliac disease is lower in primary care (0.5-1.0%) than in the endoscopy unit (1.0-5.2%), and this might affect the performance of the decision tool.

**Implications**

By using our clinical decision tool instead of routine duodenal biopsy, 58.5% (1170/2000) of patients would have avoided a duodenal biopsy yet the same number of cases of coeliac disease would have been detected.

Our data support the need for duodenal biopsy in high risk patients even if they are antibody negative. Given this observation, one option would be to serologically test the low risk group only. However, the definitions of high risk and low risk are based on current British Society of Gastroenterology guidelines, which are probably not widely available in primary care. We therefore think the most pragmatic approach would be serological testing for all patients referred for gastroscopy.

The exact antibody test needed is debatable. Many centres recommend a two step approach (tissue transglutaminase antibodies first, followed by endomysial antibodies in patients with positive results). However, for logistical reasons this approach may not be applicable to pre-endoscopy testing—the complete antibody profile may not be available by the time the patient arrives for gastroscopy. We found that using tissue transglutaminase antibodies alone was adequate and cheap and that no cases of coeliac disease were overlooked. Testing for tissue transglutaminase antibodies is the cheapest and most accurate option, as the immunofluorescence method used to detect endomysial antibodies is subjective and uses expensive tissue as the substrate (monkey oesophagus or umbilical cord).

The advent of point of care testing for tissue transglutaminase antibodies may influence clinical practice. Preliminary reports suggest that sensitivity and specificity are comparable to those seen for serology. Point of care testing might shift the onus to conduct this test from general practitioners to the endoscopy unit, where the test could perhaps be done immediately before endoscopy. This might be a more effective way of using the decision tool in the future. However, in the United Kingdom because of practice based commissioning (for primary care), many general practitioners may choose to adopt this policy as a cost effective approach.

**Cost effectiveness**

We anticipate that our decision tool will be cost effective. In our study, the decision tool reduced the workload associated with processing and reporting duodenal biopsies to 41.5% of that of the routine biopsy method. Earlier diagnosis might result in fewer consultations in primary care and possibly fewer referrals to secondary care, which would also reduce healthcare costs. In addition, a prompt diagnosis would improve the quality of life for patients with coeliac disease at an earlier stage and potentially save money by delaying onset of the complications of coeliac disease.

**Conclusion**

In this data set, pre-endoscopy serological testing combined with biopsy of high risk cases had a sensitivity of 100%. The use of this clinical decision tool may enable the endoscopist to target patients who need a duodenal biopsy. This strategy might increase the detection rate of coeliac disease.

**Contributors:** ADH helped design the study; collect, analyse, and interpret data; draft the article; and recruit patients. ADH is guarantor. SD helped analyse the data and review the final version of the manuscript. DPH, MEMA, AIL, MES, and MH helped recruit patients, analyse and interpret the data, and review the final version of the manuscript. SSC helped review the
Routine duodenal biopsy has been suggested as a way to ensure that no cases are missed at gastroscopy. WHAT IS ALREADY KNOWN ON THIS TOPIC


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WHAT IS ALREADY KNOWN ON THIS TOPIC

- The symptoms of coeliac disease may be insidious so delays in diagnosis are common.
- Routine duodenal biopsy has been suggested as a way to ensure that no cases are missed at gastroscopy.

WHAT THIS STUDY ADDS

- Pre-endoscopy serological testing and biopsy of “high risk” cases has a 100% sensitivity.
- All patients referred for gastroscopy with high risk symptoms should be biopsied irrespective of their antibody profile.

Histopathology, analyse and interpret the data, and review the final version of the manuscript. DSS conceived and designed the study. DSS helped recruit patients, analyse and interpret data, and review the final version of the manuscript.

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Clinical prediction rules for diagnosis seek to optimise the sensitivity and specificity of our diagnostic approach to a given problem. In this issue of the BMJ, Hopper and colleagues report a rare accomplishment in this regard—a decision rule that achieved 100% sensitivity in disease detection, in this case for coeliac disease.1 The rule is simple—a positive serological test for IgA antibody to tissue transglutaminase combined with being at “high risk” (having weight loss, diarrhoea, or anaemia). The rule identified every patient with the disease in a cohort of 2000 patients, all of whom underwent intestinal biopsy as the gold standard and the final diagnostic step. This is a welcome advance. As the authors emphasise, coeliac disease may affect up to one in a 100 people, only one case in seven is ever diagnosed, and an appreciable diagnostic delay of many years often occurs.2,3

This result will probably not change clinical practice, however, as current algorithms for coeliac disease already incorporate these factors. Rather, this study strongly validates this approach and allows us to estimate with some confidence the probabilities of success or failure at each step of the process. The results support the current practice of forgoing endoscopic biopsy in low risk patients with negative serology, as none of the 1170 patients meeting these criteria was found to have coeliac disease on biopsy. The study confirms that biopsy has an important role in high risk patients with positive serology. It has been suggested that this combination provides adequate evidence to diagnose coeliac disease without the need for biopsy, and a substantial proportion of patients given the diagnosis (up to 25% in one survey) have never been biopsied.4 However, 40% of high risk patients with positive serology in Hopper and colleagues’ study did not have coeliac disease when biopsied. Even acknowledging the possibility that coeliac disease can be missed on biopsy, we agree with the authors that biopsy is essential in this cohort, given the daunting prospect of lifelong adherence to a gluten-free diet.

The wisdom of biopsy in high risk patients who are tissue transglutaminase antibody negative is debatable. Although Hopper and colleagues recommend biopsy in this group, this approach identified only seven additional cases out of the 585 patients biopsied, and at least some of these cases could be predicted by testing for IgA deficiency.

This decision rule now needs to be tested in other settings,4 and the rule may fare less well because:

- The population studied was a referral cohort; the base rate of disease will probably be lower in primary care cohorts.
- Variability in assigning patients at high risk will increase if subsequent clinicians use their own definitions of weight loss, diarrhoea, or anaemia.
- The results of tissue transglutaminase antibody testing will vary more as many different laboratories will be used.
- The interpretation of biopsies will be less uniform, given the inherent variability between pathologists and differences in the quality of biopsy samples, which will come from multiple endoscopists.

The decision rule might be improved by incorporating a panel of serological markers. In particular, almost all patients with coeliac disease carry the HLA markers DQ2 or sometimes DQ8. The absence of DQ2 and DQ8 would therefore be reassuring in patients who are at high risk but are tissue transglutaminase antibody negative. Until a better rule is developed and validated, the decision rule of Hopper and colleagues seems to be the most cost effective and efficient way to assess coeliac disease.

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Operational implications of using 2006 World Health Organization growth standards in nutrition programmes: secondary data analysis

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ABSTRACT
Objective To assess the implications of adopting the World Health Organization 2006 growth standards in combination with current diagnostic criteria in emergency and non-emergency child feeding programmes.

Design Secondary analysis of data from three standardised nutrition surveys (n=2555) for prevalence of acute malnutrition, using weight for height z score (<−2 and <-3) and percentage of the median (>80% and <70%) cut-offs for moderate and severe acute malnutrition from the National Center for Health Statistics/WHO growth reference (NCHS reference) and the new WHO 2006 growth standards (WHO standards).

Setting Refugee camps in Algeria, Kenya, and Bangladesh.

Population Children aged 6-59 months.

Results Important differences exist in the weight for height cut-offs used for defining acute malnutrition obtained from the WHO standards and NCHS reference data. These vary according to a child’s height and according to whether z score or percentage of the median cut-offs are used. If applied and used according to current practice in nutrition programmes, the WHO standards will result in a higher measured prevalence of severe acute malnutrition during surveys but, paradoxically, a decrease in the admission of children to emergency feeding programmes and earlier discharge of recovering patients. The expected impact on case fatality rates of applying the new standards in conjunction with current diagnostic criteria is unknown.

Conclusions A full assessment of the appropriate use of the new WHO standards in the diagnosis of acute malnutrition is urgently needed. This should be completed before the standards are adopted by organisations that run nutrition programmes targeting acute malnutrition.

INTRODUCTION
Globally, malnutrition continues to affect many populations, with adverse effects on health, mortality, and productivity. Malnutrition is a potentiating factor in about half of the 10 million deaths among children under 5 each year, and improved nutrition is considered essential to the achievement of the millennium development goals. According to the United Nations World Food Programme, the number of nutritional emergencies has risen over the past two decades from an average of 15 a year during the 1980s to more than 30 a year since the turn of the millennium. The number of people supplied with food aid during 2005 totalled 73.1 million.

The World Health Organization’s child growth standards (referred to here as the WHO standards) are based on data from a multicentre international study and reflect how children grow under optimal conditions. As such, they are designed as a standard rather than just a reference and can be used for individual diagnoses and international comparisons. The standards were released in April 2006, and WHO is advocating their adoption as a replacement for the currently used international growth reference, produced by the National Center for Health Statistics, Center for Disease Control and Prevention, and WHO in 1978 (referred to here as the NCHS reference). Many unanswered questions remain, however, relating to the practical implementation and monitoring of nutrition programmes with the new WHO standards, including their use in emergency assessment and response.

The prevalences of global acute malnutrition and severe acute malnutrition are key indicators calculated from the weight for height index of a sample of children. They are used to monitor high risk or food insecure situations and, when certain criteria are met, to trigger alerts and leverage resources for interventions. These may include emergency feeding or other public health or livelihood programmes. A prevalence of global acute malnutrition of more than 10% is taken as indicating a serious situation.

Nutritional status can be expressed by using either the z scores method or the percentage of the median method. Z scores correspond to standard deviations from the mean value—for example, a weight for height z score of −2 corresponds to a weight two standard deviations smaller than the mean, and a z score of 1 corresponds to a weight one standard deviation larger than the mean. Percentages of the median values are simply the percentages of the reference or standard median or mean that the measurement comprises.

Global acute malnutrition includes all cases with a weight for height index below a z score of −2 or 80%
of the median, plus cases with oedema, whereas severe acute malnutrition includes those cases with a weight for height index below a z score of −2 or 70% of the median, plus cases with oedema. Whereas z score cut-offs are routinely used to assess the need for an intervention, admissions to and discharges from feeding programmes are often based on the more easily calculated percentage of the median cut-offs. The detailed planning for interventions therefore tends to be done with the expected number of admissions based on the percentage of the median indicator, in conjunction with estimates of the total population of children in the affected area. Where selective feeding programmes for children are implemented, they are generally divided into therapeutic feeding programmes for cases with severe acute malnutrition and supplementary feeding programmes for children who have moderate acute malnutrition (defined as those children without oedema but weight for height between −2 and −3 z scores or between 80% and 70% of the median).

The introduction of the WHO 2006 growth standards has been accompanied by the release of software that allows for the calculation of the prevalence of malnutrition by using z scores with both the WHO 2006 growth standards and the NCHS reference data. WHO has not released either sex combined growth standards or tables based on percentage of the median, both of which have been widely used tools in running nutrition programmes in the past.

In this paper, we use z score cut-offs and calculated percentage of the median cut-offs to compare retrospectively the prevalence of malnutrition obtained in nutritional assessments in three refugee food aid operations. We compare differences in the prevalence of total wasting and severe wasting and calculate the potential impact on the numbers of children treated in selective feeding programmes. Finally, we discuss the challenges that exist for adoption of the WHO standards in nutrition programmes.

METHODS

The anthropometric cut-offs we compare in this paper were derived from weight for height indices published in the NCHS reference and the WHO standards datasets. We used the two methods commonly used for describing the anthropometric status of children—z scores (the number of standard deviations a child is from the average) and the percentage of the median—for the comparisons.

For the NCHS reference, we tabulated the standard cut-offs for total wasting (<−2 z scores and <80% of the median) and severe wasting (<−3 z scores and <70% of the median) from published tables by using the weight for length index for lengths of 49.0-84.5 cm and the weight for height index for heights of 85.0-110.0 cm. For the WHO standards, we tabulated the same z score cut-offs for total wasting and severe wasting from the weight for length index for lengths below 87.0 cm and from the weight for height index for heights of 87.0 and above, as recommended by WHO. We also calculated and tabulated the <70% and <80% cut-off points by using the published intervals of 0.5 cm for the length and height range 49.0 to 110.0 cm. We chose this range for comparison because 49.0 cm is the lowest length included in the NCHS reference weight for height index, and 110.0 cm is the proxy height used for defining the upper inclusion age (59 months) in surveys of nutrition in children. We used Microsoft Excel 2003 to compare the cut-offs graphically.

We analysed data from three previously reported nutrition surveys in refugee camps in Africa and Asia. We filtered records to remove any cases with oedema. We did this because children with bipedal pitting oedema are classified as having severe acute malnutrition independently of their weight for height measurements, and malnutrition prevalence results calculated with the available software for the WHO growth standards (WHO Anthro 2005) fail to distinguish between children with wasting and those with oedema. Looking only at malnutrition due to wasting therefore allowed a clearer comparison of the performance of the four diagnostic criteria assessed.

We used WHO Anthro 2005 software to calculate the prevalences and 95% confidence intervals of global acute malnutrition and severe acute malnutrition, using both the NCHS reference and WHO standard z score cut-offs. We calculated the variable for age in months from the birth date but left the type of measurement variable (height or length) blank. This avoided measurement and age dependent height adjustments that are automatically implemented by WHO Anthro software in analyses using the WHO standards but not in analyses using the NCHS reference. We calculated the prevalence of malnutrition for percentage of the median cut-offs with EpiInfo 6.04d or a database and VLOOKUP formula constructed in Microsoft Excel 2003. We calculated 95% confidence intervals for these estimates by using CSample for the NCHS reference and by using EpiTable (Epi Info 6) and assuming a design effect of 2 for the WHO standards. The design effect for the surveys analysed here reflects the loss of precision due to the use of cluster sampling instead of simple random sampling. The design effect for a child anthropometric survey using 30 clusters of 30 households is routinely assumed to be 2.5

We used Newcombe’s test of paired differences to compare differences in the proportion of children eligible for selective feeding. Contemporary total population figures for the refugee camps came from registration data from the United Nations High Commissioner for Refugees, and we estimated the population of 6-59 month old children by assuming that it comprised 15% of the total.7 We estimated the number of children eligible for admission to selective feeding by multiplying the 6-59 month population by the measured prevalence of global acute malnutrition.

RESULTS

Marked, height dependent differences exist in the weight for height cut-offs used for defining severe
acute malnutrition obtained from the WHO growth standards and NCHS reference data. The graphs presented here illustrate the differences between various diagnostic cut-offs. The observed differences are relatively large when we compare the z score cut-offs but smaller when we compare the percentage of the median cut-offs. Sex did not affect the overall pattern or magnitude of the differences, and, for the sake of brevity, we display results for boys only.

Z score cut-offs
When we apply the severe acute malnutrition weight for height cut-off of $<-3$ z scores (fig 1), the largest differences between the cut-offs are seen in infants with lengths of around 60 cm, where the difference is more than 1 kg, and in children above 100 cm, where the difference is up to 0.6 kg. However, in children of lengths between 78.0 and 84.5 cm, the difference in cut-offs becomes negative by up to $-0.2$ kg. Across the length and height range corresponding to the WHO standard median heights for 6-59 months (67.6-109.4 cm), we see an overall increase in the weight for height cut-off for severe acute malnutrition, implying that children will have a higher probability of being diagnosed as having severe malnutrition with the new WHO standards. The significance of this length/height range is that it comprises the inclusion criteria for standard nutritional surveys.

When we apply the z score cut-off of $<$-2 for global acute malnutrition, we see a similar pattern but with a smaller magnitude of difference between the NCHS reference and WHO standards (fig 2). These results show that the height profile of the surveyed population is critical in influencing both the magnitude and direction of change in the prevalence of global acute malnutrition.

Percentage of median cut-offs
In contrast to the effect seen with z score cut-offs, with application of the weight for height $<$70% of the median cut-off with the WHO standards we see a decrease in the diagnostic cut-off weight for severe acute malnutrition for children over 67.5 cm (fig 3). This means that children who are assessed with percentage of the median will be less likely to be diagnosed as having severe acute malnutrition if the new WHO standards are used instead of the NCHS reference. Although the diagnostic cut-off for infants under 67.5 cm is increased, admissions from this group are relatively rare.

When we apply the percentage of the median cut-off for moderate acute malnutrition ($<$80% of the median) we see a similar pattern (fig 4), with a decrease in the probability of a positive diagnosis. Critically, as a thin child is less likely to be classified as malnourished, application of percentage of the median cut-offs in conjunction with the WHO standards is likely lead to a reduction in admissions to feeding programmes and earlier discharge of recovering patients.

Retrospective data analysis
The public health impact of applying the new WHO standards data in any nutritional assessment or programme will be strongly affected by the age profile and weight and height attributes of the population, as well as by the prevalence of oedema. Some populations may contain many children on the diagnostic “borderline” and see large changes in the diagnosed prevalence of malnutrition, whereas for other populations relatively little change may be seen. Generalising about the expected differences in the prevalence of

Fig 1 | Comparison of weight for height −3 z score cut-offs for diagnosing acute malnutrition in boys

Fig 2 | Comparison of weight for height −2 z score cut-offs for diagnosing acute malnutrition in boys

Fig 3 | Comparison of weight for height 70% of the median cut-offs for diagnosing acute malnutrition in boys
acute malnutrition detected by using the WHO standards compared with the NCHS reference, and the impact on admissions and discharge from selective feeding programmes, is therefore difficult.

To investigate what the impact of the use of WHO standards might be if they are operationally adopted, we used the WHO standard and NCHS reference data to retrospectively analyse data from three standardised nutrition surveys in stable refugee populations with moderate to high levels of global acute malnutrition. Table 1 compares the results from these case studies, showing, as expected, small differences in the prevalence of global acute malnutrition but relatively large differences in the prevalence of severe acute malnutrition, which is 1.7 to 4.2 times higher when assessed with the WHO standards.

Table 2 shows the impact on children’s eligibility for selective feeding programmes assessed with weight for height percentage of the median cut-offs. Clearly, if percentage of the median cut-offs based on the WHO standard had been applied in these operations they would have led to a substantial reduction (32-52%) in the proportion of children eligible for therapeutic and supplementary nutritional support. For example, on the basis of the registered camp population in Kenya the number of eligible children would have been reduced from 891 to 424; in the Algerian camp the number would be reduced from 1472 to 1003.

**DISCUSSION**

We have described the differences in the cut-offs for acute malnutrition between the NCHS reference and WHO standard datasets. If WHO standards are adopted in nutrition programmes without critical review and careful consideration of consequences, several potentially serious implications are likely.

Firstly, making interpretations of the seriousness of a nutritional crisis and the need for a response will be difficult where comparable trend data are not available. Decisions should remain rooted in an understanding of seasonal, regional, and annual variations in the prevalence of malnutrition, and these are only realistically possible with data generated by the continued or parallel use of the NCHS reference. Given time, comparable trend data could be generated if a dual analysis approach is adopted. Data on the relative risk of mortality associated with cut-offs based on the new WHO standards are not currently available, and established risk models will need to be recalibrated using these data.

Secondly, overall estimates of the prevalence of global acute malnutrition, and particularly of severe acute malnutrition, obtained from surveys analysed with the WHO standards are likely to be higher than estimates obtained with the NCHS reference cut-offs. This raises the potential for the misdirection of resources between emergency situations if data generated using different diagnostic criteria would not be admitted in the future, and those admitted would be discharged sooner than at present. Whether this would result in increased mortality in this population subgroup is unknown.

**Possible implications for clinical admissions**

The third potential problem concerns the admission of children to selective feeding programmes. If the WHO standards are introduced and used according to current practice, although the prevalence of acute malnutrition measured by surveys will be higher, admissions to selective feeding (therapeutic and supplementary) programmes will, if still done on the basis of percentage of the median, be lower than at present. A subgroup of children admitted under current admission criteria would not be admitted in the future, and those admitted would be discharged sooner than at present.
WHAT IS ALREADY KNOWN ON THIS TOPIC
The 1978 NCHS/WHO child growth reference curves are widely used but have some important limitations in their applicability to all populations
New 2006 WHO growth standards were designed to be a global standard, reflecting optimal growth, nutrition, and development for all children in all countries

WHAT THIS STUDY ADDS
Surveys that use the new WHO standards and a \([-3] z\) score weight for height cut-off will markedly increase the number of children identified as having severe acute malnutrition

One option that operational agencies might choose is to switch admission criteria for feeding programmes from the NCHS reference percentage of the median to the WHO standard \([\leq 3] z\) score cut-offs. The figures presented in tables 1 and 2 show that, under this scenario, the number of children eligible for selective feeding may increase overall by 1.5 to 2.1 \((\leq80\%\) of the NCHS reference median \(v < -2 z\) scores of the WHO standard). The biggest proportionate changes are likely to be seen in the numbers eligible for therapeutic feeding. These estimates need to be confirmed by studying other datasets, but they do raise serious questions about the capacity of established programmes to cope with increased patient load and about the resourcing of new relief operations.

The fourth area of concern is the divergence between measurements reported using the \(z\) score and percentage of the median methods. Although this problem has existed for some years with the NCHS reference, if the WHO standards were used to calculate both \(z\) scores and percentage of the median indices a greater divergence would exist in the estimates of malnutrition. If these data were used for assessment and planning, the gap between needs assessment (routinely done with \(z\) scores) and admissions to feeding programmes (routinely done with percentage of the median) would increase. This increased mismatch would be likely to have a detrimental effect on the planning of programmes, allocation of resources, and effectiveness of interventions.

Opportunity for harmonisation

The introduction of the WHO standards presents an opportunity for the harmonisation of indicators used in prevalence surveys and admissions to and discharges from nutrition programmes. However, the harmonisation of these indicators will need planning, training, and resources. To complicate matters further, published data are lacking on whether field staff in emergencies will have the capacity to use \(z\) scores effectively and safely.

An associated problem with the use of the WHO standards is the release of software (WHO Anthro 2005) for the analysis of anthropometric data from individuals and surveys. Although otherwise an excellent software tool, the program fails to separate cases with oedema and account for them as a separate category of severe malnutrition in its summary statistics. If not explicitly recognised by the user, this may have the effect of falsely reducing the reported prevalence of nutritional oedema. Modification of the software, to ensure its consistency with standardised reporting formats, is a prerequisite for efficient analysis of surveys with the WHO standards.

In any interim transition period using a dual analysis system, potential problems will arise if communication efforts are not strengthened to ensure that decision makers are presented with consistent and comparable data. The potential for confusion and misuse exists, thereby risking a reduction in operational effectiveness and equity. Where percentage of the median and \(z\) score results are reported, decision makers may now be presented with four different estimates of prevalence to deal with. As the history of the kcal and kJ energy units illustrates well, the international nutrition world is sometimes slow to adapt to change and some changes may be never fully implemented. An intensified effort is needed if this track record is not to be repeated with the introduction of the WHO standards.

Conclusion

The practical implications of adopting the WHO standards need to be thoroughly assessed before operational agencies start to implement programmes that use their weight for height cut-offs. If adoption of the WHO standards in nutrition programmes is to proceed, it should not be piecemeal and haphazard. Implementation needs to be coordinated, and we propose that a body comprising major UN and non-governmental implementing agencies should be rapidly established to coordinate the response to this operational challenge.

Copies of references 12-14 can be requested by email from the corresponding author.

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Managing the menopause

Helen Roberts

The transition into the menopause usually begins with elongation of cycle length, the term postmenopausal being used after one year with no periods. Most women experience menopause between 40 and 58 years of age. No menopausal symptom is universal. In Western society the commonest symptoms are hot flushes, night sweats, vaginal dryness, and sleep disturbance. Many women manage the menopause by themselves, with only about 10% seeking help from healthcare providers. Hormone replacement therapy is the most effective treatment for symptoms and although opinions are still polarised advice on its use has changed after the women’s health initiative studies.

What are the indications for hormone replacement therapy?

Menopausal symptoms

Indications for hormone replacement therapy are hot flushes, night sweats, and vaginal dryness (table 1). A Cochrane review of randomised trials showed a 75% reduction in flushes (18 fewer per week) with therapy compared with a 50% reduction with placebo.

Flushes can start while a woman is still having periods. Her perception of severity of symptoms will be the deciding factor for offering treatment, not hormone levels, as they fluctuate throughout the perimenopause. Improvements can occur within four weeks of starting therapy.

Advice from most sources, although not all, sources is to use the lowest dose of hormone for the shortest duration to give symptom relief. Short term use is also clinically appropriate as flushes disappear within a few years of menopause for about two thirds of women.

Evidence from longitudinal studies does not suggest that mood symptoms are increased at menopause and at present information is insufficient to conclude any causal relation between the transition into menopause and cognitive disturbances. Disturbances in cognition and mood are not indications for hormone replacement therapy.

Urogenital symptoms are more common after the menopause and occur in up to 50% of women. Hormone replacement therapy makes incontinence worse, but vaginal oestrogen preparations benefit dyspareunia and decrease recurrent urinary tract infections in susceptible women (table 1). Response can take one or two months and as these symptoms are not usually self limiting long term use is needed. Systemic absorption is minimal so that the risks from oral oestrogen do not apply and women with a uterus do not need to use progestogen.

Prevention of chronic disease

Long term hormone replacement therapy for the prevention of chronic disease is no longer recommended as negative outcomes outweigh positive benefits, as shown in both the oestrogen only and combined arms of the women’s health initiative studies. The participants in the studies were women aged 50-79 using 0.625 mg conjugated equine oestrogen alone or with 2.5 mg medroxyprogesterone acetate. Results showed a statistically significant increase in stroke, deep vein thrombosis, and gallbladder disease for both the combined and oestrogen only treatments, with additional increases in breast cancer and dementia (women aged >65) for combined therapy (table 2).

Statistically significant benefits were shown for fracture with both treatments and for colorectal cancer with combined therapy. The differences in absolute risk are listed on bmj.com. The risks are likely to be lower for healthier perimenopausal women using lower doses of hormone. These small increases in absolute risk for a few years are usually acceptable to women with troublesome symptoms.

Women with premature menopause usually have severe flushes requiring treatment and may often need higher doses of hormone. Evidence of other additional benefits is not substantial.

What should women do about bone?

As bone density decreases with age, advice should be given on the benefits of adequate calcium, vitamin D, and weight bearing exercise. Bone density screening for all menopausal women is not recommended;
however, guidelines do support the assessment of osteoporosis risk at menopause and measurement of bone mineral density using dual energy x ray absorptiometry for those at risk. These are women aged more than 40 with fragility fractures, those using systemic glucocorticoids for more than three months, those aged less than 65 with risk factors (for example, family history of osteoporotic fracture), and those aged more than 65. If follow-up measurement of bone mineral density is necessary readings should be taken on the same machine to reduce precision error. Treatment should be considered for those with T scores below −2.5, or below −1.5 if one major clinical risk factor is present.

As with previous studies, the women’s health initiative studies showed a decreased risk of fracture with hormone replacement therapy. Most studies have shown that long term use is required for protection. Although agreement is not general, most sources do not recommend long term treatment for osteoporosis because of the unfavourable risk-benefit ratio.

In the women’s health initiative studies, risks still outweighed the benefit for fracture even for those women at highest risk of fracture. Bisphosphonates are recommended as first line treatment and with these the benefit for fracture has only been shown for women with osteoporosis (T score ≤ −2.5).

What needs to be done before starting therapy?
A full personal and family history will highlight women with risk factors. Risk assessment for cardiovascular disease should include measurement of body mass index, blood pressure, and lipid levels. Women with previous breast cancer, coronary heart disease, stroke, dementia, or venous thromboembolism should not use hormone replacement therapy as randomised studies have shown an increased risk of further disease. Individualised risk can be assessed for women with risk factors for cardiovascular disease—that is, trial evidence can be translated to individual decisions by transforming relative risk into absolute risks. For example, hormone replacement increases the risk of stroke by 40% (relative risk 1.4). A woman with a 5% baseline risk then has a 7% (5×1.4) risk with hormone replacement therapy, which is only a 2% increase. If she has a 25% baseline risk, however, the risk with hormone replacement therapy is 35% (25×1.4), a 10% increase.

How is hormone replacement given?
Oestrogen is available as oral tablets, transdermal patches or gels, nasal sprays, and implants, although availability differs across countries. Few clinical data are available to advise women about any different safety profile with hormones other than those used in the women’s health initiative studies (conjugated equine oestrogens alone or with medroxyprogesterone acetate).

At present most women start with oral therapy at a low dose (0.3 mg conjugated equine oestrogen, 0.5–1.0 mg of 17β-estradiol or estradiol valerate) as this has been shown to relieve flushes. The dose can be increased if relief of symptoms is not adequate after a few weeks. Women who have had a hysterectomy can use unopposed oestrogen; the addition of progestogen is required for women with a uterus to reduce endometrial hyperplasia, which is increased even with low doses of oestrogen. Combined continuous regimens (oestrogen and progestogen daily) can be used when the woman has been postmenopausal for more than one year; before this, sequential regimens (oestrogen daily with progestogen 10–14 days each month) are

<table>
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<tr>
<th>Table 1</th>
<th>Grades of evidence for symptom relief at menopause</th>
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<tr>
<td>Symptoms and treatment</td>
<td>Effectiveness of treatment</td>
</tr>
<tr>
<td>Hot flushes, night sweats:</td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>Both unopposed oestrogen and oestrogen progestogen therapy are effective treatment for hot flushes</td>
</tr>
<tr>
<td>Tibolone</td>
<td>Effective for alleviating severity and reducing frequency of hot flushes</td>
</tr>
<tr>
<td>Vaginal atrophy, recurrent urinary tract infections:</td>
<td></td>
</tr>
<tr>
<td>Low dose topical oestrogen</td>
<td>Cream or tablet form or as estradiol releasing ring is an effective treatment for symptoms of vaginal atrophy</td>
</tr>
<tr>
<td>Intravaginal oestrogen therapy</td>
<td>Treatment for 6–8 months results in reduced recurrence of urinary tract infections in susceptible women</td>
</tr>
<tr>
<td>Tibolone</td>
<td>Has been shown to be effective for vaginal atrophy</td>
</tr>
<tr>
<td>Vaginal moisturiser Replens (Meda, Solna, Sweden)</td>
<td>Effective non-hormonal treatment that may offer relief from vaginal dryness</td>
</tr>
</tbody>
</table>

*Grading system from Scottish Intercollegiate Guidelines Network. A well designed meta-analysis of randomised controlled trials, or body of evidence that is consistently applicable; B very well designed observational studies or extrapolated evidence from randomised controlled trials or meta-analyses.
appropriate. Combined continuous regimens in early menopause may cause irregular bleeding, as oestrogen production from the ovaries is often still fluctuating. Use of prepacked products simplifies use; however, these may not yet be available in low dose format for all combined regimens and may mean that the hormones have to be prescribed individually. An easy rule of thumb to ensure adequate progestogen for protection of the endometrium is to extrapolate doses from those in prepackaged regimens. Low doses of progestogens such as norethisterone and levonorgestrel can be obtained from progestogen only pills.

For those women still menstruating, oestrogen should be started on the first day of the menstrual bleed and progestogen given 14 days later. Withdrawal bleeding should then start around the same time that the period would be expected.

Common side effects of hormone replacement therapy reported from randomised studies include irregular bleeding with combined regimens, which usually settles after a few months, and nausea and breast tenderness. These usually decrease over time, but in clinical practice lowering the dose of hormones reduces these side effects.

Oestrogen can also be given by transdermal patch. Although transdermal oestrogen has little effect on haemostasis, further evidence is required before we can give advice on a lower thrombotic risk compared with oral oestrogen.

Oestrogen given by implant is usually best reserved for specialised centres. Women who have had an early surgical menopause and whose symptom relief with other means of administration is not adequate may find implants useful. Symptoms may return, however, despite super physiological levels of oestradiol (tachyphylaxis). Implants are not normally recommended for women who have a uterus, as prolonged stimulation of the endometrium may occur, requiring continuation of progestogen even after the implants are stopped.

Progestogen is available as an oral tablet, transdermal patch, or intrauterine system. The intrauterinesystem gives good protection of the endometrium and, unlike other combined hormone replacement therapies, offers both contraception and less bleeding for perimenopausal women.

What are the bleeding patterns with hormone replacement therapy and how should irregular patterns be investigated?

Most women using the sequential regimen have a withdrawal bleed near the end of the progestogen dose. This is usually lighter than a period. Combined continuous regimens can give irregular spotting in the first 6-12 months of use, but at the end of the first year most women do not bleed. Endometrial investigation (ultrasonography to determine the thickness of the endometrium or pipelle biopsy) is not required before starting hormone replacement therapy unless there has been bleeding between periods or bleeding after one year with no periods.

If irregular bleeding persists during treatment compliance should be checked and cervical malignancy or infection ruled out before referring for investigation.

What advice can be given about stopping therapy?

Observational data show that for women starting hormone replacement therapy 40-50% stop within one year and 65-75% stop within two years, usually without needing to visit a healthcare provider. Good evidence is lacking on the best way to stop treatment. The initial approach could be to ask women to stop within one or two years of starting therapy to see if symptoms have gone. Women with severe return of flushes could then be advised to restart therapy but to slowly decrease the dose over the next 3-6 months. Addition of other non-hormonal treatments that help flushes has been suggested to help women who have symptoms during withdrawal, particularly those who are at high risk of adverse events while using therapy. Women with long term debilitating symptoms will need to balance symptom relief with ongoing risks from therapy.

Are there other treatments that can help menopausal symptoms?

The Royal College of Obstetricians and Gynaecologists advises that regular aerobic exercise such as swimming and running may help with flushes, as can reduction of caffeine and alcohol intake. Limited

<table>
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<tr>
<th>Table 2</th>
<th>Hazard ratios for various outcomes for women aged 50-79 years using hormone replacement therapy</th>
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<tbody>
<tr>
<td>Outcome</td>
<td>Hazard ratio (95% CI) for combined oestrogen progestogen</td>
</tr>
<tr>
<td>Stroke (mainly ischaemic)</td>
<td>1.41 (1.07 to 1.85)</td>
</tr>
<tr>
<td>Breast cancer (final results)</td>
<td>1.24 (1.01 to 1.54)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.95 (1.43 to 2.67)</td>
</tr>
<tr>
<td>Coronary heart disease (final results)</td>
<td>1.24 (1.00 to 1.54)</td>
</tr>
<tr>
<td>Dementia (women &gt;65 years)</td>
<td>2.05 (1.21 to 3.48)</td>
</tr>
<tr>
<td>Gall bladder disease and procedure</td>
<td>1.59 (1.20 to 1.97)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.66 (0.45 to 0.98)</td>
</tr>
<tr>
<td>Total fracture</td>
<td>0.76 (0.69 to 0.85)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63 (0.43 to 0.92)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.98 (0.82 to 1.18)</td>
</tr>
</tbody>
</table>
SUMMARY POINTS

Hormone replacement therapy remains an appropriate treatment for women with moderate to severe menopausal symptoms

Hormone replacement therapy should not be used for the prevention of chronic disease

Treatment should be at the lowest dose for the shortest time necessary to control symptoms

Women should be advised of the increased risk of stroke, deep vein thrombosis, and gallbladder disease with both combined and oestrogen only therapy

Combined therapy is also associated with increases in risk of breast cancer and dementia (women aged >65)

Evidence also exists for acupuncture and for paced respirations.

Tibolone, a synthetic steroid with weak oestrogenic, progestogenic, and androgenic properties, has shown benefit for flushes and vaginal dryness (Table 1). At present data are lacking from randomised studies to enable advice on outcomes such as breast cancer and cardiovascular disease.

Randomised studies have shown that progesterogens can benefit flushes (for example, Depo-Provera (Phar-macia) 150 mg (90% v 25% fewer flushes compared with placebo) or oral medroxyprogesterone acetate 20 mg daily (74% v 26% fewer flushes compared with placebo). These doses can be used in women with previous venous thromboembolism.

Progesterone cream (20 mg and 32 mg daily) has been evaluated in two randomised studies, one showing benefit (20 mg daily) for flushes (83% women improved v 19% placebo), the other not. Data are insufficient to give assurance that progesterone cream will provide adequate protection of the endometrium for women using oestrogen.

Since the publication of the women’s health initiative studies the use of bioidentical hormones for flushes has increased, usually in the form of transdermal creams or troches (similar to lozenges or pastilles). These are often a mixture of low doses of estradiol (0.5 mg) along with estriol (Biest cream) or also including estrone (Triest cream). These products are compounded in pharmacies and are not available commercially. Clinical efficacy for relief of flushes is likely to result from the estradiol component and we have no data to advise women that risks are different from conventional hormone replacement therapy.

Progestogen should be added to protect the endometrium in women with a uterus. Testing for hormones in saliva is often suggested with use of bioidentical hormones but is not thought to be useful. The treatments discussed for women with previous breast cancer are also the choices for other menopausal women with flushes.

What are the treatments for women with previous breast cancer?

Flushes are often severe for women with a history of breast cancer, either from the effects of chemotherapy and ovarian ablation or from the side effects of adjuvant therapy such as tamoxifen and aromatase inhibitors.

One randomised study of hormone use in women with previous breast cancer showed an increase in recurrence compared with placebo. Any hormonal therapy, including progesterone alone, is considered to be contraindicated for women with previous breast cancer.

Clonidine has shown some benefit for flushes compared with placebo. Transdermal clonidine 0.1 mg/day seems to be more useful than oral clonidine (0.1 mg and 0.2 mg). Side effects include dry mouth, constipation, drowsiness, and dizziness, but no effect on blood pressure at these doses. Clonidine can, however, enhance the effects of other antihypertensives, anxiolitics, and alcohol.

Both selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors have been shown to reduce flushes (60%) compared with placebo (30%), perhaps due to the role of serotonin in the pathophysiology of flushes. The benefit of these products over placebo can also be presented by the daily improvement in the number of flushes (see bmj.com).

Most of the randomised studies have been of short duration (4-12 weeks). Venlafaxine (37.5 mg and 75 mg), fluoxetine (20 mg), and paroxetine (12.5 mg and 25 mg) have all shown benefit. Advice is to start at the lower doses and titrate upwards and also to taper the dose at withdrawal. Although these drugs are generally well tolerated, possible side effects include dry

ADDITIONAL EDUCATIONAL RESOURCES

National Institutes of Health (http://consensus.nih.gov/)

Statement from a state of science conference on management of menopause related symptoms, 2005

Royal College of Obstetricians and Gynaecologists (www.rcog.org.uk/index.asp?PageID=310)

A statement from the Menopause and Hormone Replacement Study Group


Alternatives to hormone replacement therapy for the management of menopausal symptoms

Useful websites

Women’s health initiative study (www.nhlbi.nih.gov/whi/)

This website contains a videocaste, information kit, and details of publications from the women’s health initiative study


Pamphlet on oestrogen plus progestogen for consumers
mouth, dizziness, nausea, and constipation. They also have the potential to decrease libido. At present there is discussion on the possible effects of selective serotonin reuptake inhibitors on the efficacy of tamoxifen. Tamoxifen is converted to its active metabolites by cytochrome P450, and paroxetine, fluoxetine, and possible other selective serotonin reuptake inhibitors have potential to inhibit this conversion. Venlaflaxine would seem to be a weaker inhibitor.28

The anti-epileptic gabapentin (900 mg/day) has also been shown to provide benefit for flushes in women with breast cancer.30 The side effect profile may, however, restrict the use to specialised centres.25

Most of the studies of the herbal remedy black cohosh are of short duration and have had mixed results. A recent randomised trial in women with breast cancer who were taking tamoxifen did, however, find benefit for flushes over placebo.6 The commercially available product Remifen (GlaxoSmithKline, Pittsburgh, PA) has been the most widely studied. Although one case of acute hepatitis has been reported, overall the product seems safe for short term use.

Meta-analysis showed a small reduction in flushes from red clover isoflavones 40-82 mg/day. At present black cohosh and red clover are not thought to have any effects on breast or endometrium, although long term data are needed.

Other studies on phyto-oestrogens have shown mixed results, but the four trials in women with previous breast cancer found no difference in flushes with soy isoflavones compared with placebo.30 The effects on the breast of long term treatment with these products is not clear but they have been shown to cause endometrial hyperplasia.6

Vitamin E has shown a small benefit over placebo, with one less hot flush daily.25 Dehyroepiandrosterone, soy products, dong quai, evening primrose oil, or ginseng do not seem to benefit flushes.25 Replens (Meda, Solna, Sweden), a vaginal moisturiser, can be used for vaginal symptoms (table 1).24-30

ADDITIONAL EDUCATIONAL RESOURCES

Other cochrane reviews of menopausal and older women

Found little evidence on the effect of hormone replacement therapy or oestrogen replacement therapy on overall cognitive function in healthy postmenopausal women, although some small studies showed some benefit of bolus intramuscular injections of estradiol for younger surgically menopausal women


Concluded that neither hormone replacement therapy nor oestrogen replacement therapy was indicated for cognitive improvement or maintenance in women with Alzheimer’s disease


Did not support a beneficial effect of dehydroepiandrosterone supplementation on cognitive function of non-demented middle aged or elderly people


Promising although inconsistent evidence of improvement in cognition with Ginkgo. Side effects similar to placebo


All vaginal delivery systems (cream, tablets, pessary, ring) were equally effective for the symptoms of vaginal atrophy, although conjugated equine oestrogen cream caused overstimulation of the endometrium


No effect of oestrogen alone or with progestogen on the body mass index increase normally experienced at the time of menopause


Unopposed oestrogen therapy in women with a uterus was associated with increased rates of endometrial hyperplasia, irregular bleeding, and consequent non-adherence to therapy. The addition of oral progestogens given sequentially or continuously was associated with reduced rates of hyperplasia and there was a suggestion that continuous therapy over long duration is more protective than sequential therapy in the prevention of endometrial hyperplasia. Hyperplasia was more likely when progestogen was given every three months in a sequential regimen compared with every month in a sequential regimen


This review of combined hormone replacement therapy found no protective effect for any cardiovascular outcome, and increased risk of venous thromboembolic events(relative risk 2.15), pulmonary embolus (2.15), and stroke (1.44) compared with placebo
Testosterone replacement
The American Endocrine Society does not recommend the generalised use of testosterone in women. It points out that no data exist to advise women on risks from long term use. The main evidence of benefit for testosterone is for women with surgical menopause, when it was used along with hormone replacement. Improvement was found in sexual function compared with hormone replacement alone. This meta-analysis had various modalities of replacement including testosterone implants and transdermal patches. The study lasted a median of six months, with the main adverse effect being a decrease in high density lipoprotein cholesterol levels. Evidence of a treatment effect for perimenopausal women was insufficient. As testosterone is not approved for use in women in most countries, referral to specialised centres is advised.

What does the future hold?
Despite hormone replacement therapy being available for 60 years there are still many gaps in our knowledge. Ongoing longitudinal data on menopausal symptoms are needed for other ethnic groups. More research is needed on alternative therapies to tackle standardisation of dose, along with clinical efficacy. Larger randomised controlled trials for selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors are required to look at efficacy and the degree of interaction with tamoxifen.

It would be useful to have more information to advise women in the 50-59 years age group, who are the most likely users of hormone therapy for symptom relief. In the past few years subgroup analysis of results from the women’s health initiative studies has been ongoing in this age group. The number of events is small, however, and the studies were not powered to examine them. Thus many of the reported interactions for these younger women may be spurious and due to chance alone. In this age group the only significant outcome (when the confidence interval did not include 1) was the increase in risk of deep vein thrombosis with combined replacement therapy (see bmj.com). These subgroup analyses are, however, useful to generate hypotheses for much needed further study in these younger postmenopausal women. Some studies, such as the Kronos early estrogen prevention study, are under way.

Competing interests: None declared.

10 Women’s Health Initiative Steering Committee. Effects of conjugated estrogen in postmenopausal women with hysterectomy. JAMA 2006;295:1701-12.
PREGNANCY PLUS

Type 1 diabetes and pregnancy

Roy Taylor,1 John M Davison2

Pregnancy in women with type 1 diabetes remains a challenge for the patient and healthcare team alike. The scenario box on this page highlights some of the problems in achieving satisfactory pregnancy outcomes in women with diabetes. We discuss in the article the main areas of concern.

SCENARIO

Julie rang the diabetes specialist nurse having confirmed pregnancy with a home test kit. Her period was two weeks late. Although she recalled being advised about the need for prepregnancy care, she thought her glucose control was good enough (HbA1c concentration 7.9% at last check) and she had been taking a 400 µg tablet of folate acid daily. She had developed type 1 diabetes 16 years before (at age 8) and at her last annual review had no retinopathy or microalbuminuria. She controlled her diabetes with bedtime insulin glargine, plus insulin lispro (a rapid acting analogue) before meals.

An urgent appointment for the medical obstetric clinic was arranged, and telephone advice was given to achieve blood glucose levels of 3.5-5.5 mmol/l before meals and 4.0-6.5 mmol/l two hours after meals. HbA1c concentration decreased from 7.7% at presentation to 6.3% within eight weeks and was maintained around this level for the rest of pregnancy. The 19-20 week anomaly scan showed a cardiac abnormality, later confirmed as a ventricular septal defect. Blood pressure increased from 102/66 mm Hg to 124/84 mm Hg. Labour was induced at 38 weeks. Blood glucose concentration was maintained at between 5.5 mmol/l and 7.3 mmol/l through use of intravenous glucose and insulin. After a normal vaginal delivery the 4100 g baby boy had Apgar scores of 7 and 9 at 1 and 5 minutes respectively. The locum neonatal senior house officer was advised by the experienced midwives not to measure blood glucose at birth, and when it was checked three hours after the first feed it was normal for age (2.8 mmol/l). Julie’s baby remained with her on the ward.

Blood creatinine concentration decreased from 75% chance if 125-180 µmol/l; 75% chance if 180-220 µmol/l; and 60% chance if >220 µmol/l). The higher the prepregnancy creatinine concentrations, the higher the risk of permanent loss of renal function. When albuminuria is established in a woman with type 1 diabetes, the implications for timing of pregnancy should be explained to her. Diabetic nephropathy will inevitably advance, and renal function will decline over a period of months or years. Once the creatinine concentration has increased, the chance of successful pregnancy decreases.

METHODS

In writing this review, we used published information from Medline searches, search of the Cochrane databases, and personal reference archives.
Conceals wide individual variation

average fall in insulin dose of 5% between weeks 34 and 38 then increases steadily until around 28 weeks’ gestation. The dose does not change until around 18 weeks’ gestation and with standard deviations), from Taylor et al.5

Fig 1

Required. However, if moderate background changes Rechecking at 28 weeks’ gestation is all that is change will occur during pregnancy.

What is to be expected from each clinic visit. Box 1 summarises the effects of pregnancy on diabetes.

One consequence of achieving near normoglycaemia is that asymptomatic hypoglycaemia will occur more frequently, and this will lead to unawareness of hypoglycaemia.7 Women must be advised that they are at greater risk than usual of severe, unannounced hypoglycaemia and be specifically counselled about the importance of testing blood glucose concentrations before driving. Ideally a spouse or partner should be provided with a glucagon kit and trained in its use.

Retinopathy deteriorates whenever blood glucose control is suddenly tightened, as shown by several large randomised studies.6 6 In pregnancy, the extent of deterioration is strongly related to the degree of retinopathy present just before pregnancy. If retinopathy is not present on digital imaging according to the national standards for England,7 then it is highly unlikely that clinically significant change will occur during pregnancy.6 7

Rechecking at 28 weeks’ gestation is all that is required. However, if moderate background changes are present, over half of women will develop proliferative retinopathy,8 11 and full retinal screening is required at booking, 16-20 weeks, and 28 weeks.

If diabetic nephropathy is already established and serum creatinine is raised, there is an increased risk of permanent loss of renal function.8 12

How does diabetes affect the pregnancy?
The most profound potential effect is the increased risk of congenital malformations. The recent UK Confidential Enquiry into Maternal and Child Health survey showed a threefold excess of cardiac and neural tube anomalies.9 Figure 2 shows that very poor control of blood glucose leads to over 25% risk of malformation but that improved prepregnancy glucose control can decrease this almost to background levels.13-15 Even women with type 1 diabetes with normal HbA1c concentrations have intermittent, marked hyperglycaemia, and this may explain the difficulty of completely minimising the risk.16-17

Hyperglycaemia exerts its teratogenic effects during the period of organogenesis—the first 42 days of pregnancy—and pregnancy is invariably confirmed when much of this time has elapsed. This, together with delays in seeking advice from a nurse or doctor, means that frequently no effective advice to modify risk of congenital malformations can be given during the pregnancy. Diabetes confers a significant increase in risk of early spontaneous fetal loss, often as a consequence of non-viable, severe malformation.13

Prepregnancy care from specialised multidisciplinary clinics, involving optimisation of blood glucose control and prescription of folic acid, could considerably decrease the observed rates of congenital malformation. Regrettably, however, even energetic local programmes have only modest impact at best;14 and data from countries round the world suggest that achieving change is very difficult.2 3 16-28 Many patient information leaflets about pregnancy do not make clear the risks of pregnancy in diabetes. It is now routine practice to advise women to take 5 mg

Fig 1 | Data on 107 singleton pregnancies (showing means with standard deviations), from Taylor et al. 5 Average insulin dose does not change until around 18 weeks’ gestation and then increases steadily until around 28 weeks’ gestation. The average fall in insulin dose of 5% between weeks 34 and 38 conceals wide individual variation

Box 1 | Effects of pregnancy on diabetes

- Change in eating pattern
- Increase in insulin dose requirements at 18-28 weeks’ gestation
- Greater importance of tight glucose control (ideally HbA1c < 6.1%)
- Increased risk of severe hypoglycaemia
- Risk of deterioration in pre-existing retinopathy
- Risk of deterioration of established nephropathy
- Lower renal threshold for glycosuria

determined by placental function and varies in successive pregnancies in any one woman. A five year, single centre, observational study has shown that the average increase in insulin requirement is 40%, with a wide range from no change to a higher than threefold increase.5 Figure 1 shows the average time course of this change, which is helpful for advising what is to be expected from each clinic visit. Box 1 summarises the effects of pregnancy on diabetes.

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Fig 2 | The risk of all congenital malformations is increased above the background population rate of 2%, even in women with type 1 diabetes with normal HbA1c concentrations. The risk increases sharply with increasingly poor blood glucose control. Data from Rosenn et al13
of folic acid daily before conception and for the first 12 weeks of pregnancy. No direct evidence supports this advice; the consensus to offer such advice was extrapolated from information that increased folic acid intake is more effective in preventing malformations in other conditions of high risk of neural tube defects.\(^{21}\)

Macrosomia (birth weight >4000 g) occurs in about a fifth of pregnancies in women with type 1 diabetes—twice the incidence for England—\(^{22}\)—with the important corollary of an increased risk of birth injury to such babies. Shoulder dystocia occurs in about 8% of births to diabetic mothers (with risk of Erb’s palsy), compared with 3% to the background population as shown by large, well conducted observational studies.\(^2\) \(^4\) Associated with macrosomia is the greater risk of more severe trauma to the mother, with potential future problems of poor pelvic floor function. Serial monitoring of fetal growth and size by ultrasonography is essential to allow judicious planning of delivery.

Delivery at about 38 weeks’ gestation is advised for women with diabetes to minimise the risk of unexplained late fetal death. The timing and mode of delivery should be determined on an individual basis based on best possible assessments of risk to mother and baby. Macrosomia might also be a factor influencing timing of delivery, although little evidence supports this.\(^{23}\) In recent published series, delivery before 37 weeks occurred in about a third of women with type 1 diabetes, with preterm caesarean section being the greatest single contributor.\(^5\) \(^8\) \(^{24}\)

Pre-eclampsia is four times more likely to occur in women with type 1 diabetes than in women without diabetes,\(^9\) and even more likely in the presence of nephropathy (if albuminuria or microalbuminuria has been established before pregnancy).\(^{25}\) A large observational study has shown that poor blood glucose control before pregnancy does not in itself increase the likelihood of pre-eclampsia, although persistent poor control during pregnancy does increase the risk (odds ratio 1.65 for each 1% increase in HbA\(_1c\)).\(^{26}\)

Box 2 summarises the effects of diabetes on pregnancy.

### Box 2 | Effects of diabetes on pregnancy

- Need for pregnancy planning
- Risk of congenital malformation
- Risk of macrosomia
- Need for regular clinical and ultrasound monitoring
- Increased risk of pre-eclampsia
- Increased risk of miscarriage and intrauterine death before pregnancy, then this should be tapered-off as soon as possible because of the risk of congenital malformations.\(^{27}\) Methyldopa should be substituted providing that continuing treatment is required.

Treatment with high dose steroids may be required to mature the fetal lung if delivery is necessary before 34 weeks’ gestation, for asthma, or for hyperemesis gravidarum. If treatment is indicated, the inevitable and predictable increase in insulin resistance requires a prospective increase in insulin dosage. In practice, an increase of 40% at the time of the first dose will prevent loss of control.\(^{28}\) The increased dose of insulin is required until 24 hours after the last steroid dose. This will prevent the gross hyperglycaemia otherwise precipitated and is extremely unlikely to cause hypoglycaemia.

### Management of mother and baby around delivery

The risk of neonatal hypoglycaemia is increased in the presence of maternal diabetes, as the maternal hyperglycaemia triggers excessive rates of insulin synthesis by the fetal pancreas. The risk does not correlate with HbA\(_1c\) during pregnancy.\(^1\) \(^3\) However, controlling maternal blood glucose over the few hours before delivery is critical to minimise the risk of neonatal hypoglycaemia as blood glucose concentrations higher than 8 mmol/l will almost inevitably be associated with neonatal hypoglycaemia.\(^2\) Hence, maternal blood glucose concentrations of 4-8 mmol/l should be achieved using glucose and insulin infusion.\(^3\) As soon as the cord is cut, the rate of insulin infusion should be halved as insulin sensitivity returns to normal within minutes of shut-down of the uteroplacental circulation. Subcutaneous insulin administration can be resumed as soon as the mother is able to eat.

If the baby’s blood glucose is checked as a routine precaution too early in life, then low concentrations are certain to be observed (5% of babies of non-diabetic women have a blood glucose concentration of less than 1.7 mmol/l within two hours of birth).\(^{30}\) \(^{31}\) When faced with maternal diabetes, inexperienced staff tend to check the neonate’s blood glucose, with the consequence that the baby will be unnecessarily admitted to a special care unit and the mother left alone on the ward after nine months of hard struggle with diabetes. To avoid this “empty arms syndrome” it is critical to promote early feeding, with a check of blood glucose only just before the second feed. This will decrease the current

### How should drug treatment be managed?

The use of the recently introduced long acting insulin analogue glargine is one of the most important recent advances in diabetes management as it minimises the risk of hypoglycaemia despite tight control.\(^10\) Two case series totalling 174 individuals have shown no safety problems in pregnancy.\(^{26}\) \(^{27}\)

Given that swings of blood glucose are known to be deleterious, any safety problems specific to glargine are outweighed by the beneficial effects on overall control. Like most insulins, glargine is not licensed specifically for use in pregnancy, and individuals must be advised about risks and benefits. There is no single insulin regimen that suits all in pregnancy.

If a patient is taking antihypertensive treatment such as an angiotensin converting enzyme inhibitor...
separation rate (one in three cases)—two thirds of separations are potentially avoidable. If hypoglycaemia is suspected, however, then glucose concentrations should be checked.

Conclusions

If Julie (see Scenario box) had contacted her diabetes team before going ahead with her plans to conceive and if blood glucose control had been optimised, the risk of congenital malformation would have been much reduced. Care from the combined obstetric and diabetes team during pregnancy indeed allowed early detection of problems. The induction of labour at 38 weeks avoided the potential risk of unexplained late fetal death. Good blood glucose control during labour minimised the chance of neonatal hypoglycaemia, and separation of mother and baby after delivery was avoided.

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10-MINUTE CONSULTATION

Intermittent claudication

Roger W Simon, André Simon-Schulthess, Beatrice R Amann-Vesti

A 58 year old smoker presented with a six month history of pain in the left calf during walking.

What issues you should cover

Is this really intermittent claudication?
Ask about key symptoms of peripheral arterial disease, including walking distance before onset. In peripheral arterial disease, pain in the hip, thigh, and calf (rarely foot) is not present at rest, on weight bearing, or when starting to walk but occurs after a distance that is predictable (and shorter going uphill). The pain is felt in the muscle, not the bone or joint, and is relieved rapidly with rest or reduction of walking pace. Pain occurring before 200 m reflects Fontaine stage Ia peripheral arterial disease; pain at or beyond 200 m reflects stage Ila.

Main differential diagnoses
Spinal claudication manifests as weakness not pain and starts soon after standing up, with relief on sitting or bending (lumbar spine flexion). Radiculopathy relates mainly to back problems, radiates down the leg, is not relieved by resting, and may diminish by changing position. With hip arthritis, pain starts with weight bearing and is related to activity. In arthritic and inflammatory conditions, pain is continuous and intensified by weight bearing, with tenderness, swelling, and hyperthermia. With a Baker’s cyst the pain is aggravated with activity, not relieved by resting, and may have tenderness and swelling behind the knee.

Medical history
Record risk factors, family history, other cardiovascular symptoms or events, and previous peripheral vascular interventions. Pay attention to drug treatment, such as β blockers, 5-HT receptor agonists, and ergot derivatives—these can worsen existing peripheral arterial disease.

What you should do

Examine the affected leg. Look for colour and trophic changes, as well as early ulcerations suggesting critical ischaemia. Compare skin temperature with that of the other leg. A capillary refill time (established by pressing the toe firmly and noting the time it takes for the pallor to disappear) of more than three seconds indicates severe peripheral arterial disease. Examine pulses at the groin and popliteal fossa, and the pedal pulses. Absent pulses indicate an occlusion above this level. Conduct auscultation of the aortoiliac arteries in the lower abdomen and femoral arteries.

If peripheral arterial disease is suspected, the first and most important screening test is the ankle-brachial index, easily done during a consultation. Systolic blood pressure of the dorsalis pedis, posterior tibialis, or fibularis artery is obtained with a handheld Doppler and divided by the higher of the two brachial pressures. An index <0.9 confirms peripheral arterial disease.

Peripheral arterial disease is recognised as having a risk equivalent to that of coronary heart disease, making secondary prevention mandatory. Thus, immediate treatment should start with low dose aspirin (75 mg daily) and statins, regardless of the total cholesterol concentration.

Optimal control and treatment of all cardiovascular risk factors is crucial. Consequently, get blood checked for glucose and lipids. Advise patients with obesity (body mass index > 25, waist circumference ≥ 102 cm for men and 88 cm for women) to lose weight.

To stop the progression of peripheral arterial disease, a recommendation to stop smoking is essential as smoking is the strongest risk factor. Offer nicotine replacement treatment or suggest a smoking cessation programme.

Advise the patient to exercise (brisk walking) for 30 minutes twice daily to increase pain-free walking and total walking distance by stimulating collateral blood flow.

Uncomplicated intermittent claudication does not need referral to a specialist. If the patient has warning symptoms, refer quickly to a vascular specialist for further assessment and decision for angioplasty or bypass surgery. Be aware of the 5 Ps—pain, pale, pulseless, paraesthesia, paralysis—indicating an acute limb ischaemia.

USEFUL READING


Patient information sheet is available from the Vascular Society of Great Britain and Ireland (www.vascularsociety.org.uk/patient/int_claud.html)
Keeping it secret

PERSONAL VIEW Anonymous

I sat in the consulting room of a GP years my junior who documented my injuries—the 10 cm bruises on my arms and legs, the finger marks, and the scalp haematoma—with kindness and a non-judgmental compassion that made me cry. She told me my injuries were serious.

She told me even doctors end up in bad relationships, because we are human beings. She told me there was no shame in feeling lonely, terrified, and trapped. She told me I should leave.

It can’t have been easy for her: she knew my partner and my partner’s parents, yet she treated me with impartiality and respect. Doctors like to feel in control: it doesn’t come easily to us to ask for help.

It has been both humbling and liberating to experience the kindness of strangers.

I said that this attack came without warning. Of course, it was not the first: an attempt at choking during a disagreement, an unexpected blow struck with a chairback severe enough to break a rib, a beating for making travel arrangements without permission.

I simply did not want to recognise that I was living with someone who was potentially dangerous to me who just happened to be a doctor.

I know medicine to be a stressful and demanding job. Because my partner had been assaulted at work and had a recent bereavement, and I tried to make a diagnosis: post-traumatic stress disorder, bipolar disorder, unresolved childhood issues, anything that might excuse or explain this hostile stranger. Because I was so familiar with domestic violence in practice. Because I was arrogant enough to think I was indestructible and I could offer help. Because I became tired and bewildered and confused. Because I simply did not want to recognise that I was living with someone who was potentially dangerous to me who just happened to be a doctor. I am strong, though I was often reviled for being weak.

I am brave, though I was often accused of cowardice. It took all my bravery and strength to leave our home and return to my city of origin.

With the support of friends and colleagues I am recovering my personal confidence. I am thankful for the medical community and the sensitive care and understanding I have experienced. I have a responsible job. I know that I am loved and respected. I did not involve the police.

I did report my partner to the regulatory authorities, requesting a health assessment of fitness to practise. That is a hard thing for one doctor to do to another, especially someone you love. Like any patient, I have to think I will never receive feedback on the outcome of any investigation.

I have learnt much about myself as a person, a doctor, and a citizen. My life and my practice will be changed by my experience.

Partner violence is an abuse of power. It happens to men and to women, and is perpetrated by men and by women, in different sex and same sex relationships. It ruins lives. It happens to doctors.

If you are a doctor who is a perpetrator of violence, get help. If you are a doctor who is a victim of violence, get help. If you are doctor who knows of such a situation, get help. Someone’s life might depend on it.

See also Editorial p 706 and Review of the Week p 748
Home truths about domestic violence

A new film offers some important lessons for doctors who suspect cases of domestic violence, writes Piyal Sen

A man is sleeping in his bed; soon, his pyjamas are aflame. He wakes up in a panic and raises the alarm. The fire brigade and police arrive to find a woman huddled in a corner of the lawn with the children. A police officer escorts her to the police station and a detective constable aggressively interrogates her. The next day she is produced in court, formally charged, and remanded in prison. The husband dies six days later. Thus began the events leading to the trial of Regina v Ahluwalia, which introduced the concept of battered women’s syndrome for the first time as a legal defence in UK criminal courts. This term, developed by American psychologist Leonora Walker, is a type of post-traumatic stress disorder. It is characterised by a state of “learned helplessness” to explain the apparent passivity of many victims of violence, and “diminished perception of alternatives,” which suggests that the victim cannot see any way out of her situation. It can be used to support a defence of provocation.

The film Provoked is largely based on Kiranjit Ahluwalia’s life, drawn from her autobiography Circle of Light and written with Rahila Gupta of the Southall Black Sisters, a campaign group that champions the rights of Asian and African-Caribbean women in the UK. Kiranjit, an Indian housewife, had an arranged marriage with Deepak Ahluwalia, a British Asian factory worker, and was subjected to severe violence and forms of mental torture for 10 years. She ultimately set fire to her husband’s bedroom while he was asleep. The film starts with her life from the time of the attack, and follows it until her eventual release. It shows her experience in a women’s prison, her attempts to have regular contact with her children while in custody, and finally, her trial and subsequent leave to appeal. Her experience of violence in the marriage is shown through flashbacks. Other characters appear, like a volunteer from the Southall Black Sisters, a fellow female prisoner who has also killed her partner, as well as legal and medical professionals involved with the case.

The film has some powerful moments. For example, in prison, Kiranjit hesitates when asked to take off her jewellery, including the mangalsutra and kara (symbols of marriage for a Sikh woman). Later on, she says, “for the first time, I feel free.” There is also the sequence in court where Kiranjit’s QC, when discussing what is “reasonable,” turns towards Kiranjit and says, “Reasonable to whom, my lord? You? Me? To a woman who suffered violence, abuse, and humiliation of the highest order for 10 years, who feared for both her own life and the life of her young children, I myself could not, would not, presume to know what would be reasonable for such a woman.”

For a medical audience, two important lessons can be drawn from the film. The first can be drawn from the medical evidence given by a doctor in court, who had seen an injured Kiranjit in hospital and suspected that she was the victim of domestic violence, but was unable to question her privately because of her husband. A referral to a social worker at that stage, particularly as she had young children, might have helped to avert the subsequent tragedy. Now there are much clearer guidelines for doctors when seeing a suspected case of domestic violence. The Ahluwalia case played an important role in raising awareness about this problem. The other important lesson is one of offering an opinion only within the boundaries of one’s knowledge, even when pushed by lawyers in court. Kiranjit’s defence team sought the advice of a mental health professional, who refused to be drawn on the issue of provocation but mentioned her endogenous depression as grounds for supporting the defence of diminished responsibility. Her legal team, though initially unhappy, did eventually decide to use this statement in court, and this proved to be the deciding factor.

In the real Ahluwalia case, there was a retrial where a large body of psychiatric evidence supported the defence of diminished responsibility. This meant that Kiranjit suffered from an “abnormality of mind” which “substantially impaired” her responsibility for the killing. Kiranjit was freed, deemed to have already served her substantially reduced sentence. Soon after the successful outcome in the Ahluwalia case, other women also achieved similar outcomes in comparable cases. All this was not shown in the film.

Such a film should bring a message of hope to all the Kiranjit Ahluwalias who still live in our midst. For their sake, one sincerely hopes that the film gets a wide viewing. After all, the problem of domestic violence is not limited to the Asian community.

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See also Editorial p 706 and Personal View p 747
Seeing is believing

A human rights film festival in London showcased several films that document abuses from a patient’s perspective. Khalid Ali reports

This year’s Human Rights Watch Film Festival, which has just finished in London and moves to New York in June, showcases several films that document the discrimination faced in certain societies by people who are ill, or who have suffered physical attack, and are in medical need. The festival, set up by the organisation Human Rights Watch to publicise the stories of survivors of human rights abuses around the world, includes 22 films from 20 countries this year.

Rosita, a joint US and Central American documentary, tells the story of 9 year old Rosa, a Nicaraguan girl who became headline news in 2003 when she was raped and fell pregnant. Her parents, who were working in Costa Rica as coffee pickers at the time of the attack, fought for Rosa to obtain a rarely granted “therapeutic” abortion. The story is told through media footage and the words of Rosa’s parents, doctors, lawyers, and priests. As the media and the government publicise Rosa’s story, the girl is imprisoned in “hospital” to be cared for. The Catholic Church uses her tragedy to criminalise abortion and manipulates the local hospital doctors into claiming that the pregnancy is not harmful and that it should be allowed to full term. Horrifyingly, the doctors are not even allowed to treat her sexually transmitted disease, contracted through the rape, for fear of inducing abortion.

After the intervention of local human rights activists, Rosa is secretly taken back to Nicaragua for a clandestine abortion. The reaction of the church is to excommunicate the whole family and the anonymous doctors who performed the abortion. The film is a timely protest against the current legislation in Nicaragua. In October 2006 a new law enforced by the government banned all forms of abortion, including therapeutic ones, even when the mother’s life is in danger. Women and doctors face a jail sentence of up to 10 years. The repercussions of this unjust law were seen in November 2006 when a young woman was left to die from vaginal bleeding (BMJ 2006;333:1037). Doctors were unable to treat her for fear of breaking the law and facing imprisonment.

A second film, this time from the Democratic Republic of Congo, has a similar bleak opening. Lumo follows the story of a 20 year old woman who is brutally raped by the militias and is left with a fistula. Rejected by her family and fiancé and made a subject of mockery in her village because of her incontinence, Lumo finds her way to the one place that can offer solace, a hospital that helps rape survivors. The hospital, run by the charity Heal Africa and managed by a group of female counselors, “the Mamas,” offers free surgery and rehabilitation to fistula patients. As Lumo and her friends recover from surgery, they share their fears of multiple operations, as well as their hope of being cured. They all dream of going back to the outside world and living a normal life with their own families again. After two years and five operations, Lumo leaves the hospital physically cured but emotionally scarred. The film ends with a big march denouncing violence against women and a warning that the violence may still continue.

We’ll Never Meet Childhood Again (UK 2007) is a documentary that considers the difficult lives of children with HIV. A large proportion of HIV positive children in Europe live in Romania, where they are likely to be abandoned in hospitals. The documentary focuses on a group of children who live in one of the homes set up by the British charity Health Aid UK and is made up of interviews conducted between 1986 and 1996. HIV is still widely perceived as a social stigma and a terminal illness in eastern Europe. Some of the children featured are abused by their playmates and called the “ugly ones, the AIDS ones.” School headteachers refuse the children’s right to education in public schools. Along with its positive message of support and solidarity with HIV positive children, the film acts as an educational tool, dismissing false beliefs about modes of transmission of the virus.

The message from these powerful films is that healthcare professionals need to consider human suffering and discrimination in all its forms all over the world. Our duties and responsibilities are far beyond just dispensing medications. As we endeavour to heal patients’ ailments, we should also strive to fight ignorance, spread education, and champion human rights. Then and only then can we call ourselves human doctors.

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“Whatever”

“Is that you, Des?” This wasn’t a séance but a random email in my mailbox. It was a friend from school with whom I had lost contact over 20 years ago. “Of course it’s bloody well me” was my response. Three weeks later I walked into the restaurant and an older, greyer version of the only Mod in Orkney stood before me. Now he is a lawyer in Edinburgh, and we picked up where we left off. I reminded him of his revolting home made wine and he reminded me of the occasion following said wine when we smoked loose tea rolled in sticky labels. He jibed how he got a higher mark in maths, but I pointed out that regularly I thrashed him at cards (practical maths). But we did not brag about our professional success or how much we earned.

Scoring points seems to matter to people, whether it be about your clothes, your car, your house, or, of course, your children. Medicine is a hotbed of such behaviour, with superiority being our raison d’être. In the past the pecking order was clear—physician, surgeon, anaesthetist, general practitioner, and lastly the orthopaedic surgeon; we all knew where we stood and enjoyed our various sniper positions. But now we have a battalion of different hospital specialists: cardiologists, reflexologists, rheumatologists, acupuncturists, boneologists—God only knows where nurse specialists fit in. The air is now so hot with sneering volleys of bullets that all the sport has gone out of it.

Is it time to put the guns down? “Your GP said WHAT?” “HOW ridiculous,” “The diagnosis was SO obvious,” and all the rest of the rehearsed expressions and phrases need to stop. No doubt, like many GPs, I have taken abuse from patients following such remarks. My clinical acumen may be C+, but most of the time I get it right. This has taught me to bite my tongue when the shoe is on the other foot and colleagues have missed a diagnosis. The reality is that illness evolves, signs change, and patients give completely different histories to different doctors. The sniping has merely served to undermine the whole profession and erode trust with the patients. We are all in this together.

My father once told me “that if you compete then you have lost.” My children have taught me a modern version of this phrase. Next time you receive that condescending letter from a colleague, hold your hands to form a W, cock your head 30 degrees, and say loudly, “Whatever.” Silly, but highly effective.

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The Bigger Picture

Mary Black

Rotten jobs

Here are my nominations for the five worst jobs in the world for health professionals. My criteria are personal: these are jobs that seriously compromise ethical and moral standards, are difficult to justify to your children, and are likely to be a source of regret on your deathbed. Some of this work is highly paid; it would need to be. Readers are encouraged to write in and expand this list.

Head of medical services at Guantanamo Bay. Spanking new facilities in a remote location in Cuba well away from liberal laws that respect human rights. No pesky relatives and visitors to deal with. But how to explain all those bruises and dog bites?

Research scientist at any major tobacco company. Join a powerful global industry, see the world, meet interesting people—and work out how to kill as many as possible. Creatively exercise your grey cells spinning the evidence for tobacco deaths into total nonsense, undermine epidemiology and research ethics, develop youth health and social responsibility programmes with naive, poor NGOs in developing countries, and tell fairy stories about safer cigarettes. And have people walk the other way at cocktail parties.

Biochemical weapons developer. Fool around with funny new deadly gases, see lots of upended rats, and run advanced dosage-mortality curves. Create better gourmet cuisine to deliver plutonium. The World Medical Association urges all who participate in biomedical research to “consider the implications and possible applications of their work and to weigh carefully in the balance the pursuit of scientific knowledge with their ethical responsibilities to society.” I interpret this as: don’t do it. Some will cite national security etc as a patriotic reason for doing this kind of work. If someone can explain what nation, security, and patriotic mean in this globally connected world I would be grateful.

Surgeon in the commercial kidney transplant trade. Harm a poor person and save a rich one. Easy to justify the economics, but the dirty aspects of this global organ trade are all pervading.

Sports doping doctor. High financial rewards. Free tickets to major sporting events. Major scandal if you are found out—your risk being banned from your sporting association or even struck off, but only in some countries. The World Anti-doping Code of 2003 has clearly shifted the onus from the athlete to the doctor, so you can no longer pass the buck.

Hippocrates advised: first do no harm. Sound words to live and work by. None of these jobs stack up.

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Help for hypochondriacks

Every month for nearly six years, James Boswell wrote an essay for the London Magazine under the name of The Hypochondriack. By hypochondriack, Boswell meant not the man who is consumed by fear of illnesses he does not have but the one who suffers from melancholy, spleen, or the vapours. He hoped to ward off his own tendency to this condition, or these conditions, by his literary exertions.

Inauspiciously, perhaps, his first essay in the series was dated November, and he quotes a French novel that starts with the line (one wants to read on), “In the gloomy month of November, when the people of England begin to hang and drown themselves...”

If Boswell were writing his essays today, I suppose it would be as The Depressive, and he would long ago have been put on antidepressants. In Number XXXIX, he describes the hypochondriack’s symptoms: “His opinion of himself is low and desponding. His temporary dejection makes his faculties seem quite feeble. His fancy roves over the variety of characters whom he knows in the world... and they seem all better than his own. He regrets his ever having attempted distinction and excellence in any way, because the effect of his former exertions now serves only to make his insignificance more vexing to him. Nor has he any prospect of more agreeable days when he looks forward. There is a insignificance more vexing to him. Nor has he any prospect of more agreeable days when he looks forward. There is a

And then come immortal words, in opposition to the health and safety view of human existence: “But we are not to consider the world as an immense hospital”

The therapy is religious belief: “By religion, the Hypochondriack will have his mind fixed upon one invariable object of veneration, will have his troubled thoughts calmed by the consideration that he is here in a state of trial, that to contribute his part in carrying out the plan of providence in this state of being is his duty, and that his sufferings however severe will be found beneficial to him in the other world.”

The psychopharmacological remedy Boswell proposes is drink: “To be sure we know that an excess in wine which alone can move a thick melancholy, will probably make us worse when its violent operation has ceased, so that it is in general better to bear the mental malady with firmness. Yet I am not so sure but when the black distress has been of long continuance, it may be allowable to try by way of a desperate remedy, as poisons are sometimes given in medicine, what a joyous shock will produce. To have the mind fairly disengaged from its baneful foe, even for a little while, is of essential consequence. For it may then exert its latent vigour, and... be able to get the better of what pressed it down before in abject submission.”

And then come immortal words, in direct opposition to the health and safety view of human existence, which are more salient today than when they were written: “But we are not to consider the world as an immense hospital: and whenever we see a company with wine circulating amongst them, to think that they are patients swallowing a necessary potion.”

Risk factors can seriously damage your peace of mind.

Theodore Dalrymple is a writer and retired doctor.
Irina Victorovna Gannushkina

Pioneering researcher on cerebral blood flow

Irina Victorovna Gannushkina had a lifelong interest in experimental neurology. Her fundamental studies of collateral blood circulation in the brain, individual susceptibility to cerebral ischaemia, and cerebrovascular biomechanics opened new perspectives for neurology and neurosurgery clinics. She also studied neuroimmunology and demonstrated the role of autoimmune factor in the pathogenesis of stroke, traumatic brain injury, and other nervous diseases. She wrote *Collateral Cerebral Blood Circulation* (1973) and *Immunological Aspects of Traumatic and Vascular Brain Lesions* (1974) and coauthored *Hypertonic Encephalopathy* (1987) and *Immunopathology of Traumatic Brain Injury* (1996).

Irina Gannushkina was born in Moscow in 1929 into a medical family (her father was a neurologist and her mother a nurse). As a student in the paediatric faculty of the Stalin Moscow State Medical Institute N2, she became interested in pathology and spent four years at the students’ society of the chair of pathology. Here Gannushkina performed her first experimental research on changes in the permeability of capillaries after chloroform narcosis. She married her fellow student Leonard Kapuller, who later became a pathologist.

From 1954 until her death Gannushkina worked at the Institute of Neurology in Moscow. In 1955 she entered aspirantura—a three year postgraduate research programme for writing a kandidatskaya dissertation (the Russian equivalent of a PhD thesis). Initially her supervisor was Professor Leonid Smirnov—an outstanding Soviet neuropathologist—but owing to his sudden death Gannushkina had to finish her work under the guidance of Professor Boris Klosovsky. Her thesis, defended in 1960, was on the sequelae of occlusion of cortical vessels.

In 1962 Gannushkina became head of the laboratory of experimental pathology at the Institute of Neurology and held this position until she died. In 1969 she defended her doktorskaya dissertation (equivalent to a habilitation thesis in German-speaking countries) on changes in brain vessels after impairment of cerebral blood flow and became a professor of pathophysiology in 1972. In 1991 she became a corresponding member of the Soviet (now Russian) Academy of Medical Sciences and a full member in 2004.

Gannushkina described the characteristics of vascular changes and neural damage in different types of collateral blood circulation. She discovered the principles of structural reorganisation of cerebral blood vessels in response to haemodynamic load and rheological changes. These vascular changes might be reversed, which justifies reconstructive neurosurgical interventions such as extra-intracranial anastomoses of middle cerebral arteries.

Gannushkina and her colleagues studied mechanisms of ischaemic cerebral lesions and the difference between arterial and venous ischaemic lesions. She proved the possibility of the adverse effect of sudden recirculation in previously ischaemic brain tissue, which clinically manifests itself as the steal syndrome.

Since 1972 Gannushkina’s laboratory concentrated on the pathogenesis of the damage to cerebral blood vessels and brain tissue in arterial hypertension. This research revealed vulnerable parts of cerebral blood vessels, especially in occipital lobes, explaining the clinical symptoms of a hypertension crisis such as occipital headaches and visual impairments. This new concept of impaired autoregulation at the upper border of cerebral blood flow justified new principles of treatment of hypertension crises aimed at diminishing brain oedema.

In 1949 an English chemist, B A Toms, discovered that dissolving small quantities of heavy long chain molecules (polymers) in solution reduced drag during turbulent flow through a tube by up to 70%. The so-called Toms effect has been successfully applied in the oil industry. Gannushkina and her colleagues injected small doses of polymers in atherosclerotic vessels in experimental animals and observed an increase in diameter of cerebral vessels and normalisation of cerebral blood flow that lasted for a week. Long chains of DNA with molecular weight comparable to Toms’ polymers were discovered in the plasma of healthy volunteers. However, in patients with ischaemic stroke DNA concentration was much higher and DNA itself was represented mostly by short fragments (including oligonucleosomes). Such DNA “stumps” increased blood viscosity and contributed to thrombosis.

Gannushkina was better known abroad than in her home country. She participated in joint research projects and lectured in Poland, Germany, and Sweden. She was a member of the Soviet National committee of IBRO (International Brain Research Organisation) and had been a deputy chairman of the section on brain pathology at IBRO since 1979. In 1991 she was elected a fellow of the Royal Society of Medicine.

Irina Gannushkina had an open minded and kind personality. But as a head of the laboratory she was tough and demanding. Gannushkina preferred to teach others by her own example. She was a skilful operator and for many decades did animal experiments herself. She was a fighter by character. She leaves her husband, Leonard Leonidovich Kapuller, and a daughter.

Boleslav Lichterman, Irina Konorova
Irina Victorovna Gannushkina, professor of pathophysiology Moscow, and head of laboratory for experimental neurology, Institute of Neurology (b 1929, d Moscow 1953; MD), died from arterial embolism on 5 February 2007.
Abdul Razzak Jasim Al-Sheikhli

Former consultant ear, nose, and throat surgeon Croydon (b 1936; q Baghdad 1961; FRCS Ed, FRCS Eng), died from acute myeloid leukaemia on 4 February 2007.

After national service, Abdul Razzak Al-Sheikhli worked in Baghdad until 1966, when he was awarded a scholarship from the Iraqi Ministry of Health to study for his fellowship at the Royal College of Surgeons in London. After posts in general and thoracic surgery in Ipswich, South Mimms, and Southampton, he returned to Iraq in 1970 to work as a consultant in general and thoracic surgery in Baghdad. He relocated to the United Kingdom in 1973 and worked in Farnborough, Ipswich, London, and Aberdeen. In 1981 he moved to Croydon to work as a consultant ear, nose, and throat surgeon, a position he held until retiring in 2001. He leaves a wife, Sheila; two sons; and one grandson.

Stephen Al-Sheikhli

Joseph Maxime Gerald Midol Brookes

Former consultant obstetrician and gynaecologist Warrnambool Base Hospital, Victoria, Australia, and BMH Hanover, Germany (b 1930; q Cambridge/St Mary’s Hospital BMH Hanover, Germany (b 1930; q Cambridge/St Mary's Hospital, Victoria, Australia, and Aberdeen. In 1981 he moved to Croydon to work as a consultant ear, nose, and throat surgeon, a position he held until retiring in 2001. He leaves a wife, Sheila; two sons; and one grandson.

Stephan Al-Sheikhli

Peter Gordon Harries

Former consultant in preventive and industrial medicine Royal Navy (b 1930; q The London 1955; MD, FRCP, FFOM), died from metastatic prostate cancer on 26 September 2006.

Peter Harries, president, honorary secretary, and honorary member of the Society of Occupational Medicine and Dentistry (b 1939; q The London 1961; MD, FRCP, FFOM), died from metastatic prostate cancer on 26 September 2006.

Joe Brookes was a talented hooker before sustaining a back injury during a scrum collapse, which brought his student rugby career to a premature end. After house jobs he joined his father’s general practice in Leeds (1957-9). He then trained in obstetrics and gynaecology and took up a consultant post in 1963 at Warrnambool Base Hospital in Victoria, Australia, where he worked, for many years in a single-handed practice, until 1985. Joe returned to England in 1985, working in Huntingdon before working for the army in Hanover and Rinteln until he retired to Cambridgeshire in 1996. He leaves three children from his first marriage and a daughter from his second.

R Gibbons

Thomas Henry Flewett

Former director Birmingham Regional Virus Laboratory (b 1922; q Belfast 1946; MD, FRCPath, FRCP), d 12 December 2006.

Tom Flewett was the first to name one of the most common causes of diarrhoeal diseases, rotaviruses, during the course of his seminal research into the causes of gastroenteritis. He also identified two new species of adenoviruses, as well as confirming the presence of caliciviruses, astroviruses, and faecal coronaviruses. His work on rotaviruses brought him international fame both as a virologist and an electron microscopist. He was a WHO consultant in many countries where childhood diarrhoea was a major problem. His laboratory in Birmingham was a WHO Reference and Research Centre for Rotavirus Infections from 1980 until his retirement in 1987. A founder member of the Royal College of Pathologists, Tom showed what could be done by dedication, underpinned by sound technical knowledge, and made it fun. His other great love was golf. Predeceased by his wife, June, he leaves two daughters.

Dick Madeley

Alasdair Geddes

George James Miller

Professor of epidemiology Barts and The London, Queen Mary’s School of Medicine and Dentistry (b 1939; q Manchester 1963; MD, FRCP), died from colon cancer on 14 August 2006.

George Miller was primarily an epidemiologist interested in cardiovascular disease. In 1975 with his brother, Norman, he wrote what became the most cited paper ever published in the Lancet: that high density lipoproteins protect arteries against the development of atherosclerosis.

Later, George elegantly developed the first Northwick Park heart study investigating the associations between clotting factors and the risk of heart attacks. However, he was also interested in how the fabric of British society was shaped by land ownership, arguing in Dying for Justice that about 50,000 people in England and Wales alone die prematurely each year from causes attributable to government’s unjust forms of taxation. George was married three times and had five children.

Tom Meade

Norman Miller

Peter MacCallum

Saiyid Zafar Husain Zaidi

Former consultant paediatrician King George, Oldchurch, and Harold Wood Hospitals, Ilford and Romford (b 1933; q King George’s Medical College, Lucknow, 1955; FRCPed, FRCPCH, DCH), d 31 May 2006.

Zafar Zaidi did his paediatric residency in Ottawa and Toronto, Canada. In London he trained at Great Ormond Street and the North Middlesex Hospitals. In 1967 he was appointed to found the department of paediatrics, Aligarh Muslim University, India, becoming departmental head and professor of paediatrics. In 1972 he was appointed consultant paediatrician to King George, Oldchurch and Barking Hospitals, also working at Ilford Maternity and Rush Green and retiring in 2003. President of the Ilford Medical Society and an enthusiastic trainer, Zafar founded the paediatric department of Al Ain University (United Arab Emirates) during a year’s sabbatical. He leaves a wife; three children; and a grandchild.

Makki H Hameed
Spraying fibrin into the operation site during total knee replacement is no better at reducing postoperative blood loss than giving a dose of intravenous tranexamic acid, according to a direct, placebo controlled comparison (Journal of Bone and Joint Surgery (Br) 2007;89-B:306-9). Both agents significantly reduced blood loss compared with giving nothing.

Wanted: ground breaking, accessible initiatives to be nominated for the 2007 Integrated Health Awards. Any organisation can apply if it takes an integrated health approach to help people achieve the best possible health and wellbeing. Integrated health emphasises prevention and education and takes a more holistic approach than conventional medicine, which, according to the Prince’s Foundation for Integrated Health, is offering the award, “tends to view the body as a machine made up of components that sometimes break down.” See [www.fih.org.uk](http://www.fih.org.uk).

Although Jehovah’s Witnesses usually refuse whole blood products, they can accept other components of blood. It all depends on the definition of “blood.” In 2000 and 2004 the official doctrine of the religion defined the “primary components” of blood as red blood cells, white blood cells, platelets, and plasma. But whether to accept fractionations of these primary components is up to individual believers. Immunoglobulins, albumin, and purified factors VIII and IX are all available to followers whose “conscience would permit” (Anesthesia and Analgesia 2007;104:753-4).

Overall dietary patterns are now thought to be a better predictor of colorectal adenomas and cancers than specific dietary components. Cluster analysis shows that people with high vegetable and moderate meat intake were at significantly greater odds of developing an adenoma compared with people with high fruit and low meat intake (Journal of Nutrition 2007;137:999-1004). This dietary pattern seems more protective than diets containing more vegetables and meat.

A meta-analysis of the effects of soft drink consumption on nutrition and health found that studies funded by the food industry reported significantly smaller negative effects than studies not funded by the industry (American Journal of Public Health 2007;97:667-75). Overall, soft drinks are strongly associated with greater energy intake and body weight and lower intake of milk, calcium, and other nutrients as well as greater risk of medical disorders such as diabetes.

When a patient’s name is spoken by a familiar voice even some patients in a persistent vegetative state produce a cerebral response, detectable by functional magnetic resonance imaging. Researchers describe seven cases of persistent vegetative state and four cases with minimally conscious states (Neurology 2007;68:895-9). Five of the patients with presumed persistent vegetative state had a cerebral response, and the two that showed the most widespread activation went on to improve to minimally conscious states within three months. Functional magnetic resonance imaging could be useful to distinguish between the two states.

Is there nothing statins can’t do? A meta-analysis of randomised controlled trials claims that statins lower blood pressure to a small but statistically significant and clinically meaningful degree (Hypertension 2007;49:792-8). The response was unrelated to age, serum cholesterol changes, or length of trial, but the effects were greater the higher the baseline blood pressure.

Canadian researchers have found a link between being diagnosed with ovarian cancer and not regularly visiting a doctor. Using case—control methods they found a greater risk of ovarian cancer among women who during the five year study period did not have a medical visit or pelvic examination or who had no regular healthcare provider (CMAJ 2007;176:941-7). Postmenopausal women were at higher risk. There’s no obvious explanation.

Weekends are good for lots of things—but not for having strokes. Statistics from the hospital morbidity database in Canada show that patients with stroke who are admitted at weekends have a higher risk adjusted mortality than patients admitted on weekdays (Stroke 2007;38:1211-15). Rural and urban settings had similar patterns, and it made no difference whether the most responsible doctor was a general practitioner or a specialist.

Apart from being a smoker and having to take drugs twice or fewer times a day, the most important independent predictor of non-adherence to repeat prescriptions for heart failure drugs was a positive response to the question “have you changed your daily routine to accommodate your heart failure medication schedule?” (British Journal of Clinical Pharmacology 2007;63:488-93). Having a highly structured daily routine was a strong predictor of adherence.