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*Limitations of rapid HIV-1 tests during screening for trials in Uganda: diagnostic test accuracy study*
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Richard Hugh Balme
Adam Turnbull

John Rashleigh Belcher
P Belcher

Robert Francis Patrick Cronin
Krishna Somers

Ernest William ("Bill") Deane
Robert Scott-Jupp
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Kathleen ("Kay") Mary de Ville
Georgina Stafford, P Jane Grubb
Julie Ann Nash
Kevin A Nash

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Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial
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Doctor ordered to pay £300 000 in libel damages
Technological challenges in diagnosis and management of HIV infection in resource limited settings

Relatively quick and cheap tests can work but must be properly monitored

With the HIV epidemic in its third decade, appropriate use of technology in resource limited settings has taken on added importance as priorities shift from detection and prevention to care and support for people living with HIV. At the same time, there is a continuing need for evaluation of and improvement in the critical diagnostic tools, such as rapid tests for HIV, which have become indispensable in settings with a high prevalence of infection.

In this week’s BMJ two studies look at such evaluations. MacLennan and colleagues examine the diagnostic accuracy and clinical utility of a simplified flow cytometry method for measuring CD4 counts that promises a more affordable alternative for routine clinical use in resource limited settings. Gray and colleagues highlight problems encountered with the use of rapid tests for HIV screening in rural Rakai, Uganda.

As the world moves towards universal access to antiretroviral treatment, healthcare providers are confronted with many complexities in providing uninterrupted lifelong care. Clinical staging of HIV disease does not fully predict immunological status, and hence CD4 cell counts remain the most effective indicator for starting therapy and assessing immunological response to drug regimens. The World Health Organization has noted that “one of the most crucial needs in the developing world is universal access to affordable and locally usable CD4 testing technology.” The current shortage of laboratories that can perform counts in resource constrained settings jeopardises the success of campaigns to scale up antiretroviral treatment and distribute lifesaving drugs to millions of people living with HIV.

Current flow cytometry methods for CD4 counting, with reagents that cost from $3 (£1.50; €2.20) to $6 per test are expensive and possibly too complex for many resource constrained settings. MacLennan and colleagues compared BlantyreCount, a simplified counting method, with TruCount for both accuracy and clinical utility at a clinic for antiretroviral therapy in southern Malawi.1 BlantyreCount comprises “primary CD4 gating” using one antibody against CD4 and side scattered light to discriminate between lymphocytes and monocytes. This single platform method reduces the costs of reagents by more than 91% and makes laboratory procedures much simpler than those for existing flow cytometry methods. The authors show that the limits of agreement for BlantyreCount and TruCount are excellent (–4.9 to 27.0 cells/µl for absolute counts in the CD4 range <400 cells/µl, and −2.42% to 2.37% for %CD4/lymphocytes) but note that even this simplified method still requires a level of technical expertise not always present in resource poor settings. More importantly, the paper correctly points out that non-reagent costs, especially capital expenses and maintenance, which often come to more than $100,000 for a flow cytometer instrument, may still limit applicability in many settings.

Gray and colleagues examine the issue of false positive tests during screening for a randomised trial of male circumcision for HIV prevention in Rakai, Uganda.2 The trial used a rapid HIV test algorithm to screen potential participants. Tests yielded “weak positive” bands that resulted in low specificity and low positive predictive values when confirmed using an enzyme immunosorbent assay and western blot. When weak positive bands were excluded, the number of false positives fell. This is an important finding because previous research had shown that algorithms combining two or more rapid tests resulted in very high levels of sensitivity and specificity.3-7

Although more research is needed to establish whether these results can be generalised to other populations and specific HIV subtypes, the study raises an important question that needs further exploration. Clearly, there is a compelling need to re-examine the performance of rapid tests in various settings using a gold standard such as enzyme immunosorbent assay and western blot to verify results. Reducing the risk of false positives is important in both research and HIV testing programmes because of the stigma associated with a positive HIV test.

What are the larger implications of these findings? Firstly, it is important that we continuously improve on existing technologies to make them more affordable, accurate, and widely available. Although the cost of flow cytometry is initially high, strategically located facilities such as regional centres for antiretroviral treatment can provide the high volume of patients needed to offset the capital investment, as long as reagents are affordable. Secondly, there is no dearth of talent in resource constrained settings; only a lack of political will to make the necessary investments in training and quality control. Finally, as HIV is such a serious and stigmatised condition, it is essential that we exercise vigilance to ensure that technologies are performing optimally. As Gray and colleagues suggest, it is prudent to routinely retest a sample of specimens using a gold standard method to maintain quality control.
Body mass index cut offs to define thinness in children and adolescents

A new chart will be most useful in countries in social, economic, and nutritional transition where both undernutrition and overnutrition are prevalent

Assessment of risk for overweight by monitoring body mass index is now recommended in developed countries and more recently in urban areas of less developed countries. Body mass index is known to track significantly from childhood, to adolescence, and then to adulthood. Body mass index should therefore be assessed and monitored during childhood and adolescence to allow for early, and perhaps more effective, intervention strategies. TM Cole and colleagues’ validated thresholds or cut offs for body mass index, recommended by the International Obesity Task Force to define and identify overweight and obesity in children and adolescents, are internationally recognised.

Rather less attention has been paid, however, to the importance of assessing body mass index to monitor undernutrition. In this week’s BMJ, Cole and colleagues extend this work to provide cut offs for body mass index to define “thinness” in children and adolescents.

Malnutrition, or more specifically undernutrition, in children has long been defined in terms of height and weight in relation to age in relation to various cut offs, which are usually based on representative samples of European or American children. The choice of cut off is fundamentally important to identify correctly those children at risk and, ideally, should be related to known outcomes for morbidity and mortality. Yet, while adult body mass index values of 25 (overweight) and 30 (obesity) are related to morbidity, evidence on morbidity related to cut offs for thinness, particularly in children, is less clear. Current cut offs for thinness in children are related to either the third or fifth centile of reference charts for body mass index and cut offs for malnutrition (undernutrition) to weight for height z scores (standard deviation scores).

In France, for instance, the third centile of the French reference chart for body mass index is recommended for defining thinness in adolescents, while the World Health Organization (WHO) expert committee on anthropometry recommends the fifth centile of the American National Health and Nutrition Examination Survey (NHANES) reference database to define thinness in adolescence. Cole and colleagues argue that the current WHO recommendations for defining thinness are inappropriate because the NHANES dataset dates from the early 1970s and is of “uncertain validity.” In addition, the latest WHO growth standards are truncated at age 5, leaving no current reference that effectively covers the age range of childhood to adolescence.

Cole and colleagues’ response to this void is to use the same technique on a sample of almost 200 000 subjects from six countries (Brazil, United Kingdom, Hong Kong, the Netherlands, Singapore, and the United States), the source of the data for the International Obesity Task Force reference standards for overweight and obesity, to generate cut offs throughout childhood and adolescence that identify the child at risk because of thinness. The chosen cut off is a body mass index of 17 kg/m² at age 18 coinciding with the WHO grade 2 cut off for thinness in adults, and to a value of −2 z scores for body mass index in Cole’s combined dataset.

In addition, cut offs of 18.5 kg/m² and 16 kg/m² are also included to coincide with WHO grade 1 and grade 3 thinness in adults and allow the distinction between different grades of undernutrition and thus different levels of risk in children. This is important, given that the prevalence of child mortality is directly related to the degree of malnutrition. Furthermore, a value of −2 z scores has the added advantage of being about 80% of the median body mass index and is equivalent to the WHO definition of wasting (low weight for height).

These new cut offs are most suitable for use with samples of children in comparative studies of the prevalence of thinness, rather than as references or standards for current or recommended body mass index by age and sex. Limitations are that they use serum panels of different geographical origin and clinical stage including a unique seroconversion panel. 

Rediscovering dignity at the bedside

It is possible to teach the ABCD of preserving patients’ dignity

It was a comfort when Gerasim sat with him sometimes the whole night through . . . Gerasim was the only one who did not lie; everything he did showed that he alone understood what was happening, and saw no need to conceal it . . . and so the relationship was a comfort to him. From Leo Tolstoy, The Death of Ivan Ilyich

The Oxford English Dictionary defines dignity as “the state of being worthy of honour or respect” or “high regard or estimation.” The 1948 universal Declaration of Human Rights and article 1 of the Charter of Fundamental Rights of the European Union recognise dignity as a human right. Improving dignity in care is a core theme in guidance from many governments across the globe. For example, in England the Department of Health launched a policy earlier this year to “create a zero tolerance of lack of dignity in the care of older people in any care setting.” But how are we to achieve dignity in care? It is easier to identify when dignity is lacking than to define what it means. So what does make care dignified?

The article in this week’s BMJ by Chochinov offers clinicians a straightforward empirical framework to help them achieve dignity conserving care. Chochinov focused on dignity after finding fluctuations in the will to live of patients approaching the end of life. Factors associated with the loss of will to live were: feeling a burden on others; depression; and other symptoms, including breathlessness. Dignity appeared to be a core concept underlying these factors. A European programme, including participants from Spain, Slovakia, Ireland, Sweden, France, and the United Kingdom, found that despite a wide range of backgrounds and situations, there was a sustained level of agreement about the meaning and experience of human dignity in the lives of participants. Three overarching themes were identified: respect and recognition; participation; and dignity in care. Loss of independence, fear of becoming a burden, not being involved in decision making, lacking access to care (including palliative care facilities), and some attitudes of staff, especially when people felt vulnerable and lacked power, were all identified as fracturing their sense of dignity. Spiritual matters, also important in dignity, are strongly associated with communication, both between professionals and patients, and between patients and families. Adapting the well known mnemonic “airway, breathing, and circulation (ABC)” Chochinov has developed

Moreover, body mass index is not a direct measure of total body fat or total body lean mass, even though it correlates surprisingly well with fat and lean tissue.

The new cut offs proposed by Cole and colleagues need to be tested in studies of the association between thinness and morbidity in children and adolescents. They are potentially most useful in countries that are experiencing social, economic, and nutritional transition such as South Africa, Brazil, China, and Russia, and in which both overnutrition and undernutrition are prevalent. Having a single chart that is consistent at both ends and is constructed from international data is helpful in both epidemiological and clinical settings.

Cut offs for thinness by age and sex defined to pass through BMI 16, 17, and 18.5 at 18 years, with the international cut offs for overweight and obesity based on BMI 25 and 30

Thin

BMI

Male

Female

Moreover, body mass index is not a direct measure of total body fat or total body lean mass, even though it correlates surprisingly well with fat and lean tissue.

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BMI

Age (years)

Male

0

10

20

30

40

Female

0

10

20

30

40
an ABCD framework for dignity conserving care that is easy to remember and understand. His A—attitude—has strong resonance across other research. Parallel work in examining training of communication skills has also shown that changing attitudes is fundamental to ensuring sustained improvements to communication skills. However, changing attitude is not as easy as checking the airway. It should begin early in training but, as Walsh has argued, many medical students hear the same message again and again without a stepwise approach to developing skills. Fallowfield found that it is possible to teach communication skills using individually suitable approaches similar to many of those outlined in Chochinov’s article.8

Perhaps changing attitudes needs to pervade all medical school teaching. When visiting a Buddhist medical school in Taiwan one of us (IJH) was impressed to see that from day one medical students were taught to respect the people who had donated their bodies for anatomy dissection. Pictures and accounts of the person during life were placed at the head of each cadaver. Before starting any examination the medical students paused and gave thanks to the person for donating his or her body for study.

The introduction of the arts in many medical school curriculums may help to achieve Chochinov’s B and C, changing behaviour and ensuring compassion. In many countries medical students are being placed within larger colleges and universities which have many faculties, including the humanities, ethics, theology, health policy, as well as the social sciences (psychology, sociology, anthropology). Understanding the different cultural meanings of symptoms, needs, and dignities is important in most countries because doctors encounter patients from different cultural and ethnic backgrounds.9 10

Ensuring dignity within a tight budget may be challenging. Chochinov’s D—for dialogue—requires time with patients. As the quotation from The Death of Ivan Ilyich shows, spending time with patients is important; this is not easy to measure in the performance targets set by healthcare funders. Thus time, dialogue, compassion, and empathy can be devalued. Here, Chochinov’s article is particularly helpful. His tables provide simple guides to the types of attitudes, behaviours, compassion, and dialogue that could be easily adopted and form the basis for teaching and providing care in many health and social care settings, both in the community and in institutions. Perhaps Chochinov’s ABCD should be the first mnemonic we teach all professionals entering health and social care, even before airway, breathing, and circulation.

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Weight and pregnancy

Women who maintain a normal healthy weight, before, during, and after pregnancy have better outcomes

Women of reproductive age are bombarded with messages about diet, weight, and body image. There is growing concern on the one hand about an epidemic of obesity, and on the other about a culture that promotes “size zero” as desirable, irrespective of a woman’s natural build. Pregnancy is one of the most nutritionally demanding periods of a woman’s life, with an adequate supply of nutrients essential to support fetal wellbeing and growth. 1 With at least half of all pregnancies unplanned, women need to be aware of the implications of their weight for pregnancy, birth, and the health of their babies. However, the potential to provide women with conflicting information about weight, weight gain, and weight loss extends to pregnancy and birth outcomes.

Over one billion adults in the world are now overweight, with more than 300 million clinically obese. 2 In the United States, the prevalence of obesity in women aged 20-39 years rose from 9% in 1960-1962 to 28% in 1999-2000. 2 While weight and obesity have long concerned women in relation to body image and lifestyle matters, the association between weight gain and adverse pregnancy outcomes is less well recognised.

A recent nationwide Swedish cohort study involving 207,534 women from 1992 to 2001 examined the associations between changes in body mass index from the beginning of the first pregnancy to the beginning of the second in relation to adverse maternal and perinatal outcomes. 3 Significantly increased rates of pre-eclampsia, gestational diabetes, pregnancy induced hypertension, and large for gestational age infants (odds of an adverse outcome were almost twofold in each case) were evident with increases in body mass index of just one to two units, and they increased progressively thereafter. An increase of greater than three body mass index units significantly increased the rate of term stillbirth, independent of obesity related diseases. Importantly, weight gain during the interval between pregnancies was strongly associated with major maternal and perinatal complications, independent of whether women were overweight (body mass index >25) by definition or not.

The key message is that women of normal weight should avoid gaining weight between pregnancies. In addition, overweight and obese women (body mass index ≥30) are likely to benefit from weight loss before becoming pregnant. However, while the authors have argued convincingly for a causal relation between maternal weight gain and adverse pregnancy outcomes, the advice given must be balanced to avoid weight swings in the opposite direction.

The association between low body mass index and subfertility is well known. Much less publicised is the association between low body mass index or substantial weight loss and pregnancy related complications, such as preterm birth and low infant birth weight. A second cohort study evaluated the impact of changing maternal nutritional status on the risk of prematurity, and specifically whether increasing or decreasing body mass index altered this risk. 4 Overall, women whose body mass index fell by five or more units between pregnancies had a higher risk of preterm birth than women whose weight remained stable or who gained weight. The increased risk was particularly pronounced for women who had already experienced a preterm birth (80% v 28%). We should ensure that women of low body mass index attain a healthy weight before conception to reduce the risk of preterm birth and low infant birth weight. We should also counsel women with a history of previous preterm birth to maintain a healthy weight to prevent recurrence. In the context of the neonatal morbidity and mortality associated with preterm birth, low body mass index is one of the few modifiable risk factors.

The challenge for healthcare professionals is in interpreting these findings and advising women accordingly. Women are at increased risk of different but equally serious adverse pregnancy outcomes if they gain or lose an excessive amount of weight between pregnancies. Although apparently conflicting, these studies show how important it is to attain and maintain a normal healthy weight during, and after pregnancy. Most women wish to achieve the best start in life for their babies. This powerful motivation could be used to achieve behavioural changes in terms of a healthy balanced diet and maintaining a stable weight within the normal range for the woman’s build. This approach offers long term health benefits for women and their babies. Certainly, any woman who has had a poor obstetric outcome should be encouraged to achieve an optimal weight before planning another pregnancy. The challenge for many women of achieving a stable body mass index cannot be underestimated, and this may require professional support and advice.

What to do with insolvent hospitals

Will politicians allow providers to fail?

The progress made by the NHS in England in converting a net deficit of £547m (£812m; $1121m) in 2005-6 into a net surplus of £510m in 2006-7 has given the government a breathing space. Yet behind the headline figures lies a picture that is more complex and promises to become more troubling as the programme of health reform gathers pace.

The net surplus in 2006-7 resulted from a gross deficit of £911m and a gross surplus of £1421m. Moreover, the gross deficit was concentrated in a small number of organisations, some of which face financial difficulties that cannot be easily resolved. To address these difficulties the Department of Health is working with strategic health authorities to identify long term solutions, focusing on 17 NHS trusts with the greatest challenges.

The experience of converting deficits into surpluses has shown that there are three main approaches to dealing with NHS providers in difficulty. The first is to develop recovery plans tailored to the circumstances of providers, often linked to the provision of loans. In many cases, these recovery plans focus on reducing pay costs by cutting the use of agency staff, eliminating unnecessary management posts, and improving the control of staff vacancies. Recovery plans have also found savings in non-pay costs, such as improving office supply purchasing, reducing furniture costs, rationalising estate costs, and improving the effectiveness of information technology.

The second approach is to merge providers with neighbouring providers that have a record of sound financial performance. The first example of this was the merger of the Heart of England NHS Foundation Trust with Good Hope Hospital NHS Trust in April 2007. In this case merger was preceded by a partnership between the two organisations in which the Heart of England trust lent its management expertise to Good Hope Hospital to convert a loss of £6m to a surplus of £1.7m. The path to a full merger was cleared by dealing with Good Hope Hospital’s historic debt through the issue of £18m of public dividend capital, with the interest on the capital being paid by the strategic health authority. Freed of the need to pay back the debt, the Heart of England trust could then take over Good Hope Hospital.

The third approach is to recognise that providers may have to “exit” the emerging healthcare market. This is an option being considered for NHS trusts with the biggest deficits and also for NHS foundation trusts that find themselves in serious financial difficulty. Financial failure on this scale is likely to be unusual, but the architects of the reforms argue that the threat needs to be real enough to create incentives for providers to continuously improve their performance. If a hospital or other provider is to close arrangements will have to be made for the continued provision of essential NHS services to the populations served by that provider. The government’s consultation document on regulation made it clear that this was the responsibility of commissioners, but this is a new role for commissioners and it is not clear that they have the ability to deal with the consequences of large scale financial failure. The consultation document also announced that proposals were being prepared to establish an insolvency regime for foundation trusts, and the time it is taking to develop such a regime is a sign of the complexity of deciding how insolvency should be handled. Foundation trusts, unlike others, are free to borrow money from commercial lenders, but the lack of an insolvency regime means that commercial lenders are uncertain about the protections available to creditors in the case of a trust failing financially.

To invoke the language of insolvency, exit, and merger is to signify the transformation that is taking place in the NHS in England as the current round of health reforms are implemented. The conundrum for the government is how to reconcile the development of a more transparent and businesslike way of dealing with financial difficulties and ultimately failure with the public’s expectation that services will continue to be available in each locality.

Also, when the consequences of competition collide with the reality of politics, will ministers follow the logic of the reforms and allow unsuccessful providers to fail, or will they intervene in the market to preserve access to services? The last time this question arose, under the Conservative government’s internal market reforms in the 1990s, politicians lost the courage of their convictions and acted to blunt the impact of competition. Government intervention was most evident in London, where additional funds were given to help hospitals in financial difficulty and commissioners were told not to move their contracts in order to prevent instability among providers. Subsequently the Tomlinson inquiry was set up to prepare a plan for the future of health services in London as politicians acknowledged that the internal market might result in unacceptable consequences for hospitals.

An early challenge for Gordon Brown as the new prime minister will be whether to do the same or to keep faith with the policies of his predecessor and accept the pain that will undoubtedly accompany the reconfiguration of services in areas where NHS providers fail financially. The way in which he responds to this challenge will provide important clues to the direction of the NHS under his stewardship.

3 Timmins N, Hewitt warns that failing hospitals will be closed. Financial Times 2005;14 May p5.
No high risk antibiotics?

I was astounded to read in the study method that Hickson et al had excluded “high risk” antibiotics (as well as some misclassified low risk antibiotics). To do so is akin to performing a trial of an agent that claims to prevent type 2 diabetes, but excluding obese patients.

Cephalosporins in particular are rapidly losing their usefulness as frontline antimicrobial agents because of their potential to cause Clostridium difficile associated diarrhoea. The loss of these highly effective agents cannot be a good thing.

Any therapy that has the potential to reduce the incidence of diarrhoea associated with C difficile should be investigated with enthusiasm, but it should be done in a meaningful way. To exclude the very people in whom it is particularly important to prevent such diarrhoea—patients taking high risk antibiotics—makes this trial of academic value only.

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Competing interests: None declared.


No proton pump inhibitors?

Hickson et al have tried to introduce true scientific method in an area chiefly governed by sales tactics and mass advertising, but an important omission is the seeming lack of any data on treatment with proton pump inhibitors. Since the target population had a mean age of 74, one could safely assume a sizeable proportion of those would be taking antisecretory treatment. Given the physiological gastric pH, and its likely bactericidal effect on the cultures tested, it would have been more than useful to include outcome data for patients taking proton pump inhibitors.

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Competing interests: None declared.


FOLIC ACID FORTIFICATION

Clarify the neurological risks

The head to head between Wald and Oakley and Hubner et al mainly focused on possible risks of cancer associated with folic acid fortification. However, there are also neurological risks from fortification.

It is unwise of Wald and Oakley to dismiss as unscientific so many reports between 1945 and 1950 of the harmful effects of folic acid in the presence of vitamin B12 deficiency, and then to select only the observations that suit their own case. They are incorrect to state only that folic acid allowed the neurological consequences of vitamin B12 deficiency to progress. The earlier authors reported that both blood and nervous system could improve and relapse but to different degrees and at different rates. This is supported by the recent study of 1459 elderly subjects in the United States after fortification showing that in the presence of vitamin B12 deficiency high serum folate concentration was associated with anaemia, macrocytosis, and cognitive impairment, whereas with normal vitamin B12 status high serum folate concentration was associated with apparent protection from cognitive impairment.

Wald and Oakley’s extreme view that there is no credible evidence of any adverse health effects from folic acid supplementation or fortification is unsustainable. The protective effect of folic acid fortification on neural tube defects is real but modest (20-43% reduction), and even after fortification young women will still need additional supplementation. Folates and vitamin B12 are important for nervous system function, including methylation and epigenetic mechanisms, and it would be wise to clarify the benefits and risks at all ages, including elderly people, before exposing everyone to excessive folic acid long term.

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Competing interests: MHW has received honorariums for consultancy work, financial support to attend meetings, and research funding from Astra-Zeneca, Bayer, Genzyme, Pfizer, Vicuron, and Wyeth. JAS has received honorariums for consultancy work and financial support to attend meetings from Novartis and Wyeth.


PROBIOTICS AND DIARRHOEA

Data are not widely applicable

We caution against extrapolating the results of Hickson et al, which support the benefit of probiotics in antibiotic associated diarrhoea. We are particularly concerned about their conclusion that a probiotic yoghurt drink, given during and after antibiotic treatment, “has the potential to decrease morbidity, healthcare costs, and mortality if used routinely in patients aged over 50.”

The magnitude of the protective effects of the probiotic yoghurt against antibiotic associated diarrhoea and Clostridium difficile infection were stark. However, important issues about the study design and conclusions were not considered or given sufficient weighting in the discussion. In particular, the highly selective inclusion and exclusion criteria are crucial in result interpretation. It took over two years to recruit 135 patients out of 1760 screened individuals, and only 113 of these were followed up for evidence of diarrhoea. Put simply, how can data pertaining to less than 7% of a potential target population be extrapolated to routine use?

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Competing interests: None declared.


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Competing interests: ER has engaged in studies of folic acid and vitamin B12 in relation to the nervous system during the past 40 years.

1 Wald NJ, Oakley GP. Should folic acid fortification be mandatory? BMJ 2007;334:1252. (16 June.)

NHS RESTRUCTURING

Consider social anthropology

Breithwaite proposes a practical strategy for coping with the restructuring of the NHS.

1 NHS organisations are distinguished only by their instability, and the costs of this are high.
2 Why do we do it?

It is a symbolic act for politicians, so what is also of interest now is the symbolism of who is appointed to lead this—and, whatever the personal characteristics of the individual, the symbolism of a surgeon sends out specific messages about doctor-led action. From a social anthropological perspective it may also represent the reaffirmation of the order of tribes in health care, which increases in importance in forming and maintaining identity for individuals as the organisational identities fail yet again.

Further useful insight from Australia is provided in the notion of “orphan knowledge”—an evocative term for what was originally an observation about knowledge management but has wider application because there are situations where organisations forget things and repeat past mistakes. Do organisations really “unlearn,” or is it because knowledge is forgotten, separated, or isolated within the organisation?

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Competing interests: None declared.

1 Breithwaite J. How to restructure-proof your health service. BMJ 2007;335:99. (14 July.)
2 Mark A. Trust me I’m not a doctor. London: Middlesex University Business School, 2003. (HRM discussion paper series No 11.)

JOURNALS AND DRUG ADVERTISING

Medical schools, take the lead

It is not only journal editors who need to take leadership in changing the culture of acceptance of drug advertising: medical schools also need to recognise their responsibility. When it comes to teaching about the ethics of marketing there is much to be done: to our knowledge, no British medical school has a policy on pharmaceutical interaction.

Our American counterparts are setting the standard: Yale, Stanford, and many other American medical schools have policies restricting pharmaceutical interaction during medical school. Their policies reflect the value of marketing representatives as a source of evidence. The BMA’s recent annual representatives’ meeting signalled the beginnings of a cultural shift in the United Kingdom. The meeting voted almost unanimously in favour of supporting medical schools in not only forming policies but dedicating time in the curriculum for teaching on professional conflicts of interest.

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Robert Hughes year 4 medical student

Competing interests: None declared.

1 Smith R. Should medical journals carry drug advertising? Yes. BMJ 2007;335:74. (14 July.)
2 Williams G. Should medical journals carry drug advertising? No. BMJ 2007;335:75. (14 July.)

Beware advertising packages

In post-Soviet Russia, almost all journals depend mostly on advertisements. The most prosperous journals bring profits for their owners, and the owners then press the journals to raise more money through advertisements. This does not reduce the pressure on the content of the journal but introduces another—the demand for more profits.

All advertisers have some influence on the content of the journals to support their advertisements. And if one advertiser succeeds in this, it will not lead to complaints from their competitors. Rather the opposite: competitor advertisers will demand that the journal provides a similar service for them. In Russia these days the publication of advertisements with the supporting “scientific” paper is the usual advertiser’s package.

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Competing interests: None declared.

1 Smith R. Should medical journals carry drug advertising? Yes. BMJ 2007;335:74. (14 July.)
2 Williams G. Should medical journals carry drug advertising? No. BMJ 2007;335:75. (14 July.)

BEING AT THE HELM FOR PATIENTS

It’s all in the listening

One serious structural problem for communication in medical encounters is the primary given to diagnosis (and other technical goals). Doctors don’t even listen properly to the first thing a patient says before launching into a series of directive questions designed to produce a diagnosis, or a technical update in a review consultation.

So we rarely discover what is really bugging patients, and we rarely take time to make a well structured plan, with adequate safety netting.

The antidote is spectacular investment in the opening and closing of a consultation, together with efforts in the middle to understand the patient’s perspective and reflect it back (expressions of empathy). This is well summarised in the “four habits model” of Frankel and Stein (the in-house method of Kaiser Permanente).

It need not take longer. But it will take much remedial training for existing practitioners. For the next generation, it cannot all be achieved in medical school. New doctors must focus on mastering the technical aspects of doctoring. The rounder consultation can really only come once doctors are caring for their own patients—that is, mastering this skill is a postgraduate enterprise.

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Competing interests: MIT is managing director of Effective Professional Interactions, which offers training for consultations with patients.

1 Richards T. Who is at the helm on patient journeys? BMJ 2007;335:76. (14 July.)
Failure to monitor independent centres prevents comparison, says watchdog

Michael Day LONDON
A “cock-up” by the UK government has impeded the ability of the Healthcare Commission to assess independent sector treatment centres (ISTCs), says the watchdog's chief executive, Anna Walker.

She says that a government oversight has impeded the commission's ability to assess the safety and quality of the centres.

The commission declared this week that the Department of Health had failed to ensure that the data collected on the controversial clinics were compatible with the data used to monitor the rest of the NHS.

The commission had aimed to review the first 23 centres, which were set up to carry out high volumes of straightforward elective surgery to cut NHS waiting lists. The commission interviewed 2000 patients, made inspections, and checked health records.

Ms Walker said that there were gaps, however, because “comparative data has not been systematically collected.

“Where independent providers serve NHS patients we must ensure we have the proper systems to provide reassurance about what is being provided,” she said.

“That is why we are calling for one system that allows comparable information to be published on all major healthcare providers, whether public or private, whether they are treating NHS patients or otherwise.”

Beginning in October, the Royal College of Surgeons will carry out its own study, funded by the Department of Health, to assess the success of operations carried out in the centres. Bernard Ribeiro, president of the Royal College of Surgeons, said, “It is imperative that patients receive a sustained, safe, and [high] quality service, which is consistent across surgical providers.”

See www.healthcarecommission.org.uk

Taranissi must stand down as licence holder at infertility clinic, authority rules

Clare Dyer BMJ
Mohamed Taranissi, one of the United Kingdom’s best known infertility specialists, will lose the licence he holds in his name for his main clinic, the Assisted Reproduction and Gynaecology Centre, the licence committee of the Human Fertilisation and Embryology Authority (HFEA) has ruled.

The committee’s decision was published this week. It said the clinic must appoint another “person responsible” to be the licence holder. Mr Taranissi will remain medical director and will continue to treat patients at the clinic. Once a satisfactory “person responsible” has been appointed, the clinic will initially be given a six month licence coupled with a full inspection.

Mr Taranissi told the BMJ that he intended to appeal against the ruling. The regulatory regime gives a right of appeal to a differently constituted licence committee. If that proves unsuccessful, the High Court can judicially review the decision on grounds of an error of law.

The licence committee concluded that the gynaecologist had breached the Human Fertilisation and Embryology Act by treating “significant numbers” of patients at a second clinic, the Reproductive Genetics Institute, without a licence. The committee did not accept that he was justified in thinking his licence for the Assisted Reproduction and Gynaecology Centre covered the Reproductive Genetics Institute.

Mr Taranissi was not granted and did not seek a treatment licence for the institute, but special directions allowing storage of sperm, eggs, and embryos at the institute will remain in force.

The licence committee concluded “that a serious breach of the act had taken place in the offering of licensable treatment in unlicensed premises through 2006.”

Mr Taranissi said in a statement, “At the beginning of 2006, the HFEA issued special directions allowing treatment at the Institute for certain patients for an initial period of three months. These special directions were further extended for another three months at the beginning of April 2006. In the meantime, we were advised by the HFEA to consider reporting treatment undertaken at both the Assisted Reproduction and Gynaecology Centre and the Institute under one licence.”

He said that an interim application form was submitted to the HFEA in February 2006, which listed the addresses of both clinics under the licence of the Assisted Reproduction and Gynaecology Centre.

“This was put before a licence committee and no problems were raised at that time. It was only in late 2006 that the HFEA told us retrospectively that we could not treat patients in both centres under the same licence, notwithstanding their earlier advice.”

See www.healthcarecommission.org.uk
Practices with poor access must improve, says health minister

Zosia Kmiętowicz LONDON

General practices in England where patients have reported difficulty getting to see a doctor have been told to improve their services.

Most patients in England are happy with their ability to get an appointment to see a GP, show the results of the biggest ever survey about access to GPs commissioned by the Department of Health. But there are pockets around the country where retaining GPs remains a problem, and some communities are less satisfied with their experience of accessing general practice.

Areas in which there are problems of access are being asked to produce local action plans to improve their services, and primary care trusts have been told by the department to use their existing powers to invite new providers to offer high quality responsive services for patients.

Alan Johnson, the health secretary, who announced the measures this week, said, “I am particularly concerned about areas of deprivation where there is greater need for GP services”.

“...I am particularly concerned about areas of deprivation where there is greater need for GP services.”

Correction: Doctor ordered to pay libel damages

In a news article by Clare Dyer (BMJ 2007;335:119, 21 Jul), we inadvertently raised by a factor of 10 the amount that Tonmoy Sharma had been ordered to pay in libel damages to MedicoLegal Investigations. The correct amount was in fact £30 000 (€45 000; $62 000) [not £300 000]. This error occurred during the editing process, affecting both the title and the text.
Health and humanitarian agencies are bracing themselves for further deterioration in conditions throughout Sudan after record levels of rainfall threaten to affect millions more people.

More than 100 people have already died, and hundreds of thousands of people have been displaced by “the worst flooding in a generation,” according to the Sudanese news agency. With even heavier rainfall forecast throughout Darfur and central Sudan and Chad, relief officials are concerned that worse is yet to come and fear serious disruption to aid corridors and protection of civilians.

The World Health Organization warned, “The Nile and Blue Nile rivers are reaching alert level. Flash floods are expected to affect North, South, and West Darfur, North Kordofan, Tendalti, and areas of White Nile. Floods are already reported in Red Sea and White Nile states, and in Khartoum.”

After touring flooded areas of Khartoum last week, Claire-Lise Chaignat, head of WHO’s cholera taskforce, told the BMJ, “Further heavy rains are expected that are believed to be even more serious than in previous years. The big concern is, of course, waterborne diseases, and thinking of the huge epidemic that swept over the 25 states of Sudan last year, there is serious concern that a cholera epidemic might start again.”

Last year more than 2000 cases of cholera were recorded in Darfur alone.

Dr Chaignat said that the Federal Ministry of Health had learnt from last year’s experiences and had been recently “actively preparing for the coming cholera season” and has already positioned emergency supplies and strengthened the surveillance system.

Britain, meanwhile, last week also encountered the worst rainfall in living memory, with over five inches recorded in a single day in some areas, leading to widespread flooding.

The Red Cross assisted in evacuating patients from Tewkesbury hospital, thousands of households have been cut off from water and electricity, and people in affected areas have been advised to boil their water.

See the disasters emergency committee at [www.dec.org.uk](http://www.dec.org.uk) and Relief Web at [www.reliefweb.int](http://www.reliefweb.int).

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**UK medical training**

The end is nigh: Oscar the cat smells doom

Janice Hopkins Tanne NEW YORK

Oscar the cat has an “uncanny ability” to predict impending death among residents of a dementia ward at the Steere House nursing home in Providence, Rhode Island—even people not known to be terminally ill.

“He’s not the friendliest cat. He keeps to himself, although he can be bribed with food,” said geriatrician David Dosa, of Brown University, who has published his findings about Oscar in the *New England Journal of Medicine* (2007;357:328-9).

Oscar, who’s usually aloof, identifies patients who will die within hours by smuggling next to them, purring, and comforting them. In the year and a half he’s lived in the third floor dementia ward, he has identified more than 25 patients who were near to death. And he’s never made a mistake, Dr Dosa told the BMJ.

“His mere presence is viewed by physicians and nursing home staff as an almost absolute indicator of impending death, allowing staff members to adequately notify families.”

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Peter Moszynski LONDON

Health and humanitarian agencies are bracing themselves for further deterioration in conditions throughout Sudan after record levels of rainfall threaten to affect millions more people.

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See the disasters emergency committee at [www.dec.org.uk](http://www.dec.org.uk) and Relief Web at [www.reliefweb.int](http://www.reliefweb.int).
UK state pension inadequate for healthy living

Roger Dobson ABERGAVENNY

The minimum income needed for older people to enjoy a healthy life in England is 50% higher than the state pension.

A single pensioner aged at least 65 years needs £131 a week, and a couple need £208 (€310; $430) a week, a study has calculated (International Journal of Epidemiology 2007 Jul 12 doi: 10.1093/ije/dym129). The state pension is £139.60, before any additional means tested benefits, for a couple aged at least 65 years.

It is £87.30 for a single person—£43.70 below the amount that the paper says is adequate for a single person.

“The results suggest that inadequate income currently could be a barrier to healthy living for older people in England,” say the authors from the London School of Hygiene and Tropical Medicine.

The researchers calculated the minimum income for healthy living (MIHL) for people aged at least 65 years who were living independently without serious disability. The calculations were based on the income required for a number of aspects of healthy living, including diet; fuel; physical activity; housing; psychosocial relationships; medical, optical, and dental care; and hygiene.

“Our findings for England indicate that the current state pension and the official safety net, the pension credit guarantee (after means testing), fall below our estimated MIHL. Moreover, the MIHL is not intended to cover the 40% of older people who have significant defined disability, with the probable additional personal costs entailed. This of course will further increase the disparity between official benefits and the proposed MIHL,” say the authors.

The researchers say that there is no guarantee that pensioners would make healthy choices but add, “None the less, it would be a shortcoming of social policy if officially designated household incomes were below a level needed to allow the basic requirements of healthy living—especially in the context of government priorities to reduce health inequalities.”

Antibiotics still overprescribed

Susan Mayor LONDON

GPs in the United Kingdom are still prescribing antibiotics for a large proportion of patients who attend with sore throat, otitis media, upper respiratory tract infections, and sinusitis despite national guidance warning against this, according to a study published this week based on analysis of the world’s largest primary care database (Journal of Antimicrobial Chemotherapy 2007;60(suppl 1):i43-7).

The study assessed antibiotic prescribing in primary care using the general practice research database of consultations and prescriptions (GPRD), which collects information on about three million patients from general practices throughout the UK.

Researchers looked for all consultations between 1998 and 2001 for conditions that might have resulted in a prescription for antibiotics.

More than 80% of patients seen with lower respiratory tract infection, urinary tract infection, sinusitis, impetigo, or conjunctivitis were prescribed antibiotics, despite the fact that UK guidance recommends against their use for most of these conditions.

Some sexually transmitted infections rising

Michael Day LONDON

The rising incidence of sexually transmitted infections (STIs) among young adults and gay men continues to cause serious concern, the UK Health Protection Agency has warned.

In its fourth annual report the agency said that in 2006 there were 4%, 3%, and 9% rises in the incidence of chlamydia, genital warts, and genital herpes, respectively, compared with in 2005.

Gwenda Hughes, head of the sexually transmitted infections section at the agency, said, “The groups who we are most concerned about are young adults and gay men, and it’s crucial that we reach these groups with messages about safe sex, including condom wearing, and the importance of getting tested if they feel they’ve put themselves at risk of contracting an STI.”

Overall the number of new sexually transmitted infections diagnosed in genitourinary medicine clinics in the United Kingdom rose by 2% from 368,341 in 2005 to 376,508 in 2006. The number of new cases of chlamydia, the most common STI, increased by 4% to 113,585 in 2006. But for other bacterial infections the news was slightly better, with falls in diagnoses of syphilis and gonorrhoea, although the incidence of these diseases fell by only 1%.

The agency’s chief executive, Pat Troop, said, “There are some encouraging trends, but it’s very early. There’s absolutely no room for complacency.

“The good news is that gonorrhoea has gone down again, but the worrying picture is that of increasing levels of viral STIs, like herpes and warts, and in particular in young adults.

It is important to remember that herpes infections are carried for life, and although the symptoms are treatable many people will continue to suffer from recurrences.”


Cells infected with Chlamydia trachomatis, the incidence of which increased 4% between 2005 and 2006
Meta-analysis says low LDL cholesterol may be associated with greater risk of cancer

Janice Hopkins Tanne NEW YORK

Patients with low concentrations of low density lipoprotein (LDL) cholesterol, lowered as a result of taking statins, are at significantly more risk of being diagnosed as having cancer compared with patients with higher concentrations of the cholesterol, a meta-analysis of 23 large studies of statins shows (Journal of the American College of Cardiology 2007;5:409-18).

The analysis found one more case of newly diagnosed cancer per 1000 patients with low achieved LDL cholesterol concentrations who were taking statin treatment (below 100 mg/dl) compared with patients with higher concentrations of the cholesterol (100-150 mg/dl). US guidelines recommend 100 mg/dl.

The study set out to investigate why and how statins sometimes increase concentrations of liver enzymes and cause rhabdomyolysis. Results showed that raised liver enzymes was 271 with high dose statin, 195 with intermediate dose, and 114 with low dose statin per 100,000 person years for each 10% reduction in LDL cholesterol (P<0.001 for all pairwise comparisons). Rates of rhabdomyolysis were also higher with higher doses of statins, although not significantly so.

The meta-analysis included 23 published trials of different statins used at a range of doses, with at least 1000 person years of follow-up. These included a total of 75,117 patients who took statins and cumulative follow-up of 309,506 person years.

The researchers found a “disturbing,” highly significant inverse relation between the lowest concentration of LDL cholesterol achieved with statin treatment and the risk of newly diagnosed cancers ($R^2=0.43$, $P=0.009$).

The cancers were of a wide range of types, including genitourinary, prostate, respiratory, and haematological cancer. The researchers saw no significant relation between relative or absolute reduction in LDL cholesterol and rates of cancer.

Richard Karas, professor of medicine at Tufts University School of Medicine in Boston, and lead author of the study, cautioned, “This analysis doesn’t implicate the statins in increasing the risk of cancer."

**“This analysis doesn’t implicate the statins in increasing the risk of cancer”**

However, certain aspects of lowering LDL with statins remain controversial and merit further research,” he said.

The study authors noted, “The body of evidence is reassuring that statin use in itself is not associated with an increased risk of cancer compared with placebo. But they said that previous studies had not answered the question addressed by their study: what is the relation between reduction of LDL cholesterol in patients treated with statins and incident cancer?

In the light of current feeling that “lower is better” for LDL cholesterol concentrations to reduce cardiovascular risk, the authors warned, “It may be prudent not to use a statin dose beyond what is required to achieve the LDL cholesterol target,” but “evidence is reassuring that statin use in itself is not associated with an increased risk of cancer compared with placebo.”

Another study showed that use of simvastatin was associated with an almost 50% reduction in the risk of Alzheimer’s disease and Parkinson’s disease and that another statin, atorvastatin, was associated with a “modest” reduction in risk (BMC Medicine 2007;5:20).

The study analysed data from the decision support system of the US Department of Veterans’ Affairs database, which contains diagnostic, medication, and demographic information on 4.5 million people.

The association between taking a statin and dementia was examined compared with patients who took cardiovascular drugs other than statins, after adjusting for factors associated with dementia or Parkinson’s disease.
Systematic reviews don’t last for ever

Systematic reviews and meta-analyses are powerful tools for informing clinical decisions. But they soon begin to show their age. Researchers recently estimated that about a quarter of reviews (23%, 95% CI 15% to 33%) need updating within two years of publication, and 15% (9% to 24%) need updating within a year.

In a sample of 100 systematic reviews indexed in the American College of Physicians Journal Club between 1995 and 2005, 57 needed to incorporate new evidence by September 2006. It took a median of three years for these reviews to become out of date, and 7% (3% to 14%) were out of date by the time they were published. Cardiovascular reviews had a shorter survival than the rest.

The researchers deliberately chose reviews likely to be relevant to practising doctors, and all the reviews in their sample mathematically synthesised the evidence on at least one outcome. So these estimates may not apply to all published systematic reviews. It seems clear, however, that this kind of evidence has a relatively short shelf life, they say. Authors and journal editors should aim for speedy publication and update reviews first if there’s a delay. Doctors should probably check for more recent evidence once reviews reach their first birthday.

Ann Intern Med 2007;147:224-33

Fludarabine plus cyclophosphamide prolongs disease-free survival in CLL

The combination of fludarabine and cyclophosphamide should be the standard treatment for chronic lymphocytic leukaemia (CLL), write British researchers. Patients treated with the combination had significantly longer progression-free survival than controls given fludarabine or chlorambucil in a trial comprising 777 mostly British adults (five year estimates 36% for combination treatment v 10% for both control groups, P<0.001 for both comparisons). Choice of treatment did not affect patients’ quality of life, which worsened during treatment for all groups. Importantly, this trial included patients aged over 70, and the combination treatment seemed to work as well for them as for younger patients.

Chronic lymphocytic leukaemia is the most common leukaemia in developed countries, and it remains incurable, says a linked editorial (p 197). None of the head to head trials published so far have reported an overall survival advantage for any first line treatment. In this one, estimates of overall survival at five years were 59% (95% CI 53% to 66%) for patients given chlorambucil, 52% (42% to 61%) for fludarabine, and 54% (44% to 64%) for fludarabine plus cyclophosphamide. These authors were disappointed by this result. But they still favour combination treatment because it was associated with the highest response rate and the longest disease-free survival.

Lancet 2007;370:230-9

Gonorrhoea increasingly resistant to fluoroquinolones in the US

Gonorrhoea remains the second most common sexually transmitted infection in the United States, and resistance to fluoroquinolone antibiotics seems to be spreading. An analysis of data from 82 064 gonococcal isolates collected by a multisite surveillance programme over the 16 years to 2003 found that 4.1% of Neisseria gonorrhoeae samples collected in 2003 were resistant to fluoroquinolone treatment, up from 0.4% in 1999. The fluoroquinolones include ciprofloxacin, ofloxacin, and levofloxacin.

The first resistant strains were found in 1991. By 1999, fluoroquinolone resistance was found in 39% of cities surveyed (10/26), and by 2003 resistance had spread to 70% of cities surveyed (21/30). Resistance to penicillin peaked in 1991, at 19.6%, but had fallen to 6.5% by 2003. Resistance to ceftriaxone, cefixime, spectinomycin, and azithromycin remains rare.

The authors note that the sentinel surveillance programme—which includes mainly men attending public sexual health clinics—may not accurately reflect the picture in the general US population, or in specific locations. Doctors should also consult local surveillance data to help inform their treatment decisions.

Ann Intern Med 2007;147:81-8

Combining aspirin and oral anticoagulants is unsafe in peripheral arterial disease

People with atherosclerotic peripheral arteries have a high risk of cardiovascular complications such as stroke and heart attack. Antiplatelet agents help lower the risk, and researchers reasoned that adding an oral anticoagulant might lower it further. But the results of a recent randomised trial were clear. Patients given both treatments were no less likely to have a stroke or a heart attack or to die from cardiovascular disease than controls given just an antiplatelet agent, such as aspirin or clopidogrel (relative risk 0.92, 95% CI 0.73 to 1.16). But they were significantly more likely to bleed. Life threatening, moderate, and minor bleeds were all more common in patients given anticoagulants during a mean follow-up of three years. Overall, they had a risk of haemorrhagic stroke more than 15 times higher than controls (15.2, 2.0 to 115.6, P=0.001). The authors looked for but failed to find any subgroup of patients who might benefit. They estimate that for every 1000 patients given anticoagulants for three years, there would be 24 fewer cardiovascular events but 28 more life threatening bleeds. The message is clear—patients with peripheral artery disease do not benefit from adding an oral anticoagulant to their

Ann Intern Med 2007;147:81-8

Ann Intern Med 2007;147:81-8
Researchers get closer to the genetics of coronary heart disease

Researchers looking for the genetic basis of coronary heart disease have found at least seven genetic variants significantly associated with symptomatic disease. The three most convincing were on chromosomes 2, 6, and 9, and together they could be responsible for 38% (95% CI 13% to 55%) of coronary artery disease in the population. The other four are entirely new, thrown up by a combined analysis of two large case-control studies in European adults.

Researchers used the new rapid genotyping technology to scan for half a million or so genetic variants (single nucleotide polymorphisms) in people with and without coronary heart disease. The “best” three were significantly associated with heart disease in both studies, which increases the likelihood that the associations were real, not statistical artefacts generated by multiple comparisons.

The genetic variant on chromosome 9 (9p21.3) looks like the strongest candidate locus so far, says an editorial (doi: 10.1056/NEJMe078121). Other researchers have already reported links between 9p21.3 and heart disease in a variety of populations using several different scanning technologies. We won’t know for some time how (or even if) these variants cause coronary heart disease, says the author. But other candidates are likely to follow soon.

Metformin remains the best treatment for type 2 diabetes

Newer, more expensive, treatments for type 2 diabetes offer no advantage over cheaper treatments such as metformin, according to a systematic review. Most agents reduce concentrations of glycated haemoglobin by around one percentage point, but metformin has a better side effect profile than the rest, say the authors. Most agents other than metformin cause weight gain; the sulfonylureas and repaglinide have a greater tendency to cause hypoglycaemia; and the thiazolidinediones have a harmful effect on low density lipoprotein cholesterol and have been linked to an increased risk of heart failure.

The authors found few reliable data on the effects of any agents on renal failure, retinopathy, neuropathy, and cardiovascular disease. Most of the 136 trials they found were short term and sponsored by the drug industry. They conclude that metformin should remain the drug of first choice for adults with type 2 diabetes, in line with current national and international guidelines. When one drug isn’t enough, doctors should probably add a second generation sulfonylurea. The authors synthesised evidence from 216 studies and two previous systematic reviews.

Ann Intern Med 2007;147(6) [epublication ahead of print 17 July]

Fruit and vegetables don’t prolong survival in women with breast cancer

Computed tomography (CT) of the coronary arteries is one alternative to traditional coronary angiography for patients with chest pain. It’s less invasive, but it exposes patients to a substantial dose of ionising radiation. There is no way of knowing the exact risks of cancer associated with each scan. But they could be substantial, particularly for young women. According to the latest estimates, coronary artery scans are associated with a lifetime risk of cancer of one in 143 for a 20-year-old woman, although the risks go down quickly with age. The risks look much lower for men of any age, and by 80 years the estimated lifetime attributable risk from one scan falls to only one in 1338.

These figures are “best guesses,” as there are no data linking real scans with real cancers, say researchers. Instead, they calculated the risks using an established model based on multiple other sources, including Japanese survivors of the atomic bomb. In their study, women were particularly vulnerable to cancers of the breast, and both sexes were prone to cancers of the lung. Risks were reduced by minimising the dose of radiation given with each scan and increased by extending the scan as far as the aortic arch.

JAMA 2007;298:317-23

A diet high in fruit, vegetables, and fibre did not improve survival for women with early breast cancer in a large randomised trial (n=3088). The women had cookery lessons and counselling to enable them to increase their daily intake to five servings of vegetables, three servings of fruit, and 30 g of fibre. They were also meant to reduce their fat intake to less than 20% of total calories, but they didn’t manage to. Their chances of a recurrence, a new primary breast cancer, or death were almost identical to a control group of women who were advised to eat the standard five portions of fruit or vegetables a day. Just over 10% of each group died during the 7.3 year follow-up (adjusted hazard ratio 0.91, 95% CI 0.72 to 1.15, P=0.43). Just under 17% of each group had a recurrence or a new primary (0.96, 0.80 to 1.14, P=0.63).

Although the two groups of women had very different diets throughout the study, they both averaged the same modest weight gain. Perhaps it’s weight loss not fruit and vegetables that makes the difference, says a linked editorial (p 335). In a previous large trial, women who ate a low fat diet and lost weight survived significantly longer than controls.

JAMA 2007;298:289-98

Metformin remains the best treatment for type 2 diabetes

Newer, more expensive, treatments for type 2 diabetes offer no advantage over cheaper treatments such as metformin, according to a systematic review. Most agents reduce concentrations of glycated haemoglobin by around one percentage point, but metformin has a better side effect profile than the rest, say the authors. Most agents other than metformin cause weight gain; the sulfonylureas and repaglinide have a greater tendency to cause hypoglycaemia; and the thiazolidinediones have a harmful effect on low density lipoprotein cholesterol and have been linked to an increased risk of heart failure.

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Ann Intern Med 2007;147(6) [epublication ahead of print 17 July]
A SPOONFUL OF ANTIGEN

Immunisation without needles could have medical and technical advantages as well as being less traumatic for children. Alison Tonks reports

Any parent who has ever taken their child to a seemingly endless series of vaccinations armed with pacifiers, lollipops, and a pack of lies about how much it will hurt must have hoped that one day someone would come up with a better way to protect infants from infections. A few may even have looked on wistfully as the oral polio vaccine went down in one and wondered why all vaccines weren’t that simple. Fortunately, scientists love their children too. For the past 15 years they have been looking for the best way to produce vaccines you can eat.

The original idea was simple. Genetically engineer an edible fruit or vegetable so that it contains a vaccine and feed it to children. Early pioneers started experimenting with carrots, bananas, tomatoes, soya beans, and corn. One team led by Charles Arntzen, the US based grandfather of edible vaccines, made it all the way to phase I human trials with potatoes engineered to produce harmless antigenic proteins from enterotoxigenic Escherichia coli, Norwalk virus, and hepatitis B virus. In a series of elegant experiments, volunteers who ate the potatoes mounted a limited immune response to all three.1-3

Now though, the science has moved on, and along with it the aspirations of Professor Arntzen and other enthusiasts. Edible vaccines have grown up during the past five years, and whole fruit and vegetables are off the menu. Scientists now see genetically engineered plants not as food but as an efficient production system for antigenic proteins that can be processed into pills or capsules containing fixed reproducible (and marketable) doses.

Earlier this summer, a team of scientists from Japan reported preliminary success with rice engineered to carry a vaccine against subunit B of the cholera toxin.4 Mice fed the rice produced neutralising antibodies in their gut mucosa that seemed to protect them from an oral challenge with the cholera toxin. Professor Hiroshi Kiyono, from the division of mucosal immunology at the University of Tokyo has high hopes for rice as a vehicle for vaccines against cholera and other pathogens but concedes they have a lot more work to do before testing the vaccines in humans. Professor Arntzen and his team at Arizona State University are getting closer with an oral vaccine against Norwalk virus grown in a type of wild tobacco. “Exhaustive laboratory experiments show that this vaccine induces a powerful immune response in mice,” he says. “Preliminary trials in humans should be underway within a year.” Others are experimenting with tobacco containing the shiga toxin from E coli.5 Plant derived vaccines against plague and anthrax are also at an early stage of development, driven by the threat of bioterrorism and funded by the research arm of the US army.

How to do it

There are essentially three ways to encourage plants to make foreign proteins from human pathogens, according to Professor Julian Ma, a leading vaccine researcher from St George’s Hospital in London. You can take a gene from a pathogen such as cholera and insert it directly into the plants cells (with a little help from a common soil bacterium called Agrobacterium), which then produce the antigenic protein you plan to use as a vaccine. But this method, called transformation, is a bit slow and yields are low. To speed things up, you can insert the gene into a virus first, then infect the plant with it. The antigenic protein is produced quickly and efficiently during rapid viral
replication. This method is faster than direct transformation but carries with it the potential environmental hazard of fully infective plant viruses.

So in the most recent twist, scientists have found a way to deconstruct the viral vector, making it a harmless factory for vaccine. “The deconstructed viral vector approach is rapidly becoming the technology of choice for scientists working on these vaccines,” says Professor Arntzen. “It’s extremely efficient and generates more protein per kilo of plant than going down the route of creating transgenic plants.” Which is just as well when you consider that in early experiments with potatoes, the concentrations of antigens in the samples were so low that volunteers had to eat at least 100 g of raw potatoes to generate an immune response.  

The latest technique works best in a variety of wild tobacco.

Do we need plant derived vaccines?  
Infectious diseases are responsible for 63% of the child deaths worldwide. Many of these deaths are preventable with the right vaccine. One in five children worldwide, or about 33 million a year, don’t even get the basic vaccines such as measles.  

So there’s an urgent need for novel vaccine technologies to help reach them. Oral vaccines from genetically engineered plants have many theoretical advantages over conventional vaccines, almost all of which must be injected. They would be needle-free, making them easier and cheaper to use. Eventually, large numbers of children could be vaccinated without help from expensively trained health professionals, without the screaming, and without adding used and bloody needles to their already hazardous environment. Plant derived vaccines may even increase compliance with voluntary vaccination programmes.

Vaccines in freeze dried plants could be transported and stored at room temperature, unlike conventional vaccines, which require an unbroken chain of refrigeration from manufacture to administration. Experts estimate that it costs $200m-$300m (£98m-£148m; €143m-€218m) a year to keep a vaccine’s “cold chain” intact.  

The costs and logistics of distribution are often too much for developing nations with poor infrastructure and unreliable electricity supply. Crops such as rice and tobacco are cheap to grow, relatively easy to scale-up locally, and sustainable long term.

Arguably the biggest advantage, however, is that plant derived vaccines taken by mouth induce immunity at the mucosal surfaces such as the gut, the first line of defence against intestinal pathogens *Vibrio cholerae* and *E coli*. Traditional vaccines given by injection induce only a systemic immune response, by which time potentially lethal infections have already broken through the mucosal defences. Mucosal vaccines, such as those being developed in rice and tobacco induce antibodies at the mucosal point of entry, as well as systemically. The World Health Organization, the US National Institutes of Health, and the Bill and Melinda Gates Foundation all believe that mucosal vaccines are a key development in the defence against pathogens that invade the body through mucosal surfaces, including HIV and influenza virus.

Getting beyond the drawing board  
The technology may be feasible but someone has to pay. And so far few companies are willing to invest the $50m-$100m it would take to produce a viable plant derived vaccine.  

Enthusiasts such as Professor Arntzen are frustrated by this lack of financial support for product development but accept that the regulatory uncertainties surrounding plant derived vaccines causes many companies to hesitate. GlaxoSmithKline and Merck spent a billion dollars each getting a recently approved vaccine against human papilloma virus to market. With sums like that at stake it’s hardly surprising that big drug companies are cautious. “We also need to consider the fact that vaccines against common infectious diseases must be affordable to the developing countries that need them most, even though this limits manufacturer’s profit margins,” notes Professor Arntzen. “Unfortunately this makes blockbuster cancer treatments or drugs for Alzheimer’s disease more financially attractive to companies in the developed world than plant derived vaccines.”

Money isn’t the only problem, however. Plant derived vaccines lie in a kind of no man’s land between farming and pharmaceuticals. The regulatory rule book is still being written. Plants that produce antigenic proteins are regulated under the same
ORAL VACCINES

Scientists are more likely to overcome regulatory hurdles with pills and capsules than whole bananas

framework as genetically modified crops in many jurisdictions. Large scale production is likely to attract similar social and political unease. How, for example, would producers stop their transgenic food crops contaminating other crops and getting into the food chain? A Canadian collaboration of scientists and ethicists is already studying these and other social objections to plant derived vaccines, hoping to head off the inevitable objections before they turn into outright social rejection of the technology.

Some leading observers and the WHO believe all plants engineered to produce therapeutics proteins, including vaccines, should be grown in greenhouses to prevent genetic drift. Professor Kiyono agrees that transgenic rice would have to be grown in hermetically sealed conditions to prevent contamination of the Japanese staple crop. The contamination issue has driven others back towards inedible crops such as tobacco: “Using tobacco avoids any concerns about contaminating the food chain. It’s ironic that...”

Regulators such as the European Medicines Agency remain uneasy, even about tobacco. “Transgenic plants producing antigenic proteins have been around for 15 years, but drug companies and regulatory agencies still think of them as a prototype technology,” says Professor Ma. Scientists are more likely to overcome regulatory hurdles with pills and capsules than with whole bananas, but they still have a lot of persuading to do. One strategy is to test the water with vaccines for animals first, and Dow Agrosciences have recently obliged by gaining a licence for a plant derived vaccine against Newcastle disease in chickens. Researchers are also testing the regulators with more familiar agents produced in plants or plant cells such as intrinsic factor, insulin, and aprotinin to see how they react. An Israeli biotechnology company Protalix recently gained the US Food and Drug Administration’s approval to start advanced human trials of their new treatment for Gaucher disease—glucocerebrosidase grown in cultures of genetically engineered carrot cells. If these and other therapeutic ventures are successful, oral vaccines grown in plants or plant cell cultures could be next.

But there’s one more hurdle to jump first—the theoretical possibility that oral mucosal vaccines might induce tolerance rather than immunity. Tolerance is a mechanism by which an orally delivered antigen might somehow disable or at least interfere with the systemic immune system. The result could be a disastrous “antivaccine” that told the body to ignore invading pathogens and not respond to infection. It may be the reason we don’t mount an immune response to food.

“Tolerance is only a theoretical possibility, but as yet no one quite understands how to overcome it,” says Professor Ma, although there’s a scientific consensus that in reality, tolerance is highly unlikely to happen. We can’t learn anything from the oral polio vaccine, which is a systemic not a mucosal vaccine.

“I sensed a little despondency initially at our recent scientific meeting in Verona” he says, “but vaccine development has always been a long slow process. The new vaccine finish line first. Who knows how long it will take, but an oral vaccine against such a high impact pathogen would be a fitting tribute to the man who first thought it might be possible to grow oral vaccines in plants.

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6 Castle D, Dalgleish J. Cultivating fertile ground for the introduction of plant derived vaccines in developing countries. Vaccine 2005; 23: 1881-5.
Only general practice can save the NHS

Why have governments been intent on undermining the morale and status of general practitioners?

The UK National Health Service is designed as an expression of social solidarity and provides universal access to health care funded through general taxation and free at the time of need. Similar systems have been developed across the Nordic countries and elsewhere but, despite frequent statements of support from all mainstream political parties, all such systems now find themselves under grave threat. Rapid advances in biomedical science are producing exponential increases in the costs and sophistication of investigations and treatments. Politicians everywhere, undoubtedly reflecting the priorities of their electorates, are unwilling to increase levels of taxation to match these increasing costs. This reluctance is easy to understand, but the identification of market forces as a solution to the worsening tension is perplexing.

Markets are motivated by the pursuit of private profit. This motivation can be used to increase efficiency and hold down wages but markets can thrive only if they can generate increasing demand for their products. Health care, despite recent efforts, is not easily packaged as a product and the relation between demand and need within health care remains intensely problematic. At what point, if ever, should demand be prioritised over need? Within a market system, how can unprofitable need, however great the suffering involved, ever be given commensurate priority?

If there is to be any hope of continuing to provide a comprehensive modern health service on the basis of solidarity expressed through taxation, resources must be allocated on the basis of need rather than demand. The current enthusiasm for market forces seems to be making this politically unacceptable and so nothing is being done about the expansionist health technology industry, which is driving demand for health care through the deliberate inflation of fear. The definitions of disease are being extended to include more people as patients and preventive medicine pursues an ever greater number of risk factors, each of which triggers a search for more technological interventions. There are three clear trends that are mutually reinforcing: the medicalisation of normal life, the industrialisation of health care, and increasing state coercion of medicine. In the UK we see the last of these in the ever increasing surveillance of clinical practice, the apparently deliberate creation of unemployment among junior doctors, and a campaign of insidious vilification of doctors. All this is counterproductive if the hope is to sustain a healthcare system founded in social solidarity.

At its best, general practice offers highly trained clinical expertise located close to the context of the lives of individual patients. Longitudinal care over time allows general practitioners to understand how illness and disease develop and thrive in certain settings and it also enables doctors to see that technological biomedicine has enormous power to heal but also to harm. All doctors working in the UK who were trained in this country have been educated to understand the continuing necessity of balancing the needs of individuals and their families against those of the population as a whole. In general practice, this has generated instincts for caution, doubt, and frugality that have underpinned the longstanding (although now rapidly eroding) cost effectiveness of the UK health service.

General practitioners have learnt from experience the benefits, both to the individual and to society, of holding the border between subjective illness and the disease categories recognised by biomedical science; of confining people within diagnostic categories only when this will be positively useful to them; and of deliberately minimising exposure to the harms of medical technology. In this way, general practice directs both the power and the rising costs of biomedical science where it can help rather than where it harms. These instincts almost certainly explain Barbara Starfield’s findings of the importance of a strong system of primary care to the health of populations. Many frail older people have a diminishing appetite for technological care and a proportionately increased need for sensitive, hands-on care. How can markets have a place in marking that distinction and enabling the necessary transition?

GPs can undertake this role only if they can hold the fear implicit in any presentation of illness within a framework of trust so that demand for unnecessary and dangerous health care can be held in check—this in turn allows the doctor to prioritise the identification of need. Trust is built on strong personal relationships and on levels of skill and expertise. Patients must be able to trust that the doctor working at the first point of contact will recognise the early signs of serious disease. This can be achieved only by rigorous training, not by fragmentation of the first point of contact or by delegation to those with less training and knowledge.

GPs work in the front line and deal with undifferentiated illness and distress. They undertake a highly skilled and high risk task on behalf of society and enable the cost effective functioning of the NHS. So why have successive governments been intent on undermining the morale and status of GPs and on eroding public trust in their contribution? Are patients’ interests really served by doctors who are subservient to commercial or political interests? Why have doctors forgotten that patients may be best served by doctors prepared to defend their clinical autonomy and the ability to allocate their time and expertise on the basis of an expert assessment of need?

All the indications are that patients and professionals remain committed to a healthcare system based on social solidarity rather than the pursuit of profit. Can we be convinced that politicians are similarly committed?

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Dignity and the essence of medicine: the A, B, C, and D of dignity conserving care

Kindness, humanity, and respect—the core values of medical professionalism—are too often being overlooked in the time pressured culture of modern health care, says Harvey Chochinov, and the A, B, C, and D of dignity conserving care can reinstate them.

The late Anatole Broyard, essayist and former editor of the New York Times Book Review, wrote eloquently about the psychological and spiritual challenges of facing metastatic prostate cancer. “To the typical physician,” he wrote, “my illness is a routine incident in his rounds while for me it’s the crisis of my life. I would feel better if I had a doctor who at least perceived this incongruity… I just wish he would… give me his whole mind just once, be bonded with me for a brief space, survey my soul as well as my flesh, to get at my illness, for each man is ill in his own way.”

Broyard’s words underscore the costs and hazards of becoming a patient. The word “patient” comes from the Latin patiens, meaning to endure, bear, or suffer, and refers to an acquired vulnerability and dependency imposed by changing health circumstances. Relinquishing autonomy is no small matter and can exact considerable costs. These costs are sometimes relatively minor—for example, accepting clinic schedules or hospital routines. At other times, the costs seem incompatible with life itself. When patients experience a radical unsettling of their conventional sense of self and a disintegration of personhood, suffering knows few bounds. To feel sick is one thing, but to feel that who we are is being threatened or undermined—that we are no longer the person we once were—can cause despair affecting body, mind, and soul. How do healthcare providers influence the experience of patienthood, and what happens when this frame of reference dominates how they view people seeking their care?

Dignity and patienthood

Answering these questions begins with an examination of the relationship between patienthood and notions of dignity. Although the literature on dignity is sparse, it shows that “how patients perceive themselves to be seen” is a powerful mediator of their dignity. In a study of patients with end stage cancer, perceptions of dignity were most strongly associated with “feeling a burden to others” and “sense of being treated with respect.” As such, the more that healthcare providers are able to affirm the patient’s value—that is, seeing the person they are or were, rather than just the illness they have—the more likely that the patient’s sense of dignity will be upheld. This finding, and the intimate connection between care provider’s affirmation and patient’s self perception, underscores the basis of dignity conserving care.

Yet, many healthcare providers are reticent to claim this particular aspect of care, which is variously referred to as spiritual care, whole person care, psychosocial care, or dignity conserving care. This reluctance is often framed in terms of lack of expertise or concern about how much time this might consume. Yet, when personhood is not affirmed, patients are more likely to feel they are not being treated with dignity and respect. Not being treated with dignity and respect can undermine a sense of value or worth. Patients who feel that life no longer has worth, meaning, or purpose are more likely to feel they have become a burden to others, and patients...
who feel they are little more than a burden may start to question the point of their continued existence.14-16

Redressing the “incongruity” that Broyard raises—that is, the separation of humanity and compassion from healthcare delivery—requires that “treatment of disease takes its proper place in the larger problem of the care of the patient.”16

The A, B, C, and D of dignity conserving care

The notion of dignity conserving care, while emerging primarily from palliative care, applies across the broad spectrum of medicine. Whether patients are young or old, and whatever their health problems, the core values of kindness, respect, and dignity are indispensable. Just as the simple “A, B, C” mnemonic (airway, breathing, and circulation) effectively summarises the fundamentals of critical care, an easily remembered core framework of dignity conserving care—the A, B, C, and D of dignity conserving care—may remind practitioners about the importance of caring for, as well as caring about, their patients.36

Attitude

“A”—attitude—underscores the need for healthcare providers first and foremost to examine their attitudes and assumptions towards patients. Attitude can be defined as an enduring, learnt predisposition to behave in a consistent way towards a given class of objects (or people), or a persistent mental or neural state of readiness to react to a certain class of objects (or people), not as they are but as they are conceived to be. The perceptions on which attitudes are based may or may not reflect the patient’s reality. For instance, might an assumption of poor quality of life in a patient with longstanding disabilities lead to the withholding of life sustaining choices?37 Might ageist assumptions mean that conversations about intimacy are rarely initiated?38 Is a health worker more likely to assume intoxication in a confused, homeless patient, before considering whether they have a metabolic disorder? Do people with chronic mental illness provoke assumptions about malingering or somatoform disorders, even before an appropriate medical examination has been done?

Examining attitudes and assumptions is a deeply personal task, requiring approaches suited to the individual (box 1). At a minimum, healthcare providers must ask some basic questions, meant to help them understand how attitudes and assumptions can influence the way they deal with patients. They are reminded that “what they believe about patients and their potential may affect them profoundly. The attitude of an expert is contagious and can become limiting.”19 As a case in point, inordinately high suicide rates were reported among Scandinavian patients with advanced cancer, who were offered no further treatment or contact with the healthcare system.20 While the rationale for this may have been based on considerations of resource allocation or medical futility, the psychological and spiritual fallout is clear: people who are treated like they no longer matter will act and feel like they no longer matter. In other words, patients look at healthcare providers as they would a mirror, seeking a positive image of themselves and their continued sense of worth. In turn, healthcare providers need to be aware that their attitudes and assumptions will shape those all-important reflections.

Box 1 | Attitudes

Questions to be asked

• How would I be feeling in this patient’s situation?
• What is leading me to draw those conclusions?
• Have I checked whether my assumptions are accurate?
• Am I aware how my attitude towards the patient may be affecting him or her?
• Could my attitude towards the patient be based on something to do with my own experiences, anxieties, or fears?
• Does my attitude towards being a healthcare provider enable or disenable me to establish open and empathic professional relationships with my patients?

Actions to be taken

• Make a conscious effort to make these questions a part of your reflection on the care of each and every patient
• Discuss the issue of healthcare providers’ attitudes and assumptions, and how they influence caring for patients, as a regular part of case reviews and clinical teaching
• Include ongoing professional development activities that have you challenge and question your attitudes and assumptions as they might affect patient care
• Create a culture among your colleagues and within your healthcare setting in which acknowledgement and discussion of these issues becomes a standard part of providing care

Box 2 | Behaviours

Disposition

• Treat contact with patients as you would any potent and important clinical intervention
• Professional behaviours towards patients must always include respect and kindness
• Lack of curative options should never rationalise or justify a lack of ongoing patient contact

Clinical examination

• Always ask the patient’s permission to perform a physical examination
• Always ask the patient’s permission to include students or trainees in the clinical examination

Although an examination may be part of routine care, it is rarely routine for the patient, so always, as far as possible, take time to set the patient at ease and show that you have some appreciation for what they are about to go through (for example, “I know this might feel a bit uncomfortable”; “I’m sorry that we have to do this to you”; “I know this is an inconvenience”; “This should only hurt for a moment”; “Let me know if you feel we need to stop for any reason”; “This part of the examination is necessary because . . . ”)
• Limit conversations with patients during an examination (aside from providing them with instruction or encouragement) until they have dressed or been covered appropriately

Facilitating communication

• Act in a manner that shows the patient that he or she has your full and complete attention
• Always invite the patient to have someone from his or her support network present, particularly when you plan to discuss or disclose complex or “difficult” information
• Personal issues should be raised in a setting that attempts to respect the patient’s need for privacy
• When speaking with the patient, try to be seated at a comfortable distance for conversation, at the patient’s eye level when possible
• Given that illness and changing health status can be overwhelming, offer patients and families repeated explanations as requested
• Present information to the patient using language that he or she will understand; never speak about the patient’s condition within their hearing distance in terms that they will not be able to understand
• Always ask if the patient has any further questions and assure them that there will be other opportunities to pose questions as they arise
Behaviour
A change, or at the very least an awareness, of one’s attitudes can set the stage for modified behaviour—the “B” of dignity conserving care. Once healthcare providers are aware that they play an important role in mediating patients’ dignity, several behaviours should logically follow (box 2). Healthcare providers’ behaviour towards patients must always be predicated on kindness and respect. Small acts of kindness can personalise care and often take little time to perform.21 Getting the patient a glass of water, helping them with their slippers, getting them their glasses or hearing aid, adjusting a pillow or their bed sheets, acknowledging a photograph, greetings card, or flowers—these behaviours convey a powerful message, indicating that the person is worthy of such attention. Such behaviour is particularly important when caring for patients with advanced disease “both because of the physical threats of dying and because of the challenge to our sense of self worth and self coherence.”

Compassion
Getting in touch with one’s own feelings requires the consideration of human life and experience

- Reading stories and novels and observing films, theatre, art that portray the pathos of the human condition
- Discussions of narratives, paintings, and influential, effective role models
- Considering the personal stories that accompany illness
- Experiencing some degree of identification with those who are ill or suffering

Ways to show compassion
- An understanding look
- A gentle touch on the shoulder, arm, or hand
- Some form of communication, spoken or unspoken, that acknowledges the person beyond their illness.

One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient.
that draws from these insights, and the awakening of compassion, many fundamental aims of dignity conserving care will already have been achieved. The practice of medicine requires the exchange of extensive information, within a partnership whose tempo is set by gathering, interpreting, and planning according to new and emerging details. As such, dialogue is a critical element of dignity conserving care. At its most basic, such dialogue must acknowledge personhood beyond the illness itself and recognize the emotional impact that accompanies illness (box 4).

Several psychotherapeutic approaches (dignity therapy, meaning-centred therapy, life review or reminiscence) engage patients in more extensive, formatted dialogue, with the intent of bolstering their sense of meaning, purpose, and dignity (see further reading in box). Dialogue should routinely be used to acquaint the healthcare provider with aspects of the patient’s life that must be known to provide the best care possible. Treating a patient’s severe arthritis and not knowing their core identity as a musician, providing care to a woman with metastatic breast cancer and not knowing she is the sole carer for two young children; attempting to support a dying patient and not knowing he or she is devoutly religious—each of these scenarios is equivalent to attempting to operate in the dark. Obtaining this essential context should be a standard and indispensable element of dignity conserving care. It will also foster a sense of trust, honesty, and openness, wherein personal information and medical facts are woven into a continuous and rich dialogue informing care.

**Conclusions**

In his 1927 landmark paper “The care of the patient” Francis Peabody wrote: “One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient.” The A, B, C, and D of dignity conserving care may provide clinicians with a framework to operationalise Peabody’s sage insight and relocate humanity and kindness to their proper place in the culture of patient care. Easy to remember and empirically based, this framework may be readily applied to teaching, clinical practice, and standards at undergraduate and postgraduate levels and across all medical subspecialties, multidisciplinary teams, and allied health professions. For anyone privileged to look after patients, at whatever stage of the human life cycle, the duty to uphold, protect, and restore the dignity of those who seek our care embraces the very essence of medicine.

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**Competing interests:** None declared.

**SUMMARY POINTS**

Healthcare providers have a profound influence on how patients experience illness and on their sense of dignity. Dignity conserving care has an important effect on the experience of patients. The A, B, C, and D of dignity conserving care—attitude, behaviour, compassion, and dialogue—provide a framework to guide healthcare practitioners towards maintaining patients’ dignity. This framework can be applied to teaching, clinical practice, and standards at undergraduate and postgraduate levels and across all medical subspecialties, multidisciplinary teams, and allied health professions.

**Further Reading**


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Limitations of rapid HIV-1 tests during screening for trials in Uganda: diagnostic test accuracy study

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ABSTRACT

Objective To evaluate the limitations of rapid tests for HIV-1.

Design Diagnostic test accuracy study.

Setting Rural Rakai, Uganda.

Participants 1517 males aged 15-49 screened for trials of circumcision for HIV prevention.

Main outcome measures Sensitivity, specificity, negative predictive values, and positive predictive values of an algorithm using three rapid tests for HIV, compared with the results of enzyme immunoassay and western blotting as the optimal methods.

Results Rapid test results were evaluated by enzyme immunoassay and western blotting. Sensitivity was 97.7%. Among 639 samples where the strength of positive bands was coded if the sample showed positivity for HIV, the algorithm had low specificity (94.1%) and a low positive predictive value (74.0%). Exclusion of 37 samples (5.8%) with a weak positive band improved the specificity (99.6%) and positive predictive value (97.7%).

Conclusion Weak positive bands on rapid tests for HIV should be confirmed by enzyme immunoassay and western blotting before disclosing the diagnosis. Programmes using rapid tests routinely should use standard serological assays for quality control.

Trial registration Clinical Trials NCT00425984.

INTRODUCTION

Rapid tests for the detection of antibodies to HIV-1 allow timely point of care provision of results and do not require the laboratory facilities needed for conventional enzyme immunoassays and western blot testing. As a consequence rapid tests have been widely used for voluntary HIV counselling and testing, antenatal surveillance, and population screening. An FDA application is now pending for an over the counter home testing kit, and the expansion of requirements for HIV testing in the developing world will require use of these rapid tests. We have, however, encountered problems with the interpretation of positive results of rapid tests during the screening of populations in rural Uganda for two randomised trials of male circumcision for the prevention of HIV. We evaluated limitations of these tests in such settings.

METHODS

The Rakai health sciences programme used rapid HIV tests to screen males for two randomised trials of circumcision for the prevention of HIV in a rural population in Rakai district of south western Uganda. One trial enrolled uncircumcised males aged 14-49 who were negative for HIV and the other uncircumcised males in the same age range who were HIV positive. The rapid tests were used to initially screen males for subsequent enrolment into these two trials.

During 2003-4 we used an algorithm incorporating three rapid HIV tests to screen potential participants for a randomised trial that enrolled males aged 15-49. The algorithm (figure) consisted of an initial screening with the rapid test Determine HIV-1/2/O (Abbott Laboratories, Abbott Park, IL). If the test result was negative the participant was given a diagnosis of HIV negative with no further rapid testing. If the test result was positive the sample was retested with the rapid test HIV 1/2 Stat-Pak Ultra Fast (Chembio Diagnostic Systems, Medford, NY). If both tests gave a positive result the participant was given a diagnosis of HIV positive with no further rapid testing. If the tests gave discordant results, the sample was further evaluated with the rapid test Uni-Gold Recombinant HIV-1/2 (Trinity Biotech, Bray, Ireland). For those samples assessed by all three tests, two positive test results were interpreted as a positive diagnosis. If two of the three tests gave negative results then the participant was diagnosed as being negative for HIV.

These rapid tests and the testing algorithm were approved by the Ugandan Ministry of Health and are widely used in Uganda and elsewhere. The tests were carried out in a field setting in small mobile laboratories set up in local buildings or tents. Tests were run on serum from blood collected and centrifuged immediately before testing. At the same time a separate serum aliquot was archived. To optimise test results the technicians were advised to ensure good lighting conditions and to use a flat table, according to the
manufacturers’ instructions. The reading of each result was timed with an electronic timer, using the duration specified by the manufacturer. Each test was read by two trained laboratory technicians, with the test card lying flat on the table. The tests were interpreted according to manufacturers’ instructions, which recommend that any band in the positive region be considered as a positive result for HIV, irrespective of the strength of the band. This algorithm for rapid HIV-1 testing is widely used in Uganda. Subsequently all samples were batch retested for quality control, using two enzyme immunoassays (Vironostika HIV-1, Organon Teknika, Charlotte, NC and Cambridge Biotech, Worcester, MA), and discordant results were confirmed by western blotting (HIV-1 Western Blot; BioMerieux-Vitek, St Louis, MO).

We tested one sample from each of 1517 participants. An initial assessment of 878 batched samples, however, suggested problems with false positive results, so after March 2004 the laboratory technicians recorded the intensity of positive bands in 639 samples. In this subgroup 125 samples tested positive for HIV, of which 37 were classified as weak positive bands (5.8%). Weak positive bands were defined as a sample with an apparent positive band that was lighter than the control positive band on the test card. We estimated the sensitivity, specificity, negative predictive values, and positive predictive values of this algorithm, compared with the results of the enzyme immunoassay and western blotting as the ideal methods. Analyses were carried out for the 1517 samples, for the 639 samples for which band intensity had been coded, and for the subgroup of tests in which we had excluded positive results coded as weak positive bands (n=602).

**RESULTS**

The study population comprised 1517 males aged 15-49. The age distribution was 15-19 (21.3%), 20-24 (27.6%), 25-29 (20.4%), and 30-49 (28.8%). Fifty one per cent were married and most (65.2%) had achieved primary or secondary education (22.1%) or higher (7.3%). Only 5.4% reported no schooling. Most were sexually active (84.3%).

The table shows the results of the rapid tests for HIV. In the total sample of 1517 tests the three rapid test algorithm had reasonable sensitivity (97.7%, 95% confidence interval 94.1% to 99.4%) and negative predictive value (99.7%), but the specificity was low (90.4%, 95% confidence interval 88.7% to 91.9%) and the positive predictive value was unacceptably low (56.3%). Overall, 129 of 295 positive test results were false positives (43.7%) and four of 1222 negative results were false negatives (0.3%). Of the 129 false positives, 123 (95%) resulted from the Determine and Uni-Gold tests. Investigation of individual lots for each test did not show evidence of defective batches.

In the subsample of 639 tests with weak bands coded as HIV positive, the specificity (94.1%, 91.8% to 96.0%) and the positive predictive value (74.0%) were still unacceptably low and the false positive rate

<table>
<thead>
<tr>
<th>Study sample</th>
<th>No of samples tested</th>
<th>Positive on EIA and western blotting</th>
<th>Negative on EIA and western blotting</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>False positives (%)</th>
<th>HIV prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All rapid tests:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Positive result</td>
<td>295</td>
<td>166</td>
<td>129</td>
<td>97.6</td>
<td>90.4</td>
<td>56.3</td>
<td>99.7</td>
<td>43.7</td>
<td>11.2</td>
</tr>
<tr>
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<td>1222</td>
<td>4</td>
<td>1218</td>
<td></td>
<td></td>
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<tr>
<td>Subsample with weak positive bands coded:</td>
<td></td>
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<tr>
<td>Positive result</td>
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<td>32</td>
<td>97.8</td>
<td>94.1</td>
<td>74.0</td>
<td>99.6</td>
<td>26.0</td>
<td>14.6</td>
</tr>
<tr>
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<td>516</td>
<td>2</td>
<td>514</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsample excluding weak positive bands:</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive result</td>
<td>86</td>
<td>84</td>
<td>2</td>
<td>97.7</td>
<td>99.6</td>
<td>97.7</td>
<td>99.6</td>
<td>2.3</td>
<td>14.3</td>
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<tr>
<td>Negative result</td>
<td>516</td>
<td>2</td>
<td>514</td>
<td></td>
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</tr>
</tbody>
</table>

EIA=enzyme immunoassay; PPV=positive predictive value; NPV=negative predictive value.
(26.0%) was high. Exclusion of the 37 samples with weak positive bands, however, noticeably improved the specificity (99.6%, 98.6% to 100.0%) and positive predictive value (97.7%) and reduced the rate of false positive results to 2.3% (2/86). Among the 37 samples coded as having weak positive bands 86.0% were HIV negative on enzyme linked immunoassay and western blotting and 8.1% had indeterminate results on western blotting. From experience indeterminate results on western blotting are almost always HIV negative on the basis of repeat enzyme immunoassay or western blotting or on polymerase chain reaction. Overall 94.1% of weak positive bands were not confirmed as positive by enzyme linked immunoassay and western blotting. Among the 37 samples with weak positive bands 70.3% had weak bands on the Determine test and 29.7% on the Uni-Gold test. This problem was not observed with Stat-Pak.

To assess the possibility that the problem with low specificity was primarily the result of observer error—that is, identification of “weak” bands when none existed—140 samples were sent for reassembly at a Center for Disease Control and Prevention laboratory in Uganda. The laboratory reported 12 weak positive bands on at least one rapid test (8.3% of samples or 2.4% of all rapid tests carried out, R Downing, personal communication, 2006). These results are compatible with the findings that 5.8% of samples showed weak bands. Moreover, among the 10 samples with weak positive bands tested by the laboratory, which were then retested by enzyme immunoassay and western blotting, nine (90%) were negative on standard serology, a finding comparable to the 94.1% observed in the Rakai setting.

**DISCUSSION**

An HIV testing algorithm consisting of three rapid tests in a Ugandan setting showed low specificity and low positive predictive values if weak bands were interpreted as positive, according to the manufacturers’ recommendations. Exclusion of results with weak positive bands noticeably improved the performance of the algorithm and reduced the proportion of false positives to acceptably low levels.

The interpretation of positive bands on a rapid test is subjective. For example, the manufacturer’s instructions for the Determine test state that any red in the patient’s window should be interpreted as positive. It is possible that the laboratory technicians reading the test overinterpreted this instruction, and it is noteworthy that the specificity was higher during the period when the technicians were asked to code the band strength (table), suggesting that they became more cautious over time.

It is possible that the weak bands reflect cross reactions with other infections that might be endemic in these rural Ugandan populations, but we have no data in this regard. One other rural programme reported similar problems with false positive results from weak positive bands (H Grosskurth, personal communication, 2005), but two other evaluations of rapid tests in urban Uganda did not report these problems. We do not know whether the interpretation of weak positive rapid test results in rural Uganda affects other testing programmes in Africa. It is possible that this problem is caused by the dominant HIV-1 subtypes D, A, and AD recombinants found in Uganda, but high rates of false positive rapid test results have been reported in the United States, suggesting that this problem is not restricted to specific viral subtypes. Our findings may only pertain to the Determine and Uni-Gold tests and not to other rapid tests. Also, because these tests were only assessed in males we cannot determine whether the findings apply to females, although a gender specific difference in test performance seems unlikely. About 50% of males enrolled in the trials were identified from a parallel population cohort, and participants were fairly representative of uncircumcised males in the general population of Rakai. (Forty five per cent of eligible uncircumcised males in the cohort volunteered for trial enrolment.) Thus, although the external validity of our findings to other populations cannot be fully defined, it is likely that the problems we encountered may occur in other settings. These observations suggest that there is a need to assess the performance of rapid tests in a variety of settings, and it would be prudent to routinely retest a batch of samples by enzyme immunoassay and western blotting to maintain quality control in programmes using rapid tests. This is of particular importance given the high rate of weak positive results by enzyme immunoassay and western blotting before the disclosure of results. The proportion of samples yielding weak positive bands was relatively low in our study (5.8%), so retesting of weak positive results by enzyme immunoassay and western blotting would not impose a heavy burden on most programmes. It would, however, require laboratory backup which could lead to delay in disclosure of results to some participants.

In summary, using an algorithm of three rapid HIV tests, we found that 5.8% of results showed weak positive bands on one or more tests and that 94.1% of Weak positive bands on rapid HIV tests are mainly false positives and should be confirmed by enzyme immunoassay and western blotting before providing a diagnosis.

**WHAT THIS STUDY ADDS**

Rapid HIV tests provide timely, point of care methods for screening and diagnosis, but interpretation of positive bands is subjective
samples with weak positive results were negative or indeterminate on enzyme immunoassay or western blotting. We conclude that weak positive bands on rapid tests cannot be interpreted as positive in serum from Ugandan populations.

Contributors: RHG prepared the manuscript. He is guarantor. FM carried out the analyses. DS and NKS were responsible for the overall management of work in Uganda. TL prepared the data files. FN oversaw the field work. PO was responsible for the HIV assays. GK was the medical officer in charge of the trials. SJR provided guidance on the interpretation of assay results and quality control for laboratory work. MJW was the principal investigator of the trial in HIV positive males and is guarantor for this component of the work.

Funding: The study was supported by the National Institutes of Allergy and Infectious Diseases, Division of AIDS, National Institutes of Health (grant No U01 AI11171-01-G2), the Fogarty International Center (grant No 2D 43 TW000010-19-A1TRP), and the Gates Foundation.

Competing interests: None declared.

Ethical approval: This trial was approved by the scientific and ethics committee of the Uganda Virus Research Institute, Entebbe and the National Committee of Science and Technology, Kampala and the Committee on Human Research, Johns Hopkins University, Bloomberg School of Public Health, Baltimore.


Accepted: 11 April 2007
Rapid HIV tests provide timely, point of care methods for screening and diagnosis, but interpretation of positive bands is subjective.

WHAT THIS STUDY ADDS
Weak positive bands on rapid HIV tests are mainly false positives and should be confirmed by enzyme immunoassay and western blotting before providing a diagnosis.

Diagnostic accuracy and clinical utility of a simplified low cost method of counting CD4 cells with flow cytometry in Malawi: diagnostic accuracy study

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ABSTRACT
Objectives To assess the diagnostic accuracy and clinical utility of a simplified low cost method for measuring absolute and percentage CD4 counts with flow cytometry.

Design A CD4 counting method (Blantyre count) using a CD4 and CD45 antibody combination with reduced blood and reagent volumes. Diagnostic accuracy was assessed by measuring agreement of the index test with two other assays (TruCount and FACSCount). Clinical utility was investigated by comparing CD4 counts with the new assay with WHO clinical staging in patients with HIV.

Setting Research laboratories and antiretroviral therapy clinic at a medical school and large government hospital in southern Malawi.

Participants Assay comparisons were performed on consecutive blood samples sent for CD4 counting from 129 patients with HIV. Comparison of CD4 count with staging was conducted on 253 consecutive new patients attending the antiretroviral therapy clinic.

Main outcome measures Limits of agreement with 95% confidence intervals between index test and reference standards.

Results The limits of agreement for Blantyre count and TruCount were excellent (cell count $\pm 48.9$ to $\pm 27.0 \times 10^3/\mu l$ for absolute counts in the CD4 range $<400 \times 10^3/\mu l$ and $\pm 2.42$ to $\pm 2.37$% for CD4 percentage). The assay was affordable with reagent costs per test of $0.44 ($0.22, $0.33) for both absolute count and CD4 percentage, and $0.11 for CD4 percentage alone. Of 193 patients with clinical stage I or II disease, who were ineligible for antiretroviral therapy by clinical staging criteria, 73 (38%) had CD4 counts $<200 \times 10^3/\mu l$. By contrast, 12 (20%) of 60 patients with stage III or IV disease had CD4 counts $>350 \times 10^3/\mu l$.

Conclusions This simplified method of counting CD4 cells with flow cytometry has good agreement with established commercial assays, is affordable for routine clinical use in Africa, and could improve clinical decision making in patients with HIV.

INTRODUCTION
CD4 counting could improve appropriate allocation of antiretroviral therapy for people infected with HIV.1 Despite initiatives to reduce the price of the necessary reagents for developing nations to $3-6 ($1.5-3.0, $2.2-4.4) per test,2 this cost is still high for Africa.3 CD4 counting with flow cytometry is perceived by many to be too complex for use in Africa. WHO guidelines state that where CD4 counting is available, adults and children over 5 years with HIV should start 

REFERENCES

Contributors: See bmj.com.
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Competing interests: None declared.
Ethical approval: This trial was approved by the scientific and ethics committee of the Uganda Virus Research Institute, Entebbe and the National Committee of Science and Technology, Kampala and the Committee on Human Research, Johns Hopkins University, Bloomberg School of Public Health, Baltimore.
antiretroviral therapy as soon as their CD4 counts drop below $200 \times 10^9/l$, regardless of clinical staging. In children under 5 years CD4 percentage of total lymphocyte count (CD4 percentage) is recommended to help decide on initiation of antiretroviral therapy.

There are two main approaches for making CD4 counting more widely available in Africa. Firstly, reduce the cost of and simplify flow cytometric CD4 counting. Secondly, develop alternative counting methods. Flow cytometry, however, is the ideal method and has high accuracy.14 High throughput is possible as about 250 samples a day can be processed.3 Effective external quality assurance schemes are available in Africa.56 Finally, flow cytometers can measure CD4 percentage as well as absolute counts.

Over recent years several technological developments have shown that flow cytometric CD4 counting could be more straightforward (see bmj.com). We investigated whether these technologies could be miniaturised to reduce costs and applied them to the FACSCalibur flow cytometer. We developed a single platform method (the Blantyre count) that could be performed with reduced reagent costs and could accurately determine both absolute and percentage CD4 with increased simplicity compared with existing flow cytometric methods. We compared our method with the existing TruCount and FACSCount CD4 counting assays for diagnostic accuracy and assessed the potential impact on clinical decision making.

**METHODS**

The study was conducted at the Malawi-Liverpool-Wellcome Trust Research Programme and Queen Elizabeth Central Hospital in Blantyre. The estimated prevalence of HIV infection among adults in Blantyre district is 22%.7 We used a FACSCalibur flow cytometer.

**Reference standards (TruCount and FACSCount assays)**

We used TruCount8 and FACSCount9 assays for CD4 counts. We chose TruCount as the reference standard because it is a commercial CD4 counting method that was developed to be used on the same instrument as the index test and generates both absolute and percentage CD4. We used FACSCount as a second reference standard because it is one of the most widely used CD4 counting technologies in Africa but requires a lymphocyte count from a haematological analyser to generate CD4 percentages.

**Index test (Blantyre count)**

We used venous blood from healthy adults anticoagulated with EDTA to develop our assay (see bmj.com for laboratory details). We calculated absolute CD4 counts ($\times 10^9/l$) and CD4 percentage and assessed repeatability of our assay and examined stability of results over five days.

We modified our assay to reduce costs further when only an absolute CD4 count (Blantyre count

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**Comparison of CD4 counts determined with three flow cytometric methods using 96 blood samples from patients with HIV with CD4 counts $\leq 400\times 10^9/l$ for absolute CD4 cell counts ($\times 10^9/l$) and 129 blood samples for CD4 cell counts as a percentage of total lymphocyte count (CD4 percentage). FACSCount CD4 percentage was obtained from FACSCount absolute CD4 counts and total lymphocyte counts from a haematological analyser. Black lines depict bias and upper and lower limits of agreement. Grey broken lines denote 95% confidence intervals for these values.**
CD4 counting comparison studies
In the main CD4 counting comparison study we included consecutive blood samples from patients with HIV sent to our laboratory for full blood count and CD4 count determination from 27 January to 17 February and from 18 April to 9 May 2006 (n=134). We measured CD4 and CD4 percentage for each sample using Blantyre count, Blantyre count (absolute), TruCount, and FACSCount assays.

We carried out a smaller study on consecutive blood samples from patients with HIV sent to the laboratory in June 2006 to compare CD4 percentages generated by Blantyre count and Blantyre count (percentage) assays (n=28). Samples were not used if they exhibited clots, were sent from outside Queen Elizabeth Central Hospital, were received after the day of blood collection or if insufficient blood was available to complete all tests. There were no other selection criteria. All blood samples from all participants meeting the inclusion criteria underwent the index and reference standard tests.

Two authors performed and read the FACSCount assay and full blood count. Two other authors performed and read TruCount and Blantyre count assays together within six hours of the FACSCount assay. We subsequently trained local laboratory technicians over two to three days to perform the Blantyre count method. Manual gating of events acquired with Blantyre count was performed blind to other results. For absolute CD4 counts, we assessed agreement only for samples with a TruCount CD4 count below $400 \times 10^9/l$ as this is the relevant range for clinical decision making. For comparisons of CD4 percentage we used all samples.

Clinical utility study
We tested a further 253 EDTA anticoagulated venous blood samples from new patients attending the adult antiretroviral therapy clinic from May to July and from September to October 2006 for CD4 count using Blantyre count. CD4 counts and clinical staging were compared for each patient. Clinical staff in the antiretroviral therapy clinic performed staging blind to CD4 count results.

External quality assurance
CD4 results were determined on six NEQAS (United Kingdom national external quality assessment scheme) stabilised blood samples from the UK between January and May 2006.

Statistical analysis
We examined agreement between each pair of methods by estimating bias and limits of agreement ($\pm$bias plus or minus $1.96 \times SD$) with 95% confidence intervals. Repeatability was assessed with coefficients of variation obtained from five repeats of assays.

RESULTS
Refinement of Blantyre count—We used 20 µl blood and 10 µl of counting beads for our assay as twice the lowest volume at which optimal assay repeatability was maintained, and 0.5 µl of each antibody. See bmj.com. Using these quantities, the costs of reagents per assay were £0.44 (€0.22, £0.33) for both absolute and percentage counts, £0.40 for an absolute CD4 count, and £0.11 for CD4 percentage alone. See bmj.com for characteristics of patients.

Absolute CD4 counts in agreement studies—The median CD4 count was $193 \times 10^9/l$ (range 0 to $1884 \times 10^9/l$) with TruCount. The mean bias when we used Blantyre count rather than TruCount for samples with a CD4 count of $<400 \times 10^9/l$ was $-11.0 \times 10^9/l$ for Blantyre count. Similarly, low biases were found for other assay comparisons (table). Limits of agreement were $-48.9$ to $27.0 \times 10^9/l$ for Blantyre count and TruCount and were within the range $-55$ to $40 \times 10^9/l$ for all other assay comparisons (table, figure).

CD4 percentage in agreement studies—The median CD4 percentage was 13.0% (range 0.0-44.0%) using TruCount. Agreement between CD4 percentage

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<thead>
<tr>
<th>Assay comparison</th>
<th>Bias (95% CI)</th>
<th>Limits of agreement</th>
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<tbody>
<tr>
<td></td>
<td>Lower limit (95% CI)</td>
<td>Upper limit (95% CI)</td>
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<tr>
<td><strong>Absolute CD4</strong></td>
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<tr>
<td>Blantyre count and TruCount</td>
<td>$-11.0$ ($-14.9$ to $-7.1$)</td>
<td>$-48.9$ ($-55.7$ to $-21.2$)</td>
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<td>$-39.3$ ($-45.3$ to $-33.3$)</td>
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<td><strong>CD4 percentage</strong></td>
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<td>Blantyre count and TruCount</td>
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<td>$-2.42$ ($-2.78$ to $-2.05$)</td>
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<tr>
<td>FACSCount* and TruCount</td>
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<td>$5.83$ ($6.87$ to $4.79$)</td>
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<td>Blantyre count and FACSCount*</td>
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<td>$-7.56$ ($-8.57$ to $-6.54$)</td>
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<td>Blantyre count and Blantyre count (percentage)</td>
<td>$0.01$ ($-0.26$ to $0.28$)</td>
<td>$-1.35$ ($-1.82$ to $-0.88$)</td>
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</table>

*CD4 percentages with FACSCount calculated from absolute CD4 count by FACSCount and total lymphocyte count from haematological analyser.
generated by Blantyre count and TruCount was excellent over the full range of values, with a bias of $-0.03\%$ and limits of agreement $-2.42\%$ to $2.37\%$. Comparison of either Blantyre count or TruCount CD4 percentage with values generated using FACSCount showed poorer agreement. Blantyre count and the Blantyre count (percentage) variant could be used interchangeably for CD4 percentage with excellent limits of agreements (table, figure).

Repeatability of Blantyre count—We calculated coefficients of variation on five repeats of our assay on four blood samples with mean CD4 values 718, 712, 260, and $191 \times 10^9/l$ and mean CD4 percentage 40.3%, 42.9%, 15.0%, and 13.8%. Mean (SD) coefficients of variation were $5.2\%$ (2.7%) for absolute CD4 count and 2.5% (0.8%) for CD4 percentage.

Accuracy of Blantyre count—in tests on six stabilised blood samples (CD4 count $117 - 1269 \times 10^9/l$ and percentage $7.28\% - 60.73\%$) from NEQAS with our assay, five of six absolute CD4 counts and five of six CD4 percentages were within 1 SD of the NEQAS value, with one result of six between 1 and 2 SD of this value for each test. Blantyre count values were on average 95% of the absolute NEQAS CD4 count and 97% of the CD4 percentage.

Stability of aged samples—CD4 T cell and lymphocyte populations could be clearly distinguished and gated over the five days of the stability study, with a blood sample with day 1 CD4 count of $487 \times 10^9/l$ and CD4 percentage of 36.1%. Daily coefficients of variation for absolute counts remained below 6% and for CD4 percentage below 2.5%. The mean absolute CD4 count stayed within 10% and the CD4 percentage within 5% of the day 1 values.

Clinical staging and CD4 counts for new patients attending antiretroviral therapy clinic—Of the new patients attending the antiretroviral therapy clinic, 76% (193/253) were clinical stage I (n=77) or stage II (n=116), while 24% (60/253) had stage III (n=51) or stage IV (n=9) HIV/AIDS. Twenty five (32%) patients with stage I disease and 48 (42%) with stage II disease had a CD4 count <$200 \times 10^9/l$. Eleven (22%) patients with stage III and one (11%) patient with stage IV HIV/AIDS had a CD4 count $>350 \times 10^9/l$.

DISCUSSION

Within Malawi, we have developed an affordable accurate method of counting CD4 cells with flow cytometry by refining and miniaturising existing technology. Increasing affordability by reducing reagent costs is a critical step in making this available in countries with limited resources. Currently the reagent cost of a comparable commercially available flow cytometric assay in Africa is $5.04 (€2.52, £3.74). As we were able to reduce costs of reagents to $0.44 (€0.22, £0.33) per assay, there is the potential for 91% cost savings. This would increase to 98% if only CD4 percentage is required but would decrease if the costs of competing tests are reduced.

Cost reduction was not achieved at the expense of accuracy. Over the CD4 count range of $0 - 400 \times 10^9/l$, our assay showed minimal bias and excellent agreement compared with established CD4 counting methods (TruCount and FACSCount). Determination of CD4 percentage by Blantyre count and TruCount methods showed excellent agreement over the full range of CD4 percentages. The good performance of Blantyre count in the NEQAS immunophenotyping scheme further shows the accuracy of this method.

As well as reducing the assay price, the modifications in our assay have simplified CD4 counting with flow cytometry and it has proved straightforward to train technicians.

Strengths and weakness of study

We carried out this work in a country where affordability is of chief importance. We looked at both absolute and percentage CD4, which have previously been neglected. The limits of agreement are similar to those of previous comparison studies of flow cytometry. By miniaturising the present assay, we managed to reduce reagent costs further compared with previous studies.

Even with the simplifications introduced, however, CD4 counting with flow cytometry requires a level of technical skill not always present in resource poor settings, a reliable power supply, and a cold chain for reagent supplies. A flow cytometer represents a large capital outlay, although donor funding is sometimes available to help provide such instruments.

The simplified nature of the Blantyre count method means that this technology could be operated on less complex instruments than the FACSCalibur. Such an instrument could be manufactured at lower cost and would be simpler and less expensive to maintain.

Blantyre count could make the greatest impact on the care of children under 5 with HIV. Appropriate determination of CD4 percentage has often been neglected by investigators seeking to produce affordable CD4 counting. Determination of CD4 percentage alone by the Blantyre count (percentage) variant is not only much cheaper than determining absolute CD4 counts but also technically easier and is much more accurate than using a FACSCount instrument and haematological analyser. CD4 percentages were also more stable than absolute counts over five days in the same sample.

The determination of CD4 counts with Blantyre count in the antiretroviral therapy clinic confirms that use of WHO clinical staging criteria alone for deciding who should start antiretroviral therapy is suboptimal.

What would it cost?

Consideration of the economic feasibility of using the Blantyre count in Malawi has to include the capital cost of the flow cytometer (about $100 000), the annual service contract (about $10 000), and the salary of a laboratory technician (typical monthly salary $500) as well as reagent prices. Use of the Blantyre count method would be most cost effective with a limited number of flow cytometers operating at high sample throughput in regional centres and a coordinated system for transporting samples to these centres from peripheral clinics.
WHAT IS ALREADY KNOWN ON THIS TOPIC
CD4 counting is the main laboratory investigation for monitoring people with HIV but is often deemed too expensive and too complex to perform in resource poor settings.
CD4 counting with flow cytometry can be made more affordable by the use of simple technical modifications, but CD4 percentages required in children under 5 years and miniaturisation of blood and reagent volumes have received little attention.

WHAT THIS STUDY ADDS
Technical modifications of flow cytometry with miniaturisation can simplify and reduce the cost of absolute and percentage CD4 counts while maintaining diagnostic accuracy. This CD4 counting method could improve clinical decision making in patients with HIV disease in settings with limited resources.

Objective
To determine cut offs to define thinness in children and adolescents, based on body mass index at age 18 years.

Design
International survey of six large nationally representative cross sectional studies on growth.

Setting
Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States.

Subjects
97 876 males and 94 851 females from birth to 25 years.

Main outcome measure
Body mass index (BMI, weight/height²).

Results
The World Health Organization defines grade 2 thinness in adults as BMI <17. This same cut off, applied to the six datasets at age 18 years, gave mean BMI close to a z score of −2 and 80% of the median. Thus it matches existing criteria for wasting in children based on weight for height. For each dataset, centile curves were drawn to pass through the cut off of BMI 17 at 18 years. The resulting curves were averaged to provide age and sex specific cut-off points from 2-18 years. Similar cut offs were derived based on BMI 16 and 18.5 at 18 years, together providing definitions of thinness grades 1, 2, and 3 in children and adolescents consistent with the WHO adult definitions.

Conclusions
The proposed cut-off points should help to provide internationally comparable prevalence rates of thinness in children and adolescents.

INTRODUCTION
Much has been written about the epidemic of child obesity but malnutrition in infants, children, and adolescents poses a considerably larger public health problem internationally, and in the developed world anorexia nervosa is the third most common chronic condition of adolescence. Obesity and malnutrition represent opposite extremes on the spectrum of adiposity, and both are routinely quantified in terms of weight and height relative to the child’s age. Yet the classification of malnutrition in later childhood and adolescence is currently unsatisfactory because of the lack of suitable cut offs for international use.

BMI has been used since the 1960s to assess obesity in adults and more recently in children. International BMI cut offs for child overweight and obesity, based on data from six countries, have been developed. The

Body mass index cut offs to define thinness in children and adolescents: international survey

Tim J Cole,1 Katherine M Flegal,2 Dasha Nicholls,3 Alan A Jackson4

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INTRODUCTION
Much has been written about the epidemic of child obesity1 but malnutrition—meaning undernutrition—in infants, children, and adolescents poses a considerably larger public health problem internationally.2,3 and in the developed world anorexia nervosa is the third most common chronic condition of adolescence.5 Obesity and malnutrition represent opposite extremes on the spectrum of adiposity, and both are routinely quantified in terms of weight and height relative to the child’s age.7 Yet the classification of malnutrition in later childhood and adolescence is currently unsatisfactory because of the lack of suitable cut offs for international use.8

Fifty years ago Gomez introduced his malnutrition classification of weight below a specified percentage of median weight for the child’s age.9 This included three components: a measurement, a reference for age adjustment, and a set of cut offs.10 Later Seoane and Latham proposed splitting weight for age into weight for height and height for age,11 allowing underweight to be defined as wasting or stunting, or both.12 Subsequently Waterlow et al recommended the use of z scores for the definitions of underweight, wasting, and stunting, with the cut offs defined in terms of standard deviations (SDs) below the median rather than as percentages of the median.13 This ensures that the false positive screening rate is constant across age as applied to the reference population.10

In 1983 the World Health Organization (WHO) formally recognised the US National Center for Health Statistics (NCHS) classification14 as the international reference15 and has used it since to classify children as underweight, wasted, or stunted, each based on a cut off of −2 SDs.16 Wasting in particular is assessed with the NCHS/WHO weight for height reference, which compares the child’s weight to the average weight of children of the same height.17 This ignores the child’s age, which allows nutritional status to be assessed when age is not known. It also assumes that, on average, children of a given height weigh the same whatever their age; in infancy and adolescence, however, the weight-height relation depends on age.18,19

This can be seen by considering the index weight/heightp, where the height power p is allowed to vary with age. The index is adjusted for age and sex by dividing it by the same ratio based on median weight and height for the child’s age and sex.1 For a weight for height index such as NCHS, the value of p is the ratio of the percentage growth rates in weight and height at each age, so it is largest when weight is growing fastest relative to height—that is, in infancy and adolescence when p is 3 or more as against 1.5 in mid-childhood.18 In later adolescence, as weight growth continues after height growth has stopped, p increases to infinity and height adjustment becomes impossible. This is an important general limitation of weight for height references in that they cannot be used in adolescence.18,20 For this reason the NCHS weight for height reference was truncated at age 10 in girls and 11.5 in boys.14

The weight/heightp index can alternatively be adjusted for height for age, where p is chosen to make the index uncorrelated with height among children at
each age. This leads to a different pattern of \( p \) changing with age, with \( p=2 \) in infancy, rising to 3 in adolescence and then falling back to 2 in adulthood.\(^{19,21-23} \) Cole suggested fixing \( p \) at 2—that is, the body mass index (BMI).\(^{21} \) This is now used throughout infancy, childhood, adolescence, and adulthood.

BMI has been used since the 1960s to assess obesity in adults\(^ {24,25} \) and more recently in children.\(^ {26,27} \) Many countries now have their own national reference centile charts for BMI for age.\(^ {28-30} \) International BMI cut offs for child overweight and obesity, based on data from six countries, have been developed.\(^ {31} \)

The WHO 1995 expert committee\(^ {16} \) endorsed the use of BMI for assessing thinness in adolescence, based on the BMI reference data from Must et al,\(^ {32} \) and the recently published 2006 WHO growth standard also includes BMI for children aged 0-5 years.\(^ {33} \) However, this is insufficient for international use because the BMI cut offs from Must et al were based on US data from the early 1970s and the WHO standard is restricted in age. Thus there are no valid BMI cut offs for assessing underweight or wasting in adolescents or children over 5 years.

The international BMI cut offs for child overweight and obesity cover the age range 2-18 years and are based on the adult cut offs of 25 and 30 at 18 years.\(^ {31} \) They have been widely used, with over 1100 citations in the seven years since publication. It would be logical to produce BMI cut offs for underweight using the same principle. However, underweight does not have the same meaning in adults and children. In adults, underweight or thinness indicates low BMI, whereas in children underweight is low weight for age and wasting is low weight for height.\(^ {16} \) We have extended the adult term of thinness to children, meaning low BMI for age.

**METHODS**

**Subjects and data**

We used the same methods as those used by the International Obesity TaskForce (IOTF) for the international overweight and obesity cut offs.\(^ {31} \) We obtained BMI data from nationally representative surveys of children in six high and middle income countries: Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States (table 1).\(^ {31} \) Each survey had over 20 000 subjects aged 6-18 years, and height and weight were measured with standard methods and quality control measures to minimise measurement error. Four of the datasets came from one-off surveys, while the British and US data were pooled from surveys collected over a period of time. The US data came from the national health examination surveys II and III, and the national health and nutrition examination surveys (NHANES) I and II, while for comparison Must et al used NHANES I data for their BMI reference.\(^ {32} \) The Brazilian and US surveys used multi-stage sampling designs, and their data were analysed with survey weights. A total of 192 727 subjects were involved, 97 876 males and 94 851 females from birth to 25 years (table 1).

**LMS method**

We analysed each dataset using the LMS method, which summarises the distribution of BMI by age and sex in terms of three curves called L (lambda), M (mu) and S (sigma).\(^ {30} \) The M curve is median BMI by age, the S curve is the coefficient of variation of BMI, and the L curve expresses the skewness of the BMI distribution in terms of the Box-Cox power needed to transform the data to near normality. Any required BMI centile curve is defined in terms of the L, M, and S curves as follows:

\[
M(1+L\times S\times z^{-1/L})
\]

where \( z \) is the z score corresponding to the required centile (for example, \( z=0 \) gives the median M or \( z=0.67 \) gives the 75th centile) and the values of L, M, and S vary with age and sex.

The reverse process, of converting a child’s BMI to a z score, involves the equation:

\[
z=\left(\frac{(BMI/M)^S-1}{L\times S}\right)^{1/L}
\]

where the values of L, M, and S are for the child’s age and sex. Note that the ratio BMI/M in the second equation, multiplied by 100, corresponds to BMI expressed as a percentage of the median (BMI%). So BMI% and z are linked in a way that depends on the variability S and skewness L, which in turn depend on age.

Conventionally a BMI centile chart is based on a prespecified set of centiles (for example, 3rd, 10th, 25th, 50th, 75th, 90th, 97th)\(^ {36} \) or z scores (−2 to +2 in increments of two thirds of a z score).\(^ {41} \) Here by contrast, quasi-centile curves are constructed to pass through a given BMI cut off at a given age (we chose 18 as it was the oldest age with data available in all six datasets). To do this the required BMI is substituted into the second equation and the corresponding z

---

**Table 1** | Six nationally representative datasets of BMI in childhood (n=192 727)

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Description</th>
<th>Age range</th>
<th>Sample size</th>
<th>Age range</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>1989</td>
<td>Second national anthropometric survey</td>
<td>2-25</td>
<td>15 947</td>
<td>2-25</td>
<td>15 859</td>
</tr>
<tr>
<td>Great Britain</td>
<td>1978-93</td>
<td>Data pooled from five national surveys</td>
<td>0-23</td>
<td>16 491</td>
<td>0-23</td>
<td>15 731</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>1993</td>
<td>National growth survey</td>
<td>0-18</td>
<td>11 797</td>
<td>0-18</td>
<td>12 168</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1980</td>
<td>Third nationwide growth survey</td>
<td>0-20</td>
<td>21 521</td>
<td>0-20</td>
<td>20 245</td>
</tr>
<tr>
<td>Singapore</td>
<td>1993</td>
<td>School health service survey</td>
<td>0-19</td>
<td>17 356</td>
<td>6-20</td>
<td>16 616</td>
</tr>
<tr>
<td>US</td>
<td>1963-80</td>
<td>Data pooled from four national surveys</td>
<td>2-20</td>
<td>97 876</td>
<td>0-25</td>
<td>94 851</td>
</tr>
</tbody>
</table>

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Table 2: z scores corresponding to different BMI cut offs at age 18, averaged by sex across six datasets

<table>
<thead>
<tr>
<th>Centile</th>
<th>16</th>
<th>17</th>
<th>17.5</th>
<th>18.5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Mean z score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−2.6</td>
<td>2.4</td>
<td>−1.9</td>
<td>1.8</td>
<td>−1.6</td>
</tr>
</tbody>
</table>

Table 3: z scores corresponding to BMI 17 at age 18 by sex across datasets

<table>
<thead>
<tr>
<th>Country</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Great Britain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singapore</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An important question here is which cut off is the more appropriate, the 5th centile or −2 SD. WHO recommended the −2 SD criterion back in 1977, while the 5th centile was a pragmatic alternative at a time when a −2 SD BMI cut off was not available. For this reason we feel that −2 SD is the more appropriate cut off to use.

On this basis, the simplest way to transfer the child cut offs from weight for height to BMI is to treat the two −2 SD cut offs as equivalent. Weight for height is weight adjusted for height while BMI for age is weight adjusted for height and age. So if weight for height were independent of age, as it is at certain ages, then the two cut offs would coincide. At other ages the variability in BMI is theoretically slightly less than for weight for height, as variability caused by age is adjusted for. Against that, the height adjustment for BMI is imperfect later in childhood, so on balance the variability is likely to be similar for the two indices.

Thus the optimal cut off for our purposes would be a value of BMI at age 18 that coincided with a previously published adult cut off and which was also close to a child BMI cut off of −2 SD. But this introduces ambiguity as the z score corresponding to a given cut off will depend on the growth reference used. Here we use the six datasets as internal references to test the alternative cut offs. We also investigate the relation between z score and BMI%.

RESULTS

Table 2 gives BMI z scores and centiles corresponding to various published BMI cut offs at age 18, averaged across the six datasets, where the centiles correspond to the sex averaged z scores. In general the results are similar for boys and girls, and the cut offs range from the 0.6th to the 10th centile. BMI 18.5 is on the 6th centile and approximates to a z score of −1, while BMI 17 is on the 3rd centile and close to z score −2, and hence is near optimal for our purposes.

Table 3 looks at the BMI cut off of 17 in z score terms by dataset. The four Western countries are close to z score −2.0 in females and −2.1 in males, while the data from Hong Kong and Singapore are near to −1.4. The centiles indicate the prevalence of thinness in each country at age 18 when the survey was done, at which time the East Asian children were appreciably thinner.

Figure 1 shows the separate thinness curves for BMI 17 at age 18 by country and sex. Within each graph the country curves are largely superimposed and more so for girls than boys. Looking at the individual countries, Brazil is relatively low in both sexes while Hong Kong is high in boys, and for Singapore the boys’ curve stands out at age 6.

The BMI cut off of 17 is not only near to z score −2, it is also the WHO definition of thinness grade 2 in adults. Thus the WHO classification provides a bridge between child and adult, in that a young person with BMI 17 at age 18 is both a borderline thin adult (grade 2) and a borderline thin child (z score −2). For this reason we propose to use the cut off of 17 plus the other...
two WHO cut offs of 18.5 and 16 as the basis for our classification.

Figure 2 shows the thinness curves by country for BMI 18.5 at age 18, where the agreement between datasets is closer than for figure 1. Singapore is again anomalous at age 6, notably in the boys, probably because of the absence of data below this age.

Figure 3 shows the same curves for a cut off of BMI 16, where the agreement between countries is noticeably poorer, particularly in the boys, reflecting the greater extrapolation into the tails of the BMI distributions.

Figure 4 shows the composite curves for cut offs 16, 17, and 18.5, obtained by averaging the individual curves in figures 1, 2, and 3. To avoid a discontinuity at age 6 we smoothed the mean values with and without Singapore between ages 6 and 8. Table 4 gives the values of the curves by exact half year from 2 to 18 years, and values for intermediate ages can be obtained by interpolation.

Table 5 shows the relation between BMI% and BMI z score at different ages, averaged across the datasets by sex, where the centiles correspond to the sex averaged z scores. Up to 6 years a z score of −2 corresponds to BMI 85% of the median, while from 14 years the same z score matches BMI 80%. This shift with age is caused largely by the sharp increase in variability in BMI that occurs between 6 and 12 years. The plot of the coefficient of variation of BMI (the S curve) against age by country shows it clearly, where all six countries follow the same pattern of an early plateau then a rise, then a later plateau.

**DISCUSSION**

We propose that a BMI of 17 at age 18 is a suitable cut off to use as the basis for an international definition of thinness in children and adolescents. Three different criteria lead to this conclusion: BMI 17 is the WHO...
grade 2 cut off for thinness in adults; BMI 17 at age 18 corresponds to a mean z score of −2 using our data (table 2); and, again with our data, BMI 17 at age 18 is 80% of the median (table 5). The latter two criteria mean that in childhood the new cut off will be similar in z score and % of the median terms to those used before, notably the WHO definition of wasting—that is, weight for height below −2 SD or 80% of the median.

WHO defines thinness in adolescents as BMI below the smoothed 5th centile for age from Must et al cut offs that at age 18 are 17.5 for males and 16.7 for females. For comparison a cut off of 17 applied to our US data in table 3 (four surveys including NHANES I) corresponds to the 1st centile in boys and 2nd centile in girls. Using a cut off nearer the 2nd than the 5th centile seems reasonable in that WHO, which has always used a −2 SD cut off, opted for the 5th BMI centile of the Must et al reference only because there was no alternative. Using 17 as the cut off would unify the two WHO definitions of thinness, for adults and adolescents, while extending its use to children too.

We have tried to avoid potential confusion between the terms “wasting” and “underweight” in children by adopting the term “thinness,” which WHO uses to mean low BMI in adults and adolescents. We extend the definition to include low BMI for age in children, linked to the adult definition through the fulcrum of BMI 17 at age 18. It is important to recognise, however, that thinness is not simply the opposite of fatness—a low BMI is more strongly correlated with lean mass than fat mass.

Pelletier and Frongillo emphasise that most mortality related to malnutrition occurs with mild or moderate malnutrition so there is a need to distinguish between grades of malnutrition. In addition to our primary cut off of 17 we propose two secondary cut offs: 18.5, long used by WHO in adult studies and for grade 1 thinness, and 16, used for grade 3 thinness. Thus our three cut offs correspond to the WHO graded definition of thinness.

Surprisingly, given its key role in the assessment of malnutrition, weight for height is poorer than weight for age or mid-arm circumference for predicting mortality. Pelletier’s review summarises eight studies that compare anthropometric indicators for predicting mortality and shows that weight for height is consistently the least effective. Pelletier suggests that increased measurement error may explain this, but other possibilities are the use of weight for height rather

### Table 4: International cut-off points for BMI for thinness grades 1, 2, and 3 by sex for exact ages between 2 and 18 years, defined to pass through BMI of 16, 17, and 18.5 at age 18, obtained by averaging data from Brazil, Great Britain, Hong Kong, Netherlands, Singapore, and US

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Boys</th>
<th></th>
<th>Girls</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16</td>
<td>17</td>
<td>18.5</td>
<td>16</td>
<td>17</td>
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<tr>
<td>2.5</td>
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<td>14.92</td>
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<td>14.57</td>
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<td>13.47</td>
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datasets median, by age from 2-18 years, averaged by sex across six datasets. The centiles of BMI are compared (including the BMI 25 and 30 cut offs31). The BMI growth chart for assessment of young children. The centiles on the WHO BMI chart overlap with our proposed cut offs. In females the BMI growth chart for assessment of malnutrition. The lack of an adjustment for puberty is another limitation of the cut offs. BMI is known to be higher in male excess.52 Adjustment for this would make the cut offs proposed here allow this to be tested. The main strength of the cut offs is their ability to differentiate between fat mass and lean mass, therefore it is an imperfect measure of either adiposity or leanness. In children it correlates with fat mass more strongly at the upper end of the adiposity spectrum (where fat mass makes up a larger proportion of weight) than at the lower end.49 So in thin children BMI is a better predictor of lean mass than fat mass. We believe that none of these differences invalidates the underlying principle of the cut offs, which is to provide a simple yet “good enough” tool to compare prevalences across populations that are inevitably heterogeneous. As with any screening tool its sensitivity and specificity need testing in the field. The main strength of the cut offs is their ability to compare rates of prevalence of thinness across countries, regions, and time. The cut offs avoid the conventional concept of a reference population in that they include data from several disparate populations, so they are at the same time representative of several countries and of none. This duality increases the perceived generalisability of the cut offs, even though they clearly cannot be universally representative. Instead a

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Malnutrition in children and adolescents is a serious public health concern. It is better assessed as thinness (low body mass index for age) than as wasting (low weight for height). There are no suitable thinness cut offs for this age group.

WHAT THIS STUDY ADDS

A new graded definition of thinness in childhood and adolescence is proposed, based on pooled international data for BMI and linked to the WHO recommended adult cut off points of 16, 17, and 18.5 at age 18. The thinness cut off linked to 17 is close to the wasting cut off based on −2 z scores. The new definitions should encourage direct comparison of trends in child and adolescent thinness worldwide.

Finally, we emphasise that these cut offs need to be tested against new data; they are offered as a way forward and not as a definitive statement. But we hope they will prove helpful in providing a unified definition of thinness in children and adolescents based on thinness in adults. They can also be used in conjunction with the corresponding international definition of overweight and obesity.

We thank Carlos Monterro (Brazil), Sophie Leung (Hong Kong), Machtiel Roede (Netherlands), and Uma Rajan (Singapore) for allowing us access to their data.

Contributors: TJC and DN had the original idea. TJC did most of the statistical analyses, wrote the first draft, and is guarantor. KMF did further analyses of the US data. DN provided expertise on eating disorders and AA provided expertise on malnutrition. All authors participated in the discussion and interpretation of the results and contributed to the final paper.

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Competing interests: None declared.

Ethical approval: Not required.

20. Flegal KM, Wei R, Ogden C. Weight-for-stature compared with body mass index-for-age growth charts for the United States from the...


Accepted: 18 May 2007
Children presenting with wheeze are likely to have either atopic asthma or episodic viral wheeze; distinguishing between these has important implications for management.

If it’s wheeze it must be asthma, and if it’s asthma it must mean bronchodilators and inhaled corticosteroids—simple enough. Indeed, as asthma is so common this paradigm might seem to be logical. The large scale international study of asthma and allergy in childhood (ISAAC) found that the United Kingdom, Australia, and New Zealand had among the highest prevalences, with 15% of children affected. Asthma is more complicated, however, especially in children. We are often uncertain whether children who wheeze do have asthma, and some people say that diagnosing asthma in very young children is not possible. An increasing body of evidence suggests that asthma is a complex disorder and that different patterns of illness have different underlying pathogenesis.

Many studies have investigated various treatments in older children with classic allergic asthma, yet relatively few have considered the many young children who have recurrent wheeze. Many common treatments now have a good evidence base, but gaps still exist, such as treatments for the most difficult and severe childhood asthma. Therapeutic advances include both new drugs and new licences for older drugs. For example, the new drug omalizumab and montelukast are now licensed down to 6 months of age. Yet despite an increasing number of therapeutic options, children still die from asthma (23 recorded deaths in 2002). With this in mind, this first of two articles will review the features of the two most common patterns of childhood wheezing illnesses: atopic asthma and episodic viral wheeze. The second review will focus on management.

How do patients present?

If one feature consistently points to a diagnosis of asthma, it is wheeze. Wheeze is the end result of narrowing of small airways due to processes that include oedema of the airway wall, contraction of smooth muscle, and mucus plugging. A study of parents of wheezing children found that some thought that wheeze was a sound such as whistling, squeaking, or gasping, whereas others defined it as a different rate, style, or timbre of breathing, and some thought it was the same as coughing. This is an important reminder that reported wheeze might not be wheezing after all. Associated with asthmatic wheeze is the observation of variable or reversible airways obstruction. Over the 1980s, however, with an increased recognition of allergy, “asthma” became synonymous with “atopic asthma.” For many people, asthma became wheeze plus allergy plus bronchial hyper-responsiveness. However, this approach failed to recognise those young children and indeed older children and adults who wheeze only with colds, strongly suggesting more than one phenotype of wheezing illnesses.

Atopic asthma

The most widely recognised phenotype of wheeze is atopic asthma. This commonly presents as the school aged child who complains of episodic wheeze, cough, and shortness of breath, often with identifiable triggers and other signs of atopy, such as eczema and hay fever. Atopic asthma is more common than non-atopic childhood asthma; as many as 85% of school aged children with asthma are atopic. This type of asthma is classically associated with eosinophils and mast cells. Many studies have identified these cells in bronchial tissues and secretions of people with asthma. Increased numbers of eosinophils are known to be associated with increased symptoms of asthma, and using eosinophils as a guide to adjusting corticosteroid treatment has been shown to be an effective strategy for treating asthma in adults.

One area of diagnostic difficulty in childhood asthma is chronic cough. Cough is a common complaint in childhood; up to 10% of preschool and early school aged children have chronic cough without wheeze at some time. Although childhood asthma may present with cough, most children who cough without wheeze...
do not have asthma (box 1). Isolated chronic cough is a poor marker of asthma and, without other typical features of asthma, should always raise the strong possibility of an alternative cause. However, cough predominant or cough variant asthma undoubtedly exists, possibly because sometimes wheeze is not easily identified. It is associated with bronchial hyper-responsiveness or reversible airways obstruction, both key features of asthma. Demonstrating these features can help to identify children with cough predominant asthma. In the absence of these features, a short trial of asthma treatment may aid the diagnosis of asthma. Establishing that improvement in cough is due to treatment rather than coincidence is, however, important, as postviral cough will spontaneously improve. A return of symptoms on discontinuing treatment supports asthma as the diagnosis.

Episodic viral wheezing
Before the 1980s, wheezy and “chesty” young children were commonly referred to as “wheezy bronchitics.”

**Box 1 | Causes of chronic cough in childhood**

- Chronic suppurative lung disease
  - Cystic fibrosis
  - Immune deficiencies
  - Primary ciliary dyskinesia
  - Recurrent pulmonary aspiration
  - Retained inhaled foreign body
  - Chronic bronchitis
  - Congenital causes (such as Mounier-Kuhn syndrome) and other less common causes

- Environmental pulmonary toxic agents
  - Exposure to tobacco smoke
  - Other environmental pollutants (such as biomass combustion particles)

- Airways lesion
  - Compression—for example, lymph nodes, vascular ring
  - Malacia, often with an airway infection

- Upper airway disease
  - Adenotonsillar hypertrophy
  - Rhinosinusitis

- Oesophageal/swallowing problems
  - Aspiration
  - Neuromuscular disease
  - Tracheo-oesophageal fistula

- Interstitial lung disease
  - Autoimmune disorders
  - Cytotoxic drugs/irradiation

- Others
  - Protracted bronchitis
  - Recurrent viral bronchitis
  - Acute respiratory infections and postinfections, pertussis-like illness (parapertussis, adenovirus, mycoplasma, and Chlamydia)
  - Increased cough receptor sensitivity
  - Functional respiratory disorder (habitual cough or “vocal tic”)
  - Asthma/asthma-like conditions
  - Non-asthmatic eosinophilic bronchitis and allergy
  - Side effects of drugs

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**Fig 1 | Timeline of wheeze—a useful tool in the clinic**

This describes an illness triggered by the common cold and leading to mucous hypersecretion, inflammation, and bronchoconstriction. Wheezy, rattling children are a common phenotype that we recognise as different from children with atopic asthma: so called “episodic viral wheezers.” These children are not considered truly asthmatic and are not included in most studies of the epidemiology of asthma. However, their acute episodes are similar to those of older children labelled as having asthma. Episodic viral wheeze is common; 30-50% of preschool children have at least one episode. Some young children with atopic asthma start with a pattern of episodic viral wheeze before more persistent features surface, but most of those with pure episodic viral wheeze tend to outgrow their symptoms as they get older. Emerging data on pathophysiology support this as a distinct phenotype. One reason why these children wheeze with viruses is likely to be that they are born with smaller airway dimensions than those who do not wheeze. In one study, bronchoalveolar lavages were taken from asymptomatic preschool children with atopic asthma, those with episodic viral wheeze, and healthy controls having routine surgery. Those with atopic asthma had increased numbers of eosinophils and mast cells compared with episodic viral wheezers, who were similar to controls. An experimental viral infection of adults with episodic viral wheeze showed a predominantly neutrophilic inflammatory response without any evidence of eosinophilia. This pattern of neutrophil activation has also been shown in children with episodic viral wheeze. The link between inflammation and wheeze, however, is likely to be complex; evidence from the same group indicates that eosinophils may play a role in episodic viral wheeze independent of atopy.

Much remains to be understood about the interaction between viruses and wheezing episodes. Viruses are the major trigger for acute asthma attacks in children and adults. We know that respiratory syncytial virus infection is associated with recurrent wheezing for several months and occasionally years after bronchiolitis. Emerging evidence indicates that subtle differences in the responses of the innate and adaptive immune systems might be responsible for the development of virus associated wheeze. For example, some people with asthma have a reduced interferon γ response to rhinovirus, suggesting a predisposition to viral infection, whereas others have a heightened response with reduced symptoms during colds. A better understanding of why some children wheeze only
with viruses and others wheeze with many triggers may one day allow us to target treatments more effectively.

**Other causes of wheeze**
Other conditions can sometimes cause a wheezy chest (table). These should be considered in children who do not display key features of asthma, have additional clinical features (table), or do not respond to conventional asthma treatment.

**What are the key features in the history and examination?**
As with most initial assessments, diagnosis and management are informed by identifying recognised patterns in the history and assessing the severity with additional information gained from the physical examination. Mapping the pattern over time (fig 1) is useful not only in making a diagnosis but also in assessing severity and guiding treatment. Box 2 provides a guide to history taking and examination.

**What investigations might help?**
If the child does not respond to initial treatment or needs high doses, some specific tests may help to secure the diagnosis and assess severity more objectively.

**Peak expiratory flow monitoring**—Usually used in children over 5 years, peak expiratory flow monitoring is useful to establish diurnal variation and the severity of obstruction. Routine measurement is likely to be of limited value, with a significant drop-off in reliability of recordings made over long periods of time. Normal peak expiratory flow values vary widely, so each child should use his or her “personal best” as a guide to how obstructed they are. Consider using peak expiratory flow monitoring in short bursts, especially when treatment is being changed.

**Allergy testing**—This is not necessary in routine practice. However, where features are atypical or simple

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### Alternative diagnoses in wheezing children

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<th>Clinical clues</th>
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<td>Bronchopulmonary dysplasia</td>
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<td>Compromised host defence:</td>
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<td>Immunodeficiency</td>
<td>Recurrent bacterial infections and failure to thrive</td>
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<tr>
<td>Cystic fibrosis</td>
<td>Persistent cough and poor nutrition</td>
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<tr>
<td>Primary ciliary dyskinesia</td>
<td>Persistent nasal discharge and otitis media</td>
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**Sudden onset in previously well child**

| Aspiration of foreign body | History of aspiration in most. Unilateral reduced breath sounds |
| Persistent wet cough       |               |
| Compromised host defence:  |               |
| Cystic fibrosis            | Poor growth, clubbing, abnormal chest shape, nasal polyps |
| Immunodeficiency           | Recurrent bacterial infections and failure to thrive |
| Bronchiectasis             | Purulent sputum |

**Postviral wheeze**

| Postbronchiolitic wheeze   | Can persist for several months. Diagnosed in absence of other alerting signs |
| Obliterative bronchiolitis | Hyperinflation and fine crepitations. Disabling respiratory symptoms |

GORD=gastro-oesophageal reflux disease.
Pattern of illness

Box 2  A guide to history taking and examination

Pattern of illness

- Ask about wheeze, cough, and breathlessness (especially on exercise)
- Clarify parents’ understanding of wheeze
- Identify triggers (such as “colds,” cold air, dust, pets, and pollens)
- Identify interval (between episodes) symptoms
- Map the pattern over time (fig 1)
- Identify presence of hay fever and eczema
- Ask parents if they have atopic illnesses
- Inquire into features that may suggest an alternative diagnosis (table)

Severity of illness

- Degree of breathlessness—ability to play, run, or walk; too breathless to feed or talk
- Use of treatments—number of puffs and frequency of inhaled bronchodilator; frequency of use of oral corticosteroids
- Emergency healthcare access, including level of treatments given
- Frequency of acute episodes*
- Number of days of school missed*

Examination

During episodes

- Look for widespread wheeze
- Look for increased effort of breathing—ability to do activities and to talk, alertness, oxygen saturations
- Assess pulse rate
- Assess peak expiratory flow (in children over 5 years)
- Assess response to bronchodilator and demonstrate reversible airways

Between episodes

- Look for hyperexpansion and Harrison’s sulci (fig 2)
- Look for clues to other diagnoses (table)

*Very frequent episodes indicate that day to day control may not be adequate and identify a very vulnerable group of children

Conclusion

Different phenotypes of wheeze are seen in childhood. With the approach set out in this review a child can usually be determined to have atopic asthma, non-atopic asthma, or episodic viral wheeze; with an episodic pattern, persistent features, or both; and with a mild, moderate, or severe pattern. This should help to guide the physician in tailoring treatment to suit the individual child. More detailed guidance on points in the history, examination and investigations that aid
diagnosis can be found in the British Thoracic Society/Scottish Intercollegiate Guidelines Network guideline. Contributors: All authors contributed to the collection of data and to the text of the paper. MM is the guarantor. Provenance and peer review: Commissioned; externally peer reviewed.

Can I help you?
So, you want to work for a few weeks, maybe as an “expert,” in a developing country? Fine. Drawing on our experiences of both giving and receiving such help in several sub-Saharan countries, we can give some tips on making your trip a success.

Get real—Don’t expect to make a big difference. You won’t. If you’re lucky, you might make a tiny one. Be self sufficient—Don’t expect to be looked after. Attending to the needs of visitors can be exhausting and not worth the effort. Arrange your own travel and accommodation via the internet. There will be taxis at the airport: take one. Forget funding—NGOs will not employ strangers for a few weeks. They can be surprisingly bureaucratic and will demand reports. Pay your own way. You can go anywhere for less than $1000 ($500) and then live well on $50 a day. Forget litigation—Your defence society may look sympathetically on voluntary work. If not, don’t worry. You will not be sued. Forget snakes, just get the jabs and take the tablets—the biggest risks are malaria, alcohol, and road accidents. Get off the minibus if the driver is intoxicated. Take your mobile phone—You are visiting a different continent, not a different planet. Stay celibate—Take post-exposure prophylaxis if you will be risking HIV infection at work.

Learn the lingo—Trying to greet patients in their language will raise a laugh and be appreciated. Stay cool—When thwarted by the lack of drugs or baffled by Byzantine care systems, do not vent your frustrations on the staff. They may share your feelings. Remember life went on there before you arrived and will do so again after you leave. Take a torch—in towns do not go out after dark: you may escape being mugged, but falling into a pothole is quite likely. Arrange personal medical insurance. Be honest—Do not promise further help unless you know you will deliver. Be polite—Ask permission before taking photographs of patients. Provide feedback—Once you’re back home, email comments, photographs, and thanks to your hosts. Copy any reports or articles on the trip to them. Compromise—Keep asking how you can help. Do not do only what you want to. Try to do what those who work there want. Have fun—Keep your sense of humour. If you don’t have one, don’t go.
NICE GUIDELINES

Psychosocial interventions and opioid detoxification for drug misuse: summary of NICE guidance

Stephen Pilling,1 John Strang,2 Clare Gerada3 on behalf of the Guideline Development Groups

Why read this summary?
Drug misuse is an increasing problem that not only impairs the physical and mental health of people who misuse drugs but also negatively affects their families and wider society (for example, in its association with crime). Recently expanded drug services in the United Kingdom involve general practitioners to a considerable degree, who care for at least a third of opioid misusers in treatment. Many clinicians remain pessimistic, however, about the possible benefits of any treatment and how to engage drug users in treatment.1 This article summarises two new National Institute for Health and Clinical Excellence (NICE) guidelines that identify the most effective, safe detoxification regimens for primary and secondary care, and effective ways to promote patient engagement.2 3

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 (*).

Opioid detoxification

General principles
For all patients who are opioid dependent and have expressed an informed choice to become abstinent, services should:
- Offer detoxification as a readily available and effective treatment option;
- Provide detailed information about detoxification and the associated risks, including:
  - The physical and psychological aspects of opioid withdrawal, including the duration and intensity of symptoms
  - How such symptoms may be managed, including non-pharmacological approaches
  - The loss of opioid tolerance after detoxification, and the ensuing increased risk of overdose and death from illicit drug use (this risk may be potentiated by alcohol or benzodiazepine use)
  - The importance of continued support, and psychosocial and appropriate pharmacological interventions, to maintain abstinence, treat comorbid mental health problems, and reduce the risks of serious adverse events (including death) that may arise as a result of reduced opioid tolerance;
- Offer a community based detoxification programme routinely, except to individuals who:
  - Have not benefited from previous community based detoxification
  - Need medical and/or nursing care because of significant additional physical or mental health problems
  - Require complex polydrug detoxification (for example, concurrent detoxification from alcohol or benzodiazepines)
  - Are experiencing considerable social problems that may substantially limit the benefit of a community based detoxification programme.

Pharmacological interventions

- Offer buprenorphine or methadone as first line treatment, depending on:
  - Whether the patient is receiving maintenance treatment with either drug, as detoxification should normally be started with the same medication
  - The service user’s preference;
- Consider lofexidine, particularly for those with mild or uncertain dependence, but warn patients that this necessitates the use of adjunct medications to manage withdrawal symptoms such as nausea, vomiting and shivering as lofexidine may not sufficiently attenuate the noradrenergic storm, and that outcomes are likely to be no better than for buprenorphine or methadone;
- Do not use clonidine routinely because its outcomes are likely to be no better than for buprenorphine or methadone and because of the associated risk of hypotension;
- Do not use opioid antagonists (such as naltrexone) to precipitate or accelerate withdrawal as it seems to increase severity of withdrawal, necessitates the use of increased adjunctive medication, and no consistent
Further information about the guidance

Methods
The guidelines were developed according to NICE guideline methodology (see www.nice.org.uk/page.aspx?o=114219) by the National Collaborating Centre for Mental Health. The collaborating centre convened a development group of clinicians and patient and carer representatives for each guideline to oversee the work and develop the recommendations. The groups conducted extensive systematic reviews of the clinical and economic literature and assessed the quality of this literature. The guidelines were through an external consultation with stakeholders. The development groups assessed the comments, reanalysed the data where necessary, and modified the guidelines. NICE has produced four different versions of each guideline: a full version; a quick reference guide (which combines both guidelines); a version known as the “NICE guideline” that summarises the recommendations; and a version for patients and the public. All these versions are available from the NICE website (see www.nice.org.uk/CG051 and www.nice.org.uk/CG052). Future updates of the guidelines will be produced as part of the NICE guideline development programme.

Evidence exists for improved long term outcomes;
- Do not routinely use drugs such as benzodiazepines, minor analgesics, or antidiarrhoeals to manage opioid withdrawal symptoms. This is to reduce the risks associated with specific drugs, drug interactions, and problems with adherence. Only use these medications when clinically indicated;
- Do not offer ultrarapid detoxification under general anaesthesia or heavy sedation (where the airway needs to be supported) owing to the risk of serious adverse events, including death.

Psychosocial interventions in drug misuse
Formal psychosocial interventions have not been widely used in UK drugs services, but the evidence reviewed by NICE shows that increased use of these interventions can bring real benefits.

Individual healthcare staff
- Offer opportunistic brief interventions focused on motivation to people in limited contact with services (for example, those attending a needle and syringe exchange or primary care settings). These interventions should:
  - Comprise one or two sessions of 10-45 minutes’ duration
  - Express empathy with the service user; explore ambivalence about drug use and possible treatment options; and provide non-judgmental feedback aimed at increasing motivation to change behaviour;
  - Routinely provide information about self help groups, often based on 12-step principles (for example, Narcotics Anonymous and Cocaine Anonymous).

Drug misuse services
- Consider introducing contingency management as part of a phased implementation programme led by the National Treatment Agency to reduce illicit drug use and/or promote engagement with services for people in methadone maintenance programmes or who misuse stimulants.

- Contingency management should include:
  - Incentives such as vouchers or privileges, contingent on each presentation of a drug negative test result (for example, free from cocaine or non-prescribed opioids); such vouchers may be exchanged for goods or services, and privileges to increase the service user’s choice (for example, use of take-home methadone doses); vouchers should have monetary values that start at about £2 (£3; $4) and increase with each additional, continuous period of abstinence;
  - Drug tests (three tests a week for the first three weeks, two tests a week for the next three weeks, and once weekly thereafter until stability is achieved); urine analysis is the preferred method of testing, but oral fluid tests may be used as an alternative.

- For those at risk of physical comorbidity from drug misuse, consider material incentives (such as shopping vouchers of up to £10 in value) on a one-off basis or over a limited duration, contingent on concordance with specified harm reduction activities, particularly for:
  - Hepatitis B or C and HIV testing
  - Hepatitis B immunisation
  - Tuberculosis testing.

Overcoming barriers
In recent years drug treatment has focused on harm reduction rather than abstinence as a goal, but the evidence on detoxification makes clear that abstinence is an effective treatment option. Furthermore, although psychosocial interventions for drug misuse are not well developed, the evidence suggests that they can bring real benefits, in part through increasing the value of currently used treatments.

Contingency management has been little used in the UK, is open to misunderstanding by clinicians and the general public, and will require considerable training of staff and service development if it is to be introduced appropriately and effectively. It involves a new way of thinking, with the use of positive incentives instead of negative approaches such as the withholding of treatment. The evidence is that, particularly with this patient population, behaviour can be positively shaped with incentives, whereas threats and punishment have little influence. Overseas trials involving more than 5000 patients across more than 25 studies have consistently shown that such an approach reduces illicit drug use, is cost effective, and improves engagement in harm reduction and treatment programmes.

To tackle these challenges, it is proposed that the National Treatment Agency in the UK will establish a network of demonstration centres, which will develop
materials to support a phased implementation of contingency management, support staff training and supervision programmes, and assess the relative value of different incentive systems.

Contributors: SP drafted the paper, and all authors contributed to its revision and the final draft. SP convened both guideline development groups. JS chaired the NICE guideline on psychosocial interventions, and CG chaired the NICE guideline on detoxification.

Competing interests: Both JS and CG have received funding from pharmaceutical companies and government agencies for advisory services, and both are members of the UK Department of Health Clinical Guidelines on Drug Misuse and Dependence Group.

INTERACTIVE CASE REPORT
A patient with suspected miscarriage is found to have hypertension, renal failure, and thrombocytopenia: case outcome

Chris M Laing,1 Rhy Robert,2 Liz Lightstone,3 Alison Graham,4 Terry H Cook,5 Shaun Summers,3 Charles D Pusey6

Four weeks ago we described the case of a 46 year old woman who presented with possible miscarriage, severe hypertension, acute renal failure, pulmonary oedema, microangiopathic haemolytic anaemia, and seizures (BMJ 2007;335:1372. 30 June). The diagnoses we considered were malignant hypertension, intrinsic renal disease, a primary microangiopathic process—such as haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura, or eclampsia with HELLP syndrome. She was started on intermittent haemodialysis, an angiotensin converting enzyme inhibitor, and plasma exchange (BMJ 2007;335:44. 7 July). A magnetic resonance imaging scan of the brain showed posterior leucoencephalopathy consistent with hypertensive encephalopathy.

Her platelet count, metabolic abnormalities, and breathlessness improved and she had no further seizures. At one week she was well but remained dependent on dialysis. Bisoprolol and amloplipine were added to control her blood pressure.

Renal Doppler ultrasound showed poor renal perfusion so we performed angiography to exclude renovascular disease. This showed normal renal vessels (fig 1), suggesting a microangiopathic infrarenal process.

Renal biopsy demonstrated florid myxoid intimal thickening in interlobular arteries (fig 2), widespread acute tubular damage, and glomerular ischaemic changes. There was little thrombotic change to suggest haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura. These appearances are consistent with a diagnosis of malignant hypertension or scleroderma renal crisis.

The table summarises the other investigations and blood tests. These were negative except for a strongly positive speckled antinuclear antibody at a titre of more than 1/1000. The staining pattern was consistent with anti-RNA polymerase antibodies and this was confirmed with immunoprecipitation.

Anti-RNA polymerase antibodies are strongly associated with scleroderma renal crisis, and we consider...
The patient’s immunological profile and results of other investigations

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result (normal range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibody</td>
<td>Positive, speckled 1/1000; anti-RNA polymerase</td>
</tr>
<tr>
<td>Anti-neutrophil cytoplasmic antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-scleroderma-70 antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-topoisomerase antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-double stranded DNA antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-complement C1q antibodies</td>
<td>Negative</td>
</tr>
<tr>
<td>Complement C3</td>
<td>1.11 g/l (0.7-1.7)</td>
</tr>
<tr>
<td>Complement C4</td>
<td>0.18 g/l (0.16-0.54)</td>
</tr>
<tr>
<td>Anti-phospholipid/anti-cardiolipin antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>IgG</td>
<td>5.9 g/l (0.3-16.5)</td>
</tr>
<tr>
<td>IgA</td>
<td>0.96 g/l (0.3-4.0)</td>
</tr>
<tr>
<td>IgM</td>
<td>0.51 g/l (0.5-2.0)</td>
</tr>
<tr>
<td>Renal angiography</td>
<td>Normal</td>
</tr>
<tr>
<td>Magnetic resonance imaging of adrenals</td>
<td>Normal</td>
</tr>
<tr>
<td>Spot plasma adrenaline</td>
<td>0.76 nM (0.00-1.00)</td>
</tr>
<tr>
<td>Spot plasma noradrenaline</td>
<td>3.2 nM (0.5-5.0)</td>
</tr>
<tr>
<td>Random adrenocorticosterone</td>
<td>5.1 ng/l</td>
</tr>
<tr>
<td>Random cortisol</td>
<td>222 nM</td>
</tr>
<tr>
<td>Long dexamethasone suppression test final cortisol</td>
<td>80 nM</td>
</tr>
</tbody>
</table>

A clotting screen is essential to differentiate between causes of microangiopathic haemolytic anaemia. These can be either thrombotic microangiopathy or disseminated intravascular coagulation, possibly related to an obstetric calamity, sepsis, malignancy, or acute inflammation such as acute pancreatitis. In this case, normal clotting studies support the diagnosis of thrombotic microangiopathy.

The box lists the causes of thrombotic microangiopathy. In each situation, end organ injury will be exacerbated by hypertension. For this patient, initial management must focus on urgent treatment of her accelerated hypertension, which may even switch off the thrombotic microangiopathy. She needs immediate admission to a unit with facilities for invasive monitoring. Intravenous furosemide and nitrate infusion are appropriate if clinical signs of fluid overload are present. In acute renal failure, the response to furosemide is usually poor, and haemofiltration (or haemodialysis) should be started early. However, circulating volume can be reduced in accelerated hypertension and medical management is different, with arterial vasodilation needed rather than diuresis and venodilation.

In this case, the differential diagnosis includes haemolytic uraemic syndrome—thrombotic thrombocytopenic purpura—possibly associated with pregnancy or shigatoxin—anticardiolipin antibody syndrome, and scleroderma renal crisis. In idiopathic haemolytic uraemic syndrome—thrombotic thrombocytopenic purpura, vascular injury occurs in the context of reduced factor H activity, reduced plasma exchange is often used, the evidence is not strong, and benefit may be limited to patients with

this to be the diagnosis. Her hypertension may have precipitated miscarriage on this occasion, but the cause of the earlier miscarriages is less clear.

Scleroderma renal crisis primarily affects young and middle aged women and presents with acute renal failure and hypertension. There may be no prior symptoms of systemic sclerosis, but the history of Raynaud’s offered a diagnostic clue in this patient. Other features of malignant hypertension such as encephalopathy, seizures, pulmonary oedema, and microangiopathic haemolytic anaemia may complicate this illness.

Angiotensin converting enzyme inhibitors may facilitate microvascular remodelling and prevent progression of renal impairment; they are used widely in this disease. Intravenous vasodilatory therapy, usually with prostacyclin, is recommended, and dialysis may be required. The benefit of plasma exchange in secondary microangiopathy is controversial and was instituted in this case because initially we could not exclude thrombotic thrombocytopenic purpura as a primary diagnosis.

The prospects for renal recovery are poor in patients who need dialysis at diagnosis. This patient is currently well on haemodialysis three times a week, although she still requires oral antihypertensives. She is currently awaiting renal transplantation.

We welcome contributions of interactive case reports. Cases should raise interesting clinical, investigative, diagnostic, and management issues but not be so rare that they appeal to only a minority of readers. Full details of criteria are available at bmj.com/cgi/content/full/326/7389/564/DC1

Commentary: Nephrologist

Robin Woolfson

A clotting screen is essential to differentiate between causes of microangiopathic haemolytic anaemia. These can be either thrombotic microangiopathy or disseminated intravascular coagulation, possibly related to an obstetric calamity, sepsis, malignancy, or acute inflammation such as acute pancreatitis. In this case, normal clotting studies support the diagnosis of thrombotic microangiopathy.

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antibodies to ADAMTS13 or problems with volume overload.1

The pregnancy test is negative in this patient and she has no history of shigatoxin infection. Her miscarriages probably occurred during the first trimester, and the normal activated partial thromboplastin time excludes a lupus anticoagulant, although anticardiolipin antibodies could still be present. The history of Raynaud’s phenomenon raises the possibility of underlying connective tissue disease. A diagnosis of acute scleroderma renal crisis is supported by the presence of strongly positive antinuclear antibodies and anti-RNA polymerase antibodies, together with the renal histology. Absence of cutaneous changes is unusual, however, and might favour a unifying diagnosis of accelerated hypertension with incidental serology. In a recent report of 115 cases of acute scleroderma renal crisis, patients were mostly female (81%), had diffuse cutaneous disease (78%) and anti-RNA polymerase antibodies (59%), and outcome was predicted by renal histology.2

The renal biopsy was consistent with accelerated hypertension or scleroderma renal crisis with widespread ischaemia. Doppler ultrasound showed poor renal perfusion with normal proximal arteries confirmed on renal angiography. By this stage, the diagnosis was much clearer and a dynamic renogram would have confirmed minimal uptake with poor prognosis due to irreversible tissue injury and avoided the need for selective angiography.


Commentary: View from clinical education

Ed Peile

This interactive case discussion is interesting from an educational viewpoint. The case presentation is one of the most complex that has featured in this series, and it attracted thoughtful responses from clinicians of many specialities and levels of experience. It was good to see a medical student reasoning his way through the dilemmas posed by this patient’s presentation. Most responses showed evidence of more than a “stab in the dark” approach to diagnosis and management of the complex case.1

Clinical reasoning approaches in the responses included generating diagnostic hypotheses and testing them; using pattern recognition; and the process of “chunking” information and constructing schema excluding some pathways and exploring others (such as acute or chronic renal failure; primary or secondary hypertension). These processes are used by experts and novices alike (in differing proportions and to different effect) in test situations.2

What is less certain is how clinicians respond to complex and demanding cases like this, where the stressful situation involves volatility, uncertainty, complexity, ambiguity, and delayed feedback and information flow (VUCAD).3 We need more evidence about the reasoning processes that clinicians use in complex medical situations (rather than evidence from artificial tests of reasoning used in research) if we are to understand, let alone teach, the skills that clinicians need to determine appropriate priorities in managing a case presentation such as this.

Comprehensive mapping of clinical judgments, decision making, and analysis led Jack Dowie to stress the importance of a comprehensive Bayesian stochastic decision model that places equal weight on knowledge and input of values.4 But can we realistically expect doctors to use such complex modelling processes when dealing with desperately ill patients?

For teaching purposes I illustrate the patient’s presentation as a circle which expands as history, examination, and investigation add to our knowledge (figure). The clinician constructs a square frame composed of two adjacent sides that represent “diagnosis”...
and two that represent “management.” The clinician’s frame is “squared down” to meet the expanding rings of the emerging patient picture. Actions result when the management possibilities are reduced to an appropriate choice to frame what we now know about our patient. The process is dynamic and is repeated when decisions are made. In this case, a decision to admit the patient is made early on, and the dialysis decisions of early management follow rapidly and logically. The diagnosis becomes clearer as emergency management proceeds.

Although research into understanding effective complex clinical decision processes is necessarily complex, we may benefit from keeping simple models in our heads as we teach.

Competing interests: None declared.

Commentary: Author’s reply

Chris M Laing

We hope that readers have found this interactive case report interesting and educational. The rapid responses—from many countries, specialties, and grades—have been informative. We would like to thank BMJ readers for taking such an interest in the case and taking time to post their responses.

This patient presented with scleroderma renal crisis and features typical of accelerated hypertension—acute renal failure, pulmonary oedema, microangiopathic haemolysis, and hypertensive encephalopathy. We agree with many responders that investigation for her illness certainly warranted investigation. Investigation of accelerated hypertension may include endocrine testing, renovascular studies, serology, and renal biopsy. In our experience, white patients with this presentation often have an underlying cause.

As regards her management, basic resuscitation, adequate monitoring, and safe and timely transfer to a specialist unit were crucial. We used nitrates for pressure control in view of her volume overload and pulmonary oedema, followed by ultrafiltration and oral therapy. Some of the blood pressure agents suggested by responders would be equally efficacious, as would prostacycline. Most guidelines recommend initial lowering of diastolic pressure to 100-105 mm Hg over two to six hours, with an initial drop of no more than 25%. This can then be lowered to 85-90 mm Hg over several weeks. Acute dialysis (or haemofiltration) was clearly needed, and we felt early plasma exchange was justified given the possibility of primary TTP.

Our patient had an overwhelming illness, which evolved extremely rapidly—apparently “out of the blue.” She had a fortnight of intensive treatment and investigation and then had to adjust rapidly to the prospect of long term dialysis. She coped with these demands remarkably well.

In spite of advances in technology, mortality from acute renal disease remains high. Patients with such disease often present to non-specialists. Early recognition and treatment, with early involvement of nephrology and critical care services, is essential for a good outcome.

Competing interests: None declared.

Knifeless lung surgery

The 70-year-old patient had been admitted many times for exacerbations of his chronic obstructive pulmonary disease for the past several years, and he could barely walk despite the numerous bronchodilators and anticholinergic drugs he was taking. Recently, he was brought with severe breathlessness once again, but this time he did not respond and was referred to a tertiary care hospital for the management of respiratory failure.

He was put on a ventilator, and a few hours later he had a cardiac arrest. He was successfully resuscitated, but he then developed pneumothorax after the resuscitation. Fortunately, he responded well to ventilator therapy and intercostal drainage. A few days later he was discharged.

When he returned for follow-up, I noticed marked improvement in his dyspnoea. The beaming patient told me that he was cured of his disease. Examination and assessment of lung function confirmed his improvement. When I went through his discharge notes, I saw how his COPD had been “cured.”

The patient had large emphysematous bullae in either lung, and these were ruptured during cardiac resuscitation. Luckily, the resulting pneumothorax was managed effectively. These emphysematous bullae compressed the adjacent normal lung tissue, so their obliteration allowed normal functioning of the lung tissue. This resulted in marked improvement in lung function and clinical symptoms.

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Labour pains

Wendy Savage, champion of women’s rights in childbirth, is back with a polemical look at who controls birth and who controls doctors, writes Duncan Double

In 1985 Wendy Savage made medical headlines when she was suspended from practice over charges of incompetence in managing five obstetric cases. The charges centred on births where she was accused of having delayed performing caesarean sections.

After an inquiry conducted in the full blaze of publicity Savage was finally reinstated as senior lecturer in obstetrics and gynaecology at the London Hospital Medical College and honorary consultant at The London Hospital. *A Savage Enquiry* was her gripping account of these events. In it she wrote, “I and many of my supporters saw my suspension as part of the continuing struggle about who controls childbirth.”

In this new book Savage describes for the first time what happened to her when she returned to work. The book focuses on the problems that arise when doctors disagree among themselves. Interpersonal difficulties in her department persisted, despite the recommendations of various reports that working relationships should be improved. Ten years from the last day of her inquiry she was told of an anonymous complaint about her management of a further five cases. This time she resisted external assessment, and the matter fizzled out, though leaving her exhausted. She went on sabbatical before retiring a few years later, having also earlier become honorary professor at Middlesex University.

This book, which includes contributions from other authors, returns to the themes identified in the first book—for example, asking what services women want and who decides what they get—and considers what still needs to be done.

Savage describes the damage that gossiping causes to the reputation of doctors who are wrongfully suspended. Her experience leads her to conclude that such doctors are seen as “different” or “difficult,” often because they are more conscientious than others or act as whistleblowers. John Hendy, who was Savage’s barrister for the inquiry and who has continued to gain considerable experience in medical disciplinary cases at Old Square Chambers, which specialises in such cases, observes that personal malice or professional jealousy may in some cases play a role in trumping up charges, but these factors are almost inevitably impossible to prove.

The book indicates how suspension from work can be devastating. One woman surgeon, not yet in a position to divulge the full details of her case, writes anonymously about her experience. She is not unusual in having felt suicidal about her situation.

The book also highlights the importance of academic freedom, so that unorthodox or new opinions can be furthered. This is essential if we are to train doctors to think. Medicine is not an exact science. Attitudes and approaches vary on a spectrum from doctor centred to patient centred. A doctor centred bias can be reinforced by an overemphasis on physical abnormalities at the expense of dealing with difficult personal issues. Inevitably, with any one doctor there is an interaction between the degree of patient and doctor centredness. But Savage realises that most doctors achieve the right balance.

Of course, there are a few rogue doctors. Good clinical governance depends, however, on supporting the vast majority of sound clinicians. It actually makes health organisations less safe for patients if this is not the case. Michael Goodyear, an academic oncologist from Canada, says in his chapter, “Cultures of excellence not only value their workforce but let them know they are valued.”

Savage was accused of being non-interventionist. This was primarily because she was prepared to give women choice about a trial of labour in circumstances in which other obstetricians might have moved more directly to caesarean section. It is still a requirement of the General Medical Council’s *Good Medical Practice* to respect colleagues and not allow personal views to affect professional relationships adversely. In particular, malicious and unfounded criticisms should not be made that may undermine patients’ trust in the care or treatment they receive or in the judgment of those treating them.

One of the contributors, Marsden Wagner, writes from the international perspective of having been director of women’s and child health at the World Health Organization. He suggests that the real function of tribunals such as the Savage inquiry is to punish deviant professional behaviour that could threaten the income, style of practice, prestige, and power of mainstream doctors. Is medicine really in such a vulnerable state? Medicine is hardly a total cultural deceit—but those who point out the respects in which it is deficient may be perceived as being outside the acceptable range of medical practice.

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Four bodyguards and the perils of unmasking scientific truths

PERSONAL VIEW Felix I D Konotey-Ahulu

To be chosen to deliver the keynote address at the Martin Luther King Jr Foundation’s award banquet took me completely by surprise—and to find that four bodyguards had been assigned me shook me rigid. Nobel laureates Linus Pauling and Max Perutz, along with Hermann Lehmann, Roland Scott, A C Allison, Graham Serjeant, and I, were among a select few invited to Philadelphia to receive an award “for outstanding research in sickle cell anaemia.” But why was I asked to deliver the keynote address, with Pauling and other abnormal haemoglobin heavyweights on the platform? Was it, perhaps, because I was the only person to have sickle cell disease clinic in the world? Or because I was then director of the largest sickle cell disease centre in the world? Was it, perhaps, because a foundation commemorating a black person wanted to “show off” the only black African among haemoglobin heavyweights on the platform? Was it, perhaps, because I was the only person to have traced hereditary disease in his forebears, with named patients, generation by generation back more than three centuries? Or was it the statement made a few weeks back in New York by Professor Helen Ranney of the Albert Einstein University College of Medicine: “There is no single clinical experience in the United States comparable to that of Dr Konotey-Ahulu”?

Such “perhaps hypotheses” competed in my brain when I arrived in Philadelphia, that day in 1972. I walked out of the hotel to post a letter to my wife in Ghana. Just as I was about to cross a road, I heard a voice behind me: “Doctor! Doctor!! Do NOT cross that road. Where are you going?” The hugely built American (black) took the letter from me before dropping the bombshell: “I am one of your four bodyguards.”

The award organisers, who came within minutes of my call, explained that the text of my lecture alerted them to several problems. I had distinguished between sickle cell trait and sickle cell disease (sickle cell anaemia) because the terms were being used interchangeably, with disastrous consequences, by people who should know better. People with the trait (one abnormal gene) cope better than people with two normal genes with falciparum malaria, which kills sickle cell disease patients (two abnormal genes) quicker than people with two normal genes. I had questioned published work which claimed that black Army recruits exercising at an altitude of 4000 ft collapsed and died because of sickle cell trait. I had asked: “How could black sickle cell traits run and beat the whole world at the Olympic Games at Mexico City, at an altitude of 8000 ft (double the altitude at which people with sickle traits had been said to perish)?”

Why did I need four bodyguards? The organisers said I needed protection because I used data from an article by James Bowman, who had named seven US insurance companies that loaded the premium of black people with sickle cell trait, thus making lots of money on healthy people, who had to pay 150% for health insurance. I explained that where one person in five has the sickle cell trait, one in five sudden deaths in adults from whatever cause would be in people with sickle trait. Moreover, to make insurance recommendations for only “black” sickle cell trait, without mention of “white” sickle trait in people from Greece, Cyprus, Turkey, India, and Saudi Arabia—many of whom lived in the US—was not medical science.

I was determined not to allow a waiting list to form. I thought, “I’ll show them how I can organise an efficient service and get operations done at the same rate as I see patients in clinic.” How naive I was. Within two years I was operating on people who had been on the list for a year. It was shocking and frustrating—it felt like being impotent. The operating sessions

Liste d’attente? Pourquoi?

PERSONAL VIEW John Petri

“Doctor, when can I have my operation?”

“Well, my dear, in a few weeks I suppose.” I was learning fast.

I walked into my first UK consultant job from a similar job in France 13 years ago. At first my patients were easy to please, because there was no waiting list in my orthopaedic firm. But I can take no credit for this, because mine was a newly created job, and at first I had to steal patients from colleagues to have something to do. Otherwise, however, waiting lists were omnipresent and, apparently, an unavoidable fact of life. Still, how unavoidable could they be? I had had no waiting list in France. In fact I had to translate from English to explain to my French wife what it meant: “Liste d’attente.” She knew you could get stuck on a liste d’attente while desperately trying to reach a representative of the French bureaucracy over the phone, but a surgical liste d’attente? She was horrified.

I was determined not to allow a waiting list to form. I thought, “I’ll show them how I can organise an efficient service and get operations done at the same rate as I see patients in clinic.” How naive I was. Within two years I was operating on people who had been on the list for a year. It was shocking and frustrating—it felt like being impotent. The operating sessions
were short and few, only three and a half hours twice a week. Then half of that time was taken up with “sending for the patient,” anaesthetising, positioning, and cleaning the theatre between operations. Sometimes something would get in the way of even this slow routine, and the reasons to cancel operations were innumerable: unavailable instruments, unavailable porter, lack of beds, and unexpected medical problems. I spent more time in the coffee room than in theatre.

The most amazing aspect of all this was that nobody was talking about the causes of waiting lists. If I asked, people looked at me condescendingly as if I were deluded. If pressed, they would mention “lack of surgeons” as the cause. How could it be “lack of surgeons” if I was doing half as many operations as when I was in France?

Early on during my time in the NHS I had to translate from English to explain to my French wife what “waiting list” meant. “Liste d’attente.” She was horrified

I met a more experienced orthopaedic consultant, who had come from Belgium. I asked how he could stand such slow and inefficient surgical activity. “I tried to change the system but I gave up,” he said. “I was inefficient surgical activity.” I tried to change the NHS but that it was usually bad news; for they said that they often reported on the NHS but that it was usually bad news; for once they wanted to report good news.

In January 2006 I was invited to meet the then prime minister, Tony Blair, who, asking, “Do they pay you more than other surgeons?” was surprised that I wasn’t.

The flocks of surgeons who were supposed to come and see how you can more than double the number of operations did not materialise. But my trust remained delighted with the results and, at the beginning of 2007, half of the patients in my operating sessions were drawn from other surgeons’ waiting lists. One thing did happen. I did not pay much attention to it because I expected it but later came to realise how important it was: my income from private practice was halved.

I do not blame my colleagues for not showing much interest in my work, although I could do without the reputation of being one who does “conveyor belt surgery.” Why should they work harder for less money? Perhaps the government should try to create incentives to get rid of the widespread inefficiency in the NHS. Any health system can work only if the health professionals want to make it work. It’s the job of politicians to make them want it.

As for me, all I wanted was to give the NHS good value for money and to prove a point. Next week I am moving to Switzerland. I shall certainly have a job explaining to the Swiss what surgical waiting lists are.

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The organisers advised me to leave names of the insurance companies out of my lecture. Even so, they could not run the risk that I would be bumped off before the lecture.

I had to translate from English to explain to my French wife what “waiting list” meant. “Liste d’attente.” She was horrified

I met a more experienced orthopaedic consultant, who had come from Belgium. I asked how he could stand such slow and inefficient surgical activity. “I tried to change the system but I gave up,” he said. “I was just making enemies.” Well, I did not care about making enemies. Firstly I had to show that we did too few operations. I collected data to compare my hospital with one of similar size and activity that I knew well in France. I presented the results at an audit meeting. In the NHS we had twice as many surgeons, anaesthetists, and theatre staff as in France and were doing less than half as many operations. Then I wrote a short paper showing that, by introducing a few changes and adding another operating theatre to the two we were already using in orthopaedics, we could increase the number of operations by 73%. I was so excited that I sent my plan to all the surgeons in the hospital and to the then health secretary Frank Dobson. The reply came from his office after three months. It was long and sounded like a party political broadcast. It could be summarised by the sentence, “Thank you for your interest, we are already doing all that is necessary.”

My colleagues had not even replied, except one who was convinced that it would not work. Fortunately the management supported me, and we went through the many steps that it takes to build a new theatre. Just before that I was allowed to run a pilot scheme, hijacking a second theatre for my Thursday morning list. I would operate in one theatre while the next patient was being prepared in the second. In six months my waiting time fell from one year to a few weeks. It took another three years before I could finally run regular “dual lists.” Finally I was operating in the way I wanted to. Bliss!

We measured the “surgeon’s utilisation” going up from 50% to 95%. In 2005 I had no waiting list and I started operating on my colleagues’ patients. I won a Medical Futures award, and finally my story could become public. Television crews came to our theatres, which became temporarily known as “studio 1” and “studio 2.” I never had so many senior house officers assisting me. We were also visited by a television crew from TF1, a national French channel. When I asked why they were interested they said that they often reported on the NHS but that it was usually bad news; for once they wanted to report good news.

In January 2006 I was invited to meet the then prime minister, Tony Blair, who, asking, “Do they pay you more than other surgeons?” was surprised that I wasn’t.

The flocks of surgeons who were supposed to come and see how you can more than double the number of operations did not materialise. But my trust remained delighted with the results and, at the beginning of 2007, half of the patients in my operating sessions were drawn from other surgeons’ waiting lists. One thing did happen. I did not pay much attention to it because I expected it but later came to realise how important it was: my income from private practice was halved.

I do not blame my colleagues for not showing much interest in my work, although I could do without the reputation of being one who does “conveyor belt surgery.” Why should they work harder for less money? Perhaps the government should try to create incentives to get rid of the widespread inefficiency in the NHS. Any health system can work only if the health professionals want to make it work. It’s the job of politicians to make them want it.

As for me, all I wanted was to give the NHS good value for money and to prove a point. Next week I am moving to Switzerland. I shall certainly have a job explaining to the Swiss what surgical waiting lists are.

John Petri is orthopaedic specialist, John Paget NHS Foundation Trust, felix@konotey-ahulu.com

The organisers advised me to leave names of the insurance companies out of my lecture. Even so, they could not run the risk that I would be bumped off before the lecture.

I had to translate from English to explain to my French wife what “waiting list” meant. “Liste d’attente.” She was horrified

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Speccy-four-eyed-social-misfit-geek

My head nodded and then jolted in reflex. Bleary eyed, I glanced at my wife over my copy of the Lancet. The Lancet was my “take me seriously” badge as an aspiring new principal in general practice. “What are you reading?” I asked my wife. “Harry Potter,” she replied. I sniffed contemptuously and went back to my dry old parchment.

On Saturday Harry Potter and the Ghostly Hallowes, the final volume of the adventures of J K Rowling’s boy wizard, thumped on to my doorstep. My subscription to the Lancet, however, has long lapsed.

Harry’s parents are murdered and he is dumped on unloving in-laws. There is no social work meeting, no counselling, no antidepressants—Harry is just locked in a cupboard, with a few hand-me-downs and domestic chores. There is no complaining, no whining. When Harry discovers that he is a wizard, does he go around bragging and shooting his mouth off? No. He is then sent to a boarding school, which unusually has no recreational drugs, no underage sex, and no skiing trips—just bullying, Quidditch, and “he who must not be named.” Harry might be a hard working, speccy-four-eyed-social-misfit-geek (fertile medical school material), but he is honest, loyal, determined, and brave. Even though he is a fictional character, his story tells us more about the psychology of life than the Diagnostic and Statistical Manual can.

Narrative and fictional writing are more popular than ever. But scientific writing remains the preserve of the few. There is a vast array of specialist journals, but most lie unread in neat piles under the stairs. There is a perception that these journals are controlled by a small group of detached, conservative, academic oligarchs, more interested in protecting their own turf than in the day to day reality of their jobbing colleagues. There are few landmark papers, the conclusions in many papers are mere fiction, and the “science” is just simple observation of the real magic—nature. Specialist medical journals can learn from fiction. They need to broaden their appeal by exploring the narrative of medicine—the humour, ethics, pain, and politics of the specialty. This is not a question of dumbing down, for the only stupid thing is not realising that medicine is more about heart than brains.

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

Heads you lose

Ever since Hippocrates supposedly urged “First do no harm,” doctors have been inextricably associated with squandering lives in the name of political and religious ideology. From the Alexandrian anatomists who dissected living convicts in the 4th century BC to the Nazi Physicians’ League, doctors have bent their talents to state-sponsored murder.

None, however, has contributed more to the cause of terror—albeit unintentionally—than the well meaning French physician Dr Joseph Ignace Guillotin. A respected doctor with a lucrative practice in pre-revolutionary Paris, Guillotin was a professor of the Paris Faculty of Medicine. A disciple of reason, he helped investigate and condemn the hypnotism craze brought to Paris by the charlatan Mesmer. In the same spirit of enlightenment, he called for sweeping reforms of the capital’s atrocious hospitals and asylums.

Espousing revolutionary idealism, the progressive doctor was elected a deputy to the National Assembly in 1789. After persuading the assembly to establish a Health Committee, which he chaired, Guillotin set about modernising French medical education and practice. And it was with the same reforming zeal, in the rosy dawn of the new republic, that the good doctor turned his attentions to the iniquity of capital punishment.

Keen to extend the principle of equality to the republic’s criminals, Guillotin proposed that anyone executed should be beheaded; previously the nobility alone had enjoyed this privilege while commoners suffered a long, agonising death by hanging. In order to render this end as humanitarian as possible, he advocated a fast, foolproof, and painless decapitation machine.

Eloquently arguing his case before the assembly, he enthused: “The device strikes like lightning, the head flies, blood spouts, the man has ceased to live.”

Contrary to popular belief, Guillotin did not invent, design, build, use, or die by his eponymous contraption, nor was it even the first machine devoted to beheading; there had been earlier devices in Scotland and elsewhere. The French model was designed by a Parisian surgeon, Antoine Louis, built by a German musical instrument maker, and tested on corpses and live sheep. Initially, its nicknames included the “Louisette” after its surgeon designer and the “Mirabelle” after its ardent supporter the comte de Mirabeau. But soon after its first use, to execute the murderer Nicholas Pelletier on 25 April 1792, “la guillotine” acquired its enduring sobriquet.

After his device had removed around 40000 heads during the Reign of Terror, Guillotin undoubtedly came to regret his humanitarian mission, especially when he narrowly escaped death from a brush with his own creation. He made some amends by championing Jenner’s smallpox vaccine before dying, peacefully, in 1814. He may be less easily forgiven for bequeathing England its Department of Health, inspired by its French revolutionary predecessor. Wendy Moore is a freelance writer and author, London wendymoore@ntlworld.com

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

Dr John Arbuthnot was Queen Anne’s personal physician and a close friend of Jonathan Swift and John Gay (of The Beggar’s Opera). He was a polymath: as well as holding MDs from Edinburgh and Cambridge, he was a classical scholar and mathematician. He was a pioneer not only of medicine but of political science. Arbuthnot understood the way of the world so well that one of his works might serve as a guide to modern life.

In 1712, he published his Proposals for Printing A very Curious Discourse, in Two Volumes in Quarto, Intitled A Treatise of the Art of Political Lying, With an Abstract of the First Volume of the said Treatise. Alas, he never completed his great work, or even started it, but nevertheless left very useful hints to governments, opposition parties, and managers in the NHS. I would recommend a copious reprint and its dissemination to all those interested (or do I mean stakeholders?)—at public expense, of course. The work is very short, and even with all the necessary feasibility studies, pilot projects, inevitable overruns, and so forth, the cost wouldn’t be more than a few millions. It would improve the quality of political lying in this country no end.

The Proposals treat several important philosophical matters, such as “Whether the right of coinage of political lies be wholly in government.” The author concludes, very sensibly, that “as the government of England has a mixture of the democratically in it, so the right of inventing and spreading political lies is partly in the people” and that “the abundance of political lying is a sure sign of true English liberty.”

Arbuthnot, an experienced physician after all, has much to say on the rules of what he calls Pseudology. He suggests that lies should be either miraculous (in modern terms, the promise of eternal life through genetic engineering) or terrifying (in modern terms, the elimination of the whole human race by a new virus). “Terrible objects,” says Arbuthnot, “should not be too frequently shown to the people, lest they grow familiar.” He says “it is absolutely necessary that the people of England should be frightened with the French king . . . once a year,” but that the too-frequent resort to scares “has produc’d great indifferency in the vulgar of later years.” Here is a valuable lesson for epidemiologists.

Obviously, Arbuthnot had the future NHS in mind when he remarked: “No man spreads the lye with so good a grace as he that believes it.”

for modern terms, the promise of eternal life through genetic engineering) or terrifying (in modern terms, the elimination of the whole human race by a new virus).

Obviously, Arbuthnot had the future NHS in mind when he remarked: “No man spreads the lye with so good a grace as he that believes it.” However, he does warn the politician and the manager of the dangers of “believing their own lies, which has prov’d of pernicious consequence of late,” among which is that of “having regulated their affairs upon eyes of their own invention.” The reason for this is that they have “too great a zeal and inteniness in the practice of this art, and a vehement heat in mental conversation, whereby they persuade one another, that what they wish, and report to be true, is really so.”

Lies, of course, like all other human inventions, should be fit for purpose. “As to the duration of lyes . . . they are of all sorts, from hours and days to ages; there are some which, like your insects, die and revive again in a different form; . . . good artists, like people who build upon a short lease, will calculate the duration of a lye surely to answer their purpose; to last just as long, and no longer, than the turn is served.” Does this sound familiar? Perhaps a reprint isn’t needed after all.

Theodore Dalrymple is a writer and retired doctor.

MEDICAL CLASSICS

Middlemarch by George Eliot

First published 1871-2

George Eliot (real name Mary Ann or Marian Evans) is arguably the greatest of Victorian novelists and Middlemarch is her undisputed masterpiece. Virginia Woolf famously hailed it as “one of the few English novels written for grown-up people.” The events described by this monumental work, which was published in 1871-2, are set 40 years earlier in the fictitious market town of the title. Eliot was born in 1819 in Nuneaton and it is not improbable that Middlemarch was based on nearby Coventry.

At the centre of the novel are the parallel stories of a physician, Dr Tertius Lydgate, and the saintly Dorothea Brooke, both of whom in different ways aspire to improve the lot of mankind. Dorothea is an idealist out to change the world and particularly address local social inequalities. Dr Lydgate is passionate about reforming the medical profession and his personal practice. But both make errors of judgment, in particular in their respective marriages to unsuitable partners, and by the end of the novel their lofty ambitions remain unrealised. Middlemarch contains several clinical cases, and it is a great tribute to Eliot that the English physician and pathologist Sir James Paget (1814-99) described all the cases as being flawless in clinical detail. In many ways the novel was way ahead of its time, and some of the medical and social areas it covered are still important issues today, as the following examples demonstrate.

The effect of social inequalities on health. “Life in cottages might be happier . . . if they were real houses fit for human beings.” Lifestyle and health: “She had brought up her children . . . not to over-eat themselves . . . which . . . habit she considered the chief reason why people needed doctors. Lydgate pleaded for those whose fathers and mothers had over-eaten themselves . . .” Holistic care: “He cared not only for ‘cases,’ but for John and Elizabeth, especially Elizabeth.” The potential for a medical school locally: “A fine fever hospital in addition to the old infirmary might be the nucleus of a medical school here . . . and what would do more for medical education than the spread of such schools over the country?” This did happen in June 2007, 135 years later, as Warwick Medical School obtained its charter as an independent medical school. Approximately 25% of the hospital clinical teaching for this medical school now takes place at George Eliot Hospital NHS Trust.

Lydgate’s research interest is to discover the “primitive tissue” from which all others are derived. Eliot portrays this as a futile endeavour, but in retrospect it seems a remarkable anticipation of stem cell research. Lydgate is the first to introduce the stethoscope to Middlemarch. Eliot’s final message in Middlemarch is that we must be meliorist in this often tragic world. Ours is to do to whatever we can to make the lot of humankind better.

Vinod Patel, associate professor in clinical skills, Warwick Medical School; vinod.patel@geh.nhs.uk

John Morrissey, clinical lead for diabetes and associate specialist, George Eliot Hospital NHS Trust, Nuneaton

THEO DOUGLAS HURST AS ULYSSUS IN THE BANDSTAND SCENE FROM THE BEGGAR’S OPERA
Zinovy Solomonovich Barkagan

Haematologist who introduced the concept of disseminated intravascular coagulation

Zinovy Solomonovich Barkagan is internationally recognised for his pioneering research on snake bites and blood coagulation. He wrote about 20 monographs and chapters in Russian manuals on haematology, oncology, and the antiphospholipid syndrome, as well as coauthoring several hundred papers.

Zinovy Barkagan was born in Odessa, a cosmopolitan city on the Black Sea in the south of Russia and the birthplace of many outstanding Soviet poets and writers. He explained this phenomenon with his “formula of genius”—everyone in Odessa ate a lot of fish and shrimps. Indeed, Barkagan hesitated in his choice between literature and medicine. He combined his medical studies during the second world war at Alma-Ata in Kazakhstan with evening classes at the journalism faculty of the literary institute evacuated from Moscow.

In 1950 he defended his kandidatskaya dissertation (the Russian equivalent of a PhD thesis) on vascular reactivity in the cold in arterial hypertension. Owing to an anti-Semitic campaign in the last years of Stalin’s life, he was forced to leave Odessa for Stalinabad (now Dushanbe, Tajikistan), where he worked at a local medical institute as assistant professor and eventually as acting chair of hospital therapy. There he came across numerous deaths from snake bites and the bites of black widow spiders (Latrodectus tredecimguttatus).

The only treatment was to apply a rubber tourniquet, which often resulted in amputation of the hand or leg and seldom saved lives. Barkagan suggested sucking out the venom by mouth. Nowadays this method of treating snake bites is given in all manuals of emergency medicine. To prove the safety of this method Barkagan performed experiments on himself, holding the venom of the Levantine viper (Vipera lebetina) and the carpet viper (Echis carinatus) in his mouth before and after having damaged the mucosa. His doktorskaya dissertation (a second thesis required for professorship in Russia), defended in 1964, was dedicated to diagnosing and treating venom poisoning from snakes and arthropods in Middle Asia. Barkagan considered changes in blood coagulation (hypercoagulation) to be the key point of venom poisoning. He admitted that he first came across this idea from reading Zahira-i Kharaqmshahi (The Treasure of the Shah of Khoresm) by Abu Ibrahim Jurjani (1045-1137).

In 1956 Barkagan moved to a newly established medical institute in Barnaul (capital of the Altai region in western Siberia), where he was the propadeutic (preclinical) chair of internal medicine till 1997. He worked in Barnaul for half a century until his death. He organised the first laboratory to diagnose and treat impairments of haemostasis, and for many years it was the only one in the eastern part of the former Soviet Union, later becoming the Siberian Centre for Haemophilia and the Altai Haematological Centre.

Barkagan suggested treating disseminated intravascular coagulation with massive transfusion of serum (plasma) instead of whole blood. He also emphasised the role of disseminated intravascular coagulation in sepsis. He viewed sepsis as an infection that results in the formation of microthrombi and requires huge doses of antibiotics and serum transfusion or plasmapheresis.

The efficacy of treating the crush syndrome with plasmapheresis, frozen serum, and heparin was demonstrated during the earthquake in Armenia in 1989. It helped to avoid amputation and achieved a tenfold decrease in acute renal failure and death.

Barkagan and his colleagues also contributed to the diagnosis and treatment of arthropathies in haemophilia. They described a secondary rheumatoid syndrome in haemophilia (known as the Barkagan-Egorova syndrome) and developed an original method of rehabilitation after haemophilic haemorrhages using external fixation techniques.

Two decades ago he started his fight against habitual miscarriages. Up to 80% of affected women have the antiphospholipid syndrome. Plasmapheresis and heparin during the whole pregnancy successfully allow carriage to term in all such cases. Women from many countries, including the United States and Sweden, came to Barnaul to give birth, but now this treatment is routine.

Barkagan was an honoured science worker of the Russian Federation (1982), a state prize laureate of the USSR (1987), a corresponding member of the Russian Academy of Medical Sciences (1993), a director of the Altai branch of the Haematological Scientific Centre of the Russian Academy of Medical Sciences, doctor honoris causa of the University of Minnesota (USA), and an honorary citizen of Barnaul.

He founded a haematological school. Thirty two of his pupils defended doktorskaya and 82 kandidatskaya dissertations. His lifestyle contradicted conventional dogmas. He was a chainsmoker, neglected sports, worked at night, and did not eat much. Until his last days he preserved a childlike capacity for amazement.

His wife, Ida Mikhailovna (née Proctor), a paediatrician, predeceased him in 1995. He leaves two children and four grandchildren. His memory will be commemorated in Barnaul by a plaque at the house where he lived and a bust in the campus of Altai Medical University, and it is expected that the local authorities will name a street in his honour.

Pavel Vorobyov
Boleslav Lichterman
Zinovy Solomonovich Barkagan, haematologist, professor emeritus of Altai State Medical University, Barnaul (b 1925, q Odessa 1946; MD), died from a heart attack on 27 December 2006.
Richard Hugh Balme

Former consultant in geriatric medicine East Berkshire district (b 1923; q Oxford 1947; DM, FRCP), died from vascular dementia on 3 December 2006. After house appointments at The London Hospital, Richard Balme spent two years in the Royal Air Force, mostly in Egypt. After three years as medical registrar at The London and a year at Johns Hopkins Hospital in Baltimore, he led the team from The London’s academic unit that introduced haemodialysis for acute renal failure. In 1959 he was appointed consultant physician to the Metropolitan and Bethnal Green Hospitals in east London, introducing gastrointestinal fibreoptic endoscopy and cardiac monitoring and arrest procedures, and setting up one of the first postgraduate centres for general practitioners in the east end. In 1975 he moved to east Berkshire as consultant physician in geriatric medicine, retiring in 1984. Predeceased by his wife in 1993, he leaves three children and six grandchildren.

Adam Turnbull

John Rashleigh Belcher

Former consultant thoracic surgeon North West Thames region and Middlesex Hospital (b 11 January 1917; q St Thomas’ Hospital 1939; FRCS, MS), d 13 January 2006. John Belcher was the ninth generation doctor (father to son) in his family, graduating while still aged 21. He joined the Royal Air Force Volunteer Reserve, the experiences of his postings enabling him to gain his FRCS and MS by 1945. John promoted operative treatment of emphysematous cysts and lobectomy for lung cancer, and performed over 1000 closed mitral valvotomies even as fourth operations. He published widely and wrote Thoracic Surgical Management. President of the Society of Thoracic and Cardiovascular Surgeons of Great Britain and Ireland in 1980, with the British Council he set up cardiothoracic units abroad. A devoted family man with wide musical tastes, a compulsive gardener, and an accomplished amateur artist and photographer, he leaves three children; his wife, Jacqueline, died soon after him.

P Belcher

Robert Francis

Patrick Cronin

Former professor and dean of medicine McGill University, Montreal, Canada (b 1926; q McGill 1953; FRCP, FRCPc, FACP), died from a heart attack on 13 January 2007. The son of the author A J Cronin, Patrick Cronin moved to the United States at the outbreak of the second world war. His BA at Princeton was interrupted when he enlisted in the Royal Canadian Air Force in 1943, transferring to the British Army in 1945-7; he gained his BA a record 52 years later. A cardiologist, Patrick was best in broad-based internal medicine. With the Canadian International Development Agency, he set up exchange programmes with developing countries. He helped set up a medical university in Karachi in 1976, serving in the Aga Khan health services for 15 years. In his retirement he collected and collated his father’s works. He leaves a wife, Sis (Shirley); three children; and five grandchildren.

Krishna Somers

Ernest William (“Bill”) Deane

Former general practitioner Christchurch, Dorset (b 1918; q Cambridge/The London 1941; MA), died from heart failure on 18 February 2007. On qualifying, Bill Deane served as surgeon lieutenant in the Royal Naval Volunteer Reserve until 1946. He then joined his father in general practice in Christchurch, remaining there for 38 years. Outside work, Bill loved sailing, competing in the 1948 Olympic trials and the 1949 Fastnet race. His successes in long distance motor rallies included several alpine and Monte Carlo rallies and winning the RAC rally in 1958. In 1949 he became one of the youngest magistrates, continuing to sit on the Christchurch bench until 1981. A founder member of Christchurch Rotary Club, he was also medical officer to Mudeford lifeboat for many years. He leaves a wife, Ruth, and two children from his first marriage.

Robert Scott-Jupp

Kathleen (“Kay”) Mary de Ville

Former prison medical officer (b 1926; q Royal Free 1950), died from metastatic breast cancer on 9 December 2006. Julie was born in Malta GC but grew up and was educated in Gosport. After qualifying Julie held appointments at Walton Hospital, Liverpool, and then started anaesthetist training in Bradford in 1984, gaining the FRCA in 1990. In 1991 Julie won the Liverpool Society of Anaesthetists’ Janssen prize and Forrest medal. She joined the anaesthetic department at Whiston Hospital in 1995, becoming lead consultant for day case anaesthesia. Julie was diagnosed with breast cancer in 2003 and endured a year of intensive treatment. The cancer was in remission until 2006. Julie died in St John’s Hospice, Wirral. She leaves her mother, Joan, and two brothers.

Kevin A Nash

Julie Ann Nash

Consultant anaesthetist Whiston and St Helens Hospitals, Merseyside (b 1959; q Liverpool 1982; FRCA), died from metastatic breast cancer 9 December 2006. Julie joined the anaesthetic department at Whiston Hospital in 1995, becoming lead consultant for day case anaesthesia. Julie was diagnosed with breast cancer in 2003 and endured a year of intensive treatment. The cancer was in remission until 2006. Julie died in St John’s Hospice, Wirral. She leaves her mother, Joan, and two brothers.

Georgina Stafford

P Jane Grubb

ADVICE

We will be pleased to receive obituary notices of around 250 words. In most cases we will be able to publish only about 100 words in the printed journal, but we can run a fuller version on our website. We will take responsibility for shortening. We do not send proofs. Please give a contact telephone number and, where possible, supply the obituary by email to obituaries@bmj.com
A “sweet tooth” seems to be inherited, at least in part. A genome-wide linkage analysis in Finland indicates that the craving for sweet foods and their pleasantness and the frequency of choosing sweet foods shows significant heritability. The chromosome 16p11.2 is implicated for people who often choose to eat sweet foods. Minerva presumes that a similar genetic picture may be found in people with many dental caries (American Journal of Clinical Nutrition 2007;86:55-63).

Critically ill newborns are often at the centre of debate about end of life care and quality of life. A Dutch study of 30 babies who died within two months of birth reports that most deaths were attributable to withholding or withdrawing treatment because prolonging treatment couldn’t be clinically justified. In some babies the decision to stop treatment was made on the level of predicted suffering. Potentially life threatening drugs were rarely the cause of death (Pediatrics 2007;120:e20-8).

A technique being developed to knock out genes in human tissues grown from mesenchymal stem cells in the laboratory could replace the need for transgenic knockout mice. Much of the research is supported by the Dr Hadwen Trust, a UK medical research charity that promotes alternatives to experimentation on animals, which is targeting the area of greatest growth—animals used in genetic experiments. If the technique succeeds it could end the reliance on mouse models of human physiology (www.drhadwentrust.org.uk).

The quality of chest compressions is more important than the timing of defibrillation, according to research on pigs (Chest 2007;132:70-5). Optimal chest compressions, either as an initial intervention or after defibrillation, brought about successful resuscitation, with fewer shocks needed. Suboptimal compressions before delivering a shock failed to achieve successful resuscitation.

The “left handers life choices survey” aims to be the most widespread survey of the careers and interests of left handed people. Economic research shows that the earning power of left handed men is 15% more than for right handed men, and certain professions are particularly suited to the traits of left handed people, especially those requiring a high degree of creativity or artistic flair. Surgeons might be more likely to be right handed because of the traditional layout of operating theatres and the design of surgical tools. To participate go to www.lefthandersday.com.

Fear is delaying men from consulting general practitioners, says a study in the British Journal of Health Psychology (2007;12:403-20). Interviews with 20 men with prostate disease found that fear about what their symptoms might mean and perceived pressure to live up to a macho image in front of male doctors were common reasons for avoiding the doctor. Male general practitioners were often thought of as having negative attitudes towards male patients. Male patients also had poor knowledge about their own physiology.

Drawing on evidence in Dame Janet Smith’s third Shipman inquiry report, the Ministry of Justice is proposing new changes to the existing cremation regulations, which date from 1930. Under the proposals bereaved families will have the right to inspect the medical forms of a relative who has died and will be able to alert the medical referee to any concerns they have about unexpected symptoms or features relating to the case. The aim is to “prevent another Shipman” (www.justice.gov.uk).

Exclusive breastfeeding is the best way for HIV positive mothers to feed their babies. For women who don’t know their HIV status, promoting exclusive breastfeeding has the potential to reduce postnatal HIV transmission. These findings from a Zimbabwean study indicate that patterns of breast feeding may be more amenable to change through education than adoption of safer sexual practices (American Journal of Public Health 2007;97:1249-54).

“Pharmageddon” is the prospect of a world in which medicine and drugs produce more ill health than health, and when medical progress does more harm than good. Both Social Audit (www.socialaudit.org.uk) and Health Action International (www.healthaction.org) have raised the concept, and Social Audit is offering a number of prizes of money for thoughtful responses of fewer than 350 words published on their website, which will be fed into next year’s conference on the topic.

After the somewhat simplistic report on hand washing from the chief medical officer, BMJ readers may prefer to get a copy of the winter 2006 issue of Emerging, the newsletter of the Plexus Institute, on methicillin resistant Staphylococcus aureus (MRSA). It contests that the core problem about MRSA is that it requires a complex human response, and the solution has to involve the entire community. One promising approach is “positive deviance,” which is a process of social change based on the recognition that every community has people who solve problems better than others who have exactly the same resources (www.positivedeviance.org).