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*US editor's choice:* **Salty story**
Douglas Kamerow
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**Salt and cardiovascular disease**
Francesco P Cappuccio

**Postmenopausal hormone therapy**
Deborah Grady, Elizabeth Barrett-Connor

**Preventing ventilator associated pneumonia**
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BMJ  2007;334:873, doi:10.1136/bmj.334.7599.873-c

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Career focus

Read this week's articles on
Salt and cardiovascular disease
Legislation to cut levels of salt in processed food is necessary and justified

Blood pressure is the most powerful predictor of stroke and other cardiovascular events. The importance of salt (sodium chloride) intake in determining blood pressure and the incidence of hypertension is well established. Furthermore, randomised controlled clinical trials of moderate reductions in salt intake show a dose dependent cause-effect relation and lack of a threshold effect within usual levels of salt intake in populations worldwide. The effect is independent of age, sex, ethnic origin, baseline blood pressure, and body mass.

Prospective studies, with one exception, also indicate that higher salt intake predicts the incidence of cardiovascular events. While widespread support exists for reducing salt intake to prevent cardiovascular disease, the lack of large and long randomised trials on the effects of salt reduction on clinical outcomes has encouraged some people to argue against a policy of salt reduction in populations.

In this week’s BMJ, Cook and colleagues report the long term effects of reduced dietary sodium on cardiovascular disease in people participating in the controlled randomised trials of hypertension prevention follow-up studies (TOHP I and II). More than 3000 participants without hypertension were randomised to a reduced sodium intake for 18 months (TOHP I) or 36-48 months (TOHP II), or to a control arm. The reductions in sodium intake were 44 mmol/day and 33 mmol/day (equivalent to ~2.6 g and ~2.0 g of salt), respectively. The results show that people originally allocated to either sodium reduction group had a 30% lower incidence of cardiovascular events in the next 10-15 years, irrespective of sex, ethnic origin, age, body mass, and blood pressure. The benefits exceed those estimated by a recent meta-analysis. Cook and colleagues’ study is the first to report a beneficial effect of dietary salt reduction on cardiovascular outcomes based on randomised control data.

The study strengthens the support for dietary recommendations for lower salt intake to prevent cardiovascular disease in the general population. In 1985, the World Health Organization recommended that the average salt intake should be reduced to 5 g per day or less. However, few countries have policies for targeted reduction in salt intake.

Differences exist between developed and developing countries. In Westernised countries, people derive salt mostly from bread and processed food and only a small proportion comes from discretionary use (up to 20%). A population wide policy of salt reduction in developed countries can only be implemented with the collaboration of the food industry. Over the years, however, the need to sustain a profitable market has led to opposition from the food industry or slow progress.

In England and Wales some progress has been made, but levels of salt intake are still far from the government’s recommendation of 6 g of salt per day. Future options are to do nothing, to establish voluntary target levels of salt for a wide range of foods, or to legislate so that the food industry has to comply. Given the inertia of the past 20 years, the first option would not contribute to progress. The “voluntary” option would support existing work, but it is unlikely to achieve the set targets. The recent position of the industry in rejecting the “traffic light” proposal for labelling, whereby highly salted foods would carry a red alert warning, is one measure of the gap still remaining. The legislation option would require the food industry to reduce the salt content of processed food to within set levels. The experience in Finland suggests that legislation has added value to the previous option and at this stage is necessary and justified.

Conversely, in many developing countries, like those of sub-Saharan Africa, where the main source of salt is still discretionary, community based and context specific initiatives can be effective and should be pursued, given the increasing burden of cardiovascular disease related to hypertension.

Without considerably modifying the environment by allowing greater availability of low salt foods, people in developed countries will find it difficult to exercise their “choice” when trying to reduce dietary salt. Doctors and health professionals have long used dietary counselling to deliver non-pharmacological management of hypertension. Advising patients to reduce salt intake with a lifestyle package quickly delivered in a busy primary care setting is ineffective, however. A baseline assessment of salt intake (through a 24 h urinary collection for the measurement of sodium) is not part of the UK’s National Service Framework requirements and is not included in the Quality and Outcome Framework. The current system is therefore unlikely to make health professionals and consumers more aware of how much salt people eat or to increase motivation and knowledge on how to reduce it. In a climate of scarce healthcare resources, one of the most cost effective ways to reduce the burden of cardiovascular disease is being overlooked. And yet the evidence gets stronger.
Postmenopausal hormone therapy

Symptoms should be treated with lowest effective dose of hormone therapy for the shortest time possible

In March 2007, the North American Menopause Society (NAMS) published an updated position statement on the use of hormone therapy in postmenopausal women.1 NAMS recommends hormone therapy, which is a highly effective treatment for hot flushes and vaginal atrophy,2 as first line treatment for women with moderate to severe symptoms. It is also effective for preventing osteoporotic fractures.3,4 but NAMS recommends that hormone therapy for this purpose should be weighed against potential harm and that other approved preventive treatments such as bisphosphonates should be considered. These recommendations are clear, simple, and based on solid evidence from many randomised controlled trials.

However, NAMS recommendations are less clear in several other areas. For example, after clearly stating that hormone therapy increases risk of venous thromboembolic events and stroke, no advice is provided about how clinicians and patients should use this information. Similarly, NAMS notes that risk of breast cancer is increased in women who use oestrogen plus progestin for five years or more, but no recommendation is given about its use in women at high risk of breast cancer. The statement also notes that treatment with hormone therapy in women over 65 years increases risk for dementia,5,6 and that no evidence is available regarding effects on dementia from clinical trials in younger women, but there is no clear statement that hormone therapy should not be used to prevent dementia.

NAMS published a position statement on use of postmenopausal hormone therapy in 2004, and since then no large randomised trials have been published that would require revision of guidelines. What then has changed since the earlier statement? The main changes in the new position statement reflect the belief of NAMS panelists that, if used during or shortly after the menopause, hormone therapy may not increase risk of coronary heart disease. Evidence to support cardiovascular disease outcomes: observational follow-up of trials of hormone prevention. BMJ 2007 doi: 10.1136/ bmj.39147.604896.55.

1 He FF, MacGregor GA. How far should salt intake be reduced? Hypertension 2003;42:1093-9.

Pneumonia occurring during mechanical ventilation (ventilator associated pneumonia) is the most common infection acquired by patients in intensive care. Reported rates range from 9% to 67% and 4.4 to 15.7 cases per 1000 ventilator days.¹ In this week’s BMJ, a systematic review by Chan and colleagues² assesses the effect of oral decontamination with antiseptics on ventilator associated pneumonia and mortality in mechanically ventilated adults.

Ventilator associated pneumonia prolongs lengths of stay in intensive care and hospital, and it increases costs of care and possibly increases mortality.³ ⁴ The prevention of this infection is therefore a high priority for infection control in intensive care.⁵ Preventive procedures deal with three broad areas: prevention of cross transmission; upper digestive tract colonisation and the risk of inhalation; and maintenance and care of the artificial and natural airways.⁶ ⁷ Because the oropharynx and upper intestinal tract are the major sources of organisms causing pneumonia in intensive care, they would appear to be good targets for preventive measures.

Many studies have assessed prevention using antimicrobials administered via various routes, alone or combined. “Selective digestive tract decontamination,” which uses various combinations of systemic and topical (oropharyngeal and intestinal) antibiotics has generated the largest number of trials, summarised in at least eight successive systematic reviews, including one by the Cochrane group.⁸ In the latest update, which included 36 trials involving 6922 patients, topical and combined systemic antibiotics reduced respiratory tract infections (odds ratio 0.35, 95% confidence interval 0.29 to 0.41). Mortality was also reduced with the combination (0.78, 0.68 to 0.89), but not with topical (intestinal, with or without oropharyngeal) antibiotics alone, despite a comparable effect on rates of pneumonia.⁹ Selective digestive tract decontamination has not been accepted widely¹⁰ ¹¹ because of controversy about the balance of benefits and risks—particularly on overall use of antibiotics and selection of resistant microorganisms with prolonged use—and uncertainty

Preventing ventilator associated pneumonia

Oral antiseptic agents should be part of a multi faceted preventive care package

never be directly confirmed or refuted, because the low absolute rate of coronary heart disease among peri-menopausal women would require many thousands of perimenopausal and early postmenopausal women to be randomised to treatment or placebo for more than a decade. Even if the timing hypothesis is true, little evidence exists that other risks of hormone therapy vary with time since menopause. Finally, the timing hypothesis has little impact on clinical care. Even if we reject the timing hypothesis and assume that the overall risks documented in the women’s health initiative trials apply to younger women, the absolute risk associated with taking hormone therapy for a few years to treat menopause symptoms is low, and worth the benefit of symptom relief.

The NAMS position statement is not an evidence based guideline as defined by the UK National Institute for Health and Clinical Excellence or the US Preventive Services Task Force. A search of Medline (but not other databases) was performed, but data were not systematically abstracted or synthesised. References are provided in a bibliography, but it is not possible to determine which studies were used to support specific recommendations. NAMS uses a consensus process, in which selected experts are given recent references and asked to provide their opinions. The position statement is based on agreement among at least two thirds of the panel—more a majority than a consensus. NAMS is to be congratulated for providing financial disclosures of panel members, but it is concerning that these are so extensive.

Another worrying aspect of the 2007 NAMS position statement is that it suggests that use of postmenopausal hormone therapy is complicated. While some details are unclear or complex, the basic approach to using postmenopausal hormone therapy is clear and simple: treat bothersome menopausal symptoms with the lowest effective dose of hormone therapy for the shortest time possible and do not use it to prevent disease.


Preventing ventilator associated pneumonia

Oral antiseptic agents should be part of a multi faceted preventive care package.
by differences in design, populations studied (medical versus surgical or mixed), duration of mechanical ventilation, and type and frequency of antiseptics applied. For example, 60% of patients included in the review had received cardiac surgery and had a short (mean <48 h) exposure to mechanical ventilation and treatment. However, in subgroup analyses, the effect size was comparable with short (<48 h) or longer duration of mechanical ventilation, although it was significant only in the larger group of surgical patients. Further studies should deal with these problems and confirm the efficacy of antiseptics, especially in larger groups of medical patients in intensive care who receive prolonged mechanical ventilation.

Preventing ventilation associated pneumonia is difficult, because of the insertion of an indwelling device within a contaminated area. Only substituting invasive mechanical ventilation with non-invasive ventilation, when appropriate, can circumvent this problem. However, implementing a group of multifaceted and targeted preventive measures—including education of personnel, semirecumbent positioning of patients, care of ventilator circuit, and no-touch suctioning—can substantially reduce rates of infection. The data now available, while still limited, suggest that oropharyngeal care with antiseptics may be included in such preventive strategies. However, as is the case for antibiotics, the risk of a long term effect of widespread use of antiseptics on the emergence and spread of bacterial resistance to these agents needs to be considered.

3 Heyland DK, Cook DJ, Griffith LE, Keenan SP, Bruin-Buisson C, for the Canadian Critical Care Trials Group. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. Am J Respir Crit Care Med 1999;159;1249-56.
10 Siegers P, Speekenbrink RG, Ubbink DT, van Ogtrop ML, de Mol BA. Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: a randomized controlled trial. JAMA 2006;296:2460-6.
STIGMATISING SEX WORKERS

BMA public health doctor’s claims lack evidence

There is no epidemiological evidence to support the recent statement by Spencer Jones that 70% of all sexually transmitted infections (STIs) in Birmingham are circulating in a pool of prostitutes and their clients.1 Surveillance data routinely collected by clinics for genitourinary medicine (GUM) and analysed by the Health Protection Agency do not include the proportion of STIs diagnosed in sex workers or their clients. Furthermore, data from the “Safe Project,” a dedicated sexual health promotion service for Birmingham’s sex workers, indicates that over the past year, the prevalence of STIs among the 208 sex workers attending this targeted service was low (chlamydia (1.9%), HIV (0), gonorrhoea (2.9%), and syphilis (1%)).

More recently a local enhanced surveillance programme introduced for syphilis indicated that, although commercial sex work or reported use of sex workers were identified among those found to be infected with syphilis, just 5% of the total number of syphilis diagnoses were attributable to this group.

Trends in HIV infections in Birmingham are similar to those seen nationally, and there is no evidence that contact with commercial sex workers is a significant risk factor in those newly diagnosed with HIV infection.2,3

Overall the claims made by the chairman of the BMA public health committee seem to be without substance. As a public health doctor he has a duty not only to ensure that important public health issues are discussed but also to check out the facts before going public.

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Competing interests: None declared.

1 Day M. BMA public health doctor is accused of stigmatising sex workers. BMJ 2007;334:767. (14 April.)

For debate: Should prostitution be legalised and regulated?

The BMA’s annual public health conference is an opportunity for doctors to air public health issues and debate them, to challenge each other and establish what is known and what is not known.1 The specialty of public health takes evidence based medicine at least as seriously as other specialties, but from time to time it is important to free oneself from its fetters.

On 29 March a motion was put forward from the West Midlands region (that I drew up): “That this conference believes that the key to prevention of sexually transmitted disease is two-fold: (i) school based education that ensures that all children understand the risks associated with unprotected sexual intercourse before they become sexually active, and (ii) the legalisation and regulation of prostitution.” The first part of the motion was accepted by the conference. The second part was taken “as reference”: a polite way of saying, go back and work on this more.

The BMA press office issued a press release ahead of the conference to excite press interest.1 I believe it included reference to part (i) of the motion, which I would not have endorsed. A news agency reported that I had said that 70% of sexually transmitted infections (STIs) are in people working in the pay for sex sector, when in fact I said that 70% of frequent fliers in STI clinics come from this sector.

My reason for submitting the motion seems to have served its primary purpose: to open up some debate. I urge colleagues to consider that it is as important to think about the “big picture” of what is going on in our society as well as what is going on in any specialty.

Certainly that is what we believe we have to do in public health. The question is, should prostitution be legalised and regulated? It is an honest question.

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Competing interests: None declared.

1 Day M. BMA public health doctor is accused of stigmatising sex workers. BMJ 2007;334:767. (14 April.)

Public health policy must be based on sound evidence

Discussions around regulatory frameworks in commercial sex require careful use of terminology. A widely circulated report of the BMA’s annual public health conference seems to be advocating the legalisation and regulation of sex work in order to submit prostitutes to regular testing.1 2 This approach is not only unjustified, and an affront to human dignity and rights, but an inappropriate diversion of scarce NHS resources. Furthermore, it would be ineffective and dangerous.3 Coercion of sex workers merely drives them further underground and alienates them from the services they need, leading to a breakdown in sexual health practices, and an increase in sexually transmitted infections.4

The major health problems among sex workers are related to stigmatisation, to which this report contributes further.1 Inaccurate and inflammatory statements such as these reported comments are likely to lead to increased levels of violence against them, as seen in Ipswich, and will even place outreach workers at risk.

It is unfortunate that Spencer Jones’s statements are being attributed to the BMA, giving them an undeserved authority, and hence credibility. They do
not reflect BMA policy, and the BMA needs to clarify this with some urgency, look to its accountability, and return to evidence based practice.

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Competing interests: None declared.


2 Day M. BMA public health doctor is accused of stigmatising sex workers. BMJ 2007;334:767. (14 April.)


INTENSIVE CARE

Help for patients and relatives

The DIPEx (Directory of Individual Patient Experiences) Research Group at the University of Oxford publishes a website of patients’ experiences of health and illness. There is a module on intensive care (www.dipex.org/IntensiveCare) where you can read and watch interviews with patients of all ages talking about their experiences.1

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Competing interests: None declared.


COX-P2

Drug management of COPD

In the second step of prescribing for long term management of chronic obstructive pulmonary disease, McVor and Little recommend the addition of a long acting β2 agonist (LABA) to a short acting β2 agonist as needed, supplemented by stepwise addition of regular short or long acting anticholinergic inhalers.1 I agree with this, and it is supported by evidence; tiotropium has advantages over a LABA. The National Institute for Health and Clinical Excellence (NICE) also recommends adding a LABA in its COPD guideline (No12, 2004).2 At that time there was no evidence to show whether this was a useful combination, but now evidence shows the addition of a LABA to tiotropium has no additional benefit over tiotropium alone,3 so this is not really a suitable option.

The authors’ next step is to add an inhaled corticosteroid or a combination of inhaled corticosteroid and a LABA as a single inhaler. If an inhaled corticosteroid is to be used in COPD then it should be in line with the NICE guideline. Evidence that a combination inhaler such as Seretide (fluticasone propionate and salmeterol) produces clinically important benefit over and above the separate components is lacking.4

If a patient on regular tiotropium and, as needed, a short acting β2 agonist requires additional drug treatment then I suggest that the two options are to add an inhaled corticosteroid (as per NICE guidance) or add an oral mucolytic. To assess the effectiveness of drug therapy I suggest using five recommended questions (similar to using three questions in asthma).5

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Competing interests: None declared.

1 McVor A, Little P. Chronic obstructive pulmonary disease. BMJ 2007;334:796. (14 April.)


COELIAC DISEASE

Decision tool needs to be developed for children

The decision tool for coeliac disease developed by Hopper et al is restricted to adults. However, coeliac disease often presents in childhood with different symptoms and signs.1,2 It may therefore be inappropriate to use the clinical characteristics suggested by Hopper et al when dividing children into high and low risk groups with respect to coeliac disease.

The second part of the clinical decision tool of Hopper et al is testing with tissue transglutaminase autoantibodies.1 Also here clinicians need to consider the implications of age. In a recent review by Rostom et al,3 the pooled sensitivity of human tissue transglutaminase IgA autoantibodies was lower in children (95.7%) than in adults (98.1%); more false negative cases can therefore be expected.

The clinical decision tool proposed by Hopper et al should be adapted for children, and thereafter tested prospectively in an unslected population.

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Competing interests: None declared.


SHIFT WORK

The view from Denmark

As a junior doctor I worked all the different work rotas imaginable, both full time and flexibly, for seven years—and in three countries (the United Kingdom, Malaysia, and Denmark).1 Now I work full time in Denmark but just 37 hours a week, maybe 40 on a bad week, and this includes on-call hours.

How does the Danish public health system function with such reduced doctors’ working hours? Perhaps it is because Denmark has more doctors (they are still looking for more), and doctors are more efficient at time keeping during an average working day. The department I work in performs over 200 cleft cases and 150 free breast flaps in a year, plus all the skin cancer cases and burns injuries. These figures are similar to those of London teaching hospitals.

The downside? The training takes longer, but who cares if you can still have a good social and family life as well as enjoy your work? And there is no special treatment for women either: both parents are entitled to a shared maternity or paternity leave of up to nine months.

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Competing interests: None declared.

Contract has not meant better care, say doctors

Lisa Hitchen LONDON

Only 12% of consultants in England believe that patient care has improved under the new consultants’ contract, a critical report by the National Audit Office (NAO) says.

The contract was implemented in 2003 and was supposed to provide better services for patients; increase productivity through improved management of consultants’ work; and reward consultants for their NHS work through higher pay. It is based on an agreed “job plan” made up of 10 programmed activities of four hours each. The contract is the first update since the NHS was formed in 1948.

But a survey from the NAO of 2361 consultants compared time spent before and after implementation on patient care and showed no increase in time spent on direct care.

It also found that although consultants are paid an average of 25% more for doing the same or fewer hours than three years ago, their morale has fallen, with some admitting to adopting a “clockwatching attitude.” Hours of work have decreased since the contract came in, from an average of 51.6 to 50.2 a week.

“The contract has yet to deliver the full value for money to the NHS and the public that the Department [of Health] expected,” it says.

In negotiations it was agreed that the contract would be based on an average working week of 43 hours, although most consultants work longer hours.

Staff at 208 NHS acute and mental health trusts were asked their opinion of the contract. Most (90%) thought the contract had been implemented in a hurry. Although half felt that their job plan did not reflect their working hours, 70% thought that their new salary better reflected their workload. Only 11%, however, thought that time spent on clinical care had increased.

Costs seem to have been underestimated by the Department of Health, which originally set aside an extra £565m (£831m; $1131m) over three years for the contract but had to add a further £150m after trusts reported that it was more expensive than predicted.

Trusts didn’t limit costs when working out job plans so they agreed to more hours than budgeted for, which led to overspending, the report points out. Eighty four per cent of the chief executives asked said that they did not think the contract was fully funded.


Exodus of medical staff strains Iraq’s health infrastructure

John Zarocostas GENEVA

The exodus of Iraqi doctors fleeing the escalating violence—including targeted threats, kidnappings, and murder of medical staff—is threatening the country’s strained health infrastructure, say humanitarian relief experts.

“Health facilities are stretched to the limit as they struggle to cope with daily emergencies caused by mass casualties,” said Angelo Gnaedinger, director general of the International Committee of the Red Cross (ICRC).

Mr Gnaedinger told a recent conference in Geneva on the needs of refugees and internally displaced persons in Iraq and in neighbouring countries, “Patients and medical staff are threatened or targeted. As a result, medical personnel are fleeing the country in large numbers, leaving health facilities short of staff.”

A report by the ICRC published this month on the situation of civilians in Iraq says, “According to the Iraqi Ministry of Health, more than half the doctors have left the country.”

At the end of last year, 18 000 of the 34 000 doctors had left the country, according to reports confirmed by Iraq’s Ministry of Health, say ICRC officials.

The UN Refugee Agency (UNHCR) estimates that about 1.9 million Iraqis are displaced within the country, and that as many as two million have fled abroad—mainly to neighbouring countries, such as Syria and Jordan.

A 2006 study by the Washington based Brookings Institution, cited by an International Federation of the Red Cross and Red Crescent Societies report on Iraq, estimated that 2000 doctors had been killed and 250 kidnapped.

The Iraqi Red Crescent Society, which cooperates closely with the ICRC, has had 14 of its staff and volunteers killed and 45 abducted, 12 of whom remain unaccounted for, and has witnessed numerous attacks on its offices, warehouses, and convoys, says Mr Gnaedinger.

But some senior UN officials say that the Brookings Institution estimate is rather conservative and that the numbers are probably much higher but difficult to quantify. WHO officials say it is hard to estimate numbers of doctors killed or kidnapped because of the lack of accurate data.
US Supreme Court approves ban on “partial birth abortion”

Janice Hopkins Tanne NEW YORK

The nine member US Supreme Court ruled five to four last week to ban the “partial birth abortion” procedure in the United States. The court upheld a federal law banning the procedure that was passed by Congress in 2003. The law had been challenged in the courts for lacking an exception to protect women’s health, not just their lives.

Many commentators called the decision the most important ruling on abortion in 30 years, and women demonstrated in front of the Supreme Court in protest at the ruling (right). Abortion will be an important topic in next year’s presidential election. Potential Democratic candidates criticised the court’s decision and potential Republican candidates approved it, including former mayor of New York Rudy Giuliani, despite the fact that he has said he supports abortion rights.

Seven years ago, the Supreme Court overturned a state law that banned “partial birth abortion” because it did not have an exception to protect women’s health (BMJ 2004;328:1398), and it has several times struck down abortion laws that did not have a health exception. The federal law states that the procedure is never medically necessary and the Supreme Court upheld the federal law despite its previous decisions requiring a protection for women’s health.

The law defines a partial birth abortion as a procedure in which the doctor “deliberately and intentionally vaginally delivers a living fetus until, in the case of a headfirst presentation, the entire fetal head is outside the body of the mother, or, in the case of a breech presentation, any part of the fetal trunk past the navel is outside the body of the mother, for the purpose of performing an overt act (usually the puncturing of the back of the child’s skull and removing the baby’s brains) that the person knows will kill the partially delivered living fetus.” The number of such abortions carried out each year in the US is thought to be between 2200 and 5000.

The American College of Obstetricians and Gynecologists said that the procedure might be the safest but its view had been disregarded. Dr Douglas Laube, president of the college, said that the decision “leaves no doubt that women’s health in America is perceived as being of little consequence.”

The college, Planned Parenthood, the American Civil Liberties Union, the Center for Reproductive Rights, the National Abortion Federation, and many other organisations criticised the court’s decision. They said it was a step towards prohibiting abortion. Pro-life, anti-abortion groups applauded the decision.

Breast cancer fell when women stopped hormone replacement

Janice Hopkins Tanne NEW YORK


Women’s use of hormone replacement fell substantially after the Women’s Health Initiative study showed an increased risk of cardiovascular events and breast cancer in women using a combination of oestrogen and progestogen called Prempro (JAMA 2002;288:321-33, 366-8).

Incidence of breast cancer fell sharply between 2002, when the JAMA study results were released, and levelled off in 2003, said researchers from MD Anderson Cancer Center, the US National Cancer Institute, and the Los Angeles Biomedical Research Institute. The decrease occurred only in women aged at least 50 and was more evident in cancers that were oestrogen receptor positive. Their study, based on data from nine cancer registries in the surveillance epidemiology and end results (SEER) programme of the National Cancer Institute, includes about 9% of the US population.

In contrast, in the 1990s, incidence of breast cancer increased in older women by about 0.5% a year. Although other factors might have had an effect, “only the use of hormone-replacement therapy changed substantially between 2002 and 2003,” the authors write.

In 2001-4, when incidence in older women was falling, breast cancer among women younger than 50 rose by 1.3%.

By 2005, prescriptions for Prempro, the combined hormone replacement therapy pill, had dropped 90%, and those for conjugated equine oestrogens by 60%, Donald Berry, chairman of biostatistics at MD Anderson Cancer Center in Houston, Texas, told the BMJ.

“It’s pretty likely that hormone replacement therapy doesn’t cause breast cancer but fuels it,” he said. There is “a possibility” that some breast cancers might remain indolent but are encouraged to grow by hormone replacement, he said. When a woman stops hormone replacement, the cancer might slow its growth, or stop, or even regress. “The rapidity of change [of incidence in the study] suggested that clinically occult breast cancers stopped progressing or even regressed after discontinuation of the therapy,” the authors wrote.

As for the effect of hormones in oral contraceptives, which the study did not look at, he told the BMJ, “We don’t know.”

Stopping postmenopausal hormone replacement might delay the occurrence of clinically detectable tumours or might lead to long term reduction.
Better legislation and its enforcement are needed to reduce the number of deaths and injuries associated with road traffic crashes in young people throughout Europe, a report published by the World Health Organization warns this week.

Almost 32,000 people younger than 25 years in the WHO European region die after injuries caused by road traffic every year, making it the third leading cause of death in this age group. About half of the children younger than 15 years old who are killed die as pedestrians, whereas people aged 15-24 years are most likely to die while driving a car or motorcycle.

The policy briefing says that children and young adults need special consideration because they may not have the necessary skills and experience to handle road environments that have been designed for adults. Some of the factors that put them at more risk include speed; alcohol; not being conspicuous; not using crash helmets, seatbelts, and child restraints; and design of roads and vehicles that lack inherent safety features.

Russia, Lithuania, Latvia, Portugal, and Greece are the countries with the greatest mortality caused by road traffic among 0-24 year old people.

The policy briefing, *Youth and Road Safety in Europe*, is available at [www.who.org](http://www.who.org).

### Abstinence education has no effect on US teenagers’ sexual activity

**Janice Hopkins Tanne** NEW YORK

Although the United States spends about $88m (£44m; €65m) a year teaching teenagers to abstain from sex outside marriage, young people in the programmes are just as likely to have sex as those who don’t receive counselling, a new study says.

Teenagers who received abstinence education did not delay sexual activity any longer than those in a control group. When they became sexually active they had the same number of partners and were as likely to use condoms or other contraceptives as those who had not been counselled.

Sharon Camp, president and chief executive officer of the Guttmacher Institute, which studies reproductive issues, said, “This rigorous, well designed study adds to and confirms previous research findings that abstinence only education programmes are ineffective and a waste of taxpayer dollars.” She called for more comprehensive programmes that not only teach abstinence but also provide information on contraception and safe sex.

Federal funding of abstinence programmes was established by the 1996 Personal Responsibility and Work Opportunity Reconciliation Act. Individual states provide additional funding. The US has more than 700 programmes.

A study commissioned by the US Department of Health and Human Services and conducted by Mathematica Policy Research looked at 2507 teenagers from four groups representing urban and rural areas and different socioeconomic levels. The students were randomly assigned to a programme group that received abstinence education or to a control group that received the usual health, family life, and sex education services in their schools or communities.

Students were 11 or 12 years old when they began the programmes in 1999 and the programmes lasted one to three years. The study followed them for four to six years, at which point their average age was 16.5 years.

The report is at [www.mathematica-mpr.com](http://www.mathematica-mpr.com).
IN BRIEF

US approves bird flu vaccine: The US Food and Drug Administration approved a human vaccine against the H5N1 influenza virus on 17 April, marking the first such approval in the United States. The vaccine, manufactured by Sanofi Pasteur, will only be available through public health officials for people who are at increased risk of exposure to H5N1.

Scottish charity offers funding for pain research: Medical Research Scotland is inviting applications for research projects on pain relief after it recently received an anonymous legacy of almost £500 000 (£740 000; $1m), which stipulated the money be used for research into pain relief. Grants for research projects will be to a maximum of £15 000. See www.medicalresearchscotland.org.uk.

Prosecutors drop appeal against man cleared of helping in suicide: Public prosecutors in the Netherlands have dropped their appeal against the acquittal of philosopher Ton Vink, of the suicide support group Horizon, who had been charged with helping a 53 year old woman commit suicide. Prosecutors could not prove his actions crossed the line between offering support and actively directing her actions (BMJ 2007;334:228-9).

Psychotic psychiatrists would prefer atypical antipsychotics: A survey of psychiatrists’ preferences for treatment should they become mentally ill shows that for psychosis atypical antipsychotics were generally favoured, with risperidone getting most votes. The survey, which had a response rate of 59% from 921 psychiatrists, shows that psychotherapy and antidepressants were both endorsed as treatments for mild to moderate depression, and citalopram, fluoxetine, and venlafaxine were the three preferred antidepressants. Electroconvulsive treatment received the backing of a large majority of psychiatrists (Scottish Medical Journal 2007;52:17-9).

Patients will top up inadequate services, group claims: NHS patients in the United Kingdom will turn to the private sector as a result of cuts and longer waiting times, according to a report for the campaign group Doctors for Reform. The authors include Karol Sikora, professor of cancer medicine at Imperial College School of Medicine. He says that patients are “topping up” NHS care with private treatments in places where services are patchy. Free at the Point of Delivery: Reality or Political Mirage is at wwwDoctorsforreform.com.

Inquiry will study removal of Sellafield workers’ body parts

Owen Dyer LONDON
An independent inquiry will look into claims that body parts were removed from deceased workers at Sellafield nuclear power plant in Cumbria without their families’ consent.

Michael Redfern QC, the barrister who led the inquiry into the retention of children’s organs at Liverpool’s Alder Hey Hospital, will examine what procedures were followed, whether consent was obtained, and what use was made of the tissues, said Alistair Darling, the trade and industry secretary, last week.

Sixty five cases in which tissue was taken from deceased former workers have been identified by British Nuclear Fuels, the company that today operates Sellafield. The workers all died between 1962 and 1991.

Mr Darling said that medical records indicated that 23 samples were taken after a coroner’s inquest and 33 after a coroner’s postmortem examination. Three requests for analysis arose from legal claims, while another was made by an individual before death. Yet another was carried out on what was described as a “legally correct basis.” In the four remaining cases there is no clear record of what prompted the request for tissue samples, he said.

Mr Darling stressed the limited nature of the records. He said, “They do not provide an audit trail which would show in every case who asked for such an examination under what authority and for what purpose. Nor do they disclose whether or not the appropriate consent from next of kin was received.”

Hospital patients should be assessed for

Susan Mayor LONDON
Every hospital patient should be assessed for their risk of developing venous thromboembolism (VTE), an expert working group has recommended to the Department of Health in England.

The latest figures show that about 30 000 people die from venous thromboembolism a year in English hospitals. The government set up the expert working group to explore how best practice and guidance could be promoted and implemented to reduce the risk of venous thromboembolism.

The group recommends a mandatory documented assessment of the risk of the condition for every patient admitted to hospital and evidence based interventions according to their level of risk.

The Department of Health should set core standards for the NHS and the independent sector for assessing the risk, and hospitals’ compliance with these standards should be monitored by the Healthcare Commission, the group recommends.

The report from the expert group comes in the same week as publication of evidence based guidance from the National Institute for Health and Clinical Excellence (NICE) about preventing venous thromboembolism in patients having surgery.

The guidance recommends
Reform of patients’ forums unnecessary, MPs say

Zosia Kmietowicz LONDON
A bill going through the UK parliament that abolishes patients’ forums and replaces them with larger bodies has been criticised by MPs. They say evidence is lacking of any benefit and that the bill risks losing the patient volunteers who have brought about valuable changes in the health service over the past three years.

The Local Government and Public Involvement in Health Bill proposes establishing Local Involvement Networks (LINks) in the place of patients’ forums, 400 of which have been established in England since December 2003.

The new bodies will cover social care as well as health and are intended to attract a wider and more representative sample of the community to consult on the provision of services, including young people and ethnic minorities, something patients’ forums have failed to do.

However, in a report, MPs from the cross party health committee conclude that they are “not convinced that PPIFs [patient and public involvement forums] should be abolished.”

They add that patients’ forums could have been allowed to evolve into the larger organisations envisioned by the government in its proposed bill by merging them.

“Merging the existing PPIFs to form LINks would have been much less disruptive for volunteers and would have reduced the risk of significant numbers of them leaving. Once again the Department [of health] has embarked on structural reform with inadequate consideration of the disruption it causes,” says the report.

MPs are also angry that the bill modifies section 11 of the Health and Social Care Act, 2001, which places a duty on health authorities and trusts to consult patients and the public when planning or changing the services that they provide. Under amendments consultation is only needed for “significant” changes—a modification the report says is unnecessary and which will weaken the obligation for providers to consult patients about changes to services.

The report calls for greater clarity as to the functions and remit of LINks, their funding, and how they will be made accountable, something which is not made clear in the proposed bill, it says.

Sharon Grant, chairwoman of the Commission for Patient and Public Involvement in Health, said, “We concur with its [the report’s] substantial conclusion that the current proposals to reform the system for a public voice in health are flawed.”

The Department of Health announced in July 2005 that the commission, which was set up to oversee the forums, is to close in July this year.

The report, Patient and Public Involvement in the NHS, is available at www.parliament.uk

More than 90% of US doctors receive drug company favours

Bob Roehr WASHINGTON, DC
Ties between American doctors and the drug and medical devices industries are ubiquitous, concludes a large national US survey of doctors.

An analysis of the 1662 responses to the survey, which was supported by the non-profit Institute on Medicine as a Profession, found that 94% of respondents reported some form of relationship with drug companies (New England Journal of Medicine 2007;356:1742-50). The most common benefits of such relationships were receiving food in the workplace (reported by 83% of respondents) and receiving free drug samples (78%), while more than a third (35%) were reimbursed for attending professional meetings or training, and a quarter (28%) were compensated for consulting or enrolling patients in clinical trials that were beyond the cost of those trials.

The authors found differences between the six medical specialties studied—anesthesiology, cardiology, family practice, general surgery, internal medicine, and paediatrics—as well as by sex and place of employment.

They divided industry support into four categories: samples, gifts, reimbursements, and payments. They found that cardiologists were the greatest beneficiaries of industry largesse in three of the four categories. The exception was reimbursements, where internists scored more highly.

Anaesthesiologists scored moderately highly only in terms of receiving gifts.

risk of thromboembolism

that most surgical patients are offered compression stockings to wear while in hospital and says that many patients will also benefit from wearing inflatable “boots” in operations.

The guidance also recommends that blood thinning drugs, such as low molecular weight heparin or fondaparinux, should be given to all people having orthopaedic surgery and to other surgical patients who are at high risk of developing thromboembolism. For people having surgery to mend a broken hip, this blood thinning drug should be continued for four weeks.


Venous thromboembolism (above) is known as the silent killer
Former staff at CMAJ launch open access journal

David Spurgeon QUEBEC

Canada’s first paperless, open access, online medical journal was launched last week [www.openmedicine.ca]. Its origins lie in a dispute about editorial independence that led to the firing of senior editors at CMAJ, the journal of the Canadian Medical Association, and the resignation of most of its editorial board (BMJ 2006:332:687).

The new journal’s mission is “to facilitate the equitable global dissemination of high-quality health research; to promote international dialogue and collaboration on health issues; to improve clinical practice; and to deepen the understanding of health and health care.” It is not for profit, editorially independent, and will not charge subscription fees or run drug advertisements.

Six of the editorial team at Open Medicine were formerly editors at CMAJ and left after the dispute. Ten editorial board members at CMAJ resigned and now are on the board of Open Medicine.

Open Medicine’s publisher is John Willinsky, a professor in the education faculty of the University of British Columbia. Its co-editors are Anita Palepu, an internist at St Paul’s Hospital, Vancouver, and Stephen Choi, an emergency physician at the Ottawa Hospital.

Dr Palepu, one of the six editors who left CMAJ, says she thinks that the editorial interference at CMAJ led to the move to create the new journal. “It was a catalyst,” she explained.

She said that Open Medicine was applying for charitable status. It hoped to get operating funds from research libraries, institutional memberships, and foundations that share its mission, and also from non-drug, classified, and career advertising. A research group has already offered $C5000 (£2200; €3300; $4500) for three years.

“So, I am encouraged, but I really have no empirical data to say [whether] this is going to work or not.”

Paul Hébert, editor in chief of CMAJ since January, said, “I wish them well. Launching a medical journal is no small feat and it’s very hard work.

“Since I’ve taken on the job, the CMA [Canadian Medical Association] has decided to invest heavily in the journal, and they basically want to make this journal weekly within five years. We’re already increasing and enhancing the quality of the science.”

UK leads initiative to reduce cost of drugs in poor countries

Robert Short LONDON

A new organisation is being set up to increase transparency in the regulation, procurement, distribution, and sales of drugs in developing countries. Its objective is to drive the cost of drugs down to levels that patients can afford.

The UK led initiative, called the Medicines Transparency Alliance, has just had its first stakeholder meeting and will be launched in the coming months. It will run pilot projects in up to nine countries. Its aim is to publish information on the amount, quality, and price of drugs in poor countries; to allow patients to see what they should pay and give them confidence in the quality and safety of the drugs; and to create a forum in each pilot country that will bring together patients, doctors, non-governmental organisations, and those involved in supplying drugs.

Hilary Benn, secretary of state for international development, said at the stakeholder meeting: “One third of the world’s population has no access to the drugs they need to help them fight disease, and up to 30% of drugs available in the poorest countries are fake or substandard. Even when the right medicines are available they are unaffordable for the majority of people in developing countries, with mark-ups of up to 500% by some pharmacists.”

The UK Department for International Development is also creating an international advisory body to inform it of new developments and to identify ways to obtain and deliver drugs at sensible prices to the developing world. At an international conference on access to drugs, hosted jointly by the department and the Lancet, the department’s undersecretary of state, Gareth Thomas, challenged the drug industry, non-governmental organisations, and governments to find new ways to ensure that drugs reached people in developing countries at affordable prices. He invited participants at the conference to contribute to further debate at the department and to put themselves forward to join the advisory body.

“Finding new, innovative solutions—through new partnerships and networks, bringing down costs, accelerating research, and jumping over legal hurdles—is vital if we are to get serious about improving access to medicines for the poorest people of the world,” said Mr Thomas.

Presentations at the conference showed that success in reducing the cost of drugs in developing countries is not just about obtaining discounts from the industry and engineering flexibility in patent rights—the subjects of media attention. Access to drugs is affected by every aspect of the supply process, delegates heard. Relevant factors included research into and development of treatments for neglected diseases; patent control over the manufacture and sale of drugs; competition with generic drugs; and the supply chain by which the drugs are delivered.
Working in industry’s silken but firm embrace

Geoff Watts LONDON

“I probably spend more time thinking and talking about science now than I did in academia. Disease states, pathways, cell types . . . every day I’m faced with major scientific issues across a range of areas.”

The man making this surprising observation—surprising to him as well as to me—is Patrick Vallance. Until a year ago he was professor of clinical pharmacology at University College London (UCL); now he’s GlaxoSmithKline’s senior vice president for drug discovery. And nor is his more frequent engagement with science the only surprise he’s encountered since he changed jobs.

“Many of the projects we’re working on in drug discovery are higher risk and more forward looking than some of the things I saw coming through grant panels in academia—the sort of thing that might have been rejected as too speculative. I also realised that I had never previously sat down and talked about what things would look like in 2012 or 2015. That’s an everyday discussion in this industry. There’s no alternative.”

But what prompted him, in his mid-40s, to move into industry? As much as he now relishes the surprise aspects of his work, they clearly don’t account for the job change because he wasn’t anticipating them. So, was it boredom with the academic world, perhaps?

“It certainly wasn’t that I was fed up. I was very happy at UCL running my research group and a big division of medicine.” He had though served for two years on the scientific advisory board of the drug company, enjoyed it, and discovered (another surprise) “a breadth and depth of science and practical outcomes of science, which I found invigorating.”

Although his reasons for accepting GlaxoSmithKline’s offer were, he insists, entirely positive, he imagines that some people will have been thinking predictable thoughts. He laughs: “You’ve sold out; you’re going to be paid more; you’re no longer interested in the same things you were.”

The rewards, of course, can’t be denied. Nor can the facilities. To have met at the company’s headquarters in Greenford, Middlesex, on the date we had agreed would have been tricky for me. No problem, said Vallance’s assistant. The company has a foothold in central London. This turns out to be a smart townhouse in Berkeley Square. And Vallance remarks that the infrastructure and support on which he can now count frees him to do more of the work for which he was hired. It’s a marked departure from an administratively overburdened life as a senior academic.

The work itself involves responsibility for drug discovery—“the part of the process that goes from the initial hit of a chemical on a target through to proof of concept in the clinic”—throughout the whole company. In giving Vallance the job, GlaxoSmithKline knew it was taking on someone who’d been prepared to criticise the industry even while sitting on its scientific advisory board. Giving evidence about clinical trials to a Commons’ select committee on health in December 2004 Vallance said that “some studies funded by industry have been more helpful to marketing than to advancing clinical care” and that “some of the design flaws in commercial studies may be conceived to exaggerate benefit or to obscure access to the clinically important result.”

This conflict between commercial and scientific imperatives is surely what lies at the root of the discomfort that some doctors feel about joining industry. In clinical medicine all decisions (theoretically, anyway) are driven by facts, reason, and benefit to patients.

But drug companies have commercial departments that, although eager to deploy objective evidence if possible, also exploit other forms of persuasion. Image, emotion, prejudice, and a variety of other influences that contribute to successful marketing can lie uncomfortably with the norms and values of scientific medicine.

Vallance concedes that in this respect there can be “tension” within the industry. But pointing out that vested interest isn’t confined to drug companies, he quotes his own experience of attempts to change practice within the NHS and what can happen when reason comes up against entrenched positions or the political realities of the way the service is organised.

“I’m not sure how sound it is, jurisprudentially, to defend your own position by pointing out that the other guy’s behaviour isn’t perfect either. But it’s an understandable response to the holier than thou faction among academic critics of the drug industry.”

In his evidence to the select committee, Vallance said that the National Institute for Health and Clinical Excellence (NICE) should consider setting defined targets for new treatments. The idea would be to bring academics, clinicians, patients’ groups, and industry into the target setting process before a specific product is developed or even considered.”

Meanwhile he would like to see more movement between academia and industry. And not just through career change but for career development periods lasting a few years. Academia, he thinks, could learn a thing or two from the hard realities of industry. As his experience shows, to work within its silken but firm embrace can be intellectually invigorating.
Be sparing with red cell transfusions in critically ill children

Intensivists should think carefully before giving red cell transfusions to critically ill children, say researchers. A cautious policy that triggers a transfusion only when the haemoglobin concentration drops to 70 g/l (7 g/dl) or below looked safe in a recent trial, and substantially reduced children’s exposure to potentially harmful blood products.

The trial included 637 children who were critically ill but stable. All were in paediatric intensive care units. One group had a transfusion threshold of 70 g/l, whereas controls were given red cells when their haemoglobin concentration fell to 95 g/l.

Twelve per cent of both groups (38/320 v 39/317) developed new or progressive multi-organ failure. Fourteen children (4%) died in each group. Restricting transfusions made no difference to infection rates, organ dysfunction scores, or duration of illness. But it did reduce children’s exposure to red cells by 44% (0.9 v 1.7 transfusions per child). Adverse events were closely matched.

The trial was designed specifically to find out if the two strategies were equally safe, and the authors are confident that more judicious use of leucocyte reduced red cells does stable children no harm. The picture may be different for premature babies or children who are hypoxic, haemodynamically unstable, or bleeding.


HRT linked to ovarian cancer

Hormone replacement therapy (HRT) is associated with an increased risk of ovarian cancer in postmenopausal women, according to a large cohort study from the United Kingdom. The risk is small but potentially important and adds up to one extra ovarian cancer for every 2500 women taking HRT for five years. The authors estimate that HRT has been linked to 1300 additional ovarian cancers and 1000 additional deaths in the UK since 1991.

The study tracked more than 900 000 postmenopausal women for an average of seven years. More than 2000 women developed ovarian cancer and 1591 died of it during that time. The relative risk of cancer among current users of any HRT was 1.20 (95% CI 1.09 to 1.32), and the relative risk of death was 1.23 (1.09 to 1.38). The increased risk was confined to women who took HRT for five years or more. Past users were unaffected.

The extra cancers were not due to differences between women who do and do not use HRT, as the authors adjusted their analyses for a dozen potential confounding factors including age, wealth, parity, history of hysterectomy, smoking, body mass index, and time since the menopause.

It’s still unclear how or why these hormonal products cause ovarian cancer in older women (if they do). Similar products are protective in premenopausal women.


New treatment fails to save patients with cardiogenic shock

Cardiogenic shock after myocardial infarction is often lethal. The urgent search for better treatments led scientists to the nitric oxide pathway, which is activated during a heart attack and causes vasodilation and myocardial depression. Preventing the release of nitric oxide by inhibiting the enzyme responsible, nitric oxide synthetase, did not produce the expected survival benefit in a recent placebo controlled trial, however.

The drug tilarginine was so clearly ineffective that researchers stopped recruiting early on the grounds that continuing the study was futile. Patients given the drug were just as likely to die within a month (48%, 97/201) as those given a placebo (42%, 76/180). Tilarginine had no discernible effect on longer term mortality (six months), and it didn’t help speed up the resolution of heart failure.

Perhaps the drug failed because it disabled all three isoforms of the enzyme, not just the most harmful one, writes one commentator (pp 1711-3). Or perhaps we simply don’t know enough about the nitric oxide pathway to predict reliably what will happen when we inhibit it. But for now it seems clear that non-selective inhibition of nitric oxide synthetase should not be attempted in patients with cardiogenic shock complicating acute myocardial infarction.

JAMA 2007;297:1657-66,1711-3

Epoetin is a tempting sideline for dialysis units in the US

Patients with chronic kidney disease often need synthetic erythropoietin to prevent anaemia and keep transfusions to a minimum. But evidence is emerging of systematic overtreatment by some dialysis facilities in the United States. The problem seems to be linked to a perverse reimbursement arrangement with Medicare, whereby facilities can and do profit from treating patients with epoetin, the leading agent.

Four out of five American patients on dialysis are treated in profit making facilities, usually large corporate chains. A careful comparison of these facilities with “not for profit” dialysis units such as those affiliated with hospitals showed a clear difference in treatment patterns. At the end of 2004 (the most recent data available), profit making facilities used more erythropoietin per patient each week, chased and achieved higher haematocrit values, and adjusted patients’ doses more aggressively than not for profit units. Patients treated in profit making facilities were more likely to have haematocrit levels higher than the

HRT and relative risk of ovarian cancer

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<td>1.14 (1.01 to 1.28)</td>
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</tr>
<tr>
<td>Other</td>
<td>7.0</td>
<td>84/31.9</td>
<td>1.22 (0.98 to 1.53)</td>
<td></td>
</tr>
</tbody>
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Adapted from Lancet 2007 doi: 10.1016/S0140-6736(07)60534-2
36% target level recommended at the time by national guidelines and by the Food and Drugs Administration (54% v 47%).

None of these differences were explained by differences in case mix, and at least one commentator questions whether some units are overtreating patients for profit (pp 1713-6). Last year, the two largest dialysis chains made 21% and 25% of their revenue from epioptin.

JAMA 2007;297:1667-74, JAMA 2007;297:1713-6

HAART works best when patients adhere to treatment

Highly active antiretroviral therapy (HAART) is an effective treatment for HIV if patients take their drugs as prescribed. Tracking pharmacy claims for reimbursement from insurance companies is one way to measure adherence. It’s not ideal, because patients who pick up their drugs at the pharmacy don’t necessarily take them, but the method is simple and good enough to give researchers some idea of the link between adherence and viral suppression.

Researchers in South Africa used data from pharmacy claims to study HAART based on non-nucleoside reverse transcriptase inhibitors—the first line option in South Africa and elsewhere. They found a clear and linear relation between sustained viral suppression and better adherence to treatment in 2821 men and women being treated for the first time. Viral suppression started to improve once adherence reached 50%. Above this threshold, each 10% increase in adherence was associated with a 10% increase in the proportion of infected people with a viral load below 400 copies of HIV RNA/ml for a median follow-up of two years. Three quarters of the patients who filled all their prescriptions (100% adherence) reached this target (725/997).

Ann Intern Med 2007;146:564-73

Chondroitin won’t relieve the pain of osteoarthritis

A meta-analysis has shown that chondroitin is no better than placebo for reducing the pain of osteoarthritis. A linked editorial (pp 611-2) points out that many patients have a powerful belief in the supplement, and that continuing to take it probably won’t do them any harm.

In an unusual step, the researchers chose to focus their analysis on the three biggest and best trials after an initial meta-analysis showed that early trials were small, heterogeneous, poorly done, and potentially biased. As usual, poor quality trials were more likely than better quality trials to report positive results. The three best trials included 40% of all patients randomised. Most had osteoarthritis of the knee. Together, they suggest that chondroitin takes about half a millimetre off patients’ scores on a 10 cm visual analogue scale compared with placebo. The difference was insignificant statistically and barely noticeable clinically. The effect of chondroitin on joint space narrowing was hard to evaluate from the existing data, but the researchers say benefits look unlikely.

This is another example of an intervention that looks useful in early trials but proves not so useful once bigger and better trials are complete, says the editorial.

Ann Intern Med 2007;146:580-90

Researchers recommend omeprazole before endoscopy

Blood doesn’t clot well in an acid environment such as the stomach. So researchers in Hong Kong hypothesised that intravenous omeprazole might be a good early treatment for patients waiting for endoscopy after an upper gastrointestinal bleed. They were right. In a randomised trial, patients given a continuous infusion of omeprazole before endoscopy were less likely to need endoscopic treatments to stop the bleeding than patients given placebo (relative risk for the omeprazole group 0.67, 95% CI 0.51 to 0.90). The effect was similar for the subgroup of patients with bleeding peptic ulcers (0.61, 0.44 to 0.84). Treatments included injections of adrenaline around bleeding vessels and thermocoagulation.

Omeprazole didn’t reduce patients’ transfusion requirements, prevent recurrences, or save lives, and a similar proportion of each group needed emergency surgery to stop the bleeding. But patients given the drug were more likely to make it home from hospital in under three days (60.5% v 49.2%, P=0.005).

The researchers say their results confirm the notion that pre-emptive acid suppression can be beneficial for patients who are relatively stable and can afford to wait. But urgent endoscopy must remain the treatment of choice for patients who can’t.


Combination therapy helps keep patients with COPD out of hospital

Anticholinergic bronchodilators, long acting β2 agonists, and inhaled corticosteroids are the mainstays of treatment for people with chronic obstructive pulmonary disease (COPD). Many patients use combinations of all three. Good evidence to support any combination is hard to come by, partly because patients find it hard to stick to their assigned treatment for long enough to show that it works. Still, researchers keep trying, and a team from Canada recently succeeded in reporting some clinically useful results.

In a trial of 449 adults with moderate to severe COPD, the combination of tiotropium, salmeterol, and fluticasone improved lung function and quality of life and reduced admission to hospital compared with tiotropium alone. It did not prevent exacerbations, one of the key aims of treatment. About 60% of patients in each group had an exacerbation requiring treatment with systemic steroids or antibiotics. In a third arm, adding salmeterol to tiopropium worked no better than tiopro- pium alone.

As expected, the dropout rate was high. More than 40% of patients treated with either tiotropium (74/156) or tiotropium plus salm- etrol (64/148) failed to complete their treatment. Many started using inhaled steroids. This crossing over between groups means the negative results from this trial (on exacerbations) are less secure than the positive ones (on admission to hospital), say the authors.

Ann Intern Med 2007;146:545-55
The Bill and Melinda Gates Foundation is the world’s biggest grant giving charity and has done much to raise the profile of global health. But critics claim its special brand of philanthropy is damaging health systems in developing countries and distorting aid priorities. Hannah Brown reports

Ask anyone with a passing interest in global health what the Gates Foundation means to them and you’ll likely get just one answer: money. In a field long fatigued by the perpetual struggle for cash, the foundation’s eagerness to finance projects neglected by many other donors raised high hopes among campaigners that its impact on health would be swift and great. And with the commitment last June by America’s second richest man, Warren Buffet, to effectively double the foundation’s $30bn (£15bn; €22bn) endowment,1 hopes of substantial health achievements grew higher still.

But despite Bill Gates’s prediction at a press conference to mark Buffet’s pledge that there was now “No reason why we can’t cure the top 20 diseases”2 observers are starting to question whether all this money is reaping sufficient rewards. For although the foundation has given a huge boost to research and development into technologies against some of the world’s most devastating and neglected diseases, critics suggest that its reluctance to embrace research, demonstration, and capacity building in health delivery systems is worsening the gap between what technology can do and what is actually happening to health in poor communities. This situation, critics charge, is preventing the Gates’s grants from achieving their full potential.

As one of the Gates Foundation’s three main focuses, along with global development and its US programme, global health projects receive a substantial amount of the charity’s annual spending. To date, almost half of all awards have been in this area, a total of $6bn. When the Gates Foundation first started this generous spending in 2000, it was greeted with enthusiasm as a refreshing alternative to the staid, sluggish agencies that had until that time dominated global health. More nimble than the bureaucratic intergovernmental organisations of the UN system, including the World Health Organization, the Gates Foundation won respect for prioritising research gaps, promoting new financing mechanisms, and embracing partnerships with key global health actors.

However, the foundation’s business-like approach has also gained its fair share of detractors. A commitment to results oriented spending ensures that money is linked to measurable and demonstrable outcomes. But although this strategy makes accounting easier to handle, it has perpetuated vertical, disease specific funding strategies that damage health systems in developing countries, according to David Sanders, director of the School of Public Health at the University of the Western Cape, South Africa.

These vertical programmes, which are a longstanding feature of many global health initiatives, lead to fragmentation of health systems because they require separate planning, staffing, and management from other health services.3 Although the programmes can efficiently meet short term targets, Professor Sanders says such successes come at the expense of sustainable improvements in health. “Unless there has been a very concerted effort at preserving local capacity and ensuring retention of staff then it is not a sustainable approach,” he says. What is more, he adds, vertical programmes tend to distort government priorities in developing countries, even if local ministers are committed to broad health system improvements. “Even if governments develop coherent policies and integrated plans it is quite difficult to hold that line when your big funders—with more money than those countries’ overall health budgets—want to focus on single diseases, often using a single technology rather than a more comprehensive approach,” explains Professor Sanders.

Technology versus delivery
Whereas the foundation contests claims that it is neglecting the strengthening of health systems, co-chairs Bill and Melinda Gates...
have made no secret of the fact that they see breakthrough technologies as key instruments in global health. The foundation described its policy to the BMJ: “Effective and affordable health tools aren’t available for many diseases. For this reason, we have focused on a significant portion of our grant-making on discovering and developing new vaccines, drugs, and other technologies that could save millions of lives.” However, Anne Mills, of the London School of Hygiene and Tropical Medicine, London, says that unless the foundation starts bridging the existing knowledge gap between proved technologies and how best to deliver them to communities, the problem will just get worse. “When money goes into new technologies you are just going to see more need for evidence on delivery systems to get them into practice,” she explains.

Professor Sanders also believes the Gates Foundation’s penchant for technological solutions limits the public health impact of its programmes because it ignores the realities of life in developing countries. “It is pretty clear that in the countries that I am acquainted with in southern and eastern Africa, the biggest problem is not lack of technology but systems to implement it; health systems have been seriously weakened by years of underfunding as a result of economic crises and structural adjustment,” he says.

One of the starkest examples of the technology-delivery divide is the GAVI Alliance (formerly known as the Global Alliance for Vaccines and Immunisation), a partnership established with a grant from the Gates Foundation in 2001. The alliance was set up at a time when worldwide immunisation rates were poor after steep rises in the 1980s—led mainly by Unicef—had waned. “Vaccination coverage had stagnated and in Africa it was at a miserable 50%,” explains Professor Sanders. GAVI had the primary aim of enticing the drug industry to produce more and new vaccines. But, says Professor Sanders, “We can’t even administer the old vaccines to children in Africa.”

GAVI has since begun investing directly into health system support for vaccine delivery, but Lincolin Chen, president of the New York based China Medical Board and an associate at Harvard University’s Global Equity Initiative, says that the foundation has not yet achieved an ultimately effective balance. “I don’t think Gates’ investments are yet adequately balanced in closing the gap between what we know and what we can deliver,” he says. “I can understand Gates saying ‘That’s not what a foundation can solve; it is too messy’ but I look at the Rockefeller 100 years ago. It worked the whole system: the human resources in medical education and research, the necessary technologies, and the requisite social institutions for global health. Arguably, Rockefeller’s huge investments in modern scientific medical education and establishing the field of public health were even more important than [its funding of] the discovery of penicillin and yellow fever vaccine. Gates has the opportunity to better balance its catalytic investments for the 21st century,” he says.

Growing criticism

The foundation is also attracting negative comments from other quarters. Grant recipients note that it is getting slower at processing applications and often seems to be giving mixed signals on funding priorities. “[The foundation] is at an uncomfortable stage,” says Professor Mills. “It’s not as quick and fast as it used to be and not as predictable as more established research funders.” While the increasing tiresome administrative processes can be explained by increased interest following Warren Buffett’s donation, the Gates Foundation admits it might need to grow. “We are expanding our internal capacity to keep pace with the growing endowment and interest,” a spokesperson said.

Critics also frequently chide the organisation for its choice of predominantly northern institutions when awarding grants, citing substantial funding commitments for the Seattle based Programme for Appropriate Technologies in Health and several academic institutions, including the London School of Hygiene and Tropical Medicine and Harvard University. But the most recent bout of negative publicity emerged after a minor scandal about the foundation’s endowment investments. An investigation by the LA Times published in January this year revealed that, although the foundation refuses to put money into tobacco companies, it is not averse to buying stock in firms responsible for releasing harmful pollutants or keeping prices of HIV drugs unaffordably high.6 The foundation caused further consternation among health campaigners in its response to the investigation: after initially announcing a review of its investment policies in the wake of the LA Times’ reports, it later issued a detailed statement explaining that no changes would be made.8

David McCoy, editor of Global Health Watch, sees this move as “Exposing the hypocrisy of the Gates Foundation and the double standards that it employs.” He says that the foundation’s decision exemplifies the fact that it is prepared to confront only obvious health problems while continuing to ignore the wider political and social issues. Dr McCoy notes the irony behind the fact that the foundation’s enormous wealth is derived
from the very distortions and injustices in the global political economy that keeps billions of people impoverished and unable to access health care. “The mere fact that we have one individual able to concentrate and accumulate so much wealth points to more fundamental questions about the way that the global political economy is organised, and we need a bigger discussion about how to shift the proceeds of economic growth to more people,” he says. He adds that while even grand-scale grant giving may seem to be a beneficial action, philanthropy can actually make underlying social and economic problems—the true determinants of health—more difficult to resolve because it can hinder health system development.

Finally, as with all private philanthropic organisations, the Gates Foundation attracts criticism for the simple reason that its money is private and therefore not really open to public accountability. According to Dr McCoy, the large degree to which the foundation has become a funder of independent academic institutions, non-governmental organisations, global health agencies, and even journalists raises concerns about self-censorship and a reluctance to subject itself to proper scrutiny. The foundation counters that it is continuously striving for openness through providing detailed information about grants on its website and seeking external opinions on some funding requests.

For some, however, having to rely on the foundation’s commitment to accountability is not sufficient, given the influence it enjoys. Anne-Emanuelle Birn, Canada chair in international health at the University of Toronto, thinks that because the foundation only funds most initiatives, and selectively picks good performers, that its decisions influence other donors’ choices about where to put their money. This means, according to Dr Birn, that although the Gates Foundation’s grants may not be making a huge impact on the ground, it is substantially affecting global health priorities.

“When the Gates Foundation invests there are a whole range of bilateral agencies and governments that are interested in joining on,” says Dr Birn. “Organisations want to be associated with what are perceived to be successful initiatives.” And this influence on how taxpayers’ money is spent should, she argues, confer greater responsibility. Dr Birn, Dr McCoy, and Professor Sanders all share the belief that the Gates Foundation—and Bill Gates himself—should use its profile and clout in financial circles to lobby for changes to improve the economic condition of developing countries as well as funding health programmes.

**Positive effect**

One thing observers do not contest is that in the seven years since the foundation was set up, it has been a key advocate for global health as an issue of international concern. “The field is not treated any more like a charity side show in part because Gates entered with money and has given the field visibility,” says Professor Chen. And importantly, the foundation’s existence has prompted the traditional global health actors to take a much-needed look at what niche they can occupy now. For example, says Professor Mills, “because Gates is coming with an awful lot of money it has stimulated the [Unicef, UN Development Programme, World Bank, and WHO sponsored] Special Programme for Research and Training in Tropical Diseases to rethink its core business and to take a much-needed look at what niche they can occupy now. For example, says Professor Mills, “because Gates is coming with an awful lot of money it has stimulated the [Unicef, UN Development Programme, World Bank, and WHO sponsored] Special Programme for Research and Training in Tropical Diseases to rethink its core business...”

The foundation has also created a more stable environment for research. Professor Mills says the scale of the funding available through the foundation has enabled a different approach to research from that allowed by the necessarily restricted traditional sources of global health funding. “The research agenda surrounding potential new tools, such as intermittent presumptive treatment of malaria in infants, can now be addressed in a set of coordinated studies, rather than piecemeal as funding permits,” she explains.

However, to make the organisation more successful in terms of global health outcomes, she agrees that it must extend its funding to aid countries with policy choices and decision making. “My hope is that Gates will come to realise they do have to engage with health systems research...”

John Harris is a freelance journalist

**Competing interests:** None declared.


The past 18 months of headlines about the National Health Service have been dominated by deficits. But even if finance is likely to make fewer headlines after May when the health department is expected to announce that the service has at least technically broken even, debate over money is not about to go away.

Indeed, financial management will affect doctors and other health workers every bit as much over the coming years as in the past one—even if this time its expression will not so obviously be about frozen posts, real redundancies, reduced training opportunities, and cancelled or slipped orders for supplies and equipment.

The whole financial framework of the NHS is changing to a more commercial model, which is likely to remain in place whoever becomes the next prime minister. The changes revolve around the drive towards foundation trust status; the framework around that; and the requirements that Monitor, the foundation trust regulator, will be applying to applicants.

Balancing the books
First the framework. Over recent years, several financial fiddles that had allowed the NHS to hide its true financial position have progressively been eliminated. These include capital to revenue transfers, which allowed trusts to eat into their capital to meet annual requirements in order to balance the books. Another is unplanned support—the sort of dodge whereby an NHS organisation in surplus lent money, sometimes literally overnight, to another in deficit so that both sets of books seemed to balance. Planned support has also been stopped, in the sense of formal brokerage sanctioned by health authorities, from one organisation to another.

These changes, as Patricia Hewitt, the health secretary, is keen to tell anyone prepared to listen, have begun to bring to an end a situation where, to put it crudely, parts of the NHS in the north and the midlands, which have the highest health needs but tended to end up in surplus, ended up lending money, interest free, to organisations in the south, which had healthier populations but tended to overspend. The money owed was often not paid back.

Eliminating the fiddles has helped reveal the service’s true financial position. To that extent it has, by the reckoning of the health department’s chief economist, contributed to the deficits the NHS ran up in the 2004 and 2005 financial years.

In their place will come interest-bearing loans that hospitals will have to pay...
Takeovers and mergers

Where does that leave hospitals currently heavily in debt? Having, as before, to draw up recovery plans. In some cases, however, they are likely to be taken over by foundation trusts. The first such takeover has just happened. Heart of England, a foundation trust that in its first year made a £5m (£7m; $10m) surplus on its £265m turnover, has effectively acquired nearby Good Hope Hospital in Birmingham which, a year ago, had an accumulated deficit of around £20m on a turnover of just over £100m.² 3

Good Hope’s board had judged it “no longer financially viable”: a polite way of saying insolvent. Heart of England was initially given a management contract which this month turned into a takeover—not a traditional NHS merger. Heart of England was given a few million pounds in one-off payments, effectively as a sweetener. And £17.5m of Good Hope’s accumulated deficit was turned into public dividend capital—capital effectively underwritten by the Treasury—and put on Heart of England’s books. The foundation trust will pay a low rate of interest—around 3-3.5%—on capital which is technically repayable but in practice is rarely repaid.

In the past, the money effectively loaned to cover Good Hope’s historic debt would have sat on the West Midlands strategic health authority’s books as brokerage—money the health authority hoped it would one day get back to spend on services. What has happened instead is that the authority has now accepted that it will not be repaid. In effect, it has written the money off. The health service and the public sector as a whole, however, have not because Heart of England will pay the Treasury interest on the money that can at least notionally be said to be being recycled back into NHS finances. Repayment depends, of course, on Heart of England remaining a going concern, with Monitor having moved the trust’s rating for financial strength down a notch for taking on the additional risk of Good Hope. This may sound like a technical accounting change. In practice, however, it is more than that. It gives the NHS a way to write off debt at one level without actually writing it off at another—in effect putting an obligation on Heart of England to service the debt.

No similar takeovers are in the immediate pipeline. But such deals are a potential double win for the health department. They get more hospitals to foundation status more quickly, and they provide an answer for some of the 15 to 20 NHS trusts that are in such deep financial trouble that the department believes their position to be irrecoverable within 10 years.

Such takeovers “won’t be the solution in every case,” Patricia Hewitt has said, but they “may well be the solution in some cases.”¹ These changes affect clinicians because they add to the growing number of hospitals being subjected to the foundation trust financial regime.

Looking after the pennies

The third part of the change, and the one that will most directly affect clinicians, is service line reporting. This entails breaking down a hospital’s services by specialty—or even subspecialty and procedure—and working out which ones make money and which ones lose it under the tariff, the NHS price list now used to pay for procedures.

This information is important to foundation trusts, which have to make a surplus in order to invest. Bill Moyes, chairman of Monitor, says: “Where they have unprofitable lines, trusts can see whether that is due to staffing levels, or inefficient use of theatres, or other issues they can tackle. If they are being efficient and it is still unprofitable, that may suggest that the tariff is wrong—so this type of work can be used to help refine the tariff.”

“Where that is not the case, they could have a discussion with their primary care trust about whether doing higher volumes—more cases—would make it profitable, or whether they should exit the service and let someone else do it.”⁴

To some, such a commercial approach may seem to cut across the ethos of the NHS. But in the hospitals that have piloted it—Chelsea and Westminster, University College London Hospitals, and Frimley Park in Surrey—at least some of their leading clinicians say it is helping to redesign services. Once clinicians are given the data and are able to examine the reasons why a service is unprofitable, it puts them in the driving seat of redesign. In other words it produces engaged clinicians, not top down orders simply to pare budgets or save money.

At present, a foundation trust can be required to provide anything that a primary care trust designates to be a core service. But as the range of NHS suppliers increases “the time may come when a foundation trust may be able to walk away from an [unprofitable] service, provided we are confident that the primary care trust has alternative suppliers,” Mr Moyes says.

Service line reporting is gradually being rolled out across existing foundation trusts, but Monitor will eventually expect all applicants for foundation trust status to have such data. “Once they have the information, they would be pretty stupid not to use it,” Mr Moyes says. And at the same time, the Healthcare Commission is taking steps to measure quality using the same service line approach.

All of this is bringing some of the disciplines of business and the commercial world to NHS provision. It brings challenges for clinicians. But at least some of the changes also bring opportunities, not least for greater control over how services are designed and how they operate.

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1 Timmins N. Hospital trusts to be free of rule. Financial Times 2007 Mar 28:2.
4 Timmins N. Hospitals told to focus on profit centres. Financial Times 2007 Mar 12:3.
Bad blood

An inquiry has begun into the infection of thousands of people with haemophilia in the United Kingdom who contracted hepatitis and HIV in the 1970s and 1980s. Rebecca Coombes reports

What’s the story
An independent inquiry into how thousands of UK people with haemophilia came to be infected with contaminated blood in the 1970s and 1980s opened last week. The opening was rather dramatically marked by allegations aired on the BBC that UK doctors ignored warnings that could have prevented these patients becoming infected with HIV and hepatitis C. Several patients also claimed that they were unknowingly placed in trials to test the infectivity of blood products, were secretly tested for HIV infection, and were not informed of positive results until years later in some cases.

The story has been unfolding for decades. In the 1970s and 1980s in the United Kingdom 4670 patients with haemophilia were exposed to hepatitis C through contaminated NHS blood and blood products, and of this group 1243 were also exposed to HIV. So far 1757 of these patients have died, and many more are now terminally ill. Haemophilia, the condition in which one of the clotting proteins in blood (most commonly factor VIII) is either missing or insufficient, is treated by injection of the missing protein. The protein can now be created through recombinant technology. But in the period when the infections occurred it was derived from the pooled plasma of many thousands of donors. So if any of the sources were infected with a bloodborne virus, the whole batch would be contaminated. During this time large amounts of the clotting agent factor VIII were imported from the United States, where commercial suppliers paid high risk donors (widely called “skid row donors”), such as prisoners, for their blood.

Who’s saying what?
Successive UK governments have refused to hold a public inquiry, saying that politicians, civil servants, and doctors did not know of the dangers of factor VIII in time for its use to be stopped. This assertion was disputed by several of the patients and relatives giving their account of what happened at the independent inquiry in Westminster last week.

One, Robert Mackie, said: “They are saying they didn’t know about the AIDS virus. I’m sorry, but by June 1983 the European commissioners put out a warning that all haemophiliacs in Europe were to be informed of the risks of AIDS. Why weren’t we warned of the risks?”

Carol Grayson told how her late husband, Peter, was given blood contaminated with HIV and hepatitis C. He was given diagnoses of HIV in 1985 and hepatitis C in 1994, and he died in 2005, at the age of 47. Mrs Grayson told the hearing that doctors “failed properly to explain the danger to patients and explain where the treatment was sourced so patients could be part of the joint decision making process.” She drew comparisons with the Tuskegee syphilis scandal in the US, in which some patients were not told they had syphilis so that doctors could monitor the progression of the disease.

What has the media coverage been like?
To coincide with the opening of the inquiry in Westminster, the BBC current affairs television programme Newsnight ran a special film last week, which used official documents that have only recently resurfaced after being “lost” for decades to back up claims that UK doctors, scientists, civil servants, and politicians were aware of the threats to patients but failed to
Computer molecular model of the clotting agent factor VIII

**TIMELINE: FACTOR VIII, HEPATITIS, AND HIV**

**1966**  The first blood clotting products for haemophiliacs are produced. The first commercial factor VIII concentrate is produced by Baxter’s Hyland division

**1970s**  Britain imports huge quantities of factor VIII from the US  
(BM) 1998;316:489-90

**1974**  The World Health Organization warns Britain not to import blood from countries with a high prevalence of hepatitis, such as the United States

**1976**  A drive to invest in making the UK self sufficient in blood products begins, but the initiative is not followed through

**1982**  First UK patient with haemophilia to be given diagnosis of AIDS

**1983**  US Food and Drug Administration regulations for the collection of plasma exclude donors from high risk groups

**MAY 1983**  Dr N Galbraith of the Public Health Laboratory Service writes to Dr Ian Field of the health department: “I have reviewed the literature and come to the conclusion that all blood products made from blood donated in the USA after 1978 should be withdrawn from use until the risk of AIDS transmission by these products has been clarified.” Nevertheless, a health department letter the same month concludes that the suggestion “is premature in relation to the evidence and unbalanced in that it does not take into account the risks to haemophiliacs of withdrawing a major source of their factor VIII supplies.” No restrictions are placed on imported concentrates, except on those for children under the age of 4 years and for people with mild haemophilia

**APRIL 1989**  A number of people with haemophilia begin a civil action against the health department  
(Source: Tainted Blood [www.taintedblood.info])

The documents were obtained by relatives of some of the people who have died. Of greatest note was a letter from the head of the UK’s public health surveillance centre warning the health department about the risk of HIV infection from factor VIII after Britain’s first case in Cardiff. The letter, dated May 1983—before most haemophiliac patients became infected with HIV—says that all US blood products made from donations after 1978 should be banned. However, the health department continued to allow imports to be used, saying that the risks were outweighed by the need to keep people with haemophilia supplied with factor VIII.

The UK had a desperate shortage of factor VIII. Despite calls from the World Health Organization in the mid-1970s for countries to be self sufficient in blood products, all UK efforts failed dismally, because of underfunding and lack of political will.

Documents released last week by a group called Tainted Blood [www.taintedblood.info], made up of relatives of deceased patients, show that fears about blood products being infected with hepatitis C were circulating as early as 1976 and that similar fears about HIV were around by 1982. The Newsnight programme questioned scientists’ and doctors’ motives in keeping quiet about the risks of imported blood products. It pointed to one official document that reflected the need to find “virgin haemophiliacs,” those who hadn’t already received any possibly contaminated blood products from abroad. These patients would be very valuable in testing the infectivity of newer, heat treated products, which had just come on the market and were supposed to be safer.

**What happens next?**

The new inquiry will investigate the circumstances surrounding the supply of contaminated blood to patients. Although not an official public inquiry, it has considerable weight. Chaired by a member of the House of Lords and former solicitor general, the inquiry sits in the Palace of Westminster and, for the next four months, will hold public hearings in which evidence will be provided by civil servants, patients, and politicians, among others.  
(www.archerchbp.com)  Lord Morris of Manchester, credited with getting the inquiry off the ground, said that the inquiry “seemed the only way to restore public confidence in the safety of blood supplies and Whitehall’s ability to react to new viruses.”

Rebecca Coombes journalist, London  rcoombes@bmjgroup.com
Single-payer systems spark endless debate

Whenever Americans lapse into their periodic “conversations” on health reform, a single-payer health system is proposed by some as the panacea and condemned by others as “socialised medicine.” Rarely are the pros and cons of single-payer systems fairly debated.

In single-payer health systems, the entire population shares one health insurance carrier, usually the central or provincial government. Such systems should not be confused with “socialised medicine,” in which the government also owns and operates the healthcare delivery system. Single-payer health systems typically are just social insurance grafted onto pluralistic delivery systems, which may include investor owned, for-profit enterprises. Canada’s and Taiwan’s health systems are classic examples of this genre, as is the government run Medicare system for elderly people in the United States for the services it covers.

To their proponents, single-payer health systems offer several distinct advantages over pluralistic health insurance systems, such the American system. Firstly, single-payer systems are the ideal vehicle for implementing an egalitarian social ethic, if that is what the citizenry desires. Such systems can apply the same terms of healthcare delivery to all of its citizens, regardless of the patient’s socioeconomic status, including styles of rationing and the fees paid for given treatments. It is not so in the US. The Medicaid programme for the poor run by state governments, for example, pays physicians and hospitals significantly lower fees—sometimes less than half—than those paid for commercially insured patients. These differential prices signal to providers in the system. Providers predictably and rationally respond to market forces. Canada’s and Taiwan’s health systems offer several distinct advantages over pluralistic health systems. For instance, physicians in Taiwan’s single-payer system, for example, utilisation trends and healthcare spending can be tracked electronically almost in real time. By contrast, in the United States, paper based claims processing is still common among the myriad of private health insurers, and total national health spending can be roughly estimated only with a lag of a year or more. Furthermore, claims processing in the US engages armies of costly intermediaries who translate nomenclature used by providers into the differing nomenclatures used by third party payers, who help patients claim reimbursements from insurance carriers, who help physicians bill private insurers, and who help insurers defend themselves against over-billing by providers. In a recent article entitled “Billing Battle: Fights Over Health Claims Spawn a New Arms Race,” the Wall Street Journal (14 February 2007) reported that American insurers and physicians were spending billions of dollars fighting over insurance claims, and that some consulting firms now earned handsome profits by helping both sides in this arms race with customised software.

The built-in pitfalls of single-payer systems, however, must be acknowledged as well.

Firstly, single-payer systems allocate disproportionate market power to the buy side of health care, which allows government to keep prices at the minimum necessary to keep providers in the system. Providers understandably may question the fairness of so asymmetric a distribution of market power in a health system. To be sure, the low prices it forces on the system allow society to provide more real health care for a given budget than could be delivered in a more expensive pluralistic system, and it also makes universal health insurance coverage more affordable. On the other hand, the extremely low profit margins it yields the provider of health care makes single-payer systems less hospitable to innovation in healthcare products and services and in the organisation of healthcare delivery, areas in which the US excels, sometimes to excess.

Secondly, in single-payer systems spending on health care is pitted against other government priorities and easily falls victim to the politician’s perennial desire to campaign on tax cuts. The barebones technology, physical amenities, and queues that unduly low global budgets in single-payer systems tend to beget inevitably trigger political forces for turning the system over to allegedly “more efficient” private market forces. Canada is in the midst of a debate on this issue.

Single-payer systems have poor political prospects in countries that hold sacred the right of individuals to jump queues with their money. For instance, in the United States where, it seems, it is considered ever more acceptable for moneyed elites to purchase for themselves superior access to prestigious private schools and universities, a higher quality healthcare experience, superior access to the political process, and even superior justice.

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The author wishes to thank Tsung-mei Cheng, author of “Taiwan’s New National Health Insurance Program: Genesis and Experience So Far” (Health Affairs May/June 2003;22:61-76) for her valuable contributions to this column.
Waking up from the DREAM of preventing diabetes with drugs

A drug to prevent diabetes would be attractive. But despite promotion of recent research evidence, Victor Montori, William Isley, and Gordon Guyatt argue that we are not there yet.

Diabetes affects about 4% of the world population and is associated with important costs, both in financial and human terms. The high prevalence, increasing incidence, and associated costs makes preventing diabetes a public health priority. The diabetes reduction assessment with ramipril and rosiglitazone medication (DREAM) trial recently showed that rosiglitazone reduced the risk of diabetes in people at risk. The results have prompted aggressive marketing of rosiglitazone as a preventive therapy; some clinicians are already responding to this initiative. We argue that the strategy will bring harms and additional costs while the benefits for patients remain questionable.

Preventing diabetes

Several randomised trials have shown that modest weight loss and physical activity can greatly reduce the risk of diabetes. The Diabetes Prevention Program documented a 58% relative risk reduction (confidence interval 48% to 66%) in high risk individuals; other trials have shown similar results.

Nevertheless, the possibility of preventing diabetes with drugs has caught the imagination of the drug industry. The medicalisation of pre-disease states and risk factors has become increasingly common, including targets of precursors of hypertension, osteopenia, and obesity. The prospect of marketing existing drugs to otherwise healthy people greatly expands the market for obesity. The prospect of marketing existing drugs to otherwise healthy people greatly expands the market for diabetes.

Effectiveness of drugs

Several trials have assessed the ability of drugs to prevent diabetes (box). Overall, except for metformin, the evidence is inconsistent and comes from trials of limited methodological quality. Two trials included drug discontinuation phases to determine if the drugs had changed the natural course of diabetes or was merely treating diabetes. Both discontinuation studies found that the proportion of diabetes diagnoses remained lower in the intervention arm; a third to half of the patients, however, were lost to follow-up and did not provide discontinuation data. Furthermore, the follow-up period after treatment was much shorter than the treatment time. None of the trials showed a reduction in the risk of diabetes complications.

DREAM is a large randomised controlled trial that enrolled patients with impaired fasting glucose concentrations or impaired glucose tolerance and assigned them to high dose rosiglitazone or placebo. The trial effectively concealed allocation, adhered to the intention to treat principle, and achieved negligible loss to follow-up after a median follow-up of three years.

The trial’s primary outcome was a composite end point of death and the diagnosis of diabetes. It was stopped early after almost 1000 primary end points had accumulated because of benefit in the treatment arm (table 1). The authors noted that for every 1000 people treated with rosiglitazone 8 mg/day for three years, about 144 people who would otherwise cross the glucose threshold we call diabetes will not do so; four to five patients without congestive heart failure will develop the condition.

<table>
<thead>
<tr>
<th>Evidence for drug prevention of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
</tr>
<tr>
<td>• Consistent evidence from 3 randomised trials</td>
</tr>
<tr>
<td>• The Diabetes Prevention Program (DPP) found metformin reduced the 3 year risk of diabetes (relative risk 0.69, 95% confidence interval 0.57 to 0.83), but lifestyle change was more effective</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Troglitazone (no longer available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two trials found troglitazone was effective in preventing diabetes:</td>
</tr>
<tr>
<td>• Study in women with a history of gestational diabetes had large loss to follow-up</td>
</tr>
<tr>
<td>• The DPP discontinued the trial arm because of fear of liver toxicity. Relative risk of diabetes diagnosis after 1 year of troglitazone was 0.25 (P&lt;0.001), but the effect disappeared in the year after drug discontinuation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angiotensin converting enzyme inhibitors, angiotensin receptor blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Systematic reviews of trials in hypertension, heart failure, and coronary disease that assessed diabetes as a secondary or post hoc outcome found large preventive effects</td>
</tr>
<tr>
<td>• DREAM trial failed to confirm the effect</td>
</tr>
</tbody>
</table>

Table 1 | Results of DREAM trial of treatment to prevent diabetes

<table>
<thead>
<tr>
<th>End point/side effect</th>
<th>Rosiglitazone (n=2635)</th>
<th>Placebo (n=2634)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point*</td>
<td>306 (11.6)</td>
<td>686 (26)</td>
<td>0.40 (0.35 to 0.46)</td>
</tr>
<tr>
<td>Death from all causes</td>
<td>30 (1.1)</td>
<td>33 (1.3)</td>
<td>0.91 (0.55 to 1.49)</td>
</tr>
<tr>
<td>Diagnosis of diabetes</td>
<td>280 (10.6)</td>
<td>658 (25)</td>
<td>0.38 (0.33 to 0.44)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14 (0.5)</td>
<td>2 (0.1)</td>
<td>7.0 (1.6 to 30.9)</td>
</tr>
<tr>
<td>Oedema</td>
<td>174 (6.8)</td>
<td>124 (4.9)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*Composite of death from all causes and diagnosis of diabetes.
Use of a composite end point

The apparent motivation for the use of death and diabetes as the primary end point was fear that death could act as a competing risk (the intervention could reduce the development of diabetes by increasing the risk of dying). Unfortunately, the hypothesis is implausible, and the resulting composite end point is potentially misleading because of a large gradient both in importance to patients and in frequency of events and treatment effects. Rosiglitazone had no effect on all cause mortality, an outcome of great importance to patients.4

We have reported previously that readers should beware of trials in which investigators choose composite end points with large gradients in patient importance, event frequency, and treatment effects.15 An analysis of composite end points in cardiovascular trials showed that end points of least importance to patients often contributed most events.16 In this situation, readers must focus on the effects of treatment on the components.17 Thus, considering this trial as showing a 60% reduction in the risk of death or diabetes is a mistake. We should instead consider the apparent benefits of a 62% reduction in diabetes.

Are patients better off taking pills to prevent diabetes?
The biochemical diagnosis of type 2 diabetes is a surrogate end point. From the standpoint of the health system, diagnosis of diabetes is a surrogate for increased use of healthcare resources, at least in the short term. Whether early drug use would reduce long term expenditure is unproved. Equally efficacious lifestyle interventions are far less costly to implement and may well reduce costs in the long run, particularly when applied to populations.

From the standpoint of the patient, the diagnosis of diabetes is a surrogate for challenges with employment and insurability, need for frequent clinic visits and tests, need for self monitoring and drug use, inconvenience, cost, anxiety, and short term (such as hypoglycaemia) and long term complications (such as microvascular and macrovascular complications, depression). For patients to celebrate the finding that taking a pill reduces the risk of receiving a diagnosis of diabetes one key condition needs to apply: patients should be better off.

Table 2 presents the short and long term outcomes important to patients that we might expect in a cohort of 10000 patients who take rosiglitazone for three years to prevent diabetes, and 10000 who do not, based on a simplified modelling exercise (see bmj.com for assumptions and estimations).

Downsides of taking pills to prevent diabetes
To show that rosiglitazone has truly prevented diabetes, the DREAM investigators are conducting a discontinuation study to see if the drug has delayed the diagnosis of diabetes after discontinuing treatment. If diabetes is present after rosiglitazone withdrawal, the effect of the drug was actually treatment of diabetes. Tuomilehto and Wareham, in an editorial accompanying the DREAM publication in the Lancet, use epidemiological data to show that up to now the glucose lowering effect of rosiglitazone can completely explain the trial’s findings.19

Table 2 shows that, even under the most optimistic assumptions, patients offered rosiglitazone for prevention will end up taking more pills. Thus, neither patients who value preventing diabetes in order to avoid taking drugs, nor a society concerned with cost minimisation, benefit from early use of rosiglitazone.

Patients at risk of developing diabetes may fear the diagnosis and its consequences. Taking rosiglitazone to prevent diabetes may plausibly reduce this anxiety; alternatively, the daily reminder of the pill may increase anxiety. The finding that one third of patients with screen detected diabetes experienced distressing anxiety when they were exposed to early intensive treatment (compared to one fifth of patients who did not have early intensive treatment) suggests that increased anxiety is a real possibility.20

Both DREAM and the prospective pioglitazone clinical trial in macrovascular events (PROactive) trial found

Table 2 | Outcomes important to patients in decision to use rosiglitazone to prevent diabetes

<table>
<thead>
<tr>
<th>End point</th>
<th>Rosiglitazone (n=10 000)</th>
<th>No rosiglitazone (n=10 000)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient years of use of ≥1 diabetes drug at end of trial (3 years)</td>
<td>30 000</td>
<td>3 650</td>
<td>—</td>
</tr>
<tr>
<td>No of patients with new diagnosis of diabetes at end of trial (3 years)*</td>
<td>1060</td>
<td>2500</td>
<td>0.38 (0.33 to 0.44)</td>
</tr>
<tr>
<td>Projected patient years taking ≥1 diabetes drug at 10 years, assuming 3% annual incidence of diabetes</td>
<td>43 637</td>
<td>33 856</td>
<td></td>
</tr>
<tr>
<td>Projected patient years taking ≥1 diabetes drug at 10 years, assuming 8% annual incidence of diabetes</td>
<td>52 566</td>
<td>33 856</td>
<td></td>
</tr>
<tr>
<td>Diabetes related outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety about diabetes</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Costs and inconvenience associated with glucose self monitoring</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Costs and inconvenience associated with medical care</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Cardiovascular end points (myocardial infarction, stroke, cardiovascular death) at 3 years</td>
<td>120</td>
<td>90</td>
<td>1.39 (0.81 to 2.37)</td>
</tr>
<tr>
<td>Cardiovascular end points at 10 years</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Heart failure at 3 years</td>
<td>50</td>
<td>10</td>
<td>7.03 (1.6 to 30.9)</td>
</tr>
<tr>
<td>Heart failure at 10 years</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Retinopathy, nephropathy, or neuropathy</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Common adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral oedema at 3 years</td>
<td>680</td>
<td>490</td>
<td>1.46 (1.1 to 1.8)</td>
</tr>
<tr>
<td>Weight gain (kg) at 3 years†</td>
<td>2.0</td>
<td>−0.2</td>
<td>—</td>
</tr>
<tr>
<td>Peripheral oedema or weight gain at 10 years</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Rare adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone fractures at 4 years‡</td>
<td>632</td>
<td>373</td>
<td>1.77 (1.3 to 2.2)</td>
</tr>
<tr>
<td>Macular oedema</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

*Assuming that clinicians immediately prescribe diabetes drugs (metformin) to patients who have diabetes diagnosed given that they were already receiving limited lifestyle interventions in DREAM.
†From the DREAM slide set (www.ccc.mcmaster.ca/dream.htm).
‡From the ADAPT trial 18
§Risk ratio.
glitazones increased the risk of heart failure.14 Thus, patients hoping to avoid cardiovascular complications may develop one such serious complication as a result of taking the drug.

Evidence is emerging of other serious side effects of glitazones. These include macular oedema with risk of blindness (probably rare22), and bone loss with risk of fracture and loss of independence and death in older women with diabetes. In a community based observational study, Schwartz and colleagues estimated that older women with diabetes taking glitazones for five years could lose 3% of their whole body bone density.18 Furthermore, a four year trial found the risk of fractures in men and women with a new diagnosis of diabetes was 6.3% in those taking rosiglitazone versus 3.7% in those taking metformin or glibenclamide.22

Benefits of diabetes prevention with glitazones

One key issue is whether early drug treatment reduces the risk of developing complications of diabetes. The risk of developing cardiovascular complications in the DREAM cohort with impaired glucose regulation was very low. Thus, although the results seem to favour placebo, the estimates are very imprecise (table 1). This contrasts with many small randomised controlled trials showing that glitazones reduce cardiovascular risk factors and surrogate markers and with the results of the PROactive trial, which found no significant reductions in all cause mortality, non-fatal myocardial infarction, and stroke among patients taking pioglitazone.23 Consistent high quality direct evidence linking diabetes prevention with glitazones with reduction of complications associated with diabetes remains lacking (table 2).

How can we use our current knowledge to inform patients of the potential benefits of glitazone to prevent diabetes? We can tell patients at 25% risk of requiring a diabetes drug that we are going to give them a 100% chance of receiving that drug for three years in order to reduce their risk of requiring it in the future to 10%. This is a best case scenario. Furthermore, it is unclear how long, if at all, that reduced risk of need will extend.

In general, humans prefer immediate benefits to long, if at all, that reduced risk of need will extend.

Conclusion

When drugs are promoted for prevention, and the number of patients at risk of the target condition is very large, the expanded exposure to the drug may lead to important harm. Nevertheless, people at risk may be prepared to tolerate rare serious side effects when the benefits are clear. However, the benefits of rosiglitazone on outcomes important to patients remain speculative.

Because of the risk of harming people with no or minimal symptoms, the threshold for use of drugs in otherwise healthy people must be set high to get the required data for rosiglitazone requires large and long randomised controlled trials measuring its effect on outcomes important to patients and use of healthcare resources. Clinical use of glitazones to prevent diabetes is, at present, impossible to justify because of unproved benefit on patient important outcomes or lasting effect on serum glucose, increased burden of disease labelling, serious adverse effects, increased economic burden, and availability of effective, less costly lifestyle measures.

REFERENCES

24 Accepted: 12 March 2007

SUMMARY POINTS

Lifestyle changes and certain drugs are effective in preventing the diagnosis of diabetes

No trial has shown that prevention with drugs improves outcomes important to patients. Lifestyle changes are equally effective, much safer, and cheaper. Clinical use of glitazones for prevention cannot be justified.
Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP)

Nancy R Cook, associate professor,1 Jeffrey A Cutler, former senior scientific adviser,2 Eva Obarzanek, research nutritionist,2 Julie E Buring, professor,1 Kathryn M Rexrode, assistant professor of medicine,1 Shiriki K Kumanyika, professor of epidemiology,3 Lawrence J Appel, professor of medicine,4 Paul K Whelton, president and chief executive officer,5 for the Trials of Hypertension Prevention Collaborative Research Group

ABSTRACT
Objective To examine the effects of reduction in dietary sodium intake on cardiovascular events using data from two completed randomised trials, TOHP I and TOHP II.

Design Long term follow-up assessed 10-15 years after the original trial.

Setting 10 clinic sites in 1987-90 (TOHP I) and nine sites in 1990-5 (TOHP II). Central follow-up conducted by post and phone.

Participants Adults aged 30-54 years with prehypertension.

Intervention Dietary sodium reduction, including comprehensive education and counselling on reducing intake, for 18 months (TOHP I) or 36-48 months (TOHP II).

Main outcome measure Cardiovascular disease (myocardial infarction, stroke, coronary revascularisation, or cardiovascular death).

Results 744 participants in TOHP I and 2382 in TOHP II were randomised to a sodium reduction intervention or control. Net sodium reductions in the intervention groups were 44 mmol/24 h and 33 mmol/24 h, respectively. Vital status was obtained for all participants and follow-up information on morbidity was obtained from 2415 (77%), with 200 reporting a cardiovascular event. Risk of a cardiovascular event was either inversely13 14 or directly15 associated with increased risk of cardiovascular disease. In Scottish,16 Finnish,17 and Japanese18 studies, a single measure of urinary excretion was directly correlated with increased risk of coronary heart disease or stroke, although this direct relation has been disputed by some.19 In one lifestyle intervention trial reporting cardiovascular outcomes, there was a non-significant trend towards reduced cardiovascular disease in those assigned to a reduced sodium intervention.20

The causal effect of sodium reduction on subsequent morbidity and mortality are limited and inconclusive. Several ecological studies support a direct association between higher sodium intake or urinary sodium excretion and mortality from stroke.11 12 Prospective studies generally suggest a direct association despite imperfect measures of sodium intake, although results are mixed. Analyses of the national health and nutrition examination follow-up study (NHEFS) found that dietary sodium intake was either inversely21 14 or directly22 associated with increased risk of cardiovascular disease. In Scottish,16 Finnish,17 and Japanese18 studies, a single measure of urinary excretion was directly correlated with increased risk of coronary heart disease or stroke, although this direct relation has been disputed by some.19 In one lifestyle intervention trial reporting cardiovascular outcomes, there was a non-significant trend towards reduced cardiovascular disease in those assigned to a reduced sodium intervention.20

The causal effect of sodium reduction on subsequent disease can best be tested directly in a randomised trial. Interpretation of non-experimental studies, such as those cited above, is complicated because of methodological concerns. Trials of sodium reduction, however, have not been large enough or lasted long enough to provide adequate data on clinical outcomes.20

We followed up participants in two randomised lifestyle intervention trials—the trials of hypertension prevention phase I (TOHP I)9 and phase II (TOHP II)9—for subsequent cardiovascular outcomes. Both
Individual and weekly group counselling sessions were provided during the first three months, with additional counselling and support less frequently for the remainder of follow-up. Participants in the control group followed their usual diets and were given general guidelines for healthy eating. The follow-up period for the lifestyle interventions was 18 months. The final data were collected in 1989 to early 1990. In the intervention group, the net decrease in sodium excretion from baseline to 18 months was 44 mmol/24 h, and net changes in systolic/diastolic blood pressure were −1.7/−0.8 [P<0.01 and <0.05, respectively].

TOHP II

The second TOHP trial tested the effects of weight loss and sodium reduction on incident hypertension and blood pressure over three to four years. The design was a 2×2 factorial, with intervention groups of weight loss alone, sodium reduction alone, a combination of weight loss and sodium reduction, and a usual care group. Participants were aged 30-54 years, weighed 110-163% of desirable weight, and had average blood pressure of 83-89 mm Hg for diastolic and <140 mm Hg for systolic without antihypertensive medication. A total of 2382 participants were randomised into the trial from December 1990 to March 1992 at nine clinic sites. The active sodium reduction intervention was similar to that in TOHP I. Individual and weekly group counselling sessions were offered initially, with less intensive counselling and support thereafter, specific to sodium reduction. Mini-modules to reinforce the content were offered in the later years of the intervention. The final data were collected in March 1995.

In keeping with the factorial design, effects of the sodium reduction intervention were analysed by grouping data for the two sodium reduction interventions (alone or with weight loss) and for the two non-sodium reduction groups (usual care or weight loss alone). At 36 months, the pooled active sodium groups experienced a net decrease in sodium excretion of 33 mmol/24 h, with no significant blood pressure reduction. The sodium reduction alone group experienced a net 40 mmol/24 h reduction in sodium excretion with corresponding blood pressure reductions of 1.2/0.7 mm Hg compared with usual care, which was significant (P=0.02) for systolic blood pressure only. The sodium reduction only intervention resulted in lower incidence of hypertension, with a relative risk of 0.82 (P=0.05) compared with usual care.

Follow-up study

The observational follow-up for cardiovascular disease began in 2000, about 10 years after the end of TOHP I and five years after the end of TOHP II, and ended in 2004-5. We collected data on all events occurring since the end of the trials. The TOHP coordinating centre conducted the follow-up centrally by mail and phone. Questionnaires were posted beginning in January 2000, followed by phone calls as needed. We sought detailed information on cardiovascular and other
health outcomes. We sent additional questionnaires to responders at two year intervals through early 2005, with interim annual postcards for collection of address changes and study outcomes.

Our prespecified primary outcome was cardiovascular disease, a composite of myocardial infarction, stroke, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), or death with a cardiovascular cause. We repeated analyses excluding CABG and PTCA, and to examine consistency of results and eliminate any potential diagnostic bias, we also repeated the analysis for total mortality.

On notification of occurrence of a potential non-fatal outcome, we sought consent to obtain medical records. A study physician, blinded to randomisation assignment, reviewed the records to validate the reported outcome using standardised criteria. We also searched the national death index to identify deaths to December 2003 among those who did not respond to the questionnaires.

There were 297 non-fatal outcomes reported, including multiple reports per person. We obtained consent to examine medical records for 216 (73%) and obtained records for 196 (91%) of those with consent. Of the reported outcomes with records, we confirmed occurrence of cardiovascular disease in 178 reports (91%), including multiples reports per person. We included in these analyses all first reported outcomes, except for those that did not meet our criteria on record review.

We collected information on self reported sodium intake on the final follow-up questionnaire sent in 2004-5, which asked participants about their current preferences for salty and low sodium foods (“like a lot,” “like some,” “dislike some,” or “dislike a lot”) and whether they “always,” “usually,” “sometimes,” or “never” use low sodium products, read food labels for sodium, or keep track of daily intake of sodium (mg). We examined these data by randomised group to assess long term patterns of sodium use after the trial. Because of potential changes after a diagnosis related to a cardiovascular disease we included in these analyses only those who did not experience a study outcome.

Table 1 | Characteristics of participants in TOHP I and II according to allocation to sodium reduction intervention or control group. Numbers are means (SDs) unless stated otherwise

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TOHP I</th>
<th>TOHP II</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention (n=327)</td>
<td>Control (n=417)</td>
<td>P value</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (%) of men</td>
<td>232 (71.0)</td>
<td>299 (71.7)</td>
<td>0.82</td>
</tr>
<tr>
<td>No (%) according to race:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>255 (78.0)</td>
<td>319 (76.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>Black</td>
<td>64 (19.6)</td>
<td>87 (20.9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (2.4)</td>
<td>11 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>43.4 (6.6)</td>
<td>42.6 (6.5)</td>
<td>0.074</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.7 (14.3)</td>
<td>82.8 (13.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.1 (3.8)</td>
<td>27.1 (3.6)</td>
<td>0.88</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>124.8 (8.5)</td>
<td>125.1 (8.1)</td>
<td>0.57</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>83.7 (2.7)</td>
<td>83.9 (2.8)</td>
<td>0.43</td>
</tr>
<tr>
<td>Sodium excretion (mmol/24 h)</td>
<td>154.6 (59.9)</td>
<td>156.4 (60.5)</td>
<td>0.70</td>
</tr>
<tr>
<td>Change to end of trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in weight (kg)</td>
<td>~0.2 (3.8)</td>
<td>0.2 (3.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>Change in sodium excretion (mmol/24 h)</td>
<td>~55.2 (76.9)</td>
<td>~11.3 (77.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure.

*In TOHP II (a 2×2 factorial trial), participants were grouped according to whether they did or did not receive reduced sodium intervention. Hence, active sodium reduction group includes those assigned to sodium reduction alone and to sodium reduction plus weight loss, while control group includes those assigned to weight loss alone and to usual care.
In a sensitivity analysis using logistic regression we performed an intention to treat analysis treating non-responders as non-events. Results were similar and are not reported. Because mortality follow-up was virtually complete, we included all randomised participants in analyses of mortality alone in a full intention to treat analysis. We conducted additional analyses within subsets defined by age, sex, race, baseline body mass index, and assignment to a weight loss intervention. We analysed questions on current sodium preferences after the trial as binary outcomes using $\chi^2$ tests. Analyses were conducted with SAS version 8.2 and SPlus version 6.2.

**RESULTS**

A total of 744 participants were randomised to a sodium intervention or control in TOHP I and 2382 in TOHP II (fig 1). Baseline characteristics were evenly distributed, except for age, which was higher in the sodium reduction intervention group in each trial (table 1).26 27 Change in weight was similar, and change in sodium excretion was greater among those randomised to sodium reduction interventions.

We obtained follow-up information on cardiovascular outcomes or death for 2415 participants (77%). Follow-up rates were similar in the sodium intervention and control groups, with higher response among those in TOHP II (table 2). We had information on mortality for all participants, including non-responders. Two hundred participants (8% of the responders) experienced study outcomes.

The crude rate of cardiovascular disease was somewhat lower among those assigned to the sodium reduction intervention (P=0.21 in stratified analysis) than corresponding controls (table 2). After adjustment for baseline characteristics, particularly the imbalance in age, there were significant differences between groups. Figure 2 shows adjusted cumulative incidence rates of cardiovascular disease by trial and intervention. After we controlled for clinic site, demographic information, and randomisation to a weight loss intervention (in TOHP II), the estimated reduction in relative risk of cardiovascular disease among those in the sodium reduction versus control interventions was 25% (relative risk 0.75, 95% confidence interval 0.57 to 0.99, P=0.04). Additional adjustment for baseline weight

---

**Table 2** Response to follow-up and cardiovascular disease and total mortality according to allocation to sodium intervention or control group

<table>
<thead>
<tr>
<th>Follow-up response</th>
<th>Intervention (%)</th>
<th>Control (%)</th>
<th>P value (pCMH*)</th>
<th>Odds ratio or hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1169/1518 (77.0)</td>
<td>1246/1608 (77.5)</td>
<td>0.75 (0.62)</td>
<td>0.93† (0.78 to 1.11, P=0.42); 0.93‡ (0.78 to 1.11, P=0.42)</td>
</tr>
<tr>
<td>TOHP I</td>
<td>231/327 (70.6)</td>
<td>311/417 (74.6)</td>
<td>0.23</td>
<td>—</td>
</tr>
<tr>
<td>TOHP II</td>
<td>938/1191 (78.8)</td>
<td>935/1191 (78.5)</td>
<td>0.88</td>
<td>—</td>
</tr>
<tr>
<td>Cardiovascular disease (among responders in TOHP follow-up)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>88/1169 (7.5)</td>
<td>112/1246 (9.0)</td>
<td>0.19 (0.21)</td>
<td>0.79¶ (0.57 to 0.99, P=0.044); 0.70** (0.53 to 0.94, P=0.018)</td>
</tr>
<tr>
<td>TOHP I</td>
<td>17/231 (7.4)</td>
<td>32/311 (10.3)</td>
<td>0.24</td>
<td>0.48** (0.25 to 0.92, P=0.027)</td>
</tr>
<tr>
<td>TOHP II</td>
<td>71/938 (7.6)</td>
<td>80/935 (8.6)</td>
<td>0.43</td>
<td>0.79** (0.57 to 1.09, P=0.16)</td>
</tr>
<tr>
<td>Total mortality (among all randomised)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>35/1518 (2.3)</td>
<td>42/1608 (2.6)</td>
<td>0.58 (0.64)</td>
<td>0.81¶ (0.52 to 1.27, P=0.35); 0.80** (0.51 to 1.26, P=0.34)</td>
</tr>
<tr>
<td>TOHP I</td>
<td>10/327 (3.1)</td>
<td>14/417 (3.4)</td>
<td>0.82</td>
<td>0.76** (0.33 to 1.74, P=0.52)</td>
</tr>
<tr>
<td>TOHP II</td>
<td>25/1191 (2.1)</td>
<td>28/1191 (2.4)</td>
<td>0.68</td>
<td>0.83** (0.48 to 1.41, P=0.49)</td>
</tr>
</tbody>
</table>

*From Cochran-Mantel-Haenszel test stratifying by trial.
†Odds ratio from logistic regression adjusted for trial, clinic, age, race, sex, and weight loss intervention.
‡Odds ratio additionally adjusted for baseline weight and sodium excretion.
¶Myocardial infarction, stroke, revascularisation, or death due to cardiovascular cause.
**Hazard ratio from Cox regression analysis stratified by trial and adjusted for clinic, age, race, sex, and weight loss intervention.

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Fig 2 Cumulative incidence of cardiovascular disease (CVD) by sodium intervention group in TOHP I and II, adjusted for age, sex, and clinic
and sodium excretion strengthened the association (0.70, 0.53 to 0.94, \(P=0.02\)). Effect estimates were similar, although less significant, after further adjustment for change in weight during the trials (0.74, 0.55 to 1.01, \(P=0.06\)). Results were similar when we analysed them separately by trial. Analyses for interactions indicated that effects of the sodium reduction intervention were similar across categories defined by sex (\(P=0.98\)), race (white \(v\) black \(P=0.79\), white \(v\) other \(P=0.63\)), age (30-44 \(v\) 45-54 years, \(P=0.43\)), body mass index (<25 \(v\) ≥25, \(P=0.34\)), and active weight loss intervention overall (\(P=0.55\)) or within TOHP II only (\(P=0.17\)) (table 3). When we excluded revascularisation procedures from the composite outcome, 124 participants experienced cardiovascular disease (76 myocardial infarctions, 19 strokes, six both, and 23 cardiovascular deaths with no previous reported myocardial infarction or stroke). The fully adjusted point estimates were similar to those for the primary outcome, but were not significant (0.72, 0.50 to 1.03, \(P=0.07\)).

Sixty seven of the 3126 participants died; 35 in the intervention groups and 42 in the comparison groups. The magnitude of risk reduction in this full intention to treat analysis was consistent with results for the primary outcome (table 2 and fig 3). After adjustment for baseline characteristics, including weight and sodium excretion, there was a 20% lower mortality among those in the sodium reduction intervention (0.80, 0.51 to 1.03, \(P=0.06\)). Results were similar for each trial. Twenty five deaths were due to cardiovascular disease; 10 in the intervention groups and 15 in the comparison groups (0.62, 0.28 to 1.40, \(P=0.25\)).

![Cumulative mortality](image.png)

**Fig 3** Total mortality by sodium intervention group in TOHP I and II, adjusted for age, sex, and clinic

The final follow-up questionnaire in 2004-5 about sodium use after the trial was received from 1400 (65%) of the 2164 event-free participants, with a higher response among those in the sodium reduction intervention in TOHP I (77% \(v\) 66% in intervention \(v\) control).
WHAT IS ALREADY KNOWN ON THIS TOPIC
Randomised trials in people with and without hypertension show reduction in blood pressure with lower sodium intake. Few observational studies and virtually no trial data exist on the effect of sodium intake on subsequent cardiovascular disease.

WHAT THIS STUDY ADDS
Reduction in dietary sodium intake also seems to prevent cardiovascular disease.

control, respectively, P=0.01). In the two groups, 48% versus 32% (P<0.001) reported that they disliked salty foods, and 71% versus 64% (P=0.003) reported that they liked low sodium or unsalted foods. Additionally, 47% versus 29% reported that they usually or always used low sodium products (P<0.001); 66% versus 44% read food labels for sodium (P<0.001); and 28% versus 20% at least sometimes kept track of their daily intake of sodium (P<0.001) in the two groups, respectively.

DISCUSSION
In this long term follow-up of two completed lifestyle intervention trials, people with prehypertension assigned to a sodium reduction intervention experienced a 25-30% lower risk of cardiovascular outcomes in the 10 to 15 years after the trial. This magnitude of risk reduction was evident in each trial, in most subgroup analyses, and in various sensitivity analyses, such as those that excluded coronary revascularisation from the composite outcome, with total mortality as the trial outcome, and with an alternative set of adjustment variables. Although several of these subsidiary analyses did not achieve a conventional level of significance, the magnitude of risk reduction tended to be similar.

Strengths and weaknesses
Our follow-up study was of sufficient size and duration to assess the effects of sodium reduction on cardiovascular outcomes based on randomised trial data. Despite its relatively small size as a trial of clinical outcomes, it provides some of the strongest objective evidence to date that lowering sodium intake, even among those without hypertension, reduces the risk of future cardiovascular disease. Previous studies have been observational, relying on suboptimal measurements of dietary sodium intake, which is extremely difficult to measure. Many observational studies had a single assessment of dietary sodium intake, and many relied on dietary recall methods, which tend to be inaccurate and to underestimate actual sodium intake. Such problems with measuring sodium intake may explain the inconsistent and sometimes paradoxical findings. Observational studies measuring sodium excretion have found a more consistent positive association. Our study has several additional strengths. Firstly, participants were demographically heterogeneous, and all had prehypertension, placing them at increased risk of experiencing cardiovascular outcomes.

Secondly, measurements of dietary sodium intake during the trial phase were based on carefully collected repeated assessments of 24 hour urinary excretion. Observed baseline sodium excretion was in agreement with the average self reported intake of 3600 mg (156.6 mmol/24 h) seen in data from the national health and nutrition examination survey (NHANES) 1999-2000. One limitation of the study is the less than complete rate of follow-up. As a long term observational study of completed trials, however, the rates of follow-up (100% for mortality and 77% for morbidity) were relatively high. The response rate was similar by intervention group and thus unlikely to bias the results. In addition, analysis of total mortality, an outcome that is completely objective and virtually complete, showed a lesser but consistent reduction in risk.

A further limitation is the lack of direct measurement of blood pressure, weight, and sodium intake during follow-up, though questionnaire data support the presence of long term effects of the intervention. The intervention groups reported significantly better adherence to a reduced sodium eating pattern. Although we cannot rule out social desirability bias in reporting, the findings are supported by evidence that preference for salt can decrease after about three months on a reduced sodium diet. Persistence of adherence to intervention, albeit attenuated, has been observed at one year follow-up for other dietary modifications even in the absence of continued counselling. Maintenance of dietary sodium changes may be relatively better than for some other aspects of dietary change. If we assume the attenuation of effect that is often seen in studies of dietary change, these results might underestimate the potential public health benefits of policy changes to improve adoption and long term adherence to lower sodium intakes.

Other research
Long term clinical trials evaluating the efficacy of sodium reduction on clinical events have not been conducted because of logistic and feasibility considerations. There is, however, some evidence that sodium reduction has long term beneficial effects on blood pressure, even in the absence of continued intervention. In a 15 year follow-up study of infants who were given low sodium formula during their first six months, blood pressure was lower in the intervention group and thus unlikely to bias the results. In addition, analysis of total mortality, an outcome that is completely objective and virtually complete, showed a lesser but consistent reduction in risk.

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Besides its effects on blood pressure, an expanding body of evidence suggests that a high sodium intake has detrimental cardiovascular effects independent of blood pressure. High sodium intake increases extracellular sodium concentrations and may adversely affect vascular reactivity and growth and stimulate myocardial fibrosis. Additionally, several cross-sectional studies and one small clinical study have documented a direct relation between sodium intake and left ventricular mass. The latter mechanisms may explain the sizeable reduction in cardiovascular disease, despite the relatively modest effects on blood pressure seen during the TOHP trials.

Results of our follow-up study reinforce recommendations to lower dietary sodium intake as a means of preventing cardiovascular disease in the general population. To date, policy recommendations have relied to a large extent on a consistent body of evidence that sodium reduction lowers blood pressure, an aetiologically relevant, well accepted, and modifiable cardiovascular risk factor. High blood pressure, however, is not a cardiovascular event, and there has been a call for large scale, long term trials of sodium reduction with clinical outcomes. Our study provides unique evidence that sodium reduction might prevent cardiovascular disease and should dispel any residual concern that sodium reduction might be harmful.

In conclusion, sodium reduction, previously shown to lower blood pressure and prevent hypertension, also seems to prevent cardiovascular disease. The TOHP interventions reduced sodium intake by about 25% to 33%, approaching current recommendations for a 50% decrease in the amount of sodium in food in the United States. The observed reduction in cardiovascular risk associated with this sodium decrease was substantial and provides strong support for population-wide reduction in dietary sodium intake to prevent cardiovascular disease.

We thank David Gordon, Jean MacFadyen, and their staff at the TOHP coordinating centre for their efforts in conducting the follow-up study.

Contributors: NRC had primary responsibility for designing, conducting, analysing, interpreting, and reporting data from the follow-up study. JAC, EO, KMR, and PKW contributed to the design and conduct of the study, and all authors assisted in the interpretation of study results and critical revision of the manuscript. NRC is guarantor.

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Competing interests: None declared.

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31 Mattes RD. The taste for salt in humans. Am J Clin Nutr 1997;65:692-7S.


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Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis

Ee Yuee Chan, nurse educator,1 Annie Ruest, infectious diseases consultant,2 Maureen O Meade, associate professor,3 Deborah J Cook, professor3

ABSTRACT
Objective To evaluate the effect of oral decontamination on the incidence of ventilator associated pneumonia and mortality in mechanically ventilated adults.
Design Systematic review and meta-analysis.
Data sources Medline, Embase, CINAHL, the Cochrane Library, trials registers, reference lists, conference proceedings, and investigators in the specialty.
Review methods Two independent reviewers screened studies for inclusion, assessed trial quality, and extracted data. Eligible trials were randomised controlled trials enrolling mechanically ventilated adults that compared the effects of daily oral application of antibiotics or antiseptics with no prophylaxis.
Results 11 trials totalling 3242 patients met the inclusion criteria. Among four trials with 1098 patients, oral application of antibiotics did not significantly reduce the incidence of ventilator associated pneumonia (relative risk 0.69, 95% confidence interval 0.41 to 1.18). In seven trials with 2144 patients, however, oral application of antiseptics significantly reduced the incidence of ventilator associated pneumonia (0.56, 0.39 to 0.81). When the results of the 11 trials were pooled, rates of ventilator associated pneumonia were lower among patients receiving either method of oral decontamination (0.61, 0.45 to 0.82). Mortality was not influenced by prophylaxis with either antibiotics (0.94, 0.73 to 1.21) or antiseptics (0.96, 0.69 to 1.33) nor was duration of mechanical ventilation or stay in the intensive care unit.
Conclusions Oral decontamination of mechanically ventilated adults using antiseptics is associated with a lower risk of ventilator associated pneumonia. Neither antiseptic nor antibiotic oral decontamination reduced mortality or duration of mechanical ventilation or stay in the intensive care unit.

INTRODUCTION
Ventilator associated pneumonia remains a leading cause of morbidity and mortality among mechanically ventilated patients, with the incidence ranging from 9% to 27% and a crude mortality that may exceed 50%.1-4 Aspiration of bacteria from the upper digestive tract is important in the pathogenesis of this infection.4-5 Two different interventions aimed at decreasing the oral bacterial load are selective decontamination of the digestive tract, involving administration of non-absorbable antibiotics by mouth and through a nasogastric tube, and oral decontamination, which is limited to topical oral application of antibiotics or antiseptics.

Previous meta-analyses of selective decontamination of the digestive tract found a significant reduction in rates of ventilator associated pneumonia among treated patients.5-14 The use of this intervention is, however, limited by concern about the emergence of antibiotic resistant bacteria.15,16 Oral decontamination alone therefore may be more attractive because it requires only a fraction of the antibiotics used in selective decontamination of the digestive tract. To date, trials of oral decontamination using antibiotics have generated conflicting results, some suggesting benefit16,17,19,20 and others showing no benefit.21,22,23,24

One alternative to oral decontamination with antibiotics is to use antiseptics, such as chlorhexidine gluconate or povidone iodine. In contrast to antibiotics, antiseptics act rapidly at multiple target sites and accordingly may be less prone to induce drug resistance.25 Observational studies suggest that antiseptic oral decontamination can reduce ventilator associated pneumonia,21,22 but randomised controlled trials are not convincing.23,25-27 Recently a meta-analysis of four trials on chlorhexidine failed to show a significant reduction in rates of ventilator associated pneumonia.24 Two subsequent randomised controlled trials, however, suggested benefit from this approach.28,29

Current guidelines from the Centers for Disease Control and Prevention recommend topical oral chlorhexidine 0.12% during the perioperative period for adults undergoing cardiac surgery (grade II evidence).3 The routine use of antibiotic or antiseptic oral decontamination for the prevention of ventilator associated pneumonia, however, remains unresolved.3 Despite the lack of firm evidence favouring this preventive intervention, a recent survey across 59 European intensive care units from five countries showed that 61% of the respondents used oral decontamination with chlorhexidine.25
We carried out a systematic review and meta-analysis to estimate the effect of oral decontamination using topical antibiotics or antiseptics on ventilator associated pneumonia and mortality in mechanically ventilated adults.

METHODS

With the assistance of a professional librarian we searched for relevant randomised controlled trials using the Ovid version of Medline (1966 to May week 3, 2006) and a maximally sensitive strategy. We modified this search for Embase [1980 to week 21, 2006] and CINAHL [1982 to May week 3, 2006]. We also searched CENTRAL (the Cochrane Central Register of Controlled Trials, the Cochrane Library, issue 1, 2006) and the Cochrane Database of Systematic Reviews, issue 1, 2006. We screened previous meta-analyses and the references lists from all retrieved articles for additional studies. Further searches were carried out in two trials registers (www.clinicaltrials.gov/ and www.controlled-trials.com/) and on the web postings from conference proceedings, abstracts, and poster presentations. We also contacted authors and experts in the specialty.

Study selection and data extraction

We included published and unpublished randomised controlled trials testing the effect of oral decontamination on the incidence of pneumonia and mortality in adults requiring mechanical ventilation in an intensive care unit. We considered any type or combination of antibiotics or antiseptics. We had no language restrictions. Trials on selective decontamination of the digestive tract, observational studies, editorials, and commentaries were excluded.

Two independent reviewers (EC and AR) screened all titles and abstracts for inclusion. One reviewer (AR) was blinded to author, journal, institutional affiliation, and date of publication. We then independently assessed each selected reference for detailed evaluation. Interobserver agreement on the selection of articles for inclusion was measured with Cohen’s (unweighted) κ statistic. Two reviewers (EC and AR) also independently abstracted relevant trial characteristics, and disagreements were resolved by discussion. We contacted authors of the primary studies for clarifications as necessary.

Quality assessment

Two reviewers (EC and AR) independently appraised the quality of included trials. We evaluated randomisation, allocation concealment, blinding techniques, clarity of inclusion and exclusion criteria and outcome definitions, similarity of baseline characteristics, and completeness of follow-up. We considered randomisation to be true if the allocation sequence was generated using computer programs, random number tables, or random drawing of opaque envelopes. Alternate treatment allocation was classified as non-random. Allocation was considered concealed if it involved a telephone call to a central site, used opaque sealed envelopes, or was executed centrally by the pharmacy. Allocation was categorised as unconcealed when described as open or directly managed by the study investigators or when the methods were unclear. A study was considered blinded when patients, caregivers, and data collectors or outcome assessors were blinded, or when it was reported as double blind by the authors. We contacted authors to clarify methodology as necessary.

Data synthesis

We grouped trials according to the specified prophylactic agent used for oral decontamination. The two broad categories were randomised controlled trials in which oral antibiotics were tested against no prophylaxis and oral antiseptics were tested against no prophylaxis.

The primary outcomes were incidence of ventilator associated pneumonia and mortality. We used the authors’ definition for ventilator associated pneumonia if it included clinical and radiological criteria. As such, we excluded trials that used the clinical pulmonary infection score alone. We considered mortality in the intensive care unit in the absence of hospital mortality data. Secondary outcomes were the group mean duration of mechanical ventilation and stay in the intensive care unit. We also combined trials on antibiotics and antiseptics for the primary outcomes of ventilator associated pneumonia and mortality, in light of the a priori expectation of a similar magnitude and direction of treatment effect.

Meta-analysis was carried out using Review Manager 4.2 [Cochrane Collaboration, Oxford] and a random effects model. The pooled effects estimates for binary variables were expressed as relative risk with 95% confidence interval, whereas continuous variables were expressed as mean differences with 95% confidence intervals. We tested the difference in estimates of treatment effect between the treatment and control groups for each hypothesis using a two sided z test with statistical significance considered at P<0.05. We calculated the number of patients needed to treat (NNT, with 95% confidence interval) to prevent one episode of ventilator associated pneumonia during the period of mechanical ventilation, using the formula:

$$NNT = 1 / (RRR \times \text{median CER})$$

where RRR is the summary relative risk reduction and median CER is the median of the control events rates for all trials.

We used Cochran Q and I² statistics to assess for heterogeneity of results. We predefined heterogeneity as low, moderate, and high with I² of above 25%, 50%, and 75%. The a priori hypotheses to explain heterogeneity were method of allocation (smaller treatment effect in concealed compared with unconcealed allocation), blinding technique (smaller treatment effect in blinded compared with unblinded studies), patient population (smaller treatment effect in medical or mixed patients compared with selected surgical or trauma patients), and duration of ventilation (smaller
treatment effect in patients with mean duration of ventilation of 48 hours or more compared with less than 48 hours. The purpose of the first two analyses was to evaluate whether two critical methodological qualities influenced results.30 We also carried out a post hoc subgroup analysis to investigate the influence of alternative approaches to the diagnosis of ventilator associated pneumonia (quantitative culture of bronchoalveolar lavage fluid or protected specimen brush compared with non-quantitative culture of endotracheal aspirate or other criteria).

We compared relative risk estimates between subgroups using a two sided z test on the log relative risks, and expressed as a ratio of relative risks with its 95% confidence interval.31

The three trials with three arm comparisons were analysed as follows. In two studies,17,18 owing to the similarity of the control arms, we pooled them and compared the results with the treatment group. In the third study19 we excluded one of the two control arms from analysis because it incorporated both antibiotics and chlorhexidine.

To evaluate potential publication bias we constructed a funnel plot for the primary outcome of ventilator associated pneumonia, using odds ratio as the measure of effect, and visually inspected it for asymmetry. We also carried out Egger’s regression intercept and Begg’s rank correlation tests to assess this asymmetry formally. Analysis was done using Comprehensive Meta-analysis version 2.2.040 (Biostat, Englewood, NJ). We considered a one tailed P value of less than 0.05 as significant.

**RESULTS**

Eleven randomised controlled trials totalling 3242 patients met the inclusion criteria (table 1 and fig 1). Nine were published between 1994 and 2006,10-11 and two were published in abstract form.12,13 Four trials (1098 patients) assessed the effectiveness of antibiotic oral decontamination, whereas seven (2144 patients) evaluated the effectiveness of antiseptic oral decontamination. In the antiseptic category one trial tested Iseganan as the decontaminant.14 Iseganan is a synthetic variant of a porcine protegin, which is a natural antibiotic peptide released by neutrophils in response to invasion by microbes. Details of the excluded studies are available on request.18,19,21,23,32-37

All included studies were parallel design randomised controlled trials and were published in English. Most included general mixed patients in intensive care. Nine studies compared active treatment with placebo and two5,6 used “standard oral care” as the control. In all trials except five,5,6,8 the prophylactic regimen was given until extubation. Few studies reported on confounding strategies to prevent ventilator associated pneumonia.38 Three trials mentioned semirecumbent positioning5,6 and only one trial controlled for route of intubation and management of humidification using a ventilator circuit.6,8

The diagnostic criteria for ventilator associated pneumonia differed across trials (table 1). Several trials used quantitative microbiology to confirm ventilator associated pneumonia: three3,5,12 required a quantitative culture of bronchoalveolar lavage fluid or protected specimen brush, two used quantitative cultures of bronchoalveolar lavage fluid or endotracheal aspirate,5,6 and one used quantitative cultures of endotracheal aspirates.10 The other trials used either semiquantitative techniques5,7,13 or did not require microbiological confirmation,9 whereas in one trial the criteria were unclear.5,6 Except for three trials, the inclusion criteria included an anticipated duration of mechanical ventilation of 48 hours or more. Patients were ventilated for a mean duration of more than 48 hours in all but one trial.9 Seven trials reported duration of mechanical ventilation as means and standard deviations; eight trials reported duration of stay in the intensive care unit as such. One trial14 reported both of these outcomes as median and range values; these results were not included in the pooled analyses.

Interobserver agreement on the selection of trials for potential inclusion based on reading the titles and abstracts was excellent (Cohen’s unweighted $kappa=0.84$, 95% confidence interval 0.64 to 1.03). Interobserver agreement on the inclusion of relevant studies after detailed evaluation was also excellent ($kappa=1$).

Eight of nine authors responded to our requests and provided additional information on trial design, key quality features, and outcome data. Table 2 shows the methodological quality of included trials.

**Primary outcomes**

Ventilator associated pneumonia

Results from 11 trials (3242 patients) were available to examine the effects of oral decontamination on rates of ventilator associated pneumonia. Meta-analysis of four trials (1098 patients) testing antibiotic oral decontamination did not show a statistically significant reduction
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Follow-up</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergmans 2001*</td>
<td>Mixed</td>
<td>Obase with gentamicin, colistin, and vancomycin, 4 times daily until extubation, death, limited to 21 days</td>
<td>Control A, placebo in intensive care unit with patients receiving topical antimicrobial prophylaxis; control B, placebo in intensive care unit with no topical antimicrobial prophylaxis</td>
<td>Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations, including quantitative culture of bronchoalveolar lavage fluid or protected specimen brush. Mortality in hospital</td>
<td>Until extubation or death</td>
<td>Local and industry</td>
</tr>
<tr>
<td>De Riso 1996**</td>
<td>Cardiothoracic (open heart surgery)</td>
<td>Chlorhexidine 0.12% 15 ml preoperatively and twice daily postoperatively until discharge from intensive care or death</td>
<td>Placebo</td>
<td>Ventilator associated pneumonia: Centers for Disease Control and Prevention criteria.† Mortality in hospital</td>
<td>Until discharge from intensive care unit or death</td>
<td>Local</td>
</tr>
<tr>
<td>Fournier 2000*</td>
<td>Medical or surgical</td>
<td>Chlorhexidine 0.2% gel three times daily during stay in intensive care unit until 28 days, discharge from intensive care, or death</td>
<td>Standard treatment</td>
<td>Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations and quantitative culture of tracheal aspirate or bronchoalveolar lavage fluid, or both. Mortality in intensive care unit</td>
<td>Until discharge from intensive care unit or death</td>
<td>Local</td>
</tr>
<tr>
<td>Fournier 2005†</td>
<td>60% medical, 40% surgical</td>
<td>Chlorhexidine 0.2% gel three times daily during stay in intensive care unit until 28 days</td>
<td>Placebo</td>
<td>Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations and quantitative culture of tracheal aspirate or bronchoalveolar lavage fluid, or both. Mortality in intensive care unit by day 28</td>
<td>Until 28 days in intensive care, discharge from intensive care unit, or death</td>
<td>Local, and industry provided study drug</td>
</tr>
<tr>
<td>Koeman 2000*</td>
<td>Mixed</td>
<td>Treatment A, chlorhexidine 2% in white petrolatum vehicle four times daily until diagnosis of ventilator associated pneumonia, death, or extubation; treatment B, chlorhexidine 2% and colistin four times daily</td>
<td>Placebo</td>
<td>Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations and semiquantitative culture of tracheal aspirates. Independent adjudication committee determined if patients had ventilator associated pneumonia. Mortality in intensive care unit</td>
<td>Until extubation, discharge from intensive care unit, or death</td>
<td>Local</td>
</tr>
<tr>
<td>Kollef 2000†</td>
<td>83% non-trauma, 27% trauma</td>
<td>Iseganan 3 ml (9 mg) six times daily until 14 days. Treatment discontinued if patient developed ventilator associated pneumonia or was extubated</td>
<td>Placebo</td>
<td>Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations, including quantitative culture of bronchoalveolar lavage fluid or non-directed bronchoalveolar lavage fluid. Mortality in intensive care unit by day 28</td>
<td>Until 21 days or death</td>
<td>Industry</td>
</tr>
<tr>
<td>Lagner 1994*</td>
<td>General intensive care</td>
<td>Gentamicin gel four times daily until extubation. All received oral amphotericin B and oral disinfection with phenylhydrargram boricum and hexetidine</td>
<td>Placebo</td>
<td>Ventilator associated pneumonia: clinical and radiological investigations and positive culture of tracheal secretions. Mortality in intensive care unit</td>
<td>Until extubation</td>
<td>Not reported</td>
</tr>
<tr>
<td>MacNaughton 2004*</td>
<td>Medical or surgical (including trauma)</td>
<td>Chlorhexidine 0.2% oral rinse twice daily until extubation or death</td>
<td>Placebo</td>
<td>Ventilator associated pneumonia: leucocytosis and pyrexia &gt;38°C; deterioration in arterial blood gases; chest signs; new consolidation on chest radiography; and significant semiquantitative culture of non-directed bronchoalveolar lavage fluid. Mortality in intensive care unit</td>
<td>Not available</td>
<td>Local</td>
</tr>
<tr>
<td>Rios 2005*</td>
<td>Medical or surgical (including trauma)</td>
<td>Polymyxin B and gentamicin gel three times daily until 24 hours after extubation</td>
<td>Placebo</td>
<td>Ventilator associated pneumonia: clinical, radiological, and bacteriological, including positive quantitative culture of tracheal secretions. Mortality in intensive care unit</td>
<td>Until 28 days after ventilator associated pneumonia diagnosis or discharge from intensive care unit, or hospital discharge</td>
<td>Local</td>
</tr>
<tr>
<td>Segers 2005*</td>
<td>Cardiothoracic</td>
<td>Chlorhexidine 0.12%, nasal ointment, and 10 ml oropharynx rinse four times daily on allocation and admission to hospital until extubation or removal of nasogastric tube</td>
<td>Placebo</td>
<td>Ventilator associated pneumonia: Centers for Disease Control and Prevention criteria (no microbiological confirmation required). Mortality in hospital</td>
<td>Until 48 hours after discharge</td>
<td>Local</td>
</tr>
<tr>
<td>Seguin 2000*</td>
<td>Surgical (severe closed head trauma)</td>
<td>Povidone iodine 10% 20 ml reconstituted to 60 ml with sterile water to nasopharynx and oropharynx six times daily until extubation</td>
<td>Control A, saline rinse 60 ml; control B, standard treatment</td>
<td>Ventilator associated pneumonia: clinical, radiological, and bacteriological investigations including positive quantitative culture of bronchoalveolar lavage fluid or non-directed bronchoalveolar lavage fluid. Mortality in intensive care unit</td>
<td>Until discharge from intensive care unit</td>
<td>Not funded</td>
</tr>
</tbody>
</table>

*Published and unpublished data. †Trial stopped early. ‡Unclear if clinically defined ventilator associated pneumonia or microbiology confirmed ventilator associated pneumonia.
in ventilator associated pneumonia rates (relative risk 0.69, 0.41 to 1.18; P=0.18; I²=59.4%; fig 2). Pooled analysis of the seven trials (2144 patients) that tested the effect of antiseptic oral decontamination on ventilator associated pneumonia showed a significant reduction (relative risk 0.56, 0.39 to 0.81; P=0.002; I²=48.2%). The 11 trials combined favoured oral decontamination (relative risk 0.61, 0.45 to 0.82; P<0.001; I²=52.5%). Fourteen patients [NNT 14, 10 to 31] would need to receive oral decontamination with one of these methods to prevent one case of ventilator associated pneumonia.

Table 3 summarises the four a priori subgroup analyses. An informative comparison was possible for only two subgroups in the antiseptic trials, because either none or one comparison group existed for the other subgroups. Blinded trials yielded a more modest treatment effect than unblinded trials; medical or mixed populations also seemed to derive a more modest treatment effect compared with surgical or trauma patients. Table 3 also shows the post hoc subgroup analyses on diagnostic criteria for ventilator associated pneumonia where it was possible to compare the subgroups only in the antibiotics trials. Trials that used quantitative culture of bronchoalveolar lavage fluid observed a trend towards greater treatment effects compared with those that relied on less invasive diagnostic methods.

**Overall mortality**

Results of all 11 trials were available for the analysis of mortality (fig 3). Meta-analysis of the four trials that tested antibiotic prophylaxis found no effect on overall mortality (relative risk 0.94, 0.73 to 1.21; P=0.63; I²=34.8%). The pooled analysis of the seven antiseptic trials (2144 patients) also showed no effect on mortality (0.96, 0.69 to 1.33; P=0.82; I²=42.7%). Pooling the 11 studies produced similar results (0.97, 0.80 to 1.18; P=0.74; I²=34.3%).

**Duration of mechanical ventilation**

Overall seven trials (1760 patients) contributed to the analysis of duration of mechanical ventilation. Neither the pooled mean difference for prophylaxis using

### Table 2 | Methodological quality of included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomisation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Explicit inclusion and exclusion criteria</th>
<th>Base-line similarities‡</th>
<th>% Patients analysed for ventilator associated pneumonia divided by total No of patients randomised</th>
<th>Exclusions after randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beng-</td>
<td>Allocat-</td>
<td>Executed by pharmacy</td>
<td>Described as double blind</td>
<td>Yes</td>
<td>Yes</td>
<td>92.2</td>
<td>Early extubation or death (≥46 hours)</td>
</tr>
<tr>
<td>mansn</td>
<td>ions in block of 4</td>
<td>Unnamed</td>
<td>Described as single blind</td>
<td>Yes</td>
<td>Yes</td>
<td>Presumably 100</td>
<td>Not available</td>
</tr>
<tr>
<td>De Riso</td>
<td>Computer generated list</td>
<td>Executed by pharmacy</td>
<td>Patients, caregivers, outcome assessors</td>
<td>Yes</td>
<td>Yes</td>
<td>Presumably 100</td>
<td>Not available</td>
</tr>
<tr>
<td>Four-</td>
<td>Block randomisation stratified by site</td>
<td>Sealed envelopes by pharmacy</td>
<td>Described as double blind</td>
<td>Yes</td>
<td>Yes</td>
<td>99.6</td>
<td>Protocol violation: oral topical antibiotherapy needed</td>
</tr>
<tr>
<td>Koeman</td>
<td>Computer randomised tables stratified by centre</td>
<td>Executed by pharmacy</td>
<td>Patients, caregivers, data collectors, outcome assessors</td>
<td>Yes</td>
<td>Yes</td>
<td>100</td>
<td>None</td>
</tr>
<tr>
<td>Kolle</td>
<td>Computer generated list</td>
<td>Central telephone</td>
<td>Patients, caregivers, data collectors, outcome assessors</td>
<td>Yes</td>
<td>Yes</td>
<td>97.8 (only 87.7 completed the study. Unclear if those withdrawn, missing, or lost to follow-up were evaluated for ventilator associated pneumonia)</td>
<td>Did not receive study drug</td>
</tr>
<tr>
<td>Lagg-</td>
<td>Computer generated randomisation in time blocks†</td>
<td>Open</td>
<td>Described as double blind</td>
<td>Yes</td>
<td>Yes</td>
<td>76.1</td>
<td>Early extubation (&lt;5 days), enteral nutrition</td>
</tr>
<tr>
<td>Mac-</td>
<td>Block randomisation by random table</td>
<td>Executed by pharmacy</td>
<td>Described as double blind (patients, caregivers, investigators)</td>
<td>Yes</td>
<td>Unclear</td>
<td>100</td>
<td>None</td>
</tr>
<tr>
<td>Nau-</td>
<td>Random opening of opaque envelopes</td>
<td>Executed by pharmacy</td>
<td>Patients, caregivers, data collectors, outcome assessors</td>
<td>Yes</td>
<td>Yes</td>
<td>82.8</td>
<td>Decision to limit therapeutic efforts, death, or early extubation</td>
</tr>
<tr>
<td>Seg-</td>
<td>Computer randomised list</td>
<td>Executed by pharmacy</td>
<td>Patients, caregivers, data collectors, outcome assessors</td>
<td>Yes</td>
<td>Yes</td>
<td>96.3</td>
<td>Selective decontamination of digestive tract, withdrew consent, surgery cancelled or death before surgery</td>
</tr>
<tr>
<td>Segu-</td>
<td>Computer randomised list</td>
<td>Sealed envelopes</td>
<td>Data collectors, outcome assessors</td>
<td>Yes</td>
<td>Yes</td>
<td>89.1</td>
<td>Brain death, early extubation</td>
</tr>
</tbody>
</table>

*Published and unpublished data.
†Information obtained from Liberati et al.14
‡Age, sex, severity of disease, and, where available, systemic antibiotic treatment and ulcer prophylaxis usage.
antibiotics (−4.02 days, −9.43 to 1.40; P=0.15; I²=0%) or antiseptics (0.24 days, −1.01 to 1.48; P=0.71; I²=40.4%) showed an effect on duration of mechanical ventilation. The combined mean difference for all trials was 0.04 days (−1.15 to 1.23; P=0.95; I²=31.6%; fig 4).

**Duration of stay in intensive care unit**

Overall eight trials (2113 patients) contributed to the analysis of the duration of stay in the intensive care unit, which did not seem to be influenced by prophylaxis using either antibiotics (2.30 days, −4.10 to 8.69; P=0.48; I²=0%) or antiseptics (−0.30 days, −0.78 to 0.19; P=0.23; I²=83.5%). The combined mean difference for all trials was −0.28 days (−0.76 to 0.19; P=0.24; I²=77.8%; fig 4).

**Publication bias**
The funnel plot for ventilator associated pneumonia was asymmetrical, suggesting the existence of unpublished small studies with negative findings (fig 5). Formal statistical tests did not, however, support the presence of publication bias: Egger’s regression intercept (intercept −1.32, −3.59 to 0.95; one tailed P=0.111) and Begg’s rank correlation (Kendall’s τ with continuity correction −0.22; one tailed P=0.175).

**DISCUSSION**
The effectiveness of prophylactic oral decontamination to prevent pneumonia in patients undergoing mechanical ventilation has remained controversial since its introduction, due partly to discordant results of individual trials. We analysed antibiotic and antiseptic prophylaxis as two distinct approaches to oral decontamination. Our results suggest that antiseptic prophylaxis is effective at preventing ventilator associated pneumonia. More evidence is needed before firm conclusions can be made about antibiotic oral decontamination, although effects may be similar. This review included twice as many participants in the antiseptic trials than antibiotic trials, reflecting more precise results for the analysis of antiseptics.

We found that neither antibiotic nor antiseptic oral decontamination influenced overall mortality, duration of mechanical ventilation, or duration of stay in an intensive care unit. Our review was underpowered to detect any effect on mortality, and the small sample size limited the interpretation of the secondary outcomes.

**Comparison with previous studies**

Previous meta-analyses examining the effect of prophylaxis using selective decontamination of the digestive tract reported a significant reduction in the incidence of ventilator associated pneumonia.6-14 The most recent meta-analysis indicated that such an intervention combined with prophylactic intravenous antibiotics reduces overall mortality.14 In comparison our review suggests that oral antiseptic prophylaxis alone...
can significantly reduce the incidence of ventilator associated pneumonia, but not mortality. Our meta-analysis on antiseptics differs from the findings of Pineda et al, who pooled four trials on chlorhexidine and did not report lower rates of ventilator associated pneumonia (odds ratio 0.42, 0.16-1.06; P=0.07).24 Our results also extend those of Chlebicki et al, who did not find a statistically significant benefit using the more conservative random effects model after pooling seven trials on chlorhexidine (relative risk 0.70, 0.47-1.04; P=0.07), although their results were significant with the fixed effects model.30 Our systematic review included a larger dataset with two more recent trials,46,47 involved clarification of data from several authors, and explored heterogeneity with more subgroup analyses.

Possible explanations and implications

The lack of effect on secondary outcomes may raise concern about the accuracy with which ventilator associated pneumonia was diagnosed, given that the antiseptic trials, despite showing a substantial reduction in ventilator associated pneumonia rates, failed to show similar benefit for these secondary outcomes. It is possible that the combination of clinical, radiological, and microbiological criteria without the use of quantitative investigations using cultures of bronchoalveolar lavage fluid, which may have a high sensitivity but low specificity,40 may contribute to an overestimation of the ventilator associated pneumonia rates in these trials, and a greater observed treatment effect.

To ensure that the lack of effect on patients’ secondary outcomes did not arise from the differences in the diagnostic criteria used by the primary trials, we carried out a post hoc subgroup analysis on the basis of diagnostic criteria for ventilator associated pneumonia (differentiating between trials using invasive quantitative culture of bronchoalveolar lavage fluid or protected specimen brush versus other less invasive approaches). Only one of the antiseptic trials used invasive quantitative criteria, rendering further analysis not possible. Our analysis for the antibiotic trials was inconclusive, showing a trend towards a greater treatment effect for the trials that used the more invasive diagnostic criteria (table 3). An analysis combining all trials on antibiotics and antiseptics also suggested the same trend [invasive quantitative criteria’s relative risk 0.45, 0.21 to 0.98 vs less invasive criteria’s relative risk 0.66, 0.47 to 0.93], although the comparison of these relative risks was not conclusive (ratio of relative risks 0.68, 0.29 to 1.58; P=0.37). Nevertheless, a recent large multicentre trial found no difference in clinical outcomes or subsequent overall antibiotic use when a diagnostic approach of quantitative culture of bronchoalveolar lavage fluid was compared with non-quantitative culture of endotracheal aspirate among non-immunocompromised patients not suspected of harbouring high risk organisms.41
Our a priori subgroup analyses suggest that trials with an unblinded design and those enrolling surgical or trauma patients tended to yield qualitatively larger treatment effects than blinded trials and those enrolling medical or mixed critically ill patients. The former result is consistent with previous work showing that trials of lower methodological quality tend to report greater treatment effects.\(^{43}\) Specific surgical or trauma patients often have fewer comorbidities than medical or mixed patients, which may explain the trend towards a greater treatment effect in the former population. However, these subgroup results are best viewed as hypothesis generating.

The finding that antiseptic oral decontamination can reduce the incidence of ventilator associated pneumonia could have important implications for lower healthcare costs and a reduced risk of antibiotic resistance compared with the use of antibiotics. It may not be prudent to adopt this practice routinely for all critically ill patients until strong data on the long term risk of selecting antiseptic and antibiotic resistant organisms are available. Nevertheless, antiseptic oral decontamination seems promising.

**Strengths and weaknesses of the study**

The strengths of this review include the comprehensive search for relevant randomised controlled trials, duplicate screening, selection, assessment of methodological quality and data abstraction, and use of the random effects model (which takes heterogeneity into account) to combine trial results. We separated and then combined the antibiotic and antiseptic trials, anticipating that the underlying pathophysiology could lead to a similar treatment effect across the trials,\(^{13}\) and because an overall treatment effect is of interest in examining the relation between oral flora and lung infection during critical illness.

We inspected funnel plots to evaluate potential publication bias for ventilator associated pneumonia. We also undertook formal statistical tests. These did not show the presence of publication bias for the combined 11 antibiotics and antiseptic trials. However, the power of these tests is generally low. Although our literature search was comprehensive, it is possible that we missed other relevant trials. In addition, these trials were heterogeneous with respect to populations enrolled, regimens used, outcome definitions, and analysis strategies, contributing to differing relative risks across the trials. Other limitations of the trials we included were exclusions after randomisation, mainly due to early extubation, early deaths, or protocol violations. Some trials did not explicitly report whether the number of patients analysed reflected the total number of patients randomised (table 2) such that we were unable to abstract the intention to treat analyses from all trials. Finally, we could not obtain unpublished data from some authors on the mean duration of mechanical ventilation and stay in an intensive care unit.

**Unanswered questions and future research**

Our systematic review supports the use of antiseptic oral decontamination. Research to date does not

### Table 3 | Subgroup analyses comparing effect of oral decontamination using antibiotic or antiseptic with no prophylaxis on incidence of ventilator associated pneumonia

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Antibiotic oral decontamination</th>
<th></th>
<th>Antiseptic oral decontamination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative risk (95% CI)</td>
<td>No of studies (No of patients)</td>
<td>Ratio of relative risks (95% CI); P value*</td>
</tr>
<tr>
<td>Allocation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concealed(†)</td>
<td>0.73 (0.42 to 1.28)</td>
<td>3 (1031)</td>
<td>—</td>
</tr>
<tr>
<td>Unconcealed</td>
<td>0.26 (0.03 to 2.19)</td>
<td>1 (67)</td>
<td>—</td>
</tr>
<tr>
<td>Blinding:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinded(‡)</td>
<td>—</td>
<td>—</td>
<td>NA(§)</td>
</tr>
<tr>
<td>Unblinded</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Patient population:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical or mixed</td>
<td>—</td>
<td>—</td>
<td>NA(§)</td>
</tr>
<tr>
<td>Selected surgical or trauma</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of ventilation (hours):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq48)</td>
<td>—</td>
<td>—</td>
<td>NA(**)</td>
</tr>
<tr>
<td>(&gt;48)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ventilator associated pneumonia diagnostic criteria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative culture of bronchoalveolar lavage fluid</td>
<td>0.58 (0.28 to 1.22)</td>
<td>2 (935)</td>
<td>0.74 (0.16 to 3.53); P=0.71</td>
</tr>
<tr>
<td>Non-quantitative culture of aspirate or others</td>
<td>0.78 (0.20 to 3.12)</td>
<td>2 (163)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Comparison of estimates in each subgroup (for example, concealed versus unconcealed trials).
†Concealed = reported as open, or unclear.
‡Patients, caregivers, and data collectors or outcome assessors blinded, or reported as double blind.
§None were blinded.
¶None were surgical or trauma patients.
**None were ventilated for \(>48\) hours.
address which antiseptic is preferred, since all but one trial evaluated chlorhexidine. We cannot recommend precise methods for chlorhexidine administration owing to the wide variation of treatment regimens among studies. These included varying concentrations (0.12%, 0.2%, 2%), sites of application, forms of agent (oral rinse, gel), and frequencies and techniques of application. Nevertheless, our findings suggest that the concentration of chlorhexidine may be a consideration. In trials with cardiac surgery patients at low risk for developing ventilator associated pneumonia owing to a short duration of intubation, chlorhexidine 0.12% was effective in reducing ventilator associated pneumonia. However, among medical or mixed intensive care populations, a higher concentration may be necessary. Chlorhexidine was not effective in most of these trials at 0.2% concentration but was effective at 2%. As for the only trial that used povidone iodine, the agent was found to be effective in preventing ventilator associated pneumonia among 98 patients.
patients with head injuries with a persistent score of 8 or less on the Glasgow coma scale requiring mechanical ventilation for 48 hours or more.68

To our knowledge no trial directly compares antibiotic with antiseptic oral decontamination. Further investigations comparing antibiotic with antiseptic oral decontamination while incorporating stringent infection surveillance would be worthwhile. Whether either antibiotic or antiseptic oral decontamination favourably influence important patient outcomes such as duration of mechanical ventilation or duration of stay in the intensive care unit should be evaluated in rigorously designed and adequately powered randomised trials.

CONCLUSIONS

This systematic review suggests that in mechanically ventilated patients, antiseptic oral decontamination prophylaxis reduces the incidence of ventilator associated pneumonia. More evidence is needed before firm conclusions can be made on the effect of antibiotic oral decontamination. These results should be interpreted in light of the moderate heterogeneity of trial results and possible publication bias. Neither of these two approaches to decontamination seems to affect mortality, duration of mechanical ventilation, or stay in the intensive care unit, although these trials are underpowered for these latter outcomes, and the summary of trials to date does not yet represent the optimum information size.44 Therefore more evidence is needed before firm conclusions can be made on the full effect of oral decontamination using antiseptics and, particularly, antibiotics.

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Ethical approval: Not required.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Selective decontamination of the digestive tract reduces the incidence of ventilator associated pneumonia

Oral decontamination requires only a fraction of the antibiotics used for selective decontamination

WHAT THIS STUDY ADDS

Oral decontamination using antiseptics reduces the incidence of ventilator associated pneumonia

Neither antibiotic nor antiseptic oral decontamination reduces overall mortality or duration of mechanical ventilation or stay in intensive care


Fig 5 | Funnel plots assessing publication bias for ventilator associated pneumonia

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Accepted: 28 January 2007
Anorexia nervosa
Jane Morris, Sara Twaddle

Anorexia nervosa has the highest mortality of any psychiatric disorder. It has a prevalence of about 0.3% in young women. It is more than twice as common in teenage girls, with an average age of onset of 15 years; 80-90% of patients with anorexia are female. Anorexia is the most common cause of weight loss in young women and of admission to child and adolescent hospital services. Most primary care practitioners encounter few cases of severe anorexia nervosa, but these cause immense distress and frustration in carers and professionals. We describe the clinical features of anorexia nervosa and review the current evidence on treatment and management.

How good is the evidence for managing anorexia nervosa?

Ironically, this most lethal of psychiatric disorders is the Cinderella of research. It is hard to engage patients with anorexia for treatment, let alone research. Furthermore, the complexity of coordinated approaches used in most specialist centres may overwhelm conventional research methods.

High quality evidence on the effects of starvation on the body is available to guide physical aspects of care. Genetic studies, including twin and family studies, and more recently gene analysis, have shed some light on causes, but few randomised controlled trials of treatment exist. In contrast, many randomised controlled trials are found on the management of normal weight bulimia nervosa. Unfortunately, these interventions have a poor response in anorexia nervosa.

This review is based on searches in PubMed, Medline, and PsycLIT for treatment of anorexia nervosa and related eating disorders, and the National Institute for Health and Clinical Excellence (NICE) clinical guideline. We found no category A evidence (at least one randomised controlled trial as part of a high quality and consistent body of literature (evidence level 1)), and only family interventions met category B criteria (well conducted clinical studies but no randomised controlled trials (evidence levels 2 and 3) or extrapolated from level I evidence). NICE uses category C recommendations (expert committee reports or clinical experience of respected authorities (evidence level 4) or extrapolation from level 2 or 3) to provide guidance where high quality formal evidence is absent.

Two Cochrane reviews cover antidepressant treatment for anorexia nervosa and individual psychotherapy for adults with the disorder. The reviews are based on only seven and six small studies, respectively, all of which had major methodological limitations. A further electronic and hand search of papers published more recently is supplemented by work in press, conference presentations, and some personal communications with the relatively small group of international experts in the field.

What are the hallmarks of anorexia nervosa?
The core psychological feature of anorexia nervosa is the extreme overvaluation of shape and weight. People with anorexia also have the physical capacity to tolerate extreme self imposed weight loss. Food restriction is only one aspect of the practices used to lose weight. Many people with anorexia use overexercise and overactivity to burn calories. They often choose to stand rather than sit; generate opportunities to be physically active; and are drawn to sport, athletics, and dance. Purging practices include self induced vomiting, together with misuse of laxatives, diuretics, and “slimming medicines.” Patients may also practise “body checking,” which involves repeated weighing, measuring, mirror gazing, and other obsessive behaviour to reassure themselves that they are still thin (box 1).

What is it like to experience anorexia nervosa?
At first I believed my thoughts were normal when I looked in the mirror— you don’t expect your eyes to lie. I felt such self loathing that I drastically reduced my food intake and did a lot of exercise. I felt better about myself and decided that once I’d lost a pound or two I would eat normally again. When it came to it I was too scared. It felt good to lose a couple of pounds but it became addictive. If I did a certain amount of exercise one day, the next day I had to do at least the same amount. I ended up feeling physically rubbish, but my mind said ‘I’m a horrible person who deserves pain. Paranoia sets in. You’re convinced people think you are fat even when they say you are not. Your mind tells you they are lying, until you find you can’t trust anyone. Living with anorexia is a constant battle between two evils. On one hand eating feels like an evil thing, but other people see that very belief as the evil. When I feel I really must starve or exercise I get angry with the nurses. Other times it’s a relief though, because at least they take the responsibility away from me.

S, aged 17
What causes anorexia nervosa?

Anorexia has no single cause. It seems that a genetic predisposition is necessary but not sufficient for development of the disorder. Twin and family studies, brain scans of affected and unaffected family members, and a current multicentre gene analysis support observations that anorexia is found in families with obsessive, perfectionist, and competitive traits, and possibly also autistic spectrum traits.

Anorexia nervosa is precipitated as a coping mechanism against, for instance, developmental challenges, transitions, family conflicts, and academic pressures. Sexual abuse may precipitate anorexia but not more commonly than it would trigger other psychiatric disorders. The onset of puberty and adolescence are particularly common precipitants, but anorexia is also found without apparent precipitants in otherwise well-functioning families.

How is anorexia nervosa diagnosed and assessed?

The diagnosis is usually suspected by family, friends, and in younger patients school before a doctor becomes involved. When weight loss is well concealed, presenting features may include depression, obsessive behaviour, infertility, or amenorrhoea. Alternatively, weight loss may be thought to be secondary to allergies or other physical conditions.

A positive diagnosis of psychologically driven weight loss can be made in most patients, without the need for a battery of complex investigations to reach a diagnosis of exclusion. Basic medical investigations, blood tests, electrocardiography, weighing, and measuring the patient provide an opportunity for the patient to return (to discuss the results) and can uncover psychological problems.

If the patient refuses to be weighed it is worth persisting gently and exploring their fears. Doctors should not collude with the illness, but should advise against harmful behaviours such as running marathons, skiing, or undergoing in vitro fertilisation when at low weight.

It falls to primary care to recognise and manage relapses as well as first episodes of the illness, and to support patients and families in appropriate use of services. General practitioners may need support from a specialist in eating disorders, and early referral for more detailed assessment and advice gives patients the message that their illness is of genuine concern.

How is serious physical risk managed?

The level of physical risk should be assessed at diagnosis. No safe cut off weight or body mass index exists. Survival analyses show that death is unusual where low weight is maintained purely by starvation. Death is more likely if the patient’s weight fluctuates rapidly than if it is stable, even if the body mass index is below 12. Risk is also increased if the patient frequently purges or misuses substances.

<table>
<thead>
<tr>
<th>Box 1</th>
<th>ICD-10 (international classification of diseases, 10th revision) criteria for anorexia nervosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All five criteria must be met for a definite diagnosis to be made</td>
<td></td>
</tr>
<tr>
<td>• Body weight is maintained at least 15% below that expected (either lost or never achieved) or body-mass index is 17.5 or less. Prepubertal patients may fail to gain the expected amount of weight during the prepubertal growth spurt</td>
<td></td>
</tr>
<tr>
<td>• Weight loss is self induced by avoiding “fattening foods” together with self induced vomiting, purging, excessive exercising, or using appetite suppressants or diuretics (or both)</td>
<td></td>
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<tr>
<td>• Body image is distorted in the form of a specific psychopathology whereby a dread of fatness persists as an intrusive, overvalued idea and the patient imposes a low weight threshold on himself or herself</td>
<td></td>
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<tr>
<td>• A widespread endocrine disorder involving the hypothalamic-pituitary-gonadal axis is manifest in women as amenorrhoea and in men as a loss of sexual interest and potency (except for the persistence of vaginal bleeds in women who are taking replacement hormonal therapy, usually the contraceptive pill). Concentrations of growth hormone and cortisol may be raised, and changes in the peripheral metabolism of thyroid hormone and abnormalities of insulin secretion may also be seen</td>
<td></td>
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<tr>
<td>• If onset is before puberty, the sequence of pubertal events will be delayed or even arrested (growth will cease; in girls the breasts will not develop and primary amenorrhoea will be present; in boys the genitals will remain juvenile). After recovery, puberty will often complete normally, but the menarche will be late</td>
<td></td>
</tr>
</tbody>
</table>
Compulsory treatment for anorexia nervosa is clearly indicated by mental health legislation in acute emergencies where the patient is unable to accept treatment. In most countries this means detention in hospital. Legal responsibility becomes less clear once the immediate danger of death or irreversible deterioration has passed. Many centres invoke longer detention orders to continue compulsory refeeding to a healthier weight.

**Box 2 | Psychotherapies available for managing anorexia nervosa**

**Individual therapy**
- Structured individual treatments are usually offered as a weekly one hour session with a therapist trained in the management of eating disorders and in the therapy model used
- **Cognitive analytic therapy**
  - This psychotherapy uses letters and diagrams to examine habitual patterns of behaviour around other people and to experiment with more flexible responses
- **Cognitive behaviour therapy**
  - This psychotherapy explores feelings, educates patients about body chemistry, and challenges the automatic thoughts and assumptions behind behaviour in anorexia
- **Interpersonal psychotherapy**
  - This psychotherapy maps out a person’s network of relationships, selects a focus—such as role conflict, transition, or loss—and works to generate new ways to deal with distress
- **Motivational enhancement therapy**
  - This psychotherapy uses interviewing techniques derived from work with substance misuse to reframe “resistance” to change as “ambivalence” about change, and to nuture and amplify healthy impulses
- **Dynamically informed therapies**
  - These therapies may also result in weight gain and recovery provided the patient is aware of the risk of irreversible physical damage or death and acknowledges that certain boundaries (for example, that they must be weighed weekly, examined monthly by a doctor, and admitted to hospital if weight continues on a downward trend) are observed. The therapies involve talking, art, music, and movement

**Group therapy**
- There is little evidence that therapy for patients with anorexia benefits from being delivered in group sessions rather than individual sessions; in fact, group therapy may even worsen the problem. However, dialectical behaviour therapy offers structured groups in parallel with individual sessions. This therapy teaches skills that help patients to tolerate distress, soothe their feelings, and manage interpersonal relationships

**Family work**
- The term ‘family work’ covers any intervention that harnesses the strengths of the family in tackling the patient’s disorder or that tries to deal with the family’s stress in the face of it. It includes family therapies, support groups, and psychoeducational input
- **Conjoint therapy**
  - Evidence points to the effectiveness of the Maudsley model of family therapy and similar interventions focused on eating disorders. Whole families—or at least the parents and the patient—attend counselling sessions together, which can cause intolerable emotional stress
- **Separated family therapy**
  - The patient and the parents attend separate meetings, sometimes with two different therapists. This form of therapy seems to be as effective as conjoint therapy, particularly for older patients, and involves lower levels of expressed emotion
- **Multifamily groups**
  - Such groups provide a novel way of empowering parents by means of peer support and help from a therapist. Several families, including the patient, meet together for intensive sessions that often last the whole day and include eating together
- **Relatives’ and carers’ support groups**
  - These groups range from self help meetings to highly structured sessions led by a therapist that aim to teach psychosocial and practical skills to help patients with anorexia to recover while avoiding unnecessary conflict. Most encompass at least some educational input about the nature of anorexia

**TIPS FOR NON-SPECIALISTS**
- Recovery takes years rather than weeks or months, and patients must accept that they should attain a normal weight—refeeding alone may lead to relapse
- Trends should be monitored by weighing, which needs to be managed skillfully so it does not become a battleground
- No cut off weight or body mass index exists because many other factors influence risk
- Substance misuse—including alcohol, deliberate overdoses, or misuse of prescribed insulin—greatly increases risk
- Weight fluctuations and binge-purge methods (rather than pure restriction) increase risk
- Depression, anxiety, and family arguments are probably secondary to the disorder, not underlying causes, so the anorexia should be treated first
- Medication has little benefit in anorexia and the risk of dangerous side effects is high in malnourished patients
- Try to involve the family—encourage calm firmness and assertive care

Without this, the risk of repeated cycles of detention and relapse exists. In practice, patients in extremis can often be treated with their consent. Voluntary treatment is more likely when the clinician is experienced at managing anorexia and can confidently assess and tolerate fairly high levels of risk in the interests of collaborative therapeutic relationships, rather than coerce patients. Even legal measures of compulsion may be used in a helpful therapeutic way, though, and should not be avoided at all costs.

The best place to admit patients with life threatening anorexia is not always obvious. An acute medical ward—especially one that specialises in endocrinology, gastroenterology, or diabetes—is usually better than a general psychiatric ward. Some non-specialist medical wards have nurse specialists, who are experienced in managing patients with eating disorders. These nurses can help translate recommendations into practice and “troubleshoot” for the furtive compulsions of anorexia.

**What is the currently accepted best management?**

Anorexia takes an average of five or six years from diagnosis to recovery. Up to 30% of patients do not recover. This makes meaningful follow-up of interventions crucial but difficult. Coercive approaches may result in impressive short term weight gain but make patients more likely to identify with and cling on to the behaviour associated with anorexia.

Overall prognosis for patients with eating disorders is independent of whether treatment is received or not. Discredited behavioural regimens for anorexia involved incarceration in hospital, with removal of all “privileges” (visitors, television, independent use of bathroom), which were given back as a reward for weight gain.

Hospital admission is still strongly correlated with poor outcome. Long term prognosis is worse for patients compulsorily detained in an inpatient facility
How is weight gain achieved?
In countries where all treatment is given in hospital, refeeding is an early intervention. Subsequent treatment helps patients tolerate, maintain, or regain normal weight. This may also be the preferred approach for children and young adolescents, where long periods at low weight are detrimental to growth and development. Hospital refeeding needs physiological fine tuning and may expose the patient to iatrogenic complications such as infections, the sequelae of passing tubes, and the effects of being exposed to a “proanorexia” culture (by mixing with other patients who have anorexia).

A second approach temporarily accepts low weight, if weight is stable and regularly monitored, while patients or their families take responsibility for refeeding. It is helpful to provide dietetic expertise separately from psychotherapy. One study found that unsupported dietetic advice without parallel interventions had a 100% dropout rate.15 Weight gain is slower with this second approach, but it is more likely to be maintained. This approach avoids many iatrogenic risks. However, clinicians still need access to medical wards for physical emergencies.

What is the role of psychotherapy?
Short term structured treatments such as cognitive behaviour therapy and interpersonal psychotherapy, which are effective in other eating disorders, have not helped so far in patients with anorexia. One report found no difference in outcome between behaviour therapy and cognitive therapy.16 The preliminary results of a New Zealand study of cognitive behaviour therapy and interpersonal psychotherapy compared with usual treatment were disappointing.17 A cognitive behaviour therapy based “transdiagnostic” treatment for all eating disorders, including cases of anorexia where body mass index is above 15, has shown promise however.18

Expert consensus favours long term, wide ranging, complex treatments using psychodynamic understanding, systemic principles, and techniques borrowed from motivational enhancement therapy and dialectical behavioural therapy (box 2). These treatments should be delivered in various settings that cater for the level of intensity and degree of medical monitoring and care needed. The coordinated working of a wide range of medical and psychiatric services that do not usually work together will be needed. Because of the age group affected, and the time span involved, patients’ care often undergoes many transitions. These are peak times for relapse and decompensation.

Early on, especially in younger patients, motivation for treatment lies with parents, schoolteachers, or medical professionals. The guiding principle of motivational enhancement is to acknowledge and explore rather than fight the patient’s ambivalence about recovery. Treatment is more effective when the therapist and the patient work together against the anorexia. Such a relationship may allow the patient to be treated without having to invoke the Mental Health Act. Motivation is not an all or nothing battle to be won before treatment can start—it must be actively engendered throughout the treatment.

Family work is the only well researched intervention that has a beneficial impact.19 Family work teaches the family and patient to be aware of the perpetuating features of the disorder. Fury, anger, and fighting lead to entrenched symptoms but too much permissiveness encourages the illness by allowing it to become an accepted response to stress, or—if the family will do anything to encourage the patient to eat—a route to providing “secondary gain” from the illness. Support of carers is essential to maintain the firm but sympathetic boundaries conducive to recovery.

Early studies on teenagers with relatively recent onset anorexia showed that therapy involving the whole family was superior to treating just the patient. Further studies showed that, if tolerated, sessions involving the family and patient together gave the best promise however.

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals
- National Institute for Health and Clinical Excellence (www.nice.org.uk)—Several guidelines are available that cover anorexia nervosa, bulimia nervosa, and atypical eating disorders
- American Psychiatric Association (www.psych.org/psych_pract/treatbg/pg/EatingDisorders3pg_04-28-06.pdf)—A recently published guideline on the treatment of patients with eating disorders
- The Edinburgh Anorexia Nervosa Intensive Treatment Team (www.anitt.org.uk)—This site contains a detailed clinical pathway for anorexia nervosa
- Institute of Psychiatry/Maudsley Hospital (http://www.iop.kcl.ac.uk/)—This site has good information and downloadable PDFs on medical complications of eating disorders and is kept up to date with research development

Resources for patients and carers
- Eating Disorders (www.edauk.com)—The Eating Disorders Association site has good information about the eating disorders network in the United Kingdom, resource lists, and details of local self help and support groups
- National Institute for Health and Clinical Excellence (www.nice.org.uk)—This site also contains a patient and carer version of the NICE guidelines
SUMMARY POINTS

Anorexia nervosa has the highest rate of mortality of any psychiatric disorder. It is best to make a positive diagnosis of psychologically driven weight loss, rather than reach a diagnosis by exclusion. Short term structured treatments—such as cognitive behaviour therapy—are not effective, and longer term therapies that incorporate motivational enhancement techniques are recommended. Focused family work is effective in adolescents and young adults; counselling can involve the family as a whole or the patient and their family can be treated separately. To date, no effective drugs are available to treat anorexia.

results in terms of the family’s psychological adjustment, but that weight gain was greater when families were seen separately from the patient. Both types of family intervention were more effective than individual work. More recently, “multi-family groups” have been piloted.

The Maudsley group compared individual focused dynamic therapy, dynamically informed family therapy, individual cognitive analytic therapy, and “treatment as usual” over the course of a year. The dynamically informed therapies—both family and individual—produced the best results. The study showed that severely ill adults with anorexia could be managed as outpatients, and it highlighted the benefits of continuity of care by one therapist and of the expertise provided. However, nothing can be concluded about the specific model of therapy provided.

Is drug treatment effective?

The evidence base for the use of drugs in anorexia nervosa is poor. Antidepressants are often used to treat depressive symptoms but have limited success. The well documented benefits of antidepressants in bulimia nervosa do not extend to anorexia, and the benefit from selective serotonin reuptake inhibitors in preventing relapse after weight gain is unclear. Case reports describe the benefit of antipsychotic drugs such as olanzapine to promote weight gain. This success may be attributable to symptomatic relief of anxiety and increased appetite, rather than any effect on core pathology. Harmful effects of drugs, particularly the appearance of a long QT interval, with the risk of dangerous cardiac dysrhythmias, are more likely in patients who are malnourished and have electrolyte abnormalities.

What affects recovery and what is the prognosis?

A premature mortality rate of 20% was seen in an inpatient cohort, and a large proportion of cases took six to 12 years to resolve. Bingeing and vomiting at low weight greatly increase mortality compared with purely restrictive starvation. Comorbidity is associated with bleaker prognosis. More recently, full recovery has been demonstrated even after 21 years of chronic severe anorexia nervosa.

Criteria are available for assessing recovery from anorexia nervosa. The capacity to undertake normal levels of exercise and activity are also important. If the patient is given renutrition and care to protect against irreversible damage during the acute illness, cardiovascular function, immune function, fertility, and bone density can all return to healthy levels. Bone recovery takes years rather than months, so patients should protect the spine and pelvis in particular against gymnastic activity too early after weight gain. Even when a person has developed the crucial motivation to tolerate weight gain and explored the possibility of living with values other than those imposed by the cult of thinness, psychological recovery is difficult as the challenges of a rekindled adolescence must be faced.

Competing interests: None declared.

If tetanus is suspected, take a complete drug history and administer procyclidine

Although taking a travel history from patients returning from travelling abroad is important, occasionally it may be misleading. The ability to extract information that will help to establish the correct diagnosis remains the clinician’s most important diagnostic tool.

Case report
A 28 year old woman presented to the accident and emergency department with tightness and twitching across the facial muscles, upwards rolling of the eyes with deviation of the head and gaze to the right, and stiffness of the neck muscles. The symptoms were associated with sweating and tachycardia at a rate of 130 beats/min. Further clinical examination and imaging were unremarkable. She had no history and no evidence of skin breaks or dental or ear infection. All the blood tests were normal, including the electrolytes, C reactive protein, and white cell count.

The patient had returned from Kenya four weeks previously, where she had been on a safari holiday. Before going to Kenya, she had had all the necessary vaccinations and had started taking Malarone (proguanil with atovaquone) for malaria prophylaxis.

Ten days before her presentation, she had had colicky left flank pain with nausea and vomiting. Her general practitioner prescribed trimethoprim followed by ciprofloxacin for a presumed urinary tract infection. She had no medical history of note. The patient was using oral contraception but had no clear history of further concomitant medication. She did not know her immunisation status for tetanus.

We believed that the symptoms were consistent with tetanus, and after discussion with the infectious diseases specialist, diazepam, intravenous tetanus immunoglobulin, and metronidazole were administered. The patient was admitted to the high dependency unit for overnight observation, where her symptoms resolved completely one to two hours after receiving the specific immunoglobulin and diazepam.

The next day, after transfer to the infectious diseases unit, it emerged that the patient had started taking metoclopramide the day before her presentation. This had been prescribed by her general practitioner because of persistent nausea; the general practitioner confirmed that a tetanus boost vaccination had been given the previous year.

The patient’s symptoms had resolved six to eight hours after onset—acute dystonic reaction caused by metoclopramide was diagnosed. A “yellow card” report was submitted to the Medical and Healthcare Products Regulatory Agency, which runs the yellow card scheme for collecting information in the United Kingdom from health professionals and patients on suspected adverse drug reactions.

Discussion
This case highlights the importance of obtaining a complete drug and immunisation history in any patient suspected of having tetanus. The report describes a case where tetanus was misdiagnosed and focuses on the main differences between tetanus and acute dystonic drug reactions. Distinguishing features include the age of the patient, presence or not of wounds, recent medication, the nature of the involuntary movements (in this case oculogyric), and the duration of symptoms.

In the absence of skin injuries, tetanus is unlikely. A diagnostic and therapeutic step in this setting would have been the administration of an anticholinergic antiparkinsonian drug such as procyclidine, which would have rapidly alleviated the dystonic symptoms.

To highlight the differences and similarities, we describe below the two conditions.

Acute dystonias and dyskinesias
Dystonia is a syndrome of sustained muscle contractions resulting in twisting, repetitive movements, or abnormal postures. Acute dystonias usually present as bucolingual (pulling sensation of the tongue), torticollic (twisted neck, facial muscle spasm), oculogyric (rolling or deviated gaze), tortipelvic (abdominal rigidity), and/or opisthotonic (spasm of the entire body).

The extrapyramidal system modulates motor function using excitatory cholinergic and inhibitory dopaminergic neurotransmitters. The inhibitory dopaminergic receptors are susceptible to blockade by antinemetics, neuroleptics, and other drug groups (table). The potential adverse extrapyramidal effects are acute
Drugs that can cause dystonic reactions

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>Alfentanil</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Flecainide</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenytoin</td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Monoamine-oxidase inhibitors</td>
<td>Phenelzine, tranylcypromine</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Fluvoxamine, paroxetine</td>
</tr>
<tr>
<td>Tricyclic</td>
<td>Amitriptyline, amoxapine (discontinued in UK)</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Metoclopramide, domperidone</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Diltiazem</td>
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<tr>
<td>Neuroleptics</td>
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<tr>
<td>Butyrophenones</td>
<td>Benperidol, haloperidol</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Fluphenazine, perphenazine, prochlorperazine</td>
</tr>
<tr>
<td>Sedatives</td>
<td>Midazolam</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Cocaine</td>
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</table>

dystonic or dyskinetic reactions, parkinsonism, and tardive dyskinesias.

The duration of the symptoms is proportional to the half life of the drug—generally several hours. Anticholinergic medications (procyclidine, benztropine) restore the excitatory-inhibitory balance within minutes. This step is both therapeutic and diagnostic.

Acute dystonias may be confused with partial seizures, tetanus, strychnine poisoning, and electrolyte imbalances. Often no history is offered at all: the patient may not be able to speak or make the connection between symptoms and drug, or may not admit to taking psychotropic medication.

Incidence of dystonias caused by metoclopramide

The most common adverse extrapyramidal effect of metoclopramide is acute dystonias, with an incidence of 0.2%. The incidence is higher in patients receiving higher doses, in children, and in young adults. About 70% of dystonic patients are female. Only 479 reports of suspected metoclopramide related extrapyramidal reactions were reported in the UK for 1967-82: 455 were for acute dystonias, 20 for parkinsonism, and 4 for tardive dyskinesias. The low incidence rate in the UK is the result of under-reporting of adverse reactions.

Tetanus

The symptoms of tetanus are caused by the potent neurotoxin tetanospsamin, produced by Clostridium tetani. The exotoxin is disseminated through the bloodstream and the lymphatic system. It is taken up by the neuromuscular junctions, where it migrates retrograde trans-synaptically along the axons and accumulates in inhibitory synapses, resulting in the blockage of inhibitory impulses and muscle rigidity.

The toxin moves from the contaminated site to the spinal cord at a rate of 75-250 mm/day, a process which takes 3-14 days. The toxin binding is irreversible; recovery takes about one month, and it depends on the sprouting of new axonal terminals. Less than 2.5 ng per kilogram of tetanospsamin is lethal.

The four clinical types of tetanus are cephalic, local, generalised, and neonatal; 50-75% of patients with generalised tetanus present with trismus (lockjaw) and risus sardonicus. As the disease progresses, patients have generalised muscle rigidity. Sensation remains preserved and patients feel severe pain. Seizures, respiratory failure, glottic spasm, and sympathetic hyperactivity (tachycardia, hypertension) can result in death.

Clinical manifestation and duration of symptoms are clearly different from the oculogyric or any other dystonic movements.

Incidence

On average, 8-10 cases of tetanus are reported annually in the UK.7 The incidence decreased after national tetanus immunisation was introduced in 1961. Most cases occur in people aged over 60 years, who have not participated in the immunisation scheme.

Contributors: KD was the on-call receiving physician in the infectious diseases unit. CL was the on-call consultant and in charge of the patient’s management, and RM helped to write the article.

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Competing interests: None declared.

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Endpiece

A powerful diuretic

Madame, so it is I have this night after midnight taken your medicine, for the which I heartily thank you, for it hath done me much good, and hath caused the stone to break, so that I now void much gravel. But for all that, your said medicine hath done me little honesty, for it made me piss my bed this night, for the which my wife hath sore beaten me, and saying it is in stone to break, so that I now void much gravel. But for it hath done me much good, and hath caused the


Submitted by Philip Radford, retired general practitioner, Taunton
Give dipyridamole with aspirin instead of aspirin alone to prevent vascular events after ischaemic stroke or TIA

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Competing interests: I was involved in the cited report on clopidogrel and dipyridamole1 and in planning a trial (of aspirin alone or with these agents) that did not proceed as a potential sponsor wished to modify it. I am on the Antithrombotic Trialists’ Collaboration’s steering committee and received £500 from Sanofi in 1998 to speak on the Trialists’ results at a general practitioners’ educational meeting. I’m also a member of the No Free Lunch movement.

Sources of evidence box, references, figure and table are on the longer version on bmj.com

KEY POINTS
• In patients with a prior ischaemic stroke or transient ischaemic attack, adding the antiplatelet drug dipyridamole (modified release formulation, 200 mg twice daily) to aspirin reduces the relative risk of vascular events (stroke, myocardial infarction, or vascular death) by a fifth
• In patients already receiving current secondary preventive treatment, the average annual risk of a vascular event is no more than 5%; adding dipyridamole prevents one further vascular event for every 100 patients treated each year
• Headache may occur in up to a third of people taking dipyridamole but usually settles in one to two weeks

The clinical problem
Strategies to prevent vascular events (stroke, myocardial infarction, or vascular death) after an ischaemic stroke or transient ischaemic attack (TIA) include using aspirin, which is the most widely tested single antiplatelet drug for this purpose.1 2 Adding dipyridamole further reduces the risk in patients who have had an ischaemic stroke or transient ischaemic attack.

The evidence for change
Sources of evidence are in the box on bmj.com.1-3

The second European stroke prevention study (ESPS-2) found, in 3299 patients with a prior ischaemic stroke or transient ischaemic attack, that dipyridamole plus aspirin significantly reduced the relative risk of vascular events by about a fifth compared with aspirin alone.1 4 5 However, pooled data from previous randomised trials in several thousand patients at high risk of vascular events (about 1800 of whom had a prior ischaemic stroke or transient ischaemic attack) did not find that adding dipyridamole reduced vascular events.1 5 6 The contrasting ESPS-2 results were attributed to chance; the very low daily dose (50 mg) of aspirin used compared with previous trials; or the particular daily dose and preparation (400 mg modified release v 5 300 mg standard preparation) of dipyridamole used.1 7

The recently published European/Australasian stroke prevention in reversible ischaemia trial (ESPRIT) compared aspirin plus dipyridamole versus aspirin alone in 2739 patients with a prior ischaemic stroke or transient ischaemic attack.8 The resulting relative reduction in vascular events was the same as in ESPS-2, and a meta-analysis of all randomised trials comparing the combination with aspirin alone in patients with a prior ischaemic stroke or transient ischaemic attack largely reflected the results of the ESPS-2 and ESPRIT trials.8

Assuming a baseline risk of vascular events of 5% a year, the annual risk in the aspirin only arm of ESPRIT (reflecting well the risk in patients already receiving current secondary preventive treatments), the addition of dipyridamole would prevent about 10 vascular events per 1000 patients treated per year.9

Neither large trial found an excess of major bleeding in patients allocated the combination compared with aspirin alone. However, both reported a higher rate of premature cessation of treatment in the combination than in the aspirin arm, mainly as a result of adverse effects (particularly dipyridamole induced headache, which may occur in up to a third of people receiving dipyridamole but usually settles in one to two weeks and might be reduced by dipyridamole dose titration).1 4 8

Barriers to change
Doctors or patients may perceive that the small absolute benefit is not worth while, and adherence may be limited by adverse effects and the difficulties for a predominantly elderly population to take additional medication. As rapid intravenous injection of dipyridamole reduces blood pressure when it is used as a coronary vasodilator in stress echocardiography and thallium imaging, anxieties have been expressed about dipyridamole in patients with ischaemic heart disease.7 However, in ESPRIT, long term oral dipyridamole did not affect blood pressure, and the benefits of adding dipyridamole to aspirin were similar in those with and without ischaemic heart disease.5 9 Cost may be a barrier, as in the United Kingdom modified release dipyridamole 200 mg twice daily costs £102 (£150; £200) a patient per year, compared with £5 a patient per year for aspirin 75 mg daily.10

How should we change our practice?
Ensure first that
• The diagnosis of ischaemic stroke or transient ischaemic attack is correct (which generally requires prompt specialist assessment and appropriate investigations)
• Existing secondary preventive strategies (such as lifestyle advice, aspirin, and reduction in cholesterol and blood pressure) have been or are being considered and used where appropriate
• No reason (such as atrial fibrillation) exists to consider anticoagulants instead of antiplatelet treatment
• The patient is already taking and tolerating aspirin, the most appropriate dose being 75-150 mg daily as higher doses produce more gastrointestinal side effects and lower doses may be less effective.1 7

Then discuss with the patient (or proxy) the likely absolute benefit of adding modified release dipyridamole 200 mg twice daily (that is, on average about a 1 in 100 chance per year of benefitting) versus the potential for adverse effects and the inconvenience of extra pills. Start dipyridamole if the patient wishes; it can be continued long term if tolerated and if no contraindications develop and funding allows.
Statins, saving lives, and shibboleths

PERSONAL VIEW Tim Blackman

There is little doubt that inequalities in health are difficult to tackle. In England the gap in life expectancy between rich and poor has continued to widen, despite health inequalities increasingly being brought into the mainstream of performance management in the NHS. However fast the most deprived areas or disadvantaged groups improve their health, everyone else’s health improves faster. It sometimes seems that the most effective contribution to tackling inequalities in health that the professional classes could make is to be a little less healthy and die a little earlier.

In fact the government’s strategy for health inequalities is now more akin to redistributing health than to redistributing income or wealth. Health is being redistributed pharmacologically by statins, antihypertensives, and nicotine replacement therapy. This is creating the paradoxical situation of a medical rather than a social model of public health, and a key role for pharmaceutical companies in a new definition of prevention based on drugs. The use of statins, for example, in the effort to narrow health inequalities has seen the term “primary prevention” get redefined not as upstream interventions in social and economic conditions but as treating people with risk factors but no observable disease.

Current government policy recognises the wider determinants of health and is committed to policies on tax credit, housing, and family support targeted at those most in need to tackle these determinants. Recognition seems, however, to be growing that these are weak interventions for closing gaps in health outcomes because everyone else’s incomes, housing, and family opportunities just improve faster.

Drugs seem to offer an opportunity to redistribute health, and quickly. The looming 2010 target for narrowing the life expectancy gap in England by 10% is focusing effort on pharmacological interventions among people in their 50s and 60s. This is the equivalent of teachers in schools focusing their efforts on students at risk of only achieving D grades in their GCSEs so that they are tipped into the A*-C category, which is the performance measure. As soon as someone is saved from a lethal heart attack before 75, he or she counts towards the target, even if he or she dies one day later.

Although extending these treatments as widely as needed is laudable, having so many people taking drugs can hardly be regarded as a public health achievement. Yet the NHS is proving remarkably good at these approaches. The reason for this is because the NHS is a sickness service, which is what is good at and what it should focus on. Every attempt to push public health up the NHS agenda gets undermined by acute services trumping public health in budgetary, political, and media contests, or additional tranches of money getting diverted to priorities that are always more urgent than the slow and unglamorous interventions needed to improve the public’s health.

If it seems a heresy to argue for the NHS to be the sickness service that is so often claimed in public health circles to be its weakness, then another shibboleth of public health is partnering working. This is held to be the solution to the silos of separate acute, primary, social care, and housing services that fail to “join up” and tackle “cross cutting” issues like health inequalities. Partnerships, however, are often marked by poor accountability, lack of leadership, and ambivalent commitment. This is because the partnership is expected to be something new rather than simply a meeting of organisations, each of which has its own clear purpose. The theory of shared priorities and targets is always a good one; the practice is hard to find.

So where should the responsibility and resources for public health and tackling health inequalities lie? The obvious answer is with local councils, beyond the appetite of acute services, beyond the quick fix of statin prescriptions, and in the clarity of a single organisation with clear accountability and leadership as an agent of public health. Partnerships between local government and the NHS would then become a true meeting of the two sides of health, prevention, and treatment. In so far as treatment patterns may undermine the wider effort to narrow health inequalities, local councils’ scrutiny committees could be charged with guarding against this by focusing their work on equity in health care.

Where could extra resources for a major local government public health function come from? From acute care, with the plans announced by the services reconfiguration white paper “Our health, our care, our say” to shift spending from acute services to primary care and prevention transferring this spending instead to local government. It would then be a decision for local councils as to whether the best use of this funding would be to transfer it back to the NHS or to use it, for example, to cut the local waiting list for social housing or to improve school meals. Whatever it did, it would have to be mindful of its health inequality targets, which would now lie clearly with the local council as its responsibility.

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A film that allows doctors to see the world from the patient’s perspective, p 905

The beauty (or the pain) of studying medicine is the sheer volume of eponymous conditions encountered. While much time is spent in memorising their names, we rarely pause to wonder who the name behind the eponymy was, what he or she did, and how they did it. This compendium will serve curious minds well.

The Dictionary of Medical Biography is not a dry collection of facts that only a keen student or a medical historian might pore over. Rather, the insightful and well written essays go beyond merely listing individuals and recording their medical or scientific achievements. For one thing, the articles illustrate the contrasting personalities of some of modern medicine’s unlikely champions. Some were loud and proud—for example, Thomas Bartholin, who discovered the sublingual duct and vulvovaginal gland, both of which now bear his name. He claimed that he “was capable of producing a text faster than fungi could shoot up” after many of his manuscripts and texts were destroyed in an estate fire. Then there were the eccentric ones, like John Hughlings Jackson. The BMJ ran a five page obituary on the neurologist when he died in 1911. Pity the editors of his 300 papers, as he revised his writings several times, each redraft lengthier than the last. His definition of epilepsy alone took 11 pages. He read pulp novels and “any rubbish that was handy”—and his students referred to him as “the Sage.”

And then there are the humble ones, who are, unsurprisingly, the most inspiring. The man behind Burkitt’s lymphoma, Denis Parsons Burkitt, is known more for his humility, we learn, than his discovery of the haematological cancer and the link between low fibre diet and bowel cancer. He lived all his life according to what his mother told him as a boy: “Disappointment—His appointment—you only need change one letter.”

In this dictionary of some 1100 entries, anecdotes abound, but they’re carefully chosen to illustrate a point. It’s fun to discover Frederick Banting’s three line protocol for experiments on dogs in John MacLeod’s laboratory, which was scribbled on a piece of paper: “Diabetes. [sic] Ligate pancreatic ducts of dogs. Keep dogs alive till acini degenerate leaving islets. Try to isolate the internal secretion of those to relieve glycosuria.”

The initial reception to Banting’s findings was lukewarm, and MacLeod ended up sharing much of the credit for the discovery, which Banting thought undeserved. Banting’s initial presentation to the American Physiological Society was unimpressive, and MacLeod had to clarify the work for the audience. After a few more attempts the effect of insulin in reducing glucose levels in diabetic patients was recognised, and the rest, of course, is history.

At their best, the legends of Chinese medicine are page turners. Consider Bian Que and Chunyu Yi, both venerated for their knowledge in the study of mai (arterial pulses). Chunyu Yi was born in 205 bc and his memoirs are the basis for his entry. Even earlier, about 500 bc, Bian Que had refined traditional Chinese medicine so well that he was reported to have revived two important people, including the Prince of Guo, from a coma—using only acupuncture needles.

In a world where Western medicine dominates, it is easy to ignore the diverse systems of medicine still prevalent around the world. Helpfully, the editors includes introductory essays on Islamic, Chinese, South Asian, South East Asian, and Japanese systems of medicine.

Biographies are written not only to inform but also to inspire. This compendium is a wonderful counter to Oscar Wilde’s cynicism—“Every great man nowadays has his disciples, and it is always Judas who writes the biography.”

Bian Que had refined traditional Chinese medicine so well that he was reported to have revived the Prince of Guo from a coma.
More than a career for my daughter

FROM THE FRONTLINE
Des Spence

Medicine is boring. I gaze through the wire mesh window into the car park with the mis-spelt graffiti painted in white emulsion. Medicine is humdrum: the same people, the same complaints, the same practised spoi ls. It’s a similar existence for consultants, but at least they have the respite of an occasional game of table tennis in the mess. The only glamour in medicine is the faded copies of Hello magazine in our waiting rooms. Apparently many doctors would not recommend a medical career. Would I recommend it to my daughter?

The realisation hits us hard—once we have outgrown the stupidity of youth—that we will never cure cancer, that our “intelligence” is merely a product of working like a dog, and that all those people who seem to bumble through life earn more money. We have other frustrations too: working shifts, dysfunctional colleagues, insensitive managers, and the constant political interfering and unworkable, grandiose, and simplistic commitments that come with every looming election. And we are the meat in the sandwich between the slices of blame and compensation, just waiting to be eaten.

But I am glad that as an idealistic and drippy 12 year old I was driven to become a doctor. Indeed, being a doctor is a privilege. Clearly I might be lying, insane, or just plain stupid, and possibly all three, but with medicine it is the people that make the job—the colleagues, the nurses, the reception staff, the cleaners, and the porters—all in it together and committed to the patients.

Despite everything medicine remains a vocation, not just a career. It is about upholding medical traditions, seizing responsibility, and maintaining absolute confidentiality and, at the centre of it all, trust. Unfortunately, a medical career is often an automatic afterthought on receipt of three A grades at A level: “You could do medicine.” But becoming a doctor is a personal commitment, entailing an emotional response, and is not something that can be rationalised. And it is the mismatch between youthful expectations and the reality of medicine that is the root of much professional unhappiness.

But despite the wire mesh on my windows, the nine clinical sessions a week, and a 40 year tour of duty, I am grateful. This is what I signed up for. In time we learn to ignore the political initiatives, dump unread all the circulars, and smile while pretending to listen.

I will never recommend medicine as a “career” to my daughter, nor to anyone else for that matter—it is nothing to do with me; it’s their decision.

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Myths and realities

DRUG TALES AND OTHER STORIES
Ike Iheanacho

You must have heard the one about the man who woke up in a bath full of ice, with two incisions on his back. He’d been drugged the night before by a criminal gang, who then stole and sold his kidneys for illicit transplantations. It’s definitely true. The bloke down the pub says that his stepsister’s hairdresser swears blind that he knows someone who used to live in the same street as the poor guy it happened to.

There’s something for everyone in a good myth. The originator has the satisfaction of discovering or inventing the event or idea. Subsequent narrators can then embellish and spread the details—unburdened by conscience or the need for corroboration—to intrigue the gullible, who get a kick from being entertained or horrified. And sceptics get to feel superior by arguing how the whole thing could not possibly be true.

Big phama has quite a record in the creation and dissemination of myths. However, the industry would probably rather be seen as a debunker. For instance, the Association of the British Pharmaceutical Industry, which represents major UK companies, recently reissued a “media briefing” entitled “Information about medicines: myths and realities.”

Focusing on the restrictions that limit companies’ direct provision of information to patients, the document attacks supposedly prevalent views relating to this area.

For example, according to the briefing, it’s a myth that “the industry can’t be trusted to provide honest information.” Tell that to those who regularly find half truths and worse in drug companies’ promotional material, despite the various legal and other safeguards against such deception. Odder still are some of the other “myths.” For example, where is the hard evidence of widespread belief and active propagation of the notions that “consumers do not want information,” that “being ‘more informed’ does not benefit the patient” and that “patients are not in a position to understand or interpret information about medicines”?

The rest of the “myths” are similarly unimpressive, also coming across as crude devices for making the briefing’s central point: companies would like the right “to provide more high-quality, non-promotional information to benefit patients and carers.” The suggestion that this is the industry’s main motivation is a pretty big myth in itself.

Of course, businesses are entitled to highlight genuine views, concerns, and misapprehensions of clients, customers, or the wider public. But in the court of public opinion the drug industry can be a terrible witness and a lousy advocate.

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On the detection of fakes

Medical books these days don’t have such good titles as they once had. The other day, for example, I came across a book that I had long wanted to possess, published in 1843: On Feigned and Factitious Diseases Chiefly of Soldiers and Seamen, On the Means Used to Simulate or Produce Them, and On the Best Modes of Discovering Impostors. It was by Hector Gavin MD, who at the time was surgeon to the London Orphan Society and to the British Penitent Female Refuge. These days, of course, no British female is penitent.

The book was the prize essay in military surgery in the University of Edinburgh for 1835-6, written when Gavin was 20 years old. We mature physically earlier these days, but it seems they matured intellectually earlier in those days. At 20 I had hardly ever seen a sick person, let alone one feigning sickness.

Feigned sickness was particularly common among soldiers and sailors because, in the days before so many insurances, only they had much to gain by the practice (those whom the author calls “indulged females,” and slaves on the plantations, are the other classes the author regards as peculiarly susceptible to feigned sickness). Gavin was at pains to be fair to men in the armed services, for he recognised that to declare a sick man fit was cruel in its consequences and sometimes led to death. On the other hand, he is eloquent on the hand on the dangers of allowing malingerers to get away with it; but at a time when medicine was so underdeveloped, it must often have been difficult to distinguish the real from the fake.

He says something that has a certain resonance today in a land such as ours in which the numbers of sick people have so overtaken the numbers of the unemployed, to the delight of government statisticians, doctors, and the unemployed themselves: “Medical certificates must not be compared as a practice (as they have been) to that of alms-giving; in the best hands they are liable to great abuse; and however pure and disinterested the motives, much evil not infrequently results from them—none more than the inevitable depreciation of the medical character, which cannot fail to follow from their being given in a careless or lax manner.” This is enough to make one blush.

A passage concerning the detection of fakes brought a memory back to my mind: “Flying or migratory pains are very common among soldiers and sailors, and are known by the cant name of the all-overs.” And one method of detecting a fake is to ask him whether he has such and such a physically impossible symptom.

I recall a professor using this technique to demonstrate the false nature of a woman’s complaints. He got her to say that she suffered from pain, even in her hair. QED. The story didn’t have a happy ending, though. The next ward round was interrupted by the sight of her falling from the roof of the hospital past the ward windows. She killed herself. Gavin himself had an unhappy ending. He became an associate of Edwin Chadwick and the other sanitary reformers and went out to the Crimea to bring a little sanitation to the British troops. His younger brother, a veterinary surgeon, was also there. As Gavin gave his brother his revolver to look after one evening, it went off and wounded him fatally in the stomach. His brother died from cholera 18 days later.

Theodore Dalrymple is a writer and retired doctor.

BETWEEN THE LINES Theodore Dalrymple

“Medical certificates must not be compared as a practice (as they have been) to that of alms-giving; in the best hands they are liable to great abuse”

MEDICAL CLASSICS

Wit

Film released 2001

Few if any films deal with death and dying with such clarity, simplicity, and eloquence as Wit, which was made for American television. Emma Thompson adapted the original play for the screen and takes the leading role of Dr Vivian Bearing. Her title is not medical but academic: she teaches metaphysical poetry at a US university and has a reputation of being both brilliant and unforgiving to students who fall short of her high standards.

The entire film takes place in hospital, from the moment when she is told that she has a severe form of cancer by the ever ebullient Dr Kelekian (Christopher Lloyd), through to the closing shot as the camera retreats from the room where Dr Bearing has wrestled with death and succumbed.

On the course I run at the University of Bristol, called “Doctors in the movies,” this is the film that I show in its entirety to the medical students, and they are invariably moved by its power and tenderness. We are so used to films that live on melodrama, cheap emotion, and obvious insights that to be faced with something as subtle and delicate as this is almost overwhelming; the tears we shed have been earned, not forced.

Anyone working in the medical world can learn much from Wit. There are no villains, yet the brash Kelekian and his intern sidekick Jason epitomise a certain male obtuseness, forever focused on some abstract goal, making them overlook the human being in front of them. A particularly excruciating scene involves Jason giving Dr Bearing a gynaecological examination with a degree of awkwardness, insensitivity, and thoughtlessness that would make any medical student vow never to display such a lack of care. Jason is bright, but for him, as for Kelekian, the patient is a means to an end, not a person. Susie, though—Bearing’s nurse—is another matter; the scene where she and Vivian sit and suck ice lollies could have been saccharine but is instead moving.

The reason that the film is so effective is in the title—it is a film of great wit. Not in the sense that it is stuffed with Wildean witicisms, but because it has a trenchant and sardonic intelligence that is unusual, to say the least. The technique of voiceover commentary is so often used to cover up a film’s failings, but here it allows us to bear witness to Bearing’s experiences. She expresses her frustration at the hospital’s mechanistic approach, at the boredom of endless hours of doing nothing, at her frustration at the hospital’s mechanistic approach, at the boredom of endless hours of doing nothing, at the physical suffering she endures. Above all, the film allows us to see the world from the perspective of the patient, one who is intelligent enough to know that its unkindnesses are not deliberate. When you watch this film you consider how you would行为 if you were the doctor, the intern, the nurse, or the patient. And you can’t ask much more of a film than that it should make you both think and feel.

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Moving: Emma Thompson as Dr Vivian Bearing.
Beryl Corner

Pioneer of newborn care

Beryl Corner, distinguished paediatrician and pioneer of newborn care, died at the age of 96 on 4 March 2007. Within two years of qualifying she had acquired both the MRCP and MD and the following year was appointed honorary physician to outpatients at the Bristol Royal Hospital for Sick Children, the first paediatric post in the south west of England. She was 26.

In 1942, when among many other duties, Beryl was already providing an almost singlehanded paediatric service for Bristol, she was invited to take over responsibility for the care of all newborn infants in the corporation’s hospitals. Her first action was to visit Dr Victoria Mary Crosse, who had set up a service for newborns in the corporation’s hospitals. In 1945 Beryl Corner was one of the first three women to be elected to membership of the British Paediatric Association. Two years later she was appointed consultant paediatrician to what became the United Bristol Hospitals and South Western Regional Hospital Board. Besides being a clinical lecturer in child health and examiner to the Central Midwives Board, she served on many committees both local and national, including the Ministry of Health Advisory Committee on Prematurity. On behalf of the World Health Organization and the British Council, she undertook many training projects in South East Asia.

Beryl’s distinction was recognised in many ways. In 1959 she was a founder member of the Neonatal Society. In 1963 she was elected president of the paediatric section of the Royal Society of Medicine. Other presidencies followed, including that of the Society for the Study of Inborn Errors of Metabolism, the Bristol branch of the BMA, and the Bristol Medico-Chirurgical Society. She was also president of the Medical Women’s Federation (UK) in 1968-9, and of the Medical Women’s International Association in 1978-80. In 1996 the University of Bristol presented her with the degree of MD, honoris causa, and in 2006 she received an OBE.

Beryl’s retirement in 1976 gave her time for her many other interests. A magistrate since 1962, she was deeply involved in the work of the prison and probation services. She was also devoted to her old school, and served for many years on its council, becoming president in 1994. She was a life member of the British Red Cross and was also deeply committed to the activities of Christ Church, Clifton. A keen violinist, Beryl was a founder member of Southmead Hospital Orchestra and a director of the Bristol Music Club. Perhaps closest of all to her heart though, were the newborn apes at Bristol Zoo, some eight of whom she cared for.

Beryl’s colleagues regarded her as indestructible. She took accidents, hip replacements, and a helicopter evacuation following a flash flood abroad, all in her stride. A very small person, her intellect remained as sharp as ever until the stroke shortly before her death. It is hard to imagine Bristol without her huge white Mercedes moving in stately fashion through the traffic without anyone apparently at its wheel. It struck fear into the heart of many a motorist.

Nor were the motorists the only ones to feel fear. When she came on a ward round even the innocent wondered what they might have done wrong. Beryl had been schooled in a hard, male-dominated medical world in which women doctors were not to be taken seriously. She had to be tough to survive; and survive she did in fine style. Yet, to her friends and junior colleagues, especially if they were women, she gave unstinted encouragement. She took a tremendous interest in medical students and young doctors in training, inspiring them with her dedication and talent, and providing them with friendly and sometimes also financial support.

Peter Dunn
Beryl Corner, leading paediatrician and researcher Bristol (b 1910; q Royal Free 1934; OBE, JP, MD, FRCP, MD Hon (Bristol), FRCPCH (Hon)), d 4 March 2007.
Heidar Mahmoud Al-Sad

Associate specialist in clinical oncology Essex County Hospital, Colchester (b 1946; q Alexandria, Egypt, 1972; DMRT), died from lung cancer on 25 August 2006. One of 10 siblings born in a village on the West Bank of the Jordan, Heidar never forgot his Palestinian roots, supporting several charities there. He spent six months in Iraq as an engineering student but then changed to medicine. He worked for a short time in Libya before coming to England to study oncology. Ironically he soon developed Hodgkin’s disease, but he continued to work as a senior house officer during chemotherapy and radiotherapy. After three years as a registrar in Coventry, Heidar returned to Colchester with sessions at the newly opened St Helena Hospice and Essex County Hospital, thus helping to cement the relationship between the two. He leaves a wife, Lynne, and a daughter.

Fayez Ayache, William Pratt

Michael Alan Casson

Former general practitioner Didsbury, Manchester (b 1931; q Manchester 1955; BSc, DRCOG, MRCP), d 12 November 2006. Selected for a BSc in physiology, Mike spent time in pathology, virology, and public health medicine before joining Rudi Friedlander in a private general practice serving the local south Manchester population and the Jewish, frequently German refugee, community. Mike’s approach was one of intellectual rigour, a joy of the job, and meticulous care of his patients. He revelled in company and loved skiing. Mike retired from general practice in 1997 but stayed up to date to see certain patients and develop a thriving insurance medical practice. He completed the paperwork for his last consultation minutes before leaving for an operation from which he expected to recover quickly and return to work. He leaves a wife, two sons, and four grandchildren.

David Casson

Don Bosco Fernandez

Former general practitioner Edzell, Angus (b 1935; q Madras Medical College 1960), d 25 March 2007. Bosco Fernandez came to the United Kingdom in 1972 for higher studies. He worked in Ashington and then Darlington, moving to Scotland in 1974. He worked at Stracathro Hospital for three years and at Sunnyside Hospital for six before joining a general practice in Edzell in 1984. From 1985 until he retired in 1999 Bosco was the general practitioner for Edzell. He was a past president of the Rotary Club and at the time of his death was vice president of the Probus Club of Brechin and due to be president in June 2007. He was a keen gardener with a special interest in bonsai, nurturing a bonsai tree which he had brought from India 22 years before. He leaves a wife, Cecilia; four sons; and 10 grandchildren.

Ranjit Fernandez

Iain Michie

Former lieutenant colonel Royal Army Medical Corps and consultant physician for Argyll, County Hospital, Oban (b 1932; q Edinburgh 1955; FRCPed), died from organ failure on 10 June 2006. Iain Michie was born and educated on the Isle of Skye and spoke Gaelic. After national service he extended his commission as consultant physician. At Wheatley Military Hospital he published on neurological syndromes associated with congenital cervical and cranio-cervical abnormalities and, when serving overseas, on porphyria and leishmaniasis in Aden. He then headed the medical department of Queen Mary’s Military Hospital, Millbank, and studied cardiovascular and respiratory function in Chelsea Pensioners. In 1971 he won the Leishman memorial prize (Royal Army Medical Corps). In 1972 he was appointed consultant physician for Argyll and developed the current comprehensive service based in Oban. He retired early in 1992 after nephrectomy for hypernephroma. Predeceased by a daughter, he leaves a wife, Ray, and two daughters.

R Frew

Emily Madge Moore

Former medical officer in family planning and psychosexual medicine (b 1918; q Royal Free Hospital 1947), died from primary lung cancer on 6 December 2006. Madge Moore, or Emily as she later preferred, was a founder member of the Institute of Psychosexual Medicine. After marriage and a family she worked in school health, infant welfare, and family planning, here realising the need for training to help people with sexual problems. She set up psychosexual services in Hounslow and Weybridge and worked in youth advisory clinics for the Brook Clinic, Woking and the West London Hospital, and as student health consultant at Surrey University. She lectured widely and became involved with Marriage Guidance (Relate), Cruse, and the Samaritans in Walton on Thames and Weybridge. In retirement she set up psychosexual medicine clinics in Barnstaple and the North Devon Hospital. She leaves a husband, Bryan; three daughters; and six grandchildren.

Heather Montford

ADVICE

We will be pleased to receive obituary notices of around 350 words. In most cases we will be able to publish only about 100 words in the printed journal, but we can run a fuller version on our website. We will take responsibility for shortening. We do not send proofs. Please give a contact telephone number and, where possible, supply the obituary on a disk or by email to obituaries@bmj.com.
Spanish doctors are more likely to drink and drive than other university graduates, according to a study of self-reported behaviour in *BMC Public Health* (2007;7:55). Nurses of both sexes and female doctors were 1.2 times as likely to “drink-drive” as non-health workers. But male doctors were even less responsible, being twice as likely to drink-drive as non-health workers. Drink-driving behaviour was related to other “unsafe” practices, such as binge drinking, drinking every day, not wearing seat belts, and being a former smoker.

Men may have a biological clock ticking away after all. Scientists say that current studies in animals are confirming that ageing can affect male as well as female fertility (*Science* 2007;316:383-4). In species in which females mate with many males it seems advantageous to mate with males of intermediate age, whose sperm is likely to win in competition with younger and older males. When older males do successfully mate, the offspring may end up genetically less fit.

To try to reduce the risk of aspiration after treatment for locally advanced head and neck cancer, a US team devised a study to assess the benefits of offering “swallowing therapy” (*Oral Oncology* 2007;43:352-7). All patients were free of cancer at the time of follow-up, a median of 25 months later. Swallowing therapy improved the severity of dysphagia and reduced the need for tube feeding, but a significant number of patients still had chronic severe aspiration. A better outcome requires new strategies, say the authors.

Disrupting the environmental transmission of the flu virus may be the only viable way to protect the public in an influenza pandemic, especially where antiviral drugs and vaccines might be in short supply. Two obvious ways to do this are to use facemasks and ultraviolet light. Reusable facemasks should be stockpiled, say the authors, because the supplies of disposable ones are likely to be inadequate. Ultraviolet light directed overhead may be useful in hospitals and nursing homes (*American Journal of Public Health* 2007;97(supp 1):S32-7).

A former British Airways pilot says that doctors and dentists can learn a thing or two from the aviation industry (*Summons: Journal of the Medical and Dental Defence Union of Scotland*, spring 2007: 8-9). Health care and aviation have two key similarities—both operate in environments that are unforgiving of error, and both require effective teamwork. Health care should note from aviation how to shorten the “learning timeframe,” he says. “Safety is not a single event or even something that we ‘do.’ Safety is a notion which should inform our every action.”

Bariatric surgery—laparoscopic or open stomach banding—brings about far more positive outcomes than simple weight loss (*British Journal of Surgery* 2007;94:449-56). Measures of health related quality of life, including wellbeing, health distress, depression, perceived attractiveness, and self-worth, all improved over five years even though not all excess weight was lost. Productivity at work and physical activity also increased. Where the body mass index fell to less than 30, quality of life scores were similar to people of normal weight.

The emergence of community-acquired methicillin resistant *Staphylococcus aureus* (MRSA) in Northern Ireland offers worrying implications for the population. An otherwise healthy teenager presented with a cellulitic toe and, rather unusually for MRSA, the bug turned out to be sensitive to ciprofloxacin on in vitro testing (*Ulster Medical Journal* 2007;76:68-71).

A consultant writing in the QJM says that his team is officially “overperforming” (2007;100:251-2). They’d done more work than predicted and were asked to work less hard for the remainder of last financial year. The trouble is that they were only “in breach” of one of a number of local contracts, so for patients living in a different catchment area it was business as usual. Not only did this introduce another form of postcode discrimination, the writer says, “it’s beginning to resemble totalitarianism.”

Patients who get nosebleeds severe enough to warrant nasal packing are usually admitted to hospital—but is this necessary? A retrospective review of 116 patients who were managed after the implementation in 2004 of a local protocol, which is followed by junior doctors in the emergency department, found that only 17 patients needed admitting (*Journal of Laryngology and Otology* 2007;121:222-7). Forty six had been discharged with nasal packing in situ, and only seven patients returned because of bleeding. In all, 39 admissions had been prevented, avoiding the risk of hospital-acquired infection.

Minerva has a tendency to monitor her own bowel habit, but very little is known about what constitutes a “normal” bowel habit in women. A large survey of women with no bowel disease found a huge diversity in what is considered normal (*Diseases of the Rectum and Colon* 2007;50:351-8). Indeed, one daily bowel movement is not the norm. Older women and women who’ve had children report more faecal incontinence, and one third of all women experience some faecal incontinence. Disturbances to the usual pattern were most commonly caused by foods, followed by menstruation, stress, and childbirth.