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Minerva

Minerva
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Primary prevention of age related macular degeneration

Current evidence does not support a protective role for dietary antioxidant vitamins

In this week’s BMJ, Chong and colleagues present a systematic review and meta-analysis of the effectiveness of dietary antioxidants, including supplements, in the primary prevention of age related macular degeneration.1

Age related macular degeneration is one of the most important causes of visual loss in older people. The number of people affected will increase as populations age.2 Two types of age related macular degeneration exist. Geographic atrophy is a sharply demarcated area of depigmentation caused by atrophy of the retinal pigment epithelium; neovascular degeneration occurs when new blood vessels grow under the retinal pigment epithelium leading to haemorrhage and scarring. Age related macular degeneration is diagnosed in people aged 50 or more when no other obvious cause for degeneration exists.

New treatments are being developed rapidly. In the past two years, intraocular injections of agents that interfere with angiogenesis have been licensed for use in this condition.3 These bind to vascular endothelial growth factors to prevent endothelial cell proliferation and neovascularisation. Although improved treatments are always encouraging for people with age related macular degeneration, visual loss arising from the growth of new vessels is usually permanent, and no effective treatments exist for geographic atrophy. Research into why age related macular degeneration develops, with a view to preventing it, continues.

The incidence of many diseases increases exponentially with age. One common theory for the aetiology of many age related diseases, including age related macular degeneration, is that they arise as a result of the cumulative effects of oxidative stress.4 The systematic review by Chong and colleagues summarises the results of seven prospective studies and three randomised controlled trials evaluating the association between dietary intake of antioxidant vitamins and minerals (such as vitamin C, vitamin E, various types of carotenoids, and zinc) or dietary supplements (vitamin E and β carotene) and age related macular degeneration.1 This is the first such review of usual dietary intake—previous reviews have considered randomised controlled trials of supplements.5

The prospective studies show that people with relatively high dietary intakes of antioxidant nutrients are no more or less likely to develop the condition than those with relatively low intakes. The possible exception to this is high dietary intake of vitamin E, which was associated with a 20% reduced odds of age related macular degeneration. The significance of this finding depended on which studies were included in the meta-analysis. Further studies are needed to confirm its relevance.

Dietary intake is difficult to measure accurately. In observational studies it is difficult to be sure that a fair comparison is being made, because people with different diets also differ in many other ways. In spite of these caveats, evidence of a strong protective effect of the dietary antioxidants studied was lacking. Obviously, a well balanced diet containing fruit and vegetables has many other health benefits and should still be recommended. In addition, included studies were carried out on relatively well nourished populations in the United States, Australia, and Europe, and the results may not apply to populations with different dietary intakes.

Three randomised controlled trials provide good evidence that vitamin E or β carotene supplements do not prevent age related macular degeneration (one of these trials is included in abstract form in the review but has since been published†). Although generally regarded as safe, vitamin supplements may have harmful effects. People who smoke may be at increased risk of lung cancer if they take β carotene,7 & and vitamin E supplements may increase risk of heart failure in people with diabetes or vascular disease.9

While antioxidant vitamin supplements cannot be recommended as a public health measure to reduce the incidence of age related macular degeneration, people with early stage disease may benefit from supplements containing vitamin C, vitamin E, β carotene, and zinc.10 The recommended combination and doses of antioxidant vitamins and minerals is found in only a few commercial supplements and should be taken on specialist advice,11 with appropriate consideration of the possible benefits and harms for the individual.

Do other options exist for primary prevention of age related macular degeneration? The strongest risk factors for this condition—age and genetic factors—are not preventable, although genetic research will provide new insights into the causes of the disease and therefore its prevention. High concentrations of polyunsaturated fats are found in the retina, but evidence for a protective effect of dietary fatty acids in this condition is inconsistent.12 Smoking is the only preventable risk factor that has been associated with the condition in most observational studies.13 Currently, reducing the prevalence of smoking is probably the most effective method of reducing the population burden of this common cause of visual loss in older people.

All references are on bmj.com
Data sources and performance measurement

Measuring outcomes is necessary but difficult to get right

In this week’s *BMJ*, Westaby and colleagues compare the value of two sources of data for determining mortality 30 days after congenital cardiac surgery—hospital episode statistics (HES) and the central cardiac audit database. They find that the central cardiac audit database is more complete than HES, but that individual centres need investment to improve the completeness and accuracy of their data. Their investigation follows a study published in the *BMJ* in 2004 that used HES to compare mortality from congenital heart surgery in different UK centres. The study suggested that Oxford had significantly higher mortality than the national average, and the results were reported widely by the media. So have we learnt anything new about the relative value of routinely collected versus specifically collected sources of data?

Routinely collected patient data are regularly analysed to investigate outcome. Equally regularly the results are contested by the specifically collected dataset, which is often designed to measure the very thing being looked for. So why use routinely collected data to draw clinical conclusions at all? The advantages include pragmatism, wide coverage, low cost, and easy access. The disadvantages include superficial or inaccurate coding and potentially damaging generalisations.

HES data from the National Health Service (NHS) are widely used to produce outcome information and more recently to publicise differences between hospitals. Data produced for administrative and financial purposes that are centred on the organisation not the patient may never be as complete as data derived from clinicians.

Huge datasets also invite misuse of statistical methodology—the significance of correlations is a product of the number of data points, not necessarily its relative importance. Chance findings will occur if many tests are done on the same data; association is not the same as causality. Nonetheless, the sheer scale of the HES database makes it attractive and it has become a rich source of hypothesis generation and evidence on outcomes. The database has been used to investigate associations between case volume and outcome (for example, oesophagectomy and repair of aortic aneurysms), to search for potentially useful predictors of outcome (for example, excess mortality associated with delay in operation after hip fracture), to carry out quasilongitudinal studies to track changes in outcome related to changes in clinical practice (for example, acute urinary retention and prostatectomy), follow-up after emergency admission, and changes in mortality after paediatric cardiac surgery, and increasingly to predict individual outcomes in patients at high risk.

Results that conflict with HES data have often been reported—for example, the relation between hospital volume and outcome and the predictive factors for poorer outcome in certain patients. This is not just a contest of science and statistics but of politics, hearts, and minds. As Westaby and colleagues note, the media rapidly picked up on the conclusion based on HES data that Oxford had significantly higher mortality after paediatric cardiac surgery than the national average.

While recognising that there are problems in special datasets too—timescales and numbers of episodes are often smaller, making it more likely to miss a rare event or true difference, and collecting outcome data on your own performance may bias the case mix of patients selected for intervention—Westaby and colleagues conclude that HES data should not be used for comparisons within specialties.

Patients do not necessarily trust official data sources. We need to know if they will trust information collected by doctors who analyse their own data and claim that their performance is sound. The NHS has recently appointed a new medical director, Professor Sir Bruce Keogh, who is famous for his leadership of British cardiothoracic surgeons in measuring outcomes and making them public. This appointment sends a clear signal to staff, the public, and the media about the importance of measuring outcomes.

It is unclear how much patients change their choice of provider based on such knowledge, or how much employers manage their clinical staff with an eye on comparative performance, however intuitively it seems important. With all its potential problems, HES has more to offer than league tables of performance. Better knowledge will flow from a collaboration of all sound analyses, based on complete data, that are accurately coded by clinicians who have an interest in the outcome. This can only lead to more complete and contextualised data being released into the public domain.

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Participation in mammography screening
Women should be encouraged to decide what is right for them, rather than being told what to do

In April 2007, the American College of Physicians—the largest medical specialty society in the United States—issued new guidelines on screening mammography for women aged 40-49. Rather than calling for universal screening, the guidelines recommend that women make an informed decision after learning about the benefits and harms of mammography. The last time a major US policy organisation made such a recommendation all hell broke loose. In 1997, a consensus panel of the National Institutes of Health concluded “that the data currently available do not warrant a universal recommendation for mammography for women in their forties. Each woman should decide for herself whether to undergo mammography.” This recommendation generated intense reactions in the press, public, and government. Most stories in the press suggested that women should be screened and others directed anger at the panel for “failing” to recommend screening. The panel’s chair was summoned before congress, and a US senate resolution in favour of screening was unanimously passed— a rare act of bipartisanism. After a few months of intense political pressure, the National Cancer Institute contravened the panel’s conclusions and recommended that women in their 40s should be screened.

In contrast, the reaction to the recent guidelines was muted. The press carried a few stories—a few of which were critical—but there were no senate resolutions and no hearings to cross examine the leadership of the American College of Physicians.

The possible reasons for these dramatically different reactions are that the American College of Physicians may not have the same visibility as the National Institutes of Health panel; journalists and readers may be tired of the mammography debate; and politicians may be preoccupied with other matters. But a more positive explanation is that the public and profession increasingly accept that cancer screening has both benefits and harms. Perhaps we are finally moving beyond the debate about what women should do and are ready to focus on how to help women make the best decision for themselves.

So how can clinicians help? The first step— exemplified by the recent guideline—is to acknowledge that women face a real choice. Screening entails trade-offs that are hidden by slogans such as “If you haven’t had a recent mammogram, you may need more than your breasts examined.” These messages are meant to persuade women to do what is right, as decided by the people who write them. But no right choice exists, because screening has mixed effects—some women will benefit (by avoiding death from breast cancer) but others will be harmed. So the next step is to ensure that women understand what is likely to happen if they do or do not undergo screening.

The table shows estimates of the benefits and harms of screening mammography for women in their 40s and (for context) older women. Despite the wealth of published literature, the numbers are still controversial, and any of the figures could be criticised. The table is not meant to be the final word on mammography but to convey the order of magnitude of its effects. Furthermore, the data are based on averages, so the risks will be different for women at high risk (such as those with a strong family history of early breast cancer). And of course, the numbers are only a start. If we seriously want to promote informed decisions, we must ensure that women understand the data and have some context for judging how big (or small) these numbers are.

The main benefit of screening is to avoid death from breast cancer. The relative risk of death from breast cancer for women who are screened is 0.85 for those in their 40s and 0.78 for those 50 and older. These figures may underestimate the efficacy of screening because

### Summary of data on benefits and harms of screening mammography every 1-2 years for 10 years

<table>
<thead>
<tr>
<th>Benefits and harms</th>
<th>Age group of women (years)</th>
<th>40-49</th>
<th>50-69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 year risk of death from breast cancer*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No screening</td>
<td></td>
<td>3.3/1000 (0.33%)</td>
<td>8.9/1000 (0.89%)</td>
</tr>
<tr>
<td>Screening</td>
<td></td>
<td>2.5/1000 (0.25%)</td>
<td>6.0/1000 (0.6%)</td>
</tr>
<tr>
<td>Avoidance of death from breast cancer</td>
<td></td>
<td>0.8/1000 (0.08%)</td>
<td>3/1000 (0.30%)</td>
</tr>
<tr>
<td>Harms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient has at least one false positive screening examination that results in additional testing</td>
<td>100-500/1000 (10-50%)</td>
<td>100-500/1000 (10-50%)</td>
<td></td>
</tr>
<tr>
<td>Patient has at least one false positive screening examination that results in unnecessary diagnosis and treatment for breast cancer</td>
<td>2.5/1000 (0.25-0.5%)</td>
<td>3/1000 (0.30-0.90%)</td>
<td></td>
</tr>
</tbody>
</table>

*The 10 year chance of dying from breast cancer for American women aged 40-49 and 50-69 (2002-4) came from the National Cancer Institute. We calculated the risk for the two sets of women using the risk reduction of mammography for each age group4 after adjusting for non-compliance in trials14 and national estimates of mammography uptake in each age group about 10 years earlier according to the National Center for Health Statistics. This approach assumes that the total risk of death from breast cancer is the weighted average of the risks faced by women who are and are not screened.

1We applied estimates of the proportion of screen detected cancers that are overdiagnosed (low 10%, high 30%) to the rate of screen detected breast cancers in trials of women ≥55 and those 40-49.

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Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

BMJ 2007;335:731-2 doi: 10.1136/bmj.39350.590625.80
Screening for abdominal aortic aneurysm

Can save lives but only if operative mortality is low

A recent Cochrane review has updated our knowledge about screening asymptomatic people for abdominal aortic aneurysm, with respect to their mortality, subsequent treatment for the aneurysm, and the cost effectiveness of screening. Four completed randomised controlled studies—Chichester, Viborg, Western Australia, and the multicentre aneurysm screening study (MASS)—with 127,891 men and 93,422 women (only the Chichester trial included women) aged from 65-83 years were included to a cut-off date of 26 January 2007. This excluded the more recent seven year follow up of men in MASS, acceptance rates (of people agreeing to be screened) ranged from 63.1% (Western Australia) to 82.0% (MASS).

In men aged 65-79 years screening significantly reduced the risk of mortality related to aneurysm (relative risk 0.53 (confidence interval 0.42 to 0.68). This was achieved at the expense of doubling the rate of aneurysm surgery. However, for studies in men, the review reported no significant reduction in all cause mortality. Although the Western Australia trial found a reduction in all cause mortality (from the time of screening and not randomisation), the authors note that the interval between randomisation and screening could have introduced a bias, such that screening did not account for the reduction. However, the recent update from MASS also hints at a possible benefit in all cause mortality in men who were screened (estimated hazards ratio 0.96, 95% confidence interval 0.93 to 1.00), so a further update of the Cochrane review may be needed.

MASS produced a cost effectiveness analysis at four years with 47 fewer deaths from aneurysm equating to £28,400 (£42,000; $58,000) per life year gained and £36,000 per quality adjusted life year. At seven years this had fallen to £12,334 per life year gained and is likely to fall even further after 10 years. The Viborg trial derived a very different figure (£620 per life year saved), and the reason for this disparity seems opaque, although health economists should be able to shed some light on the reasons for the disparity.

The trials have provided evidence to suggest that screening in itself does not impair quality of life, although this is not covered in the Cochrane review.

Data are still lacking on the potential benefits or harms of screening in women. False positives cause short term anxiety, inconvenience, and sometimes unnecessary biopsies, but we think that overdiagnosis is the most important harm of screening. Overdiagnosis is the detection of lesions that meet the pathological criteria for cancer but would not progress to cause symptoms or death. Such lesions lead to overtreatment. Because we do not know which cancers are overdiagnoses, we treat everybody. But women who are overdiagnosed can only be harmed by treatment—they cannot benefit because no treatment was needed. Harms include disfiguring surgery, side effects of chemotherapy or hormonal therapy (such as nausea, fatigue, and hair loss), and injury from radiation.

Overdiagnosis is a counterintuitive phenomenon, and few women know about it. Because we cannot identify overdiagnosis during life, we do not hear stories from women harmed in this way by screening (in contrast, we routinely hear stories from women whose lives were “saved” by screening). But once informed about the possibility of overdiagnosis, most women say they would factor it into their decision about screening.

Estimating the chance of overdiagnosis is challenging as it cannot be measured directly. Screening trials consistently show an excess of breast cancer diagnoses in the intervention group, which does not go away with time, making it possible to estimate the proportion of screen detected breast cancers that are overdiagnoses. We used a range of published data to calculate the numbers shown in the table. The new guideline is an improvement because it integrates informed decision making into policy recommendations—a refreshing change in a field dominated by soundbites and slogans. But why should this advance be limited to women in their 40s? And why just American women (only women over 50 are routinely invited for mammography in the UK)? Whether a woman is in her 40s or older—on either side of the Atlantic—screening for breast cancer involves benefits and harms. Rather than telling women what they should do, policy makers should encourage women to make a decision that is right for them.

All references are on bmj.com
harms and costs for screening women, although at least one group suggests it may be cost effective and the screening of high risk women was supported by the current president of the Society for Vascular Surgery in the United States. All these data are supportive of a national screening programme, and at a time when the NHS is considering the cost implication of establishing such a programme for men aged 65 years, the seven year follow-up data from MASS with the lower cost per life year gained are especially timely. 

Correctly, the mood is in favour of aneurysm screening, but the following policy problems still need to be tackled. How can screening uptake be improved in those at highest risk (such as those in the lowest socioeconomic groups)? How can screening be refused to men older than 65 years and women at highest risk (such as smokers and those with a strong family history of aneurysm)? How and where should patients with screen detected aneurysms be managed?

All the screening trials, as well as other randomised trials of aneurysm treatment, report operative mortality of about 5% for open elective surgery (as used in all the screening trials) for aneurysms ≥5.5 cm in diameter, the general threshold for intervention. Randomised trials show that operative mortality is lower from endovascular repair (<2%) than from open repair (<5%), although endovascular repair costs more. Not only may medical treatment, including statins, further improve operative mortality and life expectancy in those found to have abdominal aortic aneurysms, there is now the expectation that statins and other new treatments will slow the growth of small aneurysms found by screening. Screening should do no harm. However, a recent evaluation of administrative and clinical databases looking at predictors of risk of death in hospital suggests that in England the in-hospital mortality for non-ruptured abdominal aortic aneurysm repair is 10.2%. A systematic review using the same dataset emphasised that although the worst mortality rates were from low volume hospitals, excellent results were achievable in occasional low volume hospitals. These data show that operative results of hospitals are central to whether screening saves or loses lives. We must tackle how acceptable mortality can be achieved across the whole country, perhaps using the protocols that led to such an acceptable mortality in the 41 EVAR trial centres. Without such safeguards, screening for abdominal aortic aneurysm may not bring the expected results and instead may cause regret about the new screening programme.

All references are on bmj.com

Modernising Medical Careers laid bare
Another fine mess the Department of Health has got doctors into

“Although a deeply damaging episode for British medicine, from this experience must come a recommitment to optimal standards of postgraduate medical education and training. This can only occur if a new partnership is struck between the profession and the DH [Department of Health], and between Health and Education. Each constituency has been found wanting thus far. In future, each must play its part. An aspiration to clinical excellence in the interests of the health of the population must be paramount.”

So concludes Professor Sir John Tooke’s inquiry into Modernising Medical Careers (MMC). This initiative, “an honest attempt to accelerate training and assure the fundamental abilities of the next generation of doctors” almost foundered over the failure of its main component, the centralised selection into run-through specialist training. In response, the government announced an independent inquiry into MMC, the interim report of which was released this week. While Tooke’s report runs through the reasons for the failure of the medical training application service (MTAS), these have been extensively covered in a previous report. Sir John’s canvas was much wider. His panel “explored the background and context—in medical terms the predisposing or aetiological factors—that may have contributed to the perceived problems with MMC, rather than simply focusing on MTAS.”

So, what went wrong? Wherever Sir John shone his torch he found debilitating vagueness and frailty. He found no evidence of a consensus on the educational principles guiding postgraduate medical training and that mechanisms for creating such a consensus are weak. The management of postgraduate training is hampered by unclear principles, a weak contractual base, a lack of cohesion, a fragmented structure, and, in England, deficient relationships between academia and service. No consensus exists over doctors’ roles at various career stages, which hampers planning of the medical workforce. A vacuum exists in policy regarding the potentially massive increase in trainee numbers. And so on.

At the press conference launching his report, Sir John refused to name and shame the guilty parties, but because he listed governance and risk management as most at fault they are most likely to reside at the Department of Health. In mitigation, responsibility for MMC was split between two people and the biggest headaches—MTAS—and the surfeit of eligible international medical graduates—were outside the responsibilities of both of them.

This week, the government announced that there would be no national IT system for job applications

NEWS, pp 737, 738
VIEW & REVIEWS, p 775

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Competing interests: TD’s wife qualified in the European Economic Area and shortlisted and interviewed for the London Deanery.

Provenance and peer review: Commissioned, not externally peer reviewed.

BMJ 2007;335:733-4
doi: 10.1136/bmj.39364.512685.80
next year and that it was launching a consultation exercise over training jobs for medical graduates from outside the European Economic Area. How had the stewardship of medical training deteriorated to such an extent at the Department of Health? Benign or malign neglect? Conspiracy to further depersonalise doctors or cock-up? Once again Sir John would not be drawn, but the manifest organisational failures of the department would suggest that conspiracy was beyond its skill set.

The bottom line is that the department has wrested control of doctors’ training from the medical profession and has proved itself unequal to the task. One of Tooke’s “corrective actions” concerns the Postgraduate Medical Education and Training Board, set up to regulate postgraduate medical education in the wake of the Bristol inquiry. He wants it merged with the General Medical Council, which already regulates two of the three components of medical education (undergraduate education and continuing professional development). Crucially, “it is a body that reports to Parliament, rather than through the monopoly employer [Department of Health].”

Doctors don’t emerge unscathed. “Forensic” analysis of meeting records shows they were well represented on the various delivery and advisory boards—one figure in the report lists an alphabet soup of 19 different representative bodies, with their dates of attendance. But in sum their influence was “suboptimal.” Their frequent calls for trialling and delay went largely unheeded, and they reported being deterred from questioning policies. On occasion, they weakened their impact by speaking up for their individual consistencies rather than for the profession as a whole, according to the report.

The report recommends that the medical profession urgently needs to develop a way of providing coherent advice on matters that affect the entire profession, without giving details of what this might look like. And it wants a consensus on the role of doctors to be agreed by the end of 2008. Sir John admits it’s a tall order, but it would coincide with the 150th anniversary of the Medical Act, something that obviously appeals to a doctor who quotes William Osler and medical historian Roy Porter in his foreword.

For the doctor on the ward or in the clinic the biggest changes will be those recommended for the structure of postgraduate training. The need for a broad based beginning, flexibility, and the promotion of excellence recur like a mantra throughout the report. Sir John says this part of the report was heavily influenced by the workshops he held throughout the United Kingdom, which involved 450 trainee doctors. They said that they wanted to be much better than “just good enough” for their jobs (hence the report’s title, *Aspiring to Excellence*).

The report recommends that the link between foundation years one and two is broken, allowing the second foundation year to become the first of a three year core training programme (along with the current first and second years of specialist training HST1 and ST2). Up to half a dozen defined core programmes (including ones in surgery, medicine, and general practice) are envisaged, which would involve six appointments of six months each. These core programmes would serve as stems for subsequent specialty training.

Entry into higher specialty training after the core programme would be based on marks obtained in national assessment centres for the specialty in question, together with structured CVs and interviews for shortlisted candidates at deanery level.

General practice training “must be extended to five years to assure the skill base of that part of the medical workforce that is going to become increasingly important, with rising longevity, increasing co-morbidity, and shifts of care to the community.” And the future of doctors in fixed term specialty training appointments and in the non-consultant career grade needs to be sorted out.

If Tooke’s recommendations for the early years of training sound familiar it is because they resemble the proposals for senior house officer training set out in *Unfinished Business*, a consultation paper dating from 2002. Its principles were that training in these early years should begin with a broad based programme and be flexible to trainees’ needs, providing opportunities to leave and re-enter. However, a subsequent document reported that “thinking had moved beyond the basic specialist programmes foreseen in *Unfinished Business*” towards a single “run-through approach,” a shift recently discussed in these pages. Tooke’s comment, “although whose thinking and with what authority is not entirely clear,” could stand as his verdict on this whole sorry chapter of Modernising Medical Careers.

And as to the next chapter? Richard Hayward captures the challenges well in his personal view this week, “the MTAS fiasco (for which all parties must share responsibility) stands as a dire warning to government and medical profession alike of trying to reform health care without cooperation between the two. Expect the current rocky ride to continue until and unless the government and the community of independent medical practitioners find common ground—something that will require a shift of culture on both sides if the NHS is really to benefit.” Tooke has provided the roadmap for postgraduate medical education and training.
LETTERS

NICE TRANSPARENCY

Let cost effectiveness models be open to scrutiny

In light of the recent ruling over the National Institute for Health and Clinical Excellence’s (NICE) decision on donepezil,1 2 we wish to comment on the adversarial system of drug evaluation and the inadequacy of NICE providing read only versions of cost effectiveness models for the purposes of reviewing their decisions.

The assertion that “NICE is not in a position to deal with the reality of restrictions being placed on the models by those who supply them”3 is not defensible. NICE could specify terms and conditions to technology assessment groups (TAGs) to allow full disclosure of what, after all, is publicly funded research. Indeed, they should be disclosed under the Freedom of Information Act, with non-disclosure acceptable only when in the public interest.

Recently, the Sheffield TAG published a correction to a cost effectiveness model for multiple sclerosis treatment caused by a coding error.3 This model underpinned a high profile and novel shared risk policy.4 Because even the simplest deterministic models need thousands of calculations, usually coded by one person, errors are hardly surprising. More sophisticated simulation models use complex computational routines, the detail of which is rarely scrutinised. Under current TAG contracts NICE cannot quality assure these models. Furthermore, a recent objective comparison of validated health economic models for diabetes found wide variability.5

The current adversarial system of economic evaluation is unacceptable to all stakeholders. Cost effectiveness models could be produced by consensus under the joint direction of NICE and industry. This would reduce costs and hasten access to health technologies that all agree are good value for money.

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Competing interests: DJC and CP have worked for several drug companies in the preparation of NICE submissions. SA has represented the Royal College of Pathologists in a previous NICE appeal. Pharmatelligence is a health outcomes consultancy, mainly to the drug industry; it has received neither instruction nor payment from the industry about this letter.

1 Chalmers I. The Alzheimer’s Society, drug manufacturers, and public trust. BMJ 2007;335:400. (25 August.)

THE PRIMARY CARE MARKET

More questions than answers

Pollock et al ask “how will National Health Service spending be accounted for in the new primary care market?”1

When I asked to see the financial details of the contracts with private providers the reply was, “I can confirm that the department holds details of the cost of the Walk in Centre and general medical services, however it is not currently prepared to release this information.”

With all the talk of competition, some questions remain. Why are personal medical services, alternative medical provider services, and private contractors not offered the same capitations as general medical service contractors, determined by an allocation formula that takes account of patients’ needs?2 Why did the advisory board for alternative medical provider contracts contain several of the private companies that are now providing primary care services?3

A final detail, the Barking and Dagenham surgery and walk-in centre (that reputedly received £5m (£7m; $10m) for a five year contract) is not catering for 7000 patients yet—that is the number of patients who will potentially be registered at the end of the five year period.4 How many patients are registered for primary care services and at what cost is known by the Department of Health only for the time being.

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Competing interests: None declared.

3 The NHS confederation. APMS core group meeting. 21 July 2004, London. www.bmj.com/cgi/content/ full/335/7622/DC1.

ALCOHOL INDUSTRY

Brazil’s market is unregulated

Farrell warns of the health implications of the unwelcome partnership between the alcohol industry and the health sector.1 Brazil has one million selling points for alcohol in a population of 180 million. These points can sell alcohol at any time of day, to anybody, including minors. We have a very aggressive advertising strategy on television that reaches millions of children. In recent research on a random sample of drivers, 30% of them had alcohol in their blood.

Brazil is by any account an unregulated market for alcohol, and the alcohol industry is trying to keep it that way. This lack of regulation contributes to the 10% increase in consumption each year.

If that were not enough, the alcohol industry has approached health professionals to advocate a harm reduction approach as the best policy for tackling this problem in Brazil.

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Competing interests: None declared.

DeclaratioN of Helsinki

Dead

Servicing the overarching interests of the drug and medical device industry, the United States has apparently successfully intervened in the past (and still tries) with provisions that weaken the protection of human subjects, taking the document farther and farther from the principles and intent of the Nuremberg Code. The World Medical Association, it appears, has been party to medical malpractice in its most wanton manifestation. Fortunately, unlike the Nuremberg Code, most courts of law do not rely on the Declaration of Helsinki for guidance.

The answer to Goodyear et al’s question—“Declaring Helsinki—alive or dead?”—seems to be that the Declaration of Helsinki is dead on the basis of no brain waves, no heart beat, and a rapidly bloating, blow fly infested, stinking cadaver.

Cynically, one must ask “what is the purpose of current efforts to ‘harmonise’ the ethics and legalities of clinical trials in countries with no device regulatory system?” How can one “harmonise” the practice of numerous unethical experiments conducted by researchers with no “internalised ethical values?” How can one “harmonise” wholesale failure to internalise ethical values?” As the ethicist Arthur Caplan said, “In many ways, rats and mice get more protection as research subjects in the United States than do humans.”

Efforts to change the Declaration of Helsinki that come from the US should be recognised for what they represent. The United States and the US Federal Drug Administration have abdicated oversight of human subjects research, as indicated by a recent report of the US Department of Health and Human Services inspector general, “. . . federal health officials did not know how many clinical trials were being conducted, audited fewer than 1% of the testing sites and, on the rare occasions when inspectors did appear, generally showed up long after the tests had been completed.”

Perhaps it is time to turn to the Canadian Ottawa Statement, to which the authors approvingly refer.

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Competing interests: JHN read and commented on the authors’ original draft.


What to do about CAM?

Doug Kamerow seems excessively tolerant of people who make lots of money out of unproved and disproved treatments.1

I prefer the straight talking of his compatriot, Gerald Weissmann, “If the trend persists, perhaps MIT (Massachusetts Institute of Technology) or Cal Tech will march in step with the medical schools and offer prizes for integrative alternative or alternative engineering.”2 Or Wallace Sampson, “It is time for Congress to defund the National Center for Complementary and Alternative Medicine (NCCAM).” After ten years of existence and over $200 million in expenditures, it has not proved effectiveness for any ‘alternative’ method. It has added evidence of ineffectiveness of some methods that we knew did not work before NCCAM was formed.3

That is something that could be done—the expenditure on NCCAM is now close to $1bn (£0.5bn; €0.7bn).

In the UK National Health Service, primary care trusts are, quite rightly, withdrawing funding from homeopathy. Tunbridge Wells Homeopathic Hospital will close and the Royal London Homeopathic Hospital is in great danger.4 5 Something has been done, at last.

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Competing interests: None declared.

1 Kamerow D. Wham, bam, thank you CAM. BMJ 2007;335:647. (29 September.)
2 Weissmann G. Homeopathy: Holmes, Hogwarts, and the Prince of Wales. FASEBJ 2006;20:1755-8
3 Sampson W. Why the National Center for Complementary and Alternative Medicine (NCCAM) should be defunded. www.quackwatch.org/01QuackeryRelatedTopics/nccam.html.
5 DC’s improbable science. The Royal London Homeopathic Hospital (RLHH) has problems. 2007. www.dsccience.net/improbable.html#fh3.

More Going Ape

Psychosocial interventions?

Given that the serotonin theory of depression has been dismissed as a myth propagated by the drug industry,1 and given the efficacy of psychosocial interventions, I was surprised that Pop considered only a pharmacological approach when treating a depressed gorilla.2

While even the most enthusiastic evangelists of cognitive behaviour therapy might acknowledge the limitations of cognitive restructuring in a gorilla, more pragmatic activity scheduling and behavioural activation both have a good evidence base as stand alone treatments for depression.

Damasio conceptualised emotional experience as being embedded within visceral and musculoskeletal states.3 In depression, reduced efferent activity from the peripheral nervous system can be stimulated by dance movement therapy, another proved treatment for depression.4

Ayurvedic philosophy, and more recently Harrison et al,5 have shown an association between low mood and overcrowding. This could be the case at the zoo, and a letter in support of rehousing, the ubiquitous default intervention of the helpless psychiatrist, might have been useful.

Dian Fossey observed the importance of social hierarchy in gorilla groups, and Pop’s patient’s withdrawal from the role of alpha male may have precipitated an existential crisis characterised by a failure to negotiate Erikson’s final task of development—integrity versus despair. Or in the words of The Jungle Book King Louie, “I’m (was) the king of the swingers, the jungle VIP. I’ve got to the top and then had to stop and that’s what’s bothering me.”

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Competing interests: None declared.

Tooke inquiry calls for major overhaul of specialist training for medical graduates

Lynn Eaton LONDON

Doctors’ postgraduate training needs to be completely reformed after the “sorry episode” of Modernising Medical Careers (MMC), John Tooke recommends in a highly critical report.

Professor Tooke’s interim report, published on Monday, calls for the national computerised application system to be scrapped and for an end to the “run through” training introduced as part of MMC.

And he wants to see UK medical graduates automatically guaranteed a place on the first year of foundation training (F1). They would then, however, be expected to take a national examination at the end of the F1 year. This would give them a national rating that they would use to compete for training positions at a local level. Candidates from other European Union countries would also be able to apply for these posts, but not at the F1 stage.

However, the issue of medical graduates from outside the EU must also be dealt with, said Professor Tooke. “That’s not to say that they have not made a fantastic contribution to the NHS in the past—and currently.”

But when it costs £200 000 (€290 000; $410 000) to £250 000 to train a UK medical graduate, said Professor Tooke, “some common sense has to prevail.”

Professor Tooke, dean of the Peninsula Medical School, was asked in April by the then health secretary, Patricia Hewitt, to investigate the failed implementation of the government’s Modernising Medical Careers programme. His interim report will be followed by six weeks’ consultation, and then by a final report at the end of the year. His proposals, if accepted, could be fully implemented within two or three years, he believes.

Under his proposals, medical graduates who successfully complete their F1 year and gain entry to the medical register would then move into core specialty training, lasting three years. Trainee doctors would spend six sessions of six months each in one of a small number of defined core programmes (including medicine, surgery, and family medicine).

At the end of the core specialty training they would compete for the next round as a specialist registrar. After this round they would emerge as either specialists or GPs. Appointment to a consultancy might entail a further examination. The report recommends that GP training should be extended from three to five years.

He was highly critical of the way the Department of Health had managed the whole Modernising Medical Careers project, which was managed by two separate people, the chief medical officer and the director of workforce. To add to the problems, Professor Tooke said, neither the computerised medical training application service (MTAS) nor non-EU overseas medical graduates fell within the remit of either of the two senior managers.

Commenting on the failings of MTAS Professor Tooke said, “Many of the problems were through the rushed implementation. Why, given the importance of this project, would you want to rush it? The process was not adequately managed.”

See News p 738 and Editorial p 733

The report is at www.mmcinquiry.org.uk.

### STRUCTURE OF MEDICAL POSTGRADUATE TRAINING, AS RECOMMENDED BY TOOKE INQUIRY

<table>
<thead>
<tr>
<th>Medical student</th>
<th>Preregistration doctor</th>
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<th>Specialist registrar</th>
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<td>Medical degree</td>
<td>Computer adaptive tests</td>
<td>Specialty assessments at selection centres</td>
<td>Competitive selection process</td>
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<td>Full GMC certification</td>
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<td>F1 year</td>
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<td>Core specialty training</td>
<td>Competitive selection process</td>
<td>Certificate of completion of training</td>
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<td></td>
<td>Trainees attend “graduate school”</td>
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<td>Places guaranteed for UK medical graduates</td>
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Source: Aspiring to Excellence: Findings and Recommendations of the Independent Inquiry into Modernising Medical Careers
many trusts fail to monitor impact of patients’ complaints

Zosia Kmietowicz LONDON

NHS trusts in England are failing to act on and learn from the complaints they get, says the national healthcare watchdog.

Results from the Healthcare Commission’s first ever audit of complaints handling in the NHS show that the way in which complaints are followed up varies greatly.

The commission identified the 10% of trusts that were most at risk of not meeting the core standard set down by the government on handling complaints. These 32 trusts, together with 10 others selected because they handled complaints well, were inspected by the commission in February and March this year.

The core standard requires trusts to make complaints procedures accessible, to act on concerns and make changes where appropriate, and to ensure that complainants are not discriminated against.

The inspectors found that only two of the 32 poorly performing trusts had adequate arrangements in place across all standards, 12 had areas for improvement, six were at risk of not complying with the core standard, and 12 had a significant lapse that could affect their rating in the commission’s annual health checks.

The commission could have issued a total of 96 notifications to the 32 poor performing trusts: one for each of the three standards. How- ever, overall the commission issued 25 notifications to 18 trusts. Most of these (14) related to discrimination against complainants.

The main concern was that no system was in place to monitor whether complainants had a detrimental effect on patients’ subsequent care.

Is Anyone Listening? A Report on Complaints Handling in the NHS is available at www.healthcarecommission.org.uk

patients admitted as emergencies should

Zosia Kmietowicz LONDON

Nearly four in 10 patients who are admitted to hospital as emergencies receive suboptimal care that in many cases is detrimental to their outcome, a UK study has found.

The latest report from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) says that such patients should be seen by a senior doctor within 12 hours and that standardised forms should be introduced across the NHS to make it clear that this has happened.

NCEPOD, an independent charity that aims to improve the delivery of health services, reviewed the care given in the first 24 hours and over the next seven days to more than 3000 adults admitted to 363 hospitals in England, Wales, Northern Ireland, and the Isle of Man on two predetermined dates in February 2005. It found that trainee doctors are failing to recognise the severity of very sick patients when they are first seen in accident and emergency departments.

The report cites the example of a patient who was admitted to hospital from a nursing home and was assessed in the emergency department by a junior doctor but was given no treatment plan. When the patient was assessed by a consultant 17 hours after arriving in the emergency department the patient’s condition had deteriorated.

government scraps national training application system

Lynn Eaton LONDON

A national computerised system will not be used for matching junior doctors to specialist training posts next year, the Department of Health has confirmed.

Instead deaneries will organise their own recruitment process for posts in England in 2008, and junior doctors’ start dates will be staggered, the health minister Ben Bradshaw has said. He has also announced plans to re-examine the current policy allowing medical graduates from outside Europe to apply for jobs in the United Kingdom.

Abandoning a national computerised system will leave deaneries responsible for advertising their own vacancies and issuing their own application forms (which will ask for CV type information). A maximum of three recruitment processes will take place each year, although the main intake will continue to be in August, particularly for the first year of specialty training.

“We have learned important lessons from the difficulties with this year’s recruitment process and have apologised to junior doctors for any distress caused to them and their families,” said Mr Bradshaw. “We said we would listen to doctors and their representatives, and today’s announcement reflects this.”

He added that any future system would be “rigorously tested and agreed with doctors, the NHS, and others involved.”

The Department of Health has also launched a consultation on how best to manage applications for foundation and specialty training programmes from medical graduates from outside the European Economic Area (EEA). The consultation ends on 22 October. One suggestion is that jobs should be filled by non-EEA applicants—including applicants with limited leave to remain in the UK, such as those on the highly skilled migrant programme—only if no suitable EEA applicant was available.

This year in England nearly 28,000 trainee doctors applied for around 15,500 posts. The health department says that overseas graduates outnumbered UK graduates applying for posts.

It warns that competition will be more intense in 2008 and forecasts a ratio of applicants to posts closer to 3.1. More than half of the applicants are likely to have trained outside Europe.
see consultant in 12 hours

Despite aggressive treatment the patient died 24 hours later.

Overall the review found that 40% of patients were not seen by a consultant within 12 hours of admission. In half the cases poor documentation made it impossible to determine when a consultant saw the patient.

The authors judged that in 16% of cases the time to the first review by a consultant was unacceptably long, which may have worsened the outcome.

Part of the problem may be the fact that consultants caring for 69% of the patients had other duties to perform while on call, and 21% were doing more than three duties at the same time. In addition, 15% of units did not have 24 hour access to computed tomography and 7% did not have access to conventional radiography.

The report calls for all patients admitted as emergencies to be seen by a consultant within 12 hours and for consultants on call to be available to deal with emergency admissions.

The report is available at [www.ncepod.org.uk](http://www.ncepod.org.uk).

Darzi promises easier access to GPs and 150 new health centres

**Zosia Kmietowicz LONDON**

The health minister Ara Darzi was criticised last week for not having consulted widely enough before publishing his review of the NHS. But his report was welcomed by many commentators for the extra funding that it promised for new technologies.

In his interim report, which was launched earlier than expected, Lord Darzi has promised better access to GPs, a new health innovation council to develop and deploy high technology health care, infection screening for all patients admitted to hospital, and annual infection control inspections in acute trusts.

Lord Darzi insisted that his vision for a world class NHS throughout England would be achieved by giving greater power to local NHS staff and others with an interest in developing health services. He said, “This is not about imposing more changes from the centre. Effective change needs to be led locally, driven by clinicians and others working in partnership across the service.”

To improve access to GPs Lord Darzi said that 100 new practices would open in areas with the worst provision and that new money would be made available to create 150 new GP run health centres that would be open seven days a week from 8 am to 8 pm. Another plan in the report is for at least half of all new and existing general practices to open their doors on Saturday mornings or one or more evenings each week, the Department of Health announced.

The health innovation council will be chaired by Lord Darzi and will be jointly funded by the health department and the Wellcome Trust to the tune of £100m (£145; $204m) over the next five years.

Although some of the report’s proposals will not be developed until the full report is launched next year, to coincide with the 60th anniversary of the NHS, others—such as access to GP services—will be acted on immediately, said the secretary of state for health, Alan Johnson.

The package of changes to improve access to GPs is “a massive investment in primary care provision and will benefit millions of patients across the country,” Mr Johnson said.

However, Iona Heath, a GP in north London and chairwoman of the Royal College of General Practitioners’ international committee, said that the proposals were a mismatch between what GPs had negotiated with the government in their contract and what was being planned. “The contract excludes GPs from working outside the hours of 8.30 am to 6.30 pm so I don’t see quite how it [the proposed increased access] is supposed to work,” she said.

If the thinking behind longer opening hours was to introduce shifts for GPs then this would destroy the balance between access and continuity, where patients could see the same doctor, said Dr Heath.

Richard Vautrey, deputy chairman of the BMA’s General Practitioners Committee, called for doctors’ leaders to be included in talks about key issues such as access to GPs and infection control.

The interim report is at [www.nhs.uk/ournhs](http://www.nhs.uk/ournhs).
Nobel prize is awarded for work leading to “knockout mouse”

Geoff Watts LONDON

The award of the 2007 Nobel prize in physiology or medicine to three gene technologists has been widely applauded by biologists. They believe that the three scientists’ achievements will play a major part in revealing the extent of genetic influences in human disease.

Rather less enthusiastic is the animal rights lobby. The work for which Mario Capecchi, Martin Evans, and Oliver Smithies were awarded the prize led to the development of the quaintly but aptly named “knockout mouse.” Now an essential tool of laboratory research into the role of genes, its creation reversed a fall in the number of experiments carried out each year on animals.

The Nobel citation talks of the trio’s discovery of “principles for introducing specific gene modifications in mice by the use of embryonic stem cells.” Working independently, Professor Capecchi, of the University of Utah, and UK born Professor Smithies, of the University of North Carolina, showed how such modifications could be brought about by using homologous recombination, the natural process by which our maternally and paternally derived chromosomes are able to swap sections of their genetic material.

The outcome of these exchanges is an increase in the genetic variation in a population, fostering the emergence of new characteristics through which natural selection brings about evolutionary change.

Professors Capecchi and Smithies showed that this recombination mechanism could be exploited to incorporate completely new DNA—new genes, in other words—into a genome. It was work by the third of the trio, Professor Evans, of the University of Cardiff, that allowed this principle to be exploited in the production of genetically modified animals.

Working with stem cells from early mouse embryos, Professor Evans first showed how to grow them in culture. He went on to inject stem cells of one mouse strain into the embryo of a different strain, then implanted the embryo into a surrogate mother. The mice born from this procedure turned out to be a mosaic of cells: some of one strain, some of the other.

He then used a retrovirus able to integrate its own genes into mouse DNA to genetically modify mouse embryonic stem cells. This time the resulting mice were a mosaic of normal cells and of others carrying the viral DNA. Further breeding allowed him to produce mice in which the germ line had been altered, so ensuring that all cells in all their offspring carried the alien genetic material.

In the 1980s the technologies devised by the three researchers were brought together to create animals with specific genetic abnormalities.

The great strength of the new technique lies in the possibility it offers for gene targeting. In essence this involves using a length of DNA to inactivate a particular gene: to “knock it out.” This allows researchers to investigate the effects of single genes.

Commenting on Professor Evans’s contribution, Martin Rees, president of the Royal Society, described the award as fitting recognition for groundbreaking research. “He is a world leader in mammalian genetics, and his research has undoubtedly increased our understanding of human diseases,” said Lord Rees. “Stem cell research has immense potential. It is a field where UK scientists have made pioneering contributions and maintain a powerful presence.”

Scientists welcome ruling on patent on breast cancer gene

Rory Watson BRUSSELS

The European Patent Office has rejected an appeal by the US drug company Myriad Genetics and the University of Utah against an earlier decision revoking the patent concerning the BRCA1 gene and its applications.

The ruling has been welcomed by European researchers working on tests for a predisposition to breast and ovarian cancer. Dominique Stoppa-Lyonnet, head of the genetics department at the Institut Curie in Paris, said: “This is an important decision, since it means we can continue our work without fear of being attacked for infringing a patent.”

The decision is the latest stage in a long running battle between European public health practitioners and the US company. Myriad Genetics was granted the patent in November 2001 and handed over its rights to the University of Utah Research Foundation three years later, while keeping an exclusive licensing agreement.

The patent relates to the BRCA1 gene isolated from the human genome, to mutant forms of that gene, and to its use in diagnosing predisposition to breast and ovarian cancer. Among other things the patent describes diagnostic methods designed to identify mutant forms of the gene and to facilitate early detection of enhanced susceptibility to these forms of cancer.

Soon after the patent was awarded,
Inventors of “gay bomb” and BMJ authors win Ig Nobel prizes

Jeanne Lenzer BOSTON

A novel weapon under investigation by the US Air Force has won this year’s Ig Nobel peace prize. The Ig Nobel awards, given for science that “first makes you laugh, then makes you think,” were given to recipients from five continents by six winners of the actual Nobel prize last week at Harvard University.

The unusual weapon, confirmed by Pentagon sources, is a “gay bomb” [http://blog.washingtonpost.com/offbeat/12 Jun, “Sunshine project uncovers US military ‘gay bomb’”]. The project, which officials say has now been scrapped, was to come up with a device to release unspecified hormones that could be absorbed through the skin or lungs, thereby incapacitating soldiers who—according to the plan—would be too busy swooning over each other in homosexual ecstasy to waste any time dashing about planting roadside bombs.

The Pentagon did not respond to inquiries from the BMJ about possible future plans for its “make love not war” initiative.

Brian Witcombe, a consultant radiologist from Gloucester, won this year’s Ig Nobel medicine prize for his article in the BMJ, “Sword swallowing and its side effects” (BMJ 2006;333:1285-7). Dr Witcombe said: “I was interested in swallowing disorders.”

He accepted the prize jointly with his coauthor, Dan Meyer, a sword swallow from Antioch, Tennessee, who swallowed a 60 cm sword before an awestruck audience at the ceremony. Dr Witcombe said he was surprised that sword swallows use real, not trick, swords.

The biology prize went to Johanna van Bronswijk, of the Eindhoven University of Technology, the Netherlands, for doing a census of “all the mites, insects, spiders, pseudoscorpions, crustaceans, bacteria, algae, ferns, and fungi with whom we share our beds each night.”

The erectile dysfunction drug sildenafil (Viagra) made its first showing at this year’s Ig Nobel ceremony. Patricia Agostino and her colleagues at the Department of Science and Technology at the Universidad Nacional de Quilmes, Argentina, found that sildenafil can alleviate symptoms related to jet lag—in hamsters. In an interview with the BMJ/Dr Agostino’s colleague, Diego Golombek responded to concerns that the erectile side effects of the drug might lead pilots to reach for the wrong joy stick. Dr Golombek said that although his team had yet to conduct clinical trials in humans, he believed that sildenafil might enhance safety in the air, not detract from it, as the drug “speeds up production of cyclic GMP [guanosine monophosphate], allowing faster re-entrainment of circadian rhythms,” so pilots would not be jet lagged.

Government backs down on merger of regulatory bodies

Adrian O’Dowd LONDON

The government has decided not to merge the United Kingdom’s two regulatory bodies in the field of human reproduction and embryo research. But it gave approval for the creation of human-animal embryos (“inter-species embryos”) for the purposes of research into disease, with the agreement of the regulator.

The Department of Health’s previous proposal to merge the Human Fertilisation and Embryology Authority (HFEA) and the Human Tissue Authority (HTA) has been formally dropped.

The decision was announced as part of the government’s formal response last week to a report published in August by a committee (representing both houses of Parliament) that scrutinised the draft bill on human tissues and embryos (BMJ 2007;335:224-5, 4 Aug).

The public health minister, Dawn Primarolo, said there was now a clear way forward for the draft bill, which represented a major overhaul of the law on assisted human reproduction and embryo research. The bill is likely to be included in the Queen’s Speech next month.

Ms Primarolo said the idea to merge the HFEA and the HTA to become a new Regulatory Authority for Tissue and Embryos had been dropped after consultation with stakeholders.

“This bill will allow legitimate medical and scientific use of human reproductive technologies for research to flourish in this country, while giving the public confidence that they are being used and developed sensibly with appropriate controls in place,” she said.

The government’s response is available at the publications and statistics section of www.dh.gov.uk.
IN BRIEF

Bush vetoes children’s health bill: George Bush has vetoed a bill that would have expanded US health insurance coverage to four million uninsured children for five years, at a cost of $35bn (£17bn; €25bn). Democrats and some Republicans in Congress hope to override the veto on 18 October. See p 749.

Chinese doctors agree not to use prisoners’ organs: The Chinese Medical Association has issued a statement agreeing that the use of organs of executed prisoners for transplantation, except for members of their immediate family, should be forbidden. The promise to change current practice comes after years of international condemnation.

Older Dutch people seek help for alcohol problems: Demand for alcohol related outpatient care among Dutch people aged 55 or over has risen by 80% since 1996. In younger groups the rise is 35%. People aged over 55 now account for one in five patients seeking such treatment, data from the National Alcohol and Drugs Information System show. See www.sivz.nl.

Polish doctors strike over low pay: The crisis in Poland’s health system escalated after 2000 doctors resigned this week in protest against low pay and poor working conditions, and a further 1000 doctors staged strikes, ahead of parliamentary elections in three weeks’ time.

Ombudsman upholds complaint by woman who was denied a scan: A woman who was refused funding to undergo a scan of her lungs was had her complaint against Health Commission Wales upheld by the Public Services Ombudsman last week. She had been refused funding to undergo a scan of her lungs has had her complaint against Health Commission Wales upheld by the Public Services Ombudsman.

Pakistan nurses strike over long hours: More than 1000 nurses at the Queen Elizabeth hospital in Lahore staged a 24 hour strike demanding shorter hours. They are working an average of 12 hours per shift, with some working 14 hours.

More US pregnant women are using antidepressants: The proportion of pregnant women in the United States who use antidepressants is now nearly 6.6%. Of 118 935 deliveries between 2001 and 2005, 6.6% of women were prescribed an antidepressant during pregnancy (American Journal of Obstetrics and Gynecology doi: 10.1016/j.ajog.2007.07.036).

UK is failing heavily addicted smokers, college report says

Susan Mayor LONDON

Heavily addicted smokers do not get enough support to help them quit, warns a UK report published last week. It calls for better access to nicotine replacement treatment as part of a harm reduction strategy.

It proposes that a new nicotine regulatory authority be established to oversee all aspects of regulation of nicotine products and to coordinate efforts to end the advantage that cigarettes currently have in the marketplace over alternative products such as gums and patches.

The report, published by the Royal College of Physicians, argues that smokers smoke mainly for the effects of nicotine, that nicotine itself is not especially hazardous, and that providing nicotine in an acceptable and effective form such as cigarette substitutes could save millions of lives. It recommends changing the regulations governing nicotine products so that substitutes are as easy to buy as cigarettes and so that they can provide a higher level of nicotine than is provided by the substitutes currently available.

Current regulatory systems governing nicotine products in most countries, including the United Kingdom, actively discourage the development, marketing, and promotion of substitute products to smokers, the report says. In contrast, cigarettes are relatively unregulated, giving them an unfair advantage in the marketplace.

John Britton, professor of epidemiology at Nottingham University and chairman of the royal college’s tobacco advisory group, said, “Smokers smoke because they are addicted to nicotine, but it isn’t nicotine in cigarette smoke that kills: it’s the hundreds of other toxic chemicals that come with it.”


Bristol-Myers Squibb made to pay $515m

Janice Hopkins Tanne NEW YORK

Bristol-Myers Squibb and its subsidiary Apothecon have agreed to pay more than $515m (£255m; €365m) in a settlement with the US Department of Justice and the Office of the United States Attorney for Massachusetts to resolve allegations involving their drug marketing and pricing practices.

The Department of Justice said in a press release that the “settlement covers a wide assortment of illegal marketing and pricing practices.”

The department said that from about 2000 to mid-2003 Bristol-Myers Squibb made illegal payments to doctors and other healthcare providers to induce them to purchase the company’s drugs. The payments were made in the form of consulting fees and expenses to participate in consulting programmes, advisory boards, and preceptorships. Some of the programmes involved trips to luxury resorts. From 1994 to 2001 Apothecon paid illegal remuneration to retail pharmacies and wholesalers to buy its drugs. The government alleged that in paying this illegal remuneration the company and its subsidiary submitted false and fraudulent claims to the US government healthcare programmes.

The government also said that from 2002 to 2005 Bristol-Myers Squibb promoted its atypical antipsychotic drug aripiprazole (sold as Abilify) for use in children and for treating dementia related psychoses. The drug is approved only for use in adult patients with schizophrenia or bipolar disorder. The company’s sales representatives urged doctors and healthcare providers to prescribe the drug for off-label use in children and in adults with dementia related psychoses in nursing homes.

In addition, the government said that the
**Systematic review shows no evidence that individualised herbal treatments are effective**

Susan Mayor  LONDON

No good evidence exists that individually tailored prescriptions of a mixture of herbs are effective, concludes a systematic review published last week.

The study reviewed all available studies of individualised herbal medicine for any indication (Postgraduate Medical Journal 2007;83:633-7). The researchers, from the Universities of Exeter and Plymouth, found only three randomised controlled trials out of 1300 studies they identified that they considered were of sufficient quality to draw meaningful conclusions. These three trials showed no convincing evidence of benefit.

One trial, involving patients with osteoarthritis of the knee, showed a non-significant trend favouring active treatment over placebo. However, the researchers said that this trend probably resulted from large differences at baseline and regression to the mean.

In a trial of patients with irritable bowel syndrome, individualised herbal treatment was better than placebo in four of the five outcomes tested but was inferior to a standardised herbal treatment (a mixture of herbs not tailored to the individual) in all outcomes.

In the third trial they looked at, individualised herbal treatment was no better than placebo in preventing chemotherapy induced toxicity.

The researchers warned: “Individualised herbal medicine, as practised in European medical herbalism, Chinese herbal medicine, and Ayurvedic herbal medicine, has an extremely sparse evidence base and there is no evidence supporting its use in any indication.

“The paucity of data supporting the effectiveness of individualised herbal medicine, and the important safety concerns associated with this particular form of phytomedicine, should be taken into account by policymakers.”

In an accompanying editorial Edzard Ernst, professor of complementary medicine at the Peninsula Medical School at the University of Exeter, considered that the public was in danger of confusing different types of herbal medicine.

He explained that phyotherapy (plant therapy practised by a health practitioner), which includes use of specific herbs, such as St John’s wort, that contain a range of pharmacologically active ingredients and for which data on effectiveness are “reasonable,” is often confused with traditional herbal medicine, in which practitioners prescribe individual mixtures of herbs and over the counter remedies that are based on plants and sold as dietary supplements.

Professor Ernst argued that properly conducted clinical trials should be carried out as part of improving the regulation of herbal medicines.

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**German pharmacists are investigated for using unregistered drugs in chemotherapy**

Annette Tuffs  HEIDELBERG

More than 100 pharmacies in Germany are being investigated for importing drugs not registered in Germany for use in the preparation of intravenous chemotherapy. Two companies in Denmark and the Isle of Man that import and export drugs are also being investigated.

The district attorney in Mannheim said in a press release that the main charge being considered was one of fraud, because the chemotherapy drugs were bought at low prices abroad but had been illegally sold at the high price of registered drugs in Germany.

The chief financial victims of the alleged fraud seem to be the insurance companies, because they were charged inflated prices. The problem came to light when a health insurance company noticed irregularities in the billing for courses of chemotherapy.

It is not yet known whether patients were harmed. The district attorney said it was possible that fake drugs were used, as well as drugs that were ineffective or did not contain enough of the active ingredient.

Insurance companies have probably lost several million euros, because one course of chemotherapy costs between €15000 (£10000; $21000) and €25000. The German Society of Haematology and Oncology says that about €900m is spent every year on intravenous chemotherapy in Germany. The profit margin for the individual pharmacy preparing the infusion is normally between 10% and 50%.

Of the 21 000 independent pharmacies in Germany, only 300 have a licence to prepare intravenous chemotherapy.
Flu vaccines help older people live longer

**EFFECTIVENESS OF FLU VACCINE**

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Flu vaccines prevent infection in younger adults. But do they prevent illness and death in older people—the largest target group? A large observational study of data from three health maintenance organisations (HMOs) in the US shows that during 10 flu seasons in the 1990s, vaccination of older people was associated with a 27% reduction in hospital admissions for pneumonia or flu (adjusted odds ratio 0.73, 95% CI 0.68 to 0.77) and a 48% reduction in deaths (0.52, 0.50 to 0.55).

The authors considered the possibility that vaccinated people were fitter or looked after themselves better than unvaccinated people, but they found no evidence of a “healthy vaccinee effect.” Benefits were smaller in seasons when the available vaccine didn’t match the circulating strain of virus particularly well. This suggests that the observed effects are real and not simply the result of confounding, says a linked editorial (p 1439).

So flu vaccines work for older people living at home in the US. But they could work better. The immune system weakens with age, and more immunogenic vaccines are needed to compensate, says the editorial. Better coverage would also help. In this study, only 58% of HMO members over 65 were vaccinated.

What’s new in the other general journals

**SHORT CUTS**

**WHAT’S NEW IN THE OTHER GENERAL JOURNALS**

Alison Tonks, associate editor, BMJ atonks@bmj.com

**People with low back pain have a good choice of treatments**

Cognitive behaviour therapy, exercise, spinal manipulation, and interdisciplinary rehabilitation are the best non-drug treatments for low back pain lasting more than four weeks, according to a systematic review. All of them worked better than placebo or sham treatment in randomised trials—they reduced pain and improved function by 10-20%. Acupuncture and a style of yoga called vinyasa yoga may also be helpful, but the evidence isn’t particularly good. Evidence on back schools, interventional therapy, laser treatment, lumbar supports, transcutaneous electrical nerve stimulation, traction, and ultrasonography is even worse, and guidelines based on the review don’t recommend them.

Patients with acute pain (lasting less than four weeks) may get some relief from warming the lower back with a heated pad or blanket, says the review. Spinal manipulation is the next best option, although again the benefits are modest.

Another systematic review by the same authors identified paracetamol and non-steroidal anti-inflammatory drugs as moderately effective treatments for acute and chronic low back pain. The linked guidelines say they are a reasonable first line choice. Most patients can expect a 10-20% improvement in pain. Opioids or tramadol can be useful for people who need stronger pain relief, but there is always a risk of dependence. So use a short course and reassess.

The review reported that muscle relaxants such as tizanidine help relieve acute pain, and tricyclic antidepressants have small to moderate effects on chronic pain. But systemic steroids do not work for anyone.

**Ann Intern Med** 2007;147:492-504; 505-14; 478-91

**Implantable cardioverter defibrillators given more often to men**

Two recent studies showing that women are less likely than men to get an implantable cardioverter defibrillator may be bad news for women, says a linked editorial (p 1564). Alternatively, the findings may be bad news for men, as it is far from clear that these devices improve quality of life or survival in real patients who are older and sicker than the participants of randomised trials.

In one cohort of Medicare beneficiaries (aged over 65) with heart failure or cardiomyopathy, men were twice to three times more likely to be treated with an implantable cardioverter defibrillator than women. But treatment made no difference to their risk of death (hazard ratio 1.01, 95% CI 0.82 to 1.23). These results are troubling, says the editorial, and hard to explain. The authors adjusted their analysis for age, comorbidity, and the probability of treatment.

A second cohort study included patients admitted to hospitals participating in a quality improvement programme. Only a third of eligible patients had an implantable defibrillator by the time they went home. Women missed out, and so did men and women from ethnic minorities.

Health inequalities for women and other groups are not new, says the editorial. But in this case, the usual hunt for root causes should be accompanied by a critical re-evaluation of the role of implantable cardioverter defibrillators in real world practice.

**JAMA** 2007;298:1517-24; 1525-32

**Donepezil fails to reduce agitation in people with dementia**

Memory loss and other cognitive impairments are the hallmarks of dementia. But many patients are also agitated and confused, and these symptoms cause most distress to carers. Few effective drug treatments exist. Donepezil is the latest to fail in clinical trials.

**BMJ** 13 OCTOBER 2007 | VOLUME 335
It had no effect on symptoms of agitation in 272 patients with Alzheimer’s disease living with carers or in care homes in the UK. This double blinded placebo controlled trial lasted 12 weeks. Donepezil helped to slow cognitive decline, but only slightly. The drug made an adjusted difference of only 7 points on the 100 point scale of the severe impairment battery, and only 1.5 points on the 30 point scale of the standardised mini-mental state examination. These small effects may not mean much to patients or their carers.

This trial, and others reporting disappointing results with atypical antipsychotics, leave doctors with few options, says an editorial (p 1441). Non-drug treatments for agitation such as music therapy, aromatherapy, and training for carers may work better, and several guidelines recommend them as a first step. But evaluation is still at an early stage. N Engl J Med 2007;357:1382-92

DNA test outperforms cytology in Dutch cervical screening

Testing for DNA from human papillomavirus is a more sensitive cervical screening tool than traditional cytology. DNA testing picks up more high grade lesions. It also picks them up earlier, according to a randomised trial.

Women in the Dutch screening programme were screened with cytology or with a combination of cytology and DNA testing. Five years later, all the women had both tests done.

As expected, combined testing picked up significantly more high grade lesions than cytology in the first round of screening (68/8575 vs 40/8380; 70% increase, 95% CI 13% to 151%, P=0.007). In the next round, the women in the combined group still had fewer high grade lesions than controls (24/8413 vs 54/8456; 55% decrease, 28% to 72%, P=0.001). DNA testing had allowed earlier detection of persisting lesions, not just those likely to regress spontaneously. The total number of lesions detected was similar in both groups.

Should national screening programmes now add DNA tests to routine cervical cytology? Not yet, say the authors. These results should be verified first, then someone needs to look carefully at costs. But if all goes well, a testing protocol that picks up serious lesions earlier could mean a longer screening interval for women. Lancet 2007 doi: 10.1016/S0140-6736(07)61450-0

Measure blood pressure both day and night

Blood pressure helps predict risk of cardiovascular disease and death, and since the early 1990s doctors have been told that blood pressure measured during the night is a better predictor than blood pressure measured during the day. This may not be true, say researchers.

Pooled data from six cohorts in Europe, Asia, and South America suggest that daytime blood pressure is just as good as night time blood pressure for predicting fatal and non-fatal cardiovascular events. Night time blood pressure and the ratio of night time to daytime blood pressure are good for predicting deaths only. So if you want the full picture, it is important to take measurements for at least 24 hours, say the authors. The blood pressure ratio may not be as useful as many doctors think.

This analysis included more than 7000 adults followed up for nearly 10 years. There were 387 deaths from cardiovascular disease, 420 strokes, and 390 coronary events. So the researchers’ estimates are probably the most accurate so far.

Daytime blood pressure wasn’t a particularly good prognostic indicator in people taking antihypertensive drugs. Perhaps 24 hour measurements should be interpreted differently in this subgroup, says a linked comment (p 1192). Lancet 2007;370:1219-29

Young children living in the southern plains of Nepal are often deficient in zinc. Replacing it had no effect on mortality or infectious illnesses in a large cluster randomised trial, however. More than 20,000 children aged 1-35 months took tablets containing zinc or a placebo for up to three years. Overall rates of death were about the same in each group (316 vs 333 deaths; hazard ratio 0.92, 95% CI 0.75 to 1.12). Diarrhoea, dysentery, and respiratory infections were the most common causes of death. The authors found a suggestion that zinc might reduce mortality in children over 12 months, but the result was not significant (0.80, 0.60 to 1.06). Zinc supplements had no effect on the risk of diarrhoea, dysentery, or respiratory illness in a linked substudy.

Disappointed by their equivocal results, the authors pooled their data with three other large trials from South Asia and Africa. The analysis confirmed their negative findings on overall mortality, but the extra power turned the hint of benefit for older children into a statistically significant result (0.82, 0.70 to 0.96).

It seems likely that extra zinc helps at least some children in some regions, says a linked comment (p 1194). But it is too early to recommend universal supplementation. Lancet 2007;370:1230-9

Zinc supplements don’t save lives in Nepal
New drug approved for age related macular degeneration

Three randomised controlled trials of ranibizumab and two of pegaptanib, involving 1511 patients with age related macular degeneration, have shown that both drugs are beneficial. Patients receiving either drug preserved visual acuity to the extent that they were more likely than controls to be able to live independently, read or watch television, or not deteriorate to legal blindness (acuity 6/60 or less). Adverse events were mild to moderate and short lived, and treatment remained effective after two years.

No head-to-head comparison of the drugs has been carried out, and the five studies are too heterogeneous to enable meta-analysis. The study was commissioned on behalf of the National Institute for Health and Clinical Excellence (NICE), whose preliminary guidance approves prescription of ranibizumab alone, but only for the wet form of the disease. Further guidance is due shortly.


Cannabis is bad for the airways

Cannabis smoking has a dose related deleterious effect on tests of airflow obstruction, large airways function, and hyperinflation. A study of 166 cannabis smokers (of whom 91 also smoked tobacco), 92 tobacco smokers, and 81 non-smokers found that one joint of cannabis has a similar effect on the airways as 2.5-5 cigarettes. However, in contrast with tobacco, cannabis was not found to predispose to emphysema, as judged by computed tomography of the lung.

Thorax 31 Jul 2007, doi: 10.1136/thx.2006.077081

Less chest illness reported in upgraded social housing

Residents in 49 “upgraded” council houses (social housing) in a deprived area reported fewer asthmatic and other chest symptoms than those in 69 control council houses. The council houses had been randomly assigned to being reroofed, rewired, double glazed, better insulated, and fully centrally heated. (The control houses were upgraded the following year.) The authors conclude that it is feasible to conduct randomised trials on such community-wide interventions.

J Epidemiol Community Health 2007;61:771-7

Magnetic resonance imaging can define type of arthritis

In 41 patients with arthritis whose disorder remained unclassified despite conventional clinical, biochemical, and radiological tests, more precise diagnosis proved possible with contrast enhanced magnetic resonance imaging of the hand and whole bone scintigraphy.

Two rheumatologists reviewing the images categorised 13 patients as having rheumatoid arthritis, 8 osteoarthritis, and 11 “other” inflammatory disorders; they were unable to categorise the remaining nine patients. Two years later, 11 of the 13 patients with rheumatoid arthritis fulfilled accepted diagnostic criteria for the disorder, with one being recategorised as having psoriatic arthritis and the other as having self limiting non-specific disease. No patient originally categorised as not having rheumatoid arthritis subsequently developed that condition.

As early treatment of rheumatoid arthritis is considered essential for improved clinical outcome in the disorder, the investigators suggest incorporating their investigative procedures into initial evaluation of unclassified arthritis.


Meningitis impairs memory

Adult survivors of bacterial meningitis are at risk of cognitive impairment. Data from three prospective studies, comparing 155 patients who survived pneumococcal or meningococcal meningitis with 72 matched controls, show impairment in 32% of patients and 6% of controls. Performance was affected across a range of memory tasks and tasks of “attention/executive” function (the speed and fluency of understanding and performing a task such as card sorting) but not tasks involving intelligence or psychomotor function. In general, patients were cognitively slower than controls. The only difference found between causative organisms was a greater risk of memory impairment after pneumococcal disease—these patients tended to be more ill on presentation. No advantage was found in those who had received dexamethasone in the acute stage, and impairment was stable over time.

J Neurol Neurosurg Psychiatry 12 Mar 2007, doi:10.1136/jnnp.2006.110023

Organic pollutants may affect learning

Exposure to persistent organic pollutants, largely ingested from the fat in animal products, has been shown to be associated with learning disability and attention-deficit disorder in children, as reported by parents. Blood levels of the seven most commonly detected persistent organic pollutants were measured in 278 children aged 12-15 from a larger US population survey. Those with high serum concentrations of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans showed about twice the prevalence of learning disability and attention-deficit disorder than those in whom the pollutants were undetectable.

The authors are cautious in ascribing causation as their study was cross sectional, but it is probably the first such study and could imply that in some children, learning disability and attention-deficit disorder may be preventable.

J Epidemiol Community Health 2007;61:591-6
W hat links Parkinson’s disease, exercise intolerance, diabetes, and organ failure in sepsis? Anything common to such a disparate group would need to be quite fundamental, and there aren’t many things more elementary than generating the energy needed to stay alive. This is the job of the mitochondrion—the dynamo of the cell—and recent research indicates that it contributes to a wide range of diseases.

Mitochondria are thought to have started off as free living prokaryotes that were engulfed by the ancestors of modern nucleated cells millions of years ago. One of the features hinting at their previous lives is that they have retained some of their own DNA. Although the role of these tiny intracellular organelles is vital, their relevance to clinical practice has often seemed obscure. Cell biologists worked out how mitochondria make energy four decades ago. Since then medical students have had to trace out how, after a glucose molecule is broken down, electrons from its oxidised metabolites move along a series of mitochondrial membrane bound proteins, building up an electrochemical energy gradient that can be harnessed to make adenosine triphosphate (ATP), the main energy source for cellular reactions. But they have usually struggled to relate this to anything encountered on the wards.

Some clinicians may have encountered one or two of a handful of disorders attributed to mutations in mitochondrial DNA such as the maternally inherited Leber’s hereditary optic neuropathy, which results in degeneration of the optic nerve. But diseases related to such mutations were regarded as rare, affecting perhaps one or two per million in the population, and the province of a few specialists.

Rising from obscurity

This view has now changed, says Doug Turnbull of Newcastle University’s mitochondrial research group. Because almost all tissue types rely on mitochondria to generate energy, genetic disorders causing mitochondrial dysfunction can manifest themselves at any age and in any organ system, often in several. Cells in muscle, the liver, the retina, and the central nervous system all perform highly energy intensive tasks, making these tissues particularly susceptible.

Reviewing epidemiological data, Professor Turnbull and colleagues suggest the minimum prevalence for single gene mitochondrial disorders is likely to be 1 in 5000, placing this among the most common types of human inherited disease.1 “Primary mitochondrial disease is seen to be much more common than previously thought,” he said. “These were rarities that used to be seen by very specialist neurologists, yet the incidence of these abnormalities in the population is much greater than we had previously considered.”

Leber’s hereditary optic neuropathy is the most common single gene mitochondrial disease, and the mutations most frequently associated with it are found in 2% of those registered blind in Australia.2 Researchers have identified more than 100 mutations in mitochondrial DNA that cause disease, and over 130 mutations in nuclear DNA have also been associated with disorders of mitochondrial dysfunction.3

In recognition of the importance of mitochondrial disease, the NHS this year designated three centres in London, Newcastle, and Oxford as referral points for diagnosis and management of these disorders. Since mitochondria and their internal DNA are inherited along the maternal line, and relevant nuclear genes can also be passed on, the centres also provide genetic counselling.

“In terms of clinical practice, our current understanding might make people think more about mitochondrial disease as the cause of the symptoms, and if that turns out to be correct, then they might look at other complications of mitochondrial disease,” Professor Turnbull said. “If you look at somebody who has paralysis of the eye muscles, which is quite a common presentation in patients with mitochondrial disease, if they have mitochondrial disease then they might be at increased risk, say, of developing...
diabetes or cardiomyopathy, and therefore you would try to screen for things which are potentially treatable."

**Role in major disease**

In addition to monogenic disorders, scientists are also discovering that mitochondria have a secondary role in many more diseases. One of the most common, and potentially most important, presentations of mitochondrial dysfunction is diabetes, which is after all a disorder of altered fatty acid and carbohydrate metabolism. How mitochondria contribute to the disease is not entirely clear, but some mutations in mitochondrial DNA are associated with type 2 diabetes, as are some changes in genes regulating mitochondrial biogenesis—the process of organelle growth, maintenance, and replication.

“In many major diseases people are now looking at mitochondria,” said Mervyn Singer, professor of intensive care medicine at University College London. Sepsis is one such area. “You get an excessive amount of inflammation in sepsis, but how do the released cytokines and mediators actually cause the organs to fail? And if the organs fail, how do they then recover? There is minimal cell death, so one way to view organ failure is as a protective mechanism akin to hibernation,” Professor Singer said.

Many changes that occur in acute critical illness switch off mitochondria, such as the release of inflammatory mediators like nitric oxide. “You have many factors conspiring at the same time to inhibit the activity of mitochondria, damage them, or reduce turnover of new mitochondrial protein,” he added. “It all implicates a mitochondrial pathology as being core to the process of organ failure. If the patient gets better, then, if this hypothesis is correct, the mitochondria must start functioning to provide the necessary energy for normal metabolic processes.”

He points out that antibiotics are among the most potent inhibitors of mitochondrial biogenesis. Perhaps this is hardly surprising considering the organelle’s prokaryotic origins, but he adds that perhaps this means the way infections are treated may also be delaying recovery. “From a sepsis point of view we have made relatively minimal inroads into treating patients with new drugs in the last 20 years.

“We are sorely in need of completely new therapeutic paradigms. What excites me is that if we can target either factors causing damage to mitochondria, or perhaps encourage their earlier activation or regeneration, the affected organs may start functioning sooner. This would undoubtedly save lives, improve morbidity, and shorten stay, all crucial goals worth aiming for.”

Mitochondria have also turned out to be central to the process of programmed cell death. Failure of this process is important in cancer, and researchers are looking at ways that mitochondrial dysfunction may be involved in tumour development. And because mitochondria generate energy, it is unsurprising that mutations in their DNA have a role in exercise intolerance. Changes in genes coding for membrane bound proteins that transport electrons in the mitochondria have been associated with extreme and premature muscle fatigue.

Another factor that has turned researchers’ heads towards mitochondria is the realisation that molecular damage from reactive oxygen radicals is important in the pathogenesis of a huge range of disorders. With their chain of oxidation reactions, mitochondria are the main source of oxygen radicals in the cell. Damage to mitochondria from oxygen radical production may hold the key to a whole group of neurodegenerative diseases, such as Parkinson’s disease, says Auckland based neurologist Barry Snow.

“Until recently we really had a great deal of difficulty understanding the pathogenesis of these diseases,” he said. “We still don’t know what causes them, but there is a strong feeling that there must be a common process in these diseases. There is a common pattern—they are more common in older people, have a gradual progression, a lack of overt inflammation—and gradual mitochondrial failure actually fits all those criteria very nicely.”

Dr Snow is running a phase II clinical trial of an antioxidant drug that is designed to accumulate in mitochondria and protect them from damage from oxygen radicals. There is some evidence that antioxidants are depleted in mitochondria in neurodegenerative diseases, and one small trial found that an untargeted antioxidant, coenzyme Q10, helped slow the progression of Parkinson’s disease.¹

The interior of a mitochondrion has a strong negative charge, however, making it difficult for antioxidants to enter. The drug in the trial, called MitoQ, combines the antioxidant activity of coenzyme Q10 with a positively charged domain to help it get into the mitochondrion. Dr Snow’s trial has recruited 128 patients who have recently had Parkinson’s disease diagnosed but who are not yet receiving drug treatment for symptoms. He is following them for a year to see whether the disease progresses more slowly in those taking MitoQ. “It is hard to prove, but all the circumstantial evidence points towards oxidative damage in mitochondria being involved in Parkinson’s disease. And in the early onset familial forms of Parkinson’s, which are very rare but point to aspects of the mechanism, a lot of those mutations turn out to be in mitochondrial proteins,” said Michael Murphy, leader of the mitochondrial dysfunction group at the Medical Research Council Dunn Human Nutrition Unit at Cambridge University, who was involved in designing MitoQ.

“If it works then it would be the first time anyone has successfully targeted mitochondrial oxidative damage in a disease. That would be quite an interesting breakthrough,” said Dr Murphy. “Oxidative damage seems to be involved in a wide range of diseases, so if it worked in one the same approach might work in heart damage or liver damage or whatever. Even in things like sepsis we might expect it to work.”

Successful treatments targeting mitochondria are still some way away, and Professor Turnbull emphasises that the main clinical application of the growing appreciation of their importance in disease is a higher profile for mitochondrial disorders. “It is really about awareness of these diseases, and being aware that there are other potential complications or potentially important genetic implications of establishing a diagnosis,” he said. “The research directing understanding about the mitochondria and about the patients is leading directly to ideas about ways in which we might target treatment for patients with mitochondrial problems. We are much more hopeful about things than we were before, but we still have a very long way to go.”

**Competing interests:** None declared.

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After the demise of President Bill Clinton’s health reform plan in 1994, I posed for readers of JAMA (1997;278:1446-7) this question: “As a matter of national policy, and to the extent that a nation’s health system can make it possible, should the child of a poor American family have the same chance of avoiding preventable illness or of being cured from a given disease as does the child of a rich American family?”

That question has long been answered in the affirmative in most other industrialised nations. In the United States it evokes irritation. Of the several letters triggered by my question, all but one were from physicians. None of them answered the question but instead attacked me as a socialist “with the ancient propagandistic use of children.” Only one letter, penned by Richard A Epstein, a law professor at the University of Chicago, addressed my question head on, with a resounding “no.” He argued: “His [Reinhardt’s] proposal for equal treatment perversely requires more care to children of poor parents than to children of rich ones, precisely because the rich families can more easily avoid injury and illness and can better pick up any slack in health care delivery.” Not one letter answered my question in the affirmative.

Unlike citizens of other nations, Americans have never been able to decide whether children are a national treasure for whose welfare the state should take primary legal and financial responsibility—or are more in the nature of human pets who are owner, so to speak, by their parents and for whose welfare the parents should take primary legal and financial responsibility—albeit within a legal framework that strictly prohibits the maltreatment or egregious neglect of either children or animals. Unable to settle that question, Americans naturally have trouble also settling the question I raised in JAMA.

These issues come to mind on the day President George W Bush has vetoed a bill that would extend health insurance coverage under the State Children’s Health Insurance Program (SCHIP) (News in Brief doi: 10.1136/bmj.39363.548715.DB).

That programme is administered and partially funded by the states, although the federal government funds 70% of a state’s spending on SCHIP, up to an annual cap that varies by state. The programme had originally been enacted in 1997 to extend insurance coverage to near poor children—those in families with incomes above 133% of the federal poverty line, the threshold for coverage by the Medicaid federal health insurance programme for poor people. Since that time SCHIP has had an important role in reducing the number of uninsured children in families below 200% of the poverty line, although anywhere between five and eight million children remain uninsured, depending on whether that status is defined as “uninsured for the entire past year” (about five million) or uninsured at the time of a survey (the higher figure).

SCHIP formally expired on 30 September. There has been general agreement that it would be extended for another five years. The political battle has been mainly over the level of federal funding that would be authorised for the next half decade.

Congress, controlled by the Democrats, had sent the president a bill authorising an additional $35bn (£17bn; €25bn) of federal funds for the next five years, on top of the $25bn baseline budget for a mere five year extension of the existing programme. This would allow the states to expand the programme to include children in families above the 200% threshold. To put this increase in perspective, the president’s total budget request for the 2008 fiscal year is $2.9 trillion; the budget request for the Iraq and Afghanistan wars for the same year is $190bn.

President Bush had proposed a budget increase of only $1bn a year ($5bn over the next five years). The Congressional Budget Office has estimated that at traditional rates of inflation of healthcare costs, this increase would not even have maintained current enrolment levels. Arguing that “poor kids should come first,” the president would require states to enrol at least 95% of children in families living below 200% of the federal poverty line before permitting the use of federal funds for any expansion of SCHIP above the 200% threshold—a target that most states would probably not be able to meet. Finally, in vetoing the bill the president remarked, “I believe in private medicine, not the federal government running the healthcare system.”

The battle over SCHIP is a classic US health policy debate in which seemingly technical jargon such as “crowding out” private insurance, arguments over the relative “efficiency” of private versus government medicine, and endless body counts on the number of children actually without health insurance camouflages much deeper and chronic ideological divisions.

When I wrote my commentary for JAMA a decade ago I was not at all seeking to use children as a tool of socialist propaganda. Rather, I sincerely—and naively, it turns out—believed that Americans could at least settle on the distributive ethic that should govern health care for the US children who are effectively disenfranchised. Alas, Americans cannot agree on the role of children in their society, from conception through to adulthood, let alone on their children’s right to health care. Thus the kids must muddle through as usual—through the ideological muddle of the nation’s adults.

Uwe E Reinhardt, professor of political economy, Princeton University, Princeton, NJ, United States reinhard@princeton.edu
Head to head

Should young people be given antidepressants?

Andrew Cotgrove, clinical director, Pine Lodge Young People’s Centre, Cheshire and Wirral Partnership NHS Foundation Trust, Chester CH2 1AW andy.cotgrove@cwpt.nhs.uk

Yes

Depression and obsessive-compulsive disorder cause considerable distress in young people. These disorders affect emotional, educational, and social development. To deny these vulnerable groups the possibility of receiving antidepressants would be to withhold one of the few evidence-based treatments available to them.

There are genuine reasons to question their use. Nevertheless, the evidence indicates that the benefits of these drugs outweigh the risks when used in the appropriate clinical context. I shall focus on the use of selective serotonin reuptake inhibitors (SSRIs) because this is the group of antidepressants for which the evidence in young people is strongest and it is the use of these drugs in depression that has been most controversial.

Quality of evidence

The criticisms of research into SSRIs include an exaggerated reporting of efficacy, selective reporting of measures, short follow-up periods, poor reporting of adverse effects, and underplaying the large placebo effects. Participants were mostly recruited by advertising and self-referral and common comorbidities, including suicidality, were excluded. In the first half of the decade there was also selective publication of studies with more positive results.

However, objective meta-analysis of the studies shows a significant benefit over placebo for some SSRIs. It is not surprising then that the Medicines and Healthcare Regulatory Authority and the National Institute for Health and Clinical Excellence (NICE) both concluded that SSRIs can be used for the treatment of depression in young people. Recent studies without many of the earlier methodological flaws—for example, the adolescent depression antidepressant and psychotherapy trial (ADAPT)—have added further evidence to support the use of SSRIs in treating depression.

Risks and benefits

So, if the drugs work, what about the risks? Earlier publications tended to play down the risks, particularly that of increased suicidality. When this came to light there was an understandable flurry of adverse publicity. However, a meta-analysis that included previously unpublished studies showed the benefits outweighed the risks, at least for fluoxetine.

A more recent meta-analysis confirms an increase in suicide related events in young people with depression taking SSRIs compared with placebo, but the difference is small (4.8% vs 3%) and there have been no suicides in any of the studies to date. Two studies found a decrease in suicidality with fluoxetine during treatment. Overall, although there is an increase in suicidality, the risk is small and can be reduced further by careful monitoring.

Evidence for other treatments

Are there other treatments for depression in young people that make the use of antidepressants unnecessary? There is some evidence for the efficacy of psychological treatments such as cognitive behaviour therapy, interpersonal therapy, and family therapy, but the effects are small. The treatment for adolescents with depression study (TADS) suggested that cognitive behaviour therapy alone was no different from placebo and was a significantly poorer treatment than SSRIs alone. NICE, partly in consideration of evidence from TADS that suggested cognitive behaviour therapy combined with SSRIs reduced suicidal behaviour, supported the use of psychological therapy as first treatment of moderate or severe depression but was clear that fluoxetine should be offered if the young person does not respond.

Two studies reported since the publication of the NICE guideline have shown no benefit for combined treatment over SSRIs alone. In patients with moderate to severe depression ADAPT found no added value in combining cognitive behaviour therapy with fluoxetine. These studies support the case for fluoxetine alone being the treatment of choice for more severe depression.

Obsessive-compulsive disorder

Antidepressants are also used to treat obsessive-compulsive disorder. NICE included 14 randomised controlled trials in its analysis of the efficacy of SSRIs for obsessive-compulsive disorder in young people. It concluded that the evidence supported the use of SSRIs and recommended fluvoxamine or sertraline, which have been licensed for this disorder. It found no significant increase in suicidal behaviour, but, because of remaining uncertainty about risk, recommended cognitive behaviour therapy as the first line treatment. NICE also recommended the use of the tricyclic antidepressant clomipramine if SSRIs are ineffective.

Informed choice

Worrying methodological errors, publication bias, and omissions of evidence in the conduct and reporting of some SSRIs trials have rightly alarmed the medical profession and the public. However, careful and objective review of the evidence shows that antidepressants have a place in treating young people with depression or obsessive-compulsive disorder. Parents and young people need to be told the risks and benefits, given advice, and be supported in choosing an evidence-based treatment. Removing antidepressants from this choice would take away one of the few potentially effective interventions for these disabling conditions.

Competing interests: None declared.

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BMJ | 13 OCTOBER 2007 | VOLUME 335
Depression is disabling a growing proportion of children, but evidence on treatment is disputed. **Andrew Cotgrove** believes drugs are a vital part of the armoury but **Sami Timimi** is unconvinced that they are helpful or safe.

**NO**

The medical profession had endorsed the use of selective serotonin reuptake inhibitors (SSRIs) well before any of the big studies in children were published.¹ Now that studies have been done, the evidence is clear: the drugs are not effective in young people and can increase suicidal behaviour. Continuing to use SSRIs in young people is not good value for money, dangerous, and ethically unsound.

It is well established that tricyclic antidepressants are not effective for childhood depression.² The evidence suggests SSRIs are no better. None of the studies on SSRIs for childhood depression have, on outcome measures reported by patients or parents, showed significant advantage over placebo.³ No data regarding rates of self harm, presentations to emergency or mental health services, or school attendance were presented in any of the studies, leading the reviewers to conclude that investigators exaggerated the benefits and downplayed the dangers of SSRIs for children. A subsequent systematic review found that unpublished trials showed that newer antidepressants were even less effective and more harmful for children than suggested by the published trials.⁴

Despite this, one antidepressant, fluoxetine, was spared. National guidelines concluded that it was the only antidepressant with a favourable balance of benefit over risk.⁵ Given its similar pharmacological properties, there is no theoretical reason why fluoxetine should have a significantly different profile from other SSRIs; and indeed it doesn’t. The treatment of adolescent depression study (TADS)⁶ is the most influential study backing fluoxetine and provides a good example of how the publicity does not match the published findings.

**Misrepresentation**

The investigators claimed to show an advantage for fluoxetine, especially when combined with cognitive behaviour therapy. However, the way they reported their data was flawed.⁷ The study included a double blind comparison of fluoxetine against placebo and an unblinded comparison between cognitive behaviour therapy alone and fluoxetine with cognitive behaviour therapy. The lack of patient blinding and placebo control in the last two groups is likely to exaggerate the benefit seen in participants receiving fluoxetine with cognitive behaviour therapy because they had more face to face contact and knew (as did their doctors) that they were not receiving placebo. Furthermore, the poor response in the group receiving only cognitive behaviour therapy is inconsistent with other published studies, raising questions about the quality of the psychotherapeutic intervention in this study.⁸

Comparing results across all four groups is therefore misleading. The valid finding from the study is the lack of a statistical advantage for fluoxetine over placebo on the primary end point, the children’s depression rating scale. Despite the exclusion of known suicidal behaviour, the study found a trend to more suicidal behaviour (six attempts in the fluoxetine groups versus one in the no fluoxetine groups). This result is consistent with that of other trials of SSRIs. Putting together that result with the lack of clinically important advantage over placebo on most measures and similar findings in the previous studies comparing fluoxetine and placebo,⁹ the profile for fluoxetine is similar to that of all other SSRIs—it has little efficacy and is potentially dangerous.

However, we should spare a thought for the beleaguered doctor. Given the high placebo response, many doctors will see improvements after prescribing an antidepressant for a young person in distress and subsequently attribute improvements to the drug. This high placebo response may thus reinforce prescribing, and it has been difficult for many doctors faced with a distressed young person to accept that SSRIs may be ineffective.

**Role of journals**

Distorted reporting hasn’t helped this situation. Major medical journals have published papers on antidepressants for children in which the message (affirmations of efficacy and safety) is at odds with the reported outcomes (of no statistical significance, dubious clinical importance, and increased rates of suicidal behaviour). Thus many of the abstracts do not mention lack of significance on the primary measures. Others such as the recent adolescent depression antidepressant and psychotherapy trial (ADAPT)¹⁰ didn’t even include a placebo arm, giving the (false) impression that SSRIs have already been shown to be more effective than placebo.

Marketing spin has taken precedence over scientific accuracy. One reason for doing the studies in the first place was to justify well established prescribing patterns. It created a trend which has become difficult to reverse despite the evidence. But reverse it we must, as it is neither value for money nor clinically useful, may have resulted in a small but tragic number of avoidable suicides, and contributed to a trend of inappropriately medicalising common emotional states and experiences.¹¹ Most states of childhood distress are self limiting and do not require extensive intervention, but when intervention is necessary psychotherapy has a well established record of effectiveness.¹²

**Competing interests:** None declared.

**References** are on bmj.com

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**WHERE DO YOU STAND ON THE ISSUE?**

**Tell us on bmj.com**
Use and misuse of preimplantation genetic testing

Detection of genetic diseases before implantation for couples at risk helps ensure healthy children, but testing for aneuploidy does not improve the chances of live birth in normal infertile women, say Peter Braude and Frances Flinter

A randomised trial in the New England Journal of Medicine has rekindled the acrimonious debate about the efficacy and appropriateness of testing for chromosomal imbalance (aneuploidy) before implantation in older infertile women having in vitro fertilisation. These women have such a poor prognosis of having a child by in vitro fertilisation that many will latch on to any promise that might improve their odds. This is the second randomised trial that shows no benefit from preimplantation genetic screening, yet advocates are unwilling to accept the findings. We examine the place of genetic testing of embryos in modern medical practice and possible future uses.

Preimplantation diagnosis

Preimplantation genetic diagnosis (PGD) was developed as an alternative to prenatal diagnosis and possible termination of an affected pregnancy for couples at risk of passing on a serious genetic disease to their children. It has an important place in preventing transmission of inherited conditions where the child has a high risk of dying early (such as spinal muscular atrophy), of severe mental or physical disability (such as unbalanced chromosome translocations), or of diseases such as Duchenne muscular dystrophy or cystic fibrosis that develop in childhood and shorten lifespan. In some cases the effect of the disease is so severe that it results in repeated early miscarriage (chromosome imbalance) or later fetal, neonatal, or infant death. Each of these conditions can be detected before implantation, provided the mutation within the relevant gene is known, through the family tree, or the specific chromosomal rearrangement has been identified.

The technique was developed in the United Kingdom in the late 1980s and first used to avoid transmission of adrenoleucodystrophy and X linked mental retardation. Embryos were generated in vitro from couples who were generally fertile but had an affected child or a family history suggesting they were at high risk of an affected child. DNA was extracted from the single cell, amplified by the polymerase chain reaction, and tested for the specific mutation or, in the case of a sex linked disease, the presence of a Y chromosome associated genetic sequence (fig 1).

The development of fluorescence in situ hybridisation (FISH), allowed specific chromosomes to be identified under the microscope, making sex selection simpler, and also enabled identification of embryos carrying unbalanced forms of translocations and other chromosome rearrangements.

The latest development in preimplantation genetic diagnosis is embryo haplotyping. This process allows the identification of a chromosome in the embryo that is likely to be carrying an inherited disorder through knowledge of the pattern of closely linked markers in an affected child or other family members. The main advantage of embryo haplotyping is that it does not require precise details of the mutation to be known, only which gene is implicated and the pattern of its inheritance in the family. This makes the development of a specific test for a disease faster and the diagnosis from a single cell biopsy more secure. It has superseded sex selection for couples at risk of having a son with a sex linked disorder because unaffected male embryos can be identified easily and considered for transfer.

Despite its use for over 15 years, relatively few centres offer preimplantation diagnosis, and many

<table>
<thead>
<tr>
<th>Condition</th>
<th>No of pregnancies/oocyte retrieved (%)</th>
<th>No of pregnancies/embryos transferred (%)</th>
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<tr>
<td>Chromosomal rearrangements*</td>
<td>62/404 (15)</td>
<td>62/234 (26)</td>
</tr>
<tr>
<td>Autosomal dominant disorders†</td>
<td>88/517 (17)</td>
<td>88/385 (23)</td>
</tr>
<tr>
<td>Sex linked disorders‡</td>
<td>120/635 (19)</td>
<td>120/483 (25)</td>
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<tr>
<td>Autosomal recessive disorders§</td>
<td>161/669 (24)</td>
<td>161/561 (29)</td>
</tr>
</tbody>
</table>

*Reciprocal and robertsonian translocations.
†Myotonic dystrophy, amyloid polynuropathy, adenosomatus polyposis coli, Charcot Marie Tooth disease, achondroplasia, Marfan syndrome.
‡Duchenne muscular dystrophy, haemophilia, fragile X syndrome, etc.
§Cystic fibrosis, β thalassaemia, sickle cell anaemia, spinal muscular atrophy.

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Accepted: 17 August 2007

Fig 1| Single blastomere being removed from 8 cell, day 3 embryo for preimplantation genetic diagnosis

This article was printed on bmj.com on 6 September 2007: http://bmj.com/cgi/doi:10.1136/bmj.39314439491.AD
of these send samples away for analysis rather than testing themselves. In the UK, there are now four centres with their own laboratories in London, one in Nottingham, and one in Glasgow, each doing 5-150 cases a year.

Success of preimplantation diagnosis

European data show that the chance of a successful outcome after preimplantation diagnosis depends on the type of genetic condition—whether it is autosomal recessive or dominant, sex linked, or a chromosome rearrangement (table 1). This is because the proportion of embryos likely to be unaffected varies with the inheritance of the disorder.

Since most couples who have preimplantation diagnosis are fertile, it had been thought that the pregnancy rates would be higher than when in vitro fertilisation is used for infertility. However, that assumption has not been substantiated. This is not really surprising, since not only do the embryos available for transfer have to survive the biopsy with good morphology but they must also be free of the genetic disorder. This requirement for the coincidence of two factors reduces the number of embryos suitable for transfer, and in many cases there may be none.

Success is most strongly related to the number of embryos available for biopsy, which in turn is related to the number of good quality eggs obtained after gonadotrophin stimulation, and this declines as the woman gets older. If suitable embryos are available for transfer, clinical pregnancy rates are around 25% regardless of the pattern of inheritance, although some clinics report higher successes than this. Data are not yet available on the number of live births per cycle attempted, which would take into account the likelihood that because of age or other factors, patients may not even get to egg collection.

Preimplantation genetic screening (PGS)

The age related decline in the chances of a live birth after fertility treatment with in vitro fertilisation is related to the decline in the number and quality of eggs. The chances of conception can be restored almost totally by using donor eggs from young women (fig 2). Since sporadic aneuploidy rises with maternal age it was proposed that the use of fluorescence in situ hybridisation to screen embryos for common aneuploidies (chromosomes 13, 16, 18, and 21) in older women would improve the outcome of in vitro fertilisation. As a consequence, preimplantation genetic screening for aneuploidy in women who have repeated failure of in vitro fertilisation or repeated miscarriage has become the most common use of embryo biopsy.

Despite the wide application of screening in patients who are desperate for a successful pregnancy, especially in the United States, until recently it has not been properly validated. Two recent randomised trials found no improvement in the chances of live birth per cycle started; one even showed a reduction. In part this is explained by the fact that embryo biopsy inevitably reduces the number of embryos available for transfer: some do not survive, test results may be unclear, and mosaicism between embryo cells may result in some normal embryos being identified as unsuitable for transfer.

Proponents of screening are reluctant to accept these findings, finding fault with the trials’ methods and criticising the clinics’ ability to perform biopsy. However, a technique that only works in certain enthusiasts’ hands and cannot be translated for general use may have little to recommend it.

Furthermore, those units have not conducted properly controlled studies to show that screening does improve outcome in their hands or which groups of patients benefit. Until then, the widespread use of this expensive technology (an additional £2000–£4000; €2880–€5760; $4000–$8000) by in vitro fertilisation centres is arguably unethical.

Inequity of access

Funding for fertility treatment in the UK is in a state of turmoil with the eligibility rules for receiving support varying widely. Unfortunately, preimplantation genetic diagnosis has been caught up in the rationing of funding for fertility treatment, as many primary care trusts do not appreciate the difference between the use of in vitro fertilisation to overcome infertility and its use in fertile couples to avoid the birth of a child with a serious genetic disorder. An innovative arrangement has been achieved in southeast England, where a consortium, informed by a committee of experts, advises on the appropriateness of a request for NHS funding, taking into account the patient’s circumstances, the severity of the disorder, and their prospects for success. The consortium generally recommends providing two treatment cycles to couples with a reasonable chance of success—that is, if the woman is younger that 40 at the time of referral and does not already have an unaffected child, which is in line with advice from the Genetics Commissioning Advisory Group.

Since requests for funding for preimplantation diagnosis are likely to be infrequent, extension of such an arrangement across the UK would help achieve equity and would avoid the understandable confusion with infertility treatment. Better still would be the institution of a national policy and funding through the NHS National Commissioning Group.
**SUMMARY POINTS**

Preimplantation genetic diagnosis can avoid transmission of serious genetic disease. Funding of preimplantation genetic diagnosis needs to be separated from infertility treatment. Decision making is likely to grow as technology allows more diseases to be detected. Evidence is lacking that screening for aneuploidy improves the success of in vitro fertilisation in older infertile women.

**ANALYSIS**

**Future use**

Preimplantation genetic diagnosis is about to change dramatically. Improvements in molecular technology and greater understanding about genetic causes of serious medical disorders will change the referral pattern of couples seeking testing. Until now, it was thought reasonable to limit the use of preimplantation diagnosis to disorders for which prenatal diagnosis was already generally accepted. Future use is likely to expand into areas such as the exclusion of embryos with genes that predispose to adult onset disorders, for which requests for prenatal diagnosis are more unusual. Some people with a genetic predisposition for certain cancers may choose to have preimplantation diagnosis despite the variable penetrance, lethality, and age of onset, and this may even become the largest indication for referral.

As the success rate improves and the repertoire of diseases for which tests are available increases, the number of couples and their offspring who could benefit from preimplantation diagnosis will rise greatly. It will be especially valuable for couples who benefit from preimplantation diagnosis despite the variable penetrance, lethality, and age of onset, and this may even become the largest indication for referral.

We thank Paul Scriven, Caroline Mackie Ogilvie, Alison Lashwood, and Yaloub Khalaf for helpful comments.

**Competing interests:** None declared.

**Contributors and sources:** PB is head of the department of Women’s Health at King’s College London; He is a member of the Human Fertilisation and Embryology Authority and chair of the scientific advisory committee to the Royal College of Obstetrician and Gynaecologists; FF is a member of the Human Genetics Commission, and has been active in the preimplantation genetic diagnosis centre at Guy’s and St Thomas’ since its inception.

**Provenance and peer review:** Commissioned, externally peer reviewed.


**CORRECTIONS AND CLARIFICATIONS**

**Should folic acid fortification be mandatory? Yes**

In both the print and web versions of this Head to Head article by Nicholas J Wald and Godfrey P Oakley (BMJ 2007;334:1252, 16 Jun) the word “deficiency” appears unnecessarily in the discussion of whether folic acid exacerbates B-12 deficiency. The relevant sentence should read: “...high dose folic acid can reverse the arrest of DNA synthesis that causes a B-12 macorcytosis [not B-12 macrocystosis deficiency],”

Also, during editing for the print version, several headings were omitted; readers are advised to consult the full version on bmj.com, which includes headings stating the four concerns that the article rebuts: that folic acid may exacerbate B-12 deficiency; that folic acid may make B-12 deficiency worse; and that folic acid is a form of folate that does not occur in nature.

**Eczema in pregnancy**

A series of unfortunate events during the typesetting of this Practice article by Sophie Weatherhead and colleagues led to the affiliations of two of the authors getting mixed up in the print version (BMJ 2007;335:152-4, 21 Jul). Their correct details are: Stephen C Robson, professor of fental medicine, Uterine Cell Signalling Group, Institute of Cellular Medicine; and Nick J Reynolds, professor of dermatology, Dermatological Sciences, Institute of Cellular Medicine, Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne. The email address for Professor Reynolds, the corresponding author, is correct.
Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis

Elaine W-T Chong, PhD candidate; Tien Y Wong, professor of ophthalmology; Andreas J Kreis, ophthalmology fellow; Julie A Simpson, senior lecturer; Robyn H Guymer, associate professor of ophthalmology

ABSTRACT
Objective To evaluate the effectiveness of dietary antioxidants in the primary prevention of age related macular degeneration (AMD).

Design Systematic review and meta-analysis.

Data sources Search of seven databases without limits on year or language of publication, and retrieval of references in pertinent reviews and articles.

Methods Two reviewers independently searched the databases and selected the studies, using standardised criteria. Randomised clinical trials and prospective cohort studies were included. Of the 4192 abstracts initially identified, 12 studies (nine prospective cohort studies and three randomised clinical trials) met the selection criteria and were included. Data extraction and study quality evaluation were independently reviewed, using standardised criteria. Results were pooled quantitatively using meta-analytic methods.

Results The nine prospective cohort studies included 149,203 people, with 1878 incident cases of early AMD. The antioxidants investigated differed across studies, and not all studies contributed to the meta-analysis of each antioxidant. Pooled results from prospective cohort studies indicated that vitamin A, vitamin C, vitamin E, zinc, lutein, zeaxanthin, α carotene, β carotene, β cryptoxanthin, and lycopene have little or no effect in the primary prevention of early AMD. The three randomised clinical trials did not show that antioxidant supplements prevented early AMD.

Conclusions There is insufficient evidence to support the role of dietary antioxidants, including the use of dietary antioxidant supplements, for the primary prevention of early AMD.

INTRODUCTION
Age related macular degeneration (AMD) is the leading cause of severe visual loss in people aged over 50 in the developed world. Early AMD is characterised clinically by yellow deposits known as drusen and changes in pigmentation of the retina. Late AMD develops when there is an ingrowth of new blood vessels that bleed into the subretinal space (exudative or “wet” type) or when the macula atrophies (geographic atrophy or “dry” type). Both these conditions usually lead to severe loss of central vision. The pathogenesis of AMD is unclear; older age, genetic markers, and cigarette smoking are the only risk factors consistently reported. Although new treatments have emerged, they are suitable only for the small proportion of people with “wet” AMD. No treatments are available for the “dry” form, and there is little to offer for the primary prevention of AMD in older people.

Dietary antioxidants have long been suggested as useful for preventing the development and progression of AMD. The retina, with its high oxygen content and constant exposure to light, is particularly susceptible to oxidative damage. A large randomised clinical trial, the age related eye disease study (AREDS), showed that patients with intermediate AMD treated with high dose antioxidant supplements (vitamins C and E, zinc, and β carotene) had a 28% reduction in the risk of progression to advanced AMD compared with placebo (odds ratio 0.72, 99% confidence interval 0.52 to 0.98). That study did not specifically examine whether antioxidant supplements were effective for the primary prevention of early AMD in people without signs of this condition.

Because oxidative damage could cause drusen to form, antioxidant supplements may be beneficial in the earliest stage of AMD. Randomised control trials and observational studies have been conducted in well nourished Western populations, but evidence of the role of dietary antioxidants as a primary preventive measure for AMD remains unclear. Some studies indicate that diets rich in antioxidants may protect against the development of signs of early AMD, and the common perception is that a diet rich in antioxidants can protect against AMD.

We performed a systematic review and meta-analysis of the role of a range of dietary antioxidants—vitamins A, C, and E; zinc; lutein and zeaxanthin; α carotene; β carotene; β cryptoxanthin; and lycopene—in the primary prevention of AMD. We considered only randomised clinical trials and prospective cohort studies for inclusion.

METHODS
Data sources We conducted a systematic review of seven databases, including PubMed (1950 to February 2007), Web of
Articles identified through seven databases (n=4192)

Articles and abstracts excluded on the basis of title and abstract (n=4103)

64 articles and 25 abstracts retrieved for detailed evaluation
85 English
4 other language (translated to English)

54 studies and 23 abstracts excluded
- 6 RCT (and 4 abstracts) on AMD progression
- 8 RCT (and 4 abstracts) AMD not outcome measure
- 1 cohort study (and 3 abstracts) did not evaluate specific nutrients of interest
- 1 duplicate abstract
- 24 non-dietary (serum) exposures
- 1 retrospective cohort study
- 4 (and 4 abstracts) case control studies
- 10 (and 7 abstracts) cross sectional studies

Final: 10 studies and 2 abstracts evaluated
- 8 cohort studies (and 1 abstract)
- 2 RCT (and 1 abstract)

Fig 1 | Flow chart of study selection process

Science (1900 to February 2007), Embase (<1966 to February 2007), Medline (1950 to February 2007), Cochrane library (including the Cochrane Central Register of Controlled Trials, 1800 to February 2007), abstracts from the Association for Research in Vision and Ophthalmology (ARVO; 1962 to February 2007), and the National Institutes of Health clinical trial databases31 (up to February 2007).

Systematic search of these databases used the terms “diet or nutrition or supplement* or carotenoids or antioxidants or trace elements or trace minerals or vitamin* or zinc or selenium or iron or copper or lutein or zeaxanthin or beta carotene* or carotenoids or or carotenoids or carotenoids or lycopene or vegetables or fruits” and “age-related macular degeneration or age related maculopathy or macular degeneration or retinal degeneration or drusen or choroidal neovascularization or geographic atrophy”. The search strategy used both keywords and MeSH terms. No limits were placed on the year or language of publication. All articles in other languages were translated to English. References identified from bibliographies of pertinent articles or books were also retrieved.

Studies and participants

Randomised control trials and prospective cohort studies evaluating dietary antioxidants or antioxidant supplements in the primary prevention of AMD (that is, no disease to early or late AMD) were considered for inclusion. We specifically excluded studies in which all participants had early AMD, as these studies evaluated antioxidants for secondary prevention of AMD (progression of early to late AMD).

For studies to be included, five criteria needed to be met: a clear definition of exposure (dietary intake of vitamin A, vitamin C, vitamin E, zinc, lutein and zeaxanthin, α carotene, β carotene, β cryptoxanthin, lycopene); participant follow-up for one year or longer; clear definition of AMD as the outcome; appropriate statistical techniques to adjust for key potential confounders (for example, age and cigarette smoking); and estimates of odds ratio, relative risk, or the primary data to calculate these ratios. In studies that did not present an odds ratio or relative risk comparing highest to lowest fifth or fourth of intake, we contacted authors for this information.41 w4

Outcome measures

The primary study outcome was early AMD (defined as soft drusen with or without retinal pigmentary changes), and late AMD (wet or dry AMD) was the secondary study outcome.

Selection of studies

Two reviewers (EW-TC and AJK) independently searched the seven databases, which included grey literature (unpublished work with limited distribution, such as conference abstracts; excluding grey literature that meets the pre-specified inclusion criteria from meta-analyses results in exaggerated effect sizes32). The search strategy found 4192 abstracts. We excluded studies if the title and abstract were not relevant, and obtained papers for all potentially relevant studies if the abstract contained insufficient information for exclusion.

Data extraction and study quality

Data extraction and evaluation of the study’s quality were done independently by two reviewers (EW-TC and AJK). Data were extracted using a standardised extraction form, and methodological quality was assessed by using the validated Downs and Black instrument for cohort studies,33 34 one of the best tools for assessing observational study designs.35 The QUOROM statement checklist was used for randomised control trials.36 The scores from these instruments were rated as high, moderate, or low quality. Disagreement between the reviewers was resolved by discussion with senior investigators (TW and RG). For two studies, the authors were contacted successfully to clarify details or to provide additional information about their study.41 w4

Data synthesis

All meta-analyses were done with RevMan 4.2.8 software (www.cc-ims.net/RevMan), using fully adjusted odds ratio or relative risk in the meta-analyses. The standard error of the natural logarithm (ln) of the odds ratio was calculated from the 95% confidence intervals using the formula

\[ \text{ln}[\text{upper limit of CI}] - \text{ln}[\text{lower limit of CI}]/3.92. \]

Heterogeneity between studies was tested with the I² statistic.37 If the I² statistic was \( \leq 30\% \) the fixed effect model was used to pool studies; otherwise, the random effects model was used. Sensitivity analyses, excluding unpublished abstracts and including only studies rated as high quality, were performed where possible. Where possible, we evaluated publication bias by
plotting a funnel plot; publication bias is unlikely if the funnel plot shows a symmetrical inverted V shape.

**RESULTS**

**Description of studies**

Of the 4192 abstracts screened, 89 were from potentially relevant studies, of which 77 were excluded because they did not meet the inclusion criteria (fig 1). The remaining 12 studies comprised nine prospective cohort studies (including one published only as an abstract) and three randomised control trials (including one abstract). Reviewers agreed completely on study eligibility. Tables 1 and 2 summarise the design features and participants’ characteristics in these studies.

**Prospective cohort studies**

When duplicate publications and abstracts were excluded, the nine prospective cohort studies selected comprised seven independent studies including 149 203 people and 1878 incident cases of early AMD. As the antioxidants investigated differed across the studies, not all studies contributed to the meta-analysis of every antioxidant. All of the cohort studies recruited participants between 1980 and 1994; in three studies,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Prospective cohort studies evaluating antioxidants and their association with the primary prevention of early age-related macular degeneration (AMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author, year</strong></td>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>Christen, 1999*</td>
<td>Physician health study 1</td>
</tr>
<tr>
<td><em>Cho, 2001</em></td>
<td>Nurses health study and health professional follow-up study</td>
</tr>
<tr>
<td>Van Leeuwen, 2005*1</td>
<td>Rotterdam eye study</td>
</tr>
<tr>
<td>Flood, 2002*2</td>
<td>Blue Mountain eye study</td>
</tr>
<tr>
<td>Moeller, 2006*7</td>
<td>Carotenoids in age-related eye disease study</td>
</tr>
<tr>
<td><em>Cho, 2004</em>3</td>
<td>Nurses health study and health professional follow-up study</td>
</tr>
<tr>
<td>Van den Langenberg, 1998*8</td>
<td>Beaver Dam eye study</td>
</tr>
<tr>
<td>Flood, 2006*9</td>
<td>Blue Mountain eye study</td>
</tr>
<tr>
<td>Chong, 2006*10</td>
<td>Melbourne collaborative cohort study</td>
</tr>
</tbody>
</table>

*The three studies that evaluated antioxidant intake and its associations with late AMD.
†Duplicate publication: Flood 2006 used in lutein and zeaxanthin pooled results instead of Flood 2002.
dietary data had been recorded before 1988 as they were a subset of another long term study. All studies were published in the past 10 years and were conducted in the United States or other Western countries. One cohort study included only women and another only men. In most studies, participants were 49 years or older, but two included participants in their early 40s. Follow-up was 5-18 years (mean 9 years). Three studies were population based and four included volunteers and health professionals. Most studies had initial participation rates of ≥80%; one study had a participation rate of 64% but reported no difference in prevalence of self reported AMD between participants and non-participants; another did not report the participation rates. The follow-up rates for most studies were over 75%. With the exception of the physicians’ health study, which evaluated self reported use of antioxidant supplements (and did not contribute to the pooled results), all studies used previously validated food frequency questionnaires to evaluate intake of antioxidants.

The assessment and definition of AMD varied between studies (table 1). All studies adjusted for age and smoking in their analyses. Most studies analysed the risk of AMD by comparing the highest fifth or fourth of antioxidant intake to the lowest fifth or fourth; one study evaluated the risk of AMD per standard deviation increase of lutein and zeaxanthin intake, but the authors, when requested, provided the odds ratio for AMD comparing the highest fifth of lutein and zeaxanthin intake to the lowest fifth. The other author who we contacted provided us with a detailed spreadsheet of the hazard ratio of the various antioxidants that were investigated. The two reviewers agreed on the quality of the study in seven of the eight published cohort studies, and resolved disagreement by discussion.

Randomised controlled trials

Three randomised control trials, including one abstract, evaluated antioxidant supplementation in the primary prevention of AMD (table 2). The vitamin E, cataract, and age related maculopathy trial (VECAT) evaluated vitamin E versus placebo supplementation in an Australian population, while the alpha tocopherol and beta carotene (ATBC) trial evaluated vitamin E or β carotene supplementation, or both, versus placebo in Finland. Neither of these trials found that antioxidant supplements were effective for primary prevention of AMD.

Dietary antioxidants and early AMD

Figures 2 and 3 show the point estimates for vitamin A, vitamin C, vitamin E, zinc, lutein and zeaxanthin, α carotene, β carotene, β cryptoxanthin, and lycopene in the different studies comparing the highest versus the lowest fifth or fourth of intake for early AMD.

For vitamin A, all three cohort studies that contributed to the pooled analysis reported null associations, and the pooled odds ratio of early AMD, in a comparison of the highest to the lowest vitamin A intake category, was 0.98 (95% confidence interval 0.81 to 1.18). For vitamin C, three of the four studies reported positive associations and one reported an inverse association. Because of heterogeneity between studies (P=0.15, I²=43%), results were pooled by using the random effect model, and the pooled odds ratio was 1.11 (0.84 to 1.46). For vitamin E, of the three published cohort studies that contributed to the pooled results, two reported an inverse association and one a null association. The Rotterdam eye study, which reported a statistically significant finding, contributed 60% weight to the pooled result, an odds ratio of 0.83 (0.69 to 1.01). When we pooled results from the two high quality studies, the odds ratio of vitamin E was 0.75 (0.59 to 0.94).

For zinc, two of the four studies reported positive associations, one reported a null association, and one an inverse association. The Rotterdam eye study reported a borderline significant finding and again dominated the pooled result (63% weight). The pooled

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study</th>
<th>Follow-up</th>
<th>Population (sample size, age (years))</th>
<th>Definition of AMD</th>
<th>No of cases</th>
<th>Antioxidants investigated</th>
<th>Relative risk (95% CI)</th>
<th>Randomisation and adequacy of allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor, 2002</td>
<td>Vitamin E, cataract, and age related maculopathy trial (VECAT)</td>
<td>4 year incidence</td>
<td>Population based, Australia (1193, 55-80)</td>
<td>Wisconsin age related maculopathy grading system (WARMGS) and international classification</td>
<td>69</td>
<td>Vitamin E 500 IU (335 mg/day) v placebo</td>
<td>Early AMD 1.05 (0.69 to 1.61); late AMD 1.36 (0.67 to 2.77)</td>
<td>High quality</td>
</tr>
<tr>
<td>Teikari, 1998</td>
<td>Alpha-tocopherol and beta-carotene study (ATBC)</td>
<td>6 year prevalence</td>
<td>Population based, Finland (941, 265)</td>
<td>Modified international classification</td>
<td>269</td>
<td>Vitamin E (50 mg/ day), β carotene (20 mg/day) or both v placebo</td>
<td>Any AMD: vitamin E only 1.27 (0.84 to 1.93); α carotene only 1.10 (0.76 to 1.79); both 1.14 (0.75 to 1.74)</td>
<td>Moderate quality</td>
</tr>
<tr>
<td>Christen, 2009</td>
<td>Physicians’ health study</td>
<td>7-12 years</td>
<td>Male doctors, USA (21 216)</td>
<td>Drusen or pigment change, plus visual acuity ≤20/30</td>
<td>532</td>
<td>α carotene (50 mg every other day) v placebo</td>
<td>Any AMD: 0.97 (0.82 to 1.15)</td>
<td>Insufficient information (abstract)</td>
</tr>
</tbody>
</table>
odds ratio of zinc for early AMD was 0.91 (0.74 to 1.11).

Six cohort studies contributed to the meta-analysis of lutein and zeaxanthin. Of these, four reported null associations, one a positive association, and one an inverse association. None of the findings in these studies was statistically significant, nor was the heterogeneity between studies (P=0.80, I²=0%). Results were pooled by using the fixed effect model, and the odds ratio for participants in the highest relative to the lowest lutein and zeaxanthin intake category was 0.98 (0.86 to 1.13), and it was 0.96 (0.82 to 1.12) when we excluded results from the abstract from the model. The symmetrical shape of the funnel plot indicates that publication bias is unlikely (fig 4).w8w9

Four published cohort studies evaluated the associations between α-carotene, β-carotene, β-cryptoxanthin, and lycopene and early AMD and contributed to the pooled results of these antioxidants (fig 3). For α-carotene, pooled results yielded an odds ratio of 1.05 (0.87 to 1.26). For β-carotene, two of four studies reported null associations, one a positive association, and one an inverse association; none was significant. The Rotterdam eye study contributed greatly (53% weight) to an odds ratio of 1.04 (0.86 to 1.25). For β-cryptoxanthin, the pooled odds ratio of four studies was 1.01 (0.85 to 1.22), and for lycopene it was 1.07 (0.90 to 1.28).

When sensitivity analyses including only population based, high quality studies for the nine investigated nutrients were performed the pooled odds ratio for the nutrients, apart from vitamin E, did not change greatly.

Dietary antioxidants and late AMD

Of the eight published cohort studies, only three provided point estimates for the risk of late AMD (table 1).w3w4w6 As each evaluated different antioxidants, we were unable to pool these results. Cases were few and odds ratios had wide 95% confidence intervals.

<table>
<thead>
<tr>
<th>Vitamin A</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flood 2002w2</td>
<td>0.90 (0.55 to 1.47)</td>
<td>14.5</td>
<td>0.90 (0.55 to 1.47)</td>
</tr>
<tr>
<td>Cho 2004w3</td>
<td>1.15 (0.83 to 1.60)</td>
<td>32.5</td>
<td>1.15 (0.83 to 1.60)</td>
</tr>
<tr>
<td>Van Leeuwen 2005w1</td>
<td>0.91 (0.70 to 1.18)</td>
<td>53.0</td>
<td>0.91 (0.70 to 1.18)</td>
</tr>
</tbody>
</table>

All studies (fixed effect) Test for heterogeneity: I²=0% Test for overall effect: P=0.83

<table>
<thead>
<tr>
<th>Vitamin C</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Langenberg 1998w8</td>
<td>1.12 (0.47 to 2.65)</td>
<td>8.7</td>
<td>1.12 (0.47 to 2.65)</td>
</tr>
<tr>
<td>Flood 2002w2</td>
<td>1.60 (0.91 to 2.82)</td>
<td>16.9</td>
<td>1.60 (0.91 to 2.82)</td>
</tr>
<tr>
<td>Cho 2004w3</td>
<td>0.84 (0.62 to 1.13)</td>
<td>35.4</td>
<td>0.84 (0.62 to 1.13)</td>
</tr>
<tr>
<td>Van Leeuwen 2005w1</td>
<td>1.21 (0.93 to 1.58)</td>
<td>39.0</td>
<td>1.21 (0.93 to 1.58)</td>
</tr>
</tbody>
</table>

All studies (random effect) Test for heterogeneity: I²=42.9% Test for overall effect: P=0.47

<table>
<thead>
<tr>
<th>Vitamin E</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Langenberg 1998w8</td>
<td>0.80 (0.39 to 1.65)</td>
<td>7.0</td>
<td>0.80 (0.39 to 1.65)</td>
</tr>
<tr>
<td>Cho 2004w3</td>
<td>1.04 (0.75 to 1.45)</td>
<td>33.0</td>
<td>1.04 (0.75 to 1.45)</td>
</tr>
<tr>
<td>Van Leeuwen 2005w1</td>
<td>0.74 (0.58 to 0.95)</td>
<td>60.0</td>
<td>0.74 (0.58 to 0.95)</td>
</tr>
</tbody>
</table>

All studies (fixed effect) Test for heterogeneity: I²=23.2% Test for overall effect: P=0.06

<table>
<thead>
<tr>
<th>Zinc</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Langenberg 1998w8</td>
<td>0.96 (0.49 to 1.87)</td>
<td>9.1</td>
<td>0.96 (0.49 to 1.87)</td>
</tr>
<tr>
<td>Flood 2002w2</td>
<td>1.20 (0.69 to 2.08)</td>
<td>13.4</td>
<td>1.20 (0.69 to 2.08)</td>
</tr>
<tr>
<td>Cho 2003w5</td>
<td>0.68 (1.04 to 1.94)</td>
<td>14.7</td>
<td>0.68 (1.04 to 1.94)</td>
</tr>
<tr>
<td>Van Leeuwen 2005w1</td>
<td>0.80 (0.62 to 1.03)</td>
<td>62.8</td>
<td>0.80 (0.62 to 1.03)</td>
</tr>
</tbody>
</table>

All studies (fixed effect) Test for heterogeneity: I²=0% Test for overall effect: P=0.34

Fig 2 | Pooled odds ratio for early AMD (highest v lowest dietary intake categories of vitamins and zinc)

DISCUSSION

Age related macular degeneration remains the leading cause of visual loss in the United Kingdom and other developed countries. Oxidative damage in the retina has been hypothesised as a key process involved in development of early AMD. Antioxidants are thought to prevent AMD by reducing the photo-oxidative damage from blue light in the oxygen filled environment of the retina, which is rich in polyunsaturated fatty acids that are highly susceptible to oxidation.w40

Previous studies and reviews have largely focused on the role of dietary antioxidants and supplements in the secondary prevention of AMD—that is, preventing progression to late AMD in people with signs of early disease. Our analysis examined the role of dietary antioxidants and supplements in primary prevention and found that a range of dietary antioxidants, including vitamins A, C, and E, zinc, lutein and zeaxanthin, α-carotene, β-carotene, β-cryptoxanthin, and lycopene, have little or no effect: pooled odds ratios ranged from 0.91 to 1.11, with the exception of vitamin E, which had a modest borderline protective association (0.83, 95% confidence interval 0.69 to 1.01).

Comparison with other studies

We found few randomised clinical trials, none of which found that vitamin E and β-carotene supplements prevented early AMD.w10w12 The studies we evaluated were largely derived from populations in the United States or other developed Western nations, where participants are well nourished. Although we included both population based and volunteer based studies, the pooled odds ratio for the nutrients investigated, with the exception of vitamin E, did not change greatly in our sensitivity analyses of population based and high quality studies.
For vitamin E, the borderline significant pooled odds ratio, especially from the two high quality studies, suggests that vitamin E may be associated with a reduced risk of early AMD. Results from the two randomised control trials do not support a protective effect of vitamin E supplementation, given in doses 2.5-fold to 15-fold higher than the highest dietary range estimated from these cohort studies. The vitamin E, cataract, and age related maculopathy trial reported a relative risk for early AMD of 1.05 (0.69 to 1.61) comparing vitamin E intake of 335 mg/day versus placebo, and the alpha tocopherol and beta carotene trial reported an odds ratio for any AMD of 1.27 (0.84 to 1.93) for vitamin E intake of 50 mg/day versus placebo.

The alpha tocopherol and beta carotene trial reported an odds ratio for any AMD of 1.17 (0.76 to 1.79) for β carotene intake of 20 mg/day versus placebo, and the physicians’ health study reported a relative risk of 0.97 (0.81 to 1.15) for β carotene (50 mg every other day) versus placebo. These results are consistent with data from prospective cohort studies. The pooled odds ratio of dietary β carotene intake for early AMD was 1.04 (0.85 to 1.27), comparing the highest (range of intake of 62.1-11.9 mg/day) to the lowest (2.1-2.3 mg/day) category of dietary β carotene.

Carotenoids have been shown to be good filters of harmful blue light, and their antioxidative properties have been demonstrated in vitro. Two of these carotenoids, lutein and zeaxanthin, are found in the macula in concentrations higher than in other parts of the body. However, results from our review suggest that high antioxidant levels in the healthy retina do little to prevent the development of early AMD. A Cochrane review showed that antioxidant supplements may have a role delaying the progression of early to late AMD. These contrasting results could imply that uncontrolled oxidative chain reactions of reactive oxygen species may have begun in eyes with AMD at early or intermediate stage, and thus high antioxidant levels at this stage of the disease process may be effective in slowing progression of AMD. The Cochrane review reported a protective effect from multivitamin supplementation (pooled odds ratio 0.68, 99% confidence interval 0.49 to 0.93) and a protective effect of zinc supplementation (0.73, 95% confidence interval 0.58 to 0.93) in preventing the progression of AMD. Both findings were mainly based on data from the age related eye disease study. No protective effect was seen for vitamin E supplementation (1.05, 0.80 to 1.53; derived only from the vitamin E, cataract, and age related maculopathy trial). A Cochrane review reported a protective effect from the vitamin E, cataract, and age related maculopathy trial.

Strengths and weaknesses of the study

We sought to be as comprehensive as possible, in accordance with guidelines for meta-analyses, and performed an extensive search through seven databases, including grey literature, and did not limit our searches by language or time. Inclusion of grey literature has also been shown to reduce the likelihood of publication bias and of overestimating pooled estimates. Although only six studies evaluated lutein and zeaxanthin, the funnel plot showed an inverted

### Table: Odds ratio (95% CI) for lutein and zeaxanthin intake for early AMD (highest v lowest dietary intake categories of carotenoids)

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lutein and zeaxanthin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cho 2004</td>
<td>2.9</td>
<td>1.22</td>
<td>0.54 to 2.75</td>
</tr>
<tr>
<td>Van den Langenberg 1998</td>
<td>4.6</td>
<td>0.93</td>
<td>0.49 to 1.76</td>
</tr>
<tr>
<td>Flood 2006</td>
<td>9.9</td>
<td>0.74</td>
<td>0.48 to 1.15</td>
</tr>
<tr>
<td>Chong 2006</td>
<td>22.9</td>
<td>1.08</td>
<td>0.81 to 1.44</td>
</tr>
<tr>
<td>Van Leeuwen 2005</td>
<td>28.5</td>
<td>1.00</td>
<td>0.77 to 1.29</td>
</tr>
<tr>
<td>Moeller 2006</td>
<td>31.3</td>
<td>0.98</td>
<td>0.77 to 1.25</td>
</tr>
<tr>
<td>All studies (fixed effect)</td>
<td>100.0</td>
<td>0.98</td>
<td>0.86 to 1.13</td>
</tr>
<tr>
<td>Test for heterogeneity: $I^2=0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $P=0.82$</td>
<td></td>
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</tr>
<tr>
<td><strong>α-carotene</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van den Langenberg 1998</td>
<td>7.1</td>
<td>0.55</td>
<td>0.27 to 1.10</td>
</tr>
<tr>
<td>Flood 2002</td>
<td>13.3</td>
<td>1.30</td>
<td>0.78 to 2.16</td>
</tr>
<tr>
<td>Cho 2004</td>
<td>30.5</td>
<td>1.10</td>
<td>0.79 to 1.54</td>
</tr>
<tr>
<td>Van Leeuwen 2005</td>
<td>49.2</td>
<td>1.06</td>
<td>0.82 to 1.38</td>
</tr>
<tr>
<td>All studies (fixed effect)</td>
<td>100.0</td>
<td>1.05</td>
<td>0.87 to 1.26</td>
</tr>
<tr>
<td>Test for heterogeneity: $I^2=26.9%$</td>
<td></td>
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<tr>
<td>Test for overall effect: $P=0.59$</td>
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<tr>
<td><strong>β-carotene</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van den Langenberg 1998</td>
<td>5.2</td>
<td>0.74</td>
<td>0.32 to 1.71</td>
</tr>
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Cigarette smoking remains the only widely accepted modifiable risk factor for the primary prevention of AMD. There is insufficient evidence that antioxidant supplements prevent the onset of AMD. Cigarette smoking remains the only widely accepted modifiable risk factor for the primary prevention of AMD and patients seeking advice on AMD prevention should be encouraged to stop smoking.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

Age related macular degeneration (AMD) is the leading cause of visual loss in older people. Antioxidants have been hypothesised to reduce oxidative damage to the retina, but the effectiveness of dietary antioxidants in the primary prevention of AMD is unclear.

WHAT THIS STUDY ADDS

Dietary antioxidants had little or no effect in the primary prevention of early AMD in well nourished Western populations. Cigarette smoking remains the only widely accepted modifiable risk factor for the primary prevention of AMD.
RESEARCH

Ethical approval: Not required.
Provenance and peer review: Not commissioned; externally peer reviewed.

1. Bressler NM. Age-related macular degeneration is the leading cause of blindness. JAMA 2004;291:1900-1.
2. Congdon NG, Friedman DS, Tien T. Important causes of visual impairment in the world today. JAMA 2003;290:2057-60.
37. Accepted: 30 July 2007
Comparison of hospital episode statistics and central cardiac audit database in public reporting of congenital heart surgery mortality

Stephen Westaby, consultant cardiac surgeon,1 Nicholas Archer, consultant paediatric cardiologist,2 Nicola Manning, associate specialist fetal cardiology,3 Satish Advani, consultant paediatric cardiologist,4 Catherine Grebenik, consultant anaesthetist,3 Oliver Ormerod, consultant cardiologist,9 Ravi Pillai, consultant cardiac surgeon,1 Neil Wilson, consultant paediatric cardiologist2

ABSTRACT
Objective To verify or refute the value of hospital episode statistics (HES) in determining 30 day mortality after open congenital cardiac surgery in infants nationally in comparison with central cardiac audit database (CCAD) information.
Design External review of paediatric surgical outcomes in England (HES) and all UK units (CCAD), as derived from each database.
Setting Congenital heart surgery centres in the United Kingdom.
Data sources HES for congenital heart surgery and corresponding information from CCAD for the period 1 April 2000 to 31 March 2002. HES was restricted to the 11 English centres; CCAD covered all 13 UK centres.
Main outcome measure Mortality within 30 days of open heart surgery in infants aged under 12 months.
Results In a direct comparison for the years when data from the 11 English centres were available from both databases, HES omitted between 5% and 38% of infants operated on in each centre. A median 60% (range 0-73%) shortfall occurred in identification of deaths by HES. As a result, mean 30 day mortality was underestimated at 4% by HES as compared with 8% for CCAD. In CCAD, between 1% and 23% of outcomes were missing in nine of 11 English centres used in the comparison (predominantly those for overseas patients). Accordingly, CCAD mortality could also be underestimated. Oxford provided the most complete dataset to HES, including all deaths recorded by CCAD. From three years of CCAD, Oxford's infant mortality from open cardiac surgery (10%) was not statistically different from the mean for all 13 UK centres (8%), in marked contrast to the conclusions drawn from HES for two of those years.
Conclusions Hospital episode statistics are unsatisfactory for the assessment of activity and outcomes in congenital heart surgery. The central cardiac audit database is more accurate and complete, but further work is needed to achieve fully comprehensive risk stratified mortality data. Given unresolved limitations in data quality, commercial organisations should reconsider placing centre specific or surgeon specific mortality data in the public domain.

INTRODUCTION
The inquiry into congenital heart surgery deaths in Bristol was widely publicised, became a political issue, and has had a profound effect on surgical practice in the United Kingdom. Irrespective of the intense controversy generated by public reporting of mortality statistics in the American healthcare system, the Department of Health has insisted on a similar policy for cardiac surgical outcomes in the UK. The Freedom of Information Act allows external bodies to access hospital statistics irrespective of whether they are complete, accurate, and substantiated. In these circumstances, any reporting agency has a responsibility to present factual information. Public reporting is particularly sensitive in the realm of paediatric mortality.

The Bristol inquiry used hospital episode statistics (HES) to compare outcomes with those of other congenital cardiac surgical units in the UK. Spiegelhalter and colleagues subsequently debated the validity of this approach. In 2004 the BMJ published a manuscript from the “Dr Foster” Unit at Imperial College, London, which described HES for mortality in congenital heart surgery. The authors applied detailed statistical analysis to non-risk assessed HES data submitted by hospital clerical staff in most but not all UK congenital cardiac surgical centres. The clinical teams did not verify the data. The paper suggested that one unit, Oxford, had significantly higher mortality than the national average for open (with cardiopulmonary bypass) operations in infants and drew damaging conclusions. The information was widely published in the lay press.

The Oxford unit questioned the results before publication, and the central cardiac audit database (CCAD) did so afterwards. A paper based on the CCAD had found no detectable difference in 30 day or one year survival between any of the 13 UK tertiary centres for congenital heart disease for the first year the database operated nationally. In contrast, the Dr...
Foster paper suggested that Oxford had outlying mortality for open procedures between 1991 and 2002 in infants less than 1 year, with a probability of this happening by chance alone of less than 0.0002. A multidisciplinary team therefore carried out an investigation to establish the difference between the mortality reported in the BMJ paper and carefully verified death rates for Oxford and other centres. We now report the findings of this investigation.

METHODS
Dr Foster epidemiologists obtained HES by using the Office of Population Census and Surveys classification of operation and procedures, fourth revision (OPCS4) codes for open cardiac operations in children from the 11 centres in England between April 1991 and March 2002. HES data are not available for Northern Ireland and Scotland. The Dr Foster group used a list of OPCS4 procedure codes, which were classified as either open or closed cardiac operations on the basis of information from the United Bristol Healthcare NHS Trust. HES does not have a flag to determine whether or not a procedure is done on cardiopulmonary bypass. For several complex paediatric cardiac surgical procedures, no OPCS4 codes were available and no hierarchical system existed where more than one operation was done. HES recorded only deaths that occurred at the hospital where the operation took place and during the same admission as the surgery. Procedures that were difficult to define by OCP5 codes were excluded from the analysis. Aylin and colleagues used HES to compare mortality within 30 days of surgery for each of the 11 centres in England with the average mortality of all centres combined. Their report then focused on mortality in hospital within 30 days of surgery in infants less than 12 months of age who had heart operations under cardiopulmonary bypass.

Thames Valley Strategic Health Authority instigated the investigation reported here, in conjunction with the Oxford Radcliffe Hospitals Trust at the request of the Department of Health. The aim was to compare mortality as reported by the administrative HES database and the clinically based CCAD for infants aged under 12 months who had cardiac operations with cardiopulmonary bypass in the UK irrespective of the site of death. The CCAD began collecting data from all centres only in 2000. Consequently, both datasets provided comprehensive statistics between 1 April 2000 and 31 March 2002, and this was the period used for comparison of data completeness and accuracy. HES and the CCAD provided primary data from their datasets, which enabled a direct comparison of the number of deaths by each hospital with the total

<table>
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<th>CCAD data</th>
<th>Missing CCAD outcomes (%)</th>
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*Number of recorded open cardiac operations in infants aged <12 months.
†Number of deaths within 30 days of operation reported in cohort.
‡All centres in England.
number of cases. We reanalysed HES data provided by Aylin and colleagues for the specific two year period.

The minimum dataset used by the CCAD includes date of death and is linked with the Office of National Statistics by using National Health Service number, to track mortality irrespective of place of death. In the CCAD, most cases with unknown outcomes were patients recorded as non-UK residents. These patients (averaging 8% but zero for Oxford and one other centre) were predominantly coded as private patients and lost to follow-up after leaving the UK. In order to have a longer time period for comparison of performance of centres, we also examined CCAD data for 2000-3 by investigation as the most up to date information available at the time (CCAD tracks outcomes at 12 months as well as 30 days after surgery and then validates it).

The clinicians from all 13 UK centres continuously collected detailed information for the CCAD dataset on a prospective basis, and dedicated cardiac data managers from the hospital database at each centre submitted the data. The data are validated by annual multidisciplinary team visits to the clinical departments to confirm the accuracy of the information. This was a period when CCAD submissions had reached a high level of compliance and accuracy. Overall data provision for the CCAD dataset against benchmarked procedures was 96.8% at this time; completeness for individual fields ranged from 75% to 100%. When CCAD outcome data could not be recorded or verified (for instance when overseas patients had returned home and could not be traced) the data point was recorded as missing. We used outcomes for infants aged under 12 months who had surgery with cardiopulmonary bypass at the 11 centres in England to provide direct comparison with the HES data supplied by Dr Foster for the study period.

The findings presented are a simple comparison between HES and CCAD statistics for the number of patients operated on and mortality within 30 days. We also provide the CCAD recorded mortality statistics for all the centres between 1 April 2000 and 31 March 2003 compared with the national average as an update on the report of Gibbs and colleagues.6

RESULTS

In the study period 2000-2, CCAD data included between five and 147 more operations for each centre than the HES data (median 23). Compared with CCAD data, HES omitted between 5% and 38% (median 15%) of infants operated on in each centre (table). The system used for reporting of postoperative deaths by HES resulted in a median shortfall of 40% (range 0-73%). In centre A, with the largest number of operations, 38% of all patients were missed by HES and only 27% of the total deaths were recorded. HES failed to track between 44% and 70% of deaths in four other centres (fig 1). As a result, HES underestimated the mean 30 day hospital mortality at 4% compared with the CCAD derived figure of 8%.

In CCAD, between 1% and 23% of outcomes were missing in nine of the 11 English centres. Because of this, 30 day mortality could be higher in these centres. Oxford had the fewest open cardiac operations and provided the most complete statistics under direct comparison. From the CCAD outcome information, Oxford reported all deaths and had 98% and 100% completeness for all data points over the two year period. The 10% mortality for open heart surgery in infants for 2000-2 was not different from the mean for all centres (8%) (fig 1). The missing deaths from other centres in HES led to the suggestion that Oxford had an outlying mortality because of the artefactually low national mortality produced from HES data. Figure 2 shows the CCAD recorded 30 day mortality compared with the national average mortality of 8% for all 13 UK centres for the three years between 1 April 2000 and 31 March 2003. These figures refine information available from the report of the first year of CCAD results.6

DISCUSSION

Principal findings

Hospital episode statistics (HES) did not provide reliable patient numbers or 30 day mortality data. On average, HES recorded 20% (5-38%) fewer cases than the central cardiac audit database (CCAD) and captured only between 27% and 78% of 30 day deaths in
nine of the 11 centres in England. HES did not record operations on non-UK residents and detected only deaths that occurred in the hospital where the operation took place and during the same admission as the surgery. No validated data exist with which to compare HES before 2000, but we have no reason to suppose that it was more reliable before that time.

Accordingly, the non-verified HES information was an unsuitable platform on which to base sophisticated statistical analysis. The Dr Foster paper did not present an accurate account of cardiac surgical activity or mortality in infants and consequently placed spurious and harmful conclusions in the public arena.

Strengths and weaknesses of the study
This study provides a comprehensive appraisal of congenital cardiac surgical activity in the UK between 1 April 2000 and 31 March 2002 and highlights the substantial discrepancy between HES and CCAD. Aylin and colleagues stated that Oxford had excessive mortality on the basis of data collected between 1999 and 2000 and adjusted for procedure. Given that CCAD validated data were available only after 2000, we can refute that claim only from that time onwards. Equally, we did not adjust our data comparison for procedure. So far, none of the studies has attempted to stratify children by risk according to functional status or comorbidity.

The Thames Valley Strategic Health Authority review highlighted previous CCAD reviews of independently validated data, which show that all UK units produce similarly acceptable results. CCAD data also showed that Oxford had the lowest mortality for non-cardiopulmonary bypass operations in infants aged under 12 months and was in the middle of the spectrum for all cardiac operations in this age group.

Although it provides the gold standard for collection of cardiac data in the UK, CCAD was imperfect in that some non-UK residents were lost to follow-up. This occurred particularly in high volume centres with overseas links. Some deaths within 30 days of operation could have been missed if the patients died abroad. CCAD now makes increasingly strenuous efforts to verify data at each congenital heart centre. Multidisciplinary CCAD team visits to all 13 UK centres guarantee a thorough approach for this system. Both cardiology and surgical teams are aware of the importance of accurate data submission. Providing an accurate description of a complex cardiac operation on an unusual heart defect can sometimes be very difficult, given the restrictions in database entry. Clinicians must enter the information of best fit. In contrast, clerical staff involved in HES submission are disadvantaged by less specialised knowledge and motivation to provide comprehensive and accurate data.

Strengths and weaknesses in relation to other studies
Referencing their own publications, Aylin and colleagues suggested that HES data were of “significant quality to be used for analysis.” They have also stated that “patients where the outcome was unknown made little difference to the overall mortality.” Information from our study indicates that these statements are wrong. Other authors have clearly shown the weaknesses and dangers of administrative databases when presenting cardiac mortality data in the public arena. In a recent paper, Shahian and colleagues compared clinical and administrative data sources for report cards on coronary artery bypass graft surgery in hospitals in Massachusetts. They found a 27.4% disparity in the volume of isolated coronary artery bypass graft surgery, a significant difference in observed in-hospital mortality, and an inappropriate classification of a centre as an outlier on the basis of inaccuracies in administrative data. Various statistical methods produced different risk adjusted mortalities. The administrative dataset was more prone to errors in coding of procedures and incorrect case numbers, non-standardised mortality end points, misalignment of data sources with intended use, absence of critical clinical variables, failure to differentiate comorbidities from complications, and inability to safely define outliers. In an editorial discussion of Shahian’s paper, Ryan concluded that the public reporting of mortality statistics must be based on data of the highest quality derived from prospectively gathered, validated, and audited clinical sources and not from unverified administrative datasets.

Meaning of the study
Publication of inaccurate statistics, particularly regarding paediatric deaths, detracts from rather than enhances public confidence. Data management requires resources, but most of the units were not funded to collect and validate data effectively. If mortality statistics are to be released, their quality must be beyond reproach. Precise database definitions, uniform training of data managers, and periodic external audit are essential. Adequate ascertainment of relevant deaths and complete recording of patient episodes are also needed.

The media are eager to publish leagues tables of performance. Dr Foster has pioneered this approach by providing newspapers with information for heart disease and other topical aspects of health care in return for a fee. Government agencies and the media increasingly tend to use administrative data for hospital profiling because they are inexpensive and available in a short time frame. Marshall and Spiegelhalter have questioned the reporting of performance indicators to provide explicit ranking of institutions. Their key messages were that league tables are unreliable statistical summaries of performance and that institutions with smaller numbers of cases may be unjustifiably penalised or credited in comparison exercises. Any performance indicator should be reported with its associated statistical sampling variability.

Uncertainty about the public reporting of unit specific mortality statistics
We believe the UK to be the first country to follow some American states by placing non-risk stratified
WHAT IS ALREADY KNOWN ON THIS TOPIC
Hospital episode statistics have been used to compare activity rates and mortality between centres, but their reliability has been questioned.

WHAT THIS STUDY ADDS
The congenital cardiac audit database is more accurate and complete than hospital episode statistics, but individual centres need further investment to improve completeness of data. The value of placing unit or surgeon specific mortality statistics in the public domain is in doubt, given the poor quality of data, imprecision of risk stratification, and confrontational media agenda.

The congenital cardiac audit database is more accurate and complete than hospital episode statistics, but individual centres need further investment to improve completeness of data. The value of placing unit or surgeon specific mortality statistics in the public domain is in doubt, given the poor quality of data, imprecision of risk stratification, and confrontational media agenda.

We appreciate the role of the Thames Valley Strategic Health Authority, Oxford Radcliffe NHS Trust, and Roger Boyle in the work to resolve this problem. We thank P Aylin and officers of the congenital cardiac audit database for providing their data for the review.

Contributors: SW and RP operated on the patients and were involved in collecting and validating the data and writing the manuscript. CG was one of the paediatric cardiac anaesthetists and was involved in validating data. NA, NM, SA, and NW collected and validated data and contributed to the manuscript. OO participated in the investigation to compare HES and CCAD data. NA is the guarantor.

Funding: None.
Competing interests: None declared.
Ethical approval: Not needed.
Provenance and peer review: Not commissioned; externally peer reviewed.

3 Westaby S. League tables, risk assessment and an opportunity to improve standards. Br J Cardiol (Acute Interv Cardiol) 2002;9:5-10.
Preventing childhood obesity: two year follow-up results from the Christchurch obesity prevention programme in schools (CHOPPS)

Janet James, health promotion specialist nurse,1 Peter Thomas, professor of health care statistics and epidemiology,3 David Kerr, consultant physician2

ABSTRACT
Objective To assess the long term effects of an obesity prevention programme in schools.
Design Longitudinal results after a cluster randomised controlled trial.
Setting Schools in southwest England.
Participants Of the original sample of 644 children aged 7-11, 511 children were tracked and measurements were obtained from 434 children three years after baseline.
Intervention The intervention was conducted over one school year, with four sessions of focused education promoting a healthy diet and discouraging the consumption of carbonated drinks.
Main outcome measures Anthropometric measures of height, weight, and waist circumference. Body mass index (BMI) converted to z scores (SD scores) and to centile values with growth reference curves. Waist circumference was also converted to z scores (SD scores).
Results At three years after baseline the age and sex specific BMI z scores (SD scores) had increased in the control group by 0.10 (SD 0.53) but decreased in the intervention group by −0.01 (SD 0.58), with a mean difference of 0.10 (95% confidence interval −0.00 to 0.21, P=0.06). The prevalence of overweight increased in both the intervention and control group at three years and the significant difference between the groups seen at 12 months was no longer evident. The BMI increased in the control group by 2.14 (SD 1.64) and the intervention group by 1.88 (SD 1.71), with mean difference of 0.26 (−0.07 to 0.58, P=0.12). The waist circumference increased in both groups after three years with a mean difference of 0.09 (−0.06 to 0.26, P=0.25).
Conclusions These longitudinal results show that after a simple year long intervention the difference in prevalence of overweight in children seen at 12 months was not sustained at three years.

INTRODUCTION
Childhood overweight and obesity is an international problem, with 10% of school age children estimated to be overweight.1,2 In the United Kingdom, obesity in children increased from 9.9% in 1995 to 13.7% in 2003.3 Although the UK government has set an ambitious target of stopping this escalating trend by 2010, a recent publication forecasts that there could be further increases, with 19% of boys and 24% of girls aged under 10 predicted to be obese by 2010.4

Numerous studies have been conducted with the aim of preventing obesity in children and young adults, many of which have been based in schools.5–6 A recent revised Cochrane review7 considered 22 studies, including 10 long term and 12 short term projects, most of which were school based and focused on multiple interventions, while some had more specific approaches. The review reported that in most cases the interventions did not significantly affect the weight of the children. One reason for the disappointing results might have been that most of the projects were too short in duration to be effective.

One school based intervention described by the Cochrane review as a good quality randomised controlled trial was the Christchurch obesity prevention project in schools (CHOPPS), also sometimes referred to as the “ditch the fizz” project. This project was started in August 2001 and was completed over one school year. It was based in six junior schools in southern England and included children aged 7-11. The intervention focused on discouraging children from consuming carbonated drinks and involved one hour of additional health education during each of the four school terms. The intervention is described in more detail elsewhere.8 The original project produced a modest reduction in the number of carbonated drinks consumed and a significant reduction in the number of children becoming overweight or obese.9 Further anthropometric measures were taken two years after completion of the original project (three years after baseline) to assess any longitudinal effects.

METHODS
Two years after completion of the original project one investigator ([J]) took additional longitudinal measurements. She had also completed the original measurements and conducted the education programme. Because of lack of funding we were unable to collect further drink diaries at this time.

Several different methods are used to assess overweight and obesity in children. We defined overweight...
and obesity using the 1990 British centile charts, in which children above the 91st centile are classified as overweight.

In the original project, the children in the three year groups attended junior schools in Christchurch, Dorset. Three years after baseline, the two older year groups had progressed to secondary schools and were tracked using school leaving lists. Most were attending three local secondary schools. From the original sample, 90 children had moved out of the area and 43 were attending secondary schools that were either outside of the project area or had fewer than six children from the original project attending. We traced 511 children from the original sample and carried out measurements on 434, 67% of the original sample (figure).

Outcome measures

One investigator (JJ) took anthropometric measures of height (without shoes) to the nearest 0.1 cm using the Portable Leister height measure (Seca, Marsden) and weight (in light clothing) measured to the nearest 0.1 kg on medical scales (Seca 770, Marsden). We converted body mass index (weight (kg)/(height (m)^2)) to z scores (SD scores) and to centile values using the 1990 growth reference disc (Child Growth Foundation). The z score (SD score) accounts for the child’s age and sex and represents the deviation compared with an average child of the same sex and age. Waist circumference was measured at the point of flexure as the child bends to one side, with 1 cm deducted to account for clothing. Waist circumference was converted to z scores (SD scores) with the 2001 McCarthy references for waist circumference. Our primary outcome measures were the change in BMI z score and the prevalence of overweight.

Statistical methods

The sample size of 376 calculated for the original project was based on changes in consumption of carbonated drinks. This sample size had 90% power to detect mean differences in z score (SD score) for BMIs of 0.49, 0.42, 0.35, and 0.34 (assuming intracluster correlations of 0.1, 0.05, 0.01, and 0.001, respectively) between the intervention and control groups. As we were able to gather data on 434 children three years after baseline and using data from the 12 month follow-up we can refine this sample size calculation. In the original 12 month follow-up the intracluster correlation for the change in z score (SD score) over 12 months was −0.003 (assumed to be 0) and the SD was 0.44 in both groups combined. Thus at three years with a sample size of 434 and assuming an SD of 0.44 and an intracluster correlation coefficient of 0, the study had 90% power to detect differences of 0.14 between control and intervention groups.

The original design was a cluster randomised controlled trial, with class being the cluster. Data were aggregated for each cluster and the two sets of clusters compared by using the independent samples t test. Subsequently, because of the nature of the school environment and the progression of children to different schools, the clusters have not remained intact and some children were lost to follow-up. This resulted in some clusters having few children in them, and so reducing the validity of that method of analysis for the follow-up data. We therefore analysed the interval scaled data in this paper with MLwiN (version 2) using multilevel models to take into account variance within clusters. For binary data we implemented a logistic model using the same software. This has resulted in the 12 month analysis presented here not being identical to that in the original report. We used a 5% significance level.

RESULTS

In the original project we collected baseline anthropometric measures from 644 children (321 girls). Of these, 434 children (209 girls) were re-measured three years later. There was no significant difference in the baseline z scores between children in the control and intervention groups who were present or missing at the final measurements. The average age was 8.6 (range 7.0-10.9) at the start of the project and 11.6 (10.0-13.9) at the three year follow-up.

Table 1 shows the BMIs, centile z scores (SD scores), and waist circumference z scores (SD scores) at baseline, 12 months, and three year follow-up. We also analysed data for each measure of change from baseline using baseline values, sex, and secondary school as covariates or cofactors. This made no material difference to the significance levels or mean changes between control and intervention group.

Table 2 shows the change in prevalence of overweight and obesity according to the 1990 British centile charts, with children above the 91st centile classed as overweight. As previously reported, at 12 months there was a significant difference between the control
and intervention groups but three years after baseline the difference was smaller and no longer significant.

**DISCUSSION**

A simple 12 month school based intervention focused on reducing consumption of carbonated drinks resulted in significant differences in the proportion of overweight children in the control and intervention groups. After two years and three years after the completion of the study, however, the difference was no longer significant, and the number of overweight children had increased in both groups, although the prevalence was still higher in the control group. In the three year follow-up, the only difference approaching significance was for the change in centile z score (SD score). Given the lack of a trend at 12 months this may well be a chance finding. The study had sufficient power to detect a difference of 0.14 or more, but the observed difference was only 0.10. The study was originally powered to detect differences in consumption of carbonated drinks, and so we cannot rule out a type II error.

The original project was different from many other school based interventions in that the intervention was specific and promoted a healthy diet based on the balance of good health. It focused specifically on discouraging the consumption of carbonated drinks. Several recent studies have further confirmed the association between these drinks and obesity, as has a systematic review and meta-analysis of 88 studies. The role of these drinks as a causative agent of obesity is also recognised by the World Health Organization. One reason suggested for this association may relate to the high glycaemic index and that they provide “empty” calories. The physiological effect on satiety from energy ingested in liquid form is thought to be different from that from solid foods and this may in part be due to faster transit times and reduced gastric distension. Therefore the additional energy from these drinks may not be detected as easily by the body and individuals may not compensate for this additional energy by consuming less later.

**Limitations**

A proportion of children were lost to follow-up; although 67% of the original cohort were measured at three years. Because of the natural progression of children at school, the original clusters did not remain intact and therefore we had to use a different method of analysis from the original study. Unfortunately because of financial and time limitations we were not able to measure any further changes in consumption of carbonated drinks, or the socioeconomic status and pubertal status of these children.

The original project provided hope that a simple intervention could be beneficial in preventing obesity, but our new results show no effect two years after the end of the intervention. Evidence suggests that it would be beneficial for the whole population to decrease consumption of soft drinks, as these drinks have a high energy intake with little nutritional benefit. The recent UK obesity guidelines from the National Institute for Health and Clinical Excellence (NICE) highlight the important role that schools can play in promoting healthy lifestyles. Obesity is a complex condition, and another report suggests that specific interventions may ignore different interlinking influences. It remains unclear whether specific interventions or those that focus on all aspects of the diet and physical activity are the most successful. Perhaps the true impact of any school based intervention can effectively be evaluated only if the interventions are continuous.

---

**Table 1** Change in body mass index (BMI), centile SD scores (z scores), and waist SD scores (z scores) at 12 months and 3 years after baseline

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>Mean difference (95% CI), P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (n=486)</td>
<td>17.5 (2.36)</td>
<td>17.2 (2.14)</td>
<td>0.24 (−0.16 to 0.64), P=0.24</td>
</tr>
<tr>
<td>After 12 months (n=474)</td>
<td>18.3 (2.85)</td>
<td>17.8 (2.45)</td>
<td>0.59 (0.11 to 1.06), P=0.02</td>
</tr>
<tr>
<td>After 3 years (n=434)</td>
<td>19.7 (3.36)</td>
<td>19.0 (3.21)</td>
<td>0.68 (0.06 to 1.30), P=0.03</td>
</tr>
<tr>
<td><strong>Change in BMI from baseline†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 12 months (n=455)</td>
<td>0.71 (1.45)</td>
<td>0.62 (0.79)</td>
<td>0.10 (−0.11 to 0.31), P=0.56</td>
</tr>
<tr>
<td>After 3 years (n=418)</td>
<td>2.14 (1.64)</td>
<td>1.88 (1.71)</td>
<td>0.26 (−0.07 to 0.58), P=0.12</td>
</tr>
<tr>
<td><strong>Centile z score (SD score)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (n=486)</td>
<td>0.53 (0.98)</td>
<td>0.44 (0.98)</td>
<td>0.08 (−0.09 to 0.26), P=0.36</td>
</tr>
<tr>
<td>After 12 months (n=474)</td>
<td>0.63 (1.07)</td>
<td>0.44 (1.01)</td>
<td>0.20 (0.01 to 0.38), P=0.04</td>
</tr>
<tr>
<td>After 3 years (n=434)</td>
<td>0.63 (1.12)</td>
<td>0.39 (1.17)</td>
<td>0.24 (0.02 to 0.46), P=0.03</td>
</tr>
<tr>
<td><strong>Change in centile z score (SD score)‡ from baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 12 months (n=455)</td>
<td>0.05 (0.57)</td>
<td>0.03 (0.30)</td>
<td>0.02 (−0.06 to 0.11), P=0.60</td>
</tr>
<tr>
<td>After 3 years‡ (n=418)</td>
<td>0.10 (0.53)</td>
<td>0.01 (0.58)</td>
<td>0.10 (−0.00 to 0.21), P=0.06</td>
</tr>
<tr>
<td><strong>Waist circumference z score (SD score)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (n=486)</td>
<td>0.85 (0.94)</td>
<td>0.83 (0.91)</td>
<td>0.03 (−0.14 to 0.19), P=0.76</td>
</tr>
<tr>
<td>After 12 months (n=474)</td>
<td>0.99 (0.93)</td>
<td>0.88 (0.87)</td>
<td>0.11 (−0.05 to 0.27), P=0.19</td>
</tr>
<tr>
<td>After 3 years (n=434)</td>
<td>0.96 (1.22)</td>
<td>0.80 (1.07)</td>
<td>0.15 (−0.06 to 0.37), P=0.17</td>
</tr>
<tr>
<td><strong>Change in waist circumference z score (SD score) from baseline†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 12 months (n=455)</td>
<td>0.08 (0.64)</td>
<td>0.08 (0.47)</td>
<td>0.01 (−0.09 to 0.12), P=0.81</td>
</tr>
<tr>
<td>After 3 years (n=418)</td>
<td>0.09 (0.99)</td>
<td>0.01 (0.66)</td>
<td>0.09 (−0.06 to 0.26), P=0.35</td>
</tr>
</tbody>
</table>

*Based on maximum number of children in each cluster.  †Based on children with data at baseline and 12 months or 3 years.  ‡Primary outcome.

**Table 2** Prevalence of overweight at 12 months and 3 years after baseline

<table>
<thead>
<tr>
<th></th>
<th>Control (%)</th>
<th>Intervention (%)</th>
<th>Odds ratio (95% CI), P value</th>
<th>Risk difference* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>20.6</td>
<td>17.4</td>
<td>0.79 (0.50 to 1.26), P=0.33</td>
<td>3.2% (−4.23% to 10.6%)</td>
</tr>
<tr>
<td>After 12 months (n=474)</td>
<td>28.5</td>
<td>18.7</td>
<td>0.58 (0.37 to 0.89), P=0.01</td>
<td>9.8% (1.83% to 17.8%)</td>
</tr>
<tr>
<td>After 3 years† (n=434)</td>
<td>30.2</td>
<td>25.6</td>
<td>0.79 (0.52 to 1.21), P=0.28</td>
<td>4.6% (−4.3% to 13.5%)</td>
</tr>
</tbody>
</table>

*Calculated assuming an intracluster correlation of 0.  †Primary outcome.
We thank the headmasters, teachers, parents, and children at the participating schools. We also thank David Phillips for discussion and advice and Julia Knott for assistance with data entry.

Contributors: JJ and DK developed the original idea. JJ delivered the education programme, carried out the anthropometric measurements, and analysed the data. All authors contributed to writing the manuscript. PT provided statistical and methodological advice. DK directed the project and is guarantor.

Funding: Internal resources within Bournemouth Diabetes and Endocrine Centre. JJ received a research scholarship from the Florence Nightingale Foundation (Band Trust Scholarship).

Competing interests: DK had a child attending one the schools involved in the original project.

Ethical approval: Dorset research and ethics committee approved the study.

Accepted: 2 August 2007
Diagnosis and management of cervical cancer

Patrick Petignat,1 Michel Roy2

Cervical cancer is the second most common cancer in women worldwide, with more than half a million new cases diagnosed in 2005.1 The disease disproportionately affects the poorest regions—more than 80% of cases are found in developing nations, mainly in Latin America, sub-Saharan Africa, and the Indian subcontinent.1 Cervical cancer is an important cause of early loss of life as it affects relatively young women. Important advances have taken place in the diagnosis and treatment of this cancer in recent years. Surgery or chemoradiotherapy can cure 80-95% of women with early stage disease (stages I and II) and 60% with stage III disease (table).2-5

Sources and selection criteria
We searched the literature to identify all relevant articles published from 1966 to March 2007 (PubMed and Cochrane database) using a combination of the terms “cervical cancer”, “diagnosis”, and “management”. Variables of interest were cervical cancer, surgery, chemotherapy, radiotherapy, chemoradiotherapy, complications of treatment, recurrence, and follow-up. Much of the clinical management discussed in this review was based on meta-analyses, systematic reviews, and phase III randomised controlled trials (RCTs).

What causes cervical cancer?
Infection with high risk types of human papillomavirus is the main cause of cervical cancer.6 This has obvious implications for primary prevention (vaccination) and secondary prevention (screening) of this disease.

How is cervical cancer diagnosed?
When a lesion is visible with the naked eye, conisation is contraindicated, and a cervical biopsy will usually provide the diagnosis. Conisation is indicated when frank invasion cannot be ruled out by a colposcopically directed biopsy, or when colposcopy is unsatisfactory and the results of a smear test show a high grade lesion.

Pathology
Squamous cell carcinoma accounts for about two thirds of all cervical cancers. Adenocarcinoma has many histological variations and is found in 15-25% of cases. Unusual histological variants include clear cell carcinoma, neuroendocrine carcinoma, and adeno-squamous carcinoma. Tumour grade (well differentiated, moderately differentiated, and poorly differentiated), depth and width of invasion, and presence (or absence) of invasion of lymphovascular space are prognostic factors that should be adequately assessed.

Cervical cancer is a clinically staged disease
The International Federation of Gynaecology and Obstetrics (FIGO) staging system is the most commonly used (table).7 It takes into account the results of the physical examination, colposcopy, histopathology (cervical biopsy or conisation), radiography (for example, chest radiography, intravenous pyelography, and barium enema), and endoscopy (for example, cystoscopy or sigmoidoscopy). Suspected invasion of the bladder or the rectum should be confirmed by biopsy.
What is the value of imaging techniques?
Computed tomography or magnetic resonance imaging is often used to define lymph node status and to assess the extent of local disease. Because they rely on size and morphological criteria to recognise lymph node metastases, it is difficult to identify normal sized nodal metastases using these methods. A recent prospective study with histopathological results as a reference found that combined positron emission tomography and computed tomography may be useful for detecting smaller nodal metastases.

What is the value of surgical staging?
Surgical staging includes pelvic lymphadenectomy and para-aortic lymphadenectomy. Many investigators have reported excellent results after surgical staging, but the only RCT found no survival advantage of surgical staging over clinical staging. A non-randomised comparison of extraperitoneal and transperitoneal surgical staging found that both techniques had similar accuracy and surgical complications, but a lower rate of enteric complications after irradiation was noted with the extraperitoneal approach. Laparoscopic extraperitoneal approaches may take advantage of both laparoscopy and retroperitoneal dissection. Compared with FIGO clinical staging, surgical staging improved the accuracy of diagnosis in 24% of stage IB tumours, 52% of stage II tumours, and 45% of stage IIIB tumours.

Is clinical staging still the gold standard?
Evidence now shows that computed tomography, magnetic resonance imaging, positron emission tomography, and surgical staging are better than clinical staging for identifying the true extent of the disease. However, none of these methods has been incorporated into the FIGO staging system yet. The main reason is that cervical cancer is most prevalent in developing countries, and staging methods should be universally available, standardised, and comparable around the world. There is also still a lack of consensus about the best imaging modality and the value of surgical staging. Future FIGO staging systems may consider incorporating some of these investigations into the classification.

Managing early stage disease
FIGO stage IA1
Patients with stage IA1 disease should be diagnosed on the basis of conisation using a technique that does not result in cauterised margins, which may obscure surgical margins. The importance of involvement of the lymphovascular space in stage IA1 disease is not clear, but most practitioners favour radical surgery or radiation if it is present.

FIGO stage IA2, IB1, and IIA (figure)
Radical hysterectomy is the treatment of choice for young healthy patients because it preserves ovarian function. Radiotherapy is thought to be equally effective for patients with early stage cancer. An RCT comparing primary surgery with primary radiotherapy in 347 patients with stage IB-IIB cervical cancer showed that disease-free and overall survival for the two groups were the same.

Is fertility sparing surgery an option?
Radical trachelectomy involves removal of the cervix with parametrial tissue after pelvic lymphadenectomy. It is a curative procedure designed to retain fertility in young women with early stage cervical cancer. About 50% of women with cervical carcinoma are under 40 and may be eligible for this treatment. To date, more than 350 cases have been reported. Cure rates are comparable to radical hysterectomy, and women who later try to conceive have more than 50% chance of pregnancy. Radical trachelectomy is emerging as an acceptable alternative for patients with early stage cervical cancer who wish to preserve fertility.

What is the role of sentinel lymph node biopsy in cervical cancer?
The goals of sentinel lymph node mapping are to avoid complete pelvic lymphadenectomy and to identify alternative lymphatic drainage sites. Preliminary results of observational studies have shown that when a sentinel lymph node is metastatic on frozen section, radical surgery can be omitted in favour of radiotherapy. Whether full pelvic lymphadenectomy can safely be omitted after a negative sentinel lymph node biopsy is still unclear.

FIGO stage IB2 (figure)
Patients with stage IB2 disease (tumour >4 cm) are poor candidates for primary radical surgery because most will ultimately need adjuvant radiotherapy. Chemoradiotherapy is the treatment of choice. An RCT showed that adding weekly cisplatin to pelvic radiotherapy before hysterectomy reduced the risk of
When should adjuvant radiotherapy be added?

Patients with early stage disease have an intermediate risk of recurrence postoperatively if they have two of the following factors: large tumour size, deep stromal invasion, or involvement of the lymphovascular space. An RCT evaluating 277 women with stage IB disease (radiotherapy versus “no further treatment”) and at least two risk factors showed that adjuvant radiotherapy decreased the rate of recurrence and improved disease free survival. However, the two groups showed no overall difference in survival. Therefore, despite the positive findings, options regarding adjuvant radiotherapy for surgical patients with selected risk factors remain debatable.

When should chemoradiotherapy be added?

Patients with early stage disease have a high risk of recurrence postoperatively if they have one of the following risk factors: positive nodes, parametrial invasion, or positive surgical margins. Such patients should receive adjuvant cisplatin based chemoradiotherapy after hysterectomy, as shown by an RCT.

Managing advanced stage disease

FIGO stage IB, III, and IVA

Three RCTs have shown that improvements in progression free survival and overall survival are greater for chemoradiotherapy than for radiation alone in patients with locally advanced stage IB-IIA disease. Benefits have been confirmed by a Cochrane review. Platinum based chemoradiotherapy is now the standard of care for these patients. The role of neoadjuvant chemotherapy followed by radical surgery is currently being studied by the European Organisation for Research and Treatment of Cancer.

FIGO stage IVA

Treatment is only palliative in patients with stage IVA disease, so quality of life and toxicity profiles must influence the choice of treatment. The only RCT to identify a chemotherapy regimen that gave these patients an overall survival advantage and that included quality of life measurements compared cisplatin with cisplatin plus topotecan. Progression free survival and overall survival favoured combination chemotherapy, but toxicity was more common, although it did not significantly reduce quality of life.

Follow-up

The aim of follow-up is to detect relapse at a stage where salvage treatment has the best chance of being effective and to monitor and treat treatment related toxicity. Most recurrences occur in the first two years after primary treatment. Physical examination includes rectovaginal examination, nodal assessment (especially supraclavicular), and cervical smears. Examinations should be performed every three to four months in the first three years. Thereafter, they should be performed every six months and after five years annually. Pain, vaginal bleeding, and gastrointestinal or genitourinary dysfunction must be investigated.

Treating recurrent disease

Recurrent cervical cancer is almost always incurable and less than 5% of patients who develop recurrence are alive at five years. Patients who develop pelvic recurrence after radical hysterectomy may be salvaged with chemoradiotherapy if they have not previously been irradiated. Central pelvic recurrences after radiation or chemoradiotherapy may undergo curative surgery with pelvic exenteration in the absence of metastatic disease.

Conclusions

Over the past few years, in most industrialised countries women with cervical cancer have benefited from improved imaging techniques, better treatments (including chemoradiotherapy), and more conservative surgical approaches. In low resource settings—where facilities for radiology, chemoradiotherapy, and supportive care are limited or unavailable—it is...
important to identify which resources fill healthcare needs most effectively and to consider alternative approaches. In the near future, the best way to improve mortality and morbidity from cervical cancer will probably be to focus on primary prevention with prophylactic vaccines against human papillomavirus.

We thank Martin Tramer for his constructive comments.

Contributors: This paper was jointly written by PP and MR. PP is guarantor. Funding: No external funding. Competing interests: None declared. Provenance and peer review: Commissioned; externally peer reviewed.


PREGNANCY PLUS

Epilepsy in pregnancy

Torbjorn Tomson,1 Vilho Hiilesmaa2

This article explores the therapeutic problems that arise when a patient with epilepsy on treatment becomes pregnant and needs both effective seizure control and attention to the safety of her fetus.

Epilepsy is usually managed by neurologists or general practitioners. Managing epilepsy during pregnancy is a major therapeutic challenge, as the potential adverse effects of antiepileptic drugs on the fetus must be balanced against the maternal and fetal risks associated with uncontrolled seizures. The situation we describe is ideal as our patient told her neurologist of her plans to become pregnant (see Scenario box). In such cases, the patient can receive counselling and treatment changes can be put in place before conception, whereas in many cases the woman is already pregnant when she alerts her doctors. Switching from valproate to lamotrigine was successful in our patient, but the effects of such switches are unpredictable. Some patients will have relapses or an increase in the frequency of seizures, which may prompt trials of other drugs. Some women may need to revert to the original treatment to control seizures—in this case valproate at the lowest effective dosage. Any switches between antiepileptic drugs should be accomplished and assessed before conception to avoid risks to the fetus induced by maternal seizures.

This article focuses on the management of women who have seizures before pregnancy and not those who have them for the first time during pregnancy, such as women who develop eclampsia.

How common is epilepsy in pregnancy?

Population based studies indicate a prevalence of epilepsy in pregnant women of up to 0.7%, although register based studies have reported prevalences of 0.2-0.4%. Women other than those with epilepsy take antiepileptic drugs, however, as they are increasingly being prescribed for psychiatric disorders and neuropathic pain disorders.

Does pregnancy affect epilepsy?

Pregnancy has no effect on seizure control in most women with epilepsy. Although population based studies indicate that symptoms deteriorate in 15-30% of women, they improve in a similar proportion of women. This could partly reflect random fluctuations. In a prospective international study of 1736 pregnancies, about 60% of women remained seizure free throughout pregnancy. Delivery and labour carry an increased risk, with 2-5% of women with epilepsy having seizures at these times. Antiepileptic drugs may differ with respect to efficacy during pregnancy. Fewer women were seizure free on oxcarbazepine, and dose increases during pregnancy were more frequent with oxcarbazepine and lamotrigine. This may be related to changes in the pharmacokinetics of these drugs during pregnancy (box 1).

How do seizures affect pregnancy?

Although the absolute risk is low, a larger than expected proportion of maternal deaths in the United Kingdom is caused by epilepsy. This may be accounted for by seizures in women who stop taking their drugs when...
they realise that they are pregnant. This illustrates the importance of effective treatment. While other seizure types have negligible effects, tonic-clonic seizures increase the pressure in the pregnant uterus, and may lead to trauma if the patient falls. They can also cause lactic acidosis, which is transferred to the fetus. However, recent reports suggest that the number of stillbirths in adequately treated women with epilepsy is similar to that in the background population. There is no hard evidence of increased risk of obstetric complications, such as pre-eclampsia, premature delivery, or placental abruption. The seizures or the epilepsy itself are unlikely to contribute greatly to the increased risk of birth defects reported for women with epilepsy.

Epilepsy is not an indication for early induction of labour or elective caesarean section. Caesarean section is needed if frequent tonic-clonic seizures or other seizures greatly impair cooperation in the forthcoming labour and delivery. A caesarean delivery may be necessary if a generalised tonic-clonic seizure occurs during labour. Refractory status epilepticus in the third trimester of pregnancy could also be an indication for a caesarean. These are rare occurrences and most women with epilepsy have normal deliveries.

**What are the risks to the fetus from antiepileptic drugs?**

Antiepileptic drugs have been associated with birth defects and impaired postnatal cognitive development. The risk of malformations is two to three times that expected in the general population with older generation drugs, such as phenobarbital, phenytoin, carbamazepine, and valproate. Treatment with more than one drug is associated with higher rates of birth defects. The risk for monotherapy with valproate, and probably other drugs, seems to be dose dependent. The pattern of birth defects varies with the type of antiepileptic drug. Neural tube defects have been linked to the use of carbamazepine, and particularly valproate. A recent report suggests that lamotrigine increases the risk of oral clefts.

The table summarises the evidence from recent large registries on the teratogenic effects of different antiepileptic drugs. Because teratogenic effects cannot be analysed in randomised controlled trials, the evidence comes from observational studies (at best class 2 level) and results must be interpreted with caution. These studies all indicate a greater risk for birth defects with valproate than with other antiepileptic drugs—rates range from 6% to 11% in children exposed to valproate (table). The North American epilepsy and pregnancy registry has also reported major malformations in 6.5% of 77 prospective pregnancies with phenobarbital as monotherapy, four times higher than in an external unexposed control group, but not significantly higher than three other antiepileptic drugs combined from the same registry. However, other retrospective and prospective cohort studies have not revealed higher malformation rates with phenobarbital than with carbamazepine. Except for lamotrigine, data on pregnancy outcome for new antiepileptic drugs are too scarce to assess their teratogenicity.

Data on effects of antiepileptic drugs on cognitive development in the offspring of mothers treated in pregnancy are less conclusive. However, a recent retrospective study from the UK suggests that valproate, in a dose dependent way, may be associated with significantly lower verbal IQ compared with carbamazepine and phenytoin or with unexposed children. A similar trend, although not statistically significant, was found in two small population based prospective studies.

These observational studies on pregnancy outcome need to be interpreted with caution as potential confounding factors have not been controlled for. Nevertheless, higher birth defect rates with valproate than with carbamazepine and the possibility of intellectual impairment call for caution in the use of valproate in pregnancy. Our patient was therefore switched to lamotrigine when planning her pregnancy. Any major changes in treatment should be made long before conception so that the effects of the new treatment can be assessed before pregnancy. The lowest effective dosage should be established for the appropriate drug as monotherapy. In some cases, seizure control can be maintained only with valproate. Low dose valproate (<800-1000 mg/day) may be no more harmful to the fetus than other drugs, and this dosage controls seizures in many patients.

### Malformation associated with monotherapy with different antiepileptic drugs

<table>
<thead>
<tr>
<th>Register</th>
<th>Total number of pregnancies</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish register study&lt;sup&gt;25&lt;/sup&gt;</td>
<td>1398</td>
<td>Valproate 9.7% (268)</td>
</tr>
<tr>
<td>Finnish national drug prescription registry&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1231</td>
<td>Carbamazepine 4.0% (703)</td>
</tr>
<tr>
<td>UK epilepsy and pregnancy register&lt;sup&gt;28&lt;/sup&gt;</td>
<td>3607</td>
<td>Lamotrigine –</td>
</tr>
<tr>
<td>Prospective international lamotrigine registry&lt;sup&gt;26&lt;/sup&gt;</td>
<td>802</td>
<td>Phenobarbital –</td>
</tr>
<tr>
<td>North American epilepsy and pregnancy registry&lt;sup&gt;27-29&lt;/sup&gt;</td>
<td>10.7% (149)</td>
<td>Valproate 2.5% (873)</td>
</tr>
</tbody>
</table>

Values are reported percentage of malformations (number of exposed). The registries summarised use different methodologies, have different criteria for malformations, and assess different populations. Malformation rates should therefore not be compared across studies. They are all non-randomised observational studies and do not provide class I evidence.
pronounced for lamotrigine and possibly oxcarbazepine, drugs eliminated through glucuronidation. Lamotrigine plasma concentrations can decline during gestation to 30% or less of prepregnancy values, with subsequent breakthrough seizures. Similar but more limited data exist for oxcarbazepine. However, women vary greatly in the way that pregnancy affects drug concentrations (box 2). Monitoring maternal drug concentrations is therefore recommended, particularly lamotrigine and oxcarbazepine, although evidence for the effectiveness of such monitoring in general is lacking. Ideally, one or two measurements should be obtained before pregnancy to record the patient’s optimal serum concentration. Sampling once each trimester is often recommended, but more frequent sampling could be justified for lamotrigine. A pronounced decline during pregnancy might, as in our case, prompt a dose adjustment, especially if the patient has been sensitive to changes in drug concentrations before pregnancy. In settings where such monitoring is unavailable, dosage adjustments are based on clinical grounds alone, so closer clinical follow-up might be warranted. The importance of meticulous compliance should be stressed. An increase in dosage should be considered early if there is a trend for deterioration in seizure control, especially for drugs that are known to be affected by pregnancy.

Preconception planning

Young women with epilepsy need pregnancy related counselling. Box 3 lists the problems that should be discussed. This task may fall to the treating doctor or the patient may be referred to an appropriate centre. Because around half of pregnancies are unplanned, these problems should be brought up well before pregnancy is contemplated. Box 4 outlines strategies to optimise the treatment of epilepsy in patients seeking advice before pregnancy.

Unplanned pregnancies are often diagnosed later than five to 11 weeks. By then, the most sensitive period of fetal development has already passed, so it makes little sense to change the drug because of teratogenic risks (box 5). The woman should be told that inadvertent exposure to antiepileptic drugs is not an indication for therapeutic abortion. Counselling is as important here as it is before pregnancy, and it usually helps the woman to gain a realistic perspective of the risks. The problems listed in box 3 also apply in unplanned pregnancies.

**Box 2 | Mechanisms for altered drug concentrations in pregnancy**

- Enhanced metabolic elimination through enzyme induction (most important mechanism, relevant for drugs that are metabolised)
- Impaired drug absorption (for example, caused by hyperemesis gravidarum)
- Physiologically increased plasma volume
- Decreased drug binding to plasma proteins (relevant for highly bound drugs such as phenytoin and valproate; this does not alter drug effects, but total drug concentrations may be misleading—measure unbound concentrations if phenytoin or valproate are monitored)
- Increased renal elimination

Although evidence is lacking for the effectiveness of folic acid in preventing teratogenicity induced by antiepileptic drugs, and the appropriate dosage is still debated, many guidelines recommend that women taking such drugs should take up to 5 mg of folate a day from before conception. Because of the definite, albeit small, risk of teratogenic effects of antiepileptic drugs, women taking these drugs should be offered prenatal diagnostics. Using modern targeted ultrasonography, almost all neural tube defects can be diagnosed at 12-22 weeks of pregnancy. Most of the other major structural abnormalities can also be detected, but the use of prenatal diagnostics depends on ethical issues and local legislation.

**Obstetric management and breastfeeding**

Because of the definite, albeit small, risk of teratogenic effects of antiepileptic drugs, women taking these drugs should be offered prenatal diagnostics. Using modern targeted ultrasonography, almost all neural tube defects can be diagnosed at 12-22 weeks of pregnancy. Most of the other major structural abnormalities can also be detected, but the use of prenatal diagnostics depends on ethical issues and local legislation.

Extra obstetric follow-up is not needed in seizure-free patients, as their risk of common obstetric complications is not increased. Those with seizures in pregnancy have a risk of seizures in labour, so delivery should take place in an appropriately equipped unit.

Breast feeding is generally encouraged, although
relatively high drug concentrations have occasionally been reported in children of mothers treated with some drugs, such as phenobarbital, ethosuximide, and lamotrigine. Mothers taking these drugs should be told about the possibility of drug effects on the neonate but not generally advised against breast feeding.

Conclusions

Women with epilepsy need counselling to optimise treatment before conception. Antiepileptic drugs are usually needed to control seizures despite their indisputable, albeit low, risks to the fetus. Most patients will have uneventful pregnancies and deliveries, provided adequate care and facilities are available. Our scenario is an example of good and timely practice.

Contributors: TT and VH contributed equally with individual sections to the first draft, which was prepared by TT. TT and VH jointly revised and finalised the manuscript.

Funding: None.

Competing interests: TT has received speaker’s honoraria or research grants (or both) from Emissari, GlaxoSmithKline, Janssen-Cilag, Novartis, Pfizer, Sanofi-Aventis, and UCB.

Provenance and peer review: Not commissioned; externally peer reviewed.


Box 4 | Optimising treatment of epilepsy in patients seeking advice before pregnancy

- Confirm diagnosis of epilepsy and reassess indication for treatment with antiepileptic drugs.
- Consider gradually withdrawing drugs before conception if epilepsy is in remission and the risk of recurrence is low; the woman is aware of the risk and consequences of recurrence; and there is enough time before conception to ascertain whether epilepsy remains in remission after withdrawal.
- Select the most appropriate antiepileptic drug for the patient’s type of epilepsy; avoid valproate if equally effective alternatives are available.
- Changing drugs in a woman who is seizure free is seldom justified except in the case of valproate.
- Aim at monotherapy with the lowest effective dosage.
- Document the patient’s optimal drug concentration before pregnancy.

Box 5 | Optimising treatment of epilepsy in patients who are already pregnant

- Avoidate fears of a patient with unplanned pregnancy (box 3).
- Withdrawing or changing antiepileptic drugs is rarely justified if seizures are well controlled. Risks probably outweigh potential gains.
- Monitor treatment more closely than normal; the frequency of clinical visits depends on seizure control and other factors, but once a trimester is standard; monitor drug concentrations of lamotrigine in particular and possibly oxcarbazepine.
- Adjust drug doses to optimise treatment in patients who have tonic-clonic seizures during pregnancy.
- Dosage adjustments may also be justified in patients with an increase in other seizure types and in patients who have a pronounced decline in drug concentrations.
- Reassure the patient that with adequate treatment the neurological and obstetric risks are low.
Patients with jaundice of unknown cause need their thyroid function tested to exclude an underlying thyroid problem

We report on a patient with Graves’ thyrotoxicosis, whose presentation with jaundice and hepatic dysfunction led to unnecessary investigations and a delay in management. We suggest patients with jaundice of unknown cause should have thyroid function tests performed as a part of their routine investigation.

Case report
A 36 year old labourer was referred to the gastroenterology department at his local hospital with a three month history of general malaise, myalgia, and painless jaundice. He reported a 25 kg weight loss and a change of bowel habit with pale diarrhoea and steatorrhoea, passing stools up to 20 times daily, with some darkening of his urine.

He had no medical history of note, was a non-smoker, consumed around 5 units of alcohol a week, and lived with his wife and teenage daughter. He had not travelled abroad recently and had had no occupational exposure to hepatitis or hepatotoxic chemicals or drugs. In addition, he had not received any blood products, undergone body piercings, or experienced any previous episodes of jaundice.

On clinical examination he was markedly cachetic and icteric (fig 1), with no signs of chronic liver disease or tattoos evident. He had no fever and a pulse rate of 78 beats/min, blood pressure of 134/78 mm Hg, respiratory rate of 14 breaths/min, and BMI of 23.9. We detected no lymphadenopathy or testicular atrophy or organomegaly on abdominal examination.

Results of full blood count and tests for urea, electrolytes, and random glucose were all within normal limits. Inflammatory markers were raised with the erythrocyte sedimentation rate of 47 mm in the first hour and C reactive protein of 52 mg/l. Results of routine hepatic function tests were 581 (normal range 1-22) μmol/l for bilirubin, 184 (30-115) U/l for alkaline phosphatase, 26 (5-48) U/l for γ-glutamyltransferase, 146 (5-40) U/l for alanine aminotransferase, 69 (5-45) U/l for aspartate aminotransferase, and 33 g/l (35-50) for albumin. Results of clotting and coagulation studies, and hepatitis investigations were normal, and autoantibody testing showed positive smooth muscle antibody of low titre (1:40), with negative results for other autoantibodies (mitochondrial antibodies).

Abdominal ultrasonography showed normal liver, biliary tree, and gall bladder with no evidence of biliary obstruction; computerised tomography of the abdomen also showed normal liver size and texture. Percutaneous liver biopsy showed evidence of cholestasis, and subsequent magnetic resonance cholangiopancreatography found no abnormality in the bile and pancreatic ducts.

Because of his unresolving jaundice and ongoing hepatic dysfunction with an undefined cause the initial medical team investigating his condition considered liver transplantation. He was subsequently referred to the gastroenterology department at our tertiary centre for a further opinion.

On review at our hospital by the gastroenterologists...
he was icteric and cachetic and reported a poor appetite with frequent bowel motions, and stool examination confirmed steatorrhoea. Thyroid function tests were requested as part of the routine investigation into weight loss and subsequently showed a free thyroxine (FT4) concentration of 24.8 (normal 9.8-23.1) pmol/l, free triiodothyronine (FT3) concentration 9.8 (3.5-6.5) pmol/l, and a thyroid stimulating hormone (TSH) concentration of 0.07 (0.35-5.5) mU/l, consistent with a diagnosis of thyrotoxicosis.

He was referred to the endocrinologists for further investigations and management. On examination he was not tachycardic, and there was no evidence of sweating, tremor, goitre, thyroid eye disease, or skin changes. Test results for thyroperoxidase and thyroid stimulating hormone receptor antibodies (TSAB) were both positive, 97.9 kU/l (normal <32.0) and 8.7 IU/l (<1.5) IU/l, respectively. We diagnosed Graves’ thyrotoxicosis and treated the patient with carbimazole. He began to improve clinically with resolution of his liver function over the next few weeks. He gained weight, his bowel frequency reduced, and his jaundice subsided with normalisation of his thyroid function.

He remained on a block and replace regimen with carbimazole and levothyroxine for six months. A year after his original diagnosis he remains euthyroid and well (fig 2). He has regained his original weight and test results for thyroid stimulating hormone receptor antibodies are now negative (<1.5 IU/l).

Presently he is kept under regular review at the thyroid clinic and will be treated with radioiodine if there is a relapse of his thyrotoxicosis.

Discussion
Thyrotoxicosis may be associated with various abnormalities in liver function1 and can be a cause of profound cholestasis,2 which may be associated with steatorrhoea. In this case the malabsorption caused by steatorrhoea augmented the weight loss caused by hyperthyroidism.

Thyroid hormone concentrations are important for normal hepatic function and metabolism of bilirubin.3 Lack of knowledge of the association between thyroid and liver abnormalities can lead to misdiagnosis, mistakes in management of patients, and consequent under-reporting of those patients affected. Published case series in those with hyperthyroidism show that results of liver tests can be severely abnormal and modest abnormalities are common.4,5 In certain individuals this can lead to serious morbidity and even mortality.

The liver has an important role in metabolism of thyroid hormone, and autopsies have shown hepatic inflammation, fibrosis, and centrilobular necrosis in patients with hyperthyroidism.6 The pathogenesis of hepatic dysfunction is unknown; one theory suggests the liver is damaged by the systemic effects of excess thyroid hormone. Hyperthyroidism induces an increased metabolic rate, which is associated with increased oxidative capacity and oxidative damage of tissue.7 Thyroid hormones are also known to increase production of insulin-like growth factor within the liver8 and can cause changes in fatty acid and lipid synthesis. This hypermetabolic state makes the liver more susceptible to injury, and, in addition, thyroid hormones might also have a direct toxic effect on hepatic tissue.

Other associations between liver dysfunction and thyroid disease per se or its management are also well described. Autoimmune hepatitis is associated with autoimmune thyroid disease, and raised aminotransferase concentrations may be seen before thyrotoxicosis is diagnosed.9 If these persist after correction of thyroid dysfunction, liver biopsy may be required to differentiate autoimmune hepatitis from liver involvement secondary to thyroid disease as immunosuppressive therapies are usually indicated for autoimmune hepatitis.

A strong association exists between Hashimoto’s thyroiditis and primary biliary cirrhosis.10 In those affected, autoimmune thyroid failure might occur associated with the presence of thyroid microsome, thyroperoxidase, and thyroglobulin antibodies in addition to the presence of goitre. Patients with these antibodies or hypothyroidism (either clinical or biochemical), or both, may be found in a considerable number of those with primary biliary cirrhosis.

Drug induced hepatotoxicity should be considered in those who present with hepatic dysfunction after initiation of thionamide therapy. The estimated incidence of antithyroid associated hepatotoxicity with both carbimazole and propylthiouracil is about 0.5%.11 Propylthiouracil induced hepatotoxicity, although rare, can be severe enough to cause hepatic failure with associated morbidity and mortality12; hepatic function should therefore be monitored routinely during treatment.

Contributors: PJDO wrote the paper; JHL and AJG reviewed the paper. All authors were involved in clinical management of the patient. AJG is guarantor.

Competing interests: None declared.

Funding: None.

Provenance and peer review: Commissioned; externally peer reviewed.

Why the culture of medicine has to change

PERSONAL VIEW Richard Hayward

Why haven’t doctors embraced health service reform? The thought came to me during a recent medicolegal conference with counsel. The year under discussion was 1996, and the issue was a possible delay in referral for a specialist appointment. The general practitioner’s letter to the local hospital had been annotated for an appointment “soon” by the consultant (correctly, it was agreed) and “soon” in 1996 meant three months. But before those three months were up the child had collapsed with an intracranial catastrophe and has been left severely damaged as a result. And my thought was, why did the medical profession remain generally silent for so long about waiting times which for “clinically non-urgent” surgery once stretched to well over a year? It wasn’t as if doctors weren’t aware of the problem, and I don’t buy into the idea that it was all a cynical ploy to boost private practice. When reducing waiting times became a government priority the medical response was less than enthusiastic: the most common excuse was that it involved overriding clinical priorities by managerial (non-medical) diktat—a justifiable complaint, but even so.

Tony Blair said in a conference speech not long after the 1997 landslide that the culture of medicine would have to change. What do we mean by the culture of medicine? The word I kept coming up with was independence. Consider this. Now doctors have been asked (to put it politely) by a monopoly employer to surrender a measure of their independent individual to individual business, even when we’re working in teams—indeed, the doctor-patient relationship is actually defined in the singular.

I used to sit on the selection committee for a London teaching hospital and the most common response to the inevitable ice breaker, “Why do you want to be a doctor?” was “I’ve always liked science at school and I want to work with people.” Early on, the practice of medicine is based on a culture of science oriented attention to people as individuals. Such an attitude takes priority over concern for the community as a whole—which is not to say that doctors aren’t interested in the NHS, but it’s too diffuse a focus to warm their blood. This is why recruitment to specialties such as preventive medicine and public health is so difficult, despite the fact that treating the community as a whole (for example, through improved sanitation, nutrition, and immunisation) has historically provided greater health benefits than the individual to individual treatments that most clinicians practice.

Now doctors have been asked (to put it politely) by a monopoly employer to surrender a measure of their independent individual to individual business for a community-wide or societal approach to disease, disability, and deformity. The cultural shift that is needed is seen as so threatening that even substantial pay increases have not been enough. The medical profession’s response has been interpreted by government as at best conservative, and at worst self-interested protectionism, and this has led to the profession being effectively sidelined during the process of health service reform. Even the royal colleges, who profess the improvement and protection of standards of health care as their primary function, have failed to provide a bulwark against state encroachment on clinical practice. Perhaps this is not surprising—they are headed by senior and independent practitioners, terrified that their institutions will be left completely out of the policy making loop.

So we have two contradictory forces at work. Health care has become an instrument of social policy for all developed societies, including ours, and independence is always in some degree of conflict with the state.

The MTAS fiasco stands as a dire warning to government and medical profession alike of trying to reform health care without cooperation between the two

But the government has not completed its agenda—indeed, assuming a target of the best health care the nation can afford, it never can—so more pressure is inevitable. And what better way to alter the culture of medicine than to undermine the doctor-patient relationship by doing away with continuity of care? With the start already made by GPs relinquishing out of hours care, and the depredations of shift working and the European Working Time Directive on hospital practice, a cynic might claim that the government has only to sit back and wait.

But the MTAS fiasco (for which all parties must share responsibility) stands as a dire warning to government and medical profession alike of trying to reform health care without cooperation between the two. Expect the current rocky ride to continue until and unless the government and the community of independent medical practitioners find common ground—something that will require a shift of culture on both sides if the NHS is really to benefit.

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The medical rumour mill

I winced as he shoved the cannula down alongside my vein and into the soft tissues of my forearm. “Missed,” he exclaimed, and swore. We were in the common room of the medical residency and practising gaining intravenous access on each other. Despite the beer, it hurt. Only one of our group was remotely competent at practical procedures and was accorded hero status. My pain at least gave me some insight into what it is to be a patient. All doctors should have their blood gases taken by some clumsy youth. Feeling the point of a needle repeatedly tapping our carpus might make us less quick to sign the orders for carpet bomb investigations, with all the collateral damage.

One day we will all be subjected to that most levelling of experiences: becoming a patient. Held on remand in a hospital ward, all rights removed, supervised toilet trips—hospital care is an indeterminate sentence, and our release is at the discretion of some distant authority figure. If that wasn’t bad enough, there’s an intrusive interest in the care of patients who are doctors. The medical world is small and parochial, and doctors are minor medical celebrities. Medical staff directly involved in our care maintain confidentiality—but hospitals are places where undiscovered sources indulge in that most human of pastimes, gossip.

Despite the profession’s veneer of propriety, hospital corridors hum to the constant chatter of medical gossip. This contagious superbug spreads rapidly from the hospital into the community, becoming more resistant to correction on each telling. Medical gossip is different from mere social tittle-tattle, for doctors are privy to the most sensitive and privileged of personal information. Doctors unlike any other group can have their confidentiality trampled, as gossip leaks inappropriate and misleading details to medical colleagues.

We may never be able to wash our hands completely of gossip, but there is a need to recognise that it is a problem. Promoting a culture where discussing a colleague’s illness or hospital admission is not acceptable would be a start. This would involve two fundamental steps. The first, and most obvious, is for clinicians not to be repossessed if you do not keep up repayments on your mortgage.”

Tapping our carpus might make us less quick to sign the orders for carpet bomb investigations, with all the collateral damage.

FROM THE FRONTLINE
Des Spence

Don’t mention it

Flick through a few newspapers and you’ll repeatedly come across a stark warning: “Your home may be repossessed if you do not keep up repayments on your mortgage.” This threat isn’t some random frightener but a standard feature in advertisements for property loans. As such, it provides tangible balance for those contemplating the real or imagined advantages of the deals in question.

If only the possible harms of medicines were contextualised so clearly. Instead, it’s often assumed that the general public just cannot understand risk when it comes to drug treatment. So, as the thinking goes, it’s best not to go on about harms and side effects too much for fear of needlessly frightening patients or carers.

This well meaning attitude infects much of the communication (or lack of it) between healthcare professionals and patients about drug therapy. Although avoiding balanced discussion about risk may seem pragmatic, it can represent a false economy of effort, and the presumptions underlying the avoidance approach are ultimately rubbish.

It is patronising to suggest that people who, for instance, invest financially, take out insurance, travel to hazardous areas, or, yes, buy homes are unable or unwilling to weigh up positives and negatives when it comes to prescribed treatment. Of course, the capacity to make and act on these assessments will vary widely across the population. However, this variable capacity is also true of doctors, many of whom struggle with understanding and conveying the implications of published evidence for the care of the individual patient.

Debating treatment risks has practical limitations, even for the most committed professional. Limited consultation time is an obvious example, as is the often patchy nature of the data available on adverse consequences of treatment. But a pervasive cultural factor is also at work.

It has become too easy for patients to believe that drugs can be intrinsically “safe.” This relates, in part, to the potentially misleading ways in which treatment is sometimes portrayed. A classic example is dichotomising patients into supposedly wholly distinct groups such as “treatment successes” and “treatment failures.”

This type of binary classification can be useful shorthand in detailing clinical research findings, but it deliberately overlooks continuous variation between individuals in biological constitution, function, and response. When it is echoed in the information patients receive, it feeds the dangerous notion that drug therapy is an all or nothing experience in which the treatment either works or not, or causes adverse events or not, rather than showing a range of effects in different people. No sensible mortgage provider would be so simplistic.

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DRUGS, TALES, AND OTHER STORIES
Ike Iheanacho

| BMJ | 13 OCTOBER 2007 | VOLUME 335 |
A foolish, fond old man

What was King Lear’s diagnosis? There are two problems: firstly, he was a fictional character, and secondly, he is not available for tests or examination (a problem besetting all pathographers, though it also affords them infinite scope for pleasant speculation). So, screeds have been written in the last two centuries, but we are no nearer the truth—because there is no truth to come nearer to.

Let that not detain us. If we argued only about those matters that had a potentially definitive answer we should become boringly rational. Was Lear, then, demented, and if so was the dementia of the Alzheimer’s, Lewy body, or multi-infarct type? (His variable mental states suggests the second or third.) Or was he depressed, perhaps as the result of an unresolved grief reaction to the death of his wife, mother of his three daughters? This doesn’t seem likely, since he hardly mentions her, his three daughters? This doesn’t seem likely, since he hardly mentions her, perhaps because she died so long before the action of the play starts.

Do I plump for a diagnosis? Brief psychotic episode, perhaps? Manic depressive psychosis (rapid cycling type)? Or even personality disorder?

In cities, mutinies; in countries, discord; in palaces, treason; and the bond cracked ‘twixt son and father.” In reply to which Edmund soliloquises: “This is the excellent foppery of the world, that, when we are sick in fortune . . . we make guilty of our disasters the sun, the moon and the stars; as if we were villains on necessity, fool by heavenly compulsion . . . and all that we are evil in, by a divine thrusting on.”

So let us just say, with Lear himself, that he was a very foolish, fond old man. For my money, the critical point is made by the Duke of Kent, when Lear has divided his kingdom between Goneril and Regan, excluding Cordelia because she will not indulge in any extravagant declarations of love for him. Kent says:

The youngest daughter does not love thee least,
Nor are those empty-hearted, who low sounds
Reverb no hollowness.

If Lear had realised this, then none of the tragedy and suffering would have ensued.

And here, it seems to me (this is a hobby horse of mine), Lear—the play, I mean—speaks to our age directly: for is it not the case that we live in an age of emotional incontinence, when they who emote the most are believed to feel the most?

Theodore Dalrymple is a writer and retired doctor

Is it not the case that we live in an age of emotional incontinence?

No, I prefer not to do so, if only because of the warning of Edmund (the wicked bastard son of the Earl of Gloucester) against ascribing bad behaviour to anything other than our free decision to behave badly.

His father remarks, “These late eclipses in the sun and moon portend no good to us . . . Nature finds itself scourged by the consequent effects. Love cools, friendship falls off, brothers divide.”

What was Lear’s diagnosis?

BETWEEN THE LINES

Theodore Dalrymple

First published 1985

While many were learning to “study a study and test a test” in the early 1980s, another approach was developing in a small blue collar town in Ontario, Canada, at a new medical school. Internists calling themselves clinical epidemiologists (and refusing to define clinical epidemiology) were putting together a series of articles for the Canadian Medical Association Journal called “Clinical Epidemiology Roundups.” The article series was “prepared for those clinicians who are behind in their reading.” The huge success of this series led to the expansion of the concepts in the book Clinical Epidemiology: A Basic Science for Clinical Medicine.

The book emphasises formal probabilistic reasoning as a vital aspect of medical practice. This approach would later turn medicine on its head in what would become the underpinning of “evidence based medicine.” The term is nowhere in the book; it would not be coined until 1991.

The diagnosis section breaks down the process of diagnostic reasoning by explaining the analytic process and pointing out how errors occur. The section on management urges clinicians to rely on research rather than individual experiences to estimate prognosis and to decide on the best therapy. The authors introduced the number needed to treat statistic, emphasised the crucial role of randomisation in study design, and promoted the use of confidence intervals rather than p values to understand the magnitude of effect.

The book was written by clinician-researchers with a strong contrarian streak, which was needed to shake up the status quo. In a well argued editorial written before the book, lead author David Sackett called for “the mandatory retirement of experts” (but failed to heed his own advice many years later).

These authors at the McMaster School of Medicine planted the seeds that would grow into evidence based medicine and information mastery. Opening in 1965, McMaster was the first medical school to introduce problem based learning. It was this environment of inquiry—and perhaps the labouring of young Turks in the shadow of a more established medical school just down the road in Ontario—that resulted in this iconoclastic approach to medicine embodied in the book. The book is dedicated to H L Mencken, Kurt Vonnegut Jr, Douglas Adams, and (wink, wink) the emperor’s new clothes.

Over 30 years later, evidence based medicine would be named “a medical milestone” by BMJ readers. To understand the genius of EBM, one only has to explain what it means to friends and relatives outside of medicine. An explanation of how decisions should be based on the best evidence rather than solely on personal experience will be met with a reaction I often hear: “You mean you have to TEACH doctors to do this?”

It is just a sign of how any discipline, once it cloisters itself away from the greater world, can go off on the wrong trail, branching away from science to the boggy marsh of intuition, opinion, and reason revered as clinical experience. The return of empiricism as embodied in evidence based medicine, and its slow ascendance over eminence based medicine, is in large part the result of this book.

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Selling health the Tesco way—every little helps?

Can health promotion messages learn from the techniques that Tesco and McDonald’s use?

Petra Boynton examines a new book on the subject.

Before you left the house this morning or on your journey to work you’ll probably have experienced social marketing in the form of advertisements for everything from fast food to fast cars. Some of these messages may even affect your future behaviour from where you shop to what you buy.

The influence of advertising has long been a source of debate and concern, with plenty of research indicating negative causal effects of advertising messages on health. Rather than follow this path, Hastings’ book promotes the use of techniques similar to those used by advertising and public relation agencies to influence social and health behaviours. The text will teach you how you can use the same approaches as big corporations and advertising agencies to influence how your patients understand and act on health information.

Initially I was sceptical about this claim. It reminded me of the old saying “you can’t take down the master’s home with the master’s tools.” I wondered whether we should be fighting against the influence of consumerism rather than what might be seen as colluding with it.

Fortunately that’s not what Hastings is advocating. His text takes you through the theory behind social marketing (in particular, stages of change and social, cognitive, and exchange theories). This is refreshing in an area where ideas are often not underpinned by evidence.

Hastings outlines the basic principles behind social marketing, and throughout the text there are exercises to help you consider questions that arise. For example, you are asked to consider why established corporations like McDonald’s are so successful or to consider how pharmaceutical companies promote their products to doctors—and what research questions you might ask to delve into how and why these approaches work. Through each chapter you are guided with strategies for completing social marketing, so by the end of the text you have a clearer understanding of how you might apply the ideas for yourself.

Many aspects of social marketing are controversial: the chapter dedicated to the ethics of working in this area includes how and when you deliver key messages—and what to do when your messages are in conflict with those of other stakeholder groups.

Case examples at the end of the text show social marketing at work in campaigns to combat everything from cutting speeding to promoting healthy eating. The case studies show that social marketing has been particularly effective in smoking cessation programmes. The book includes global case studies to indicate that social marketing isn’t confined to Western audiences or client groups.

Though the book shows us how we can combine research with marketing approaches, it does not go far enough in challenging how commercial organisations are also blurring research and advertising. Today, public relations campaigns fill our daily media with junk mathematical formulas, suspect surveys, and other promotional activities that lead to consumers being misled about science and being taught to mistrust health messages.

Although the social marketing pundits have cleverly learnt to turn advertising to their advantage, the public relations industry is already a step ahead. The book does little to advise on how we might challenge the PR industry’s advantage—or how to ensure that research using social marketing techniques doesn’t get lost in the sea of publicity stories that wash up on journalists’ desks every day.

Hastings opens with the concept “if it’s good enough for Tesco,” but as we know there are major problems with the ethics, activity, and environmental and consumer impact of such industries. So for some readers, copying techniques without challenging core problems may sit uneasily with their political outlook and may make it difficult for them to apply the theories in the text. That would be a shame, as the book is undoubtedly useful if you work in health promotion and education and are interested in finding new strategies for health interventions and evaluations. It gives a clear overview of a technique that you and your patients may find invaluable.

If you are struggling to find ways to help your patients give up smoking, use contraception, eat more healthily, exercise regularly, or manage their health more effectively, Social Marketing could give you some useful ideas on how you might reach people with key messages. At least, you’ll have a greater understanding about how other more dominant messages in advertising are affecting your patients’ health and wellbeing. In ad speak: it’s a win-win situation.

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You can use the same approaches as big corporations and advertising agencies to influence how your patients understand and act on health information.
William Hector Ninian Angus

Former general practitioner Southampton (b 1918; q Glasgow 1941; FRCP), died from heart failure on 12 May 2007.

William Hector Ninian Angus (“Bill”) was called up within six months of qualifying to be medical officer of 111 Squadron and served for four years in North Africa and Italy. After hospital jobs he entered into partnership in Southampton in 1950, remaining in the same practice until he retired in 1988. As well as being closely involved with local medical politics, Bill helped to set up the general practice teaching at the new Southampton Medical School. With other general practitioners, he supported the idea of teaching medical students throughout their medical course from its start. He was one of the earliest trainers in general practice in the country, training over 30 general practitioners. He leaves a wife, Sonja; two children; and four grandchildren.

Tim Billington

Shuja-Ud-Din

Former consultant in geriatric medicine York Hospitals (b 1933; q Karachi 1956; DTMH, FRCP), died from a heart attack on 3 July 2006.

In 1959, having completed his junior house physician posts in general medicine and neurology in Karachi, Shuja-Ud-Din emigrated to the United Kingdom. In 1972, after working in Kent, Devon, Hampshire, Hartlepool, and Newark, he was appointed senior registrar in geriatric medicine in west Cornwall. He was then consultant in York from 1974 until he retired in 1998. Shuja was instrumental in setting up the stroke unit at St Mary’s Hospital. With his colleagues he modernised elderly medicine from mainly long term to more acute and rehabilitative care, commissioning two 30-bedded wards at the newly built York District Hospital for acutely ill elderly patients and setting up community units for the elderly in and around York. He leaves a wife, Farzana; two sons; and a grandson.

N S Patta

Richard Cedric Horwitz

Consultant radiologist South Buckinghamshire (b 1947; q Cape Town 1972; FRCR), d 18 July 2007. After emigrating to England in 1978, Richard Horwitz completed training in radiology at Oxford before becoming a consultant radiologist for Wycombe and Amersham Hospitals in 1984. His special interest was breast imaging. He took on several management roles, including being the first clinical director of radiology, chairman of the ethics committee, and medical director of South Buckinghamshire NHS Trust. He was a driving force behind the extension and modernisation of the radiology department and setting up the breast screening service in 1989 with its first satellite unit in a general practice. He was also a skilled cabinet maker. He leaves a wife, Mary, and two children.

Carolyn Charlesworth, Anthony Bradlow
Andrew Kirk

Francis John Caldwell Roe

Independent consultant in toxicology, experimental pathology, and cancer research (b 1924; q Oxford/The London 1948; DM, DSc, FRCPath), died from complications of pneumonia on 8 August 2007.

Francis John Caldwell Roe’s research interests included the general toxicology and potential carcinogenicity of many substances, as well as mechanisms of carcinogenesis, cancer epidemiology, cancer prevention, and the pathology of laboratory animals. He served on the UK government’s committees on carcinogenicity and toxicity and the WHO Expert Advisory Panel on Food Safety, as well as numerous other national and international expert committees and scientific journal editorial boards. He became life vice president of Marie Curie Cancer Care in 1996. Two of his portrait sculptures are on display at the Royal Society of Medicine, and his study of Cuthbert Dukes is on permanent display at the Royal College of Pathologists. He leaves a wife, Brenda; four children; and seven grandchildren.

Peter N Lee

Jack Salem

Former area medical officer Trafford Area Health Authority (b 1920; q London 1943; FFCM, MRCGP), died from cerebral vascular disease on 1 October 2006.

Jack Salem was educated in France and was halfway through his medical studies in Paris when he had to escape from the Nazi occupation to complete them in London. He finished his wartime service as captain in the Royal Army Medical Corps. In 1961, after a spell in hospital practice and as a general practitioner, he joined the North Western Regional Health Authority. With the reorganisation of 1974 he became area medical officer to the new authority, retiring in 1982. His many activities included serving on the Central Committees for Community Medicine and Hospital Medical Services and on the Working Party on the State of Community Medicine. He also represented his county at chess. He leaves a wife, Elizabeth; a son; and three grandsons.

Richard Salem

ADVICE
We will be pleased to receive obituary notices of around 250 words. In most cases we will be able to publish only about 100 words in the printed journal, but we can run a fuller version on our website. We will take responsibility for shortening. We do not send proofs. Please give a contact telephone number and, where possible, supply the obituary by email to obituaries@bmj.com
Living near the surgery could get you a quicker cancer diagnosis. In northern England, patients with breast and colorectal cancer who lived further from their general practitioner’s surgery were significantly more likely than those living nearby to present with late stage disease. The probability of detecting cancer at a late stage increased by about 1% for every minute of car travel time, according to a study in the European Journal of Cancer (published online 20 September 2007).

Magnets do not relieve pain, despite the claims of those marketing them. A systematic review and meta-analysis of 29 published and potentially relevant clinical trials found that the evidence does not support the use of magnets for pain relief (CMAJ 2007;177:736-42). The analysis considered all randomised clinical trials of static magnets for treating pain from any cause.

Prudent management of women with a history of caesarean section is recommended by the authors of a Swedish study (British Journal of Obstetrics and Gynaecology 2007;114:1208-14). Compared with women who delivered vaginally in their first birth, women who had a caesarean section were at greater risk of uterine rupture in subsequent vaginal deliveries. The risk is influenced by induction of labour, birth weight, gestational age, and maternal factors. Uterine rupture, although rare, is associated with a substantially increased risk of neonatal mortality (adjusted odds ratio 65.62, 95% confidence interval 32.6 to 132.08).

Horse riders face as much danger as rugby players. Researchers in Calgary report that, among experienced riders in southern Alberta, Canada, horseback riding is more dangerous than automobile racing, motorcycle riding, skiing, and American football, and as dangerous as rugby (American Journal of Surgery 2007;193:636-40). Chest and head injuries predominated; and 7% of those injured died. Only 9% of injured riders wore helmets.

The National Prescribing Centre has announced a free interactive information service that they say will be providing high quality, evidence based educational materials and resources relating to prescribing, therapeutics, and medicines management. An additional part of the service is a discussion forum to get peers talking to each other. The website, www.npci.org.uk, is a “virtual building” that “makes searching for content really intuitive.”

Cancer patients are at high risk of developing febrile neutropenia, which is often fatal. A study of 48 cancer patients with febrile neutropenia attending one US emergency department found that those who presented frequently had no identified source of infection. One third of the whole sample had positive blood cultures, and one fifth died or required intensive care within two weeks. The costs of managing them in the emergency department were similar to the cost of a single day of inpatient care (Oncologist 2007;12:1019-26).

Histone/protein deacetylase inhibitors (HDACi) have been approved by the Food and Drug Administration for cancer treatment. But new animal research shows that these drugs also inhibit the immune system (Nature Medicine published online 7 October 2007 doi: 10.1038/nm1652). One of the many functions of HDACi is to increase the production and suppressive function of regulatory T cells. These T cells suppress the rest of the immune system, and HDACi have been shown to decrease inflammatory bowel disease and prevent rejection of heart and pancreatic grafts in mice.

The general physician is a dying breed in the United Kingdom, but in the United States they’re alive and kicking, and known as “hospitalists.” A hospitalist is usually defined as a general medical physician who, rather than referring patients to specialist teams, will manage patients from admission in the emergency department through to discharge and community based care. Patients treated by hospitalists tend to be discharged nearly one day earlier than those cared for by non-hospitalists, but the two groups had similar readmission rates and in-hospital and 30 day mortality (Archives of Internal Medicine 2007;167:1869-74).

The ideas and beliefs that parents hold about their children’s asthma drugs influence their children’s adherence to asthma management plans (Pediatrics 2007;120:e521-6). Among parents in a sample of 622 children, 77% felt that their child’s medication was necessary and 30% had strong concerns about the drugs. For 77%, necessity scores were higher than concern scores, but for 17%, concern exceeded necessity. Adherence to medication regimens increased as the difference between perceived necessity and concern scores increased.

Exposure to tobacco smoke in pregnancy may cause high blood pressure in the baby. Newborn infants of smokers had a systolic blood pressure 5.4 mm Hg higher than the babies of mothers not exposed to tobacco smoke in pregnancy. Diastolic pressures were not affected, and the association of smoking with heart rate was largely explained by confounding factors (Hypertension 2007;50:572-8).