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Otto Fleming
R G Grainger

Michael Edward Glanvill
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E M Armstrong

John Spencer Jones
Nick Spencer Jones, Chris Spencer Jones
Andrew Herd Muir
Adrian Tully

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Minerva
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Fillers
Making a difference: now it's your turn

Career focus
Read this week's articles on
Website extra
BMA chairman resigns
Remedy UK loses court case
A new diagnosis of cancer is rare in primary care, and the role of general practitioners (GPs) in diagnosing cancer can be challenging. In the United Kingdom, a GP with a list size of 1500 will on average see only 1.39 cases of lung cancer, 0.23 oesophageal cancers, 0.99 colorectal cancers, and 0.45 renal or bladder cancers each year.\(^1\) We seek to diagnose the few patients with cancer out of the many who are concerned about it or who have non-specific problems. In this week’s BMJ, a cohort study by Jones and colleagues assesses the association between alarm symptoms and a subsequent diagnosis of cancer in just under 800,000 patients in primary care.\(^2\)

Diagnostic errors are one of the leading causes of medicolegal claims against GPs,\(^3\) and they can damage the faith of our patients. However, GPs have a role as gatekeepers of health resources and more recently the added responsibility of managing a budget. Over-referral to secondary care can unnecessarily raise patients’ anxiety while awaiting investigation and waste precious resources.

What are we to make of alarm symptoms? Are certain symptoms or signs so suggestive of cancer that no further consideration is needed apart from how to write the urgent referral letter? On the face of it, the high positive likelihood ratios for cancer reported by Jones and colleagues,\(^4\) which range from 75 for rectal bleeding to around 300 for dysphagia, might suggest this. Put simply, the presence of dysphagia makes it 300 times more likely that a patient has cancer. But strangely, even this is not enough for the GP to refer because most patients with such symptoms will not have cancer. The positive predictive value (PPV) of dysphagia for cancer is only 2% in women and 5% in men; that is, more than 95% will not have cancer.

Further difficulties arise when we analyse what doctors mean when they code symptoms. Current guidelines from the National Institute for Health and Clinical Excellence (NICE)\(^4\) define dysphagia as interference with the swallowing mechanism that occurs within five seconds of having started swallowing. It advises urgent referral of dyspeptic patients with dysphagia who have “suspected cancer.” But dysphagia has been reported as a symptom in 37% of patients with erosive oesophagitis, and this resolves in most patients (83%) after treatment with a proton pump inhibitor.\(^5\)

The recent Montreal definition and classification of gastro-oesophageal reflux disease highlights this problem.\(^6\) It defines “troublesome dysphagia” as dysphagia that causes patients to alter their eating patterns or have symptoms of solid food getting impacted. Dysphagia is troublesome only in a minority of patients with gastro-oesophageal reflux disease. The Montreal classification suggests that troublesome and worsening dysphagia, especially for solids, is an alarm symptom and should be investigated. Jones and colleagues found that the PPV of dysphagia for cancer was only 0.16–0.21% if patients were less than 45 years old. GPs have to decide whether to treat young patients at lower risk who have non-troublesome dysphagia initially with a one month trial of proton pump inhibitors or automatically to refer them all.

While Jones and colleagues found the PPV of haematuria was high for urological cancer (5.5%, for men, 2.5% for women), age and sex have a strong effect—the PPV is only 0.22% for women under 45 years. If a 40 year old woman presents with a first episode of cystitis-like symptoms and haematuria, a urinary tract infection may be the most likely diagnosis, but this should be confirmed by a midstream urine specimen. In a 70 year old man, similar symptoms should be viewed with high suspicion as the PPV for urological cancer is 11.2% in such patients,\(^2\) and this is not altered by the presence or absence of dysuria.\(^7,8\) This supports the NICE guidelines, which suggest urgent referral of adults with painless macroscopic haematuria.\(^9\) Patients with symptoms suggestive of a urinary infection and macroscopic haematuria should be referred urgently if infection is not confirmed by investigation. Patients aged 40 years or more who present with recurrent or persistent urinary tract infection associated with haematuria should also be referred urgently, as urological cancer can present in this way.\(^10\)

NICE guidelines suggest haemoptysis should be investigated by chest radiography.\(^4\) If the results are negative, those aged 40 or more should be referred urgently if haemoptysis persists. Secondary care studies suggest 6-21% may have lung cancer when investigated further, and these cancers may be smaller and more curable than those detected on radiography.\(^9\) This is supported by the findings of Jones and colleagues, where the PPV was 4.1-20.4% in patients over 55 but only 0.21-0.36% in those under 45. The PPV for the younger patients in particular may be an overestimate because this is a General Practice Research Database study, which is dependent on GPs correctly coding haemoptysis. GPs may be more likely to do this if they plan to make a referral than if a small amount of blood is mixed with sputum in a young patient with a presumed chest infection.
Rectal bleeding is the most common alarm symptom in primary care identified by Jones and colleagues. It has the lowest PPV overall—only around 2%—which highlights the difficulties GPs face when presented with this symptom. Many patients with rectal bleeding fear they have bowel cancer but do not quite fit the criteria for urgent referral. Hopefully, the national bowel screening programme will improve things for the future.

The take home message is that alarm symptoms need to be considered seriously. The 2005 NICE guidelines on referral for suspected cancer provide a valuable and pragmatic tool that can help GPs make realistic referral decisions. These guidelines are now supported by evidence from primary care. However, the action that a GP takes will depend on their intimate knowledge of the patient and his or her wishes.

The value of administrative databases
Is growing but their contribution to improving quality of care remains unclear

Modern health care involves the routine collection of administrative data primarily for management and accounting purposes. Such databases include some clinical data (such as type of surgery, diagnosis, length of stay) that might be useful in monitoring quality of care. In this week’s BMJ, Aylin and colleagues have used hospital episode statistics (HES) data, which are routinely collected by the UK National Health Service, to develop statistical models for predicting hospital mortality adjusted for case mix in three well defined clinical areas—cardiac surgery, aortic aneurysm repair, and colorectal cancer.

Previous comparisons of administrative databases and clinical databases or medical notes (chart review) have found administrative databases to be lacking in three important ways—scope (the relevant data not available), data quality, and ability to adjust for factors relating to patient case mix. This has led to the credibility of administrative databases being questioned, but as a result of several high profile events, this view of HES data may be changing.

In 2001, Dr Foster used HES data to produce standardised mortality ratios adjusted for case mix using methodology proposed by Jarman and colleagues. The methodology was later adopted by the Institute for Healthcare Improvement in the United States in its drive to reduce hospital mortality. In 2002, the inquiry into the high death rates after paediatric cardiac surgery in Bristol used HES (as well as a clinical database) to show that Bristol was a statistical outlier. The inquiry report stated that HES “was [sic] not recognised as a valuable tool for analysing the performance of hospitals. It is now, belatedly.” Furthermore, the inquiry also remarked that the “dual” system (HES and the clinical database) of collecting data in the health service was “wasteful and anachronistic.” In 2004, Harley and colleagues also used HES data retrospectively to show that Rodney Ledward, the discredited gynaecologist who was the subject of the Ritchie Inquiry, was also a statistical outlier. Also in 2004, the BMJ started publishing Dr Foster case notes, which draw on analyses of HES data undertaken by the Dr Foster Research Unit.

The present study by Aylin and colleagues shows that HES based models to predict hospital mortality, in three well defined conditions, compare favourably with dedicated clinical databases. Although the choice and interpretation of some of the variables (such as year and deprivation) may be questionable, in statistical terms HES based models predict hospital mortality as well as their clinical counterparts. Clinical databases are often more costly; so are they still necessary?

In our view, it would be premature to discard clinical databases, because their purpose is not limited to predicting mortality. They may also measure longer term outcomes, incorporate rapid changes in treatments (administrative databases are constrained by inertia), and include other outcomes (such as quality of life) that are not often found on administrative databases. Furthermore, administrative databases seldom (without linkage) cover mortality adequately. In-hospital mortality is a key outcome only in a few important diseases. Other potentially useful process outcomes such as length of stay are also limited. Crucially, clinical databases are clinically owned vehicles driven to improve quality of care through a peer led educational process, as exemplified by the Department of Veterans Affairs. Currently, HES data are not.

We advocate that where HES based analyses are accurate they should be incorporated into the existing quality improvement framework alongside clinical databases. This would help clinicians to test their usefulness in delivering quality improvement and so develop
trust in the quality of HES data. Only when HES-based analyses are considered fit for purpose, after extensive comparison with clinical databases, would the criticism about “dual” databases be valid.11 Dual databases can be useful, however. For example, hospital death rates adjusted for case mix after surgery for congenital heart disease in the UK identified Oxford Radcliffe Hospital as a high outlier using HES data, but this was explained by incomplete case ascertainment in HES, which recorded 20% fewer cases than the central cardiac audit database.12

Another routinely collected data set—which unlike administrative databases has not been closely scrutinised—that is fit for purpose, clinically meaningful, and has no apparent credibility problems is laboratory data. Prytherch and colleagues13 14 showed that models for predicting hospital mortality produced from laboratory data were as good as the best models reported by Aylin and colleagues. This is even more remarkable as Prytherch and colleagues predicted deaths in general surgery and general medicine and not the specific areas selected by Aylin and colleagues.2 Most modern hospitals now have computerised laboratory databases so further research into the use of these databases is needed.

Ultimately a key purpose of data (and analyses) is to support continual quality improvement. While clinical databases have a track record in delivering improvement, the extent to which administrative databases can be incorporated into clinical quality improvement processes remains, by and large, to be seen.

### Functional foods

The Journal of Nutrition October 2001

Functional foods, also known as “nutraceuticals” or “designer foods” are foods containing supplements that are intended to improve health, and they are slowly emerging on supermarket shelves worldwide. The market is divided into two main categories. Firstly, breakfast cereals fortified with fibre and sometimes vitamins and, secondly, dairy or yoghurt drinks and yoghurts with probiotic bacteria. Manufacturers of foods, soft drinks, and drugs have invested heavily in this sector to create a market that aims to cover 5% of the value of food sales worldwide.1 By 2005, global sales were an estimated $73.5bn (£36.9bn; €54.3bn) and, although slowing, still on target to reach $167bn after 2010.2 In this week's BMJ, de Jong and colleagues3 discuss various aspects of functional foods—their effectiveness, long term safety and marketing.

There are two broad positions on functional foods. Proponents argue that they are a consumer friendly way to improve diets and fulfil the aim of nutrition as a source of preventing ill health. They see them in the forefront of “personalised medicine” and health through consumer choice. Sceptics argue that the market for functional foods is corporate and driven by the need to diversify and create niche sectors in saturated food markets. They also argue that functional foods are affordable and appealing only to the “worried well,” or worse, could be an extra burden on poor people’s finances.

Functional foods were developed and first regulated in Japan in the 1980s,4 then spread to North Europe and North America, also affluent consumer markets.5 The expansion was shaped by these regions’ particular consumer cultures and health sensitivities, not least their experience of food scandals.6 7 Consumer organisations have lobbied for controls on health claims, sound verification, and accurate labelling. Companies have concurred, but their main concern has been safety. Twenty years after bovine spongiform encephalopathy, no company wants to risk its reputation or share price on unsafe products.

Regulators and policymakers are right to keep a watchful eye on functional foods. The European Union, the world’s largest single consumer market, introduced a regulation on the use of nutrition and health claims for such foods in December 2000.6 Companies and scientists have worked with relevant regulatory bodies and organisations at different levels of governance from the United Nations to EU to national governments.8 9 10 Now that functional foods are in the market place—

7. Dr Foster. Homepage. www.dfoster.co.uk/.
Multimorbidity’s many challenges

Time to focus on the needs of this vulnerable and growing population

Patients with multiple conditions are the rule rather than the exception in primary care. In a recent study of 21 family practices in the Saguenay region, Quebec, the prevalence of multimorbidity was 69% in 18-44 year olds, 93% in 45-64 year olds, and 98% in those aged over 65, and the number of chronic conditions varied from 2.8 in the youngest to 6.4 in the oldest. Other countries report a similar burden. The number of Americans with multimorbidity is estimated to rise from 60 million in 2000 to 81 million by 2020.4

Having multiple chronic medical conditions is associated with poor outcomes: patients have decreased quality of life, psychological distress, longer hospital stays, more postoperative complications, a higher cost of care, and higher mortality. Multimorbidity also affects processes of care and may result in complex self care needs; challenging organisational problems (accessibility, coordination, consultation time); polypharmacy; increased use of emergency facilities; difficulty in applying guidelines; and fragmented, costly, and ineffective care.

Yet most research and clinical practice is still based on a single disease paradigm which may not be appropriate for patients with complex and overlapping health problems. Classic clinical trials tend to emphasise efficacy at the expense of effectiveness. In doing so, they exclude patients with multiple conditions, thereby compromising the external validity and the relevance of the trials for this population.8

Research on multimorbidity is in its infancy. So far, most research has investigated the epidemiology of multimorbidity, its effect on physical functioning, and its measurement. Much less studied is the effect of multimorbidity on processes of care and what constitutes “best care” for these patients.

Areas for potential investigation of multimorbidity fall primarily into three categories—defining and categorising the population; developing the tools needed to explore multimorbidity and its consequences; and using these tools to investigate promising processes of care.

Who are the patients with several conditions? What is their risk profile? How do we distinguish multimorbidity from related concepts such as complexity, frailty, and polypharmacy? How do we classify multimorbidity and comorbidity in terms of conditions that need disparate versus congruent treatment strategies? For example, how does the patient with coronary disease, hypertension, and diabetes differ from the one with pulmonary disease, arthritis, and depression? In which situations is a subjective or an objective measure of multimorbidity more appropriate?Investigators have begun to look at several of these complex questions, but standards have not yet been developed.10

The results of prevalence studies reveal a complex picture of coexisting diseases. We now require a clear conceptual framework that includes consistent measures of multimorbidity and permits comparisons between studies. This will facilitate the next step—investigating improved processes of care. What are the best processes for making decisions in the context of multiple, often ill defined, problems and fragmentary evidence? How should we assess the shifting priorities of patients and providers, design adaptive responses to unpredictable aspects of the illnesses, and organise multiple resources to achieve specific health goals? What affects processes of care, and what constitutes best care? Which outcomes matter to these patients in which situations? How do we implement whatever best care turns out to be?

Answers to these questions will require continual experimentation, with substantial innovation and reform in healthcare delivery and organisation. Models of collaborative, patient centered, and goal oriented care are more likely to meet the complex needs of patients with multimorbidity. Involving patients in the research process and making good use of mixed methods research designs that incorporate both patient and provider perspectives may also help answer complex clinical questions.

The study of multimorbidity is particularly appropriate for the international research community for several reasons. Research is in its infancy, and appropriate collaboration may minimise redundancy and promote efficient and timely research. Different international communities have varied access to administrative data that can be used to paint broad pictures of caring for people with several conditions. The World Health Organization has given priority during the next decade to worldwide prevention and care of chronic illness. International collaboration specifically among primary care researchers may result in patient centered and low tech care practices that can be translated into practice in varied settings and across different healthcare systems.

As a step towards facilitating this collaboration, we have started a virtual research community to discuss research questions specifically directed towards international communication on multimorbidity. The increasing number of primary care research networks in many countries also offers an ideal setting for collaboration to occur. The time has come not only to include people of all ages with multimorbidity in research efforts, but to focus on improving the care of this vulnerable and growing population.


Thromboprophylaxis for adults in hospital
An intervention that would save many lives is still not being implemented.

The evidence that pharmacological thromboprophylaxis can reduce the rate of venous thromboembolism by 60-65% is compelling. Last month the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) published guidelines on venous thromboembolism in patients having surgical procedures, which are summarised in this week’s BMJ. The risks to surgical patients, particularly those undergoing orthopaedic procedures, are well known, but most people who develop venous thromboembolism in hospital are medical patients.

The prevention of venous thromboembolism in adult patients in hospital was the main challenge to patient safety in 2001, according to a technical assessment by the Agency for Healthcare Research and Quality in the United States. In 2005, the UK government’s Health Select Committee reported that venous thromboembolism caused more than 25 000 potentially preventable deaths a year, and probably half of these deaths resulted from admission to hospital.

Despite all this evidence, mortality due to venous thromboembolism after hospital admission is still at least 10 times greater than the more widely publicised mortality due to methicillin resistant Staphylococcus aureus (MRSA). Overall, the number of deaths from venous thromboembolism in the UK each year is five times greater than the combined total number of deaths from breast cancer, AIDS, and road traffic incidents. Indeed a revised estimate, based on an epidemiological model using extrapolation from European data, suggests that about 60 000 deaths from venous thromboembolism occur annually in the UK. Autopsy data indicate that about 10% of deaths in hospital are due to pulmonary embolism.

1. BMJ 2007;334:1017-8
doi:10.1136/bmj.39210.496505.BE

EDITORIALS
Summary of expert working group’s recommendations on thromboprophylaxis for adults in hospital

Medical patients

Particularly those admitted for longer than four days, who have reduced mobility with either severe heart failure, respiratory failure, inflammatory illness, or cancer: heparin, preferably low molecular weight heparin

High risk surgical or orthopaedic patients

Mechanical prophylaxis and low molecular weight heparin or fondaparinux

Intermediate risk surgical patients

Mechanical prophylaxis and low molecular weight heparin or fondaparinux

Low risk surgical patients

Mechanical prophylaxis and early mobilisation

Despite the considerable evidence base for thromboprophylaxis, it is poorly implemented in the UK. A combination of factors may be responsible—as a result of poor education, health professionals’ lack of awareness of this condition; venous thromboembolism is often a silent disease (80% of deep vein thromboses are subclinical); and venous thromboembolism often occurs after discharge from hospital. Prescribing costs may also be a barrier to the use of thromboprophylactic drugs, but this is not clear.

The Health Select Committee reported two years ago that thromboprophylaxis was not effectively implemented in the UK—as few as 20% of eligible patients were receiving appropriate prevention. The committee recommended that NICE should produce its planned guidelines on venous thromboembolism for surgical procedures more quickly. It also recommended that an independent expert working group be set up to investigate how current best practice and guidance on venous thromboembolism could be promoted and implemented and what resources might be needed to support delivery of any strategy through existing structures. This committee was to report to the chief medical officer in July 2006.

The expert working group’s report and the chief medical officer’s response were published last month. The expert group recommended that, on admission to hospital, all adults should have a risk assessment for venous thromboembolism that is formally documented and incorporated into the hospital’s system for the Clinical Negligence Scheme for Trusts. The group also recommended that the Department of Health should set core standards aimed at ensuring 100% compliance with risk assessment for thromboprophylaxis. Moving on to prevention, the report stated that aspirin should not be used for thromboprophylaxis as it is less effective than other agents, such as low molecular weight heparin. The chief medical officer has brought the report to UK doctors’ attention and has set up another committee to implement the recommendations of the report.

The consultation phase for the NICE guidelines was highly contentious because the draft guidelines emphasised mechanical prophylaxis—using compression stockings and, during surgery, inflatable boots—rather than drugs. Indeed, concerns about the way NICE reached its recommendations partly led to the Health Select Committee’s decision some months ago to review NICE.

The published NICE guidelines review the same evidence as that in the expert working group’s report and, while both agree that aspirin should not be used, NICE has retained the emphasis on mechanical rather than chemical means of thromboprophylaxis. Furthermore, NICE classes patients aged over 60 as being at high risk rather than those aged over 40.

The Health Select Committee’s report two years ago provided an opportunity to change practice. Meanwhile, more than 25 000 people may have died needlessly each year because of the failure to implement simple thromboprophylaxis in UK hospitals.

More advice to clinicians

Concerns over the safety of single use instruments led to a moratorium in Wales on tonsillectomy, which created a cohort of patients who fulfilled the criteria for tonsillectomy but were denied surgery for more than one year.

We think that adults presenting with chronic or recurrent tonsillitis may expect as many as three or more episodes in the forthcoming six months and that these episodes are likely to result in time off work and further visits to the general practitioner. In contrast to the likely effect of intervention by tonsillectomy, we would not be able to give these patients any indication of if, or when, this was likely to change.

No randomised controlled trials have been conducted that support tonsillectomy in adults, but equally there are no studies that support denial of tonsillectomy as an alternative in patients with serious disease. As no test exists to determine if an individual patient will improve with time, “watchful waiting” is used by most clinicians as a diagnostic tool to determine whether surgery should be advised. Waiting is not a treatment in itself, and considerable morbidity may be associated with this option in some patients.

Ideally, a large scale randomised controlled trial with long term follow-up is required to examine the consequences of denying tonsillectomy to patients who previously would have been considered worthy of surgery. However, such a study may fail through lack of patient willingness to remain long enough in the control group. Furthermore, given the levels of morbidity measured in these patients and the large volumes of complaints we received from distressed patients and parents who were denied surgery, such a study may even be considered unethical.

Alun Tomkinson consultant in otolaryngology and head and neck surgery, University Hospital of Wales, Cardiff CF14 4XW Rosemary Fox specialist registrar in public health medicine Mark Temple consultant in public health medicine National Public Health Service for Wales, Cardiff CF10 3NW alun.tomkinson@cardiffandvale.wales.nhs.uk

Competing interests: None declared.


OLDER PEOPLE IN CARE HOMES

Role of primary care

Practical steps taken in primary care can improve the standard of care for older people in care homes.1 Seven years ago I presented an alternative to the reactive (“firefighting”) approach to patients in care homes to my partners. Since then we have taken personal responsibility for a care home each, managing the long term health issues of our patients and building constructive relationships with the staff and management at the six homes (142 patients) we look after.

I have also presented the general practitioners in Peterborough with the arguments in favour of a named general practitioner from a committed practice taking on responsibility for the care of all the patients in a particular care home. Historically in Peterborough, patients have not changed doctor on entering a care home. This has resulted in practices with small numbers of patients in as many as 17 different care homes across the city, and care homes needing to liaise with up to 70 doctors in 17 different practices.

Gillie E Evans general practitioner, Jenner Health Centre, Whittlesey, Cambridgeshire PE7 1EJ gillie.evans@nhs.net

Competing interests: None declared.


How to bring about changes

McMurdo and Witham bring to mind the poor level of care that so many elderly people have to tolerate in residential care.1 We underestimate how stressful it is for nurses and care assistants to provide intimate, personal care non-stop, day in day out, week after week. Unlike junior doctors, they are generally not on an upward career track. Stress may be measured by how strongly it is avoided, and staff turnover is an enormous problem in care of the elderly.
**DIPYRIDAMOLE WITH ASPIRIN**

Combination shows no advantage over aspirin alone

I disagree with Sudlow’s recommendations. The cited ESPRIT study had lots of limitations. Firstly, during the study inclusion criteria changed from a three arm to a two arm design. Secondly, patients and physicians were not blinded to the treatment regimen. The resulting confounder therefore cannot be estimated. Thirdly, possible lifestyle changes, comorbidity, and co-treatment were not under examination.

Adherence in the dipyridamole-aspirin group was much less (2.6-fold) than in the aspirin group. The on-treatment analysis showed only a small benefit for bleeding as aspirin group. The on-treatment analysis group was much less (2.6-fold) than in the under examination.

1 Sudlow C. Give dipyridamole with aspirin instead of aspirin alone to prevent vascular events after ischemic stroke or TIA. BMJ 2007;334:901. (28 April).


4 Tirschwell D. Aspirin plus dipyridamole was more effective than aspirin alone for preventing vascular events after minor cerebral ischemia. ACP Journal Club November/December 2006;145:57.


**8 BLOCKERS**

Misuse of confidence intervals threatens conclusions

The data presented in table 1 of Ong’s review leave considerable uncertainty about whether atenolol is better or worse than other β blockers. The confidence intervals for the results on other β blockers are wide (as fewer patients have been studied), and the test for interaction shows that the relative risk for atenolol, compared with other β blockers, for stroke is 1.05 (95% confidence interval 0.26 to 4.17), for myocardial infarction 1.22 (0.91 to 1.63), and for total mortality 1.21 (0.95 to 1.14). All of these confidence intervals include the possibility of no difference, and for stroke the results are compatible with atenolol being four times better or four times worse than other β blockers. It is very misleading to draw conclusions based on whether significance is achieved with either treatment alone.

Christopher J Cates general practitioner, Manor View Practice, Bushby WO23 2NH chris.cates@nhs.net

Competing interests: None declared.


**DRUG MONEY FOR PATIENT GROUPS**

Cancerbackup responds

Mintzes says that Cancerbackup does not list the possible side effects of trastuzumab or say where its funding comes from—this is not the case. Cancerbackup provides up to date and accurate information about treatment including all possible side effects, both on our website (www.cancerbackup.org.uk) and in our factsheets. We provide a full list on our website and now in our press releases of all funders.

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1 Sudlow C. Give dipyridamole with aspirin instead of aspirin alone to prevent vascular events after ischemic stroke or TIA. BMJ 2007;334:901. (28 April).


4 Tirschwell D. Aspirin plus dipyridamole was more effective than aspirin alone for preventing vascular events after minor cerebral ischemia. ACP Journal Club November/December 2006;145:57.


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We are advised by an independent clinical advisory board. Pharmaceutical companies have no influence on any decision we take. Joanne Rule chief executive, Cancerbackup, London EC2A 3JR {rgarnett@cancerbackup.org.uk

Competing interests: None declared.

1 Mintzes B. Should patient groups accept money from drug companies? No. BMJ 2007;334:935. (5 May.).

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The illusion of invulnerability

Kent claims that patient groups are not naive, value their independence fiercely, and are quite capable of spotting the strings that may be attached to funding. Many doctors have similar overconfident beliefs about invulnerability to being misled by drug companies. This illusion of invulnerability actually increases vulnerability.

In the 1840s doctors did not understand the risk of invisible microbes so were offended by the suggestion they should wash their hands. We are now going through a similar paradigm shift towards understanding the risk of invisible unintended bias from exposure to industry influence techniques. These techniques include manipulation of reciprocal obligation, which can occur without our awareness. Patient groups tend to reciprocate by lobbying governments to pay for overpriced drugs rather than lobbying the companies to reduce their prices. Funding for patient groups could be increased and the alleged problems with government funding reduced by abolishing patents to allow price competition and using the savings to fund research, education, health promotion, and other activities of patients’ groups through competitive grants.

Peter R Mansfield director, Healthy Skepticism Inc 34 Methodist Street, Willunga, SA 5172, Australia peter@healthyskepticism.org

Competing interests: Healthy Skepticism is funded by individual subscriptions and occasional small contracts. In the past 5 years we have provided services for many organisations including universities, Consumers International, Der Acznevideibtvf (Germany), Drugs and Therapeutics Information Service (Australia), Health Action International, National Prescribing Service (Australia) and the Royal Australasian College of Physicians.

1 Kent A. Should patient groups accept money from drug companies? Yes. BMJ 2007;334:934. (5 May).


4 Dana J, Loewenstein G. A social science perspective on gifts to physicians from industry. JAMA 2003;290:252-5.

For the full versions of articles in this section see bmj.com

UK NEWS Government will suspend MTAS for second round of job interviews, p 1027
WORLD NEWS Clinton brokers deal to lower price of antiretrovirals, p 1026
bmj.com Patients’ records should not be put on IT system without explicit consent, MPs told

NHS has not reaped benefits from refinancing of PFI schemes

Michael Day LONDON

An influential group of MPs has claimed that widespread financial incompetence is adding to the cost of the United Kingdom’s controversial private finance initiative (PFI).

The House of Commons Committee of Public Accounts made its new attack on the PFI after it discovered that the government had clawed back £100m (€145m; $200m) less than was predicted from the new private-public profit sharing schemes.

The committee’s chairman, the Conservative MP Edward Leigh, blamed the loss on the failure of Treasury officials to oversee key refinancing arrangements.

In 2003 the Office of Government Commerce, which then had responsibility for PFI policy, told the public accounts committee that it expected the public sector to receive between £175m and £200m from the voluntary sharing arrangements in early PFI deals. Typically, these loans were renegotiated on a more favourable basis once PFI projects had been completed and the risks involved were lower.

However, left to their own devices, officials in local hospitals had been out of their depth negotiating with their counterparts in the private sector, the committee says.

In 2002 ministers introduced changes so that public sector bodies could share in some of the financial gains when big PFI loans were rearranged. Typically, these loans were renegotiated on a more favourable basis once PFI projects had been completed and the risks involved were lower.

However, left to their own devices, officials in local hospitals had been out of their depth negotiating with their counterparts in the private sector, the committee says.

In 2003 the Office of Government Commerce, which then had responsibility for PFI policy, told the public accounts committee that it expected the public sector to receive between £175m and £200m from the voluntary sharing arrangements in early PFI deals. However, up to December 2006 the government had secured the right to gains of only £93m.

“Proceeds gained by the public sector from PFI debt refinancing under the voluntary code for the sharing of gains are currently well short of expectations” said Mr Leigh.

Update on PFI Debt Refinancing and the PFI Equity Market: 25th PAC Report 2006-07 is available at www.parliament.uk

Claims of poor cancer survival are “wrong”

Michael Day LONDON

Senior experts on cancer have defended the UK’s record on survival from cancer against claims that it is among the worst in the Western world.

Michel Coleman, professor of epidemiology at the London School of Hygiene and Tropical Medicine, said that this month’s headline grabbing report by Karolinska Institute researchers claiming that the United Kingdom was languishing near the bottom of the rich countries league table for cancer survival was “statistically crude and incorrect.”

“We don’t accept their results,” Professor Coleman said. “For France they claimed [that] the five year, all cancer survival for women was 71%. If you tell French cancer specialists that they will laugh in your face.”

Mike Richards, the UK government’s clinical director for cancer, noted that some of the Swedish researchers’ statistics on survival, which linked poor outcomes in the UK to low uptake of new drugs, concerned a period when most of the “new drugs” had yet to become available.

He predicted that the latest figures from the European cancer registries study on cancer patients’ survival and care (Eurocare), which are due this autumn, would show major improvements in survival in the UK. “And it’s interesting to think that these figures only take us up to 2002 and that there may have been further improvements since then,” he said.

The comments came as Professor Coleman announced results from his new research, conducted for Cancer Research UK, showing that 10 year survival for all cancers in England and Wales has doubled in the past 30 years.

The figures show that although survival varies widely with different types of cancer, on average a patient with cancer now has a 46% chance of being alive 10 years after diagnosis, whereas 30 years ago the figure was 24%. Overall five year survival is now 50%.

However, Professor Richards agreed with Harpal Kumar, chief executive of Cancer Research UK, that uptake of new drugs was lower in the UK than in other rich countries.

“This is something that we are concerned about,” said Mr Kumar. “We know that the UK has a lower uptake than the rest of Europe.”

(See Observations p 1034.)

More details are at www.cancerresearchuk.org

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<tr>
<th>Type of cancer</th>
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Source: Cancer Research UK
NEWS

Exploring ageing and bereavement

Annabel Ferriman BMJ
This life sized, wire mesh sculpture of a human body is part of an exhibition about loss, ageing, and memories.

The artist, Lucy Campbell-Maguire, is a GP and a hospice doctor in Manchester, who admits to being fascinated with death. Complementing the wire sculptures are large scale colour photos of her parents' skin, which demonstrate the ageing process.

Dr Campbell-Maguire says that the exhibition "poses questions around the themes of how we perceive ageing, and how it is to live with the 'ghosts' of those we have lost."

The exhibition is at the Central Art Gallery, Old Street, Ashton-under-Lyme, until 30 June.

FDA places “black box” warnings on anaemia drugs amid reports of incentives to doctors

Janice Hopkins Tanne NEW YORK
The committee of the US Food and Drug Administration (FDA) that advises on oncology drugs last week recommended new warnings on erythropoiesis stimulating drugs that are given to patients undergoing chemotherapy to counteract anaemia. Patients undergoing dialysis are also often given the drugs.

The committee said that such synthetic erythropoietins (also called epoetins or "epo drugs") were associated with an increased risk of cardiovascular events and possibly of progression of cancer. It unanimously recommended new clinical trials.

The FDA committee’s recommendations came only days after the New York Times published a story on its front page headlined “Doctors reaping millions for use of anemia drugs” (www.nytimes.com, 9 May) and the Wall Street Journal reported how Johnson & Johnson promoted epoetin alfa (www.wsj.com, 10 May “Suit details how J&J pushed sales of Procrit”).

In March the FDA called for a review of two drugs made by Amgen, darbepoetin alfa (Aranesp) and epoetin alfa (Epogen), and of Johnson & Johnson’s epoetin alfa (Procrit) (BMJ 2007;334:495, 10 Mar). Experts had questioned whether US doctors were prescribing the drugs in dosages that were too high (BMJ 2007;334:978-80, 12 May). The review of the drugs was held last week.

The FDA placed “black box” warnings on the drugs in March after a New England Journal of Medicine study reported a higher risk of death, heart attack, stroke, and hospitalisations for heart failure in patients who were not on dialysis but who were being treated to raise their haemoglobin concentrations (www.fda.gov/cder/drug/advisory/RHE.htm).

“Drug companies cannot pay doctors to prescribe pills that patients get from pharmacies. However, the New York Times reported that doctors received rebates from the drug companies and reimbursement from private insurers, with some doctors receiving higher rebates for exclusive use of a company’s drug. A spokesperson for Ortho Biotech, the division of Johnson & Johnson that sells epoetin alfa, said, “None of Ortho Biotech’s promotions are intended to have the effect of relating the prescription of epo drugs to the income of physicians or their practices. We encourage physicians to follow the guidance in the FDA approved label.”

Tackle cancer in Africa now to prevent catastrophe, say health activists

Zosia Kmietowicz LONDON
Unless urgent action is taken to try to control the rising incidence of cancer throughout Africa, many hundreds of thousands of lives will be lost to the disease, doctors and politicians warned last week.

The former UK health secretary Alan Milburn, who chaired a two day conference on cancer in Africa last week, said: “There is a potential catastrophe here, and we have an obligation to stop it. This is as much a priority as HIV and AIDS, tuberculosis, and malaria—there is no ‘either or.’”

The meeting, attended by over 130 leaders in world health and cancer control, resulted in the “London declaration on cancer control in Africa.” The document, which calls for cancer strategies that tackle prevention, early detection, diagnosis, treatment, and palliative care, will be delivered to the World Health Organization this week with a mandate to make cancer in Africa a greater priority.

Cancer accounts for 12.5% of deaths worldwide, a greater proportion than is caused by HIV and AIDS, tuberculosis, and malaria combined. It is expected that by 2020 15 million new cases of cancer will occur every year, one million of them in
New helpline for those who blow whistle on research fraud

Bryan Christie EDINBURGH

A confidential helpline has been established in the United Kingdom to offer advice and guidance to whistleblowers who think they may have uncovered cases of misconduct in medical research.

It will also be a source of expert advice to universities, the NHS, and private companies in helping them respond effectively to allegations of research misconduct.

The helpline, which was set up by the UK Panel for Research Integrity in Health and Biomedical Sciences and will be staffed by the Research Integrity Office, was launched last week at a meeting in Edinburgh.

Michael Farthing, chairman of the panel’s planning group and pro-vice chancellor for medicine at the University of London, said that although cases of research misconduct are uncommon, they can have huge consequences in human and financial terms. He described the helpline as “an attempt to bring a bit more transparency to how we deal with research misconduct in the UK.”

He added, “We want to open up the debate, and this is another way of helping [us] do that.”

Professor Farthing said that nearly all of the major cases of research misconduct have been exposed by whistleblowers but that often such people did not know where to turn to for help. “Many of us who have been involved in this area have had quite a lot of personal experience of people who have phoned us in desperation because they have experienced frustration in their own institution. Having a third party involved—even in an advisory capacity—can unlock the situation.”

The helpline is intended to provide that sort of support. It will offer guidance in the first instance and can refer callers, if necessary, to an adviser chosen from a register of experts with wide experience of handling cases of misconduct.

Professor Farthing said it is difficult to predict how much use will be made of the helpline. “It may be 20-30 calls a year, but it could be considerably less. It is difficult to know how many people out there have concerns, but I would not expect [the number] to be enormous.”

All calls will be answered in the first instance by Andy Stainthorpe, the project’s director and head of the Research Integrity Office. He said, “The telephone line is a quick and straightforward way of putting people in touch with the experts and will of course be totally confidential.”

The helpline’s number is 0844 7700644 and is open 8 am to 8 pm, Monday to Friday.

DISTRIBUTION OF NEW CASES OF CANCER WORLDWIDE IN 2000 VERSUS SALES OF ANTICANCER DRUGS

Source: Franco Cavalli (International Union Against Cancer)

Israeli surgeons put their names on study they had not done

Judy Siegel-Itzkovich JERUSALEM

The Israel Medical Association says that in future it will take action against academic fraud by investigating complaints and discouraging the relatively widespread phenomenon of “gift authorship,” in which the names of doctors not involved in research are included in the list of authors.

Its announcement comes after a recent case where a surgeon, who was presenting details of a study to a conference, claimed that six doctors had been involved in the research when in fact he had been the sole researcher. Moreover, the surgeon claimed that it was a prospective study and that informed consent had been obtained from the participants, whereas actually it had been conducted retrospectively and without informed consent.

Oleg Avrutis, a surgeon at the Bikur Holim Hospital, Jerusalem, was found by Shimon Glick, the public complaints officer at the Israeli Ministry of Health, to have falsely claimed that he and five others conducted a randomised prospective trial on nearly 1000 patients between 1992 and 1996.

The aim of the study, claimed the authors, was to compare two methods of inguinal hernia surgery: the laparoscopic approach and the Lichtenstein technique. The authors concluded that laparoscopy was superior.

The study, written by Dr Avrutis, was presented as an abstract at a conference of the European Society for Endoscopic Surgery in Barcelona in 2004.
Let fingerprints help the healing

Lynn Eaton

The soothing power of art was the theme of this year’s “Heal” exhibition at the Naughton Gallery in Belfast. The annual competition, sponsored by Queen’s University School of Nursing and Midwifery, invites artists to submit work that will enhance the physical and mental wellbeing of patients who might be feeling anxious, uncomfortable, and isolated. The settings for the final works were a paediatric ward, a ward for elderly patients, a maternity ward, a communal area in a hospice, and an accident and emergency waiting room.

“Even as far back as 1860, Florence Nightingale realised that patients’ recovery was positively affected by form, colour, and light, noticing an actual physical effect and an increase in their progress,” said Jean Orr, head of the School of Nursing and Midwifery at Queen’s.

The exhibition features nearly 30 works from artists across the north and south of Ireland and covers a variety of themes, from the healing power of the chrysanthemum through to the idea that laughter is the best medicine. Shown here is part of Fingerprint Studies no.1 by Eoin Mac Lochlainn, one of three prize winners awarded £2000. “Heal” continues until 16 June 2007. For details visit naughtongallery.org.

Zosia Kmiotowicz

On paper the idea of practice based commissioning, a major plank of the government’s modernisation programme for the NHS in England, seems to be a remarkably simple proposal, with few risks and potentially many gains.

The theory is that if general practices are given control of their own budgets for commissioning secondary care and community health services, the number of referrals to hospitals will fall, cutting hospitals’ running costs along the way. With greater autonomy, GPs will also gain the freedom to exercise their entrepreneurial and clinical skills for the good of their patients by developing community services according to local needs.

And by providing expert care closer to patients’ homes through “super clinics” in the community, GPs get to keep patients within their sights, delivering true follow-up of care and reaping professional fulfilment.

So what could possibly go so wrong? Why did Hamish Meldrum, chairman of the BMA’s General Practitioners Committee, last week declare the scheme a “shambles”?

The Department of Health launched practice based commissioning in 2004 as part of the NHS improvement plan to “put people at the heart of public services,” and GPs were able to take part from April 2005.

Government figures show that 96% of general practices have received the first part of the directed enhanced service (DES) payments for signing up to the principle of practice based commissioning (BMJ 2007;334:922, 5 May). And all primary care trusts are “providing practices with indicative budgets” to GPs holding

for delays in getting projects off the ground. Of 800 GPs and practice managers he recently questioned at meetings where he spoke about commissioning, Dr Kingsland said that less than a fifth indicated by show of hand that they had received the full DES payment.

Half of the payment of £1.90 (€2.80; $3.80) per patient is paid up front, to allow GPs to start planning to buy in services. The second half of the payment is released when practices meet the objectives outlined in their plans.

Although Dr Kingsland admits that his evidence is “soft,” his findings among practice staff who are at the “cutting edge”—committed to practice based commissioning and already engaged in it—fall far short of the uptake rate being touted by the Department of Health.

Maggie Marum, a management consultant at the National Association of Primary Care, said, “There is also almost universal resistance across the NHS to GPs holding indicative budgets. Most practices have not received any data in 2006-7 on which to base commissioning and service design decisions.”

Dr Kingsland said that his own practice has been genuinely frustrated by what should have been a simple project for the trust to approve. The project, to take over the phlebotomy service from the local hospital, was held up at the primary care trust’s committee stage 12 months after it was first conceived.

“We had planned to redeploy any profits from running the phlebotomy service into paying for a clinical psychologist. But now she [the clinical psychologist] has been employed elsewhere, and we have lost all our momentum and enthusiasm,” said Dr Kingsland.

Brian Palmer, chairman of Essex Local Medical Committee, said that primary care trusts’ financial difficulties and their short and turbulent history have led to nervousness within them.

“PCPs have only been in existence for six months, and they are now being told that they have to share their power. It would take a phenomenally strong management to be able to do that,” he said.

Stewart Drage, of the London-wide local medical committees, struggles to name two trusts out of 24 on his patch with successful commissioning projects.

“There is no incentive for primary care trusts to do it [hand over commissioning to general practices], because it is a reduction in their role if they hand over control to practices. Trusts are in deficit, and there is a large amount of distrust between GPs and managers, with little signs that they [at the trust] are going to build a protected resource for commissioning,” Dr Drage said.

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“There is almost universal resistance . . . to GPs holding indicative budgets”

Hamish Meldrum called commissioning “a shambles”
Direct to consumer advertising should not come to Europe

Ray Moynihan BYRON BAY, NEW SOUTH WALES
An international alliance of consumer and other groups has attacked the European Commission, accusing it of supporting the drug industry’s push for direct to consumer advertising in Europe.

US-style advertising of prescription drugs aimed directly at consumers is currently prohibited in Europe, and attempts to overturn the ban were firmly rejected by the European parliament in 2002 (BMJ 2002;325:990).

However, the drug industry and elements within the European Commission are pushing to change the rules so that drug companies can provide more information to patients across Europe, a move that critics argue is an underhand way of introducing advertising.

Taking a position in support of loosening the rules, a European Commission draft report that is currently out for public discussion states, “The focus should be on the availability and quality of information, and not its source,” and it says that “the pharmaceutical industry has the potential to be an important source of information,” as long as the information is reliable, objective, and non-promotional.

In a strongly worded letter sent to two commissioners early this month, the alliance, which is made up of three organisations, the International Society of Drug Bulletins, Health Action International, and Medicines in Europe Forum, claims that drug companies are “utterly incapable of providing the reliable comparative information needed by patients.”

The letter argues that patients and citizens should be protected “from the influence of advertising masquerading as ‘information.’”

A Health Action International spokeswoman, Barbara Mintzes, said it makes no sense to look to companies for objective information, because they have responsibilities to shareholders to maximise sales. “They can’t be expected to provide non-promotional information to help people make treatment choices,” she said. Ms Mintzes recently wrote an article in the BMJ saying that patients’ groups should not take funding from the drug industry (BMJ 2007;334:935, 5 May).

The European Federation of Pharmaceutical Industry Associations has hit back at the critics and claims that it does not want aggressive US-style direct to consumer advertising in Europe but simply more free information to patients.

Drugs advertisements are common in US magazines

Drug advertisements are common in US magazines

MRC says it will invent, develop, and market its own drugs

Michael Day LONDON
The UK Medical Research Council (MRC) will step up its clinical research activities, after indicating that it expects a generous share of the increase in the research budget announced by the Treasury in March.

The chief executive of the council, Colin Blakemore, said that government funded clinical trials were imminent, thanks to the increased funding.

This year’s comprehensive spending review by the government announced an above inflation rise of 2.7% a year until 2011 in the budget for the research councils. Exactly how much the MRC receives will not be announced until the autumn.

However, when asked if the MRC was expecting a generous proportion of the increase, the MRC’s chairman, John Chisholm, said, grinning: “I would have to say that biomedical research has done very well, and I don’t think there’s anything for us to worry about.”

Professor Blakemore said the extra cash would be used to expand clinical and translational research, which links laboratory work to clinical studies.

His comments follow the launch in March of the MRC’s six new translational medicine centres, which are based at the University of Bristol, the University of Cambridge, King’s College London, Imperial College London, University College London (together with the University of Newcastle), and the University of Oxford (in partnership with the Wellcome Trust Sanger Institute) (BMJ 2007;334:493, 10 Mar).

At the time of the launch he said that the new centres would form part of the MRC’s efforts to slash the time taken for its research to translate into better care at the bedside.

Professor Blakemore said that the MRC planned to invent, develop, and market its own drugs, with or without the support of the industry, so as to speed advances against rare diseases or those that are prevalent in poor countries.

To this end, at last week’s strategy briefing he announced that a groundbreaking phase II drug trial, funded jointly by the MRC and the Department of Health, was imminent.

To reduce the potentially huge costs of such a study, he said that patients would be carefully selected so that fewer were needed.

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IN BRIEF

Violence in Iraq is blamed for rise in drug abuse among children: Drug abuse among children and young people in Iraq has risen by 20% this year, a survey by local non-governmental organisations shows. Psychological effects of violence and the easy availability of narcotics are blamed for the increase.

Rare type of cholera is seen in warmer river waters: Dutch doctors are warning of possible further cases of infection with a non-epidemic type of the cholera bacterium Vibrio cholerae after a man in the Netherlands became infected after scrubbing eels caught in the IJsselmeer. Doctors believe that warmer surface water, possibly caused by global warming, is able to sustain the bacteria.

New project will test IT interventions to improve safety: The UK National Institute for Health and Clinical Excellence and the National Patient Safety Agency are collaborating on a pilot project to assess the clinical and cost effectiveness of systems based and computer based interventions to record patients’ current drug treatments and also to prevent ventilator associated pneumonia. (See www.nice.org.uk.)

US age rating of films will take smoking on screen into account: The Motion Picture Association of America has said that “depictions of smoking in movies will now be a factor when deciding what a film’s rating will be.” The ruling means that new movies in the US that contain smoking may be rated R (people aged under 17 will need to be accompanied by an adult) rather than PG-13 (parents are strongly cautioned that some material may be inappropriate for children aged under 13).

Rules on promoting baby milk are still being flouted: Almost 1.4 million children are still dying every year because they are not getting enough breast milk, says Save the Children. Twenty five years after a code was introduced to restrict the promotion of substitute milk and food products, all manufacturers continue to violate it in some way, the charity said.

Being treated unfairly increases risk of heart disease: People who feel they have been treated unfairly and who feel they have suffered injustice are at greater risk of heart disease than people who are content with how they have been treated, shows a study of 8000 civil servants who were followed up for 11 years, published in the Journal of Epidemiology and Community Health (2007;61:513-8).

Girl carrying anencephalic fetus is granted right to travel

Clare Dyer (BMJ)

A pregnant 17 year old in state care in Ireland won the right last week to travel to the United Kingdom to abort the anencephalic fetus she is carrying. The case at the High Court in Dublin has reopened a highly charged debate over abortion in Ireland, where the constitution protects the right to life of the unborn child and terminations are illegal unless there is a real and substantial risk to the life of the mother.

The Irish Health Service Executive (HSE), which has care of the teenager under an interim care order after an incident involving her mother, had written to the Passport Office pointing out that it had not consented to the issuing of a passport for her. Officials had also asked the police to stop her leaving the country, but the police wrote back saying they had no power to intervene.

After a fraught legal battle that continued in court through the May bank holiday weekend, a High Court judge ruled that the teenager, known only as Miss D, was free to travel outside the country for an abortion if she wished. Mr Justice Liam McKechnie criticised the HSE—which by the end of the hearings had done an about-face and supported Miss D’s right to travel—for ignoring her welfare and personal autonomy.

“It was strikingly daring of the HSE to use the executive to restrain, if necessary through force or incarceration, the intended travel of the applicant,” he said.

Miss D, who was 19 weeks pregnant by the time of the judgment, was supported by her mother and boyfriend in deciding to seek a termination

Clinton brokers deal to lower price of antiretrovirals

Seye Abimbola (BMJ)

The former US president Bill Clinton has brokered a deal to provide cheaper antiretroviral drugs for people with HIV in developing countries. The agreement was reached between the William J Clinton Foundation, a charity set up to foster health security and economic empowerment worldwide, and two Indian manufacturers of generic drugs, Cipla and Matrix.

The reduced prices will be available in 66 developing countries in Africa, Asia, Latin America, and the Caribbean. “Seven million people in the developing world are in need of treatment for HIV/AIDS,” said Mr Clinton. “We are trying to meet that need with the best medicine available today and at prices that low and middle income countries can afford.”

Under the deal, the first line combination of tenofovir, lamivudine, and efavirenz, taken as a single daily dose, will cost $340 (£170; €250) per patient each year. This is a reduction of 45% in low income countries and 67% in many middle income countries.

The deal was made possible by funding from UNITAID, an international drug purchasing organisation. Established in 2006 by France, Brazil, Chile, Norway, and the United Kingdom, UNITAID raises funds from a levy on airline ticket sales to support health care in developing countries. It will provide the Clinton Foundation’s HIV and AIDS initiative with more than $100m to buy second line drugs for 27 countries throughout 2008.

Philippe Douste-Blazy, the French foreign minister and chairman of the UNITAID board, said, “Every person living with HIV deserves access to the most effective medicines, and UNITAID aims to ensure that these are affordable for all developing countries.”

About 750 000 people worldwide are currently receiving drugs to treat AIDS through the Clinton Foundation.
Government will suspend MTAS for second round of job interviews for training posts

**Lynn Eaton** LONDON

In an 11th hour development, a day before a High Court hearing was due to take place on Wednesday, England’s health secretary, Patricia Hewitt, announced plans to scrap the flawed medical training application service (MTAS).

But although this has been heralded by some observers as a decision to abandon MTAS—the system for handling junior doctors’ applications for training posts—it is clear that the first round of interviews set up through the service and that have already taken place or are due to take place will still be valid.

Ms Hewitt merely announced that, rather than trying to continue with MTAS, local deaneries would notify junior doctors of the outcome of the round one interviews and that selection for the second round would be done by local deaneries, not through MTAS.

“It’s old news,” said Matt Jameson-Evans of Remedy UK, the doctors’ group that is bringing the legal action against the Department of Health. “We knew round two was going to be done by local deaneries.”

Nearly all the posts would be filled on the first round, he said, which is where Remedy UK claims that the health department has abused its power. Dr Jameson-Evans said that the department’s announcement will not affect Remedy UK’s case, which was due to be heard on Wednesday, after the *BMJ* went to press.

In her written statement to the House of Commons Ms Hewitt outlined her concerns at the security breaches that had occurred with the MTAS website and said that these would be reported to the police.

“Given the continuing concerns of junior doctors about MTAS, the system will not be used for matching candidates to training posts but will continue to be used for national monitoring,” she said.

She went on to explain that, subject to the outcome of the current judicial review, the first offers for specialty posts in hospitals in England would be made on or after 21 May 2007.

**Patricia Hewitt:** “The system will not be used for matching candidates to training posts but will continue to be used for monitoring”

Remedy UK is bringing its court action because of the problems associated with the discredited medical training application service (MTAS) (*BMJ* 2007;334:974, 12 May).

Under the system, applicants were told that they would all have one interview for each job, but only one.

The judge could order the health department, if it loses the case, to scrap its current plans to push ahead with specialist training appointments from 1 August. Instead it would have to appoint doctors to these posts on a temporary basis only, for a year, and a fairer appointment procedure would then have to be set up for next year.

Remedy UK has instructed Leigh Day and Co, a firm of lawyers that is well known for taking on controversial human rights and medical negligence cases, to fight the case. “MTAS has been a comprehensive failure,” the lawyers state in their submission to court.
Drug eluting stents are widely used “off label”

Drug eluting stents may be a breakthrough technology, but clinicians’ enthusiasm for them has already outstripped the supporting evidence, says an editorial. These products were licensed quickly on the basis of randomised trials in selected low risk patients. But it’s now clear that many people being fitted with drug eluting stents have a higher risk profile than those in early trials, usually because they are sicker or have more complex pathology.

So called “off label” use is widespread. About half the patients in two recent database studies were given their stents in circumstances outside the original regulatory specifications (pp 1992-2000, pp 2001-9). Perhaps unsurprisingly, they had higher rates of early and late complications, including heart attacks and deaths. Off label use was also associated with stent thrombosis in one study (events at one year, 1.6% of off label patients vs 0.9% of on label patients; adjusted hazard ratio 2.29; 95% CI 1.02 to 5.16).

The editorial says doctors should be aware that they are using these stents beyond the supporting evidence and should guard against the “hope and hype of a product based on limited approval data.” They should also campaign for more systematic postmarketing surveillance in the US. The current system relies heavily on isolated registries using different data standards. The registries are often paid for by manufacturers of drugs or devices.

Aspirin works best in small doses

Aspirin is the most commonly used drug in the world. In the United States alone, one third of the adult population—some 50 million people—take an aspirin a day to protect themselves from strokes and heart attacks and to help prevent a cardiovascular death. Most people take no more than 325 mg, and some considerably less. But doses up to 1300 mg a day are approved by the US regulatory authorities. What is the best dose for most people?

A systematic review concludes that patients taking aspirin long term do best on doses of 75-81 mg a day. Higher doses don’t work better but do increase the risk of side effects, especially gastrointestinal bleeding. The authors estimate that if all American patients took 325 mg a day there would be 900 000 more major bleeds each year than if their daily dose was 81 mg. Buffered or enteric coated aspirins seem no safer than traditional pills.

The authors took a close look at eight randomised trials and three observational studies comparing different doses in patients with established cardiovascular disease. The trials included nearly 10 000 people taking 30-1300 mg a day. None reported better outcomes for patients taking higher doses.

HPV vaccine highly effective in uninfected young women

Merck’s new quadrivalent vaccine against human papillomavirus (HPV) was highly effective against precancerous cervical lesions and anogenital warts in two recent trials. In young women not infected with the vaccine serotypes, vaccine efficacy was 90-100% in both trials over three years. However, the vaccine was much less effective in unselected women, some of whom were already infected or had HPV related disease.

The vaccine targets serotypes 6, 11, 16, and 18. Types 6 and 11 cause anogenital warts and some low grade neoplastic lesions. Types 16 and 18 cause most cervical cancers worldwide.

The trials have reignited the debate about who should be vaccinated and when (pp 1990-1, pp 1991-3). HPV vaccines are most needed in the developing world, where 80% of deaths from cervical cancer occur, says one commentary. But the cost of £360 (€181; $260) is probably beyond the reach of most low income countries.

In countries that can afford it, the vaccine has become a political problem rather than a public health one, says another commentary. Scientists should keep a cool head and continue to look for answers to the remaining questions. We still don’t know enough about long term safety, how long immunity will last, the optimum number of doses, or whether other potentially oncogenic HPV serotypes will take over when types 16 and 18 have been eliminated.

Banning Swedish snus makes no sense

Snus is a kind of smokeless tobacco that users take by mouth—usually by placing it under the upper lip. It’s currently banned in Australia and most of Europe, but snus is legal and popular in Sweden, where researchers have recently confirmed that it is safer than cigarettes, but not completely harmless.

In a cohort of 279 897 male construction workers, snus was not associated with an excess risk of oral or lung cancer, but users were significantly more likely to develop pancreatic cancer than men who had never used tobacco products (relative risk 2.0, 95% CI 1.2 to 3.3). Smoking was a powerful risk factor for all three cancers.

In another study, researchers calculated that legalising snus in Australia would probably produce a net gain in health benefits to the population if enough smokers switched to snus. So should the bans be lifted?

At least two commentators think they should. It makes no sense to criminalise the use of a relatively safe tobacco product but allow people the freedom to kill themselves smoking cigarettes, they write. However,
Folic acid and B vitamin supplements won’t prevent venous thromboembolism

<table>
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<th>Subgroup</th>
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<tr>
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Adapted from Ann Intern Med 2007;146:761-7

Observational studies suggest a link between high serum concentrations of homocysteine and venous thromboembolism (VTE). If the link is causal, then reducing homocysteine concentrations should help prevent deep vein thromboses and pulmonary emboli. But trials of vitamin supplements designed to do just that have been disappointing.

The latest trial randomised 5522 middle aged and older men and women to take a supplement of folic acid, vitamin B-6, and vitamin B-12 or placebo for five years. In each group, 44 participants had a symptomatic deep vein thrombosis or pulmonary embolus (or both) during follow-up (incidence rate 0.35 per 100 person-years in each group; hazard ratio 1.01; 95% CI 0.66 to 1.53). The supplement did not prevent venous thromboembolism overall, despite bringing down homocysteine concentrations compared with placebo. Neither did it work for any subgroup, including patients with the highest serum concentrations of homocysteine at baseline.

All the men and women in this trial had cardiovascular disease, or at least two major risk factors including diabetes. Both groups started the trial with mean serum homocysteine concentrations of 11.5 μmol/l, and nearly three quarters lived in Canada and North America, where folic acid is added to bread flour.

Ann Intern Med 2007;146:761-7

How pharmaceutical representatives change your behaviour

“It’s my job to figure out what a physician’s price is. For some it’s dinner at the finest restaurants, for others it’s enough convincing data to let them prescribe confidently and for others it’s my attention and friendship . . . but at the most basic level, everything is for sale and everything is an exchange.” So writes one former pharmaceutical representative in an article explaining to doctors just how drug reps work their clients. In the US an estimated 2.5 drug reps exist for every targeted doctor, and their approach to changing prescribing habits has developed into a science. Grooming doctors, known in the industry as detailing, involves profiling their psychology, tracking their prescriptions using data from pharmacies, targeting their weaknesses, and massaging their vanity, he writes. Even sceptics can be turned around with the right combination of humility and the academic veneer provided by armfuls of publications and invitations to teach. Doctors who won’t see reps are targeted through their staff instead.

Detailing is expensive—each drug costs an estimated $25-$30m (£13-15m; €18-22m) a year—but companies know that it works. How can you avoid it? You can’t. If you write enough prescriptions, they will find you.

PloS Med 2007;e150 doi: 10.1371/journal.pmed.0040150

Educational intervention helps inner city GPs detect tuberculosis

Tuberculosis is a re-emerging threat to public health in many developed countries, and primary care doctors are well placed to find it early and to make sure affected patients are treated. A simple educational intervention to encourage screening certainly worked in general practices in Hackney, where rates of tuberculosis are among the highest in the UK. A combination of education, support, computer prompts, and financial incentives increased rates of screening from 0.4% (84/23 051) to 57% (13 478/23 573) of patients registering with a general practice in a cluster randomised trial.

General practices in the intervention group also did more tuberculin tests than controls and diagnosed more active cases (47% (66/141) v 34% (54/157); odds ratio 1.68; 95% CI 1.05 to 2.68). The overall yield from screening was low, however. Most of the improvements were due to better case finding in existing patients, not better screening of new registrants.

Still, the authors think their intervention could be a useful addition to local strategies against tuberculosis, particularly in inner city areas. It won’t be enough on its own, however. The best way for developed countries to fight tuberculosis is to support control strategies well outside their own borders, says a commentary (pp 1493-4).

Lancet 2007;369:1528-34, 1493-4

Physician assisted deaths: no “slippery slope” in the Netherlands and Oregon

Rates of euthanasia and physician assisted suicide have fallen slightly since they were legalised in the Netherlands in 2002. In 2005, euthanasia accounted for 1.7% of deaths in the Netherlands, down from 2.6% in 2001 (P<0.05), according to a nationwide survey of doctors. Physician assisted suicides accounted for 0.1% of deaths, down from 0.2% in 2001 (P<0.05). Of the 9965 deceased patients studied, 8.2% were continuously and deeply sedated before death.

Doctors—most often general practitioners—chose neuromuscular relaxants as the lethal agent in almost two thirds of cases of euthanasia in 2005, opioids in about a fifth, and barbiturates in a 10th. Respondents reported 80.1% of all cases to the authorities in 2005, up from 54% in 2001. The survey had a response rate of 77.8% (5342/6860).

Physician assisted deaths are clearly not on a “slippery slope” in the Netherlands, writes one commentator from the US (pp 1911-3). The situation is similarly stable in the US state of Oregon where one in 1000 deaths is now officially physician assisted. Oregon is the only state to allow doctors to help patients end their own lives, though euthanasia remains illegal.

In what state of health has Tony Blair left the National Health Service? The story could have been one of dazzling success. If, on that May morning back in 1997 a soothsayer had told him what the results would be 10 years later, he might reasonably have expected to rank somewhere alongside Aneurin Bevan as a hero of NHS history.

Instead doctors and nurses are united in fury while voters tell pollsters that they think the service is worse than it was and they expect it to get worse still. For the first time ever, a majority of the population think the NHS would be safer in Conservative hands.

Results have never been so good, yet the public view of the NHS has never been so glum. How did this happen?

The Labour government began well with a 10 year national strategy agreed after lengthy consultation with NHS staff led by Tony Blair himself. The Wanless report uncovered the depth of need after decades of funding that almost always fell below real NHS inflation rates. The public agreed money was needed; national insurance rates were raised to pay for it.

NHS spending will have trebled by next year to £94bn (£138bn; $187bn), easily reaching the European Union average, as promised. Ever since Attlee cut back its budget before it was even launched, the NHS has been pinched for funds. It has certainly never enjoyed such a time of plenty.

Where has the money gone? Opposition parties will keep up that chant until the next election, accusing Labour of giving poor value for the cash spent. But a fair reckoning requires some memory of what the NHS was like in previous under-funded decades. Every winter there was an NHS crisis: as the BBC’s social affairs editor I used to mark it in the news diary as an expected annual event. Sometimes it was flu that had elderly patients overflowing on to trolleys in hospital corridors. But always by February and March it was money running out that caused theatre and ward closures, with surgeons left to twiddle their thumbs while waiting lists spiked up until the new financial year.

Look back down memory lane at some of the headlines before Mr Blair came to power: “400 critically ill children turned away from intensive care units in the past three months due to a chronic shortage of beds and nurses” (Mirror, 21 January 1997); “1 in 7 operations cancelled due to cutbacks” (Mirror, 18 November 1996); “Chaos mounts as wards turn away the sick” (News of the World, 28 January 1996); “Doctors reveal winter chaos in NHS” (Independent, 10 January 1997). Pictures of patients on trolleys abound among the old cuttings.

Better care

Even allowing for the usual media exaggeration, few objective NHS watchers would deny how much improvement there has been since then. In 1997, 283,866 people had waited 6 months or more for operations. By last March, ministers announced there were only 199. Back in 1997 few would have believed Tony Blair had he promised to cut waiting times to its present average of 6.6 weeks, (which does, of course, hide wild variations).

In 2003 when the target was set, 75% of patients were seen within four hours in accident and emergency departments; last year it was 98.5%. Even allowing for statistical fiddling, nobody doubts refurbished accident and emergency departments are better. There are now 20,000 more consultants and general practitioners, 70,000 more nurses, 118 new hospitals, and 188 new general practice clinics. As ever, demand rose too: there were 3% more users a year and 75% more emergency ambulance calls.

No one waiting three months now will remember waiting 18 months back then. Voters don’t do gratitude
All those are NHS in-puts—but what of real health outcomes? Tsars for cancer and heart disease saw deaths from both fall. Over 10 years life expectancy rose by 2 years, to 81.2 for women and 76.9 for men—but the hard truth is that the life expectancy graph has been on a similar steady gradient upwards for a long time and the rise may have happened anyway.

Every government vows it will shift priorities towards prevention and public health. Like every other leader, Blair failed to do that significantly, although a smoking ban will help. Every government promises to redirect resources into community services where 90% of treatment happens—but like every government, Blair’s failed to stop hospitals siphoning off the lion’s share. Mental health had early extra money, but along with all community, maternity, and health visiting services, it suffered badly in the latest sharp spending squeeze.

**Poor decisions**

Nevertheless, the Blair record is good, so why are NHS staff and voters convinced everything is worse? This has been a decade of turmoil, with zigzag reforms dictated from the top, only to be countermanded again from the top. The history of his “reforms” hardly bears repeating. First he dismantled general practice fundholding and some aspects of the Tory internal market. He set up primary care groups, remade them into primary care trusts, and then merged them again into half the number. Demolished regional health authorities were resurrected as 28 strategic health authorities and then merged again back into the original 10 regions. The public health director for the south west region provides one graphic example of what has happened on the ground in this breathless deckchair shuffling. He has held the same job since 1994, but has had to reapply for it seven times since then because of reorganisations.

With each turn of the screw, Tony Blair became more convinced that only a fiercely competitive market could jolt the NHS into better productivity. He castigated Bevan’s “monolithic” state driven model and trusted the magic of Adam Smith’s “hidden hand” to drive greater efficiency. But he made a fundamental error by putting the power in the hands of the providers and not the purchasers. He built up mighty foundation hospitals and independent treatment centres first, neglecting weak and feele primary care trusts without the managerial clout to power his great market machine. Instead, the hospitals sucked money out of the pockets of the primary care trusts’ inexperienced finance directors.

Making a market caused rows with his own party, but all this organisational stuff was of zero interest to patients. They woke up to the change only when the market began to bite in painful ways. The market demanded no deficits, no more collaborative loans between hospitals that were now supposed to compete, so in one breakneck year long-standing debt had to be tortured out of the system. This the public did suddenly notice.

How can there be deficits with so much money sloshing around the NHS? The debt squeeze accelerated “reconfigurations” that meant some 60 local hospitals would close or lose their accident and emergency or maternity services. Many of these closures had been due for years and this was just the inefficiency the market was designed to throttle, but here was the gift a resurgent Conservative opposition needed. Save Our Hospital campaigns sprang up everywhere, even sometimes where there was no threat.

Just as the deficit squeeze started to freeze posts and even to cut some jobs, news of the accidental overpayment of consultants and general practitioners reached public ears. True, there had been a shortage of doctors in 1997 and they needed a good increase, but the bungled contracts looked like money out of control. Add in the saga of the mighty Connecting for Health information technology system, which over-ran in cost and time and failed to deliver in ways that were well-predicted by all the experts. Add that to growing outbreaks of methicillin resistant *Staphylococcus aureus* and *Clostridium difficile*, and the public decided the NHS was in meltdown.

However often Tony Blair and his health ministers recite their litany of successes and improvements, public opinion heads downwards. Voters asked about the NHS said it was a disaster, although when asked about their personal experience they reported that their local services were indeed better. But they just presumed they were lucky and chose to believe increasingly lurid anecdotes in the press rather than their own experience. Few can remember a decade ago to make useful comparisons: no one waiting three months for a hip operation now will remember waiting 18 months back then. Voters don’t do gratitude.

The press, as ever 75% right wing, sense an issue to put the wind in the Tories’ sails. Bad NHS stories are a staple diet of the media second only to crime—but bad hospital stories are now multiplying exponentially. With 1.3 million NHS staff each grumbling to scores of family and friends, alienating them is politically lethal too. David Cameron may have won the hearts and minds of NHS staff with his promise of no more reorganisations—if they believe any new health minister can ever resist the temptation to disorganise everything all over again.

Blair came to power famously promising to save the NHS. He feared public support would vanish without reform. In a sense, he succeeded, as it is David Cameron who has finally had to force his party to accept a free tax funded NHS with no flirtations with top-up payments or private insurance.

Tony Blair leaves with the NHS as his Iraq on the home front. But history may be kinder in a couple of years.
**THE LOCKED CODE**

Despite numerous attempts to prevent it, patenting of genes is still legal. Geoff Watts explains the problems

A bill introduced earlier this year in the US House of Representatives had one indisputable virtue: brevity. Congressmen Xavier Becerra and Dave Weldon’s proposed Genomic Research and Diagnostic Accessibility Act would have added a new section to the US legal code. The bill ran thus: “Notwithstanding any other provision of law, no patent may be obtained for a nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies.” That was it.

Had the bill been passed it would have resolved a long running dispute over the legitimacy of patenting genes. But it was not to be. The bill ran out of time, gene patenting remains legal, and the argument goes on. Given that the patent system is long established and generally agreed to be socially desirable, why should its application to genes have proved so contentious?

For many reasons—not the least of which is a widespread reluctance to view DNA as just another chemical. The information encoded within our genes has helped to make us what we are, influences our health and longevity, and may even offer insights into our close relatives. Hence we have declarations of the kind issued by Unesco, which talks of the genome as our “common human heritage.”

The problem with conferring a special status on DNA is that the underpinning emotions can swamp any attempt at reasoned discussion. One notable example is an opinion piece by Michael Crichton, the author of *Jurassic Park*, in the *New York Times* earlier this year. “You can’t patent snow, eagles or gravity, and you shouldn’t be able to patent genes either,” he insisted. “Yet by now one fifth of the genes in your body are privately owned.” The implication—that Genentec or some other biotechnology company will soon be knocking at the door demanding payback—is of course nonsense. But this is the climate in which dialogue on the many real and multi-layered concerns raised by gene patenting is too often conducted. So how best to unpick this helically twisted mess?

**Patent decisions**

At first sight, the conventions governing patentability seem to rule out genes. As products of nature—a term that obviously encompasses any molecule of human DNA—genes are not supposed to be subject to patent law. However, bodies ranging from the courts to the European Union¹ have decided that a natural product that has been isolated, purified, or otherwise altered is patentable.

This raises the issue of invention as opposed to discovery. Patents are intended to cover only the former—although, surprisingly, the relevant US statute does use the word discovery: “Whoever invents or discovers any new or useful process, machine, manufacture or composition of matter . . . may obtain a patent.” Although the wording does muddy the waters somewhat, patents have not in practice been granted to applicants who have put no inventive effort into whatever they’re laying claim to—you never could have patented water simply by bottling it.

The further you delve into gene patenting, the more technical the issues become. When patent offices examine new applications, they use several criteria including novelty, inventiveness, and usefulness. A review published by the Nuffield Council on Bioethics succinctly summarised the position on novelty and inventiveness: “Patent offices take the view that extracting genetic information encoded by a DNA sequence is not just a matter of gaining scientific knowledge about a natural phenomenon [because] it involves the use of cloning techniques to create an artificial molecule.” In this sense the process can be described as both novel and inventive. At least that was the position until a few years ago. But technology has moved on and circumstances have changed: most notably the publication of the human genome sequence. What would have justified the issue of a patent in the 1990s might not in the 2000s.

A further complication is the relatively relaxed stance of the US Patent Office. Applications that would not satisfy the European Patent Office have found favour in its US counterpart. The same is true for another core patenting criterion: usefulness or utility. In the 1990s the US office was inundated with applications for genes or gene fragments for which the demonstration of utility was, to say the least, vague. Claims amounted to little more than saying, “This is a gene. As such it must be important, and we’ll test for it.”

In January 2001, following public consultation, the US office decided to raise the bar. It now requires gene patent claims to have a “specific and substantial and credible utility.” Officials interpret credible as meaning that the utility of the invention must have been shown to be theoretically possible—even though it need not have been shown in practice. The authors of the Nuffield report, however, think this standard is still too low. “The current state of genetics and biochemistry does not make it difficult to suggest functions for DNA

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¹ This is the “Human Genome Patent Exception” that was removed for the wet biology of the 2000s. The Human Genome Patent Exception was a clause in the European Patent Convention that allowed patents for isolated human DNA sequences. It was replaced in 2000 with the Human Genome Directive, which clarified that isolated human DNA sequences are not patentable.
sequences that are ‘theoretically possible,’ in the sense that they are not ruled out by what is already known; but this should not suffice for the award of a patent.”

Do patents matter?
The potentially adverse consequences of patenting became clear in the tangled and now notorious case of the American company Myriad Genetics and its hold over BRCA1, a gene affecting susceptibility to breast cancer. The European Patent Office granted Myriad patents on the diagnostic use of the gene. In 2002 several organisations, including the French Institut Curie, lodged objections on various technical grounds including “inadequacies in the gene sequence” and on lack of inventiveness. In January 2005 the patent office upheld the objections, prompting a celebratory press release: “It is a victory for the institute and its collaborators to issue a statement; avoiding duplication of effort; encouraging further research, etc. The arguments

Further complicating the patenting issue is that entire genes are not the only bits of DNA in question. Patents have also been filed for expressed sequence tags. These are small lengths of DNA with a nucleotide sequence identical to that found at one end of a gene. As such they’re invaluable for locating particular genes in a complete genome. Because expressed sequence tags are parts of whole genes, patents may overlap.

This also applies to single nucleotide polymorphisms or SNPs. These are small genetic variants: differences in single base pairs that occur in roughly one in every 1000 nucleotides. Some are linked to a person’s risk of specific illnesses and, importantly for drug companies, affect the body’s response to certain chemicals.

As it happens, agreement has been reached over SNPs. This followed the creation of the SNP Consortium, an international group originally comprising several drug companies and the Wellcome Trust. In an attempt to prevent patent wrangles the consortium set out to identify and map all the SNPs in the human genome and then make this information freely available.

On gene patenting in general, however, the debate continues. The arguments in favour are: allowing inventors to recoup their investment; avoiding duplication of effort; encouraging further research, etc. The arguments against are predominately about the scope and number of patents, and the consequential risks that routine discoveries will be unjustifiably rewarded, or that the practical application of knowledge will be prohibitively expensive or otherwise restricted.

The principle spelt out in the failed US congressional bill would, for good or ill, have cut through all this argument—in America, at least. But because the dispute has remained unresolved for so long, and many patents already exist, we are now in a position to begin asking if gene patenting is turning out to be good or bad in actual practice. By studying patents filed between 1980 and 2003, the University of Sussex’s PATGEN project has tried to do just this. Although its report points out that definitive answers are not yet possible, its measured conclusion seems to hint that patenting does not merit too much concern: “With the number of patent applications in decline, more stringent examination procedures and the likely restriction of the scope of patents by case law . . . the negative impact of DNA patenting may turn out to be more limited than some had feared.”

In all likelihood the future of intellectual property claims in genomic research will be neither all public nor all private but a shifting combination of the two.

Natural selection, commendably pragmatic, has always imposed a “pick and mix” regime on the evolution of the genome. A similar approach may be equally appropriate in deciding about patenting it.

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Competing interests: None declared.

8 Wellcome Trust. The SNP consortium and international hapmap project. www.wellcome.ac.uk/doc/MTD005106.html
**OBSERVATIONS**

**MEDICINE AND THE MEDIA**

**Cancer drugs: swallowing big pharma’s line?**

The media lapped up a report last week criticising the UK’s record on cancer treatment. **Rebecca Coombes** unpicks the latest round of NICE-bashing

When a report last week put the United Kingdom near the bottom of a league of developed nations for giving patients access to new cancer drugs, the press were more than happy to spread the bad news.

The drug company funded report from the Karolinska Institute, Stockholm, received a largely uncritical reception by UK newspapers, broadsheet and tabloids alike. “Cancer survival rates are worst in western Europe,” splashed the **Daily Telegraph** on its front page. The UK was the “sick man of Europe” for providing cancer drugs, said the **Independent**.

The report, paid for by Roche and published in the *Annals of Oncology* (volume 18, supplement 3, 2007), covers 25 countries, including Australia, Canada, New Zealand, South Africa, and the United States, as well as 19 European countries, and looks at access to 67 “innovative” cancer drugs. In its final verdict, the UK was yoked with Poland and the Czech Republic, as being “low and slow” in the uptake of new cancer drugs. The most stark “inequalities” in access to cancer treatment, according to the report, were for the new colorectal and lung cancer drugs, bevacizumab, cetuximab, erlotinib, and pemetrexed. In all cases UK uptake was said to be low or very low.

Access to these new drugs directly related to improved cancer survival rates, claimed co-author Bengt Jönsson, director of the Centre for Health Economics at the Stockholm School of Economics. “Our report highlights that in many countries new drugs are not reaching patients quickly enough and that this is having an adverse impact on patient survival.

In the US we have found that the survival of cancer patients is significantly related to the introduction of new oncology drugs.”

The authors said that in France, Germany, Spain, and Italy 51-52% of patients had access to cancer drugs launched after 1985, whereas in the UK only 40% of patients had access to the 67 drugs listed in the report. The UK, according to the report, had the worst five year survival rate for all cancers of the five main EU nationals. France was top, with 71% for women and 53% for men surviving five years or more, and the UK bottom with 53% and 43% respectively.

The authors pointed the finger firmly at the National Institute for Health and Clinical Excellence (NICE): “Nowhere in the world is the decisive role played by economic evaluation more evident. It was the explicit objective of NICE to avoid any significant delays in bringing innovations to the market in the UK. There is as yet no evidence that this objective is met.”

The report, and the media coverage that followed, left NICE severely rattled. It said that the report was a “rehash” of a 2005 report by the same authors and that the update failed to acknowledge NICE’s 18 month old rapid appraisal process, which fast tracks appraisals of new drugs in around six months. In a curt press statement, NICE chief executive Andrew Dillon said: “This drug industry sponsored report is flawed, inaccurate, and directly contradicts itself in places. It is the job of NICE to put the health of patients and the public first, not the profits of the pharmaceutical industry.”

Mr Dillon countered that NICE had sped up access to effective cancer treatments, with trastuzumab (Herceptin) being a case in point, and that use of NICE-recommended cancer drugs was now “higher than ever.”

From a public relations point of view, NICE associate director of external communications Lucy Betterton was not surprised that her organisation’s battering from the Karolinska Institute went unchallenged by the UK media. For example, in the **Daily Telegraph**, consultant radiographer and breast cancer patient Sarah Burnett dismissed NICE as representing “yet another hurdle for the pharmaceutical industry to clear before a treatment is made generally available.”

Ms Betterton said: “We weren’t surprised by the coverage. Cancer is such a hot topic and stories like this are easy to run. It’s a simple story—the UK has the worst access to cancer drugs and worst survival rates.
Questions like, Where does the report come from? Who paid for it? What motivated them? are more complicated and not tackled often by the press.” She said that new and expensive cancer drugs might not be any more effective than therapies already in use—a point not reflected in the Karolinska Institute report. “We look at how well a drug works compared to other treatments and whether it is good value for money. One reason a drug may not be recommended is that it isn’t sufficiently better than other drugs already available to make it cost effective for the NHS,” she said.

A lone supportive voice came in the *Guardian* from Tony Harrison, senior research fellow at healthcare think-tank the King’s Fund. Mr Harrison said that Roche and other drug companies were “basically trying to destroy NICE.” Bringing in drugs as soon as they were licensed was not necessarily good for patients or the NHS, he said. “A proper assessment of clinical evidence on the ground—as opposed to a drug company’s own trials—takes time.”

Richard Peto, professor of medical statistics and epidemiology at Oxford, told the *BMJ* that the report misrepresented the UK’s success in bringing down death rates due to cancer. He said that mortality rates in the UK could not be compared with those in other countries. “We are so good at counting deaths in this country, whereas elsewhere there are underestimates.” Unlike in other countries, researchers were able to link into national mortality statistics and automatically be notified of cancer-related deaths.

Professor Peto strongly disagreed with the report’s claim that access to the newest cancer drugs was the key to cutting cancer deaths. “The key determinant of cancer mortality is not the extent to which the latest drug is used—although there are a few exceptions, such as Herceptin. We are being strung along and new drugs are being developed that may work, but not very differently to the ones we already have.”

He said that the huge decreases in cancer mortality—he thought the best in the world currently—were largely because of a downturn in deaths caused by tobacco, and dramatically improved breast cancer survival rates, mostly attributed to the success of hormone therapies.

The Karolinska report warned that, as cancer research continued to grow, many new drugs and treatments would flood the market in coming years. “Countries urgently need to address how they are going to accommodate newer drugs into the healthcare systems and pay for them.”

But Professor Peto said that the real debate should be over drug company pricing. “Patient organisations may call for all effective treatment to be available for free, but if this was the case it would be exploited wholly by drug companies for corporate profit—they would double their prices overnight. The price rise in drugs has been unprecedented and is made more acceptable by reports like these. There is too much criticism of the NHS and not enough of these companies’ pricing policies.”


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**POLL RESULTS**

**Should patient groups accept money from the pharmaceutical industry?**

In the online poll following our 5 May Head to head debate (*BMJ* 2007;334:934-5), 16% of 230 respondents said yes and 84% said no. Here are some of the comments we received:

**NO** “An often vulnerable group of people will be influenced by the ‘nice’ drug company who understands all their problems, and the ‘bad’ doctors who won’t prescribe the new wonder drug.”

**YES** “I think that government funding is very hard to apply for. And some groups might miss out.”

**NO** “The psychological obligation to ‘return the favour’ currently makes patient groups an unwitting extension of the company’s marketing department. But I could accept the situation if the money went into an independent central fund, and groups applied to that for grants.”

**YES** “Patient groups need funding for core work as well as projects. As long as the funding source does not give conditions tied to the funds that compromise its spending and the reputation of the group, then this is acceptable and is right; whether it is from public coffers, charitable trusts or from industry.”

**NO** “For over 10 years I was involved in a significant patient group organisation and saw first hand the effect of industry partnerships. They affect the quality and type of information that patient groups distribute, particularly with respect to drugs. Also, many advisers and professionals who are appointed to conduct peer review on grants provided to researchers by these groups are connected to industry.”

**NO** “Accepting money from the pharmaceutical industry may make it difficult for patient groups to promote treatments or therapies which may run counter to the industry’s interests.”

**NO** “Some funded patient groups end up pushing for very expensive drugs, for example, Herceptin.”

**NO** “If the patient groups think the companies are philanthropic show me an example of a company providing money to a patient group when they do not have a drug on the market or in the pipeline for that patient group.”

**NO** “Too many groups are influenced by the agendas of the drug companies who use ‘educational funding’ as a way of stealth marketing.”

**NO** “As a healthcare professional and a survivor of a catastrophic illness, I know patient groups first hand. The Pharmas use skilled public relations firms to appeal to patients on an emotional level. Patients, even well educated ones, can end up feeling that the pharmas ‘really care’ about them, and feel almost honoured to be the recipients of money for groups. However, most patient groups in the US do not question the pharma role in enforcing high prices and/or lack of price regulations.”

Full poll results are available at http://resources.bmj.com/bmj/interactive/polls/accept-money-poll

See Letters, p 1020.
Anyone who doubts the Department of Health’s ability to consume cash like a forest fire should take a look at the freedom of information section of the DH website. There, after a long and ultimately successful battle by Rod Ward, senior lecturer at the University of the West of England, is published the report written in 2004 by Sir William Wells into the NHS University. It’s a tale to make the blood run cold.

I can claim a walk-on part. In May 2001 I was summoned, along with the political editor of the Times, to a briefing by the political adviser to Alan Milburn, then secretary of state for health. It was the middle of the election campaign, and to spuce up the Labour manifesto somebody had invented the idea of launching an NHS University. McDonald’s already had one, the Hamburger University, to train its staff in the finer points of fast food delivery: so did Disney, and 2000 other US corporations.

Mr Milburn’s man skilfully dished us up a scoop, fast-food style. Cooks, porters, and other low-paid staff, he told us, would be promised £300 a year to start individual “learning accounts” and at any time 100 000 NHS staff, from cleaners to consultants, would be taking courses. This was the “big idea” of Labour’s campaign, intended to echo the success of the Open University. The NHS University would be a “model of excellence” and would cost £30-50m (€44-74m; $60-100m) a year.

The story duly appeared on page one of the next day’s Times, and the NHS University was formally launched the same day by prime minister Tony Blair at the Royal Marsden Hospital in London. Did I wonder, even momentarily, if I might have been sold a pup? Possibly, but it wouldn’t have been the first time.

Troubles began almost before Mr Blair had closed his mouth. The university title is jealously guarded, and those that hold it are quite prepared to defend it. Becoming a university requires Privy Council approval, and 55% of students must be taking degree courses, a level that the NHS University could not achieve for many years, if ever. Allowing it to become established would also threaten the future of existing universities, which formed a stockade to repel the encircling Indians. They won without breaking sweat. The NHS University was forced to rename itself the NHSU, in which the U stood for nothing at all. Honestly, nothing.

That was a big psychological setback that more prudent planning might have avoided. It upset the chief executive of NHSU, Professor Bob Fryer, who had taken to calling himself vice-chancellor designate, and insisted that the university title mattered. But NHSU went ahead, recruiting staff without ever quite defining what it was about. “We have been struck, in the course of our review, by the absence of simple, clear descriptions of NHSU’s purpose and the parameters of its role,” Sir William Wells commented dryly in his now published review.

Its ambitions were huge. “Step by step NHSU is expected to assume an umbrella responsibility for all learning in health and social care,” Professor Fryer said. But its powers were limited. It could not force anybody to take its courses, alternative versions of which already existed at established universities. It made few efforts to find out what its customers actually wanted. When it did, said Sir William, it was “too little, too late.”

Cash demands began to rise. The NHSU spent £28m in 2003-4, £44m in 2004-5, and put in a bid for £73m in 2005-6. It planned a “virtual campus”—a fancy website, I think this means—that was going to cost £20-50m over five years, but that was abandoned after a similar scheme, the online electronic university, crashed after spending £9.9m of public money on a learning platform that didn’t work.

At this point health secretary John Reid, bless him, pulled the plug. Armed with Sir William’s report he was able to stop the NHSU in its tracks and merge it with the NHS Modernisation Agency and the NHS Leadership Centre into something called the NHS Institute for Innovation and Improvement. Professor Fryer was found another job. In 18 months of existence the NHSU had absorbed £72m, and trained 30 000 people, mostly in fairly basic skills.

Sir William concluded: “NHSU’s expenditure of £72m in 2003-5 can only be justified as large-scale investment which will reap major dividends in the future. This creates a potential for embarrassment if questions are asked about the value for money of NHSU . . . very rapid steps will need to be taken if the threat of embarrassment is not to be prolonged well into the future.”

Where public money is concerned, this government is pretty close to unembarrassable. But just to make sure, it suppressed Sir William’s report and denied Mr Ward’s request for it to be published, while simultaneously claiming it would be published “shortly.” When the Freedom of Information Act came into force at the beginning of 2005 he repeated the request, was turned down, and appealed to the information commissioner, who upheld his appeal. The DH then appealed to the next tier of authority, the Information Tribunal, backing down just days before that appeal was due to be heard. These are the same ministers who accuse journalists of being cynical.

Let’s leave the last word to Rod Ward, who deserves it. He said: “We need to learn some of the lessons—we spent £72m of taxpayers’ money and the management was diabolical.”

Nigel Hawkes is health editor, the Times nigel.hawkes@thetimes.co.uk
Functional foods: the case for closer evaluation

Current regulations focus on the mandatory safety evaluation of functional foods before they come to market, but Nynke de Jong and colleagues argue that the effects of such foods should also be evaluated after they have been launched.

Functional foods are modified foods that claim to improve health, quality of life, or wellbeing. These foods are intended for use in the context of a healthy lifestyle or as a means to compensate for an unhealthy one. From society’s point of view, there are several potential problems—the medicalisation of our daily food intake, the long term safety and effectiveness of these foods, and the aggressive marketing and advertising of these highly profitable products. However, functional foods need to be fully evaluated to make sure they meet current scientific and regulatory standards.

EU regulations

Several European Union regulations and directives on functional foods are currently being developed. Current rules focus mainly on the mandatory safety evaluation of new foods before they come to market; minimum and maximum safe upper values for micronutrients used for fortification; lists of permitted substances for fortification; the registration of herbal products; and acceptable nutritional and health claims.

One positive development has been the recent publication of regulations on nutrition and health claims. Nutritional claims can now be made only if the food fits a certain nutrient profile (such as below a predefined fat content or "low fat"). New claims can be issued only after being assessed and authorised by the European Food Safety Authority (EFSA) on the basis of good nutritional science. Most of the regulations and directives focus on evaluating safety before foods reach the supermarket, however—no regulations deal with aspects that arise after this point.

Market positioning of functional foods versus drugs

Similar to so called lifestyle drugs—drugs at the boundary between lifestyle wishes and health needs, such as erectile stimulants, appetite suppressants, and drugs to help people stop smoking—functional foods are designed to meet consumers’ needs and lifestyle wishes. Data on sales and market dynamics of functional foods are limited. An analysis of functional foods launched between January and April 2005 identified more than 200 new products.

Many functional foods are aimed at trying to improve gut health and heart health and are intended for people who have mild health problems or slight discomfort. The market for health drinks in the United Kingdom is fast growing, with a turnover of £316m (€464; $632) in 2005. Although some functional foods (table) might have beneficial effects on risk factors for various chronic and life threatening conditions, there is no proof that attacking these risk factors is good for general health in the free living population. Their main appeal may be particularly to worried consumers.

Possible food and drug interactions

Functional foods may influence the effectiveness of drugs and patients’ compliance. This can be illustrated by the example of phytosterol and stanol enriched products, which are intended for people with mildly raised cholesterol who do not take cholesterol lowering drugs. People in this group are often unaware of their cholesterol value. The enriched products may, therefore, be eaten only by those with substantially raised, and thus known, cholesterol values and associated higher cardiovascular morbidity, which inherently increases the potential for interactions with cardiovascular medication.

Phytosterols and stanols interact with statins to have an additive effect on reducing low density lipoprotein cholesterol values. The possible downside to this

EDITITAL by Lang

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ANALYSIS
interaction is that serum phytosterol concentrations increase during long term statin treatment, and concern has been raised about the possible atherogenic effects of phytosterols. This is why Health Canada, the federal department responsible for helping Canadians maintain and improve their health, has not allowed these foods to be sold in Canada.

Eating functional foods may also have detrimental effects on patient compliance with drug treatment; adherence to statins is known to be suboptimal. People who eat phytosterol or stanol enriched foods may alter the dose of their statins for various reasons, without consulting a doctor. A lower dose of statins can never be compensated for by the intake of functional foods.

Limited postlaunch scientific data
Once functional foods come to market, limited data are available about their impact on the community. We have little understanding of the circumstances under which these foods are eaten, whether target groups are reached, and if targeted education programmes or health policies should be recommended. Very little is also known about exposure, long term or otherwise, and safety under free conditions of use, and whether and how functional foods interfere with drugs designed for the same target. These problems have not been addressed even in the best studied of these foods—phytosterol and stanol enriched foods. There is no evidence that functional foods cause harm, but the data are limited to five to six years of use and a restricted number of users.

Scientific developments at the interface between food and pharmacology are ongoing, so data supported assessments of these foods are now possible. The development of a structured postlaunch monitoring system has been suggested but not yet implemented in Europe.

The case for postlaunch monitoring
Despite two recent reports on the subject, we are still uncertain about how many people buy and consume functional foods and about any benefit they may have, so more thorough investigations are needed. If these foods are found to be of net benefit to public health, targeted education programmes and supportive government policy should be considered. If no effect or an adverse effect is identified, the associated health claims should be re-evaluated. New regulations may also be needed.

In addition to questions about user compliance, problems such as the impact of compensating behaviour, the possible alternative use of drugs or more traditional foods, and the effect size of these approaches should also be evaluated and compared.

Postlaunch monitoring, which consists of several phases spread over time—starting with signalling and ending with a risk-benefit analysis (figure)—could deal with these uncertainties. Signalling could be performed transparently by manufacturers under supervision of and in collaboration with national food safety authorities. An EFSA committee could be mainly responsible for distributing monitoring tasks to national food safety bodies or nutrition research institutes, with national policymakers and risk managers as important intermediaries. Each monitoring question would determine which institute is assigned a particular task. Such a strategy would also mean close collaboration with those responsible for pharmacovigilance.

The ultimate result of postlaunch monitoring could be a decision support tool that helps policymakers and others such as health insurance companies evaluate the impact of health promoting strategies (traditional foods, drugs, functional foods). Intermediaries, such as doctors and dietitians, should be informed about the results so they can educate and help consumers. Practical and unbiased information on when and how to use functional foods and potential side effects and interactions could be conveyed in instruction leaflets, reference books, and on websites. In turn, the intermediaries could provide feedback on consumer experiences to the monitoring team. This would make the best possible use of the results of monitoring and extend their coverage, so that funding for postlaunch monitoring might come not only from manufacturers, but also from national and international governments and private sources.
Postlaunch monitoring programme

![Diagram of postlaunch monitoring programme]

**SUMMARY POINTS**

Functional foods are designed to meet consumer needs and lifestyle wishes and may be used as self medication

EU regulations focus on the warrant of safety before a functional food reaches the market

Postlaunch monitoring is needed to assess whether functional foods are safe and effective under customary conditions of use

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Until now, postlaunch monitoring for functional foods has been erratic. The first attempt at such monitoring (for phytosterol enriched foods) found that people who buy the product eat less than was anticipated and that no serious adverse effects have been reported to manufacturers’ consumer care lines. Data were gathered at the household level only, however, so users were not characterised and it was not possible specifically to estimate exposure.

Our unit has been mapping the effectiveness of phytosterol and stanol enriched margarine eaten by the Dutch population. The maximum effect seen over five years was stabilisation of total cholesterol values rather than the slight increase usually seen with age. Although this effect is modest, it can still reduce the risk of coronary heart disease and provide health benefits in the general population. These observations support the inclusion of effectiveness in the postlaunch monitoring programme. A future topic for research would be to evaluate the effectiveness of adding functional foods to a traditional diet compared with altering the total diet according to dietary guidelines. This single example suggests that we need to invest more in finding out what functional foods can contribute to individual and public health in relation to the promises made by manufacturers.

**Contributors and sources:** The authors are experts in postlaunch monitoring of functional foods (Nld, MGW, MCO, HV) and medicines (CHK, HGM). This draft was written by Nld, Ov, and MGW, with comments by HV, MCO, and HGM. Background studies that underpin the views presented in this paper were carried out by all authors. Nld is guarantor.

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Alarm symptoms in early diagnosis of cancer in primary care: cohort study using General Practice Research Database

Roger Jones, Wolfson professor of general practice,1 Radoslav Latinovic, database manager,2 Judith Charlton, research assistant,2 Martin C Gulliford senior lecturer in public health2

ABSTRACT

Objective To evaluate the association between alarm symptoms and the subsequent diagnosis of cancer in a large population based study in primary care.

Design Cohort study.

Setting UK General Practice Research Database.

Patients 762 325 patients aged 15 years and older, registered with 128 general practices between 1994 and 2000. First occurrences of haematuria, haemoptysis, dysphagia, and rectal bleeding were identified in patients with no previous cancer diagnosis.

Main outcome measure Positive predictive value of first occurrence of haematuria, haemoptysis, dysphagia, or rectal bleeding for diagnoses of neoplasms of the urinary tract, respiratory tract, oesophagus, or colon and rectum during three years after symptom onset. Likelihood ratio and sensitivity were also estimated.

Results 11 108 first occurrences of haematuria were associated with 472 new diagnoses of urinary tract cancers in men and 162 in women, giving overall three year positive predictive values of 7.4% (95% confidence interval 6.8% to 8.1%) in men and 3.4% (2.9% to 4.0%) in women. After 4812 new episodes of haemoptysis, 220 diagnoses of respiratory tract cancer were made in men (positive predictive value 7.5%, 6.6% to 8.5%) and 81 in women (4.3%, 3.4% to 5.3%). After 5999 new diagnoses of dysphagia, 150 diagnoses of oesophageal cancer were made in men (positive predictive value 5.7%, 4.9% to 6.7%) and 81 in women (2.4%, 1.9 to 3.0%). After 15 289 episodes of rectal bleeding, 184 diagnoses of colorectal cancer were made in men (positive predictive value 2.4%, 2.1% to 2.8%) and 154 in women (2.0%, 1.7% to 2.3%). Predictive values increased with age and were strikingly high, for example, in men with haemoptysis aged 75-84 (17.1%, 13.5% to 21.1%) and in men with dysphagia aged 65-74 (9.0%, 6.8% to 11.7%).

Conclusion New onset of alarm symptoms is associated with an increased likelihood of a diagnosis of cancer, especially in men and in people aged over 65. These data provide support for the early evaluation of alarm symptoms in an attempt to identify underlying cancers at an earlier and more amenable stage.

INTRODUCTION

More than 80% of clinical care in the United Kingdom is delivered in general practice and primary care; some general practitioners refer less than 5% of their patients each year for specialist opinions and hospital investigations.12 Referral from primary to secondary care is often triggered by a general practitioner’s awareness of so called “alarm symptoms,” features in the clinical presentation that are considered to predict serious, often malignant, disease. For example, guidelines on the identification of alarm symptoms form the core of the “two week rule” for urgent referral of patients suspected of having cancer,13 and many clinical practice guidelines specify particular symptoms that mandate urgent investigation or referral.3 However, the evidence base for the alarming nature of many alarm symptoms is weak, and general practitioners often use individual approaches to the collection and analysis of data in the course of consultations,4 often relying on personal heuristics (which may include questions thought to have high negative predictive value for the presence of serious disease).

However, diagnosis of cancer is relatively rare for the individual general practitioner, whose role may be characterised as marginalising danger, in contrast to that of the specialist, whose task is to marginalise uncertainty.6 In other words, general practitioners need to sort out the minority of patients who need urgent attention from the majority who are likely to have self limiting disorders, for which time can be used as a diagnostic and therapeutic tool.7

Haematuria—microscopic and macroscopic, with or without pain—is thought to account for approximately four consultations per thousand patients per year in primary care in the UK. The presence of painless, macroscopic haematuria is widely regarded as an alarm symptom suggesting the presence of a urinary tract neoplasm, but little information collected in the primary care setting is available to support this assertion. When Buntinx did a systematic review of published reports in 2000 he was unable to find a single primary care study, and the information on which to base decision making in primary care had been collected in referral centres.8 A subsequent study from Buntinx’s group, using a Belgian sentinel primary care network, reported an overall positive predictive value of haematuria for urological cancer of 10.3% and a sensitivity of 59.5%.9 Summerton and colleagues’ study of a haematuria clinic emphasised the
importance of looking in detail at the symptom complex associated with haematuria. Most recently, Hamilton and colleagues derived a positive predictive value for prostate cancer of haematuria alone of only 1%, and several other symptoms had greater predictive values than haematuria.

Dysphagia is a relatively common problem and is often regarded as an alarm symptom mandating urgent referral, generally for contrast radiology in view of the potential dangers of upper gastrointestinal endoscopy in patients with oesophageal obstruction. However, as in many conditions of interest, the information available to guide decision making is derived largely from secondary care settings. A recent systematic review, which identified 83 relevant studies, described wide variation in the sensitivity and specificity of alarm symptoms for upper gastrointestinal malignancies.

Haemoptysis occurs in up to 40% of patients with bronchitis, and is also seen in other less serious upper respiratory conditions, but it is an important alarm symptom for the presence of bronchial carcinoma, pulmonary tuberculosis, pulmonary embolism, and other serious cardiovascular problems, as well as systemic diseases and coagulopathies. Unsurprisingly, haemoptysis often leads to specialist referral and the use of investigations, but little information is available on the outcome of hospital referrals for haemoptysis and even fewer data are available to guide cost effective decision making in primary care. The most recent publication by Hamilton and colleagues, a population based case-control study, found generally low positive predictive values for symptoms associated with lung cancer except for haemoptysis, with a positive predictive value of haemoptysis alone of 2.4%, but with much higher positive predictive values when haemoptysis was accompanied by other symptoms such as dyspnoea, weight loss, and anorexia.

Rectal bleeding is a common symptom; community surveys indicate that between 7% and 10% of the Western adult population report rectal bleeding in a 6-12 month period and that blood is mixed with stool in up to 30% of cases. Rectal bleeding is reported by people over the age of 50 less often than in younger patients (27% versus 12%). A minority of people with rectal bleeding consult a physician, and although reasons for consultation may include worry about serious disease, anxiety about an adverse diagnosis is also likely to play a part. Because rectal bleeding is such a well recognised alarm symptom, patients who present with this condition are likely to be referred for lower bowel endoscopy or a specialist opinion after evaluation, including rectal examination, by the primary care physician. However, given the relative infrequency of a diagnosis of malignant or serious inflammatory disease, guidance is needed to help primary care physicians to select patients with rectal bleeding for whom urgent investigation or referral is most appropriate.

Few epidemiological data are available to provide an evidence base for these decisions. Buntinx’s group found a range of age dependent positive predictive values of rectal bleeding for colorectal cancer in their sentinel network study, and Lawrenson and colleagues, using the General Practice Research Database, reported an overall positive predictive value for colorectal cancer of 0% in men and 3.5% in women.

The General Practice Research Database provides a valuable resource with which to improve our understanding of the significance of these symptoms and of their predictive value for serious disease. It is the world’s largest primary care database, containing detailed clinical and healthcare information representing around 13 million patient years, contributed to by several hundred representative general practices in the UK. The structure, utility, and validity of the database and the data that can be extracted from it have been extensively described, and good evidence exists for the comprehensiveness and accuracy of the data. In this study, we set out to determine the incidence of so called alarm symptoms, and the association between these symptoms and subsequent diagnosis of neoplasms, by using a retrospective cohort design. For each alarm symptom, we specifically aimed to estimate the proportion of patients with alarm symptoms who were later diagnosed with cancer, or positive predictive value; the proportion of patients diagnosed as having cancer who previously reported the symptom (that is, the sensitivity of the symptom for detecting cancer); and the likelihood ratio of a diagnosis of cancer associated with the symptom.

METHODS

Practice and patient selection

We selected all 128 general practices that provided data of a sufficient standard from 1 January 1994 to 31 December 2000 and which provided exclusively Read coded data. We selected all 923 605 patients who were registered with these practices between 1 January and 31 December 1994 and were aged 100 years or less in 1994. From these, we identified patients whose first ever recorded occurrence of each alarm symptom (haematuria, haemoptysis, dysphagia, or rectal bleeding) was after 31 December 1994 and who had not previously been diagnosed as having any cancer. The diagnostic codes used are available from the authors.

We then evaluated each patient’s record for new occurrences of associated cancers. For haematuria, we evaluated urinary tract neoplasms, including neoplasms of the urethra, bladder, ureter, and kidney but excluding neoplasms of the prostate and other reproductive organs; for dysphagia, we evaluated oesophageal neoplasms only; for haemoptysis, we evaluated respiratory tract neoplasms; and for rectal bleeding, we evaluated colorectal neoplasms. We did this by first identifying all patients who ever had symptoms recorded for haematuria, haemoptysis, dysphagia, or rectal bleeding or who were diagnosed as having neoplasms of the urinary tract, respiratory tract, oesophagus, or colon and rectum.

We then excluded those patients whose date of first symptom or first relevant diagnosis of cancer was before 1 January 1995. In order to include only those...
patients who were previously free from cancer, we excluded all patients with a diagnosis of any other cancer than the ones of interest before the date of the first recorded symptom or before the index cancer diagnosis date if the related symptom was not recorded. In secondary analyses, we also evaluated whether the incidence of neoplasms other than those that we pre-specified was increased after the occurrence of alarm symptoms.

Analysis
To obtain information on the underlying incidence of cancer and the value of symptoms for detecting cancer, we set out to estimate, for each alarm symptom-outcome pair, the incidence of new alarm symptoms by sex in patients not previously diagnosed as having cancer; in patients with new occurrences of alarm symptoms, the proportions with related cancer outcomes diagnosed over time (positive predictive value); the incidence of outcome cancer by sex; and the proportions of cancer patients who had previous alarm symptoms in defined preceding time intervals (sensitivity).

In patients who presented with alarm symptoms, we determined whether a first diagnosis of the associated neoplasm occurred in successive quarters up to five years. As most cancer diagnoses occurred within three years of the first symptom, we evaluated the proportion of patients with symptoms who were diagnosed as having cancer in the next three years as the positive predictive value for the symptom. We calculated exact binomial confidence intervals. We compared the observed number of new diagnoses of associated cancers in patients with alarm symptoms with the number expected if the age and sex specific cancer incidence rates for the study population applied to the sample of patients who had the symptom of interest. We compared the observed and expected numbers of cancer occurrences by estimating a standardised incidence ratio with 95% confidence intervals estimated from the Poisson distribution. For a rare disease in a defined population, the ratio of observed to expected number of cancer diagnoses provides an estimate of the ratio of post-test to pretest odds of a cancer diagnosis. The standardised incidence ratio therefore provides an estimate of the likelihood ratio of a positive test.

To evaluate the sensitivity of each alarm symptom as a test for cancer, we evaluated only those patients whose first cancer diagnosis was in 1999 or 2000 to ensure that each patient had at least five years of records before the cancer diagnosis date. For each patient with a cancer diagnosis, we determined whether a record of the relevant alarm symptom existed during the preceding three years.

RESULTS
Our population consisted of 923 605 eligible patients registered with 128 practices in 1994, of whom 762 325 were aged 15 years or older. We evaluated first occurrences of alarm symptoms in patients with no previous diagnosis of cancer. We found 11 138 first occurrences of haematuria, 4822 of haemoptysis, 6003 of dysphagia, and 15 314 of rectal bleeding in patients aged 15 years or older between 1 January 1995 and 31 December 2000. Table 1 shows the age and sex standardised incidence rates for alarm symptoms and their

Table 1 | Incidence of neoplasms and alarm symptoms in population aged 15 years and older from 1995 to 2000

<table>
<thead>
<tr>
<th>Site</th>
<th>Symptom</th>
<th>Neoplasm</th>
<th>Incidence per 100 000 person years (95% CI)</th>
<th>Cases</th>
<th>Incidence per 100 000 person years (95% CI)</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>Haematuria</td>
<td>Urinary tract neoplasms</td>
<td>285.1 (278.1 to 292.2)</td>
<td>6411</td>
<td>35.6 (33.2 to 38.0)</td>
<td>883</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>Haemoptysis</td>
<td>Respiratory tract neoplasms</td>
<td>138.5 (133.4 to 143.6)</td>
<td>2938</td>
<td>45.0 (42.3 to 47.6)</td>
<td>1135</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Dysphagia</td>
<td>Oesophageal neoplasms</td>
<td>83.6 (79.7 to 87.6)</td>
<td>1884</td>
<td>21.1 (19.3 to 22.8)</td>
<td>636</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectum and colon</td>
<td>Rectal bleeding</td>
<td>Colorectal neoplasms</td>
<td>130.8 (126.1 to 135.6)</td>
<td>3372</td>
<td>4.4 (3.6 to 5.1)</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>6411</td>
<td>285.1 (278.1 to 292.2)</td>
<td>883</td>
<td>35.6 (33.2 to 38.0)</td>
<td>1135</td>
<td>45.0 (42.3 to 47.6)</td>
</tr>
<tr>
<td>Women</td>
<td>4727</td>
<td>206.0 (199.8 to 212.2)</td>
<td>330</td>
<td>10.5 (9.3 to 11.7)</td>
<td>1135</td>
<td>45.0 (42.3 to 47.6)</td>
</tr>
</tbody>
</table>

European standard population used as reference.
associated cancers in the population aged 15 years and over, using the European standard population for reference. Each group of neoplasms was more frequent in men than in women; respiratory tract neoplasms were the most frequent, and oesophageal neoplasms were the rarest. First episodes of alarm symptoms were generally between 10 and 20 times more frequent than associated neoplasms, but this was not so for haemoptysis, which was only three times more frequent than the incidence of respiratory neoplasms. The mean age at first symptom was 58.5 (SD 18.9) years for haematuria, 61.6 (18.0) years for dysphagia, 54.5 (19.4) years for haemoptysis, and 52.5 (18.8) years for rectal bleeding. Table 2 shows age specific incidence rates of symptoms.

In the next stage of the analysis, we omitted data for patients with incomplete dates for their first symptom: we excluded 30 with haematuria, 10 with haemoptysis, 4 with dysphagia, and 25 with rectal bleeding. The figure shows the distribution of related cancer diagnoses by quarter after the first recorded alarm symptom. Diagnoses of cancer were most often made in the first three months after the onset of alarm symptoms; very few diagnoses of cancer were made later than three years after symptom onset. Table 3 gives the observed numbers of new occurrences of related cancers in the first six months and three years after symptom onset, with positive predictive values and likelihood ratios for each symptom. Haematuria and haemoptysis had the highest predictive values for cancer, followed by dysphagia and rectal bleeding. In the fourth and fifth years of study, the small number of observed occurrences of cancer were similar to the number expected from background incidence rates (fig).

In secondary analyses, we searched for diagnoses of cancer other than those that we had pre-specified. After

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Age and sex specific incidence of alarm symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>No with symptom</td>
</tr>
<tr>
<td>Haematuria</td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>359</td>
</tr>
<tr>
<td>25-34</td>
<td>413</td>
</tr>
<tr>
<td>35-44</td>
<td>571</td>
</tr>
<tr>
<td>45-54</td>
<td>745</td>
</tr>
<tr>
<td>55-64</td>
<td>790</td>
</tr>
<tr>
<td>65-74</td>
<td>847</td>
</tr>
<tr>
<td>75-84</td>
<td>688</td>
</tr>
<tr>
<td>≥85</td>
<td>293</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>141</td>
</tr>
<tr>
<td>25-34</td>
<td>182</td>
</tr>
<tr>
<td>35-44</td>
<td>230</td>
</tr>
<tr>
<td>45-54</td>
<td>272</td>
</tr>
<tr>
<td>55-64</td>
<td>364</td>
</tr>
<tr>
<td>65-74</td>
<td>360</td>
</tr>
<tr>
<td>75-84</td>
<td>258</td>
</tr>
<tr>
<td>≥85</td>
<td>77</td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>87</td>
</tr>
<tr>
<td>25-34</td>
<td>181</td>
</tr>
<tr>
<td>35-44</td>
<td>374</td>
</tr>
<tr>
<td>45-54</td>
<td>521</td>
</tr>
<tr>
<td>55-64</td>
<td>522</td>
</tr>
<tr>
<td>65-74</td>
<td>659</td>
</tr>
<tr>
<td>75-84</td>
<td>645</td>
</tr>
<tr>
<td>≥85</td>
<td>383</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>682</td>
</tr>
<tr>
<td>25-34</td>
<td>1019</td>
</tr>
<tr>
<td>35-44</td>
<td>1085</td>
</tr>
<tr>
<td>45-54</td>
<td>1271</td>
</tr>
<tr>
<td>55-64</td>
<td>1201</td>
</tr>
<tr>
<td>65-74</td>
<td>1161</td>
</tr>
<tr>
<td>75-84</td>
<td>912</td>
</tr>
<tr>
<td>≥85</td>
<td>430</td>
</tr>
</tbody>
</table>
haematuria, inclusion of cancers of the reproductive organs yielded 21 additional cancers in women and 158 cancers in men, mostly cancers of the prostate. Inclusion of these cancers in the analysis would give a positive predictive value of 3.9% in women and 9.9% in men. After dysphagia, inclusion of gastric cancers yielded 17 additional cancer diagnoses in women and 30 in men. Inclusion of these cancers gave positive predictive values of 5.2% in women and 6.9% in men. Estimates based on the pre-specified cancers may be thus conservative for these symptoms. Extending the diagnostic criteria yielded only six additional cancers after haemoptysis and two additional cancers after rectal bleeding. Table 4 shows the predictive value of each alarm symptom for cancer over the next three years in six age groups, emphasising the substantial effects of both age and sex.

Table 5 shows the proportion of patients who received a diagnosis of cancer in either 1999 or 2000 and who had been recorded as having an alarm symptom in the preceding three years. Over this preceding three year period, the proportion of patients with urinary tract cancer who had previous haematuria was 58.7% in men and 51.2% in women. This represents the sensitivity of the symptom for detecting cancer. The sensitivity of haemoptysis for a diagnosis of respiratory tract cancer was 22.2% in men and 13.6% in women. The sensitivity of dysphagia for a diagnosis of oesophageal cancer was 58.3% in men and 53.8% in women, and the sensitivity of rectal bleeding for a diagnosis of rectal cancer was 33.3% in women and 25.1% in men.

**DISCUSSION**

This study provides estimates for the increased likelihood of diagnosis of a related cancer after the first episode of four common alarm symptoms often encountered in primary care. In the first three months after the first presentation with haematuria, haemoptysis, dysphagia, or rectal bleeding, the likelihood of a diagnosis of cancer was greatly increased. Over three years, the relative increase was highest for oesophageal cancer after dysphagia and lowest for a diagnosis of colorectal cancer after rectal bleeding. The increased likelihood of a diagnosis of cancer remained high during the first year after an alarm symptom but gradually declined over time and was not significantly different from background at five years. This is reflected in the predictive values for cancer that we have derived, which although significant across all age groups are striking in older patients, particularly in men and in patients with haemoptysis and haematuria.

**Strengths and limitations**

This study has the strength of a large registered and accurately characterised population, drawn from a large number of general practices. Previous studies

### Table 3 | Observed related diagnoses of cancer in first six months and three years after first alarm symptom, positive predictive value, and likelihood ratio for cancer after symptom

<table>
<thead>
<tr>
<th></th>
<th>Cumulative No of cancer diagnoses</th>
<th>Positive predictive value (%) (95% CI)</th>
<th>Expected No of cancer diagnoses</th>
<th>Likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Six months after first symptom</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematuria:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>6385</td>
<td>349</td>
<td>5.5 (4.9 to 6.1)</td>
<td>3.1</td>
</tr>
<tr>
<td>Women</td>
<td>4723</td>
<td>117</td>
<td>2.5 (2.1 to 3.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Haemoptysis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2930</td>
<td>169</td>
<td>5.8 (5.0 to 6.7)</td>
<td>1.4</td>
</tr>
<tr>
<td>Women</td>
<td>1882</td>
<td>63</td>
<td>3.3 (2.6 to 4.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Dysphagia:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2628</td>
<td>138</td>
<td>5.3 (4.4 to 6.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Women</td>
<td>3371</td>
<td>70</td>
<td>2.1 (1.6 to 2.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Rectal bleeding:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>7523</td>
<td>138</td>
<td>1.8 (1.5 to 2.2)</td>
<td>1.8</td>
</tr>
<tr>
<td>Women</td>
<td>7766</td>
<td>119</td>
<td>1.5 (1.3 to 1.8)</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Three years after first symptom</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematuria:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>6385</td>
<td>472</td>
<td>7.4 (6.8 to 8.1)</td>
<td>18.9</td>
</tr>
<tr>
<td>Women</td>
<td>4723</td>
<td>162</td>
<td>3.4 (2.9 to 4.0)</td>
<td>3.3</td>
</tr>
<tr>
<td>Haemoptysis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2930</td>
<td>220</td>
<td>7.5 (6.6 to 8.5)</td>
<td>8.7</td>
</tr>
<tr>
<td>Women</td>
<td>1882</td>
<td>81</td>
<td>4.3 (3.4 to 5.3)</td>
<td>2.5</td>
</tr>
<tr>
<td>Dysphagia:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2628</td>
<td>150</td>
<td>5.7 (4.9 to 6.7)</td>
<td>2.4</td>
</tr>
<tr>
<td>Women</td>
<td>3371</td>
<td>81</td>
<td>2.4 (1.9 to 3.0)</td>
<td>1.6</td>
</tr>
<tr>
<td>Rectal bleeding:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>7523</td>
<td>184</td>
<td>2.4 (2.1 to 2.8)</td>
<td>11.0</td>
</tr>
<tr>
<td>Women</td>
<td>7766</td>
<td>154</td>
<td>2.0 (1.7 to 2.3)</td>
<td>9.2</td>
</tr>
</tbody>
</table>
have evaluated the quality of data in the General Practice Research Database with satisfactory results,27 28 and the population of patients we have studied is likely to be similar to the general population of the UK and of other Western societies. Diagnoses recorded in the database have been shown to be generally valid, and this may be especially the case for cancer. The incidences we report are broadly similar to those reported from cancer registries, but such comparisons are approximate for several reasons. We derived our denominator data from registered rather than resident populations, and they may be inflated. We have also aggregated diagnostic categories where appropriate and excluded all cases with previous diagnoses of cancer. Our analyses included only well defined groups of associated neoplasms. We acknowledge that alarm symptoms may be caused by other serious conditions, both neoplastic and non-neoplastic, as our secondary analyses showed.

We also acknowledge that greater imprecision is likely in the recording of symptoms than of medical diagnoses, and we do not know how long the symptoms were present before they were first recorded at a general practice consultation. Previous studies have indicated that patients may delay seeking medical advice for rectal bleeding, for example, for many months and for many reasons.29 In addition, we are not able to accurately characterise the nature of some of these alarm symptoms—in the case of rectal bleeding, for example, whether the blood was fresh and accompanied by pain or was darker, mixed with stool, and painless. Different presentations are likely to carry different pathological implications; Ellis and Thompson found rectal bleeding accompanied by a change in bowel habit, without any peri-anal symptoms, to have a positive predictive value for colorectal cancer of 11.1% in their study of 319 patients consulting general practitioners about rectal bleeding.29 Similarly, we are unable to comment on whether the haematuria was painful or painless, whether haemoptysis occurred in the context of a respiratory illness, or whether dysphagia was accompanied by other upper gastrointestinal symptoms or, indeed, whether swallowing difficulties were related to fluids or to solids. Studies by Bruyninckx et al and Summerton et al both emphasised the importance of associated symptoms in patients with haematuria and their propensity to “amplify” the predictive value of a single symptom.9 10

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Observed related cancer diagnoses in first three years after first alarm symptom and positive predictive value for cancer by broad age group and sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td>Women</td>
</tr>
<tr>
<td>Haematuria</td>
<td>45</td>
</tr>
<tr>
<td>45-54</td>
<td>10 745</td>
</tr>
<tr>
<td>55 to 64</td>
<td>27 790</td>
</tr>
<tr>
<td>65 to 74</td>
<td>50 846</td>
</tr>
<tr>
<td>75 to 84</td>
<td>47 688</td>
</tr>
<tr>
<td>≥85</td>
<td>25 293</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>45</td>
</tr>
<tr>
<td>45-54</td>
<td>5 272</td>
</tr>
<tr>
<td>55 to 64</td>
<td>15 364</td>
</tr>
<tr>
<td>65 to 74</td>
<td>30 358</td>
</tr>
<tr>
<td>75 to 84</td>
<td>27 258</td>
</tr>
<tr>
<td>≥85</td>
<td>2 77</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>45</td>
</tr>
<tr>
<td>45-54</td>
<td>3 520</td>
</tr>
<tr>
<td>55 to 64</td>
<td>10 522</td>
</tr>
<tr>
<td>65 to 74</td>
<td>25 659</td>
</tr>
<tr>
<td>75 to 84</td>
<td>26 645</td>
</tr>
<tr>
<td>≥85</td>
<td>16 383</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>45</td>
</tr>
<tr>
<td>45-54</td>
<td>8 1270</td>
</tr>
<tr>
<td>55 to 64</td>
<td>33 1200</td>
</tr>
<tr>
<td>65 to 74</td>
<td>28 1156</td>
</tr>
<tr>
<td>75 to 84</td>
<td>67 930</td>
</tr>
<tr>
<td>≥85</td>
<td>12 430</td>
</tr>
</tbody>
</table>

*Total number of patients in category with alarm symptom.
Table 5 | Occurrence of alarm symptoms in three years preceding diagnosis of neoplasms for cases diagnosed in 1999 and 2000. Values are cumulative frequencies unless stated otherwise

<table>
<thead>
<tr>
<th>Cancers diagnosed in 1999 or 2000</th>
<th>Alarm symptom in preceding 3 years</th>
<th>Sensitivity (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urinary tract neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>293</td>
<td>172</td>
</tr>
<tr>
<td>Women</td>
<td>125</td>
<td>64</td>
</tr>
<tr>
<td><strong>Respiratory tract neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>302</td>
<td>67</td>
</tr>
<tr>
<td>Women</td>
<td>169</td>
<td>23</td>
</tr>
<tr>
<td><strong>Oesophageal neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>84</td>
<td>49</td>
</tr>
<tr>
<td>Women</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td><strong>Colorectal neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>237</td>
<td>79</td>
</tr>
<tr>
<td>Women</td>
<td>183</td>
<td>46</td>
</tr>
</tbody>
</table>

**Implications**

However, we believe that this new analysis offers additional information on which to base guidance for general practitioners on the management of patients presenting with alarm symptoms, four of which we have studied here. We have shown a very significantly increased risk of cancer being diagnosed in the three to six month period after presentation with an alarm symptom, with different risks attached to different alarm symptoms, different sexes, and different age ranges. The differences in age and sex specific incidence rates for these alarm symptoms are interesting. To some extent, they are likely to reflect the differential prevalence of the various cancers in men and women, but they may also be related to differences in healthcare seeking behaviour in men and women.

For haematuria, the risk of a cancer being diagnosed is greatly increased in the first three to six months after presentation, particularly in younger patients and, in the later years, in middle aged men and older women. Haematuria that is unexplained by urinary tract infection can readily be investigated by careful physical examination and fibreoptic cystoscopy and imaging of the upper renal tract, and our results suggest that these investigations should be done with a minimum of delay in patients in the highest risk groups identified in this study.

Haemoptysis has an unsurprisingly low sensitivity for a respiratory tract malignancy, most likely because of its frequent association with respiratory tract infection. However, unexplained haemoptysis is associated with a very high risk of a diagnosis of cancer, particularly in the three month period after haemoptysis, suggesting that when haemoptysis is unexplained by respiratory infection or other local factors, imaging studies should be done in a timely fashion to identify or exclude an underlying neoplasic cause.

Dysphagia is also associated with a high rate of diagnosis of oesophageal cancer, particularly in men, in the three to six month period immediately after presentation, suggesting that dysphagia unexplained by non-neoplastic diseases such as reflux oesophagitis should be investigated promptly. Recent guidelines on the management of gastro-oesophageal reflux disease have suggested that only progressive dysphagia should be regarded as an alarm symptom and that dysphagia improves with antisecretory treatment in many reflux patients, but our data suggest that progress needs to be monitored over a fairly narrow time frame if early diagnosis is to be facilitated. A recently published systematic review underlines the weakness of data available to guide clinicians on the most appropriate management of patients with dysphagia, and our data add weight to the recognition of this symptom as being significantly associated with a high risk of a cancer diagnosis in the three month period after presentation. Although database studies are unable to capture the finer details of patients’ symptom presentations, they have the major advantage of providing much greater analytical power than clinical studies, such as follow-up of prospective endoscopic series.

Finally, rectal bleeding, a common problem in the general population and a controversial topic in terms of the need for full investigation, is associated with high rates of cancer diagnosis in the 90 day period immediately after presentation. A recent study from general practice in the UK suggested that one in 10 patients presenting with rectal bleeding have colonic neoplasia, and the authors recommended full investigation of all patients with rectal bleeding on the basis of these figures. Some evidence exists that the characteristics of the bleeding are important in making a decision to investigate urgently, and, because of the ubiquity of rectal bleeding [affecting 10-20% of the general population each year], our epidemiological data need to be considered in the context of the clinical presentation and the likelihood of the bleeding (painless, dark blood, mixed with stool) being related to a colonic malignancy, although of course all rectal bleeding needs to be investigated by local examination and by digital rectal examination as an absolute minimum.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Alarm symptoms or “red flags” are often used to identify patients whose symptoms need investigation. The evidence for the “alarming” nature of some of these symptoms is weak.

**WHAT THIS STUDY ADDS**

Likelihood ratios for a diagnosis of cancer after haematuria, haemoptysis, dysphagia, and rectal bleeding are high in the first six months and fall towards unity at around three years. Predictive values for a diagnosis of cancer vary according to age, sex, and alarm symptom, and rise with age.

The data provide support for the selection of patients presenting with these symptoms in general practice and needing urgent investigation.

**Conclusions**

Taken overall, our results provide additional support for the concept of alarm symptoms in primary care—symptoms that are associated with a subsequently greatly elevated risk of serious disease being identified. The association between alarm symptoms and high rates of cancer diagnosis vary somewhat between
men and women and across different age ranges, and individual alarm symptoms have different sensitivities and specificities for a final diagnosis of cancer. The most striking associations found in our study were between haematuria and urinary tract neoplasmia and between dysphagia and oesophageal neoplasia; haemoptysis and rectal bleeding had less strong associations and predictive values.

More research in this area, using well characterised, large patient populations, should further refine the implications of alarm symptoms and, in particular, use more detailed description of the symptoms themselves and of patients’ characteristics to determine the urgency with which investigations and specialist referral need to be pursued.

Contributors: RJ had the original idea for the study, which was designed by all authors. MCG, RL, and JC extracted and analysed data. RJ drafted the paper, and all authors contributed to the final version. MCG is the guarantor.

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Genital herpes and its management

P Sen,1 S E Barton2

Genital herpes is an important public health disease and is the leading cause of genital ulcer disease worldwide. We present the latest evidence based guidelines from the British Association for Sexual Health and HIV (BASHH), the Centers for Disease Control and Prevention (CDC), and other expert committees to provide an up to date account of genital infection with herpes simplex virus (HSV), its clinical features and diagnosis, and a practical approach to management of affected patients.

Treatment regimens have largely been based on evidence obtained from randomised controlled trials, while certain new diagnostic tests are limited by lower levels of evidence obtained only from descriptive or case studies.

Sources and selection criteria
We searched PubMed (1966-2006) for relevant studies using keywords and text terms for genital herpes. We accessed the WHO and Health Protection Agency (United Kingdom) website to assess the disease burden of genital herpes and consulted guidelines on genital herpes from the British Association for Sexual Health and HIV (2001) and the Centers for Disease Control and Prevention (CDC, 2006). Additional data and references were obtained from International Union against Sexually Transmitted Infections (IUSTI) meetings, BASHH meetings, the International Herpes Management Forum (IHMF), the World STI/HIV congress, and a personal archive of references.

What causes genital herpes and how is infection acquired?
Genital herpes is caused by infection with herpes simplex virus (HSV), commonly by HSV type 2 and now increasingly by type 1. Both HSV-1 and HSV-2 infections are acquired from contact with infectious secretions on oral, genital, or anal mucosal surfaces. Genital herpes can also be acquired from contact with lesions from other anatomical sites such as the eyes and non-mucosal surfaces such as herpetic whitlow on fingers or from lesions on the buttocks and trunk.

What is the prevalence of genital herpes in the UK and worldwide?
In the UK, there was a 15% increase in the number of diagnoses of first attack of genital herpes from 16 479 cases in 1995 to 19 180 cases in 2004.1 In the United States, an estimated 40-60 million people are infected with HSV-2, with an incidence of 1-2 million infections and 600 000-800 000 clinical cases a year.2 The prevalence of genital herpes in developing countries varies from 2-74% according to the country. In some African countries that are experiencing HIV epidemics, HSV-2 is highly prevalent (≥70%), and there is evidence that genital HSV increases the risk of HIV infection and that people with both are more likely to transmit HIV infection.3

How do patients present?
First (initial) episode of genital herpes
The initial episode is the first episode of genital infection with either HSV-1 or HSV-2 (box 1). Primary genital herpes is the first episode in an individual with no pre-existing antibodies to either HSV type. A non-primary first episode is the first infection in an individual with pre-existing antibodies to the other HSV type.4,5

Recurrent genital herpes
Groups of vesicles or ulcers develop in a single anatomical site and heal within 10 days. For the first two years patients may experience an average of five clinical episodes a year, which may reduce in frequency thereafter. Genital HSV caused by type 1 infection recurs less often, and thus typing of infection may inform patient counselling.
Asymptomatic HSV infection
Most people with HSV infection have mild unrecognised or subclinical disease and are unaware of their infection. They may shed the virus intermittently in the genital tract and thus transmit the infection to their sexual partners entirely unknowingly. Subclinical shedding occurs most commonly in the first year of infection in patients with genital HSV-2 infection and in individuals with frequent symptomatic recurrences. Perianal shedding is common in HIV negative, HSV-2 seropositive men who have sex with men and are asymptomatic. Most infections of genital herpes are transmitted by people who are unaware that they are infected or who have no symptoms when transmission occurs.

How do I make a diagnosis of genital herpes?
The clinical diagnosis of genital HSV infection has a low sensitivity and specificity; laboratory confirmation of infection and typing of HSV is essential as it influences the management, prognosis, and counseling of patients.

Detection of HSV in clinical lesions—Table 1 compares the methods of detection. Take swabs from the base of the lesion or fluid from a vesicle. For culture tests it is essential that the cold chain (4°C) is maintained and appropriate media are used. Polymerase chain reaction (PCR) is the most useful test as less meticulous handling of specimens is required.

Serology—Commercial tests that use complement fixation are not type specific. Seroconversion from a zero baseline is usually diagnostic of a primary infection. In the case of recurrent infection, an immune response from a non-zero baseline may be detected. These tests cannot distinguish between initial and recurrent infections, however, and have been replaced by sensitive tests such as enzyme linked immunosorbent assay (ELISA) and radioimmunoassay (RIA). Type specific serology tests (TSSTs), which detect glycoprotein G2 specific to HSV-2 and glycoprotein G1 specific to HSV-1 infection, are the only commercially available diagnostic tools available to identify those with asymptomatic HSV infection and can effectively distinguish the two types with high sensitivity (80-98%) and specificity (≥96%). Case control studies have shown that there are certain clinical settings when these tests may help the diagnosis of HSV infection (boxes 2 and 3).

How do I manage patients with genital herpes?
First episode of genital herpes
General measures (evidence level IV, grade C, table 2) for treating patients with a first episode include cleaning affected areas with normal saline, giving analgesia (systemic or local, such as lidocaine gel), and treating any secondary bacterial infection.

Specific antiviral therapy
Aciclovir has a good record of safety and efficacy and is available in generic formulations. Other drugs, such as valaciclovir and famciclovir, have less frequent dosing regimens compared with aciclovir (box 4) but are more expensive. Randomised control trials have shown that all three drugs reduce the severity and duration of clinical attacks. None of these drugs eradicate the infection or latent virus.

There is no evidence of benefit from courses of treatment longer than five days. BASHH guidelines, however, recommend that treatment should be continued beyond five days if new lesions continue to form, if

### Table 1 | Comparison of detection methods for HSV in clinical lesions

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Viral typing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tzanck smear</strong></td>
<td>Low</td>
<td>Low</td>
<td>No</td>
<td>Shows giant cells from lesions, provides presumptive evidence of infection</td>
</tr>
<tr>
<td><strong>Virus culture</strong></td>
<td>High</td>
<td>High</td>
<td>Yes</td>
<td>Ideal test. Sensitivity declines as lesions heal</td>
</tr>
<tr>
<td><strong>Antigen detection</strong> (DFA or EIA)</td>
<td>Low</td>
<td>High</td>
<td>No</td>
<td>Low cost and rapid</td>
</tr>
<tr>
<td><strong>PCR</strong></td>
<td>Highest</td>
<td>High</td>
<td>Yes</td>
<td>Rapid but expensive. Useful in late clinical lesions. Test of choice in examination of cerebrospinal fluid. Used for research studies</td>
</tr>
</tbody>
</table>

DFA=direct fluorescent antigen; EIA=enzyme immunoassay; PCR=polymerase chain reaction.
At least one randomised controlled trial as part of the body
of literature of overall good quality and consistency
addressing the specific recommendation

Availability of well controlled clinical studies but no
randomised clinical trials on topic of recommendation

Evidence obtained from expert committed reports or
opinions or clinical experiences of respected authorities,
or both. Indicates absence of directly applicable clinical
studies of good quality

<table>
<thead>
<tr>
<th>Grades</th>
<th>Requirement</th>
<th>Equivalent evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation</td>
<td>Ia—evidence obtained from meta-analysis of randomised controlled trials; Ib—evidence obtained from at least one randomised controlled trial</td>
</tr>
<tr>
<td>B</td>
<td>Availability of well controlled clinical studies but no randomised clinical trials on topic of recommendation</td>
<td>Ila—evidence obtained from at least one well designed controlled study without randomisation; Ib—evidence obtained from at least one other type of well designed quasi-experimental study; III—evidence obtained from well designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies</td>
</tr>
<tr>
<td>C</td>
<td>Evidence obtained from expert committed reports or opinions or clinical experiences of respected authorities, or both. Indicates absence of directly applicable clinical studies of good quality</td>
<td>IV—evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities</td>
</tr>
</tbody>
</table>

Box 4 | Recommended regimens for first episode of genital herpes (1b, A)\(^4\)
---|---
Aciclovir 200 mg orally five times a day for 5-10 days or
Aciclovir 400 mg orally three times a day for 5-10 days or
Valaciclovir 500 mg to 1 g orally twice a day for 5-10 days or
Famciclovir 250 mg orally three times a day for 5-10 days

Box 5 | Recommended regimens for episodic therapy (1a, A)\(^5\)
---|---
Aciclovir 200 mg orally five times a day for 5 days or
Aciclovir 400 mg orally three times a day for 5 days or
Aciclovir 800 mg orally twice a day for 5 days or
Aciclovir 800 mg orally three times a day for 2 days or
Valaciclovir 500 mg orally twice a day for 3-5 days or
Valaciclovir 1 g orally once a day for 5 days or
Famciclovir 125 mg orally twice a day for 5 days or
Famciclovir 1 g orally twice a day for 1 day

Randomised controlled trials have shown all these regimens to be effective. Our preferred treatment is aciclovir 400 mg orally three times a day for five days because it is effective and low cost.

**Suppressive antiviral therapy (1a, A)**—Meta-analyses of randomised controlled trials have shown that suppressive antiviral therapy can significantly reduce (by 70 to 80%) the number of recurrences in patients with frequently recurring (≥6 recurrences a year) genital herpes.\(^{12}\) Box 6 shows the recommended regimen. Patients should discontinue treatment after 12 months to assess the ongoing frequency of recurrences. The timing of this should be agreed with the patient, and recurrences should be treated.

**How do I manage patients with asymptomatic HSV infection?**

A landmark study by Corey et al found that daily suppressive treatment with valaciclovir can reduce HSV-2 transmission among HSV-2 discordant heterosexual couples by 75% for clinical disease and reduce acquisition (measured by serology) by 48%.\(^{13}\) Other antiviral drugs may be effective but have not been investigated.\(^{14}\)

**What are the important points to discuss when counselling patients?**

Counselling infected people and their sexual partners is integral to the successful management of genital symptoms and signs are severe, or if the patient also has HIV. The guidelines also state that combined oral and topical treatment is of no additional benefit. Numerous over the counter and internet based topical and oral “herbal cures” are available. There is no scientific evidence for the use of essential oils, plant extracts, zinc, and L-lysine, and they have no place in the management of genital herpes.

Our preferred treatment is aciclovir 400 mg orally three times a day for seven days because it is effective, low cost, and patients comply with treatment.

**Recurrent genital herpes**

Treatment of recurrent attacks includes supportive therapy, episodic antiviral therapy, or suppressive antiviral therapy. Most recurrent attacks are mild and self limiting however, and can be managed with supportive therapy only. General measures for treating patients include cleaning the affected areas with normal saline, giving analgesia (systemic or local such as lidocaine gel), and treating secondary bacterial infection.

**Supportive therapy**—Supportive therapy includes saline bathing, the use of analgesia, and counselling of sexual behaviour and can be instituted when recurrences are mild and self limiting.

**Episodic antiviral therapy (1a, A)**—Initiate episodic antiviral therapy during the prodrome or early in an attack (Box 5).\(^{6}\) Oral aciclovir, valaciclovir,\(^{11}\) and famciclovir\(^7\) reduce the severity and duration by a median of one to two days.\(^{6,9}\) Topical antiviral therapy is less effective than systemic therapy.\(^4\)

How do I manage patients with asymptomatic HSV infection?

A landmark study by Corey et al found that daily suppressive treatment with valaciclovir can reduce HSV-2 transmission among HSV-2 discordant heterosexual couples by 75% for clinical disease and reduce acquisition (measured by serology) by 48%.\(^{13}\) Other antiviral drugs may be effective but have not been investigated.\(^{14}\)

What are the important points to discuss when counselling patients?

Counselling infected people and their sexual partners is integral to the successful management of genital
Physicians should provide counselling to help patients cope with infection and prevent sexual and perinatal transmission. We have summarised the various points that physicians need to consider and discuss when counselling patients (box 7). This guide comes from personal practices and guidance from the British Association for Sexual Health and HIV (BASHH), the Centers for Disease Control and Prevention (CDC), and the International Herpes Management Forum. Educational reading material and access to web based literature on genital herpes should be provided as part of the counselling process.

**Box 7 | Points to discuss during counselling**

- Information on the natural course of the disease, the potential for recurrent attacks, and the role of asymptomatic shedding in sexual transmission. Patients should be informed that asymptomatic viral shedding is more common in genital HSV-2 than HSV-1 infection and is most frequent in the first 12 months after the infection is acquired.
- Patients with a first episode of genital herpes should be told that this does not necessarily indicate recent infection and that genital symptoms may develop several years after the infection is acquired.
- Information on antiretroviral treatments available and their impact on infectivity. Episodic as well as suppressive therapy should be discussed with patients in respect to recurrent episodes of infection.
- Patients in a stable long term relationship where one partner is not infected may remain discordant for several years despite potential repeated exposure; they should be told that the risk of sexual transmission of HSV-2 can be reduced by the daily use of valaciclovir by the infected partner.
- Abstention from sexual activity during prodromal symptoms or when lesions are present.
- Advice to inform current and new sexual partners before initiating a sexual relationship.
- Use of condoms with new or uninfected partners, particularly in the 12 months after the first attack.
- Sexual partners of infected patients should be advised that they may be infected even if they have no symptoms. Type specific serological testing should be offered to them to determine whether they are at risk of HSV acquisition.
- Asymptomatic people who test positive for HSV-2 infection on type specific serology testing should be counselled in the same way as those with symptoms and taught to recognise the clinical manifestations of infection.
- Women with a history of genital herpes or with male partners with a history of genital herpes should inform their doctors early in any pregnancy to prevent the risk of neonatal infections.
- Pregnant women who are not infected with HSV-2 should avoid sexual intercourse with their male infected partners during the third trimester. Pregnant women who are not infected with HSV-1 should also avoid genital exposure to HSV-1 during the third trimester (such as oral sex with a partner with oral herpes and vaginal intercourse with a partner with genital HSV-1 infection).

How do I manage genital herpes in a pregnant woman?

Data from the aciclovir pregnancy registry on the use of aciclovir in pregnancy does not show any increase in the number of birth defects.

First episode of genital herpes

For women who acquire the infection in the first and second trimester treat with oral or intravenous aciclovir in standard doses and plan for vaginal delivery. For women in who vaginal delivery is planned, continuous aciclovir in the last four weeks of pregnancy will reduce the risk of clinical recurrence at term delivery by caesarean section (1b, A).

All women presenting with the first episode of genital herpes after 34 weeks’ gestation should be delivered by caesarean section. If vaginal delivery is unavoidable, treat the mother and baby with aciclovir.

Recurrent genital herpes

In women with recurrent infection caesarean section should not be performed if there are no genital lesions at the time of delivery. Daily suppressive aciclovir in the last four weeks of pregnancy might prevent recurrences of genital herpes at term and might be cost effective. If genital lesions are present at the onset of labour, experts recommend delivery by caesarean section.

What is the interaction between genital HSV-2 and HIV?

Both HSV and HIV have reached epidemic proportions in certain developing countries. Genital herpes caused by HSV-2 infection has been shown to double the risk of becoming infected with HIV through sexual transmission. The ulcers and breaks in the genital mucosa and skin caused by HSV-2 infection facilitate entry of the HIV virus. These lesions contain large numbers of CD4 lymphocytes, which are target cells for HIV. Transmission of HIV is more likely from people who also have HSV-2, possibly because of high titres of HIV in genital secretions during HSV-2 reactivation.

How do I manage genital herpes in HIV positive or immunocompromised patients?

In patients with HIV or who are otherwise immunocompromised, episodes may be prolonged, more severe, and require a longer duration of antiviral treatment (box 8). A recent study found that treatment with valaciclovir at 1 g a day significantly reduced HIV RNA genital shedding as well as the plasma viral load. These data support the hypothesis that therapy

**Box 8 | Recommended regimens for daily suppressive therapy in people with HIV**

- Aciclovir 400-800 mg orally twice a day
- Valaciclovir 500 mg orally twice a day
- Famciclovir 500 mg orally twice a day
for genital HSV infection in people with HIV reduces the risk of their transmitting HIV and may affect the natural progression of HIV infection. Further studies to investigate this are ongoing.

What about a vaccine?

To date the development of effective vaccines has not been promising. Difficulties arise because of the complexity of the life cycle of the virus (latency) and the current lack of understanding of the human mechanism of control of primary and recurrent disease. A large scale study of a gD2-AS04 vaccine is being carried out to further evaluate the protective effects in women as initial studies have shown differential effects in men and women.

Conclusions

Genital herpes is an important public health disease that can cause substantial morbidity if it is undiagnosed and untreated. Clinicians should suspect HSV infection in all patients presenting with ulcers in the genital area. Genital HSV infection increases the risk of HIV infection and people with both infections are more likely to transmit HIV to their sexual partners.

Contributors: Both authors contributed equally to the manuscript.

Competing interests: None declared

Provenance and peer review: Commissioned, peer reviewed.


9 Ashley RL. Sorting out the new HSV type specific antibody tests. Sex Transm Infect 2001;77:237-7.


16 International Herpes Management Forum. Patient information leaflets. www.himf.org/Patient/PatientResources.asp


ADDITIONAL EDUCATIONAL RESOURCES

World Health Organization (www.who.int/topics/sexually_transmitted_infections/en/)—offers factsheets and latest publications and research on genital herpes.

Centres for Disease Control And Prevention (www.cdc.gov/std/Herpes/default.htm)—offers factsheets on genital herpes.

Sexually Transmitted Diseases Diagnostics Initiative (www.who.int/std_diagnostics)


Information resources for patients

International Herpes Management Forum (www.himf.org/Patient/PatientResources.asp)—this site offers information leaflets for patients on genital herpes; the materials have been written in collaboration with people who have genital herpes to help others with the condition. The International Herpes Alliance offers support and information to those with genital herpes, those helping to manage the disease, and national patient support groups around the world. www.himf.org/Patient/PatientResources.asp

Herpes Health (Canadian site) (www.herpeshealth.ca)

Association Herpes Actualités (French site) (www.herpes.asso.fr)

Herpes Informatie Organisatie (Dutch site) (www.hiso.nl)

New Zealand Herpes Management Forum (www.herpes.org.nz)

British Association for Sexual Health and HIV (www.bashh.org/guidelines/2002/hsv_0601.pdf)—offers the latest UK management guidelines on genital herpes.

Centers for Disease Control and Prevention (www.cdc.gov/std/Herpes/default.htm)—offers facts, statistics, treatment guidelines, and other resources on genital herpes.
NICE GUIDELINES

Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients having surgery: summary of NICE guidance

Jennifer Hill, Tom Treasure, on behalf of the Guideline Development Group

Why read this summary?

Deep vein thrombosis occurs in over 20% of patients having major surgery and over 40% of patients having major orthopaedic surgery. The postoperative risk of pulmonary embolism can be as high as 5% in the highest risk groups. However, many patients are probably not currently receiving adequate prophylactic measures. This article summarises the most recent guidance from the National Institute for Health and Clinical Excellence (NICE) on how to reduce the risk of venous thromboembolism in inpatients having surgery.

Recommendations

NICE recommendations are based on systematic reviews of best available evidence. When minimal evidence is available, a range of consensus techniques is used to develop recommendations. In this summary, recommendations derived primarily from consensus techniques are indicated with an asterisk (*).

Assess patients for risk factors

Assess patients for the following risk factors, and inform all patients of the risks of venous thromboembolism and the effectiveness of prophylaxis.

- Age over 60 years
- Obesity (body mass index ≥30)
- Continuous travel of more than three hours during the four weeks before or after surgery
- Immobility (for example, paralysis or limb in plaster)
- Personal or family history of venous thromboembolism
- Varicose veins with associated phlebitis
- Active cancer or cancer treatment
- Active heart or respiratory failure
- Severe infection
- Acute medical illness
- Recent myocardial infarction or stroke
- Inflammatory bowel disease (for example, Crohn’s disease and ulcerative colitis)
- Use of oral contraceptives or hormonal replacement therapy
- Pregnancy or puerperium
- Certain specific haematological or systemic causes of prothrombotic state (such as antiphospholipid syndrome, Behçet’s disease, central venous catheter in situ, inherited thrombophilias, myeloproliferative diseases, nephrotic syndrome, paraproteinaemia, paroxysmal nocturnal haemoglobinuria).

General prevention of venous thromboembolism

- Offer all surgical inpatients a mechanical method of prophylaxis (graduated compression or antiembolism stockings, intermittent pneumatic compression, or foot impulse devices) except where contraindicated (for example, do not offer graduated compression stockings to patients with peripheral arterial disease or diabetic neuropathy.
- Offer both mechanical prophylaxis and low molecular weight heparin to all inpatients having orthopaedic surgery (and inpatients having other surgery who have one or more of the risk factors listed above). Fondaparinux, within its licensed indications, may be used as an alternative to low molecular weight heparin.
- Offer thigh length stockings (worn until usual level of mobility), but knee length stockings may be used to improve compliance or fit. The compression should be about 18 mm Hg at the ankle, 14 mm Hg at the mid-calf, and 8 mm Hg at the upper thigh.
- Healthcare professionals trained in the use of compression stockings should show patients how to wear them correctly. Monitor use and provide help if necessary.*
- Consider regional instead of general anaesthesia. If regional anaesthesia is used, plan the timing of pharmacological prophylaxis carefully to minimise the risk of haematoma.
- Encourage patients to become mobile as soon as possible after surgery and to do leg exercises if immobile.*
- Ensure the patient does not become dehydrated.*
- Consider risks and benefits of stopping pre-existing established anticoagulation or antiplatelet therapy before surgery.*
Prevention for specific types of inpatient surgery

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Patient has no risk factors</th>
<th>Patient has ≥1 risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip replacement</td>
<td>Mechanical prophylaxis plus LMWH or fondaparinux</td>
<td>Mechanical prophylaxis plus LMWH or fondaparinux (continue for four weeks)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>Mechanical prophylaxis plus LMWH or fondaparinux (continue for four weeks)</td>
<td>Mechanical prophylaxis plus LMWH or fondaparinux (continue for four weeks)</td>
</tr>
<tr>
<td>Other orthopaedic</td>
<td>Mechanical prophylaxis plus LMWH or fondaparinux</td>
<td>Mechanical prophylaxis plus LMWH or fondaparinux</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Mechanical prophylaxis</td>
<td>Mechanical prophylaxis plus LMWH (if no other anticoagulants used)</td>
</tr>
<tr>
<td>General</td>
<td>Mechanical prophylaxis</td>
<td>Mechanical prophylaxis plus LMWH or fondaparinux</td>
</tr>
<tr>
<td>Gynaecological (excluding caesarean)</td>
<td>Mechanical prophylaxis</td>
<td>Mechanical prophylaxis plus LMWH or fondaparinux</td>
</tr>
<tr>
<td>Neurosurgery (including spinal surgery)</td>
<td>Mechanical prophylaxis</td>
<td>Mechanical prophylaxis plus LMWH (except patients with ruptured cranial or spinal vascular malformations if the lesion has not been secured)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>Mechanical prophylaxis</td>
<td>Mechanical prophylaxis plus LMWH</td>
</tr>
<tr>
<td>Urological</td>
<td>Mechanical prophylaxis</td>
<td>Mechanical prophylaxis plus LMWH</td>
</tr>
<tr>
<td>Vascular</td>
<td>Mechanical prophylaxis</td>
<td>Mechanical prophylaxis plus LMWH</td>
</tr>
</tbody>
</table>

LMWH=low molecular weight heparin.

Advice to patients

- Warn patients that the immobility associated with continuous travel of more than three hours in the four weeks before or after surgery may increase the risk of venous thromboembolism.
- Advise patients to consider stopping combined oral contraception four weeks before elective surgery.
- Give patients (as part of their discharge plan) oral and written information on the signs and symptoms of deep vein thrombosis and pulmonary embolism, the correct use of prophylaxis at home, and the implications of not using the prophylaxis correctly.

Specific strategies

For recommended prevention strategies for specific types of inpatient surgery, see the table.

Overcoming barriers

Some clinicians hold strong views about the overall benefits of reducing the risk of deep vein thrombosis or pulmonary embolism with drugs that increase the risk of bleeding. The balance of risks cannot be quantified from clinical experience, and moreover, a recent adverse experience tends to affect objective consideration. The highly valued concept of clinical judgment conflicts with recognition that adherence to an evidence based guideline may be safer for doctors as well as for patients.

NICE has developed tools to help organisations implement the guidance (see www.nice.org.uk/page.aspx?q=toolkit). Further information about the guidance is available on bmj.com.

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Commentary: NICE—setting clinical standards

Gillian Leng, Michael Rawlins, Mercia Page

The clinical guidelines programme of the National Institute for Health and Clinical Excellence (NICE) is arguably the largest in the world and is unique in considering both cost effectiveness as well as clinical effectiveness. This article by Hill and Treasure is the first in a series to be published in the BMJ: each article will give a short account of key features of newly published NICE guidelines. The articles will particularly focus on areas where changes in current practice are recommended.

NICE guidelines are produced by an independent guideline development group. Its members include relevant clinicians, experts in areas such as systematic reviews and health economics, as well as at least two patients or carers. The development process is based on an internationally agreed methodology (box) and NICE has now published almost 50 clinical guidelines. In a recent survey, NICE’s guideline on schizophrenia achieved a higher total score (and by a wide margin) on all internationally agreed elements of guideline development than any of the 26 other international guidelines on the same topic.

There is no point, though, in developing clinical
Making a difference: now it’s your turn

Sitting beside your patient in a consultation, how can you make the greatest difference? How can you minimise morbidity, reduce mortality and, improve quality of life? And, if your patients wish to do all they can for their own personal health gain, where do they get most benefit?

Earlier this year, we sought your views on the greatest medical breakthroughs since 1840. Your vote concluded that the major advances were mostly in public health and at population level. But most health care occurs when doctors and patients meet one to one. We would now like to focus on the doctor-patient interface and ask you to vote on the areas you feel can make the greatest difference to personal health.

In fewer than 100 words, tell us what interventions you think offer the greatest potential benefit. We don’t want to anticipate your suggestions, but possible examples could be home based palliative care, improving cardiovascular risk factors in type 2 diabetes, reducing falls in elderly people, preventing hospital infection, avoiding prescription errors. Armed with your nominations—and the priority lists published by major national and international healthcare organisations, research bodies, and charities—we will draw up a short list. Later this year we will ask you to vote, and the result of this vote will have a major influence on the direction of the BMJ and BMJ Publishing Group in the next year.

We will focus our resources across the BMJ Group in the key areas that you identify. In the BMJ we will commission a range of relevant articles, including editorials and reviews. Detailed analyses of each condition—including morbidity and mortality—will be provided, so that in a year or two we can look back to see if there has been any change. We will promote BMJ Masterclasses where you can come a hear the experts, commission BMJ Learning to create appropriate self-assessment and learning resources, bring together the latest reviews from Clinical Evidence, look at patient management through the Drug and Therapeutics Bulletin, and work with BMJ Journals to provide more in-depth analysis of a specialist nature as appropriate.

The BMJ is more than a journal, and the BMJ Group is much more than a publisher. We want to be an active partner for doctors and patients. This is your opportunity to tell us what you would like. Make your nominations as a rapid response to this article online at bmj.com Domhnall MacAuley primary care editor, BMJ@dmacauley@bmj.com
RATIONAL IMAGING

Minimally invasive treatment for liver and lung metastases in colorectal cancer

Alice Gillams

The patient
A 59 year old woman had an anterior resection for primary Duke's C rectal carcinoma in 2004 followed by adjuvant chemotherapy. Two years later, on routine computed tomography surveillance, she was found to have liver (fig 1) and lung (fig 2) metastases.

Surveillance after resection of primary colorectal cancer
Surveillance is indicated in patients with Duke's B or Duke's C colorectal carcinoma who are potential candidates for further therapeutic intervention. The optimal surveillance strategy is a matter of debate. An ongoing trial (FACS) is looking at the cost effectiveness of intensive follow-up or no follow-up in patients with successfully resected colorectal cancer (www.facs.soton.ac.uk). Currently, most centres opt for computed tomography scans at six or 12 monthly intervals for the first two or three years, combined with regular measurements of serum carcinoembryonic antigen.

Because the liver metastases were centrally located in our patient, surgery would have involved removal of three quarters of the liver, followed by pulmonary lobectomy for the lung metastasis. Liver resection and pulmonary resection are associated with a small increase in mortality—less than 5% for liver resection and less than 2% for pulmonary resection—and combined liver and lung resection has been reported to improve survival for patients with metastases from colorectal cancer. However, in light of the substantial morbidity (<37%) associated with major liver surgery and the need for two surgical procedures, the patient opted for radiofrequency ablation to both areas (fig 3).

Our standard investigation for radiofrequency ablation is high quality, contrast enhanced, multidetector computed tomography, with occasional positron emission tomography—computed tomography or liver magnetic resonance imaging where specific questions need to be answered. These last two tests are used more often when investigating patients for liver resection; this is warranted given that resection is a more invasive and expensive procedure.

The liver lesions were ablated under general anaesthesia using an array of three water cooled electrodes. One month later, the patient had ablation of the lung metastasis, which was performed under conscious sedation (midazolam and fentanyl) with a single water cooled electrode. After ablation, she received systemic chemotherapy with oxaliplatin and fluorouracil.

Outcome
Follow-up scans performed four to five months after ablation show absent enhancement at the treated sites in the liver and lung consistent with ablated tumour (figs 4, 5).

What is radiofrequency ablation?
Radiofrequency ablation is a minimally invasive, image guided technique that delivers focused thermal energy directly to the tumour. Needle electrodes are positioned percutaneously into the tumour and an alternating current is applied which produces ionic agitation, frictional heating, and cell death. After successful ablation, computed tomography scans show an area of absent enhancement, which becomes smaller over time. Radiofrequency ablation for primary and secondary liver and lung tumours has been approved by the National Institute for Health and Clinical Excellence within the context of ongoing audit and research (www.nice.org.uk). Other focal ablative techniques for the destruction of tumour include cryotherapy, microwaves, lasers, and high intensity...
focused ultrasound, but radiofrequency ablation is the most widely used technique at present.

**Complications**
Complications after liver ablation include bleeding and abscess formation. Thermal injury to adjacent vulnerable structures, such as the bowel, can usually be avoided. Complications after lung ablation include pneumothorax (which occurs in about 40% of patients, although only 10% need aspiration or intercostal tube insertion), haemorrhage, pleural effusion, and infection. Contraindications to radiofrequency ablation include a predisposition to bleeding or, in the case of lung ablation, limited pulmonary reserve (forced expiratory volume in one second <1.0 litre). Treatment of small areas can be performed under conscious sedation; general anaesthesia is needed for larger treatments. Most patients spend one night in hospital.

**Indications**
Radiofrequency ablation is used in patients with limited numbers of moderately sized (<5 cm diameter) metastases for whom surgical resection is not an option. Surgery may be contraindicated for many reasons including the location or distribution of the tumour or associated comorbidity. As a result, only 15% of patients with liver metastases are candidates for surgery. Yet colon cancer is the third most common cause of death from cancer, and 50% of patients with colorectal cancer develop liver metastases. In the absence of imaging follow-up most patients present with extensive tumour. As both liver resection and ablation can be applied only to patients with limited disease, surveillance scans, which detect limited disease that can subsequently be treated, should help improve survival. Radiofrequency can be used in isolation or in conjunction with surgical resection or chemotherapy.

**Survival**
Although no randomised controlled trials exist to date, several centres have published results from case series of more than 100 patients. In our series of 167 patients with colorectal liver metastases who could not undergo resection, a subgroup of patients with five or fewer metastases, the largest of which measured less than 5 cm, and with no extrahepatic disease had a five year survival of 29%. Other groups report similar results. These results are not dissimilar to those for surgical resection in patients suitable for surgery, who have a five year survival of around 40%. Anecdotal evidence suggests that the combination of destruction of all macroscopically detected tumours with radiofrequency ablation followed by aggressive systemic chemotherapy improves survival the most. We therefore gave our patient systemic chemotherapy after ablation. Systemic chemotherapy is the first line of treatment for patients whose tumours are too large for them to undergo ablation or resection. This treatment aims to reduce the size of the tumour, so that surgery or ablation can be carried out.

The day was mine. Not going to work meant I could miss the battle of the bathrooms. With time I can manage without help, I told my wife. So with a quiet house I laid out my clothes and meandered down to the shower.

Firstly, the shampoo. The only bottle I can squeeze had disappeared, probably into my son’s overnight bag. I took my wife’s expensive stuff into the living room, lay on the couch, bit the bottle, and managed to get some of the gloop on to my head, the sofa, and under my arms. A sticky stride to the shower ensued and a good elbow turned on a scalding stream. The heat control was too stiff to turn, so tripping, dripping to the garage, naked with goose pimples, and feet gently marinading in Duckhams, I secured some pincers.

Turning the dial down from poaching temperature I noticed water rising over the tray and wondered if anyone else knew of the existence of a shower trap. Bending down risks a fall and a steadying outstretched arm has given way before with a resulting black eye. But by wedging my head in the corner of the cubicle I could squat down and prise up the top plate with the thin end of a pincer handle. The spray washed most of the detergent away. Moist armpits may signify adequate hydration but sticky axillae mean buggered arms.

Back to the bedroom where rolling on a strategically placed towel and a drunken dance for a little air drying were an essential prerequisite for tunnelling into clothes. Unfortunately my son had borrowed my jogging pants and tied the waistband drawstring far tighter than my sagging midriff could accommodate. Teeth and tugging released the constriction and the friction of the bed pulled them above my waist as I slithered over the side. Dressed but grounded.

Struggling up and forcing my feet into loosely tied trainers just as my children did before they could manage laces, I was almost set up for the day. Just the medication. A bite into the blister foil pack of riluzole netted a smear of tongue numbing powder. A sour taste before returning to bed to recover. Some colleagues arrived at lunchtime bringing a meal and messages from friends, workmates, and patients. They brought hope and warmth, and I don’t think it was emotionalism that reduced me to tears.

Later as I sat watching a courting pair of long tailed tits fluttering round the bird feeders in the afternoon sun I had time for reflection. My job was my life and my passion. The NHS and the Bevan principles were items of faith. But now I can turn off my mobile phone and ignore modernising medical careers.

My job was my life and my passion. The NHS and the Bevan principles were items of faith. But now I can turn off my mobile phone and ignore modernising medical careers.

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We welcome submissions for the personal view section. These should be no more than 850 words and should be sent electronically via http://submit.bmj.com. Please avoid references.
Penicillin and a series of fortunate events

The story of penicillin takes in a dirty petri dish, a refugee chemist, and a few human tears, finds Allen F Shaughnessy

Like an impromptu relay race, a series of fortunate events and unlikely connections between the right people with the right knowledge in the right places gave the world penicillin. We owe our antibiotic armamentarium to a dirty petri dish in Alexander Fleming's laboratory, a German refugee chemist, a rotten melon, and the rising popularity of soft drinks. And the whole process, in a sense, started with a few human tears.

"Penicillin: Triumph and Tragedy," by medical historian Robert Bud, traces the development of penicillin from a chemical stumbling on by accident to an idea, or perhaps an ideal, that has led to a social revolution.

This development began in 1929 when Fleming noticed a zone of inhibition around a colony of Penicillium mould on an agar plate of Staphylococcus. The story almost ended there, for Fleming could not simply siphon off the juice produced by the Penicillium mould and inject it into infected patients. The research needed to isolate the responsible chemical compound was stalled for years. It wasn’t until eight years later that Ernest Boris Chain, a German expatriate chemist, developed a method of producing a stable powder form.

After tests on only a handful of mice, the first “safety trial” was performed: a single dose given to a woman dying from cancer. The first clinical trial was performed on an infected patient, a policeman who developed sepsicaemia after a minor cut. Police constable Alexander improved dramatically with each penicillin injection—until supplies ran out and he succumbed. His initial response encouraged further testing in five patients, four of whom had miraculous recoveries.

Mould grows only on surfaces, and about 500 agar plates were needed to produce treatment for a single patient. Large scale production took penicillin to the cornfields of the Midwest of America.

Having found a method of mass production that could be adapted to penicillin production, the researchers searched for a more productive strain of the Penicillium mould. After a worldwide search, this better strain was found on a melon in a local market in Peoria, Illinois.

Soon, production of penicillin had grown exponentially, from the 40 mg first isolated by Chain in 1937 to four tonnes of pure drug produced in 1945. News—and then use—of penicillin grew rapidly. The first commercial production plant was opened by Pfizer.

The triumph of antibiotics allowed other medical technologies to take off. “Antibiotics supported surgeons, who were now confident they could manage infection and were routinely carrying out more ambitious operations. Cancer therapists could also reduce the immunity of patients without the worry of infection,” writes Bud.

On the other hand, the availability of antibiotics allowed for sloppiness in medical care: “Whereas before strict hygiene had been seen as essential to the avoidance of disaster, now a little less rigour was sometimes afforded. A Harvard professor warned in 1963 that the rapid growth in antibiotic use was due not just to clinical need, but also to understaffing, ignorance, and poor diagnosis.”

Not much has changed today, with the implicit motto in medicine of “when in doubt, antibioticise,” and “broader [spectrum] is better.” After all, how many children reach their fifth birthday without taking antibiotics for at least a week?

The tragedy of penicillin, according to the author, occurred when penicillin the chemical became penicillin the promise—offering hope, wellness, and freedom from pain and disease that would far outrun its therapeutic ability. As Bud points out, “Penicillin is so closely associated with ‘strong medicine’, scientific triumph, social improvement, and reliability that the very writing of a prescription gives hope to the patient and a sense of power to the doctor.”

Penicillin: Triumph and Tragedy, is a fascinating overview of the development and marketing of penicillin. It will have too much detail for some readers.

And what was the role of tears? In the years before noticing the antibacterial activity of Penicillium, Alexander Fleming had investigated the antiseptic properties of human tears. This led him to retrieve the mouldy plate from the rubbish because the mould might have produced a substance similar to the germ killing lysozyme he had identified in human tears. This insight resulted in countless lives saved and also transformed Pfizer, a small chemical company originally specialising in the production of citric acid for soft drinks, into the pharmaceutical powerhouse it is today.

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Food for thought

Cornwall’s beaches are full of successful professional driftwood. While they sip mochas and gossip at 100 dB, their boarding school children get drunk and snog in the dunes. We Scottish interlopers are viewed with suspicion. We lack the social badges, but we also enjoy the surf, the escape, and the high quality of Cornwall’s food. Interestingly, Cornwall’s hospitals have improved their food at no extra cost by sourcing ingredients locally.

When I was a junior doctor I lost weight, mainly because of the revolting hospital food, which varied in colour and consistency but all tasted the same. The salad bar simply involved mixing a kilogram of salad cream with cold leftovers. It was hot toast with margarine (even then butter was seen as dangerous) that sustained me.

When the food trolley doors were flung open, so were the wards’ windows, to let the stench out—a welcome relief to the institutional incubation we endured. Food was politely pushed around the plate and then straight into the slops. After dinner patients congregated in the smoking room for hot toast. But the poor souls on a prescription diet fared worse. Their mystical and utterly pointless diets consisted of fluorescently coloured jelly, and as it was “prescribed” it was forcibly spooned down. All patients lived in fear of the hospital dietitian.

Food is important to health, irrespective of the setting—so why can’t we get something as basic as hospital food right? Unfortunately, hospital food has been “medicalised.” The recipes are the concoction of the medical “expert” and the accountant. The expert, obsessed with “healthiness,” insists on blandness; the accountant, obsessed with cost, insists on cheapness. The result: NHS food is centrally manufactured on an industrial estate outside Slough and shipped out in juggernauts overnight. Each unit costs 0.03 p per polystyrene plateful. When patients elect to eat the plate rather than the food, concerned doctors prescribe expensive sip feed—merely milkshakes with comic book names and a periodic table of additives. What insanity.

The solution is to retrain most dietitians as cooks, reopen local kitchens, source local seasonal foods, and work to classic British recipes. Encourage patients to eat together, and throw in a glass of wine. Fund it by stopping doctors scanning everyone all the time.

This summer, if I am admitted to hospital with deafness after a prolonged bombardment of name dropping while on holiday in Cornwall, at least I know the food will be good.

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

Call me by my true name

I have been called many things, but Senile Prima Gravida was perhaps the most insulting. Fit as a fiddle, oozing health and vitality, I had to walk seething round the outpatient department carrying that stupid chart with the irritating slogan in big bold print on the front cover.

There are so many alternatives that would have added a touch of dignity and even glamour. Emeritus pregnancy. Master pregnancy. Senior pregnancy. Very Interesting Pregnancy (VIP). Medically Unusual and Distinguished pregnancy (MUD). Or even better, “Mary E Black’s remarkable and unique pregnancy.” But the medical jargon prevailed.

“The gall bladder in bed 23.” Luckily we hear that less as staff have it drilled into them that cases are people and people have names. And people do like their names, especially when frightened and ill.

Some patients are quite able to hold their own. An enthusiastic student nurse plonked herself down cheerfully yet a tad presumptuously at the end of an elderly patient’s bed. “I see your name is Elizabeth X. Would you like me to call you Elizabeth or Mrs X.” The reply, delivered with an understated yet withering dignity, was: “Young lady, you can call me Lady X.”

Even the medically qualified may need back-up. My doctor father, never one to stand on dignity, insisted on the use of his medical title during hospital visits towards the end of his life. He bluntly refused to go back to the best surgeon in town who had omitted to call him Dr and had brought in a medical student without asking. I eventually persuaded him that skill with the knife was preferable to nice manners when excising a large renal carcinoma.

Not everyone can speak out when they do not like or do not understand what they are being called. Children in particular get confused and worried when called by the wrong name. Medical labels can take on frightening meanings when half understood by those not fluent in English (or Latin).

So when in doubt, call things by their direct, true, and often simple names. And do it courteously and check the listener understands. I was thrilled with a sweet elderly patient with lovely manners, apple cheeks, and a discreet silver bun. The emergency call to her bedside three days after a straightforward end to end resection of large intestine revealed a horror scene. Her abdominal wound had dehisced, and intestines snaked all over the bed. “Oh Dr Black,” she pleaded, “What are these?” I opted for truth and got it right. “They’re only your guts, Mrs X. You’ve had them all your life. It just happens to be the first time you have actually seen them.”

Mary E Black is a public health physician, Belgrade, Serbia drmaryblack@gmail.com
A viol prejudice

According to Gorky, Lenin feared the music of Beethoven because it made him want to pat people’s heads, and this was a distraction from having them shot, which was so much more constructive.

Tolstoy had a similar, though of course not identical, reaction to Beethoven, in so far as the character of Pozdnyashov in the story The Kreutzer Sonata may be taken to express Tolstoy’s own views (as I think it may). The Kreutzer causes “an awakening of energy and feeling unsuited both to the time and place...” and “cannot but act harmfully.”

In the story, Pozdnyashov kills his wife because he believes she has formed a liaison with a violinist, recently returned from Paris (a sure sign of depravity), with whom she plays the sonata.

From the medical point of view, what is interesting about the story is Tolstoy’s vicious hatred of doctors, whom he regarded as corrupters of the world. He accused them of materialism, and indirectly of having been responsible for the murder. It was they, after all, who told the victim how to go about having sexual relations without risk of pregnancy, thus arousing her husband’s insensate jealousy.

You can almost see Tolstoy foaming at the mouth when he spoke of doctors. Tolstoy wrote. In a letter to A N Pleshcheyev in the year after the story’s publication, Chekhov recognised its literary merits: “Among all the mass that is written now, one could scarcely find anything else as powerful both in the gravity of its conception and the beauty of its execution.” But, he continued, “it has one fault for which one cannot readily forgive the author—that is, the audacity with which Tolstoy holds forth about what he doesn’t know and is too obstinate to care to understand. Thus his statements about syphilis... are not merely open to dispute, but show him up as an ignoramus who has not, in the course of his long life, taken the trouble to read two or three books written by specialists.”

Shall I be accused of the same fault when I quote something that Tolstoy says in connection with doctors that, my agreement with Chekhov notwithstanding, does strike me as true: “Today one can no longer say, ‘You are not living rightly, live better.’ One can’t say that to oneself or to anyone else. If you live a bad life, it is caused by the abnormal functioning of your nerves, etc. So you must go to the doctors, and they will prescribe eight penn’orth of medicine from a chemist, which you must take!”

Theodore Dalrymple is a writer and retired doctor.
OBITUARIES

Ian McGregor Leading British malariologist

Ian McGregor made a huge contribution to malariology. Equally skilled at field epidemiology and laboratory immunology, he showed that African children who survive their first two years have a long-lasting—though not permanent—immunity to malaria; that immunity can be transferred to non-immune people; that antimalarial drugs inhibit the formation of natural immunity; and that pregnant women have decreased immunity but confer immunity on newborns. He also found, contrary to belief, that malaria infection decreased a person’s immunity to other parasitic and infectious diseases.

He worked at the Medical Research Council (MRC) unit in the Gambia—it was originally a nutrition unit and later diversified into tropical diseases—and was its director for 22 years.

McGregor was born into a Glasgow tailoring family with a high regard for education. From Rutherford Academy he went to St Mungo’s College and thence to Glasgow Royal Infirmary for his clinical studies. He changed from a sports-mad schoolboy to a high-flying student, carrying off class medals in anatomy, physiology, surgery, public health, and obstetrics and gynaecology. After a year of house jobs in Glasgow he was conscripted into the army in 1946 and trained in malariology, a word he hadn’t previously met, in Gaza. When he was demobbed in 1948 he took a diploma course at the London School of Hygiene and Tropical Medicine. One of his tutors was Professor Ben Platt, director of the MRC Nutrition Unit, which had an outpost in an old military hospital in the Gambia. He recruited McGregor to see whether East African’s malnutrition was caused by malaria parasites appropriating protein.

McGregor chose Keneba, a remote village, for his research, with two nearby villages to act as controls. The area had a five month rainy season when roads became impassable and he and his team were cut off. They slept in the open until their mud huts were built, days before the five month rainy (and malarial) season began. Many years later, they were sent a land rover from the UK. It arrived in the rainy season and, as the roads were impassable, news was sent by a foot messenger carrying the telegram in a cleft stick—shades of Evelyn Waugh and Scoop.

McGregor took a census and registered births, which later meant that, for the first time in that area, children’s exact ages were known. He used these data for longitudinal studies over 25 years, finding that insecticides and antimalarials reduced childhood anaemia and hepatomegaly but not height or weight.

Unprotected adults developed immunity, and he showed that this was in the gamma globulin fraction of blood and could be transferred to non-immune adults, the serum from west Africans inducing immunity in east Africans. Using immunofluorescent techniques he showed that serum antibodies are diverse, represented past and current infection, that age-specific antibody levels were an index of how endemic malaria was in that region, and that women are more susceptible to malaria in pregnancy and probably transfer antibodies to their unborn babies.

McGregor was in charge of planning, costing, and ordering supplies to build staff accommodation. When the facility needed a well, the locals were afraid to dig it and a workman from another village left the job half done. McGregor finished it off with aplomb, and halfway through the task looked up and was surprised to see Sir Eric Pridie, the Colonial Office’s senior medical officer, who was paying a surprise visit. In the 1950s, Landsborough Thomson, the MRC head, sent Joan Small, one of his staff, to the Gambia to sort out the bookkeeping. She and McGregor fell immediately in love and married in 1954. She remained with him as his administrator.

He ran a 40 bed hospital for research. His labs were a Mecca for visiting researchers and students doing their electives. He was ambitious, hospitable, very kind to young researchers, and supportive to colleagues. He was clear thinking, prepared to listen to original ideas, and ask questions and go away to read. He was meticulous, testing ideas step by step. He loved fishing, and watching the migratory birds that fly over the Gambia. He is remembered for his lack of vanity, funny hats that kept his ears warm, good cheer, and hearty laugh.

McGregor was head of the Gambia unit from 1954 to 1974, and from 1978 to 1980, when it was otherwise without a director. He spent the intervening years working for the MRC in Mill Hill, and from 1980 was a professorial fellow at Liverpool University. He retired in 1994, aged 72.

He did a fair amount of work for the World Health Organization for 40 years, mainly on malarial control with insecticides. He published 200 papers, many of major importance, and edited, with Walter Wernsdorfer, the definitive textbook, The Principles and Practice of Malariology.

He was appointed CBE in 1968 and knighted in 1982. He was made an FRS in 1981 and was president of the Royal Society of Tropical Medicine and Hygiene from 1983 to 1985.

He retired to Salisbury, where he was active in the Royal Society for the Protection of Birds and in his village and church. He leaves a wife, Joan, and a son and daughter.

Caroline Richmond
Professor Sir Ian McGregor CBE, FRCP, director MRC Laboratories, the Gambia (b 1922; q Glasgow 1945; FRCP), died of a heart attack on 1 February 2007.
Christopher Charles Draper

Former senior lecturer London School of Hygiene and Tropical Medicine (b 1921; q Oxford 1946; MD, DPH, DTM&H), d 7 December 2006. Christopher Draper returned from national service in Japan with the Anzac Medical Service to study and later be junior lecturer at the London School of Hygiene and Tropical Medicine. In 1953 he joined the Colonial Research Service, for six years running the successful Pare-Taveta scheme in Tanzania to control malaria. He worked for three years in Nigeria on viruses and for five years in England at the Wellcome Foundation on rubella vaccine and interferon. In 1969 he returned to the London School as senior lecturer, working there, until his retirement, on rabies, schistosomiasis, Burkitt’s syndrome, and leprosy. He was a member of the WHO Advisory Committee on Malaria. In retirement he worked for the Overseas Development Agency and WHO. He leaves a wife, Katharine, and three children.

Katharine Draper

Mike Buchanan

Jessie Reid Gray Buchanan

Former assistant venereologist Leeds General Infirmary (b 1920; q Edinburgh 1943), died from chronic obstructive pulmonary disease on 2 February 2007. Jessie decided she wanted to become a doctor at the age of 5. Appointed to the female section of the venereal disease department at Leeds General Infirmary in 1946, she remained there until she retired in 1985. She enjoyed her job, as well as managing husband, son, and house. Jessie leaves a husband, Mike; a son; and two grandchildren.

Otto Fleming

Former general practitioner Sheffield and South Yorkshire (b 1914; q St George’s 1949; FRCP, MD (Vienna)), d 23 March 2007. Otto Fleming was forbidden to graduate in medicine from the University of Vienna in 1938, the year of the German annexation of Austria. He escaped to Palestine, where he joined the Royal Army Medical Corps, serving for four years as a medical orderly. He completed his training in London and for 35 years worked in general practice around Sheffield. He was a founder and active member of the Royal College of General Practitioners, the first provost of the Trent region. He requested the University of Vienna to apologise to those who could not graduate in 1938, and eventually, in 1999, it granted him and his colleagues their MD degrees. Otto was a lifelong student, studying several subjects, including Latin and economics, into his 80s and 90s. He leaves a wife, Dorothy, three children, and six grandchildren.

Peter Glanvill

Stephen John Hadfield

Former general practitioner Chard (b 1930; q St Bartholomew’s Hospital, London, 1953; MA, DOBSTRCOG, FRCPEd), d 5 February 2007. In 1936 Stephen Hadfield moved to general practice in Wiltshire and Devon. He saw war service in the Royal Air Force Volunteer Reserve, being mentioned in dispatches. In 1948 he was appointed assistant secretary of the BMA, where, in his writing and thinking, he contributed hugely to the development of general practice. He was under secretary of the BMA in 1960 and Scottish secretary from 1964 until his retirement in 1974. In 1977 he and his wife, Mary, he leaves three children and four grandchildren.

Nick Spencer Jones

Andrew Herd Muir

Michael Edward Glanvill

Former general practitioner Chard (b 1923; q St Bartholomew’s 1947; DM, MRCPG), died from ischaemic heart disease on 18 March 2007. In 1949 after national service in the Royal Air Force, Michael Glanvill joined his father in the practice he had bought in the 1930s, serving there until his retirement in 1982. A founder member of the Royal College of General Practitioners, Michael was one of the first to employ a practice nurse. A trained barrister at law, he was divisional surgeon for St John Ambulance and became a serving brother. His interests included caving, scuba diving, and, latterly, hang gliding, and he was honorary medical warden to the Mendip Rescue Organisation. In his retirement he studied Russian, obtained an Open University arts degree, and took up fly fishing. Predeceased by six months by his wife, Mary, he leaves three children and four grandchildren.

E M Armstrong

John Spencer Jones

Former consultant chest physician south east Kent (b 1924; q Guy’s Hospital 1948), died from bronchopneumonia on 11 March 2007. While a medical student, Spencer volunteered to help in the Bergen-Belsen concentration camp, where typhus and tuberculosis were rife. On his return he developed tuberculosis, which delayed his qualification and decided his specialty of chest medicine. These experiences were largely responsible for the quiet intensity with which he lived his life observing, noting, and analysing everything. He worked at the Royal Brompton Hospital before a recurrence of his tuberculosis led him to work in Davos, Switzerland, where he recovered. His enquiring mind and meticulous record keeping formed the basis of many publications. Predeceased by his wife, Phyllis, he leaves two sons and four grandchildren.

Chris Spencer Jones

Specialist in Department of Vascular Medicine, Ninewells Hospital, Dundee (b 1954; q Dundee 1977), died from a heart attack on 26 January 2007. After qualifying Andy Muir held a succession of house officer and registrar posts in Tayside before finding a niche in Ninewells Hospital. He was much admired and respected by medical and nursing colleagues for his clinical acumen and skill. Outside of medical life Andy had many interests—he was multilingual, intensely interested in continental culture and cuisine, and a talented musician. He leaves a wife, Cathy, and three children.

Adrian Tully

Jessie Reid Gray Buchanan

Former assistant venereologist Leeds General Infirmary (b 1920; q Edinburgh 1943), died from chronic obstructive pulmonary disease on 2 February 2007. Jessie decided she wanted to become a doctor at the age of 5. Appointed to the female section of the venereal disease department at Leeds General Infirmary in 1946, she remained there until she retired in 1985. She enjoyed her job, as well as managing husband, son, and house. Jessie leaves a husband, Mike; a son; and two grandchildren.

Mike Buchanan

Christopher Charles Draper

Former senior lecturer London School of Hygiene and Tropical Medicine (b 1921; q Oxford 1946; MD, DPH, DTM&H), d 7 December 2006. Christopher Draper returned from national service in Japan with the Anzac Medical Service to study and later be junior lecturer at the London School of Hygiene and Tropical Medicine. In 1953 he joined the Colonial Research Service, for six years running the successful Pare-Taveta scheme in Tanzania to control malaria. He worked for three years in Nigeria on viruses and for five years in England at the Wellcome Foundation on rubella vaccine and interferon. In 1969 he returned to the London School as senior lecturer, working there, until his retirement, on rabies, schistosomiasis, Burkitt’s syndrome, and leprosy. He was a member of the WHO Advisory Committee on Malaria. In retirement he worked for the Overseas Development Agency and WHO. He leaves a wife, Katharine, and three children.

Katharine Draper

Otto Fleming

Former general practitioner Sheffield and South Yorkshire (b 1914; q St George’s 1949; FRCP, MD (Vienna)), d 23 March 2007. Otto Fleming was forbidden to graduate in medicine from the University of Vienna in 1938, the year of the German annexation of Austria. He escaped to Palestine, where he joined the Royal Army Medical Corps, serving for four years as a medical orderly. He completed his training in London and for 35 years worked in general practice around Sheffield. He was a founder and active member of the Royal College of General Practitioners, the first provost of the Trent region. He requested the University of Vienna to apologise to those who could not graduate in 1938, and eventually, in 1999, it granted him and his colleagues their MD degrees. Otto was a lifelong student, studying several subjects, including Latin and economics, into his 80s and 90s. He leaves a wife, Dorothy, three children, and six grandchildren.

Peter Glanvill

Stephen John Hadfield

Former general practitioner Chard (b 1930; q St Bartholomew’s Hospital, London, 1953; MA, DOBSTRCOG, FRCPEd), d 5 February 2007. In 1936 Stephen Hadfield moved to general practice in Wiltshire and Devon. He saw war service in the Royal Air Force Volunteer Reserve, being mentioned in dispatches. In 1948 he was appointed assistant secretary of the BMA, where, in his writing and thinking, he contributed hugely to the development of general practice. He was under secretary of the BMA in 1960 and Scottish secretary from 1964 until his retirement in 1974. In 1977 he and his wife, Mary, he leaves three children and four grandchildren.

Nick Spencer Jones

Andrew Herd Muir

Specialist in Department of Vascular Medicine, Ninewells Hospital, Dundee (b 1954; q Dundee 1977), died from a heart attack on 26 January 2007. After qualifying Andy Muir held a succession of house officer and registrar posts in Tayside before finding a niche in Ninewells Hospital. He was much admired and respected by medical and nursing colleagues for his clinical acumen and skill. Outside of medical life Andy had many interests—he was multilingual, intensely interested in continental culture and cuisine, and a talented musician. He leaves a wife, Cathy, and three children.

Adrian Tully
The characteristics of heart rate variability may be useful for predicting which patients with infections presenting to emergency departments are likely to develop septic shock. Twenty one of 81 patients enrolled in a study developed septic shock, and regression analysis identified the “root mean square successive difference” as the characteristic that best predicted this event (Academic Emergency Medicine 2007;14:392-7). Before readers themselves go into shock, this characteristic can be automatically calculated by the machine that measures heart rate variability.

Does migraine affect cognitive function? A study in Neurology (2007;68;1417-24) suggests it does, but perhaps not as might be expected. Migraine sufferers, especially those who experience aura and those over 50, showed less decline on cognitive tasks over time than people who don’t get migraine. They did score lower on tests of immediate and delayed memory at baseline, however.

Most studies of the impact of alcohol on health have focused on men. A study in Addiction (2007;102:730-9) looks at alcohol use in women aged 35-69 who have had non-fatal heart attacks. The authors conclude that in this population of light to moderate drinkers, alcohol intake was associated with a reduced risk of myocardial infarction, compared with complete abstainers, although occasional binge drinking was related to a substantial increase in risk.

On a typical day in the United States, 75% of children watch television and 32% watch videos or DVDs. Not to be outdone, 27% of 5-6 year olds are now using a computer on a daily basis for nearly an hour, and more than a third of 3-6 year olds and a fifth of 0-2 year olds have a television in their bedroom. The reason commonly given is that this frees up television sets for other family members. The developmental impact from such media and digital obsession is not known (Pediatrics 2007; www.pediatrics.org/cgi/doi/10.1542/peds.2006-1804)

The Department of Health’s standard application form designed to streamline applications to conduct multicentre research in the United Kingdom seems to have failed in its intention. Researchers applied to 316 primary care organisations in England and Wales. They could not establish contact with 4% of organisations; six months after submission only 82% of applications had been approved and the verdict was still awaited in 13%. A total of 318 staff hours were spent completing supplementary forms, providing extra information, and chasing up dormant applications (Journal of the Royal Society of Medicine 2007;100:234-8).

Steroid sulfatase inhibitors are being developed as a potentially more potent treatment than aromatase inhibition for hormone dependent breast cancer in postmenopausal women. A novel tricyclic sulfamate ester has passed muster in the first trial of such treatment in postmenopausal women with oestrogen positive metastatic breast cancer. The drug almost completely blocked steroid sulfatase activity in peripheral blood lymphocytes and tumour tissue. In turn, this induced significant reductions in serum androstenediol and oestrogens. Disease was stable in five of the eight patients for up to seven months (Oncologist 2007;12:370-4).

Minerva was not surprised to read in a study of 16 acute psychiatric wards that at any time of the day 84% of psychiatric inpatients were “socially disengaged” and mainly inactive. Just 4% of inpatients’ time was spent in organised group activities, and many of the patients opted out of such activities altogether (Psychiatric Bulletin 2007;31:167-70).

The original Charnley hip joint has a follow-up history of more than 30 years. The Charnley Elite-Plus femoral stem is one of its younger offspring, thought to be particularly useful for younger patients. In a long term study, the survival of the femoral stem at 12 years was 99%, with revision as the end point. The prevalence of acetabular osteolysis was 10.8%. The use of a zirconia head and a modern cementing technique were crucial in preventing aseptic loosening of the femoral stem in these high risk patients (Journal of Bone and Joint Surgery (Br) 2007;89-B:449-54).

Same day discharge for patients having percutaneous coronary interventions such as stents and thrombolysis might be good when resources are tight, but is it safe? A randomised trial comparing same day discharge with overnight hospital stay found it to be safe and feasible in most (80%) patients selected, and there were no more complications with early discharge than in the overnight group (Circulation 2007;115:2299-306).