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**Arbitrariness and conventionality: actions speak louder than words**
Emma Stapleton
Folic acid and birth malformations
Despite 15 years of evidence, preventable defects still occur

With prevalences of 10-15 per 10 000 and 20 per 10 000 live births, neural tube defects and oral clefts are among the most common congenital malformations. Good evidence shows that periconceptional supplementation with folic acid reduces the risk of neural tube defects. What is less clear is the effect of folic acid supplementation on other birth defects, such as cleft lip, with or without cleft palate.

In this week’s BMJ, Wilcox and colleagues report a population based case-control study from Norway, which shows that supplementation with folic acid in the periconceptional period reduces the risk of cleft lip, with or without cleft palate, in newborns. Supplementation with 400 µg of folic acid for three months around conception was associated with a 40% reduction in the prevalence of cleft lip, with or without cleft palate, at birth (adjusted odds ratio 0.61, 95% confidence interval 0.39 to 0.96). Exposure data were obtained retrospectively one year after conception, but the reliability of the data was enhanced by evaluating information on pill bottle labels and brands. This was a large, well designed study that used high quality registries; this enabled efficient early case identification and control selection. The study supports findings from other recent studies, including a large meta-analysis. The evidence that folic acid reduces malformations is robust, but how much is needed and how it should be taken is less clear. Despite these uncertainties, 400 µg folic acid per day has been estimated to prevent a large proportion of neural tube defects. Three public health strategies for reaching this dose have been suggested. The first is for women to eat a diet rich in natural folates. However, it is difficult to reach this dose with diet alone, and folate in the diet has lower bioavailability than synthetic folic acid. The second is for women to take supplements of folic acid in the periconceptional period. This strategy is compromised by low compliance and high rates of unplanned pregnancy. Studies have shown that although mass media campaigns increased awareness up to nearly 80%, fewer than 50% of women followed the recommendations. The third strategy is mandatory fortification of staple foods (such as wheat, corn flour, or rice). This would achieve coverage in a large section of the population. Countries differ substantially in their choices of preventive strategy.

The World Health Organization has recommended supplementation with 400 µg of folic acid in the periconceptional period. Fortification of food is mandatory in an increasing number of countries (Brazil, Canada, Chile, Costa Rica, Jordan, South Africa, and the United States). In general, however, Europe has not followed, despite the finding that even suboptimal fortification (for example, 180 µg/day in the US) greatly reduces neural tube defect rates. Further support for mandatory fortification of food comes from a cohort study showing that simply recommending women planning pregnancy to take folic acid is not enough to substantially reduce the prevalence of neural tube defects at birth. Accumulating evidence of a protective effect of folic acid supplementation on the prevalence of oral cleft defects also supports the introduction of mandatory food fortification. However, in many European countries mandatory fortification has been limited by theoretical concerns. These include the potential of masking symptoms of vitamin B12 deficiency, interactions with certain drugs (antifolates), and other unrecognised adverse effects such as the risk that some women may have idiosyncratic reactions to folic acid even in small amounts (and others might need far larger doses for a preventive or therapeutic effect). But mandatory folic acid supplementation to achieve around 180 µg/day on average and 1000 µg/day at maximum holds little risk of complications. Despite this, questions about adverse effects and long term effects of mandatory food fortification remain unanswered, and any change in diet must be closely monitored.

What is Europe waiting for? A common argument is that introducing mandatory fortification to reach a relatively small group (women getting pregnant) is not a good enough reason to intervene at population level. If fortification would also reduce the burden of major disorders such as cardiovascular diseases and dementia the case might be different. The risks of these disorders increase with high plasma concentrations of homocysteine, and folic acid supplementation can reduce these concentrations in humans. However, definitive evidence (such as data from randomised controlled trials) of a protective effect of folic acid on these two diseases has yet to be found. In theory, any clinical improvement could have a long latency period, which could make it difficult or impossible to detect even in a large randomised controlled trial.

So, if this is the kind of evidence that Europe is waiting for mandatory fortification with folic acid may never happen. If this is the case, we will lose the chance of decreasing the burden of 4500 neural tube defects that occur each year in the European Union alone, not to mention the effect on cleft lip with or without cleft palate shown by Wilcox and colleagues.
Housing and health

Heating improvements may hold most promise for developing healthy housing policy

It has been known for centuries that housing and health are inextricably linked. However, most of the evidence so far comprises cross-sectional studies, which can only assess the relation between housing and health outcomes rather than provide convincing evidence that better housing improves health. A systematic review of intervention studies (carried out in 2001) found that housing improvement may lead to small improvements in self reported physical and mental health and reductions in some symptoms, but adverse effects on health are also possible.1 However, the evidence is patchy and robust study designs are rare. Of the 18 studies identified in the review, six were prospective controlled studies and only one was a randomised controlled trial.1

In this week’s BMJ, Howden-Chapman and colleagues report a large randomised controlled trial from New Zealand assessing whether insulating older houses increases indoor temperatures and improves occupants’ health and wellbeing.2 The relevance of such studies to decision making in public health is emphasised in the UK government’s Wanless report, which examined the cost effectiveness of taking action to improve the health of the whole population and to reduce health inequalities.2 The report highlighted the almost complete lack of an evidence base for the effectiveness and cost effectiveness of public health and social interventions. The report also identified the need to collect better evidence of the effects of interventions in the housing sector.

The trial by Howden-Chapman and colleagues directly addresses this need. Their study included a cost-benefit analysis.4 The findings suggest that improving the indoor environment may lead to improved self rated health (adjusted odds ratio 0.50, 95% confidence interval 0.38 to 0.68), fewer visits to a general practitioner (0.73, 0.62 to 0.87), fewer days off work (0.62, 0.46 to 0.83), and fewer days off school (0.49, 0.31 to 0.80).

In addition to the use of a randomised controlled trial design, the strengths of the study include retention of more than 75% of the original participants and a large final sample size (>3000). This in a field in which studies are small (rarely more than 200 participants) and retention is rarely more than 50%, if reported at all.1 Funding, personal commitment, and expertise are likely to explain much of this study’s success, but the research team also ensured the commitment of the housing agencies that delivered the intervention.3

The lack of consistent health impacts detected in previous prospective controlled studies may partly be explained by variation in the actual intervention delivered and the varying potential to benefit from the investment. In the New Zealand trial, not everyone in the intervention group received the full intervention package.2 3 However, area based programmes may deliver improvements regardless of individual need at baseline. In one recent controlled non-randomised study of housing led neighbourhood regeneration, about two thirds of residents reported no housing problems at baseline, so limiting the potential to improve conditions.6 The small sample sizes in previous studies often preclude further analysis of subgroup effects according to the extent of improvements. The New Zealand trial, however, may be large enough to allow investigation of a dose-response effect, taking into account the range of improvements delivered.

Heating and energy efficiency measures can improve the indoor environment and also alleviate fuel poverty (when a household spends more than 10% of its income on fuel). The combination of greater warmth and reduced household expenditure may be a key mechanism through which health effects occur. Previous
The Pharmaceutical Price Regulation Scheme
Proposals for a new drug pricing mechanism in the NHS are welcomed

Early last week, the Office of Fair Trading (OFT) published its report on the Pharmaceutical Price Regulation Scheme,\(^1\) a uniquely British mechanism for determining the prices the National Health Service pays for brand name drugs (currently costing around £8bn (£12bn; $15.6bn) a year). For 18 months the enquiry team had analysed the scheme, heard evidence, looked at arrangements in other countries, and modelled alternatives in an NHS context. Early on Tuesday 20 February it delivered its verdict: the scheme was no longer fit for purpose and needed to change.

The Pharmaceutical Price Regulation Scheme (formerly the Voluntary Price Regulation Scheme) has been running since 1956. It is a voluntary arrangement between the Department of Health and individual drug companies, which determines the prices companies can charge the NHS for their drugs.\(^2\) The scheme has helped keep drug companies based in the United Kingdom in good stead since its inception.

The question that now arises is to what extent the scheme serves the purposes of industry rather than the interests of patients. This question has been raised in at least two parliamentary health select committee enquiries in the past 13 years,\(^3\)\(^4\) but this is the first time that a detailed and specific “public” investigation has been undertaken. The enquiry team has had sufficient resources, expertise, and access to otherwise confidential material to do the job thoroughly. Moreover, the team has published the results in a detailed yet accessible manner.

The purposes of the scheme are clearly set out in the agreement of November 2004 (agreements are negotiated every five years; the current arrangement came into force in January 2005 and is due to end in 2010).\(^2\) From the start, it is clear that the goals of the scheme are compromised as they present an insurmountable conflict—the scheme is tasked to secure the provision of drugs for the NHS at “reasonable prices” while simultaneously determining prices that are high enough to “sponsor” (more recently called “promote”) the wellbeing of UK based companies. Interestingly, this has always been the way in which UK government worked to ensure that UK manufacturers were competitive in an international market.

The workings of the scheme are simple: each year companies give the Department of Health details of their historic capital (the monies they have tied up in plant, machinery, factories, raw materials, etc). After taking into account allowances for costs on research and development, promotion, and information, the department uses a formula to determine the total amount the company can charge the NHS (“return on capital”) for all of its products (its basket of drugs). To reach the permitted return, companies can price their drugs high at the time of launch. Moreover, if the return on capital is not reached each year the company can raise the prices of other drugs in its basket. Conversely, if the permitted return is exceeded, the company is required to reimburse the excess to the NHS (“in reality the reimbursements are negligible”).

The strands of the scheme are such that many of the outcomes run counter to the interests of the NHS. High prices at launch are essentially inevitable, drugs are developed (and rewarded) that do not necessarily offer clinical advantage, and the industry alone determines prices according to what they believe to be their product’s value. Moreover, as the prices have been

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Regulation of doctors

UK government white paper puts patient safety at the heart of medical practice

On 21 February 2007, the government published its white paper *Trust, assurance and safety—the regulation of health professionals in the 21st century*, which sets a framework to assure the safety of patients and quality of care. The paper considers the English chief medical officer Sir Liam Donaldson’s review of medical regulation, *Good Doctors, Safer Patients*; the Department of Health’s report, *Regulation of the Non-medical Healthcare Professions*; and subsequent consultations with professionals and lay people.

The main areas covered by the white paper are how to assure the safety of patients in situations where a doctor’s performance or conduct pose a risk, the introduction of an effective system of revalidation, and modifications to the role and function of the General Medical Council (GMC).

Patient safety is central to the proposals. At local level the value of attempts to ensure quality in the current National Health Service is recognised. In the current system poor medical performance is dealt with separately by the employer (NHS) and the regulator (GMC). This may result in a “regulatory gap,” whereby a doctor may be providing care that does not inspire the confidence of his or her colleagues and employer but his or her performance is not so poor that referral to the GMC is indicated. Under the new proposals, “GMC affiliates” (senior clinicians) are supposed to bridge this gap by providing guidance to employers on local investigations, and to enter “recorded concerns” against a doctor’s GMC registration. This novel idea, probably too expensive as a local solution, will be piloted in England at regional level.

At national level two key changes are proposed. The first is a standard of proof for adjudicating on concerns about a doctor’s fitness to practise. The previous criminal standard of proof—beyond reasonable doubt—now changes to the civil standard—the balance of probability. This change was proposed by Dame Janet Smith in the fifth Shipman report. The civil standard will be flexibly applied using a sliding scale, with serious cases needing evidence at the level of the criminal standard. Sliding scales, used by other healthcare regulators and the Financial Services Authority, have a credible track record. However, where a doctor’s reputation is at stake and a “NICE blight”). Finally, any notion of reimbursement or sponsorship would be lost. Industry will not like these changes. Because the fine details for determining perceived clinical value are not yet spelled out, companies may be concerned that prices could be forced down. They may worry that the stability of financial returns will no longer be guaranteed, which would pose difficulties in long term investment. Until now they have shared the risk of drug development with the NHS (if things went wrong they could expect reimbursement); under the new scheme they would be alone.

The OFT deserves congratulations for its enquiry into the Pharmaceutical Price Regulation Scheme and for the recommendations made. The old system is arcane and archaic and has to change, and the OFT has provided a sound basis for debate and offers an appealing alternative. The mystery is that the system was not changed years ago.

problems will be supported, and that options for rehabilitation and retraining will be made available. This is to be welcomed but will require a change in culture from both the profession and the public to avoid defensive practice and a climate of fear.

Doctors accept that revalidation is needed, and half of patients think that it already happens. The chief medical officer’s previously proposed two tier approach of relicensure (to enable doctors to remain registered to practise) and specialist recertification (to maintain the specialist and general practice registers) is endorsed.6 The new system of relicensure will be based on the generic standards in Good Medical Practice,7 will involve an annual appraisal, which will now contain a summative element, and any concerns raised by the medical director or GMC affiliate will need to be resolved. A 360º feedback tool (to give feedback on performance from several sources) will be piloted to support the process. Care will be needed to ensure that the valued developmental aspect of appraisal is not lost and that new 360º feedback tools have a positive effect on clinicians’ practices.8

Specialist recertification, the responsibility of the medical royal colleges, will be a comprehensive assessment against the standards that apply to the particular medical college. Information required may include clinical audit, simulator tests, knowledge tests, patient feedback, observation of practice, and continuing professional development activities. Standards will need to be set, agreed with stakeholders, and tested by each specialty.

Clarity is essential for individual practitioners as to what information is required for both relicensure and recertification. In terms of how the process might work in practice, doctors have been shown to prefer simple systems that have a clear structure, with support for individuals.9

The changes to the GMC are fewer than were initially proposed. Members will now be chosen by an appointment commission, with equal numbers of lay and medical members being appointed. The GMC will be accountable to parliament, but independent from government. Crucially, the GMC’s international reputation and expertise in undergraduate education is recognised and their proposed model of undergraduate, postgraduate, and continuing professional development boards is accepted.

This white paper sets patient safety at the heart of medical practice. Medical regulation has evolved. The professionally led regulation of the 1990s now gives way to partnership regulation with our patients and the NHS. Operational details need to be determined, particularly in Scotland, Wales and Northern Ireland, and many will require legislation. The challenge now is to work with our colleagues, professional groups, and patients to deliver a fair regulatory system that can inspire the confidence of all.


Management of breast cancer in women with BRCA gene mutation

Breast conservation surgery is safe in selected women when combined with adjuvant therapy

Germline mutation may account for up to 10% of breast cancers.1 Known mutations in the BRCA1 and BRCA2 genes are responsible for about 45% of breast cancer susceptibility syndromes (genetic abnormalities that put patients at high risk of developing breast cancer), which are inherited in an autosomal dominant pattern.1

Variants of the BRCA genes increase the overall risk of developing breast cancer and are also associated with a high risk of early onset breast cancer. Once BRCA1 or BRCA2 mutation has been confirmed, preventative strategies include bilateral prophylactic mastectomy and intensive screening with possible hormonal manipulation. Although prevention of primary breast cancer with mastectomy reduces the risk of breast cancer by 89.5-100%, understandably it is unacceptable to many women.2,3 This is because it has a negative impact on self image, it involves major surgery, it cannot remove all risk, and patients may find it hard to accept its theoretical benefit as not all carriers develop breast cancer.

For women with breast cancer unrelated to BRCA (“sporadic breast cancer”), breast conserving surgery combined with radiotherapy is used where appropriate and is now regarded as the standard of care.4 Conceptually, breast conserving surgery may seem unwise in women with BRCA related breast cancer because...
of the potential risk of in-breast tumour recurrence. After more than a decade of research the optimal local treatment for these women remains a source of contention.

The largest series to date examined breast conserving surgery in 160 women with BRCA mutation and found a 10 year in-breast tumour recurrence of 12%.\(^5\) In women with sporadic breast cancer, the cumulative 10 year in-breast tumour recurrence in five national surgical adjuvant breast and bowel project trials was 8.7%.\(^6\) The risk in women with BRCA mutation is therefore slightly higher than in women without, though it seems to be acceptable, as previous trials in women with sporadic breast cancer have reported in-breast tumour recurrence between 10% and 15% at 10 years. Furthermore, when women with BRCA related breast cancer were compared retrospectively with age matched controls with sporadic breast cancer, no significant difference was found in the risk of in-breast tumour recurrence, provided the women with BRCA related breast cancer had undergone bilateral prophylactic oophorectomy.\(^5\) However, women with BRCA mutation who did not have prophylactic oophorectomy had twice the rate of in-breast tumour recurrence relative to controls.\(^5\) Although the risk of ovarian cancer in women with BRCA mutation is much lower than the risk of breast cancer, bilateral prophylactic oophorectomy reduces the risk of a new breast cancer as a result of hormone deprivation.\(^7\) Prophylactic oophorectomy reduces the risk of breast cancer by about 70% in women with BRCA mutation, and short term hormone replacement therapy after surgery does not seem to negate this protective effect.\(^8\)

Apart from an increased risk of in-breast tumour recurrence, women with BRCA mutation who have breast conserving surgery also have a greater incidence of new primary tumours in the contralateral breast than women with sporadic breast cancer (42% vs 9% at 12 years).\(^9\) Bilateral prophylactic oophorectomy combined with tamoxifen reduces the risk of contralateral breast cancer by as much as 50% in women with BRCA mutation, supporting hormonal intervention.\(^9\)

Tamoxifen reduces the risk of in-breast tumour recurrence in these women, and this protective effect increases with the duration of treatment (up to four years).\(^10\)

The only specific BRCA chemoprevention studies have been small single centre trials. Several randomised controlled trials have assessed tamoxifen as a chemoprevention strategy in high risk patients, however, and post randomisation analysis of those with BRCA mutation has shown tamoxifen to be up to 50% effective in preventing breast cancer in these patients.\(^11\) In addition, tamoxifen can reduce the incidence of a second primary cancer by 50% in women with BRCA mutation.\(^11\) So what does all this mean for patients and the clinicians advising them? Overall, the evidence indicates that breast conservation is safe in selected women with BRCA related cancers when combined with optimal adjuvant therapy.\(^3\) Recent data show that women who have breast conserving surgery rather than mastectomy for breast cancer score higher on quality of life measures, and these findings are probably applicable to women with BRCA mutation.\(^12\) However, women with BRCA related breast cancer should be informed of the relative risks and benefits of bilateral prophylactic mastectomy compared with breast conservation so they can be supported in making their own decisions.

HIV funding: debate misses the point

As one who has lost five out of 11 siblings to HIV, I cannot but be aware of the magnitude of HIV. Though the figures of England and de Lay et al differ,1 2 the element of relative overspending on HIV compared with other health and social developmental sectors is obvious.

Both miss the crucial point that HIV is the only tropical disease receiving anywhere near Western rates of health funding. The reasons for this include the global nature of HIV, the wages and expenses of expatriate health workers, and the many groups working with HIV in the tropics. England could have argued that the money channelled into HIV should be spent through local national health departments. Some African non-governmental organisations and de Lay et al may argue for the status quo, which has created, in some cases to the detriment of health and governance institutions, parallel institutions as it benefits their causes. England should have presented a breakdown of how the HIV funding is being used. He may find that only a small fraction trickles down to African patients with HIV and that a significant chunk bounces back to the West.3

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PANDEMIC FLU

Look at all the evidence before stockpiling amantadine

Tsiodras et al propose testing amantadine to see if any benefits could accrue in combination with neuraminidase inhibitors in pandemic flu.1 2 The principal attraction seems to be low cost. Although they quote resistance and harms as well as lack of “any demonstrable reduction in transmissibility or pathogenicity,” this does not seem to deter them from their proposal.

Had they consulted the Cochrane Library, they would have discovered that amantadine (the only adamantane for which we have a reasonable knowledge base) relieves or suppresses symptoms if taken within 48 h, but it does not prevent infection with influenza A viruses or stop their nasal excretion. This is the key finding in a pandemic as apparently healthy individuals devoid of symptoms and feeling good because they have taken “the pill” would be spreading influenza viruses in the community through contact and droplets. Amantadine suppresses symptoms but not infection, it does not prevent or even diminish the risk of influenza communication, it causes unacceptable harms, resistance to it is widespread and swiftly induced: it is a very dangerous drug, especially in a pandemic.2

Would the authors give prophylactic amantadine to essential workers knowing it causes gastrointestinal symptoms (mainly nausea, odds ratio 2.56; 95% confidence interval 1.37 to 4.79) and insomnia and hallucinations (2.54; 1.50 to 4.31) and caused withdrawals from the trials because of adverse events (2.54; 1.60 to 4.06)?3 Would they give it to ambulance drivers, train conductors, and helicopter pilots?

If pharmaceutical intervention is required to help contain a pandemic, then neuraminidase inhibitors are far safer and more effective than adamantanes.4 No benefit, but a lot of harm will accrue with continued use of amantadine. That is what all available comparative evidence shows.

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Competing interests: TJ is the first author of both relevant Cochrane reviews. He holds no stock or shares and has not received any fees in the past five years from any organisation which could benefit or be harmed by this letter.

1 Tsiodras S, Mooney JD, Hatzakis A. Role of combination antiviral therapy in pandemic influenza and stockpiling implications. BMJ 2007;334:393-4. (10 February.)

It’s only numbers

Both England and de Lay et al play the numbers game of statistics, economy, and modelling of the future.1 2 But I guess that none of the authors is HIV positive or a doctor and so can sit safely behind a desk jettisoning numbers to the audience.

HIV, tuberculosis, and malaria are among the greatest killers of the poorest people in the world, claiming about 1 million lives each per annum, or 114 people every hour of every day, disabling the future economies and existence of the poorest nations. Yet, has the world conquered even one of the big three? If a glimmer of hope to save the future deaths came from heavy investment in immune damage from any of the big three, then every penny spent is worth while. To change public attitudes will take decades, unlike the immediate and positive effect of Princess Diana holding the hand of a patient with AIDS before the media. Until then money must be invested in trying to stem the tide of death for today and tomorrow.

“Fielding while Africa burns” is a common issue, when words from desk jockeys take centre stage and engage debate and not action. No author brings a primary solution to the table, but rather each mildly lambasts world authorities and nation leaders for fiscal mishandling. A weak debate. In the time it has taken you to read this another person has died of AIDS—a fact of life.

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Competing interests: None declared.
WHO FUNDING

World Health Organization refutes allegations

The World Health Organization categorically rejects the allegations made in a recent story in the BMJ which imply that WHO solicits money from the pharmaceutical sector through independent organisations by circumventing its own rules.1

As the BMJ correctly reports, WHO has clear guidelines against seeking or accepting funds from commercial enterprises or through third parties where there would be a conflict of interest.

When WHO does accept donations or funds from pharmaceutical companies—for example, donations of vaccines or medicines—those donations are clearly accounted for and transparently reported.

In this specific case, Dr Benedetto Saraceno was very clear. He had never asked that funds be solicited from the pharmaceutical sector, and he declined the funds that were offered.

WHO is concerned about the BMJ’s depiction of Dr Saraceno. He is a professional of deep personal integrity. In the 10 years he has been with WHO, Dr Saraceno has tirelessly worked to highlight the public health consequences and grave inequalities faced by the millions of people who are affected by mental, neurological, or behavioural disorders.

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Competing interests: None declared.


RANDOMISED TRIALS

The urge to sprinkle statistics is irresistible

We might be forgiven for believing that Glasziou et al had discovered some hitherto unknown method of causal inference.1 Instead they have merely stumbled across the way in which causes have been identified in everyday life and science throughout history.2

The “mother’s kiss” technique for removing a bead lodged in a nostril is an effective treatment not only because it has been shown to work in case reports but also because it is grounded in elementary principles of physics familiar to every child who has played with a pea shooter. It does not need statistical analysis. Yet, the authors—unable to free themselves of the urge to season the data with a sprinkle of relative risks or P values—neglect the fact that the many examples they provide of treatments with clearly observable effects are widely accepted without the need for statistical tricks.

The obsession with both randomised controlled trials and the statistical approach to causation has clouded the thinking of a generation or more of medical researchers. So much so, that the commonsense notion of causation has been relegated to little more than an afterthought. And this accounts for the dismissive approach to any data not derived from randomised trials. Perhaps, after their damascene conversion, Glasziou et al will campaign for a change in the hierarchy of evidence in favour of data from non-randomised sources.

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Competing interests: None declared.


Beware “Texas sharp shooter” in rate ratios of progression

Glasziou et al’s method of calculating rate ratios of progression (stable unchanging condition before v change shortly after the intervention) is appealing,1 but we need to be wary of a “Texas sharp shooter” effect. This effect is usually associated in epidemiology with the problem of interpreting apparent clusters of disease in space, where the geographical unit of analysis may have been chosen post hoc so as to maximise the apparent density of cases as in the joke about a Texan firing bullets into the wall of a barn and then drawing the targets around the bullet holes to show his shooting prowess.

An analogous problem may occur when calculating rate ratios in the manner described in this article, although the sharp shooting is in time, not space. In the mother’s kiss, the time period used is 10s, which gives a rate ratio of progression of 1440. However, perhaps, the bead dislodged after only 8 s, a rate ratio of 1440/0.8=1800. Alternatively, if the bead had taken 15 s to dislodge, the doctor, nurse, and mother might still reasonably have felt that they should take the credit for the happy outcome. You need to make an a priori decision about the post intervention time frame you will use—presumably based on the maximum length of time after the event you are prepared to attribute any improvement to your intervention.

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Competing interests: None declared.


MORPHINE

Double effect is a myth leading a double life

Kelly Taylor’s request to use morphine “to make her unconscious” under the principle of double effect is a puzzling choice.1

Evidence over the past 20 years has repeatedly shown that, used correctly, morphine is well tolerated and does not shorten life or hasten death.2 Its sedative effects wear off quickly, toxic doses can cause distressing agitation, and it has a wide therapeutic range. The Dutch know this and hardly ever use morphine for euthanasia.3

Palliative care specialists are not faced with the dilemma of controlling severe pain at the risk of killing the patient: they manage pain with drugs and doses adjusted to each patient, while at the same time helping fear, depression, and spiritual distress. Doctors who act precipitously with high, often intravenous, doses of opioids may do so out of compassionate panic, but they are being misled into bad practice by the continuing promotion of double effect as a real and essential phenomenon in end of life care. Using double effect as a justification for patient assisted suicide and euthanasia on the grounds that it is already being done under the rubric of double effect is not tenable in evidence based medicine.4

In end of life care double effect is a myth leading a double life.

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Competing interests: None declared.

1 Dyer C. Dying woman seeks backing to hasten death. BMJ 2007;334:329. (17 February.)


Save COX 2 inhibitors till last for cardiac patients

Susan Mayor LONDON

Cyclo-oxygenase-2 (COX 2) inhibitors should be used only as the last choice after other types of non-steroidal anti-inflammatory drugs (NSAIDs) to relieve chronic pain in people with heart disease or at high risk of it, the American Heart Association has recommended. Its statement, published online in Circulation on 26 February (http://circ.ahajournals.org doi:10.1161/circulation-aha.106.181424), was designed to end any remaining confusion about the cardiovascular risk of these agents.

The association has recommended a stepped approach to treatment. The first step should be non-pharmacological approaches, such as physical therapy and weight loss, for patients with known cardiovascular disease or with risk factors for ischaemic heart disease. Drug treatment should start with agents with the lowest reported risk of cardiovascular events, before other agents are prescribed, and at each step account should be taken of the risk-benefit balance.

First line drug choices include paracetamol (acetaminophen), aspirin, tramadol, and short term use of other narcotic analgesics. If these fail to achieve adequate pain control, the next option is non-acetylated salicylates, such as naproxen.

The association recommended NSAIDs that aren’t COX 2 inhibitors if pain is still inadequately controlled, then NSAIDs with some COX 2 activity as the next step, and lastly COX 2 selective NSAIDs.

The committee considered the risk of all three of these classes to be sufficiently high to require that patients taking them should be monitored regularly for sustained hypertension (or worsening of prior blood pressure control), oedema, worsening renal function, or gastrointestinal bleeding. See pp 436, 450.

Doctors lose power to run their profession

Clare Dyer BMJ

The General Medical Council will lose the right to decide whether doctors’ misconduct makes them unfit to practise, in the biggest shake-up of medical regulation in the United Kingdom for 100 years. The GMC will continue to set standards and investigate allegations of serious misconduct by doctors, but the right to adjudicate will pass to a separate body, probably an independent tribunal with legal, lay, and medical members.

The reform is outlined in a white paper on the regulation of doctors issued this week by the Department of Health. The GMC will have statutory responsibility for the oversight of education. Two GMC boards will cover undergraduate education and continuing professional development, and the Postgraduate Medical Education and Training Board will continue as the third. This arrangement will be reviewed in 2011 to see if “further integration is desirable.”

Under the reforms, which build on Good Doctors, Safer Patients, a review in July 2006 by Liam Donaldson, the chief medical officer for England, doctors will have their skills and competence checked every five years. Doctors who fail the revalidation process will continue as the third. This arrangement will be reviewed in 2011 to see if “further integration is desirable.”

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The civil standard would operate on a sliding scale, with stronger evidence needed in the most serious cases, so the standard would be virtually indistinguishable from the criminal standard. The GMC will have statutory responsibility for the oversight of education. Two GMC boards will cover undergraduate education and continuing professional development, and the Postgraduate Medical Education and Training Board will continue as the third. This arrangement will be reviewed in 2011 to see if “further integration is desirable.”

The loss of the GMC’s role as adjudicator was accepted by the royal colleges and by the GMC itself. Graeme Catto, its president, cited “the difficulty of being seen or perceived to act as judge and jury.” The council will also gain the right to appeal decisions that it regards as too lenient.

Most controversial for doctors is the proposed move from the criminal standard of proof—beyond reasonable doubt—to the lower civil standard—on the balance of probabilities—in fitness to practise cases.

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The three papers—Trust, Assurance and Safety: the Regulation of Health Professionals in the 21st Century; Learning from Tragedy: Keeping Patients Safe; and Safeguarding Patients—are available at www.dh.gov.uk.
UK nears European average in proportion of GDP spent on health care

Anne Griffin [BMJ]

Between 2000 and 2004 the increase in spending on health in the United Kingdom as a percentage of gross domestic product (GDP) was bigger than the increases in France, Germany, and Italy, says a new report from the Office of Health Economics (OHE).

This means that the gap between the UK and other European countries such as Germany and France in total spending on health as a percentage of GDP has narrowed. Total spending on health care in the UK rose to an estimated £120bn (€180bn; $240bn) in 2006, representing 9.4% of GDP, up from 7.1% in 2001. Referring to Tony Blair’s promise to bring NHS funding up to European levels, Jon Sussex, the OHE’s deputy director, said, “The spending side of the promise seems to have been kept.”

A rise in the numbers of doctors and nurses in the UK health services is one effect of the increase in spending on health, says the OHE. The number of doctors per 1000 people in the population rose from 1.9 in 2000 to 2.3 in 2004. Although the growth in the number of doctors per 1000 people is higher than that in other European countries, the UK still lags behind Italy, France, and Germany in the overall number of doctors per 1000 of the population. “We spend more of our money on things other than doctors,” said Mr Sussex.

By contrast, the number of nurses in the UK is among the highest in Europe: in 2005 the average was 9.3 nurses per 1000 people. In 2004 Germany had one of the highest levels of nurses, at 9.7 per 1000 of the population, followed by the UK at 9.2 and France at 7.5.

“For the money we spend we’re getting fewer doctors and more nurses,” summarised Mr Sussex.

The OHE reports other benefits of higher healthcare spending: “In parallel with the increased spending on health care there has been an improvement in key indicators of health, such as infant mortality and life expectancy.”

This year’s compendium also reported an increase in the proportion of births that were caesarean sections, to nearly one quarter. “This is not that mothers are too posh to push,” said Emma Hawe, the OHE’s head of statistics. She attributed the increase to the greater numbers of emergency caesarean sections.

Ms Hawe cited many possible causes for the rise in emergency caesarean sections, including mothers being older. The birth rate among mothers in their early 30s overtook the rate for mothers in their late 20s for the first time in 2004.

But an ageing population did not have to result in a higher rate of caesarean sections, she said.

The OHE Compendium of Health Statistics is available from [www.ohecompendium.org](http://www.ohecompendium.org).

Europe needs several years to prepare for flu

Rory Watson [BRUSSELS]

European Union countries need another two to three years of sustained effort and investment to be able to respond effectively to any flu pandemic, the Stockholm based European Centre for Disease Prevention and Control has said.

In its first review of national preparedness among 25 countries of the EU (all the countries except Romania and Bulgaria), as well as Iceland and Norway, the centre has analysed the measures that have already been taken and highlights areas where more work is needed.

Zsuzsanna Jakab, the centre’s director, acknowledges that much progress has been made over the past two years, but when presenting the report last week she identified two main challenges.

She said, “We must maintain the current political climate and momentum to continue and finish the work. That will take two to three years. We need to further develop national plans so that we have a government wide pandemic plan.”

All EU countries now have national health sector preparedness plans and are in the process of making them operational. This effort has been accompanied by considerable investment in flu research and in building up stockpiles of antiviral drugs.

However, the centre says that preparations have not reached the point where it is possible to be confident that four key responses to a pandemic will function smoothly. The primary care system must be able to deliver treatment to most of those in need of it. Hospitals should be in a position to deliver acute care to patients with flu while continuing to treat other conditions. Essential services, such as food and fuel supplies, must continue to function at the local level. And vaccines should reach primary care services within six months of the outbreak of a pandemic.

The centre’s report, which will be updated to include all 27 EU countries later this year, specified areas where improvements are still necessary:

• All health sector plans must be expanded to include business continuity plans for essential public services
• The plans must cover primary care and hospital services and address the logistics of rapidly distributing antiviral drugs to patients
• National plans must be devised so that they work with plans drawn up by neighbouring countries and not against them
• Preventive efforts against seasonal flu must be stepped up, both to reduce the thousands of deaths from the disease each year and to improve overall preparations against a more deadly strain
• Flu research should be extended.

NHS trusts don't meet standards expected for children

Robert Short LONDON

NHS trusts in England are struggling to meet the standards of services for children in hospitals laid down by the national service framework for children. This is the conclusion of a review of hospitals’ services for children by the Healthcare Commission, England’s health watchdog.

The review, which the commission carried out in 2006, looked at 157 NHS hospital trusts, two primary care trusts, and one partnership trust.

Overall 75% of trusts were rated “fair” or “weak” for the services they provide to children. Just 21% were rated as “good” and 4% as “excellent.” The six service types assessed in the review were emergency care, day case care, outpatient’s services, inpatients’ care, emergency surgery, and planned surgery.

The review found that many hospitals are not systematically providing training in the needs of children in several key areas, including basic child protection, communication, play, life support, and pain assessment.

More than half (58%) of child protection services do not meet the standard that 95% of nurses in any one service where children are treated should have up to date, basic training.

Only 24% of nurses and 7% to 9% of surgeons and anaesthetists have had formal training in communicating with children. Also, access to staff who specialise in play varies greatly.

In 8% of hospital trusts surgeons do not operate on enough children to maintain their skills to carry out surgery on very young children. And 16% of paediatric inpatient units carry out less work with young children than the recommended minimum professional level.

In 12% of hospitals there was insufficient cover by staff during the day to ensure effective life support in serious emergencies. This figure rose to 18% percent of hospitals for night cover.

The review also found that all but eight local hospitals that did not have adequate life support cover have now provided assurance that such cover is in place.

Improving Services for Children in Hospitals: Improvement Review is available at: www.healthcarecommission.org.uk.

New once a day, fixed dose antimalarial is now available

Anne Griffin BMJ

A new antimalarial combination treatment to be taken as a fixed dose once a day has been developed by a non-profit organisation for use in developing countries. The combination of artesunate and amodiaquine will be known by the brand name Coarsucam in private sector sales.

The non-patented drug is the first result of the drugs for neglected diseases initiative (DNDi), a non-profit product development organisation, and was produced in partnership with one of the world’s largest drug companies, Sanofi-Aventis. Two other major sources of funding were Médecins Sans Frontières and the European Commission.

“Tens of millions of people could benefit from this treatment each year,” said Bernard Pécout, executive director of the initiative. “The new artesunate-amodiaquine fixed dose combination has been adapted to patients’ needs.”

Artesunate is a water soluble derivative of artemisinin, which comes from the shrub Artemisia annua, long used in traditional Chinese medicine. The World Health Organization recommends treating malaria with artemisinin in combination with another antimalarial drug rather than on its own to prevent the development of resistance.

“We urgently need affordable drugs but also combination therapies with an artesunate based combination because this is the recommendation of the WHO,” said Awa Coll-Seck, executive director of the Roll Back Malaria Partnership. “We really welcome the focus of this initiative on affordable drugs and on drugs reaching a lot of children under five.”

Until now the combination of artesunate and amodiaquine was available only in multi-tablet formulations. The new drug is a single tablet, which ensures that the two drugs are taken together and in the correct proportion.

“We wanted to make it easy for patients to be compliant and to prevent resistance,” said Jean-Rene Kiechel, manager of the fixed dose artesunate based combination therapies project at DNDi. “In the field you need to have simplicity.”

The drug is also the first combination of artesunate and amodiaquine that is available at three strengths suitable for children, including for infants.

To public sector organisations the three day course of the drug will cost less than $1 for adults and less than $0.50 for children aged under 5 years. Dr Pécout said, “The fact that the artesunate and amodiaquine six dose combination drug is made so affordable right from the start and is not under patent removes a significant barrier to its availability.”

More information is available at: www.actwithasaq.org.
US health experts call for a centre to compare treatments

Janice Hopkins Tanne NEW YORK
A group of leading health policy experts has said that the United States needs a centre to compare the value of health treatments, similar to the United Kingdom’s National Institute for Health and Clinical Excellence (NICE).

The group was brought together last month in Washington, DC, by the Health Industry Forum, which is based at Brandeis University and aims to develop solutions to problems in health care; Kaiser Permanente; and the industry group America’s Health Insurance Plans. It comprised Stuart Altman, dean of Brandeis University; Gail Wilensky, former administrator of the US Healthcare Financing Administration; Kathy Buto, vice president for health policy government affairs at Johnson & Johnson; and Jack Rowe, a gerontologist who retired as chief executive officer of the health insurance firm Aetna and was previously president and chief executive officer of Mount Sinai Medical Center in New York.

The cost of health care weighs heavily on the US economy, the business community, and state and federal governments, the members agreed.

“The ability of this very rich country to continue to spend money without regard to its benefits is … coming under increasing scrutiny,” Dr Altman said. The US does not compare health benefits with costs, he said, as the UK, Australia, Canada, and Germany do.

Dr Wilensky said that US health spending, adjusted for inflation, is growing 2% to 2.5% faster than the economy. That will mean “serious distortions” to federal budgets and the economy, she said. She proposed cutting the growth in spending to 0.5% or 1% faster than the growth in the economy.

“We need to find ways to spend smarter,” she said. “Drugs and devices are all fine and important, but we need to go where the money is … in medical procedures.

“We just don’t know very much … about comparative clinical effectiveness or comparative cost effectiveness.”

She suggested a centre to compare clinical effectiveness of procedures, drugs, and devices and a separate centre to evaluate cost effectiveness.

The panelists discussed whether these centres should be part of a government department or agency, a federally funded research agency, or completely independent, or whether they should resemble respected institutions such as the Institute of Medicine or the Federal Reserve Board, which governs banking and finance.

They agreed that it should be a public-private organisation.

The group’s discussion is available at www.kaisernetwork.org/health/cast/hcast_index.cfm?display=detail&hc=2043

Misuse of prescription drugs could soon exceed that of illicit narcotics, UN panel warns

John Zarocostas GENEVA

The misuse and trafficking of prescription drugs is growing fast worldwide and is set to become as big a problem as illicit drugs, a report by the International Narcotics Control Board warns. Governments need to step up efforts to stem the problem, it says.

The diversion and misuse of narcotic drugs in the form of pharmaceutical preparations, however, also continues to be under-reported, it says.

The board recommends that all governments should “promote the rational use of narcotic drugs and psychotropic substances,” in accordance with the recommendations of the World Health Organization.

The report by the independent, quasi-judicial body, which monitors the implementation of UN drug control conventions, points out that in the past decade consumption of opioid analgesics increased by more than 100% in more than 50 countries around the world.

It says that in the United States “the gradual increase in the use of sedatives, tranquillisers and narcotic drugs other than heroin among the general population has resulted in prescription drugs becoming the second most abused class of drugs after cannabis.”

Such prescription drugs have effects, it says, that are similar to those of illicit drugs when taken in inappropriate quantities and without medical supervision.

The number of Americans who misused controlled prescription drugs “nearly doubled from 7.8 million in 1992 to 15.1 million” in 2003, it notes. The misuse of prescription drugs such as fentanyl, hydrocodone, and oxycodone, it says, has led to a rising number of deaths in North America and Europe.

Large scale diversions of buprenorphine, an analgesic that is prescribed for substitution treatment of drug dependency, have also been reported in India and in European countries such as France, where it is widely used in the treatment of heroin addicts.

During 2001-5 the global consumption of buprenorphine more than tripled from 420 million daily doses to 1.5 billion daily doses. Illicit preparations of buprenorphine have been found to be misused in Iran, Pakistan, the United Arab Emirates, the Czech Republic, Finland, Georgia, and Mauritius, among other countries.

In the United Kingdom the misuse of methadone alone or in combination with other drugs, says the study, “was implicated in 173 drug related deaths in 2005.”

Misuse of fentanyl is also a growing problem in North America, Europe, and Russia.

The 2006 annual report of the International Narcotics Control Board is available at www.incb.org.
**Guidance recommends asking pregnant women about mental health**

**Susan Mayor** LONDON

Women should be asked about their mental health as much as their physical health as part of antenatal and postnatal care, new guidance for the NHS in England recommends.

The guidance, developed by the National Institute for Health and Clinical Excellence (NICE), the body that advises on the use of treatments by the NHS, recommends that healthcare professionals should ask women in antenatal and postnatal care about their mental health on a regular basis to detect ongoing and new mental health disorders. Recent estimates indicate that as many as one in seven women experience a mental health disorder in the antenatal or postnatal period.

David Tomson, a GP and consultant in patient centred primary care at North Shields and chairman of the guideline development group, said, “This guideline really puts antenatal and postnatal mental health on the map and says to healthcare professionals and women that it is time to take mental health during this period seriously. Treating mental health problems during and following pregnancy is as important as treating physical problems such as high blood pressure, so healthcare professionals should be asking women about mental health as standard.”

To help healthcare professionals spot mental health problems at an early stage the guideline recommends asking women three simple questions: “During the last month, have you often been bothered by feeling down, depressed, or hopeless? During the last month, have you often been bothered by having little interest or pleasure in doing things? Is this something you feel you need or want help with?”

Women considered to need treatment should be fully informed of all options and make decisions in partnership with healthcare professionals. Doctors should discuss the risks of taking or not taking drugs to treat illness at every stage, taking into account pregnancy and breastfeeding.

The guideline emphasises the importance of access to psychological treatment. NICE guidance is available at [www.nice.org.uk](http://www.nice.org.uk).

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**HFEA allows women to donate their eggs for research**

**Susan Mayor** LONDON

Women in the United Kingdom can donate their eggs for research, provided that they are properly informed of the risks associated with donation and are protected from coercion, the Human Fertilisation and Embryology Authority (HFEA) ruled last week. They will be able to do so even if they are not undergoing fertility treatment.

The independent regulator of in vitro fertilisation (IVF) treatment and embryo research in the UK said in a statement, “Having considered all the information on donating eggs for research, including the risks to women and the outcomes of a public consultation, the authority has decided that women will be allowed to donate their eggs to research, both as an altruistic donor or in conjunction with their own IVF treatment.”

Women have previously been able to donate only spare eggs produced through IVF or in connection with gynaecological treatment such as sterilisation.

Angela McNab, chief executive of HFEA, said that donation for research would be allowed under the same rules as for treatment and would have clear safeguards. “These include having clear separation between the researchers and people carrying out the woman’s treatment, detailed information about the realistic outcomes of the research and the impact the donation would have, and requiring the person getting the woman’s consent [to be] independent from the research team.”

She considered that these safeguards should prevent women being coerced or misled into donating their eggs or being misinformed about the extent to which their donation might affect research.

Women donating their eggs for research will not be paid but can claim back any expenses they have incurred in taking part in the procedure.

The Royal College of Obstetricians and Gynaecologists has called for measures to ensure that egg collection is safe for women. Where eggs are donated for research purposes, the college has recommended that a research oversight committee should monitor women’s reactions to the drugs they receive to promote ovulation.

The college has also said that women should be screened for predisposition to the ovarian hyperstimulation syndrome.

Stephen Minger, director of the stem cell biology laboratory at King’s College London, said that the purpose of the research being conducted was an important consideration: “If a woman is donating eggs for research on infertility, this is not so much an issue, because the eggs are being used in a way that makes donation meaningful.”

But he thought there was more of a problem with using donated human eggs for research involving cloning, including somatic cell nuclear transfer.

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**Joint Account**

**Annabel Ferriman** BMJ

An exhibition exploring the world of conjoined twins, Joint Account, is to open at the Old Operating Theatre museum in Southwark, London, later this month.

The sculptor Shelley Wilson aims to show the psychological effects of being a conjoined twin and the trauma that such twins suffer in wanting both to be separated from their twin and to remain as one. She emphasises that she is not actually sculpting historical or living conjoined twins but using such twins as a metaphor for life.

The main exhibit of wax sculptures is being held in the Old Operating Theatre, next to Guy’s Hospital, which is Britain’s oldest operating theatre and which was hidden for almost a century in the garret of St Thomas’s Church. Joint Account is open from 10 March to 9 April at the Old Operating Theatre, 9a St Thomas Street, London SE1. More information is at [www.thegarret.org.uk/shelleywilson.htm](http://www.thegarret.org.uk/shelleywilson.htm).
### IN BRIEF

**Gates joins forces with Canada on HIV research:** Canada’s federal government will supply $111m (£50m; €73m; ¥96m) and the Bill & Melinda Gates Foundation an additional $28m to establish a new research facility to accelerate development of a vaccine against HIV.

**Deaths from cirrhosis rise in Britain:** Mortality from liver cirrhosis is still increasing in Britain despite a steady decline in most countries worldwide since the 1970s. A study in the *Journal of Hepatology* (doi: 10.1016/j.jhep.2007.01.025) says that from 1980 to 2002 the average annual increase in the number of deaths in England and Wales was 7% in men and 3% in women, while in Scotland it was 9% in men and 7% in women. The age adjusted mortality from cirrhosis in 2000-2 at all ages was 4.2 deaths per 100 000 in women and 8.9 per 100 000 in men.

**Cocoa may reduce risk of heart disease:** Cocoa may lower the risk of heart disease, says a study in the *International Journal of Medical Sciences* (2007;4:53-8), because of its high flavonoid content. It compared the Kuna people of the San Blas islands, who consume more than 900 mg of flavonoids a day, with people in mainland Panama. On the mainland cardiovascular disease was the leading cause of death (age adjusted mortality 83.4 deaths per 100 000 people), but among the Kuna mortality from this disease was 9.2.

**Merck backs down on cervical cancer vaccine:** Merck has said that it will stop lobbying US states to pass laws requiring that preteen girls be vaccinated against cervical cancer, in the face of a growing backlash among parents, doctors, and consumer groups. Merck produces the Gardasil vaccine, which costs $360 (£180; €270) for a three dose regimen. The vaccine was approved last year.

**Lombardy gives funeral options for abortions:** Doctors must now ask women specifically asked for burial. Previously the fetus was disposed of with other human tissue unless the woman specifically asked for burial. This change, voted in by the regional parliament, which is held by a centre right majority, also applies to fetuses younger than 20 weeks. Some gynaecologists object to the new rule, which they say may have negative psychological consequences for the women.

### Internet doctor is suspended for irresponsible prescribing

**Owen Dyer LONDON**

A GP who ran internet consultations for patients was last week suspended for nine months by the GMC for irresponsible prescribing.

Julian Eden was found to have acted irresponsibly, or not in the patient’s best interests, in the cases of three patients and two undercover journalists who applied for prescriptions to his website, e-med [http://e-med.co.uk](http://e-med.co.uk).

The most serious case, the GMC panel found, was that of a teenage boy, referred to as Patient A, who acknowledged in his online application that he was prone to self harm, smoked cannabis, entertained suicidal thoughts, and was in the care of child psychiatric services. Despite this Dr Eden gave him repeat prescriptions of propranolol without a face to face consultation. Patient A eventually overdosed on the drug, but he survived.

Dr Eden admitted irresponsible conduct in his prescribing to two other patients, who both became addicted. Patient X, a Swansea businessman, received 43 monthly prescriptions for the sleeping pill zolpidem over a 26 month period. Eventually he took to forging the prescriptions to save the consultation fee, until he was caught by police.

Fiona Hutson, the only patient named in the case, was able to obtain diazepam and dihydrocodeine from Dr Eden for a year without ever seeing him for a consultation.

Both patients testified that they had misled Dr Eden to obtain extra drugs.

The BMA has called for tighter controls on internet prescribing.

### Government must win over doctors to prepare for funding slowdown

**Adrian O'Dowd LONDON**

Urgent action is needed now to prepare for the slowdown of NHS funding from next year, says a report from the healthcare think tank the King’s Fund. And doctors must be better engaged with the reforms of the NHS if the slowdown is not to damage care of patients, it says.

The report argues that good forward planning will help NHS organisations to cope when funding for the health service changes during the next spending cycle, stretching from 2008-9 up to 2011-12.

The chancellor of the exchequer, Gordon Brown, is expected to announce real term cash increases in the next comprehensive spending review of between 3% and 3.5% per year for the NHS up to 2011-2, which is less than half the annual increase received by the service every year since 2000.

The King’s Fund report says that to help the NHS cope with this reduced funding the government should act now to reduce widespread variations in hospital performance, improve productivity, and win the support of health staff in its efforts to reform the health service.

The report says: “In a labour-intensive industry, doctors, nurses and other health care professionals are the key resource—not just clinically, but managerially too.

“Greater efforts should be made to involve clinicians in the management of the NHS—through responsibility for devolved budgets and involvement and ownership of strategic management decisions.”

The chief executive of the King’s Fund, Niall Dickson, said: “Everyone knows the days of massive growth in health spending will come to an end from 2008. That is bound to be difficult but it should not be a cause for despair.”

The report was produced after a summit held last year that was attended by government officials, health professionals, economists, and policy analysts. *Funding Health Care: 2008 and Beyond* is available at [www.kingsfund.org.uk](http://www.kingsfund.org.uk).
Simple measures can reduce numbers of falls in hospital

**Owen Dyer** LONDON

Nearly one in five falls in UK hospitals could be prevented if hospitals adopted simple precautionary measures, says a report from the National Patient Safety Agency.

The report draws on data from over 205,000 incidents reported to the agency’s national reporting and learning system over a year beginning in September 2005.

These incidents included at least 970 fractures, of which 530 were hip fractures. There were 26 confirmed deaths.

In an average 800-bed acute hospital trust, the report estimates, there will be around 24 falls each week and more than 1200 falls every year. The cost to the average acute trust is estimated to be a minimum of £92,000 per year.

Age is closely correlated with the risk of falling, says the report. The risk typically spikes just before noon, when patients are most active.

Community hospitals see the most falls, with an average of 8.4 incidents per 1000 bed days. The rate is 4.8 falls per 1000 bed days in acute hospitals and 2.1 per 1000 bed days in mental health units. The rate of falls varied hugely between trusts, with some community hospitals reporting 20 times as many falls as others.

The hospital’s physical environment is rarely a major factor, the report finds. Launching the findings, the agency’s director of epidemiology and research, Richard Thomson, said, “Most falls are related to the effects of illness and the ageing process, with very few due to environmental hazards such as wet floors or steps.”

While 35 out of 42 NHS organisations questioned in a voluntary survey reported that they had fall prevention policies, these are sometimes poorly focused, the report found. Many programmes overemphasise the prediction of risk in individual patients, often using unvalidated risk assessment methods, while failing to take simple preventive steps.

**WHAT PATIENTS WERE DOING WHEN THEY FELL IN HOSPITALS IN ENGLAND AND WALES (2005-6)**

![Diagram showing what patients were doing when they fell in hospitals in England and Wales (2005-6)](Image)

*Based on a random sample of 200 incident reports for each location
*Source: National Patient Safety Agency

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**Repeal law that puts “FDA on the payroll of the industry”**

**Zosia Kmietowicz** LONDON

The law that requires drug companies to pay “user fees” to the US Food and Drug Administration for every drug they submit for approval should not be renewed when it next comes before Congress, says a former editor of the New England Journal of Medicine.

Writing an open editorial in the *Boston Globe*, Marcia Angell, who worked for the journal between 1979 and 2000, most recently as interim editor in chief, said that the Prescription Drug User Fee Act has, in effect, “put the FDA on the payroll of the industry it regulates” (www.boston.com, 26 Feb, “Taking back the FDA”).

The act, which was passed by Congress in 1992, “put the fox in the chicken coop” and has changed the focus of the agency, which now serves the industry rather than the public, says Dr Angell.

Nearly all of the $300m (£153m; €230m) that the fees bring to the agency every year have been earmarked to speed up the approval process, she says, money “which the companies recoup many times over by getting their drugs to market faster.”

“But while it’s a small investment for drug companies, it’s a lot of money for the agency, and it has drastically changed the way it operates—creating a disproportionate emphasis on approving brand-name drugs in a hurry,” adds Dr Angell.

“Consequently, the part of the agency that reviews new drugs gets more than half its money from user fees, and it has grown rapidly. Meanwhile, the parts that monitor safety, ensure manufacturing standards, and check ads for accuracy have languished or even shrunk.”

In addition, the part of the agency that approves generic drugs has become so small that it takes twice as long for generic drugs to be approved as brand name drugs. Dr Angell says that there is currently a backlog of 800 generic drugs waiting to be approved. The delay works in the drug companies’ favour, as they are able to add billions of dollars to their profits while their products have no competition from generic products.

Dr Angell also criticises the agency for failing to enforce commitments given by companies at the time of approval of a drug to conduct further safety studies once the drug is on the market.
Prophylaxis with heparin prevents pulmonary embolus in medical inpatients

Anticoagulant prophylaxis with unfractionated or low molecular weight heparins reduces the risk of pulmonary embolus by about half in selected medical inpatients, according to a meta-analysis of nine randomised trials.

The trials included nearly 20,000 patients in total. Twenty of the 9915 (0.2%) patients given prophylaxis had a pulmonary embolus, compared with 49 of the 10,043 (0.5%) who had no prophylaxis (relative risk 0.43; 95% CI 0.26 to 0.71; absolute risk reduction 0.29%). The authors estimate that doctors would have to treat 345 inpatients to prevent one event.

The treated patients, all of whom had currently recommended heparin regimens, were significantly less likely to have a fatal pulmonary embolus than controls (number needed to treat, 400). But the findings for symptomatic deep vein thrombosis were borderline. Prophylaxis with heparin reduces the risk of pulmonary embolus by about half in selected medical inpatients, according to a meta-analysis of nine randomised trials.

Treatments for COPD may not prolong survival

Treatments for chronic obstructive pulmonary disease (COPD) give symptomatic relief, but it’s hard to show that they actually save lives, and some specialists are getting frustrated. “Believe it or not, we still need more data, from even larger trials” wrote one, after the latest supposedly definitive trial ran into difficulties and failed to reach a clinically useful conclusion.

The trial was large (n=6112) and compared four treatments (a long-acting β agonist, an inhaled corticosteroid, both of these combined, and neither of these) for three years in patients with COPD. Four out of 10 patients dropped out of the trial, so the findings were borderline and difficult to interpret. Combination therapy saved more lives than the placebo, but only just, and the difference was not significant in the strict statistical sense (all cause mortality 12.6% v 15.2%, hazard ratio 0.825, 95% CI 0.681 to 1.002, P=0.052).

Neither of the treatments alone reduced mortality compared with placebo.

So where do these results leave patients? Until we have better evidence, combined treatment with an inhaled steroid and a long-acting β agonist should probably be reserved for people with severe disease, says the linked editorial (pp 851-4). Others should stick with a long-acting β agonist alone. Combination treatment reduced exacerbations, improved symptoms, and protected lung function in this trial.

But patients given an inhaled steroid (alone or in combination) had a significantly increased risk of pneumonia. N Engl J Med 2007;356:775-89, 851-4

Male circumcision cuts risk of HIV by half

Two randomised trials from Kenya and Uganda have found that circumcising young men cuts their risk of HIV infection by about half. Both trials were large, well designed, and properly analysed. Both were stopped early because it became obvious so quickly that circumcision worked. Taken together with a third, previously published, trial from South Africa, these trials provide convincing evidence that circumcision helps prevent HIV infection among African men. We now have a historic opportunity to save lives in the region, says a linked commentary, we must not squander it (pp 617-9).

Big questions remain, however. Should governments and international organisations begin scaling up male circumcision all over the continent? If they should, how can it be done safely, cheaply, ethically, and with respect to the wide range of cultural sensitivities surrounding male circumcision? If they should, how can it be done safely, cheaply, ethically, and with respect to the wide range of cultural sensitivities surrounding male circumcision in Africa? There’s also concern that circumcised men will feel safer, abandon condoms, and make the situation worse.

Two experts commenting on these studies agree that male circumcision remains only part of the solution to HIV infection (pp 615,

**Cardiopulmonary bypass doesn’t cause cognitive decline**

Surgery to circumvent diseased coronary arteries can be done with or without cardiopulmonary bypass. The so-called off-pump technique is technically harder, but avoids the potentially damaging effects of aortic clamping and cannulation on cerebral perfusion. The choice of technique seems to make no difference to patients’ long term cognitive function, however.

A five year follow-up from a head to head trial comparing the two techniques showed that patients who had cardiopulmonary bypass during surgery had almost identical cognitive decline to patients who had surgery without cardiopulmonary bypass.

The original trial included 281 relatively young and fit patients from the Netherlands. They were having coronary artery surgery for the first time. About half of each group had moderate cognitive decline during the next five years (62/123 (50.4%) v 59/117 (50.4%); absolute difference 0%; 95% CI, −12.7% to 12.6%), and about a fifth had cardiovascular events. Cardiopulmonary bypass made no measurable difference to any outcome, including quality of life.

The researchers were mildly surprised by their findings, given that cardiopulmonary bypass is known to cause more cerebral embolisation than off-pump surgery. They repeated their analysis using a more demanding definition of cognitive decline, and the results were the same—about a third of each group met the definition after five years. *JAMA* 2007;297:701-8

**Controlled insulin therapy during cardiac surgery is probably pointless**

Patients having complex cardiac surgery do better if their glucose metabolism is tightly controlled postoperatively. To find out if outcomes are even better when the tight control is started during rather than after surgery, a team from the Mayo Clinic in Rochester, Minnesota, did a randomised controlled trial.

Careful use of insulin to keep glucose concentrations between 4.4 mmol/l and 5.6 mmol/l during surgery made no difference to the incidence of a composite outcome measure that included death, sternal wound infection, prolonged pulmonary ventilation, cardiac arrhythmia, stroke, and acute renal failure. In fact, the intervention group had significantly more deaths (4 v 0, *P*=0.061) and strokes (8 v 1, *P*=0.02) than the control group.

It now looks unlikely that a few hours of intraoperative glucose control has a big effect on perioperative complications and events, although a small effect is still possible. A linked editorial (pp 307-8) argues that the study was probably overambitious from the start. Since it takes several days for tight glucose control to produce measurable benefits after surgery, the benefits of starting a few hours earlier were never going to be dramatic. To rule out a small benefit, these authors would have needed thousands of patients. They recruited 400. *Ann Intern Med* 2007;146:233-43, 307-8

**In-store clinics are no threat to good primary care**

Walk-in primary care clinics are opening up in high street pharmacies and supermarkets all over the United States. Although some doctors see them as a threat, these clinics are broadly a good thing for patients, for medical professionals, and for the healthcare business, says one expert from Harvard Business School.

The clinics are typically a simple kiosk staffed by a nurse practitioner offering a few dozen diagnostic tests and treatments for simple ailments such as swimmer’s itch, “strept” sore throat, bladder infections, and minor burns. The clinics are cheap to run, easy to administer, convenient for everyone, and charge low fees—usually about $50 (£26; €38) per consultation. They also run extended hours.

The biggest company, MinuteClinic (slogan “you’re sick, we’re quick”), has kiosks in 156 locations around the country, and the marketplace is expanding rapidly.

It’s still unclear whether these clinics are here to stay, says the author of the report. But even if they don’t, an operational model based on McDonald’s hamburger chain—cheap, fast service from a limited menu—could help reshape the US primary care services. Well rehearsed concerns about standards and continuity of care remain theoretical. Good collaboration with local doctors should help secure both.

Primary care doctors should not be afraid to hand over this small piece of turf to nurse practitioners in supermarkets. Doctors are better placed to deal with patients who need more than symptomatic treatments for flu. *N Engl J Med* 2007;356:765-8

**High pulse pressure predicts atrial fibrillation**

An estimated one in four of us will eventually develop atrial fibrillation. We don’t know exactly how or why it happens. But a recent study suggests that it is something to do with the stiffening aorta and the resulting increase in pulse pressure that accompanies ageing.

In two long running cohorts (the Framingham and Framingham offspring studies), the incidence of atrial fibrillation went up by an estimated 26% for each 20 mm Hg increase in pulse pressure at baseline (adjusted hazard ratio, 1.26 per 20 mm Hg increment; 95% CI 1.12 to 1.43). The effect persisted through adjustments for at least a dozen well established risk factors for atrial fibrillation, and the researchers are fairly sure that the association is independent. The cohorts included 5331 American middle aged men and women, 13% (698) of whom developed atrial fibrillation during a mean follow-up of 16 years.

Pulse pressure—the difference between systolic and diastolic blood pressure—is a quick and easy, though indirect, measure of proximal aortic stiffness. In this study it was a more powerful predictor of incident atrial fibrillation than either mean, systolic, or diastolic blood pressure. *JAMA* 2007;297:709-15
THE BIG QUESTION

Will we be getting good doctors and safer patients?

Last week, the Department of Health announced its plans for reforming regulation of UK doctors. The BMJ asked some of those affected for their opinions.

Graeme Catto, president
General Medical Council, London

I believe that forward thinking doctors will welcome this white paper, which puts the uncertainties of recent years behind us. The emphasis on the independence of the General Medical Council—indeed of government as the UK’s dominant healthcare provider and of dominance by any single group—is right if we are to command the confidence of everyone who receives and provides healthcare. We all need a lasting settlement.

The white paper stems from the four major inquiries that tragically showed what can go wrong when a tiny number of doctors depart from the high standards that are rightly expected of them. Professional regulation, however, must primarily be concerned with supporting and embedding good practice; the majority of doctors are good doctors who strive to be better. Support for ill doctors is particularly welcome.

The central role of the medical register is recognised, together with the GMC’s four main functions: setting standards, coordinating all stages of medical education, ensuring that only appropriately qualified doctors are registered, and dealing effectively and fairly with concerns about individual doctors. These interlocking functions remain the basis for independent professional regulation built on the GMC’s accountability for the fitness for purpose of the register and fitness to practise of those on it.

The principle of revalidation, which we first suggested 10 years ago, is now accepted. We must begin relicensing and recertification as soon as practicable.

The composition of the council will be changing, with equal proportions of medical and lay members. Council members need to be there because of specific interests, competencies, and commitment to the public interest; democracy on its own will not give us the most appropriate mix. We have agreed to introduce the civil standard of proof, flexibly applied, to take account of the seriousness of the allegations and the possible consequences for the doctor. This will not result in more doctors being suspended but will enable appropriate restrictions on practice when that is necessary to protect patients.

The white paper extends our role in coordinating all stages of medical education, in defining and assuring standards of practice, and in modified plans for GMC affiliates. The further separation of adjudication is an incremental change, since we already have independent panels. Many doctors, as well as patients, have questioned whether we should both investigate and adjudicate, however well we perform the tasks.

Regulation is a dynamic process. The GMC has already made important reforms. This white paper provides a secure foundation for the GMC and for the medical profession in the years ahead.

Adam James Pringle, general practitioner, Lawley, Telford

It is sad, but unsurprising, to see the changes in medical regulation suggested in Good Doctors, Safer Patients1 being railroaded through unchanged despite the almost universal agreement among working doctors that they are fundamentally flawed (doctors.net.uk discussion forum). To quote Liam Donaldson, “There is little disagreement with the assertion that in 2006 every patient is entitled to a good doctor. Yet, there is no universally agreed and widely understood definition of what a good doctor is. Nor are there standards in order to operationalise such a definition and allow it to be measured in a valid and reliable way.”

The white paper proposes annual inspection of doctors. If this were a proposal to screen for a medical problem, it would fail to meet almost all of the World Health Organization criteria required to justify its introduction.2 We do not have a definition to measure the doctors against; nor do we have any valid and reliable test that will separate the good from the bad. It is far from clear how many doctors are expected to fail, and there is no real plan that deals with the needs of failing doctors. How can this system succeed in its aim of protecting patients?

The proposals will, however, meet the pressing political need to “do something.” It will bring large financial rewards to the royal colleges.

Most failing doctors are not malevolent but have the simple human weaknesses of physical or mental ill health. The chief medical officer recommended the provision of support services in 1999.3 The evidence that easy access to support and treatment protects the public has been clear for a quarter of a century, yet still no action has been taken.4 The chief medical officer believes 5% of doctors fail over five years. But he is choosing to re-invent medical regulation instead of proposing additional powers for the National Clinical Assessment Service, which is already referred this number of doctors but finds it cannot act effectively. It seems far simpler to give the assessment service the power (behind closed doors) to work to the civil standard of proof and to require appropriate remedial training.

The government, guided by the chief medical officer, could protect patients and support doctors by providing adequate occupational health support, giving the assessment service adequate powers to deal with failing doctors, and allowing the reformed GMC an opportunity to succeed—all of which could be done quickly and at relatively low cost. Its preference for grand schemes over practical actions comes at the expense of both doctors and patients and will in due course be seen for the folly it is.

Bernard Ribeiro, president, Royal College of Surgeons of England, London

I welcome the white paper on medical regulation and am particularly
pleased that the proposal for periodic revalidation is underpinned by a strengthened role for the medical royal colleges. This enhanced role will consolidate our commitment to safety and the highest standards of surgical care for our patients.

The revised proposals relating to the role of regional General Medical Council affiliates are welcome, as it is the strengthened role for trust medical directors. Training of these people is critical, and the white paper acknowledges that a high level of investment is needed to establish and maintain effective arrangements.

The introduction of a sliding scale in fitness to practise cases will ensure that a doctor facing erasure from the medical register is judged against an appropriately high level of proof. The GMC has already introduced changes for dealing with fitness to practise cases, and I hope that the independent adjudicating body will recognise the expertise and experience the GMC can add. We need time to absorb the changes. Successful implementation will require piloting, realistic timeframes, and adequate funding.

![Image of James Johnson, chairman of council British Medical Association, London]

James Johnson, chairman of council British Medical Association, London

I argued in November that the chief medical officer’s proposals for reforming and restructuring the General Medical Council represented a major assault on the principle of professionally led regulation. The white paper Trust, Assurance and Safety sweeps that principle aside completely and for all health professionals. Government has accepted Janet Smith’s argument that being an elected member of a regulatory body, and by implication accountable to a constituency of fellow professionals, is not compatible with acting independently in the public interest. The white paper repeatedly refers to the risk that the standing of a regulator is impaired if the public perceives it to be in hock to the profession it regulates. However, there must be an equally substantial risk that public confidence in the independence of their doctors is undermined if patients believe them to be under state control. Government needs to face up to the reality that 25 years of independent opinion polling by MORI confirms that the public trusts doctors, not politicians, to tell them the truth.

Some progress has been made since the consultation. The GMC’s role in governing undergraduate medical education has been secured with a solid, tripartite structure for undergraduate, postgraduate, and continuing education.

The proposals for GMC affiliates have been moderated and the vital responsibility of medical directors for clinical governance recognised. Proposals for relicensure and recertification still need much greater clarity, but the white paper recognises that the majority of doctors retain a lifelong enthusiasm for learning and for developing their practice.

The GMC has already separated the governance of regulation from the delivery of casework, but its good faith in so doing has not been rewarded. Instead, it further loses the right to adjudicate hearings, with its role confined to investigation and prosecution. I am unconvinced that this further separation of functions is necessary or proportionate. It does at least open up a route for the GMC, as the body that sets standards of conduct and competence, to appeal against the findings of disciplinary panels if they fail to uphold those standards appropriately.

However, if the GMC is now the prosecution service for medicine, and if a civil standard of proof is to be deployed, doctors are likely to feel that they are paying not for the privilege of professional regulation but to be policed. I understand and respect the decision of the GMC to embrace the white paper and to work with the grain of emerging public thinking on regulation. But I do have real concerns about how these changes will affect doctors’ sense of ownership of their profession and their role in shaping its future.

Professionally led regulation was never a right, nor was it just a privilege. Fundamentally, it was a responsibility on doctors to act in the public interest. Its passing will serve the interests of neither patients nor the profession.

Joyce Robins, codirector Patient Concern, London

Patients trust and respect the great majority of doctors and appreciate the skilful care they receive. We are tired of headlines exposing the few who let down the profession and shake our confidence. The measures in the government’s white paper should ensure that doctors have an opportunity to show their expertise while patients can be assured that any doctor they consult is competent and deserving of their trust.

Self-regulation has produced some spectacular failures: Harold Shipman, Bristol, Rodney Ledward, Richard Neale, William Kerr et al. Probably no one believes that another Shipman is lurking, but as Lesley Southgate, past president of the Royal College of General Practitioners, told the Shipman inquiry: “There are doctors out there who are harming patients.” It is time for change.

Patients have long believed that the General Medical Council looked after its own. Doctors finance it and therefore they expect its support. Up to now the GMC has acted as investigator, prosecutor, judge, and jury in fitness to practise cases. It is only right that these functions should be split and that an independent organisation will adjudicate.

GMC council members will no longer be elected but appointed, so that they are not chosen on a particular manifesto. The professional majority will go. This will be an improvement only if lay members are genuinely lay. Objectivity is questionable for those who work in the health service.

The most contentious measure is the change in the standard of proof in fitness to practise cases from beyond reasonable (criminal standard) doubt to the balance of probabilities (civil standard). This is about patient safety. The Family Court can take children away from their parents permanently on the civil standard of proof. In both cases the objective is prevention.

In the past, the tendency to give doctors the benefit of the doubt has ended in tragedy. Now it will be possible to act earlier on patients’ concerns—well before the point where a string of patients are dead or damaged and a doctor is struck off. The aim is protective, not punitive. No one wants to see doctors struck off. What is needed is intervention—support, supervision, retraining—before conduct can reach this level. The BMA believes that doctors will now begin to practise defensively rather than looking after the interests of their patients. We have more faith in doctors than that.

Most patients marvel that it has taken a string of scandals before the obvious necessity of medical colleges defining the skills and Research p 464 standard of performance needed for continuing membership has been recognised. The tightening up of appraisal to include a summative element is essential. The aim must be to gain an objective assurance that a doctor continues to meet the required standards. But we hope we can avoid a bureaucratic exercise with doctors wasting endless time ticking boxes.

If the changes are received in the right spirit by the profession and made to work effectively, then we can all move on, confident that the lessons of the past have been learnt.
Hitting the genetic profile button on his computer, David White, a general practitioner, gets a list of the antihypertensive drugs and doses most suited to the patient sitting in front of him. He gives the computer generated prescription to the patient. This is what Francis Collins, leader of the Human Genome Project and director of the US National Human Genome Research Institute, predicted doctors would be doing in the next few years.

In 2001, he wrote: “Genetic prediction of individual risks of disease and responsiveness to drugs will reach the medical mainstream in the next decade or so. The development of designer drugs, based on a genomic approach to targeting molecular pathways that are disrupted in disease, will follow soon after.”

This prediction now looks optimistic. “Biology is much more complex,” comments Klaus Lindpaintner, head of the Research Center for Medical Genetics with Roche. “But the idea of pharmacogenetics is certainly playing an increasingly important role in the way we think about developing drugs.”

What is pharmacogenetics?
Pharmacogenetics analyses genetic differences between individuals in their response to medicines. Professor Lindpaintner explains the attraction: “This approach promised more bang for the buck for patients and providers, with the greater likelihood of a response and reduced risk of side effects.”

Health service providers are keen to explore genetic approaches to optimising use of drugs. The UK genetics white paper in 2003 identified pharmacogenetics as a research priority. It said: “Pharmacogenetics will lead to prescribing which is more effectively tailored to the needs of the individual,” suggesting that this could reduce the waste associated with having to try out drugs before finding the best one for each patient and significantly cut the risk and cost of adverse drug reactions. The government has allocated £2.5m (€3.7m; $4.9m) for pharmacogenetic research on existing drugs. The Department of Health is also funding the first university chair in pharmacogenetics, supported by two to three full time researchers.

Drug development
To what extent are drug companies incorporating pharmacogenetic approaches into developing new drugs? Nadine Cohen, head of pharmacogenetics at Johnson & Johnson Pharmaceutical Research and Development, said: “We need to incorporate pharmacogenetics in research and development as early as possible and include it in all stages from drug discovery through to commercialisation. In drug discovery, we are trying to identify genes associated with disease, which could lead to novel targets, novel diagnostics, and enrich drug development pipelines.”

Genetic factors have been considered at an early stage of drug development for several decades in terms of how a drug is excreted, explains Munir Pirmohamed, professor of clinical pharmacology at the University of Liverpool. “In new drug development, if a drug is metabolised by cytochrome P450 2D6—a liver enzyme for which mutations are quite common—and other drugs are available, the drug won’t be developed further. So drugs are screened out at an early stage, based on pharmacogenetic issues.”

The more recent interpretation of pharmacogenetics—prescribing guided by the patient’s genotype—is still evolving, according to Professor Pirmohamed. “It is coming along, but not for everything,” he said.
“Where genetic variation between individuals is associated with variations in response to a drug, companies may proceed to look at efficacy and toxicity in that genotype-guided group.” This results in genotype guided indication at licensing.

Duncan McHale, head of molecular profiling at Pfizer UK, agrees that pharmacogenetics is being introduced into drug development. “But it is certainly not the panacea suggested in early claims of its potential impact. It has not revolutionised drug development.” He thinks that this is unsurprising in such a tightly regulated environment, where new developments have to be explored fully before being tested in people.

Current applications

Despite a lot of research in the field, relatively few drugs based on pharmacogenetic research have made it to the bedside. Oncology is the most advanced in its use of pharmacogenetic approaches. Greater understanding of the biology of many cancers has provided clear molecular targets for new drugs. And because cancers involve genetic mutations, exploring these is an obvious route for drug development.

Trastuzumab (Herceptin) is the most well known drug to result from pharmacogenomic design. It is prescribed for a genetic variant of breast cancer rather than a genetic variant of the patient, targeting the Her-2 protein. Patients are tested for the protein, not a genetic marker. Another example is imatinib. This inhibits the enzyme Bcr-Abl kinase produced as a consequence of the translocation between chromosomes 9 and 22 that occurs in chronic myeloid leukaemia. Use of genetic approaches is extending to other diseases as more about their aetiology is understood.

Pharmacogenetics is also beginning to have a role in prescription of the reverse transcriptase inhibitor abacavir to patients with HIV infection. Patients with the HLA-B*5701 allele are at greater risk of a hypersensitivity reaction to the drug. Recent studies have shown that the frequency of hypersensitivity falls from more than 5% to less than 1% if the drug is prescribed according to HLA typing, according to Professor Pirmohamed. Some centres are now routinely typing patients before prescribing abacavir. He notes: “This is an important example of pharmacogenetics that has worked. It has progressed quickly to clinical practice, only taking four years from identification of the genetic factor involved.”

There has also been interest in reviewing pharmacogenetic aspects of drugs already in clinical use. Warfarin is the most advanced in this respect, with two genetic variants in cytochrome P450 (the enzyme that metabolises warfarin) and vitamin K epoxide reductase (the target for the drug). “Looking at these two markers, together with age and body weight, gives a good degree of precision in dose requirement,” said Professor Pirmohamed. However, further studies are needed to assess whether they would be sufficiently accurate for clinical practice.

Niche markets?

Have fears that drugs would be niched by pharmacogenetics, greatly restricting potential markets, put companies off taking this approach? Roland Wolf, director of the biomedical research centre at Dundee University, thinks not: “There was concern about restricting markets by subdividing into genetic groups. But when you develop new drugs, you want to optimise the potential for a drug to succeed in phase III trials. If you can identify genetic variance that may define differences in the way the drug works, you would be crazy not to carry out genetic testing as part of clinical trial.” He points out that if a genetic variant meant that only 20% of the population responds to a new drug, a trial in the entire population might not show an advantage over an existing treatment.

Pharmacogenetics is just one approach that drug companies are using to develop new treatments, says Dr McHale. “We see pharmacogenetics as one of a range of approaches that we will use—along with transcription analysis and proteomics.” He thinks that for some drugs pharmacogenetics is key in defining the risk:benefit ratio. “But this is unnecessary for other drugs that work well and are well tolerated in the majority of people.”

Professor Lindpaintner agrees: “We kid ourselves if we think there are responders and non-responders; there are only people who respond more or less.” He warns that finding indicators that accurately predict likely responders is very challenging: “The last thing we want to do is inappropriately withhold a potentially beneficial medicine. You need a marker with high specificity and sensitivity—around 75-80%—before you can use it in diagnostic research.”

He thinks that the genotype might be the wrong place to look to biomarkers of response to most drugs. “DNA sequences are not known aside from a few rare diseases. And DNA is the most remote level from where life happens, which is at the level of proteins and small molecules. Therefore, we are more likely to see diagnostic tools at the level of protein expression.”

Way forward

Most drug companies have developed in-house expertise in genetics, but collaborations with academic research groups and biotech companies are also flourishing. One example is a serious adverse events consortium that is currently being formed as a partnership between the US Food and Drugs Agency and drug industry.

Looking to the future, predictions are much more cautious than those made a few years ago by Dr Collins. Professor Lindpaintner believes that pharmacogenetics is here to stay but we need to be realistic about its potential, which is limited given the highly complex aetiology of common diseases. They are not single gene disorders. Most are multifactorial, with genetic and environmental factors.”

Dr Wolf sees another reason why genetic approaches may not be the holy grail of new drug development. “Drugs with a wide therapeutic index won’t show much variability in response, so there is not much point in exploring the pharmacogenetics. For diseases with a readily identifiable marker—such as blood pressure for hypertension—you might as well give the drug according to blood pressure, so can do without genetics.”

“We have moved into an era of realism rather than hype in the potential of pharmacogenetics in new drug development,” concludes Professor Pirmohamed. “Genetic aspects have to be looked at in association with other factors, including environment, in the clinical use of drugs. Just because a drug doesn’t work in a patient doesn’t indicate genetic variation in response is the cause. The patient may just not be taking the drug. Genetics are just part of how patients respond to drugs.”

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Competing interests: SM has received payment for writing and communications projects from medical charities, government organisations, publishing companies, drug companies, and communications agencies.


Killing me softly

Can the prevention of suffering justify the involvement of doctors in capital punishment?

Ninety four per cent of the world’s executions occur in four countries. China executes the most people, at least 1000 and maybe as many as 8000 a year. Iran and Saudi Arabia are next, with around 100. The United States is fourth. In 2006 we killed 53 convicted murderers, down from 60 in 2005. In the 30 years since 1977, when the US Supreme Court moratorium on capital punishment ended, about 1000 Americans have been executed, a third of them in Texas, the rest in 33 other states.

Putting someone to death is not easy or pretty. As Elizabeth Weil pointed out in a recent New York Times Magazine article on the subject, each time a new method of capital punishment has been introduced it has been because the then current method was found to be barbaric and uncivilised. Death by hanging can lead to a dangling, kicking, prolonged struggle or a gruesome rope beheading. Firing squads are hard to control and sometimes inaccurate, leaving the victims alive. Gas chambers take a long time, and death by suffocation is not attractive. Electrocuton commonly results in grotesquely charred flesh and occasionally in flaming heads and other body parts. And sometimes it doesn’t work.

Which is why we now do virtually all of our executions in the US by lethal injection. Nice and clean, sterile setting, looks like a hospital. People dressed in white, alcohol swabs, cardiac monitors, intravenous lines. When all goes right, three quick intravenous injections—sodium thiopental to put the condemned to sleep, a paralysing agent so as not to offend the witnesses with any gasps or jerky movements, and potassium chloride to stop the heart—and in a few minutes, a “humane” and certifiable death.

But things don’t always go right. Several recent widely publicised fiascos have made that clear. In Florida, poorly trained technicians placed two IVs in the arms of a condemned man named Angel Diaz. Neither one was in a vein. The potassium infused subcutaneously, causing chemical burns. His painful death took more than 30 minutes, during most of which he was awake and speaking. This led Governor Jeb Bush to declare a moratorium on executions in Florida until they can figure out a better way to execute the 372 others on death row there.

And that, unfortunately, is where the medical profession comes in. If lethal injection is going to be done correctly, you need someone with medical expertise to do it. Or at least to train the people who do it and to supervise them. The US constitution specifies that no “cruel or unusual punishment” is allowed. Leaving aside for a minute the argument that capital punishment itself is cruel, certainly making people suffer needlessly is.

Surgeon Atul Gawande interviewed four doctors and a nurse who had participated in executions for a compelling article in the New England Journal of Medicine last year (2006;354:1121-9). Some of them stated that if capital punishment is legal, then executions should be done competently, and that means with medical supervision. One of the doctors compared executions to other end of life situations. When a patient is dying it is up to a physician to make sure the death is as pain-free and comfortable as possible, whether death is caused by nature or the state. And some of the participating doctors were state employees, whose job it was to care for prisoners. The men and women on death row were their patients.

Others argue that there can be no doctor-patient relationship between the doctor who facilitates an execution and the person to be executed, because the doctor is not putting the “patient’s” welfare first. Since at least 1980, the policy of the American Medical Association has been that physicians may not participate in executions because they are members of “a profession dedicated to preserving life when there is hope of doing so.” Does that take precedence over preventing the suffering that will occur if doctors are not involved in lethal injections?

Other countries don’t seem to have the same problem figuring out how to execute their criminals. Weil wrote that China has a “suite of hyper-efficient lethal-injection vans that drive around the provinces carrying trained teams that execute the condemned.” No mess, no fuss.

And that is the real problem: we don’t want a mess. We want these evil people to disappear, to be dead, but most of us don’t want to feel bad about how they died. In the more remote past, hangings were public; the citizenry attended and saw everything. Now we do it in secret, we can’t bear to watch, and we want it to be painless.

There are lots of reasons to be against capital punishment: it’s immoral, it reduces the state to the level of the killer, and it is irreversible if we find we’ve made a mistake. But if there is even one killer, one crime that is so heinous to “deserve” a capital sentence we have to accept that then we shouldn’t be killing people on behalf of the state.

Sometimes it is going to go wrong and we’re going to feel bad. If we can’t accept that then we shouldn’t be killing people on behalf of the state.

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Designing and evaluating complex interventions to improve health care

Determining the effectiveness of complex interventions can be difficult and time consuming. Neil C Campbell and colleagues explain the importance of ground work in getting usable results.

Complex interventions are “built up from a number of components, which may act both independently and interdependently.” Many health service activities should be considered as complex. Evaluating complex interventions can pose a considerable challenge and requires a substantial investment of time. Unless the trials illuminate processes and mechanisms they often fail to provide useful information. If the result is negative, we are left wondering whether the intervention is inherently ineffective (either because the intervention was inadequately developed or because all similar interventions are ineffective), whether it was inadequately applied or applied in an inappropriate context, or whether the trial used an inappropriate design, comparison groups or outcomes. If there is a positive effect, it can be hard to judge how the results of the trial might be applied to a different context (box 1).

The Medical Research Council framework for the development and evaluation of randomised controlled trials for complex interventions to improve health was designed to tackle these problems. It proposed a stepwise approach, parallel to that used in evaluating new drugs (box 2). This approach has been hugely influential internationally, but the MRC now recognises that it needs further development. We make suggestions for flexible use of the framework by providing a series of examples with lessons learnt. We focus on preliminary work before a definitive randomised controlled trial. Examples are taken from primary care, but the principles are applicable to all healthcare settings.

Overview
We found it helpful to consider phases 0, 1, and 2 of the stepwise approach as part of one larger iterative activity rather than as sequential stages (box 2). We found we needed data to clarify our understanding of the context of the research, the problem we sought to tackle, the intervention, and the evaluation (figure). Research on all these areas can be conducted simultaneously. In the following sections, we outline the important contextual considerations, describe the aim of each of three main components (problem definition, intervention, and evaluation), the key tasks necessary to meet each aim, and the conceptual and research approaches helpful in achieving the key tasks.

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Context
Context is all important. It includes the wider socio-economic background (including underlying cultural assumptions), the health service systems, the characteristics of the population, the prevalence or severity of the condition studied, and how these factors change over time. How a problem is caused and sustained, whether it is susceptible to intervention, and how any intervention could work may all depend on the context. This means that understanding context is crucial not only when designing interventions but also when assessing whether an intervention that was effective in one setting might work in others (box 3). Contexts differ between locations and change over time—for example, the introduction of financial incentives in 2004 for general practitioners to achieve targets in the management of chronic diseases changed the context of UK primary care.

The implications for researchers are twofold. They need to understand the context when designing a theoretically based intervention whose mechanism of action can be clearly described and whose validity is supported by empirical data. Secondly, when reporting trials, researchers should describe the context in which the intervention was developed, applied, and evaluated, so that readers can determine the relevance of the results to their own situation.

Defining and understanding the problem
The next step is to develop a sufficient understanding of the problem to identify opportunities for intervention that could result in meaningful improvements in health or healthcare systems. Table 1 gives the...
key components of this task, along with a worked example from our experience.

**Conceptualising the problem**
Different health problems have different levels of complexity. Some can be conceptualised in relatively simple ways, but others occur at multiple levels. In the example in table 1, high death rates in people with cardiovascular disease are affected by:

*Disease*—Atherosclerosis, risk factors (cholesterol, blood pressure, smoking), comorbidity

*Patient*—Beliefs about lifestyle, adherence to treatment, and symptoms

| The essential process involves mapping out the mechanisms and pathways proposed to lead from the intervention to the desired outcomes, then adding evidence and data to this map |

| Relation between context, problem definition, intervention, and evaluation for complex interventions |

| The essential process involves mapping out the mechanisms and pathways proposed to lead from the intervention to the desired outcomes, then adding evidence and data to this map |

| Box 1 | Illustration of problems of interpreting randomised controlled trials of complex interventions |

| Primary care mental health workers |

The NHS Plan in 2000 suggested that by 2004, primary care trusts in England should employ 1000 new primary care mental health workers to help deliver better quality mental health care. There was little underpinning evidence of the value of the role or time to evaluate whether it would be effective before nationwide implementation.

In 2002, one trust decided to pilot the role. It employed and trained five psychology graduates and assigned them to one or two practices each. Their role included direct work with clients, supporting practice teamwork, and work in the wider community. It used a pragmatic inexpensive cluster randomised controlled trial to explore the effect of these workers on patient satisfaction, mental health symptoms, and the cost effectiveness of care. Sixteen practices and 368 patients participated.

At three months, patient satisfaction (the primary outcome) was higher among patients in intervention than in control practices ($P=0.023$). However, lack of information about the active ingredient of the intervention (what the workers actually did) made this finding difficult to interpret and potentially less generalisable to other areas.

**Efforts to illuminate this “black box” by the trialists included:**

- Workers being asked to keep work diaries
- A parallel qualitative study exploring the experiences and views of trust commissioners, practice teams, workers, and patients.

Unfortunately, few workers managed to complete diaries in any detail. The qualitative study suggested that a key role of the workers was befriending patients, but it was not possible to isolate the influence of this on the trial findings. Further work on the meaning and value of befriending is now required.

**What could have been done before the trial if time had permitted?**

- Exploration of the potential effect of different facets of the mental health workers’ role
- Consideration of the local context (eg, ethnic characteristics of the population)
- Modelling of mechanisms by which care and patient health might be improved
- Design of a trial, using appropriate outcomes, to evaluate effects on these mechanisms

| Table 1 | Defining and understanding the problem for intervention: example of online behavioural intervention for people with cardiovascular disease |

<table>
<thead>
<tr>
<th>Key tasks</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Define and quantify the problem</td>
<td>Many cardiovascular deaths can be avoided by secondary prevention measures. These require health professionals to offer and monitor appropriate interventions and patients to take pills and change health related behaviours such as smoking, diet, and exercise</td>
</tr>
<tr>
<td>Identify and quantify the population most affected, most at risk, or most likely to benefit from the intervention</td>
<td>Coronary heart disease is the leading cause of death in the UK, responsible for over 110 000 deaths a year in England and affecting 2-4% of the population. People with diagnosed coronary heart disease are at greatest risk of premature death from cardiovascular causes</td>
</tr>
<tr>
<td>Understand the pathways by which the problem is caused and sustained</td>
<td>Behaviours such as smoking, poor diet, and a sedentary lifestyle increase risk of death from cardiovascular disease, whereas a healthy diet, exercise, and adherence to effective drugs reduce the risk. Theories of health psychology provide a way to link beliefs about health and motivation (eg, intention and self efficacy) with behaviour (eg, adopting a lifestyle)</td>
</tr>
<tr>
<td>Explore whether these pathways are amenable to change and, if so, at which points</td>
<td>Determinants of behaviour change, including intention and self efficacy are amenable to change</td>
</tr>
<tr>
<td>Quantify the potential for improvement</td>
<td>Lifestyle change after coronary heart disease is diagnosed is often suboptimal, leaving room for improvement. Extreme lifestyle changes have been shown to affect the progression of disease, with up to 5% regression of atheromatous stenosis. Thus an intervention that promotes lifestyle change has potential to achieve clinical improvement</td>
</tr>
</tbody>
</table>

| Box 2 | MRC framework for design and evaluation of complex interventions |

| Stepwise approach (on paper) |

**Phase 0**—Preclinical or theoretical (why should this intervention work?)

**Phase 1**—Modelling (how does it work?)

**Phase 2**—Exploratory or pilot trial (optimising trial measures)

**Phase 3**—Definitive randomised controlled trial

**Phase 4**—Implementation

**Parallel approach (in practice)**

Combine phases 0-II into one larger activity to develop understanding of the problem, the intervention, and the evaluation
Practitioner—Accessibility, prescribing practices, practices in health promotion

Health service—Availability of effective preventive and therapeutic care

Policy—Policies on preventive services (tobacco control, diet, exercise, etc)

Social context—Socioeconomic status, social support.

This is important if a decision to intervene at one level could be cancelled out or promoted by actions at other levels. For example, improving practitioners’ health promotion practices may have no effect on patients’ health behaviour if social and environmental factors obstruct response.16

Drawing on theories can help to conceptualise a problem, but having more than one level challenges us to use more than one theoretical approach. In the above example, if the problem to be tackled is individuals’ health behaviour, it may be best explained using theories from health psychology.17 It could also, however, draw on social theory to understand interactions with the social environment and organisational theory to understand health service and practitioner factors.18

Collecting evidence

A range of research methods can be used to collect evidence. In the example in table 1 researchers used systematic literature reviews, epidemiological research, and expert opinion to quantify the extent of the problem and identify the groups most at risk and the key modifiable risks. Had the factors causing and sustaining the problem been less well understood, the researchers may have had to do some primary research. For example, reasons for delayed presentation by patients with symptoms of lung cancer are poorly understood, so epidemiological and qualitative research is being undertaken to identify and quantify determinants and targets that may be amenable to intervention (international cancer research portfolio study CRU1278). Qualitative research can explore opportunities for, and barriers to, change. The findings, and extrapolations from other related research, can inform an initial assessment of how much improvement the intervention might achieve.

Developing an optimal intervention

For an intervention to have a credible chance of improving health or health care, there must be a clear description of the problem and a clear understanding of how the intervention is likely to work. The original MRC framework identified designing, describing, and implementing a well defined intervention as: “the most challenging part of evaluating a complex intervention—and the most frequent weakness in such trials.”19 Table 2 summarises the key tasks for achieving this understanding and gives an example.

Conceptual approaches

Conceptual modelling or mapping can clarify the mechanisms by which an intervention might achieve its aims. The essential process involves mapping out the mechanisms and pathways proposed to lead from the intervention to the desired outcomes, then adding evidence and data to this map. Modelling of the intervention both depends on, and informs, understanding of the underlying problem. The intervention must engage the target group and affect pathways amenable to change that are identified as important to the problem. In the example in table 2 the intervention engages the general practitioner (providing tailored advice and training), the primary care team (organising referral around a single trained general practitioner), and the patient (facilitating their provision of information).

Box 3 Importance of context in complex interventions

The Evercare programme of case management for elderly people has been shown to reduce hospital admission in US nursing home residents, reducing overall costs by about $880 (€450; £680) per nurse practitioner.20 NHS England piloted a UK version of Evercare and has since implemented community matron management for older people at high risk of emergency hospital admission. Differences in context raise uncertainties about effectiveness, however, particularly since the broader evidence that case management is effective is weak and inconsistent.21

Is the problem the same?
The US and UK share the wider context of rising healthcare costs for expanding elderly populations, one component of which is rising rates of emergency admissions. However, the problem most amenable to intervention differs in the two countries. Poor coordination of care is relatively more important in the US, and the lack of financial incentives to keep patients in the community is relatively more important in the UK.

Is the intervention the same?
UK implementation of Evercare case management differs from the US trial in several respects:

• The target population is different (all those at high risk of emergency admission in the UK v nursing home residents in the US). Effectiveness of the UK implementation therefore depends on accurately identifying patients at high risk of emergency admission, which was not possible in the pilots or initial implementation10

• In the UK, nursing home and NHS funding remains separate, so community matrons’ effectiveness largely relies on better review and coordination of existing services, which are already less fragmented than in the US.

What are the appropriate outcomes?

Case management may reduce emergency hospital admission, but it might also improve patient care in terms of other important outcomes including functional status, patient and carer quality of life, and satisfaction with services. There is also potential for adverse effects on the overall quality of care for elderly people since recruitment of community matrons from existing district nursing services may exacerbate nurse shortages. The policy focus on emergency admission may therefore be too narrow.
were numbers of appropriate referrals at baseline and findings from related interventions. Further data were provided by carefully controlled intervention studies. Identifying barriers or rate limiting steps in intervention pathways—Complex interventions can fail because of unforeseen barriers. Barriers can be cognitive, behavioural, organisational, sociocultural, or financial. They may occur early in the intervention process or during steps not previously considered or thought important. In the computer support example (table 2) some rate limiting steps were identified early when populating the intervention model with data on uptake of computer support in general practice, but others emerged during subsequent qualitative research. Early identification provides opportunities for resolution (which in this case included redesigning the software and training general practitioners on how to consult while using the software).

Optimising combinations of components in the intervention—There is no consensus on how to achieve this. Once a conceptual model has been formed, some complex interventions may be amenable to simulations or carefully controlled experimental studies outside the normal clinical setting. In our example, simulated patients were used to test the intervention with general practitioners. This identified the likely outcomes for a range of patients and allowed general practitioners to comment on how the intervention could be improved. Simulation can also be used to explore the effect of changes in dose on response, and changes in contextual influences. Early randomised studies also have a place. In the example a randomised study was used to quantify the potential for benefit by using an intermediate outcome (decisions to refer) known to be tightly linked to final outcomes (referrals). Later, in another randomised trial, the researchers attempted to optimise the intervention by including an adaptive arm. In this arm, the intervention could be modified according to practitioner feedback when use of software during consultations fell below predetermined criteria.

Developing and optimising trial parameters

The ideal evaluation provides convincing evidence of effectiveness or otherwise, without wasting resources. Table 3 lists the key tasks in designing such an evaluation.

### Conceptual methods

The development of research protocols for randomised trials is detailed elsewhere. We found three considerations particularly important for robust evaluations of complex interventions. Firstly, outcomes must link plausibly with the intervention's proposed mechanisms of action and include its potential adverse effects and other costs. Secondly, realistic estimates of recruitment and retention are essential before moving to a definitive trial. Thirdly, if randomisation is to be clustered, good (or at least plausible) estimates of intraclass correlation are needed.

### Collecting data

The conceptual model of the intervention can provide a rational guide to both intermediate and final outcome measures. Sensitive intermediate outcomes can enable small trials to provide meaningful findings during the development of the intervention (table 3). In definitive trials with negative results, they can help identify the point along the causal pathway where the intervention failed. If estimates of recruitment, retention, and intraclass correlation

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**Table 2 | Key tasks for optimising an intervention: example of computer support for assessment of familial risk of cancer in primary care**

<table>
<thead>
<tr>
<th>Key task</th>
<th>Example</th>
</tr>
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<tbody>
<tr>
<td>Identify key processes and outcome of intervention</td>
<td>The intervention sought to optimise the use of cancer genetics services available to primary care by reducing inappropriate referrals. A central problem was that referral guidelines are complicated to use and poorly implemented in general practice.</td>
</tr>
<tr>
<td>Identify mechanisms by which intervention will lead to improved outcome</td>
<td>The intervention would provide tailored advice on referral for individual patients by using computer decision support to implement referral guidelines. Systematic reviews have shown that this mechanism helps the implementation of clinical practice guidelines. Training would help practitioners to use the software, and paper questionnaires would help patients provide information to increase the accuracy of assessment.</td>
</tr>
<tr>
<td>Identify barriers to application of intervention (which may manifest as rate limiting steps)</td>
<td>Previous studies of computer support suggested that lack of use during consultations was an important rate limiting step. Lack of training and poor software design contributed to this. A qualitative study of the prototype software (RAGs) using simulated patients identified important contextual barriers (eg, time needed for data entry, and loss of doctor-patient interaction) and helped development of the software to minimise adverse effects (eg, providing an interface that encouraged shared use by doctor and patient and avoided frightening “high risk” messages appearing suddenly on screen).</td>
</tr>
<tr>
<td>Quantify potential for benefit and estimate the likely effect size</td>
<td>An experimental randomised block design study with simulated patients showed the software could improve risk assessment and double the number of appropriate referral decisions (the intermediate outcome).</td>
</tr>
<tr>
<td>Refine the target group to take account of its likelihood of responding to the intervention</td>
<td>The potential target group was all primary care practitioners. The group was refined to a single general practitioner in each practice to maximise the effect of the training and increase the frequency with which they used the software.</td>
</tr>
<tr>
<td>Consider the best achievable combination of intervention components and intensities</td>
<td>Findings from previous related research and the qualitative and experimental studies of the prototype software all helped with this. A concern was to optimise use of the software during consultations so, in addition to standard intervention and control arms, an exploratory trial included an “adaptive arm,” which permitted the software and protocols to be varied during the trial in response to comments from practitioners and reasons identified for low use.</td>
</tr>
</tbody>
</table>

**Table 3 | Optimising the evaluation: example of community based screening for genital Chlamydia trachomatis infection**

<table>
<thead>
<tr>
<th>Key task</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify feasible and valid measures of outcomes—both intermediate and final; specify the outcome on which the study will be powered</td>
<td>Key outcomes are tubal infertility and ectopic pregnancy. Research evaluating effects on these would take many years or a huge sample. A crucial intermediate outcome is whether individuals at risk of these adverse outcomes will accept screening.</td>
</tr>
<tr>
<td>Consider randomisation; randomise at the level of the intervention; but cluster randomise only if necessary</td>
<td>A feasibility study used individual randomisation, partly because cluster randomisation required a much larger sample size (about 21 times). There were, however, practical difficulties with this. Data protection legislation prevented researchers from accessing names and addresses of potential participants, so staff in each general practice had to generate the randomised mailings. This proved prohibitively expensive.</td>
</tr>
<tr>
<td>Estimate recruitment and retention rates</td>
<td>The feasibility study showed that recruitment rates in the current ethical and legal framework might make a definitive trial difficult.</td>
</tr>
<tr>
<td>Calculate sample sizes</td>
<td>A small scale feasibility study in 3 general practices informed sample size calculation for a definitive trial using both cluster and individual randomisation based on rates of acceptance of screening.</td>
</tr>
</tbody>
</table>
have not been obtained during prior research with the target group, a feasibility study may be needed to model patient flow. Such studies also enable assessment of feasibility of the methods of randomisation including acceptability to participants and suitable level to avoid contamination effects. They provide data to inform sample size calculations for the final evaluation and descriptive statistics on the baseline performance of the final outcome measures.

Conclusion
The design of an intervention depends on understanding the underlying problem and the context, what difficult processes are involved in optimising the intervention, and why the evaluation needs outcomes appropriate to the intervention mechanism. Defining and understanding the problem and its context, developing and understanding the intervention, and developing and optimising the evaluation are three substantial tasks but can be conducted simultaneously. The process of development ends with one of three scenarios. Firstly, it may become clear that the intervention is unlikely to be cost effective in the current environment and does not warrant the cost of a large randomised trial. Secondly, the evidence supporting the intervention may become so strong that there is no doubt that it will be beneficial—in which case it should be implemented. Finally, although doubt may remain about the effects of the intervention, it is sufficiently promising to warrant the costs of a definitive evaluation. In that case, the researcher who understands the underlying problem, has developed a credible intervention, and considered the key points in evaluation will be in a strong position to conduct a worthwhile, rigorous, and achievable definitive trial.

We thank St John's College, Cambridge, for hosting the group and the MRC cooperative group for their support.

Contributors and sources: This article was prepared by a working group, comprising postdoctoral general practice researchers with experience of using the MRC framework to develop complex interventions. The group was convened by the MRC cooperative group for the development and evaluation of innovative strategies for the prevention of chronic disease in primary care. Group members were selected from different institutions and were widely geographically dispersed within the United Kingdom. The working group met annually for three years (a total of 5 days), during which time we reviewed the practical experience of the members of the group, using examples, to identify the important tasks and processes that formed part of developing and defining complex interventions for evaluation. In a separate exercise, examples of practice were collated and analysed indiuctively to look for common themes and examples of divergence. The article was conceived by the working group as a whole: NCC, JE, and ALK wrote the first draft. EM and NCC wrote the final draft. All authors contributed to the concepts in the paper and to redrafting the paper. NCC is guarantor.

Competing interests: None declared.

SUMMARY POINTS
Good design is essential to get meaningful information from randomised controlled trials of complex interventions
The MRC framework was developed to improve such trials
The first three phases of the framework can be conducted simultaneously in an iterative process to better understand the problem, the intervention, and the evaluation


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Effect of insulating existing houses on health inequality: cluster randomised study in the community

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ABSTRACT

Objective To determine whether insulating existing houses increases indoor temperatures and improves occupants’ health and wellbeing.

Design Community based, cluster, single blinded randomised study.

Setting Seven low income communities in New Zealand.

Participants 1350 households containing 4407 occupants.

Intervention Installation of a standard retrofit insulation package.

Main outcome measures Indoor temperature and relative humidity, energy consumption, self reported health, wheezing, days off school and work, visits to general practitioners, and admissions to hospital.

Results Insulation was associated with a small increase in bedroom temperatures during the winter (0.5 °C) and decreased relative humidity (~2.3%), despite energy consumption in insulated houses being 81% of that in uninsulated houses. Bedroom temperatures were below 10°C for 1.7 fewer hours each day in insulated homes than in uninsulated ones. These changes were associated with reduced odds in the insulated homes of fair or poor self rated health (adjusted odds ratio 0.50, 95% confidence interval 0.38 to 0.68), self reports of wheezing in the past three months (0.57, 0.47 to 0.70), self reports of children taking a day off school (0.49, 0.31 to 0.80), and self reports of adults taking a day off work (0.62, 0.46 to 0.83). Visits to general practitioners were less often reported by occupants of insulated homes (0.73, 0.62 to 0.87). Hospital admissions for respiratory conditions were also reduced (0.53, 0.22 to 1.29), but this reduction was not statistically significant (P=0.16).

Conclusion Insulating existing houses led to a significantly warmer, drier indoor environment and resulted in improved self rated health, self reported wheezing, days off school and work, and visits to general practitioners as well as a trend for fewer hospital admissions for respiratory conditions.

Trial registration Clinical Trials NCT00437541.

INTRODUCTION

The quality of housing affects the health of the population. Improvements to housing could potentially prevent ill health, especially in sections of the population exposed to substandard housing.1 2 Several reviews of social interventions, and housing interventions in particular, have highlighted a dearth of studies in this area and the urgent need for studies from which causal inferences can be drawn.3 6 People in developed countries spend more than 90% of their time indoors, most of it in their own homes, but we know little about the specific health effects of the indoor environment.7 8 The housing, insulation and health study is a cluster randomised trial of insulating existing houses in low income communities. The study was designed as a practical intervention to improve the indoor environment at the community level.

The British Wanless report stated that “every opportunity to generate evidence from current policy and practice” should be taken to provide more robust evidence of practical interventions that might help governments formulate effective policies.9 Because evidence that improving housing can significantly reduce morbidity is limited, we focused on houses as the main unit of analysis to provide evidence for use in formulating public policy. Fitting insulation into houses, rather than intervening at the level of the individual—for example, by providing people with more clothes—could be a more cost effective and practical way to improve health.10

Badly constructed and older houses are difficult and expensive to heat. Inadequate warmth in the home can have health consequences for the occupants, particularly during winter.11 12 The efficiency of domestic energy is linked with health because money spent on energy cannot be spent on other necessities such as food.13 14 Colder houses place more physiological stress on older people, babies, and sick people, who have less robust thermoregulatory systems and are also likely to spend more time inside.15 Houses that are cold are also likely to be damp, and this can lead to the growth of moulds, which can cause respiratory
symptoms. The link between inadequate heating; damp, cold, and mouldy houses; and poor health has been highlighted in several international reports. Surprisingly, excess mortality in winter is more pronounced in temperate rather than colder climates, suggesting that houses in these regions do not adequately protect occupants from the weather.

**METHODS**

The study methods, including power considerations and randomisation, have been published previously, but a brief summary is given below. Figure 1 outlines the flow of households through the study.

**Setting**

New Zealand has a temperate climate, with mean winter daytime temperatures ranging from 10°C in the south to 16°C in the north. Two thirds of the housing stock comprises three bedroom and four bedroom stand alone wooden houses on wood or concrete piles (Statistics New Zealand, www.stats.govt.nz/default.htm). Houses usually last about 90 years and about a third have no insulation. Most people only heat the living room and occasionally a bedroom.

Our study was established in seven geographical areas, three urban and four rural, in partnership with local. We obtained ethical approval from all sites.

**Recruitment**

We selected participants for the study through local organisations, which also obtained informed consent. Each community selected 200 households. The selected households were in uninsulated dwellings; at least one household member had reported respiratory symptoms in the past year—such as recurrent wheezing or had a history of asthma, pneumonia, or chest infections; and members were planning to remain in the dwelling for the next two winters.

Sample size calculations were based on the number of people whose health status could be expected to improve

<table>
<thead>
<tr>
<th>Assessed for eligibility (n=not known)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community groups enrolled all applicants who met criteria</td>
</tr>
<tr>
<td>Excluded (n=not known)</td>
</tr>
<tr>
<td>Not meeting inclusion criteria (n=not known)</td>
</tr>
<tr>
<td>Refused to participate (n=not known)</td>
</tr>
<tr>
<td>Other reasons (n=not known)</td>
</tr>
<tr>
<td>Households randomised (n=1350)</td>
</tr>
<tr>
<td>Allocated to intervention (n=679 houses, 2262 people)</td>
</tr>
<tr>
<td>Received allocated intervention (n=628 houses; median 3 health forms, range 0-11 forms received)</td>
</tr>
<tr>
<td>Did not receive allocated intervention (n=51 households)</td>
</tr>
<tr>
<td>No baseline data returned (n=14; no health forms)</td>
</tr>
<tr>
<td>Moved before intervention carried out (n=21; median 3 health forms, range 0-8 forms)</td>
</tr>
<tr>
<td>Withdrew for various reasons (n=6; median 1 health form, range 0-2 forms)</td>
</tr>
<tr>
<td>Access problems (n=2; range 3-5 health forms)</td>
</tr>
<tr>
<td>Unknown (n=8; median 5 health forms, range 3-7 forms)</td>
</tr>
<tr>
<td>Returned health form but no house form (n=3 households, range 1-4 health forms; 1 received intervention)</td>
</tr>
<tr>
<td>No baseline data returned but houses were insulated (n=4)</td>
</tr>
<tr>
<td>Allocated to control (n=671 households, 2145 people)</td>
</tr>
<tr>
<td>Subsequently received allocated intervention (n=670 houses, median 3 health forms, range 0-11)</td>
</tr>
<tr>
<td>Did not receive allocated intervention (insulated in error n=1, 1 health form)</td>
</tr>
<tr>
<td>Returned health form but no house form (n=1 household, 1 health form)</td>
</tr>
<tr>
<td>No baseline data returned (n=19)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>Baseline data returned, but no follow-up household or individual health forms (n=71; 5 health reasons; 29 moved; 9 other; 25 unknown; overall year 1, median 3 health forms, range 1-9)</td>
</tr>
<tr>
<td>Households did not return the 2nd year house form but did return at least 1 health form (n=3)</td>
</tr>
<tr>
<td>Households did return the 2nd year house form but returned fewer health forms than in the 1st year 1 (n=132)</td>
</tr>
<tr>
<td>Discontinued intervention (n=0)</td>
</tr>
<tr>
<td>No houses had insulation removed</td>
</tr>
<tr>
<td>Analysed (n=563 households, median 3 people, range 0-9, total 1689 people)</td>
</tr>
<tr>
<td>Excluded (n=116 houses, 573 people)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>Baseline data returned, but no follow-up household or individual health forms (n=86; 6 health reasons, 6 house structure, 48 moved, 3 other, 23 unknown; overall year 1, median 3 health forms, range 0-11)</td>
</tr>
<tr>
<td>Household did not return the 2nd year house form but did return at least 1 health form (n=1)</td>
</tr>
<tr>
<td>Household did not return the 2nd year house form but did return fewer health forms than in the 1st year 1 (n=161)</td>
</tr>
<tr>
<td>Discontinued intervention (n=0)</td>
</tr>
<tr>
<td>No houses had insulation removed</td>
</tr>
<tr>
<td>Analysed (n=565 households; median 3 people, range 0-11, total 1623 people)</td>
</tr>
<tr>
<td>Excluded (n=106 houses, 522 people)</td>
</tr>
</tbody>
</table>
from “fair” or “poor” on the generalised health question in the SF-36 (short form 36) questionnaire.

**Participants**

The study comprised 1350 houses. The tenure patterns showed some divergence from the 2001 New Zealand Census: 24% of houses in the study were rented compared with 32.2% nationally; 11% were rented from public landlords, compared with about 6% nationally. About a third of the houses were in the lowest tenth of socio-economic areas, and two thirds were in the bottom three tenths, so that participants were likely to be vulnerable to ill health. Twenty per cent rated their health as poor or very poor, compared with 13% of the general population.

The initial, regionally stratified randomisation was carried out by an independent biostatistician. Table 1 shows no evidence for systematic bias.

**Intervention**

Households randomly allocated to the intervention group had their houses insulated after the baseline measures were taken in the study’s first winter (June to August 2001). The intervention consisted of installing ceiling insulation, draught stopping around windows and doors, and fitting sisalated paper beneath floor joists and a polythene moisture barrier on the ground beneath the house. The insulation, which was free to house-holders, was to government specifications (resistance specified as 0.1 W/m K) and was installed by trained community teams. (Households in the control group were insulated for equity at the end of the study after all data had been collected.)

**Outcome measures**

The study used interviewer administered questionnaires; participants’ self reported experience; as well as independent measures of use of health services, house temperature, and other environmental characteristics of the houses (table 2). Most questions had been used in previous housing surveys.

In spring 2001 and 2002, all household members 11 years and over completed a self administered questionnaire about their health, contact with the health system, smoking, and time lost from work or normal activities because of ill health. This included a subset of three SF-36 full scales (role physical, role emotional, and social functioning), the transitional health question, and a single question from two scales—general health and vitality. Care givers or parents completed a similar but age appropriate questionnaire for infants and children under 11 years.

We checked use of primary care by contacting the specified general practitioners. The number, duration, and main ICD-10 (international classification of diseases, 10th revision) codes for hospital admissions were collected through a data matching process using the unique national patient identifier number.

Participants reported daily whether they felt warm, OK, or cold, before their evening meal. The head of the household also completed an interviewer administered questionnaire in the home about household demographics, dwelling characteristics, and space heating—including estimates of the use of solid fuel. The interviewers were told to make no leading comments about the households’ insulation status. Regional electricity and gas companies supplied data on the energy consumption of each household during the study period.

**Table 1: Baseline data in a trial of insulating houses. Values are number/total number (percentage) of people**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (n=2262)</th>
<th>Control (n=2145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1185/2262 (52)</td>
<td>1112/2145 (52)</td>
</tr>
<tr>
<td>Ethnic origin*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>1106/22196 (50)</td>
<td>1001/2109 (48)</td>
</tr>
<tr>
<td>Pacific</td>
<td>501/22196 (23)</td>
<td>578/2109 (27)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>294/2262 (13)</td>
<td>248/2145 (12)</td>
</tr>
<tr>
<td>5-14</td>
<td>565/2262 (25)</td>
<td>522/2145 (24)</td>
</tr>
<tr>
<td>15-24</td>
<td>230/2262 (10)</td>
<td>236/2145 (11)</td>
</tr>
<tr>
<td>25-44</td>
<td>594/2262 (26)</td>
<td>590/2145 (28)</td>
</tr>
<tr>
<td>45-64</td>
<td>391/2262 (17)</td>
<td>362/2145 (17)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>188/2262 (8)</td>
<td>187/2145 (9)</td>
</tr>
<tr>
<td>Health rated fair or poor</td>
<td>445/2243 (20)</td>
<td>437/2131 (21)</td>
</tr>
</tbody>
</table>

Denominators vary owing to missing data.
*Ethnic origin was self defined; multiple ethnic affiliations possible.

**Table 2: Outcome measures in a trial of insulating houses**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Household</strong></td>
<td></td>
</tr>
<tr>
<td>Warmth and dampness</td>
<td>Self reported dampness and warmth</td>
</tr>
<tr>
<td>Measured temperature and relative humidity</td>
<td>Comfort charts</td>
</tr>
<tr>
<td>Energy use</td>
<td>Self reported fuel usage</td>
</tr>
<tr>
<td>Measured data from energy companies</td>
<td></td>
</tr>
<tr>
<td>Subjective fungal activity</td>
<td>Musty smell</td>
</tr>
<tr>
<td>Observed mould</td>
<td></td>
</tr>
<tr>
<td>Measured fungal activity*</td>
<td>Mould speciation</td>
</tr>
<tr>
<td>Mould mass</td>
<td>Endotoxins</td>
</tr>
<tr>
<td>β Glucans</td>
<td></td>
</tr>
<tr>
<td>Allergens*</td>
<td>Dust mite allergens</td>
</tr>
<tr>
<td>Environmental tobacco smoke*</td>
<td>Smoking behaviour</td>
</tr>
<tr>
<td>Individual Self reported health and use of healthcare facilities</td>
<td>SF-36 scales</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Days off work and school</td>
</tr>
<tr>
<td>Questions on use of healthcare facilities</td>
<td></td>
</tr>
<tr>
<td>Health risk behaviour*</td>
<td>Smoking</td>
</tr>
<tr>
<td>Measured use of healthcare facilities</td>
<td>Number of visits to general practitioner</td>
</tr>
</tbody>
</table>

*Results not reported in this paper.
In 140 randomly selected houses, we recorded temperature and relative humidity in the main bedroom, every 15 minutes, during both winters. At two randomly selected houses in each of the seven communities, temperature and humidity were also continuously recorded outside.

**Statistical methods**

We analysed the data in several ways on an intention to treat basis. As randomisation led to no discernible systematic biases, we compared the follow-up scores of the intervention and control groups and subtracted follow-up scores from baseline scores to derive change scores. The analysis of covariance (ANCOVA), the preferred approach, is presented unless otherwise indicated. ANCOVA adjusts each participant’s follow-up score for baseline score, but has the advantage of being unaffected by differences at baseline. Analyses also controlled for the clustering of individuals within households and households within regions. We routinely added sex, ethnic origin, and age group to the adjusted model; this decision was made a priori. We used SAS software (version 9.1, SAS Institute) and the Glimmix procedure for binary or normal data or STATA (version 8.2, StataCorp) and a zero inflated negative binomial model for count data.

Where odds ratios are presented, a value less than 1 represents a positive effect of insulation whereas a value more than 1 indicates a negative effect of insulation. In general, we adjusted variables for age, sex, region, and baseline values. The unadjusted odds ratios presented take account of clustering. Indicative samples of the most important outcome measures are presented here; others will be presented elsewhere.

**RESULTS**

We recruited 1350 households; baseline household information was obtained from 1309 of these households and 4407 people. At follow-up, 1128 households and 3312 people remained—an 86% retention rate for households and a 75% rate for people. The proportion of indigenous Maori people (49%) and migrant Pacific people (22%) was higher in the sample than in the national population (15% and 6%, respectively).

**Household factors**

The houses in the study were typical of low socioeconomic status dwellings. Self reporting showed that 18% were in poor or very poor condition, 89% had condensation, and 75% had mould. Building inspectors reported even worse conditions, with 53% of the houses in the 140 random subsample being in poor or very poor condition and 81% with some mould (table 3).

**Weather**

Winter in both years was broadly comparable. Mean daytime temperatures were 10.5°C and 11.3°C in 2001 and 2002.

**Indoor environment**

The odds of feeling cold always or most of the time decreased significantly in the insulated houses compared with uninsulated houses (adjusted odds ratio 0.06, 95% confidence interval 0.04 to 0.09; P<0.0001; table 4). The odds of reporting ineffective heating after intervention was significantly lower for insulated houses (0.38, 0.25 to 0.57; P<0.0001; table 4). Mean bedroom temperature increased in the insulated houses from 13.6°C to 14.2°C and in the uninsulated ones from 13.2°C to 13.4°C. Mean relative humidity decreased in the insulated houses from 68.6% to 64.8% compared with 68.3% to 66.9% in the uninsulated houses (table 5). Figure 2 shows the smoothed empirical temperature frequency (area under the curve) over a 24 hour period. Bedroom temperatures were below 10°C for an hour less in insulated houses and 45 minutes longer in the uninsulated houses.

**Reported damp and mould**

At baseline, two thirds of households reported damp and three quarters reported mould, but after insulation the odds of reported dampness decreased (0.13, 0.10 to 0.17; P<0.0001) and mould (0.24, 0.18 to 0.32; P<0.0001) decreased significantly (table 4).

**Energy usage**

Electricity and gas company data, and calculations from self reported wood and coal usage using standard calorific values, showed that a geometric mean kWh equivalent of 3899 was used in the intervention group compared with 4941 kWh in the control arm. After adjusting for baseline usage, this equated to the insulated households consuming 81% of that consumed by control households (81% effect, 72% to 91%; P<0.0006; table 4). Taking a subsample of households (n=136), who used only electricity and mains gas in both years, the estimated value of fuel

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### Table 3 | Household baseline data in a trial of insulating houses. Values are number of households affected/total number (percentage) of households

<table>
<thead>
<tr>
<th>Household factors at baseline</th>
<th>Group</th>
<th>Intervention (n=679)</th>
<th>Control (n=671)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self reports</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dwelling reported in poor or very poor condition</td>
<td>116/644 (18)</td>
<td>118/653 (18)</td>
<td></td>
</tr>
<tr>
<td>Condensation</td>
<td>566/633 (89)</td>
<td>577/640 (90)</td>
<td></td>
</tr>
<tr>
<td>Dampness not due to condensation</td>
<td>413/613 (67)</td>
<td>437/641 (68)</td>
<td></td>
</tr>
<tr>
<td>Mould</td>
<td>481/643 (75)</td>
<td>490/651 (75)</td>
<td></td>
</tr>
<tr>
<td><strong>Building inspector reports</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking reported inside the house during winter</td>
<td>264/641 (41)</td>
<td>254/656 (39)</td>
<td></td>
</tr>
<tr>
<td>Dwelling cold always or most of the time</td>
<td>452/647 (70)</td>
<td>473/651 (73)</td>
<td></td>
</tr>
<tr>
<td>Maintenance poor or very poor</td>
<td>37/70 (53)</td>
<td>36/69 (52)</td>
<td></td>
</tr>
<tr>
<td>Any mould</td>
<td>59/70 (84)</td>
<td>54/69 (78)</td>
<td></td>
</tr>
<tr>
<td>Large patches of mould</td>
<td>18/70 (26)</td>
<td>16/69 (23)</td>
<td></td>
</tr>
</tbody>
</table>
savings was around £25 (€37; $49; excluding taxes) a year.

**SF-36**

Self reported health improved significantly in the intervention group (table 6). Participants in insulated houses were significantly less likely to report poor or fair health (0.50, 0.38 to 0.68; P<0.0001). On the social functioning scale, participants in insulated houses reported 6.2 percentage point improvement relative to the control group (3.8 to 8.6); this improvement was 10.9 percentage points on the role emotional scale (P<0.0001) and 11.8 percentage points on the role physical scale (P<0.0001) (table 7). People in the intervention group had 0.56 times the odds of being in the bottom half of a reduced mental health scale (0.41 to 0.77; P=0.0003).

People in insulated houses had about half the odds of respiratory symptoms, such as recent wheezing (0.57, 0.47 to 0.70; P<0.0001) and self reported winter colds and flu (0.54, 0.43 to 0.66; P<0.0001) as those in the control group. In adults, the incidence of morning phlegm decreased significantly (0.64, 0.52 to 0.78; P<0.0001), and in children under 13 years the likelihood that the symptoms of wheezing would disturb

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**Table 4 | Household results in a trial of insulating houses. Values are number/total number of households for self reported house condition and median/geometric mean (number of households) for energy use, unless stated otherwise**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group</td>
<td>Control group</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Any mould</td>
<td>364/509</td>
<td>362/501</td>
<td>0.28 (0.21 to 0.36) P=0.0001</td>
</tr>
<tr>
<td>House cold most of the time or always</td>
<td>398/550</td>
<td>383/547</td>
<td>0.09 (0.07 to 0.12) P=0.0001</td>
</tr>
<tr>
<td>Condensation</td>
<td>487/538</td>
<td>486/535</td>
<td>0.17 (0.12 to 0.23) P=0.0001</td>
</tr>
<tr>
<td>Non-condensation dampness</td>
<td>334/519</td>
<td>324/516</td>
<td>0.23 (0.18 to 0.30) P&lt;0.0001</td>
</tr>
<tr>
<td>Heating/ineffective†</td>
<td>61/304</td>
<td>104/375</td>
<td>0.38 (0.26 to 0.55) P=0.0001</td>
</tr>
</tbody>
</table>

**Table 5 | Temperature and relative humidity in a trial of insulating houses**

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>13.6</td>
<td>13.2</td>
<td>0.40 (0.10 to 0.70) P=0.05</td>
</tr>
<tr>
<td>Relative humidity (%)</td>
<td>68.6</td>
<td>68.3</td>
<td>0.79 (0.64 to 0.97) P&lt;0.0001</td>
</tr>
<tr>
<td>Average hours/day ≥10°C</td>
<td>3.25</td>
<td>4.02</td>
<td>1.04 (0.77 to 1.16) P=0.06</td>
</tr>
<tr>
<td>Average hours/day ≥75% relative humidity</td>
<td>6.81</td>
<td>6.78</td>
<td>0.90 (0.77 to 1.05) P=0.20</td>
</tr>
</tbody>
</table>

*Question answered for both years and adjusted for baseline status, region, and amount of sunshine.
†Excludes those who reported using no heating in either year.
‡Estimated full fuel data for both years, including self reported wood, coal, and liquefied petroleum gas; adjusted for region and fuel use in year 1.
§Measured for both years on a subsample.
¶Full fuel data for both years; households use only electricity and mains gas; adjusted for region and fuel use in year 1.
∥Estimated full fuel data for both years, including self reported wood, coal, and liquefied petroleum gas; adjusted for region and fuel use in year 1.
\*Measured and self reported
electricity.
\(\) Measured only includes self reported wood, coal, and liquefied petroleum gas.
\[\] Excludes those who reported using no heating in either year.
\{\} Households with full fuel data for year 2 only; adjusted for region only.
\(\) Measured and self reported.

---

**Fig 2 | Bedroom temperatures in houses from intervention and control groups. The area under the frequency curves is proportional to the average number of hours each day below 10°C**
sleep (0.57, 0.40 to 0.81; P=0.0019) or speech (0.51, 0.31 to 0.86; P=0.012) halved (table 6).

**Days off school and work**
Children in insulated houses were reported to have half the odds of having a day off school compared with the control group (0.49, 0.31 to 0.80; P=0.004), and fewer adults reported having had a day off work (0.62, 0.46 to 0.83; P=0.0017). When we analysed the data on days off work, we added the presence of non-working adults in the house to the model a priori to account for the situation at home (such as having someone able to care for sick children).

**General practitioner visits**
We received records from general practitioners for 82% of the participants. Self reports showed that visits to general practitioners were significantly lower for insulated houses (0.73, 0.62 to 0.87; P=0.0002), but the difference was not significant according to general practitioner records (0.95, 0.81 to 1.13; P=0.58) (table 8).

**Hospital admissions**
We were able to access the National Health Index number (and therefore the hospital records) for 80% of participants. We found little overall difference in the number of people who were admitted to hospitals for all causes between the intervention group and control group (4.4% v 4.7%). For respiratory conditions such as pulmonary disease and obstructive airways diseases, however, people from insulated houses were less likely to be admitted to hospital (0.8% v 1.3%; 0.53, 0.22 to 1.29; P=0.16). For conditions other than respiratory diseases, which are less likely to be related to quality of housing, the difference between the study groups was not significant.

### Table 6 | Health outcomes in trial of insulating houses

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group</td>
<td>Control group</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>SF-36 self report scales (adults with data for both years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low vitality (bottom 3 of 6 categories)</td>
<td>445 (967)</td>
<td>450 (954)</td>
<td>290 (967)</td>
</tr>
<tr>
<td>Low happiness score (bottom half of scale)</td>
<td>158 (960)</td>
<td>147 (944)</td>
<td>81 (960)</td>
</tr>
<tr>
<td>Fair or poor general health</td>
<td>231 (977)</td>
<td>245 (964)</td>
<td>145 (977)</td>
</tr>
<tr>
<td>Self reported symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colds or flu (participants with data for both years + babies)</td>
<td>—</td>
<td>—</td>
<td>855 (1481)</td>
</tr>
<tr>
<td>Wheezing in past 3 months (participants with data for both years)</td>
<td>591 (1409)</td>
<td>598 (1366)</td>
<td>412 (1409)</td>
</tr>
<tr>
<td>Morning phlegm (adults in matched set who answered in year 2)</td>
<td>—</td>
<td>—</td>
<td>283 (965)</td>
</tr>
<tr>
<td>Sleep disturbed by wheezing (children 0-12 years, both years)</td>
<td>233 (512)</td>
<td>214 (471)</td>
<td>142 (512)</td>
</tr>
<tr>
<td>Speech disturbed by wheezing (children 0-12 years, both years)</td>
<td>73 (507)</td>
<td>72 (468)</td>
<td>35 (507)</td>
</tr>
<tr>
<td>Days off work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had days off work (adults 18-64 working in year 2)</td>
<td>195 (487)</td>
<td>223 (500)</td>
<td>149 (588)</td>
</tr>
<tr>
<td>Number of days working adults had off work</td>
<td>Count data</td>
<td>0.62 (0.46 to 0.83)</td>
<td>P=0.0017*</td>
</tr>
<tr>
<td>Number of days working adults had off work</td>
<td>Count data</td>
<td>0.63 (0.41 to 0.96)</td>
<td>P=0.033</td>
</tr>
<tr>
<td>Days off school</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had days off school (6-17 year olds in school, year 1)</td>
<td>175 (246)</td>
<td>183 (257)</td>
<td>149 (246)</td>
</tr>
<tr>
<td>Number of days 6-17 year olds had off school</td>
<td>Count data</td>
<td>0.49 (0.31 to 0.80)</td>
<td>P=0.0044†</td>
</tr>
</tbody>
</table>

Twelve babies were born in the year between the first and second winter; 7 in the intervention group and 5 in the control group, for whom we received National Health information.

All adjusted odds ratios adjusted for age group, sex, and ethnic origin.

*Also adjusted for year 1 score or status, household, and region.
†Also adjusted for household and region.
‡Also adjusted for household.
§The first set of results used a zero inflated negative binomial model; the second set is the incident rate ratio.
¶Also adjusted for region and non-working adult in house.
**Also adjusted for region and number of working adults in house.
††Also adjusted for region and number of 6-17 year olds in house.
Table 7 | Self reported SF-36 results in a trial of insulating houses. Results are mean score in adults who had data for both years, unless stated otherwise

<table>
<thead>
<tr>
<th>Scale</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group</td>
<td>Control group</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Social functioning</td>
<td>69.2</td>
<td>69.3</td>
<td>78.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.1 (3.9 to 8.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P=0.0001</td>
</tr>
<tr>
<td>Role emotional</td>
<td>63.1</td>
<td>62.4</td>
<td>77.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.8 (7.2 to 14.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P=0.0001</td>
</tr>
<tr>
<td>Role physical</td>
<td>52.5</td>
<td>52.2</td>
<td>70.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11.2 (7.4 to 15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P=0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for score at baseline, age group, sex, ethnic origin, household, and region.

Table 8 | Use of health care in a trial of insulating houses. Values are number of people (total number of people with available data) unless stated otherwise

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group</td>
<td>Control group</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Self reported visit to general practitioner</td>
<td>813 (1448)</td>
<td>769 (1396)</td>
<td>664 (1448)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.81 (0.70 to 0.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P=0.0043</td>
</tr>
<tr>
<td>General practitioner reported visit</td>
<td>814 (1390)</td>
<td>765 (1346)</td>
<td>769 (1390)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.01 (0.86 to 1.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P=0.9484</td>
</tr>
<tr>
<td>Secondary care*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admitted to hospital; main code a respiratory condition</td>
<td>7 (1379)</td>
<td>10 (1340)</td>
<td>8 (1386)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.552 (0.23 to 1.32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P=0.18</td>
</tr>
<tr>
<td>Admitted to hospital; main code a control condition</td>
<td>48 (1379)</td>
<td>56 (1340)</td>
<td>43 (1386)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.865 (0.569 to 1.312)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P=0.50</td>
</tr>
</tbody>
</table>

Outcomes were measured on people with attendance records for both years in primary care and by using a unique identifier in the second year in secondary care. All adjusted odds ratios were adjusted for age, sex, and ethnic origin.

†Also adjusted for baseline value and region.
‡Also adjusted for region.
Householders spent significantly less on heating their houses after the intervention, and these savings may have increased their effective disposable income. The finding that householder took advantage of the efficiency gains to lower energy consumption is consistent with the relatively small change in mean temperature and other empirical studies in this area. It also suggests that the improvement seen in health was not due to average temperature and humidity changes, which were relatively small, but to larger changes in exposure to very low temperatures and high humidity.

Our study showed that a relatively modest investment in insulation per house (around £700 excluding taxes, or the cost of one inpatient hospital admission) led to significant improvements in the population’s self-reported health and a lower risk of children having time off school or adults having sick days off work. Participants in the intervention group reported significant improvements in their general health, respiratory symptoms, and sense of comfort and wellbeing. We saw no reduction in visits to general practitioners according to official reports; however, the absence of a unique patient identifier in primary care means that patients’ recall of visiting several general practitioners, which is common in New Zealand, may be more accurate than the records from their main practitioner. In secondary care, where a unique patient identifier exists, we saw a trend towards fewer admissions to hospital and fewer days in hospital for respiratory conditions.

Evidence from a major British cohort study has shown that the effects of poor housing conditions are cumulative over the life course. Thus, housing interventions can have significant health multiplier effects. A conservative cost-benefit analysis of this intervention trial indicated that the tangible health and energy benefits outweighed the costs by a factor approaching 2, when calculated in present value terms at a 5% real discount rate over 30 years, and that the energy savings component covered around half the cost of the insulation.

CONCLUSION

Our study has shown that it is possible to balance the practicalities of working in partnership with communities with the rigour of a randomised controlled study. Improving the thermal properties of older houses led to warmer houses and had demonstrable health benefits. Interventions of this kind, which focus on low income communities and poorer quality housing, have the potential to reduce health inequalities. Fitting insulation is a cost-effective intervention for improving health and wellbeing and has a high degree of acceptance by the community, policy makers, and politicians.

We would like to thank Olivia James at Otara Health Inc; Jo Hunt at Opotiki Trade Training; Pounamu Skelton and the New Plymouth Office of Te Puni Kokiri; Johnina Stymes and Alberta Hunga at Te Iwi o Rakapaaka; Daya Fau at Te Wainohi o Kahungunu; Gail Chalmers and Porirua Housing Action Group; Linda Wall, June Robinson, and the Rata Branch of the Maori Women’s Welfare League; Ann Curre at Crown Public Health; the interviewers and retrofit teams; and all the householders who took part in our study. We are grateful to our community coordinators the late Ruth Nepia, Pounamu Skelton, and Jo-Ani Robinson. We also thank the general practitioners, the National Health Information Service, the energy companies who supplied us with utilisation data, and June Atkinson, who carried out the randomisation.

Funding: The Health Research Council of New Zealand, the Energy Efficiency and Conservation Authority, the Ministry of Health, Solid Energy, Oton, Christchurch City Council, Environment Canterbury, Hutt Mana Community Trust, MARA, Eastern Bay of Plenty Energy Trust, Wellington City Council, and Housing New Zealand Corporation.

Competing interests: None declared.

Ethical approval: This multicentre study was approved by the central region ethics committee.

Contributors: PH-C helped design, perform, analyse, and write up the study. AM helped design, perform, and write up the study. JC helped design, analyse, and write up the study. TC, DD, RC, NW helped design, analyse, and write up the study. CC, KSS, AW, and all the householders who took part in our study. We would like to thank Olivia James at Otara Health Inc; Jo Hunt at Opotiki Trade Training; Pounamu Skelton and the New Plymouth Office of Te Puni Kokiri; Johnina Stymes and Alberta Hunga at Te Iwi o Rakapaaka; Daya Fau at Te Wainohi o Kahungunu; Gail Chalmers and Porirua Housing Action Group; Linda Wall, June Robinson, and the Rata Branch of the Maori Women’s Welfare League; Ann Curre at Crown Public Health; the interviewers and retrofit teams; and all the householders who took part in our study. We are grateful to our community coordinators the late Ruth Nepia, Pounamu Skelton, and Jo-Ani Robinson. We also thank the general practitioners, the National Health Information Service, the energy companies who supplied us with utilisation data, and June Atkinson, who carried out the randomisation.

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WHAT IS KNOWN ON THIS TOPIC

Damp, cold, and mouldy houses are associated with poor health.

WHAT THIS STUDY ADDS

Insulating existing houses makes the indoor environment significantly warmer and drier, while lowering energy use. Fitting insulation significantly improves occupants’ self-rated health, self-reported wheezing, days off school or work, and visits to general practitioners, and results in fewer hospital admissions for respiratory conditions.
and MB helped design and write up the study. GD provided biostatistical advice. PH-C is guarantor.

10 The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. Lancet 1997;349:1341-6.
PHPSSSID=b7ef87229dce18fc6813a276606986.

Accepted: 14 December 2006
Folic acid supplements and risk of facial clefts: national population based case-control study

Allen J Wilcox, senior investigator,1 Rolv Terje Lie, professor,2 Kari Solvoll, retired,3 Jack Taylor, senior investigator,1 D Robert McConnaughey, senior programmer,4 Frank Åbyholm, professor,5 Hallvard Vindenes, consultant plastic surgeon,6 Stein Emil Vollset, professor,2 Christian A Drevon, professor3

ABSTRACT

Objective To explore the role of folic acid supplements, dietary folates, and multivitamins in the prevention of facial clefts.

Design National population based case-control study.


Participants 377 infants with cleft lip with or without cleft palate; 196 infants with cleft palate alone; 763 controls.

Main outcome measures Association of facial clefts with maternal intake of folic acid supplements, multivitamins, and folates in diet.

Results Folic acid supplementation during early pregnancy (≥400 µg/day) was associated with a reduced risk of isolated cleft lip with or without cleft palate after adjustment for multivitamins, smoking, and other potential confounding factors (adjusted odds ratio 0.61, 95% confidence interval 0.39 to 0.96). Independent of supplements, diets rich in fruits, vegetables, and other high folate containing foods reduced the risk somewhat (adjusted odds ratio 0.75, 0.50 to 1.11). The lowest risk of cleft lip was among women with folate rich diets who also took folic acid supplements and multivitamins (0.36, 0.17 to 0.77). Folic acid provided no protection against cleft palate alone (1.07, 0.56 to 2.03).

Conclusions Folic acid supplements during early pregnancy seem to reduce the risk of isolated cleft lip (with or without cleft palate) by about a third. Other vitamins and dietary factors may provide additional benefit.

INTRODUCTION

The discovery that folic acid in early pregnancy reduces the risk of neural tube defects is one of the important public health advances of recent years.1 Even before folic acid deficiency had been linked to neural tube defects, it was known to produce facial clefts in rodents.2 However, studies of an association with facial clefts in humans have provided inconsistent results,3,4 and the question remains unresolved.4

This question is especially relevant in countries where fortification of foods with folic acid has not been allowed. One of these is Norway, which has one of the highest rates of facial clefts in Europe.10 We assessed possible effects of folic acid on facial clefts in Norway through a population based case-control study.

METHODS

Study design

Infants born in Norway with orofacial clefts are treated at government expense in one of two surgical centres (Oslo and Bergen). We contacted the families of all newborn infants born from 1996 to 2001 who had been referred for surgical treatment of a cleft (either cleft lip with or without cleft palate or cleft palate only). During the same years, we randomly selected an average of four per thousand live births (identified through the medical birth registry of Norway) as controls. These babies served as controls for both case groups, with a case:control ratio of about 1:2 for cleft lip with or without cleft palate, and 1:4 for cleft palate only. Mothers and fathers provided informed consent.

Data collection

Mothers completed two mailed questionnaires. The main questionnaire collected data on demographic characteristics; reproductive history; and smoking, alcohol, drugs, and other exposures during early pregnancy. The median time from the baby’s delivery to completion of the main questionnaire was 14 weeks for cases and 15 weeks for controls (interquartile range 13-17 weeks).

After returning the main questionnaire, mothers were sent a second questionnaire on nutrition. This quantitative food frequency questionnaire was developed for the Norwegian diet and has been assessed for accuracy, validity, and reliability among diverse groups of Norwegian adults.11-13 We adapted this questionnaire slightly for women of reproductive age and asked women to recall their diet during the first three months of pregnancy. The main questionnaire and the nutritional questionnaire are available online (dir. niesh.nih.gov/direb/studies/ncl/question.htm).

We used three sources to identify non-cleft birth defects among cases: the medical birth registry (based on delivery records and hospital records during the first week of life), medical records at the hospital doing the corrective surgery, and the mothers’ questionnaire. For the analysis of “isolated clefts,” we excluded cases with a non-cleft birth defect ascertained from any of these sources.
Intake of folic acid supplements
For each of the six months preceding pregnancy and each of the first three months of pregnancy, mothers were asked whether they took folic acid supplements and, if so, the specific product name. We contacted women who reported taking folic acid and asked them to send an empty pill bottle or label to the study office, so that staff could confirm the contents and dosage.

To be consistent with previous clefts studies,7,8 we defined a three month exposure window for folic intake comprising the month before the last menstrual period and the first two months of pregnancy. (Facial structures that form the embryonic lip fuse during the fifth and sixth weeks of life, about eight weeks after the last menstrual period, whereas the palatal shelves fuse during weeks seven to 10.14) We counted women as exposed if they took folic acid for at least one month during this window; 81% of exposed women took folic acid for at least two of the three months.

Women who reported using folic acid supplements were asked in which specific months they took them and how often they took them. Among women who reported taking folic acid, we were able to confirm intake for 99% by using the product name or pill bottle label.

Specific dose was unavailable for 19% of women taking folic acid. We imputed missing doses as follows. Before 1999, folic acid supplements of 400 µg were unavailable in Norway except by prescription. Norway changed this policy in 1998,15 and 400 µg preparations became available over the counter. This change was reflected in our data: most women taking folic acid before 1999 were taking less than 400 µg, while 85% of women taking folic acid after 1998 took 400 µg or more. Accordingly, when dose was missing, we imputed 100 µg up to 1998 and 400 µg thereafter.

Women were asked similar questions about multivitamins; we again collected brand names, empty bottles, and labels for documentation. Fifty six per cent of multivitamins contained folic acid. Among those with known dose of folic acid, 70% provided 100 µg or less (median 100 µg). For women who took multivitamins containing folic acid at an unknown dose, we imputed 100 µg.

We estimated each woman’s total folic acid intake from folic acid supplements and multivitamins based on the folic acid dosage (known or imputed) and the frequency of intake. The standard recommendation in Norway (as elsewhere) is 400 µg folic acid a day in the periconceptional period.15 Fifty five per cent of women who took folic acid supplements got an average of 400-500 µg folic acid a day; only 12% got higher doses. Accordingly, we categorised perinatal folic acid intake into three groups: none, less than the current recommended daily dose (1-399 µg), and the recommended daily dose (≥400 µg). For dichotomous analyses, we assessed folic acid as <400 µg or ≥400 µg a day, consistent with previous studies.17

Intake of dietary folate
We estimated dietary folate intake by applying official Norwegian food composition tables to mothers’ responses on the food frequency questionnaire, with adjustments for the usual methods of food preparation. We categorised dietary folate a priori into quarters on the basis of the folate distribution among controls.

RESULTS
Participants
Among the nearly 300 000 women who delivered in Norway during the time of our study (1996-2001), 676 mothers had a baby with an orofacial cleft referred for corrective surgery. We excluded 24 mothers who did not speak Norwegian or whose baby died after birth, leaving 652 eligible case mothers. Of these, 88% (573) agreed to participate (377 with cleft lip with or without cleft palate and 196 with cleft palate only). We randomly selected 1022 live births within six weeks of delivery to serve as controls. After we excluded 16 mothers who were not Norwegian speakers or whose baby died, 1006 control mothers were eligible, of whom 76% (763) agreed to participate.

More than 95% of mothers were married or living as if married. Mean maternal age was 29 years, and about 40% of mothers delivered for the first time. Ten per cent of control mothers took ≥400 µg folic acid supplements as well as multivitamins in early pregnancy, 9% took folic acid alone, and 26% took multivitamins alone. Among the cases, 17% of babies with cleft lip with or without cleft palate also had some other birth defect, and 40% of those with cleft palate only had accompanying defects (table 1).

Folic acid supplement
Table 2 shows odds ratios for clefts with folic acid supplements. The crude odds ratio with folic acid of ≥400 µg/day was 0.66 (95% confidence interval 0.47 to 0.95) for cleft lip with or without cleft palate and 0.81 (0.53 to 1.26) for cleft palate only. Associations were present only among the cases with isolated clefts (that is, those with no other birth defects; data not shown). We therefore restricted subsequent analyses to the isolated clefts. Adjustment for potential confounding factors (diet and multivitamins, mother’s education, mother’s employment during early pregnancy, smoking, alcohol consumption, and year of baby’s birth) slightly weakened the association between folic acid and cleft lip with or without cleft palate and removed the association entirely for cleft palate only. Lacking any evidence of an effect of folic acid on cleft palate only (odds ratio 1.07, 0.56 to 2.03), we focused the remainder of the analysis on cleft lip with or without cleft palate.

We explored additional adjustments for parity, age of mother and father, marital status, and measures of family income, all of which produced little or no change in estimates. Results were also unchanged after exclusion of women with imputed values for folic acid.

None of the analyses, either crude or adjusted, suggested any association of low dose folic acid (<400 µg/day) with clefting. In the dichotomous analysis of folic acid (<400 µg/day or ≥400 µg/day), the adjusted
relative risk for isolated cleft lip with or without cleft palate was 0.61 (0.39 to 0.96).

Dietary folates
The estimated median intake of dietary folates (adjusted for usual method of cooking) was 205 (interquartile range 160-260) µg/day. Dietary folate intake across quarters was moderately associated with the crude risk of cleft lip with or without cleft palate (P for trend=0.03) (table 3). The relative risk for women above the median compared with those below was 0.78 (0.61 to 1.01). Adjustment for covariates weakened this above the median compared with those below was 0.78 (0.61 to 1.01). Adjustment for covariates weakened this risk slightly {0.80, 0.60 to 1.08).

Multivitamins
Intake of multivitamins around conception showed a similarly modest association with reduced risk of cleft lip with or without cleft palate (crude odds ratio 0.77, 0.57 to 1.03). Adjustment for covariates (including folic acid) again produced minimal change (0.75, 0.50 to 1.11).

Combining three sources of folic acid and vitamins
The figure shows adjusted odds ratios for eight groups of mothers, categorised by whether the mothers were above or below the median for dietary folate, whether they were taking multivitamins around conception (yes or no), and whether they were taking ≥400 µg folic acid around conception (yes or no). Women with lower measures in all three categories are the reference group. The estimated relative risk for isolated cleft lip with or without cleft palate with folic acid from the three categories is the reference group. The estimated median intake of dietary folates (based on recalled intake of fruit and vegetables) probably was not possible in earlier studies.

Strengths and weaknesses
Study design—Cases were drawn from a large and well defined population, with virtually complete ascertainment, a high participation rate (88%), and clinical confirmation of all defects. Although the participation rate was lower for controls (76%), the controls had the advantage of being drawn randomly from the entire population of births. Our study was designed to test the folate hypothesis. Women were contacted as soon as possible after delivery to reduce the recall interval.

We cannot reconstruct the mothers’ complete exposure history retrospectively, but the collection of brands, bottles, and labels allowed us to correct some errors in self report.

Data quality—Folic acid is a synthetic folate dispensed in well calibrated doses. Although error in measurement inevitably occurs (for example, owing to missing data or errors in reported frequency of intake), folic acid is estimated more reliably than dietary folates. Nutritional assessment is notoriously inexact. In addition, our measure of dietary folate (based on recalled intake of fruit and vegetables) probably

<table>
<thead>
<tr>
<th>Demographic and other characteristics of mothers and children, cases and controls, Norway 1996–2001. Values are numbers (percentages)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers</td>
</tr>
<tr>
<td>Age (years):</td>
</tr>
<tr>
<td>&lt;20</td>
</tr>
<tr>
<td>20-29</td>
</tr>
<tr>
<td>30-39</td>
</tr>
<tr>
<td>≥40</td>
</tr>
<tr>
<td>Education less than high school</td>
</tr>
<tr>
<td>Employment in early pregnancy</td>
</tr>
<tr>
<td>Folic acid supplement*:</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>1-399 µg</td>
</tr>
<tr>
<td>2400 µg</td>
</tr>
<tr>
<td>Dietary folate, µg (quarters):</td>
</tr>
<tr>
<td>0-171</td>
</tr>
<tr>
<td>172-214</td>
</tr>
<tr>
<td>215-264</td>
</tr>
<tr>
<td>≥265</td>
</tr>
<tr>
<td>Multivitamins*:</td>
</tr>
<tr>
<td>Cigarette smoking†:</td>
</tr>
<tr>
<td>No exposure</td>
</tr>
<tr>
<td>Passive only</td>
</tr>
<tr>
<td>Active, 1-5</td>
</tr>
<tr>
<td>Active, 6-10</td>
</tr>
<tr>
<td>Active, ≥11</td>
</tr>
<tr>
<td>Alcoholic beverages‡:</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1-3</td>
</tr>
<tr>
<td>4-6</td>
</tr>
<tr>
<td>≥7</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>Infants</td>
</tr>
<tr>
<td>*Any intake of folic acid supplements (either alone or with multivitamins) during month before pregnancy and first two months of pregnancy.</td>
</tr>
<tr>
<td>†Number of cigarettes per day.</td>
</tr>
<tr>
<td>‡Total number of drinks during the first three months of the pregnancy.</td>
</tr>
</tbody>
</table>
captures many aspects of good nutrition, and the observed association with dietary folate could reflect the effects of other vitamins in addition to folates.

Bias—As in all case-control studies, recall bias is a concern. We sent the main questionnaire to women around three months after delivery, much earlier than in many previous studies. Concerns about recall bias were further reduced by the specificity of the findings. In our data, the association with folic acid was strong for cleft lip with or without cleft palate but absent for cleft palate only. This is consistent with previous positive studies, which have found associations more often with cleft lip with or without cleft palate than with cleft palate only.\(^\text{2,4-7}\) Also, recall bias would presumably operate among all women who took folic acid, not only those who took the higher doses. The fact that folic acid less than 400 \(\mu g\) a day showed no association with clefts suggests a lack of recall bias.

Confounding—Confounding is a general threat to observational studies, particularly when the response rate is higher among cases than among controls. Differential participation by social class or other confounding characteristics could contribute to the observed associations. However, adjustments for social factors, alcohol, smoking, and other potential confounding variables had little impact on the estimates. This weak evidence for confounding in the analysis reduces the likelihood of residual confounding by these or other closely related factors. We cannot rule out the presence of unmeasured confounders, although such confounders would have to be strongly related to cleft lip with or without cleft palate in order to produce the observed results.

Comparisons with previous human studies
Previous evidence from epidemiological studies of folic acid and clefts has been mixed.\(^\text{3-7}\) Some ambiguity in previous studies may reflect the relatively weaker association of folic acid with clefts compared with neural tube defects. Furthermore, most of the earlier clefts studies were not specifically designed to test the folic acid hypothesis, few were able to distinguish intake of folic acid from intake of multivitamins, and none sought documentation of reported intake. Recently, van Rooij and colleagues reported a protective effect on isolated cleft lip with or without cleft palate with folic acid supplement alone,\(^\text{7}\) although this study was limited by a small sample and a haphazard set of controls. The plausibility of a specific role for folic acid in preventing cleft lip is further supported (albeit indirectly) by a study of pregnant women taking drugs that can act as folic acid antagonists.\(^\text{17}\) An increased risk of facial clefts was reported among the prenatally exposed infants. No previous studies have collected information on daily folic acid intake less than 400 \(\mu g\), and so we are unable to compare our finding of an apparent threshold effect with other studies.

Contribution of other vitamins
The finding that the relatively low levels of dietary folates (which are less bioavailable than folic acid) seemed to be weakly protective against cleft lip with

### Table 2

<table>
<thead>
<tr>
<th>Folic acid supplement ((\mu g/\text{day}))</th>
<th>All cases: crude risk</th>
<th>Isolated clefts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=377</td>
<td>n=314</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.98 (0.73 to 1.33)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.97 (0.70 to 1.35)</td>
</tr>
<tr>
<td></td>
<td>0.97 (0.69 to 1.36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.17 (0.75 to 1.84)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=287</td>
<td>n=287</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.66 (0.47 to 0.95)</td>
</tr>
<tr>
<td></td>
<td>0.58 (0.39 to 0.86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.57 (0.38 to 0.85)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.65 (0.40 to 1.05)</td>
<td></td>
</tr>
<tr>
<td>Cleft lip with or without cleft palate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=196)</td>
<td>(n=118)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>0.90 (0.54 to 1.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.92 (0.55 to 1.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.07 (0.56 to 2.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleft palate only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=114)</td>
<td>(n=114)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1.06 (0.72 to 1.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.02 (0.63 to 1.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.09 (0.67 to 1.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.98 (0.51 to 1.90)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjusted risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=377</td>
</tr>
<tr>
<td>1.0</td>
</tr>
<tr>
<td>0.97 (0.65 to 1.46)</td>
</tr>
<tr>
<td>n=287</td>
</tr>
<tr>
<td>1.0</td>
</tr>
<tr>
<td>0.97 (0.65 to 1.46)</td>
</tr>
</tbody>
</table>

*Adjusted for variables as in Table 2, plus periconceptional folic acid (less than 400, \(\geq 400 \mu g/\text{day}\)) and periconceptional multivitamin use (yes or no).

### Table 3

<table>
<thead>
<tr>
<th>Dietary folate (quartiles)</th>
<th>All (354 cases; 704 controls): crude risk</th>
<th>Subset with complete data (287 cases; 664 controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>1.0</td>
<td>Crude risk</td>
</tr>
<tr>
<td>Q2</td>
<td>0.86 (0.59 to 1.26)</td>
<td>0.86 (0.59 to 1.26)</td>
</tr>
<tr>
<td>Q3</td>
<td>0.71 (0.49 to 1.05)</td>
<td>0.70 (0.47 to 1.03)</td>
</tr>
<tr>
<td>Q4</td>
<td>0.75 (0.51 to 1.11)</td>
<td>0.74 (0.50 to 1.09)</td>
</tr>
</tbody>
</table>

Crude risk

| Adjusted risk†              |
|----------------------------|--------------------------------|
| n=377                      |
| 1.0                        |
| 0.86 (0.59 to 1.26)        |
| n=287                      |
| 1.0                        |
| 0.86 (0.59 to 1.26)        |

†Adjusted for variables as in Table 2, plus periconceptional folic acid (less than 400, \(\geq 400 \mu g/\text{day}\)) and periconceptional multivitamin use (yes or no).
WHAT IS ALREADY KNOWN ON THIS TOPIC
Folic acid supplementation in the periconceptional period reduces the risk of neural tube defects
Benefits from folates in the prevention of other birth defects have not been established

WHAT THIS STUDY ADDS
The risk of cleft lip with or without cleft palate seems to be substantially reduced by folic acid supplements during the month before pregnancy and the first two months of pregnancy
Similar benefits are not apparent for cleft palate

or without cleft palate, even though we saw no evidence for a protective effect of low dose folic acid supplements (<400 µg/day), is curious. This suggests that other nutritional factors correlated in diet with the folates may have a role in preventing cleft lip with or without cleft palate. Several observations support this possibility. Multivitamins in the absence of folic acid showed a weakly protective effect. Also, we saw a stronger effect when dietary folate and multivitamins were combined, even in the absence of folic acid supplement (figure). The possibility of other nutritional components in the causation of cleft lip with or without cleft palate may help to explain why the population distributions of cleft lip with or without cleft palate and neural tube defects are not more similar; neural tube defects are a category of birth defect strongly and specifically associated with folates. The role of unmeasured nutritional factors in combination with folic acid deserves further investigation.2

Prevalence of birth defects and population attributable risk
This study provides a population based assessment of the risk of clefting, with reasonable participation rates, documented folic acid exposure, and clinically validated outcomes. The size of the actual effect in utero is not estimable, given that unmeasured fetal losses may distort this relation.18 Even so, our data provide a basis for assessing the public health impact of folic acid supplementation. Given the current levels of folic acid supplementation in Norway, and the estimated reduction in risk from folic acid, we estimate that an additional 22% of isolated cases of cleft lip with or without cleft palate could be averted if all pregnant women took ≥400 µg of folic acid a day.

An increase in intake of folic acid has occurred in many developed nations through supplements and (in some countries) through food fortification. If our findings are correct, these increases in folic acid exposure ought to produce reductions in the prevalence of cleft lip with or without cleft palate at the population level. Results have been mixed, with reductions reported in some areas but not others.19-21 Reductions in neural tube defects at the population level have also been difficult to document,22 even though the benefits of folic acid for neural tube defects have been proved in clinical trials.1 The inherent difficulties of detecting population level changes in rare diseases may contribute to this inconclusive evidence.

Conclusion
Intake of 400 µg a day or more of folic acid in the periconceptional period seems to reduce the risk of isolated cleft lip with or without cleft palate in Norway by about a third. This apparent effect of folic acid is relevant to ongoing discussions about food fortification. If folic acid is able to prevent a major birth defect in addition to neural tube defects, this benefit should be included among the risks and benefits of fortifying foods with folic acid, a matter of ongoing controversy in many countries.23

We are indebted to the dedicated staff who did the fieldwork for this study (Maria Axcro, Nina Howland, Asse Gunn Mjåvatnet, Gunnar mid, and Lil Stallone). We thank Donna Baird, Olga Basso, Freya Kamel, Matthew Longnecker, Ron Manger, Ruby Nguyen, Dale Sandler, Min Shi, and Clarice Weinberg for useful criticisms of earlier drafts of this paper.

Contributors: All authors made substantial contributions to the intellectual content of the manuscript and all have approved the final version. AJW originated the study, designed the field work, analysed the data, contributed critical insights in interpretation of data, and had primary responsibility for writing the paper. RTL originated the study, designed and supervised the field work, helped in analysis of data, and contributed critical insights in interpretation of data. KS contributed to the design of the field study, supervised the scanning and interpretation of the food frequency questionnaire, and participated in the interpretation of data. JF contributed substantially to the design of the field study. DRMcC made substantial contributions to the cleaning of the data, did the programming for data analysis, and contributed critical insights in interpretation. F contributed to the design of the field study, provided clinical access to cases, and contributed critical insights in interpretation of data. HV contributed to the design of the field study, provided clinical access to cases, and contributed critical insights in interpretation of data. SEV contributed to the design of the field study and participated in the interpretation of data. CAD contributed to the design of the field study, designed the food frequency questionnaire, and participated in the interpretation of data. AJW is the guarantor.

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Management of kidney stones

Nicole L Miller, James E Lingeman

Urolithiasis affects 5-15% of the population worldwide.1 Recurrence rates are close to 50%, and the cost of urolithiasis to individuals and society is high. Acute renal colic is a common presentation in general practice, so a basic understanding of its evaluation and treatment would be useful. Most of the literature is retrospective, but we will try to provide an evidence based review of the management of urolithiasis and will cite prospective randomised controlled trials when available.

Sources and selection criteria
We performed a literature search to identify information on the management of urolithiasis. We searched databases including Medline and the Cochrane Library to assemble appropriate evidence based reference material.

What is the clinical presentation and initial evaluation?
Initial evaluation of the patient with urolithiasis should include a complete medical history and physical examination. Typical symptoms of acute renal colic are intermittent colicky flank pain that may radiate to the lower abdomen or groin, often associated with nausea and vomiting.1 Lower urinary tract symptoms such as dysuria, urgency, and frequency may occur once a stone enters the ureter.

Comorbid diseases should be identified, particularly any systemic illnesses that might increase the risk of kidney stone formation or that might influence the clinical course of the disease (box 1). Other important features are a personal or family history of kidney stones with previous treatments and stone analysis, and any anatomical abnormalities or surgery of the urinary tract (box 1). A complete history of drugs use can help identify those that are known to increase the risk of kidney stones (box 1).2

Assessment should include measurement of vital signs because fever may be an indication for acute intervention (box 2). Physical examination often reveals costovertebral angle or lower abdominal tenderness. Urinalysis should be performed in all patients. Microscopic haematuria combined with the typical symptoms of renal colic is highly predictive of urolithiasis, but stones may occur in the absence of haematuria.3 Positivity for nitrates or bacteria and leucocytes on urine dipstick analysis may indicate urinary tract infection, in which case urine should be sent for culture. Finally, microscopic urinalysis may identify crystals, such as the classic hexagonal crystals seen in cystinuria. In the acute setting, laboratory evaluation includes complete blood count, serum electrolytes, and measurement of renal function. A more detailed metabolic evaluation is best performed after the acute stone event has resolved.3

How is the diagnosis made?
Unenhanced helical computed tomography is the best radiographical test for diagnosing urolithiasis in patients with acute flank pain.4 Intravenous urography was formerly the gold standard, but recent prospective trials have shown that computed tomography is the best method for diagnosing ureteral calculi.5 If the symptoms are not caused by urolithiasis, computed tomography can often identify the real cause.6 Most kidney stones (box 3) are visible on computed tomography, except for stones induced by certain drugs, such as indinavir.

A plain abdominal radiograph can determine whether stones are radio-opaque and can be used to monitor disease activity. Alternatively, some clinicians prefer to use computed tomography in the follow-up of kidney stones, particularly when the stone is radio-lucent. Ultrasound is rarely used because of its relatively low sensitivity, although it is often used as the initial imaging test in pregnant patients with flank pain.6

SUMMARY POINTS
Unenhanced helical computed tomography is the best radiographic technique for diagnosing urolithiasis
Shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy have replaced open surgery for treating urolithiasis
Most simple renal calculi (80-85%) can be treated with shock wave lithotripsy
Percutaneous nephrolithotomy is the treatment of choice for complex renal calculi
Staghorn calculi should be treated, and percutaneous nephrolithotomy is the preferred treatment in most patients
Ureteroscopy is the preferred treatment in pregnant, morbidly obese, or patients with coagulopathy
Most ureteral calculi <5 mm in diameter will pass spontaneously within four weeks of the onset of symptoms

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**Box 1: Important factors to identify in the patient’s history**

Presence of systemic illness
- Primary hyperparathyroidism
- Renal tubular acidosis
- Cystinuria
- Gout
- Diabetes mellitus
- Inflammatory bowel disease
- Renal insufficiency
- Sarcoidosis
- Medullary sponge kidney

Anatomical features
- Presence of horseshoe kidney
- Previous urinary diversion
- Obstruction of the ureteropelvic junction
- Solitary kidney
- Previous renal or ureteral surgery

Previous kidney disease
- History of urinary tract infection or pyelonephritis, or both
- Family history of urolithiasis
- Detailed history of previous stone events
- Treatment
- Stone analysis

Drugs that affect stone disease
- Carbonic anhydrase inhibitors (topirimate)
- Ephedrine
- Guaifenesin
- Calcium with vitamin D
- Triamterene
- Indinavir or sulfadiazine

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**What are the indications for urgent intervention?**

Urgent intervention is most often needed in acute obstruction. Once a stone passes into the ureter, obstruction may cause reduced glomerular filtration rate and renal blood flow. Box 2 lists the indications for acute intervention. A randomised controlled trial found that ureteral catheters, ureteral stents, and percutaneous nephrostomy tubes are equally effective for decompressing the urinary tract. Bladder and renal pelvic urine should be sent for culture and antibiotic sensitivity testing. Broad spectrum antibiotics are best prescribed initially, and further antimicrobial treatment should be tailored to the results of urine culture.

While parenteral narcotics have traditionally been prescribed for acute renal colic, non-steroidal anti-inflammatory drugs such as ketorolac and diclofenac are effective in relieving pain by inhibiting prostaglandin mediated pain pathways and decreasing ureteral contractility. However, non-steroidal anti-inflammatory drugs should be avoided in patients with compromised renal function or a history of gastrointestinal bleeding.

**What are common treatments for nephrolithiasis?**

Open surgery was the mainstay of treatment for urolithiasis, but it has now been supplanted by less invasive treatments.

**Shock wave lithotripsy**

The introduction of shock wave lithotripsy in the early 1980s revolutionised the treatment of nephrolithiasis. A shock wave is generated by a source external to the patient that propagates through the body before being focused on a kidney stone. Shock waves cause stone fragmentation directly by producing mechanical stresses or indirectly by the collapse of cavitation bubbles.

Although shock wave lithotripsy is the most common treatment for urolithiasis, it can have side effects. In human and animal models it can cause acute renal injury. Computed tomography and magnetic resonance imaging have demonstrated renal injury in 63-85% of patients treated with shock wave lithotripsy. A recent retrospective case-control study with 19 year follow-up noted an association between shock wave lithotripsy and the development of hypertension and diabetes mellitus. In the lithotripsy group, diabetes developed in 16.8% of patients versus 6.6% of controls. The chronic effects of shock wave lithotripsy are an area of ongoing research.

**Ureteroscopy**

Ureteroscopy involves retrograde visualisation of the collecting system using a rigid, semi-rigid, or flexible endoscope. Improved fibreoptics and deflectability and the reduced size of ureteroscopes have expanded the use of ureteroscopy for stones in the upper urinary tract. The ureteroscope has a working channel that allows the introduction of a variety of instruments for stone fragmentation and removal.

A retrospective study showed that ureteroscopy is useful when lithotripsy fails; when complex or lower pole renal calculi are present, or when patient factors such as pregnancy, coagulopathy, or morbid obesity preclude lithotripsy. One disadvantage of ureteroscopy is that a ureteral stent, which causes considerable discomfort in some patients, is often necessary to prevent obstruction from ureteral oedema or stone fragments.

**Percutaneous nephrolithotomy**

Percutaneous nephrolithotomy involves creating an access tract into the renal collecting system through which nephroscope can be performed. The nephroscope has a working channel through which an intracorporeal lithotripsy device (lithotrite or laser) can be introduced. Stone fragments are removed using suction, graspers, or basket extraction. The technique enables stones to be retrieved for analysis, and all stone material can be removed so that the patient does not have to pass any fragments, as is common with shock wave lithotripsy and ureteroscopy. Although percutaneous nephrolithotomy is thought to be more invasive than other treatments, a large meta-analysis has demonstrated its safety and efficacy, particularly when stones are large, multiple, or complex.

**What are the guidelines for treatment selection?**

The fundamental principle guiding treatment selection is to maximise stone clearance while minimising patient
morbidity. The decision making process can be simplified by stratifying stones into clinical categories based on location (renal or ureteral) and complexity (simple or complex).

Renal calculi
The characteristics of the stones (size, number, location, and composition), renal anatomy, and clinical factors are all considered when selecting a treatment approach for renal calculi.

Simple renal calculi
Simple renal calculi are those with a stone burden of <2 cm (aggregate diameter) and normal renal anatomy. Most simple renal calculi (80-85%) can be treated successfully with shock wave lithotripsy (fig 1). However, lithotripsy may fail or be less effective when stones are larger; stones are located in dependent or obstructed parts of the collecting system; stones are made up of calcium oxalate monohydrate, brushite, or cystine; the patient is obese or has a body build that inhibits proper imaging; or it is difficult to target the stone for shock wave delivery and subsequent fragmentation. A retrospective comparison of percutaneous nephrolithotomy and shock wave lithotripsy found that as stone burden increased, the number of lithotripsy treatments and ancillary procedures increased, but stone-free rates decreased.

Percutaneous nephrolithotomy results in higher stone-free rates and lower retreatment rates than shock wave lithotripsy. Because it is more invasive, however, percutaneous nephrolithotomy is usually reserved for patients in whom shock wave lithotripsy fails or those who are unsuitable for lithotripsy. Ureteroscopy is an increasingly used alternative for treating simple renal calculi because it has similar stone-free rates to shock wave lithotripsy and morbidity is lower than with percutaneous nephrolithotomy. Ureteroscopy is especially attractive in coagulopathic, pregnant, or morbidly obese patients where shock wave lithotripsy or percutaneous nephrolithotomy are less effective or contraindicated.

Complex renal calculi
Complex renal calculi include stones >2 cm, such as staghorn calculi; stones occurring in kidneys with abnormal anatomy; and stones resistant to fragmentation. Recently published guidelines of the American Urologic Association recommend that staghorn calculi should not be treated with lithotripsy because of relatively poor stone-free rates. Ureteroscopy has been used to treat upper tract stones >2 cm, but stone clearance rates are significantly lower than with percutaneous nephrolithotomy and stones recur rapidly (10% within six months). For this reason, percutaneous nephrolithotomy is the treatment of choice for most complex renal stones (fig 2). Combined percutaneous nephrolithotomy and shock wave lithotripsy (sandwich therapy) for complex stones was commonplace in the 1990s, but improvements in percutaneous nephrolithotomy techniques have led to a decline in the need for shock wave lithotripsy. Even the largest staghorn calculi can be cleared percutaneously with the aid of secondary look nephroscopy and multiple access tracts.

The management of lower pole calyceal calculi remains controversial. A prospective randomised multicentre trial showed that percutaneous nephrolithotomy was better than shock wave lithotripsy in the clearance of lower pole calculi >1 cm (stone-free rates of 91% vs 21%). However, for lower pole calculi <1 cm, a recent prospective randomised trial failed to show a statistically significant difference in stone-free rates between the two techniques. Urolithiasis associated with aberrant renal anatomy can present a treatment challenge. All three techniques described above and even laparoscopy have been used to treat calculi in these situations.

Ureteral calculi
Ureteral calculi most commonly present with symptoms of acute renal colic. If urgent intervention is not needed (see box 2), the patient and clinician must decide whether to intervene or proceed with expectant management. The likelihood of spontaneous passage decreases as stone size increases.

An extensive meta-analysis is found that most ureteral calculi <5 mm in diameter will pass through the urinary tract spontaneously. Spontaneous passage usually occurs within four weeks after the onset of symptoms. If a stone has not been passed within four weeks, intervention is indicated, as the risk of complications such as ureteral stricture and renal deterioration increase. Therefore, observation is adequate for stones <5 mm if symptoms can be controlled and follow-up is ensured.
For the purposes of selecting treatment, ureteral calculi can be divided into categories on the basis of location—proximal or distal—with the point of division being the narrow part of the ureter over the iliac vessels.

**Proximal ureteral calculi**

Several endourological options are available for the treatment of proximal ureteral stones: shock wave lithotripsy with or without stone manipulation, ureteroscopy, and percutaneous nephrolithotomy. In 1997, the ureteral stones guidelines panel of the American Urologic Association recommended shock wave lithotripsy as the treatment of choice for stones ≤1 cm. Randomised controlled trials comparing the two techniques have reached conflicting conclusions.\(^2\) Unlike shock wave lithotripsy, ureteroscopy is not influenced by stone size and can be used to treat distal ureteral calculi >1 cm.\(^2\) Semirigid ureteroscopy has a success rate of 90-99% for treating distal ureteral stones.\(^2\) Ureteroscopy may also be the simplest solution in institutions with limited access to a lithotripter.

**Distal ureteral calculi**

Although the likelihood of spontaneous passage of stones is highest in the distal ureter, intervention with ureteroscopy or shock wave lithotripsy is often necessary. Both techniques are excellent options for symptomatic ureteral calculi <1 cm. Randomised controlled trials comparing the two techniques have reached conflicting conclusions.\(^2\) Dietary restrictions of calcium are not recommended as they may increase urinary oxalate excretion and result in negative calcium balance.\(^2\) Medical management of the recurrent or high risk stone former can be individually tailored using the results of the metabolic evaluation.

**What's new? Medical expulsive therapy**

This treatment comprises the use of drugs to help the spontaneous passage of ureteral calculi. Several drugs including calcium channel blockers (nifedipine),

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**Box 4 | Indications for comprehensive metabolic evaluation**

- Family history of urolithiasis
- Presence of bilateral stone disease
- Presence of inflammatory bowel disease, chronic diarrhoea, or malabsorption
- History of bariatric surgery
- Concurrent medical conditions associated with urolithiasis (primary hyperparathyroidism, gout, renal tubular acidosis)
- Presence of nephrocalcinosis
- Presence of osteoporosis or pathological skeletal fractures
- Stones are formed from cystine, uric acid, or calcium phosphate
- The patient is a child

**Box 5 | Components of a comprehensive metabolic evaluation**

- Analysis of stone composition
- Two 24 hour urine collections for:
  - Volume, pH, calcium, oxalate, citrate, uric acid, phosphate, sodium, potassium, magnesium, ammonium, chloride, sulfate, and creatinine
  - Cystine screen
- Measurement of serum calcium, bicarbonate, creatinine, chloride, potassium, magnesium, phosphate, and uric acid
- Measurement of blood urea nitrogen
- In cystinuric patients, evaluation as above and 24 hour measurement of cystine
- In hypercalcaemic patients, intact parathyroid hormone and 1,25 dihydroxyvitamin D
ADDITIONAL EDUCATIONAL RESOURCES


Information resources for patients

- International Kidney Stone Institute (www.iksi.org)—Website of a charitable organisation dedicated to supporting research into clinical and basic science and education to help detect, manage, and prevent kidney stone disease. It contains educational material for patients as well as a description of the ongoing research projects in the area of kidney stone disease.
- American Urological Association-Urology Health (www.urologyhealth.org)—Also contains user friendly information on the diagnosis and treatment of kidney stones.
- Patient UK (www.patient.co.uk)—This website contains comprehensive and free up to date information on various medical conditions, including kidney stones.
- National Kidney Foundation (www.kidney.org/atoz/atozTopic.cfm?topic=13)—An excellent resource for information on patients with various kidney problems such as chronic kidney disease, kidney stones, and those who need dialysis.

Contributors: NLM performed the literature search and wrote the manuscript. EJL reviewed, revised, and approved the final paper and will serve as guarantor.

Competing interests: EJL has been a consultant and adviser for Lumenis and Olympus; meeting participant and lecturer for Karl Storz; and an investigator and lecturer for Boston Scientific.

Provenance and peer review: Commissioned, externally peer reviewed.

Disorders of salt and water balance are extremely common in primary care. In many cases the cause is apparent and the result is not life threatening, but doctors should be aware of warning signs that may point to serious progressive disorders so that these can be diagnosed and managed early.

Many situations involving the use and interpretation of laboratory tests are not supported by the high levels of evidence that can be achieved when interventions are assessed, but considerable consensus guidance is available on optimal use of laboratory tests. This article considers two scenarios involving salt and water balance that may be seen in primary care and discusses when further investigations may be helpful, and it gives a summary of evidence based and consensus guidance.

Although disorders of salt and water balance are extremely common in primary care, their causes are usually apparent, and the primary clinical question that arises is whether any change of dosage or drugs is required (typically diuretics in heart failure).

Serious and rapidly progressing sodium and water balance problems are rarer, and the practitioner often needs to decide when to initiate further investigation.

**Case 1**

A 72 year old man with chronic obstructive pulmonary disease due to longstanding smoking presented to his general practitioner with a two week history of lethargy and feeling nauseated. The patient was being treated with furosemide 20 mg and enalapril 5 mg a day for congestive cardiac failure (doses unchanged over recent months). This was clinically stable, and he had been noted previously to be hyponatraemic (sodium 131 mmol/l at last check two months previously) with a moderate reduction in renal function (creatinine 124 μmol/l, estimated glomerular filtration rate 54 ml/min/1.73 m²).

On examination the patient did not have fever and his blood pressure was 146/88 mm Hg. He had slight ankle oedema, which had been noted previously, and was in sinus rhythm, rate 86 beats/min. His chest contained a few diffuse rhonchi but no focal signs. Heart sounds were normal. Electrolytes were reported as serum sodium 124 mmol/l, potassium 4.3 mmol/l, urea 6.2 mmol/l, and creatinine 111 μmol/l. He reported no change in regularity of taking his tablets, and repeat testing was arranged for one week later. This returned a sodium of 123 mmol/l. The doctor telephoned the laboratory to discuss the results.

The measured osmolality of the serum sample submitted was 256 mmol/kg water (reference range 280-301 mmol/kg in people over 60 years old), and the doctor was asked to submit a urine specimen from the patient for osmolality, which was found to be 560 mmol/kg. Urinary sodium concentration was 36 mmol/l, and random plasma glucose concentration was 6.1 mmol/l. These results were interpreted as inappropriate concentration of urine and a urinary sodium concentration that was inappropriately high in a patient with hyponatraemia and hypo-osmolar serum. After discussion with the local endocrinologist, a synacthen test was done to exclude adrenocortical deficiency. This showed adequate adrenocortical reserve: baseline cortisol 465 nmol/l rising to 780 nmol/l after 250 μg of intramuscular tetracosactrin (normal response is a rise >200 nmol/l to >550 nmol/l after 30 minutes). The doctor was advised to start giving the patient 1 litre fluid restriction pending an urgent specialist opinion.

On subsequent investigation, a plain chest x ray showed no abnormality, although thoracic computed tomography showed hilar lymphadenopathy. Subsequently, bronchoscopy showed a small hilar bronchial tumour, which was diagnosed histologically as small cell lung cancer. Fluid restriction was continued, pending assessment for chemotherapy, and his sodium concentration rose to 128 mmol/l 10 days later.

**Case 2**

A 42 year old woman with type 2 diabetes controlled by metformin and gliclazide attended her general practitioner with a two week history of lethargy and feeling nauseated. The patient was being treated with gliclazide 30 mg a day, metformin 850 mg daily, and insulin detemir 8 units daily for control of her diabetes. She had been noted previously to be hyponatraemic (sodium concentration rose to 128 mmol/l 10 days later).

On examination she did not have fever and her blood pressure was 130/70 mm Hg. She had slight ankle oedema, which had been noted previously, and was in sinus rhythm, rate 86 beats/min. Her chest contained a few diffuse rhonchi but no focal signs. Heart sounds were normal. Electrolytes were reported as serum sodium 118 mmol/l, potassium 4.4 mmol/l, urea 5.3 mmol/l, and creatinine 112 μmol/l. She reported no change in regularity of taking her tablets, and repeat testing was arranged for one week later. This returned a sodium of 112 mmol/l. The doctor telephoned the laboratory to discuss the results.

The measured osmolality of the serum sample submitted was 265 mmol/kg water (reference range 280-301 mmol/kg in people over 60 years old), and the doctor was asked to submit a urine specimen from the patient for osmolality, which was found to be 298 mmol/kg. Urinary sodium concentration was 56 mmol/l, and random plasma glucose concentration was 5.9 mmol/l. These results were interpreted as inappropriate concentration of urine and a urinary sodium concentration that was inappropriately high in a patient with hypernatraemia and hypo-osmolar serum. After discussion with the local endocrinologist, it was decided to stop metformin and reduce insulin detemir to 4 units daily, pending assessment for treatment of her diabetes.

**Summary points**

- Hyponatraemia is common in primary care; hypernatraemia is rarer
- In both conditions, the common causes are usually clinically apparent
- When great or rapid changes occur consider rarer causes
- Urine spot sodium concentration and osmolality help to differentiate the cause
- Unexpected results should raise suspicion of pseudohyponatraemia and pseudohypernatraemia

**Keywords**

- Hyponatraemia
- Hypernatraemia
- Osmolality
- Sodium concentration
- Excessive fluid intake
- Urine concentrating ability
- Adrenocortical deficiency
- Adrenocortical insufficiency
- Diabetes mellitus
- Pulmonary disease
- Congestive cardiac failure
- Bronchial tumour
- Small cell lung cancer
- Antidiuretic hormone (ADH)
- Water retention
practitioner because of increased tiredness, thirst, and polyuria over the previous six weeks. She had lost 3 kg in weight over the same period. Glycated haemoglobin (HbA1c) four months before had been 7.2%, and capillary blood glucose concentrations measured at home had occasionally been in the region of 5-8 mmol/l.

On examination she was not acutely unwell and not clinically dehydrated. Her blood pressure was 124/78 mm Hg lying and 112/70 mm Hg standing, and pulse 84 beats per minute in sinus rhythm. Urine glucose by test strip showed ++ glucose, and serum electrolyte results were reported as sodium 151 mmol/l, potassium 3.8 mmol/l, urea 8.3 mmol/l, creatinine 105 pmol/l. A random plasma glucose concentration was 7.7 mmol/l.

Her serum electrolyte results three months earlier were sodium 142 mmol/l, potassium 4.1 mmol/l, urea 4.3 mmol/l, creatinine 96 pmol/l, and her serum calcium corrected for albumin had been 2.26 mmol/l (reference range 2.20-2.62 mmol/l).

She was advised to drink plenty of fluids and to return in three days for review, during which time her doctor contacted the local laboratory to discuss her results. When she was seen again, her symptoms were still present; her repeat blood results were similar; and a urine sample, recommended by the laboratory, returned an osmolality of 210 mmol/kg. Her measured serum osmolality was 308 mmol/kg (reference range 275-295 mmol/kg).

Urine output over 24 hours was 4.6 litres. She was referred urgently to an endocrinologist, who gave her a test dose of intranasal desmopressin, which greatly reduced urine output, and urinary osmolality rose to 570 mmol/kg water. She started taking regular desmopressin while having further investigations. Anterior pituitary function testing showed no impairment of corticotrophin, gonadotrophin, or growth hormone release, and serum prolactin was within the reference range. However, her thyroid function tests showed secondary hypothyroidism with thyroid stimulating hormone of 3.1 mIU/l (reference range 0.4-5 mIU/l) and free thyroxine (FT4) of 9 pmol/l (reference range 11-23 pmol/l), and she started thyroid replacement treatment.

Subsequent magnetic resonance imaging of the brain showed that she had a craniopharyngioma, which was successfully decompressed surgically. She later had external beam radiotherapy to the residual tumour.

Discussion

Hyponatraemia

Hyponatraemia is the commonest of the electrolyte disorders. One recent study reported a prevalence of 7.2% in a community setting, rising to almost 30% in hospital inpatients. Both hyponatraemia and hypernatraemia are more prevalent in older patients. Hyponatraemia has been defined as mild (serum sodium 125-135 mmol/l), moderate (115-124 mmol/l), and severe (<115 mmol/l), but rate of change may be as important as absolute values.

In most cases the cause is apparent from the clinical setting of diuretic use or secondary hyperaldosteronism in cardiac, liver, or renal disease. The difficulties are knowing when to investigate further and how to distinguish the rarer, less obvious, causes.

Analytical imprecision and biological variation mean that differences of up to 5 mmol/l in measurement of serum sodium may be due to chance. Laboratory errors can occur, so a repeat sample is prudent to confirm an unexpected result. Changes of 5 mmol or more should alert practitioners to a potentially progressive process.

Chronic mild hyponatraemia in a patient with heart failure is common and is related to a combination (among others) of natriuresis, diuretics, and secondary hyperaldosteronism. Diagnosing renal salt and water handling disorders in patients who are taking drugs that influence salt and water handling, notably diuretics, can be difficult; where possible, a cautious reduction in the dose can occur, so a repeat sample is prudent to confirm an unexpected result. Changes of 5 mmol or more should alert practitioners to a potentially progressive process.

<table>
<thead>
<tr>
<th>Box 1</th>
<th>How should I investigate a patient with low serum sodium concentration?</th>
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<tbody>
<tr>
<td>• Establish history of fluid intake and current treatments</td>
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<tr>
<td>• Assess fluid status, to identify whether hypovolaemia or hyponatraemia is present</td>
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<tr>
<td>• Repeat to confirm and establish whether acute and changing or chronic and stable. Changes of up to 5 mmol/l can reflect non-significant variation. Persistent and stable serum sodium 132-135 mmol/l in a clinically well patient may reflect a statistical population outlier and may not require investigation</td>
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<tr>
<td>Serum sodium 125-131 mmol/l</td>
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<tr>
<td>• Check serum potassium, urea, creatinine, triglycerides, and protein and plasma glucose</td>
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</tr>
<tr>
<td>• If cause is not clinically apparent, check</td>
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<tr>
<td>• Urine sodium and osmolality if inappropriate secretion of antidiuretic hormone (SIADH) suspected:</td>
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<tr>
<td>• Urine sodium &lt;30 mmol/l suggests renal sodium loss or SIADH</td>
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<tr>
<td>• Urine osmolality &gt;100 mmol/kg water in the context of hyponatraemia is consistent with SIADH</td>
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<tr>
<td>• Exclude Addison’s disease and hypothyroidism</td>
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<tr>
<td>• Consider reset osmostat syndrome in patients with debilitating illness and stable hyponatraemia.</td>
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<tr>
<td>Serum sodium 115-124 mmol/l</td>
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<tr>
<td>• Check, as above</td>
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<tr>
<td>• Seek specialist advice unless long term stable and cause has been established</td>
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<tr>
<td>• Consider immediate admission if sodium is falling rapidly or neurological signs or symptoms are present</td>
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<tr>
<td>Serum sodium &lt;115 mmol/l</td>
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<tr>
<td>• Immediate admission usually indicated</td>
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has been cited as inappropriately high in the presence of hyponatraemia, although quoted thresholds vary and the urine osmolality may provide useful additional information to discriminate between defective renal concentration and states in which renal salt is lost.

The syndromes described as resulting from inappropriate secretion of antidiuretic hormone and chronic dilutional hyponatraemia have causes that include ectopic production, increased pituitary secretion, increased sensitivity to antidiuretic hormone, and resetting of the body osmostat in chronic disease states. The last of these usually leads to stable mild hyponatraemia.

For clinical purposes the principal differentiation is between states that are chronic and relatively stable and those producing progressively severe and rapidly worsening hyponatraemia. Severe hyponatraemia can occur with any of a large number of drugs (hence the importance of a drug history) or as a result of secretion from tumours, classically small cell lung carcinoma but also several others. It may also occur with head injury and non-malignant lung disease. Other chronic illness states can produce hyponatraemia through a similar mechanism, although this is usually mild and relatively slow to change.

Failure of the kidney to preserve sodium (urinary sodium concentrations are typically less than 10 mmol/l in hyponatraemia), combined with appropriately dilute urine, should prompt consideration of renal salt losing states, including intrinsic renal disease and endocrine causes (hypoadrenalism). Because secretion of antidiuretic hormone over-rides the body osmostat to maintain circulating volume, hyponatraemia must be excluded before any fluid restriction is considered.

Pseudohyponatraemia (redistributional hyponatraemia) may be seen in a variety of situations unrelated to salt and water homeostasis: hyperglycaemia, hyperproteinaemia, and chylomicronaemia. In these conditions serum osmolality is normal (hyperproteinaemia with chylomicronaemia) or raised (chylomicronaemia).

Hypernatraemia

Hypernatraemia is rarer in primary care, and in most cases the cause will be apparent from the clinical setting, typically gastrointestinal losses from vomiting or diarrhoea, or poor fluid intake. In case 2 the magnitude of the rise over three months acted as the indicator of a potentially progressive process.

Other than urine glucose concentrations, which may have been positive because of a low renal glucose threshold, the results in case 2 excluded poor diabetes control as a cause for her polyuria, and the finding of inappropriately dilute urine in a patient whose serum is hyperosmolar (and would under normal circumstances have been concentrating her urine in order to retain water) indicate diabetes insipidus, requiring urgent referral.

Hypernatraemia with hyperosmolar serum and inappropriately dilute urine is diagnostic of diabetes insipidus. This may be caused by defective production of antidiuretic hormone from the hypothalamus, or, more rarely, release from the posterior pituitary gland, or from loss of renal response to circulating ADH (nephrogenic diabetes insipids). Additional investigations can exclude several of the secondary causes of nephrogenic diabetes insipidus: hypercalcaemia, hypokalaemia, and drugs (notably lithium). Further characterisation of the cause of the diabetes insipids may include dynamic testing (water deprivation test under carefully supervised conditions); a challenge with desmopressin; and imaging to identify space-occupying hypothalamic lesions, classically craniohypophysiosis, or the rarer granulomatous diseases such as Wegner’s granulomatosis or neurosarcoidosis. In most cases the thirst response will attempt to correct the hyperosmolar state, and with the exception of patients such as elderly or bedbound people, who may have limited access to fluids through immobility or institutionalisation (reviewed by Milionis et al), large confirmed rises in serum sodium concentration should prompt suspicion of diabetes insipidus.

Urine osmolality must be interpreted in light of serum osmolality. Quoted “reference ranges” for urine osmolality (typically 50-1200 mmol/kg) simply reflect the range of the concentrating capacity of the kidney, which depends on body hydration status.

Pseudohypernatraemia is unusual, but it may be seen in hypoproteinaemic states when sodium has been measured by routine laboratory methods.

Evidence note

Definitions of mild moderate and severe hyponatraemia are based on a consensus opinion document; they serve only as a guide, as the rate of decline and the clinical context will influence individual patients’ responses. We found no definitions of the severity of hypernatraemia, and the guideline values offered are approximate equivalents to total body water loss, representing an approximate threshold at which oral hydration is
Arbitrariness and conventionality: actions speak louder than words

When patients present with balance symptoms, it’s essential to find out exactly what their symptoms are. Patients complaining of dizziness could mean vertigo, dysequilibrium, light-headedness, presyncope, or something entirely different. And when patients report that they suffer from vertigo, there’s every possibility that they’re using the term to mean something other than the clinical definition—a sensation of spinning or motion.

When a deaf patient signs that he has vertigo he touches his index finger to his forehead, then moves his hand in small circles next to his head. The meaning is obvious. The intention is similarly clear when a deaf patient signs that she is unsteady or off balance. British sign language (BSL) shows that the two symptoms are quite different, despite the fact that they have confusing terminology in spoken language—the words vertigo, dizziness, and giddiness being synonymous according to the Oxford Dictionary of English.

I’ve noticed my boss using similar gesticulations when clarifying a dizzy patient’s history. He’s not a BSL user, but he uses clear gestures to clarify meanings. When asking about vertigo, he circles his hand without touching his forehead, so he’s actually making the sign for a helicopter, but, because of the context, his patients understand him perfectly. If he made the same sign on an airfield, they’d probably guess that he was referring to a helicopter.

Could it be that a sign makes more sense, or has a clearer meaning, than a word? Can we define things more accurately with a gesture than with a word? I’m not a linguist, but I suspect the answer lies in a linguistic feature of signed languages which is minimal in spoken languages—arbitrariness and conventionality.

In BSL, conventional signs have a representative meaning. To see the word “baby” signed there is no doubt that it means baby. If I were to move my hands in a pedalling motion, you’d probably know I was signing “bicycle” even though nobody actually pedals a bicycle with their hands.

Conventional signs are analogous to a picture or a model, whereas the arbitrary signs (such as how, why, when) do not have a representative meaning and are analogous to a word.

With the exception of onomatopoeic expressions, few spoken words represent what is being described. The word cat, for example, doesn’t have any direct relevance to a cat, other than that we know the word cat refers to a furry domestic mammal with pointy ears.

We can imagine that conventional signs rarely stray from their original meaning. The sign for vertigo is unlikely to ever mean something other than “I feel as though I’m spinning.” In spoken language, however, the apparently arbitrary meaning of words has a tendency to evolve and to be misinterpreted and misused.

In the clinical setting, accurate information transfer between clinician and patient is vital, and communication errors have potential for disaster. Models, diagrams, and clear gestures can all be used to help clarify arbitrary terms used in speech. In linguistic terms, conventionality provides simpler communication than arbitrariness—other than that we know the word baby makes more sense, or has a clearer meaning, than a word? Can we define things more accurately with a gesture than with a word? I’m not a linguist, but I suspect the answer lies in a linguistic feature of signed languages which is minimal in spoken languages—arbitrariness and conventionality.

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In the clinical setting, accurate information transfer between clinician and patient is vital, and communication errors have potential for disaster. Models, diagrams, and clear gestures can all be used to help clarify arbitrary terms used in speech. In linguistic terms, conventionality provides simpler communication than arbitrariness—or in everyday terms, actions speak louder than words.

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The case for dedicated sickle cell centres

PERSONAL VIEW Graham Serjeant

In Jamaica the word transition means death, but in the sickle cell vocabulary of the United States it refers to the transfer from paediatrician to adult physician. Most patients with sickle cell disease are now identified at birth and are followed by paediatricians with an interest in and knowledge of the disease. Then at an arbitrary age—12, 16, or 18 years, depending on the institution—patients must leave the doctor they have known from birth and are referred to a usually unknown doctor. The result is that many patients default from follow-up at a critical time of adolescence, when they face problems of delayed physical and sexual development, enuresis, leg ulcers, priapism, and an increasing incidence of bone pain crises.

Is this disruption in clinical care necessary? Yes, the administrators say; but then we should ask whether the patients are there for the system or the system is there to serve the patients. Is it possible to provide a seamless service for clinical care of sickle cell disease? Are the demands of managing these patients sufficiently different from those of other chronic diseases to consider dedicated sickle cell centres?

Sickle cell disease is a lifelong condition in which clinical complications are generally separated by periods of relatively good health known as the steady state. Most doctors familiar with sickle cell disease believe that the best clinical service is provided by monitoring the steady state. Contact with patients two to four times a year when they are well provides clinical and haematological baseline against which to judge events of acute illness. It allows earlier detection of some complications, increases rapport between doctors and patients and their families, and provides opportunities for education, counselling, and social support. Frequent clinical examinations and blood, biochemistry, bacteriological, and other investigations enable a large database to be built up—most readily achieved through electronic data management—so that should be accessible for patient management and for research.

Who are the best healthcare personnel to provide clinical services? Currently this is the task of haematologists, not because the haematology of sickle cell disease is challenging but because few other disciplines seem interested. What is the most relevant clinical training for a disease whose spectrum of complications include hypersplenism, stroke, enuresis, gallstones, chronic leg ulcers, pulmonary hypertension, pain management, and psychological and social problems and that should also prepare healthcare staff for education and counselling? Opting for several specialists may require patients to attend several different clinics at extra cost and disruption.

Expertise within a dedicated sickle cell centre comprising doctors with experience in the clinical complications of the disease supplemented by sickle cell nurse practitioners would provide the infrastructure for training of further specialist nurses, technologists, counsellors, and doctors. Doctors with little experience are more likely to resort to blood transfusions, hospital admission, and surgery, exposing patients to unnecessary risks and using resources that may be better deployed in other ways. Clearly, specialist opinion would still be needed, especially in orthopaedics, ophthalmology, and urology, but such interventions should take place within a coordinated treatment plan.

Bone pain crises currently account for 60% to 80% of hospital admissions related to sickle cell disease, and patients view this as a major deficiency in management. Patients often perceive hostility from medical and nursing staff in emergency departments and report a lack of the sympathetic support that is helpful in resolving bone pain. The provision of daycare facilities for sickle cell patients has greatly reduced the need for hospital admission, thus decreasing costs. Most painful crises follow avascular necrosis of bone marrow, induced by skin cooling—not an intrinsically serious pathology.

Are the patients there for the system, or is the system there to serve the patients?

In this situation patients welcome day care as a reassuring alternative to hospital.

However, although day care has an important role, it should not be allowed to undermine the ability of patients and their families to cope with many painful crises at home. Several factors enable patients to reduce their analgesic requirements: knowledge of the task of haematologists, not because the haematology of sickle cell disease is challenging but because few other disciplines seem interested.

In Jamaica patients in pain often say that they only have to reach the doors of the sickle cell centre to start to feel better. Why? Because of the reassurance of seeing medical staff who know about sickle cell disease and who know about them.

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Britney tears

I shook my head at the cheapness of the clothes in the shopping centre and fretted over whether children halfway round the world had sweated to produce them. My daughter tugged my sleeve. “Has Britney gone bonkers?” she asked. Britney’s shaved head lurched from every news stand. Tattooed and in drug rehab, what has become of one of my daughter’s icons? “No, she’s sick,” I replied, “and she will get better. Don’t worry.”

Am I so short of ideas as to waste column space in this prestigious journal on the likes of Britney Spears, a washed-up teen diva? But Britney matters, because her life is mirrored in the lives of our own children: image obsessed, materialistic, and sexualised. Britney was a child star and had it all, fame and fortune beyond measure, but she was denied that most basic of needs, a childhood. Celebrity sets no boundaries, distorts friendships, and, worst of all, removes the need to compromise; they can neither love nor be loved.

But our own children are in trouble too. Society has become so child centred that we are unwilling to deny children any of their demands or to set boundaries. They are living a dream childhood where they can have it all. Inevitably, hormones and adulthood come knocking at the door. Denied the opportunity to develop the coping skills they need as adults, their lives implode—and so beckon drugs, alcohol, sex, cutting. Our antidepressants and counselling are sticking plasters on their gaping wounds. There are Britneys in every street of the country.

The corporate greed that feeds this celebrity culture is corroding the welfare of all our children. Gossip magazines and tabloid newspapers are nothing more than tasteless voyeurism, observing the subjects’ rise to fame but salivating at the spiral of decline.

We doctors are hiding in a dugout in the comfort zone of scientific medicine, so often of questionable benefit, so that we have lost sight of wider problems in society. Perhaps it is time to look over the edge and see the devastation that childhood is becoming, time to teach our children that fame and fortune are false deities, both corrupt and malevolent. Removing the television sets, the internet, and pernicious magazines from our children’s bedrooms might be a good start in limiting the influence of our celebrity culture. We may fret about the conditions of children in poor countries, but we have real problems closer to home too.

Believe it or not

Belief is an emotional state that is not susceptible to rational persuasion, said Spinoza. And, boy, could I sing a few bars of that—although my seminal experience was not at some frenzied religious festival with people slashing themselves theatrically or falling down speaking in tongues but in the cold light of the surgical ward.

When I was a surgical intern a young man was admitted with a left upper quadrant mass. Ireland was a poor country then; advanced imaging was not available, so the diagnosis largely depended on clinical examination and was a mystery until the senior registrar arrived.

“It’s an enlarged spleen,” he proclaimed. “I can feel a notch.” His certainty was such that none could gainsay him. We all had another go; sure enough, there it was clear as a day: a notch. How could we have missed it?

The news spread like wildfire around the hospital and further afield. Medical students just love their clinical signs, and they came in their thousands to palpate this wonderful notch. The senior registrar, by now rather proprietorial, would, with the touch of a showman, gently guide their hands over the patient’s abdomen. They would palpate timidly, seem confused and uncertain for a long moment—but then, as they looked at the senior registrar’s expectant face, their eyes would light up. “Yes, there it is, I can feel it, it’s a notch, most definitely a notch, a wonderful, wonderful notch, the most wonderful notch that I have ever felt.”

It was a bandwagon: the enthusiasm was infectious and overwhelming. As with the emperor’s new clothes, no one wanted to be an outsider; everyone wanted to belong, to be part of the gang. Everyone either believed they really could feel that notch or pretended they could, in case they looked stupid.

Our senior registrar’s stock rose mightily, and he bestrode the wards like a colossus. The message was clear, he opined grandly to his adoring acolytes, like a fat and obnoxious Buddha: blood tests and x rays are all very well, but at the end of the day you couldn’t beat good old fashioned clinical acumen.

Dawn came up like thunder on what Seamus Heaney might have termed “the fatal conclave” on the day of the laparotomy, the gallery packed with supporters. We opened up the patient and found … a big kidney and, to add insult to injury, a rather small and apologetic spleen. The senior registrar paled, the crowd sagged, and apologetic spleen. The senior registrar paled, the crowd sagged, detumescent with disappointment, and at the back someone started singing, “The king is in the altogether, the altogether …”

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The well versed doctor

I once met the doctor and poet Dannie Abse on a train. There is no reason why he should remember me, because I am not particularly memorable, but I was very impressed by him. The first volume of his autobiography, A Poet in the Family, is exquisitely written; and if I were dean of a medical school I would make all my students read it. Perhaps it is just as well that I am not dean of a medical school.

One has to be a doctor to appreciate fully some of the lines of Abse’s poetry. Describing, for example, a bedroom in a Holiday Inn, one of those faceless hotels that transform Tegucigalpa into Wigan and vice versa, and into which not a breath of air is allowed to penetrate from the outside world, he writes: “The room had a pyrexia of unknown origin.”

How deliciously exact that is, what a pleasure it is to roll the words around in one’s mind, savouring their felicity and poetic truth.

Which of us has not been in a hotel—usually a three star hotel—in which the temperature of the room was perfectly controlled, but at an uncomfortable temperature. Which of us, in those circumstances, has not sought in vain for the source of the heat—as one searches for the source of a pyrexia of unknown origin—or to open a window that has been specially sealed to prevent suicides among hotel guests? (Such hotels, though, are favoured by those who want to kill themselves with overdoses, and they hang a “Do not disturb” notice on their door handle. Because I have seen so many cases I now think that attempting suicide is the principal reason people do not want to be disturbed in hotel rooms—an example of the treachery of personal experience as a guide to the world.)

In his poem Tuberculosis Abse charts the change in attitude to this disease. Its significance has altered, or at least had done so in 1986 when he published the poem. Since then, of course, we have once more come to fear it because of drug resistance.

When Abse started out, tuberculosis was still so often fatal that he used to write in patients’ notes not “tuberculosis” but “acid-fast organisms,” and other doctors would write Koch’s disease, as if by softening the name you reduced its ravages.


I am younger than Abse, so when a student friend of mine was given a diagnosis of tuberculosis, no heroics or tears were necessary, beyond taking the pills for a time.

Later I developed a special interest in this condition because I treated hundreds of cases in a far distant country where I worked. Although most people were cured of the disease, tuberculosis never became banal as in Abse’s poem: “Today, an x-ray on this oblong light / Clear that was not clear. No pneumothorax, / No deforming thoracoplasty. No flaw. / The patient nods, accepts it as his right, / And is right.”

The reason tuberculosis was still dreaded where I worked was not because it was fatal but because it was evidence of witchcraft. And if at first, for whatever reason, the magic did not work, the witch was bound to try again. But before you laugh or shake your head at such foolishness, consider this: the witchcraft gets us all in the end.

Theodore Dalrymple is a writer and retired doctor.

BETWEEN THE LINES

Theodore Dalrymple

Before you laugh or shake your head, consider this: the witchcraft gets us all in the end.

In 1916 Mikhail Bulgakov, 24 years old and fresh from medical school in Kiev, was posted to a snowbound rural clinic in northwestern Russia, “thirty-two miles from the nearest electric light.” In his semi-fictionalised account, A Country Doctor’s Notebook, the young medic spends the journey to the remote hospital, worrying about how he will cope with tracheotomies and obstructed labour (he has seen only two normal deliveries at medical school), and urging himself to walk, not run.

He doesn’t have to wait long before a cart rumbles into the hospital yard carrying a young woman with a leg smashed in a flax brake, her pulse barely palpable. “‘Die. Die quickly,’ I said to myself. ‘Otherwise what am I to do with you?’” However, he horrifies himself by ordering the “feldsher,” the Russian equivalent of a physician’s assistant, to prepare the theatre for an amputation. His own adrenaline as potent as the camphor injections given to revive the patient, he saves her by removing the leg.

Later he is presented with a fetus with a transverse lie and has to examine the woman in front of the hospital’s veteran midwife: “The fact was that once the experienced Anna Nikolaevna had told me what was wrong, this examination was quite pointless.” The midwife advises a “podalic version.” The doctor gravely concurs, announce that he’s off for a cigarette, and runs to look up “podalic version” in a textbook. As they scrub in, Anna Nikolaevna recounts how his predecessor performed the procedure. “I listened avidly to her, trying not to miss a word. Those ten minutes told me more than everything I had read for my qualifying exams, in which I had actually passed the obstetrics paper with distinction.”

Such an internship, including an attack by wolves while on his way to a home visit in the middle of a blizzard, is no longer the norm for house officers (although it remains so for many doctors in the developing world). But Bulgakov’s struggle with the dark Russian winter swirling outside his window symbolises the lack of experience, loneliness, and the worry of breaking the Hippocratic oath that gnaws at the sleep of junior doctors everywhere.

Medicine was for Bulgakov a light in the dark days of Soviet repression. “Each person ought to be a doctor,” he wrote, “in the sense of disarming all the invisible enemies threatening life.”

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Don’t blame the drugs

Psychoactive drugs haven’t always been seen as an evil to society. A new book laments the “cult” of fear that now controls our relationship with these drugs, finds Allen Shaughnessy

A century ago alcohol was the prevailing demon substance. Prohibitions on drug use were few, jails were not full of drug users, and drugs derived from coca, cannabis, and poppy were in wide use by the public. Reputable doctors, scientists, and poets, along with less well known people, used these drugs in ways similar to use of caffeine and nicotine today, such as the physician who continuously used morphine for 62 years. For the most part people used these drugs without them affecting their life or functioning, their use ebbing and flowing among periods of non-use.

Popular patent medicines of the time were likely to contain one or more of these psychoactive drugs. The manufacturer Parke-Davis had tincture of cannabis and 15 coca related products. Coca-Cola originally contained cocaine and was a result of the temperance movement in the United States: with the growing threat to alcohol, the Atlanta based inventor John Pemberton removed the red wine from his popular “French Wine Cola,” added cocaine, and changed its name to Coca-Cola.

Richard DeGrandpre describes psychoactive drugs as “socially defined commodities” and not solely, as they are often portrayed, inherently powerful manipulators of our will and behaviour. He points out that “drug use and drug outcomes are ultimately artefacts of culture, not of the inherent pharmacological properties of drugs.”

Context, in other words, is everything. Take cocaine users out of their normal setting and place them in a controlled, blinded study: they can’t differentiate injected cocaine from caffeine or even placebo. Mice, when isolated and given nothing to do, will self administer cocaine until exhaustion; when put in their normal habitat and given the option of food or cocaine they will choose food as their stimulus of pleasure half the time. Each society allows drugs to unlock different forms of behaviour. The author gives the example of alcohol, explaining that we learn about drunkenness from our society and act accordingly: “Whisky in a pub in the Gorbals excuses hitting your friends with bottles; bloody Marys at a Chelsea party facilitate sexual advances towards other people’s wives.”

The cult of pharmacology is not limited to illicit drugs. Cult behaviour also exists with legal drugs, largely driven by commercial interests. Barbiturates, initially marketed as safe and non-addictive, were developed to replace chloral hydrate. Then came Meprobamate, only to be replaced by benzodiazepines, which, once again, initially thought to be non-addictive.

As the market matured and the dependence potential of benzodiazepines became known, a search for new drugs began. What I call “backward pharmacology” was used to develop the so called selective serotonin reuptake inhibitors (SSRIs). The search for SSRIs did not occur because serotonin deficit was known to be a cause of depression; rather, the drugs were developed and then a disease for their use had to be found—fluoxetine was initially investigated as an antihypertensive. It was only later that SSRIs were commercialised to fill the gap in the psychopharmacology market left by the growing negative connotations of anxiety and the changing medical opinion of benzodiazepines.

Firstly, however, the depression market had to be created. Depression in the United States in the 1950s and before was considered to be a rare disorder, with a prevalence of 0.005%. This now contrasts with a prevalence of 10% at the end of the 20th century. Given the difficulty in separating anxiety from depression, and the negative connotations of anxiety, it was a relatively easy matter to develop this previously rare disease to create the market.

However, the fact is that alcohol or drug use does destroy the lives of users and those around them. And, indeed, many people have had their lives transformed through the use of anxiolytics or antidepressants. The price for benefit to some people or preventing harm to a few has been policies depriving the many.

The desire to alter state of consciousness has been present in nearly all cultures. Along with this desire has been the categorisation of drugs as “good” and “bad.” We now have a white market of legal (“good”) psychoactive drugs, a grey market of drugs used to alter consciousness but lacking a stamp of legitimacy to do so—alcohol, nicotine, caffeine—and a black market of (“bad”) psychoactive drugs.

DeGrandpre points out these distinctions are largely based on cultural mores and not pharmacology. As I write this, though, a legal cup of caffeine sits next to my computer monitor. Meanwhile, in the mountains of Peru, workers are chewing coca leaves to get them through their day.

The theme of The Cult of Pharmacology is that our approach to psychoactive drugs, whether white market or black market, is “irrational and unpredictable, full of fear and loathing, with a strong theme of commerce running right through the center.” The book is well researched and documented and full of interesting facts. For many readers it will produce a whole new perspective that will have an impact when they reach for the prescription pad or a cup of coffee or disparage the drug user on the street.

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Brian Brendan Hickey
Former consultant general surgeon/ urologist Morriston Hospital, Swansea (b 1912; q Oxford 1933; MCh, FRCS), died from bladder cancer on 4 August 2006. After qualifying, Brian Brendan Hickey became part of the neurosurgical team at the London Hospital. He joined the Royal Army Medical Corps at the outbreak of war and served at home and in the Far East. On demobilisation, he worked as a surgeon in Mosul. He was then appointed surgeon at Morrison Hospital, where he spent the remainder of his working life, save for a period as professor of surgery in Khartoum. When he retired he became high sheriff of West Glamorgan and served on the bench as a magistrate. He leaves three children and 10 grandchildren.

Peter Viggo Egebjerg Jensen
Former general practitioner Blackpool, clinical assistant in psychiatry (b 1927; q Manchester 1953), died from hepatocellular carcinoma on 28 October 2006. Peter Viggo Egebjerg Jensen was born in Manchester to Danish parents. His Danish heritage was immensely important to him. As a general practitioner he developed a keen interest in psychiatry, psychotherapy, and medical hypnosis. In 1978 he received a needlestick injury when taking blood from a drug addict and developed hepatitis B. He recovered, but in 1982 he developed polyarteritis nodosa, probably as a result of the hepatitis. This led to his early retirement from general practice in 1985, although he continued to work as a clinical assistant in psychiatry until 1992. In 2005 he was diagnosed as having hepatocellular carcinoma, a recognised late complication of hepatitis B. He leaves a wife, Phyllis, and three children.

Mary Jensen
Peter Jensen

Joseph Lister
Former general practitioner Harrow (b 1919; q London Hospital 1943; MRCP), died from heart failure on 26 November 2006. Joseph (“Joe”) Lister designed and founded Harrow’s first purpose built group practice in 1967 and was Harrow’s longest serving general practitioner. He was chairman of Harrow Hospital and set up the Harrow Association for the Disabled. He was employment medical adviser with the Health and Safety Executive and worked on the use of whole body scanners to assess asbestosis in industrial workers. His interests included bridge, which he played to international standard, and tennis. He was president of Harrow Rotary Club. He leaves a wife, Nicky; three sons; and grandchildren.

David Lister

James Martin Stewart
Former general practitioner and police surgeon Oxford (b 1920; q Trinity College, Dublin, 1944), died from a ruptured aortic aneurysm on 12 May 2006. On qualifying, James Martin Stewart (“Martin”) joined the Royal Army Medical Corps, where he became interested in venereology. Martin then joined a practice in Oxford where he worked in venereology and developed an interest in student health. When he retired in 1986 Martin was college doctor to seven Oxford colleges. He was a police surgeon from the early 1960s and was secretary and president of the Oxford division of the BMA. Martin also sat on the local ethics committee for 15 years. He leaves a wife, Roberta; four children; and 11 grandchildren.

Alison Stewart

Frank Derek Thompson
Former consultant nephrologist St Peter’s Hospital, Harefield Hospital (b 1939; q Cambridge 1965; MA, FRCP), d 15 July 2006. Frank Derek Thompson’s background in cardiovascular and renal medicine allowed him to combine a career as nephrologist at St Peter’s hospitals and the Harefield and Mount Vernon group. When dean of the Institute of Urology and Nephrology (1985-98), he was largely responsible for its successful integration into the Middlesex/UCH Medical School and for relocation of the St Peter’s hospitals to the Middlesex Hospital. He was passionate about cricket, gardening, and bird watching and was a committed Christian. He leaves a wife, Liz, and two children.

Guy Neil d
M A Mansell
Intensive smoking cessation programmes that are administered free to patients over three months are cost effective in high risk smokers with heart disease. Compared with those receiving “usual” care of counselling and printed material given out before discharge from hospital, those who received the intensive intervention had significantly higher continuous abstinence rates at each follow-up interval. At two years, 33% had managed to kick the habit and stay clean, compared with just 9% in the usual care group. The absolute risk reduction in mortality was 9.2% with a number needed to treat of 11 (Chest 2007;131:446-52).

Recent studies indicate that the risk of stillbirth increases after a caesarean section. In an attempt to shed more light on these findings, a retrospective cohort study was conducted in an English population of women with a previous delivery by caesarean section between 1968 and 1989. This has confirmed the risk of stillbirth as 4.6 per 1000. Why this happens remains unclear, but, as the rate of caesarean deliveries is soaring, it’s likely that the risk is now much higher (BJOG 2007 Jan 25 doi: 10.1111/j.1471-0528.2006.01249.x).

There are now more obese people living on our planet than there are people who are starving, according to RTD info, a magazine on European research (December 2006;51:29). Currently at least 7% of health spending in the European Union is allocated to obesity and its medical consequences, a figure that doesn’t reflect the loss of economic activity attributable to this evolution. And hot on the heels of this epidemic comes another—“diabesity”: 80% of people with adult onset diabetes are typically overweight.

Drinking spearmint tea could reduce mild hirsutism in women. Previous reports have suggested that extracts of the spearmint plant could lower male libido, probably by reducing levels of androgens (studies in rats have confirmed this effect). Now, a small study of 21 hirsute women has found that drinking two cups of spearmint tea a day for five days significantly reduced their androgen levels, suggesting that this might become a more palatable alternative to hormone treatment to suppress androgen production (Phytotherapy Research 2007 doi: 10.1002/ptr.2074).

Another sort of tea may be just the ticket to dampen down the detrimental effects of toxic chemotherapy on the small bowel. Irinotecan is highly effective against many cancers but causes severe inflammatory damage and oxidative stress to the mucosa of the small intestine. Green tea polyphenols administered orally to mice already treated with irinotecan protected against oxidation, and these findings may be replicated in the clinical setting (Journal of Nutrition 2007;137:634-40).

Intensive statin therapy in elderly men and women with coronary artery disease provides long term protection against acute cardiac events and death as well as reducing cholesterol levels, compared with moderate doses of statins. However, the SAGE study, which compared moderate pravastatin therapy with intensive atorvastatin treatment, found that both reduced myocardial ischaemia to a similar extent. The authors say this points to there being different low density lipoprotein cholesterol-lowering thresholds for ischaemia and for major acute cardiac events (Circulation 2007;115:700-7).

Hopping rabbits are helping to test a new tissue-engineered device designed to improve healing of the anterior cruciate ligaments. The device is a biodegradable, polyester based scaffold strengthened by braiding, similar to shoelaces. The rabbits showed that it has high mechanical durability and improved ligament healing, especially when the polymer was seeded with ligament cells to encourage the growth of fresh tissue (Proceedings of the National Academy of Sciences 2007 Feb 20-23 [www.pnas.org/cgi/doi/10.1073/pnas.0608837104]).

Black henna tattoos are popular with holidaymakers, but they can also cause sensitisation to the paraphenylenediamine in hair dye, causing allergic contact dermatitis. A series of cases in the CMAJ (2007;176:445-6) all describe similar stories of young people developing erythema, oedema, and pruritis of their scalp, hairline, eyelids, or cheeks a couple of days after having their hair dyed. All of them had had at least one black henna tattoo.