

Folic acid and birth malformations

Despite 15 years of evidence, preventable defects still occur



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Competing interests: None
 declared.

Provenance and peer review:
 Commissioned; not peer reviewed.

BMJ 2007;334:433-4

doi: 10.1136/bmj.39133.386296.BE

With prevalences of 10-15 per 10 000 and 20 per 10 000 live births, neural tube defects and oral clefts are among the most common congenital malformations. Good evidence shows that periconceptional supplementation with folic acid reduces the risk of neural tube defects.^{1,2} What is less clear is the effect of folic acid supplementation on other birth defects, such as cleft lip, with or without cleft palate.

In this week's *BMJ*, Wilcox and colleagues³ report a population based case-control study from Norway, which shows that supplementation with folic acid in the periconceptional period reduces the risk of cleft lip, with or without cleft palate, in newborns. Supplementation with 400 µg of folic acid for three months around conception was associated with a 40% reduction in the prevalence of cleft lip, with or without cleft palate, at birth (adjusted odds ratio 0.61, 95% confidence interval 0.39 to 0.96). Exposure data were obtained retrospectively one year after conception, but the reliability of the data was enhanced by evaluating information on pill bottle labels and brands. This was a large, well designed study that used high quality registries; this enabled efficient early case identification and control selection. The study supports findings from other recent studies,⁴ including a large meta-analysis.⁵

The evidence that folic acid reduces malformations is robust, but how much is needed and how it should be taken is less clear. Despite these uncertainties, 400 µg folic acid per day has been estimated to prevent a large proportion of neural tube defects.^{1,2} Three public health strategies for reaching this dose have been suggested. The first is for women to eat a diet rich in natural folates. However, it is difficult to reach this dose with diet alone, and folate in the diet has lower bio-availability than synthetic folic acid. The second is for women to take supplements of folic acid in the periconceptional period. This strategy is compromised by low compliance and high rates of unplanned pregnancy. Studies have shown that although mass media campaigns increased awareness up to nearly 80%, fewer than 50% of women followed the recommendations.^{6,7} The third strategy is mandatory fortification of staple foods (such as wheat, corn flour, or rice). This would achieve coverage in a large section of the population. Countries differ substantially in their choices of preventive strategy.

The World Health Organization has recommended supplementation with 400 µg of folic acid in the periconceptional period. Fortification of food is mandatory in an increasing number of countries (Brazil, Canada,

Chile, Costa Rica, Jordan, South Africa, and the United States). In general, however, Europe has not followed, despite the finding that even suboptimal fortification (for example, 180 µg/day in the US) greatly reduces neural tube defect rates.^{7,8} Further support for mandatory fortification of food comes from a cohort study showing that simply recommending women planning pregnancy to take folic acid is not enough to substantially reduce the prevalence of neural tube defects at birth.⁹ Accumulating evidence of a protective effect of folic acid supplementation on the prevalence of oral cleft defects^{3,10-12} also supports the introduction of mandatory food fortification. However, in many European countries mandatory fortification has been limited by theoretical concerns. These include the potential of masking symptoms of vitamin B12 deficiency, interactions with certain drugs (antifolates),⁶ and other unrecognised adverse effects such as the risk that some women may have idiosyncratic reactions to folic acid even in small amounts (and others might need far larger doses for a preventive or therapeutic effect). But mandatory folic acid fortification to achieve around 180 µg/day on average and 1000 µg/day at maximum holds little risk of complications.⁶ Despite this, questions about adverse effects and long term effects of mandatory food fortification remain unanswered, and any change in diet must be closely monitored.

What is Europe waiting for? A common argument is that introducing mandatory fortification to reach a relatively small group (women getting pregnant) is not a good enough reason to intervene at population level. If fortification would also reduce the burden of major disorders such as cardiovascular diseases and dementia the case might be different. The risks of these disorders increase with high plasma concentrations of homocysteine, and folic acid supplementation can reduce these concentrations in humans.¹³ However, definitive evidence (such as data from randomised controlled trials) of a protective effect of folic acid on these two diseases has yet to be found. In theory, any clinical improvement could have a long latency period, which could make it difficult or impossible to detect even in a large randomised controlled trial.

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

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Housing and health

Heating improvements may hold most promise for developing healthy housing policy



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

In this week's *BMJ*, Howden-Chapman and colleagues report a large randomised controlled trial from New Zealand assessing whether insulating older houses increases indoor temperatures and improves occupants' health and wellbeing.² The relevance of such studies to decision making in public health is emphasised in the UK government's Wanless report, which examined the cost effectiveness of taking action to improve the health of the whole population and to reduce health inequalities.³ The report highlighted the almost complete lack of an evidence base for the effectiveness and cost effectiveness of public health and social interventions. The report also identified the need to collect better evidence of the effects of interventions in the housing sector.

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

(0.73, 0.62 to 0.87), fewer days off work (0.62, 0.46 to 0.83), and fewer days off school (0.49, 0.31 to 0.80).

In addition to the use of a randomised controlled trial design, the strengths of the study include retention of more than 75% of the original participants and a large final sample size (>3000). This in a field in which studies are small (rarely more than 200 participants) and retention is rarely more than 50%, if reported at all.¹ Funding, personal commitment, and expertise are likely to explain much of this study's success, but the research team also ensured the commitment of the housing agencies that delivered the intervention.⁵

The lack of consistent health impacts detected in previous prospective controlled studies may partly be explained by variation in the actual intervention delivered and the varying potential to benefit from the investment. In the New Zealand trial, not everyone in the intervention group received the full intervention package.^{2,5} However, area based programmes may deliver improvements regardless of individual need at baseline. In one recent controlled non-randomised study of housing led neighbourhood regeneration, about two thirds of residents reported no housing problems at baseline, so limiting the potential to improve conditions.⁶ The small sample sizes in previous studies often preclude further analysis of subgroup effects according to the extent of improvements. The New Zealand trial, however, may be large enough to allow investigation of a dose-response effect, taking into account the range of improvements delivered.

Heating and energy efficiency measures can improve the indoor environment and also alleviate fuel poverty (when a household spends more than 10% of its income on fuel). The combination of greater warmth and reduced household expenditure may be a key mechanism through which health effects occur. Previous

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Competing interests: None declared.

Peer review and provenance: Commissioned; not externally peer reviewed.

BMJ 2007;334:434-5

doi: 10.1136/bmj.39133.558380.BE

studies indicate that warmer and less humid living conditions may improve health, but they also suggest that the health benefits disappear if housing costs increase.¹

Several studies assessing the impact on health of heating improvements are now near completion, including a large quasi-experimental evaluation of the Scottish Executive's central heating programme⁷ These and the New Zealand study suggest that heating improvements may hold most promise for the development of an evidence base to inform healthy housing policy.

This new trial emphasises the benefits of investing in housing, which are not limited to health, as reductions in work and school absences were also seen. This evidence and emerging evidence from other housing studies should inform policies linking housing investment to impacts on health.

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The Pharmaceutical Price Regulation Scheme

Proposals for a new drug pricing mechanism in the NHS are welcomed



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

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

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

The purposes of the scheme are clearly set out in the agreement of November 2004 (agreements are negotiated every five years; the current arrangement

came into force in January 2005 and is due to end in 2010).² From the start, it is clear that the goals of the scheme are compromised as they present an insurmountable conflict—the scheme is tasked to secure the provision of drugs for the NHS at "reasonable prices" while simultaneously determining prices that are high enough to "sponsor" (more recently called "promote") the wellbeing of UK based companies. Interestingly, this has always been the way in which UK government worked to ensure that UK manufacturers were competitive in an international market.

The workings of the scheme are simple: each year companies give the Department of Health details of their historic capital (the monies they have tied up in plant, machinery, factories, raw materials, etc). After taking into account allowances for costs on research and development, promotion, and information, the department uses a formula to determine the total amount the company can charge the NHS ("return on capital") for all of its products (its basket of drugs). To reach the permitted return, companies can price their drugs high at the time of launch. Moreover, if the return on capital is not reached each year the company can raise the prices of other drugs in its basket. Conversely, if the permitted return is exceeded, the company is required to reimburse the excess to the NHS ("in reality the reimbursements are negligible"¹).

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

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Conflict of interest: JC gave evidence to the Office of Fair Trading enquiry team.

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

BMJ 2007;334:435-6
doi: 10.1136/bmj.39136.464421.BE

negotiated by the Department of Health on behalf of ministers, it is essentially impossible for government to argue that prices are too high.

Furthermore, there is a real risk that the work of bodies such as the National Institute for Health and Clinical Excellence (NICE) and the Scottish Medicines Consortium, at a national level, and the many drugs and therapeutics committees at a local level is undermined if money saved is centrally reimbursed in a secret deal. Finally, the system no longer appears to be sustainable as an organ of government because of its inherently conflicting goals and the level of secrecy surrounding decision making and outcomes.

The proposals in the OFT report are persuasive. Broadly, under a new Pharmaceutical Price Regulation Scheme drug prices would be negotiated at launch for each drug individually by (ultimately) an independent commission using robust evidence of the product's perceived clinical value. Representatives of NICE and the Scottish Medicines Consortium would be involved in determining the price, and presumably if they have agreed on its clinical value then the product would be available to the NHS immediately after launch (an end to "NICE blight"). Finally, any notion of reimbursement or sponsorship would be lost.

Industry will not like these changes. Because the

fine details for determining perceived clinical value are not yet spelled out, companies may be concerned that prices could be forced down. They may worry that the stability of financial returns will no longer be guaranteed, which would pose difficulties in long term investment. Until now they have shared the risk of drug development with the NHS (if things went wrong they could expect reimbursement); under the new scheme they would be alone.

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

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Regulation of doctors

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



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Competing interests: None declared.

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

BMJ 2007;334:436-7
doi: 10.1136/bmj.39135.619410.80

On 21 February 2007, the government published its white paper *Trust, assurance and safety—the regulation of health professionals in the 21st century*,¹ which sets a framework to assure the safety of patients and quality of care. The paper considers the English chief medical officer Sir Liam Donaldson's review of medical regulation, *Good Doctors, Safer Patients*²; the Department of Health's report, *Regulation of the Non-medical Healthcare Professions*³; and subsequent consultations with professionals and lay people.

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

Patient safety is central to the proposals. At local level the value of attempts to ensure quality in the current National Health Service is recognised. In the current system poor medical performance is dealt with separately by the employer (NHS) and the regulator (GMC). This may result in a "regulatory gap," whereby a doctor may be providing care that does not inspire the confidence of his or her colleagues and employer but his or her performance is not so poor that referral to the GMC is indicated. Under the new proposals, "GMC affiliates" (senior clinicians) are supposed to bridge this gap by

providing guidance to employers on local investigations, and to enter "recorded concerns" against a doctor's GMC registration. This novel idea, probably too expensive as a local solution, will be piloted in England at regional level.

At national level two key changes are proposed. The first is a standard of proof for adjudicating on concerns about a doctor's fitness to practise. The previous criminal standard of proof—beyond reasonable doubt—now changes to the civil standard—the balance of probability. This change was proposed by Dame Janet Smith in the fifth Shipman report.⁴ The civil standard will be flexibly applied using a sliding scale, with serious cases needing evidence at the level of the criminal standard. Sliding scales, used by other healthcare regulators and the Financial Services Authority, have a credible track record.⁵ However, where a doctor's reputation is at stake some doctors may feel their human rights are being violated. Also, it is the role of those adjudicating to judge the facts against a standard, and there is a theoretical risk that in setting the standard the process of judgment has already started before the facts are heard. The second change is the introduction of an independent panel that will adjudicate cases instead of the GMC and separate the role of investigation from judgment.

Against these local and national changes is a firm commitment that doctors with performance and health

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

Doctors accept that revalidation is needed, and half of patients think that it already happens. The chief medical officer's previously proposed two tier approach of relicensure (to enable doctors to remain registered to practise) and specialist recertification (to maintain the specialist and general practice registers) is endorsed.⁶

The new system of relicensure will be based on the generic standards in *Good Medical Practice*,⁷ will involve an annual appraisal, which will now contain a summative element, and any concerns raised by the medical director or GMC affiliate will need to be resolved. A 360° feedback tool (to give feedback on performance from several sources) will be piloted to support the process. Care will be needed to ensure that the valued developmental aspect of appraisal is not lost and that new 360° feedback tools have a positive effect on clinicians' practices.⁸

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

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

The changes to the GMC are fewer than were initially proposed. Members will now be chosen by an appointment commission, with equal numbers of lay

and medical members being appointed. The GMC will be accountable to parliament, but independent from government. Crucially, the GMC's international reputation and expertise in undergraduate education is recognised and their proposed model of undergraduate, postgraduate, and continuing professional development boards is accepted.

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

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Management of breast cancer in women with BRCA gene mutation

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

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

Once BRCA1 or BRCA2 mutation has been confirmed, preventative strategies include bilateral prophylactic mastectomy and intensive screening with possible hormonal manipulation. Although prevention

of primary breast cancer with mastectomy reduces the risk of breast cancer by 89.5-100%, understandably it is unacceptable to many women.^{2,3} This is because it has a negative impact on self image, it involves major surgery, it cannot remove all risk, and patients may find it hard to accept its theoretical benefit as not all carriers develop breast cancer.

For women with breast cancer unrelated to BRCA ("sporadic breast cancer"), breast conserving surgery combined with radiotherapy is used where appropriate and is now regarded as the standard of care.⁴ Conceptually, breast conserving surgery may seem unwise in women with BRCA related breast cancer because

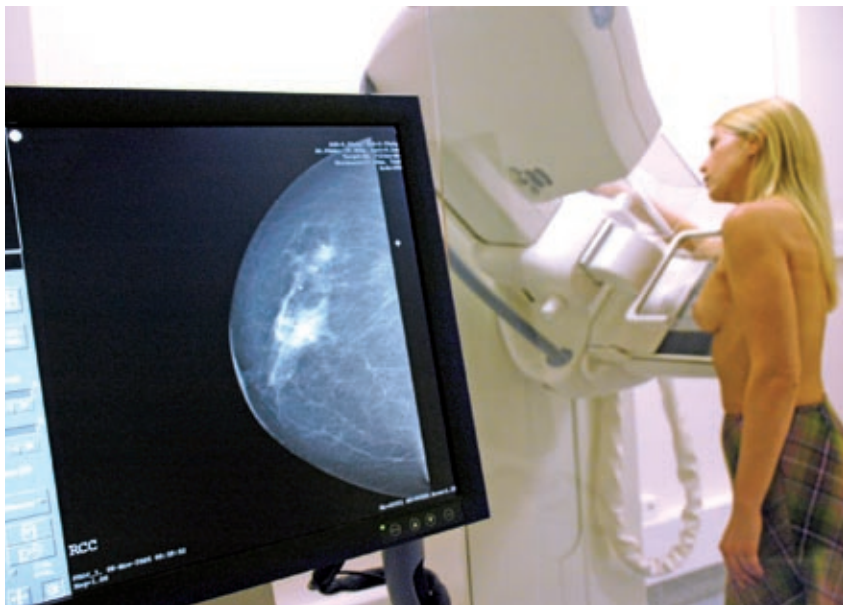
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Competing interests: None declared.

Provenance and peer review: Non-commissioned, externally peer reviewed.

BMJ 2007;334:437-8
doi:10.1136/bmj.39114.354248.80



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of the potential risk of in-breast tumour recurrence. After more than a decade of research the optimal local treatment for these women remains a source of contention.

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

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

cancer by as much as 50% in women with BRCA mutation, supporting hormonal intervention.⁵

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

The only specific BRCA chemoprevention studies have been small single centre trials. Several randomised controlled trials have assessed tamoxifen as a chemoprevention strategy in high risk patients, however, and post randomisation analysis of those with BRCA mutation has shown tamoxifen to be up to 50% effective in preventing breast cancer in these patients.¹¹ In addition, tamoxifen can reduce the incidence of a second primary cancer by 50% in women with BRCA mutation.¹¹ So what does all this mean for patients and the clinicians advising them? Overall, the evidence indicates that breast conservation is safe in selected women with BRCA related cancers when combined with optimal adjuvant therapy.⁴ Recent data show that women who have breast conserving surgery rather than mastectomy for breast cancer score higher on quality of life measures, and these findings are probably applicable to women with BRCA mutation.¹² However, women with BRCA related breast cancer should be informed of the relative risks and benefits of bilateral prophylactic mastectomy compared with breast conservation so they can be supported in making their own decisions.

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