Folic Acid and the Prevention of Neural Tube Defects

Report from an Expert Advisory Group

Department of Health
Scottish Office Home and Health Department
Welsh Office
Department of Health and Social Services, Northern Ireland

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PREFACE

In October 1991, an Expert Advisory Group was set up in response to the publication of the final results from the Medical Research Council Vitamins Study Group. Its report is addressed to all Chief Medical Officers in the United Kingdom. The Chief Medical Officers have been joined by the Chief Nursing Officers in welcoming this opportunity to commend measures for preventing one of the more common congenital abnormalities.

The Expert Advisory Group stressed that there was less evidence than they would have wished on which to base their recommendations. We are grateful to Professor Dame June Lloyd and the members of the Expert Group for their hard work in tackling several difficult decisions. It will be important to assess the effectiveness of this new programme and I endorse the recommendation that the scientific issues should be reviewed as further information becomes available.

DR KENNETH CALMAN
Chief Medical Officer
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1992

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1. Introduction

1.1 In July 1991, the results of the Medical Research Council (MRC) Vitamin Study of folic acid and other vitamin supplementation in the prevention of neural tube defects (NTD) were published [1]. The study, which was started in 1983, was a randomized double blind trial conducted in the United Kingdom and six other countries. Women who had had a previous baby with NTD, and thus who were known to be at high risk in future pregnancies, were invited to take part. A total of 1817 women were allocated, at random, to one of four groups according to whether they would receive supplementation and, if so, with which nutrients. The groups were either to receive 4 milligrams (4000 micrograms) folic acid per day, or daily multivitamin supplementation (vitamins A, thiamin, riboflavin, B_6, C and D), or both or neither. Half the women, therefore, took folic acid and half did not. 1195 had a pregnancy in which the status of the fetus or infant, in relation to NTD, was known. There were 27 NTD, 6 in the two groups receiving folic acid and 21 in the two other groups; this result suggested that folic acid offered a protective effect of 72 per cent (relative risk 0.29; 93 per cent confidence interval 0.12 - 0.71). Multivitamin supplementation without folic acid showed no significant protective effect. It was concluded that 4 milligrams (4000 micrograms) per day of supplementary folic acid can significantly reduce the risk of recurrence of NTD.

1.2 The MRC Study had been preceded by two intervention studies that suggested vitamin supplementation may be preventive (para 3.2). One used a dose of 0.36 milligrams (360 micrograms) per day [2], the other used 4 milligrams (4000 micrograms) per day [3]. The higher of the two doses was used in the MRC Study to avoid the uncertainty that would follow from a negative result using the lower dose.

1.3 In response to the result of the MRC Study, and as an interim measure, guidance was issued at once to doctors, nurses, midwives and health visitors [4]. Any woman who had borne a child with NTD and who was planning a pregnancy should be advised to take 5 milligrams (5000 micrograms) of folic acid daily and should also be encouraged to choose foods that were rich in folate (the dose was chosen because there were no 4 milligram preparations available).

1.4 At the same time, an Expert Advisory Group was convened with the following terms of reference:

> "To consider the dietary implications of the results of the Medical Research Council Vitamin Study on the prevention of neural tube defects and to make recommendations."

The Group began its work in October 1991. It held five meetings. Additional experts attended the fourth meeting*

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*Dr I Chanarin	The Clementine Churchill Hospital, Harrow, London.
Professor N C Nevin	Professor of Medical Genetics Queen's University, Belfast.
Professor J M Scott	Professor of Biochemistry, Dublin.
Professor R W Smithells	Emeritus Professor of Paediatrics and Child Health, University of Leeds.
Professor K M Laurence	Emeritus Professor of Paediatric Pathology, University of Wales College of Medicine, Cardiff, was unable to attend but gave written comments.

2. Neural tube defect: Description and prevalence

2.1 The term neural tube defect (NTD) includes anencephaly, encephalocoele and spina bifida but not hydrocephalus as a sole malformation. These conditions occur if the brain and/or spinal cord with its protecting skull and spinal column fail to develop properly around the fourth week of embryonic life. Anencephaly is a condition where most of the brain and skull are absent, and stillbirth or death very soon after delivery is inevitable. It accounts for about half of all cases of NTD. Encephalocoele, where the brain protrudes through a defect in the skull, is rare. In spina bifida, the spinal canal in the vertebral column is not closed, although the defect may be covered with skin. Infants born with spina bifida show a wide range of physical disabilities. In the more severe forms the spinal cord bulges out of the back, the legs and bladder may be paralysed, and obstruction to the fluid surrounding the brain causes hydrocephalus. Such children face a life of severe handicap. The suffering for individuals affected by NTD and for their families is substantial.

2.2 Some embryos with NTD will be aborted spontaneously. By mid-pregnancy, it can be expected that almost all cases of anencephaly and at least two thirds of those with spina bifida will be identified by estimation of alphafetoprotein levels in maternal blood and amniotic fluid and by ultrasound scan. Some parents choose to have the pregnancy terminated at this stage.

2.3 The prevalence of NTD at birth in the UK is now less than 0.3 per 1000 total births compared to about 4 per 1000 total births 20 years ago. The decline since the 1970s is mainly due to screening and selective terminations, but there has also been a reduction in the underlying incidence the reasons for which are unknown [5]. The geographical variation in birth prevalence within the United Kingdom with rates in parts of Wales, West Scotland and Northern Ireland two-

to three-fold higher than elsewhere, has also been declining.

2.4 There is an undoubted genetic/environmental interaction in the causation of NTD. If a woman or a man have had an affected offspring, or if either suffers from the condition themselves, their risk of a baby with NTD is increased about ten-fold. After two affected pregnancies, it is increased by about twenty-fold.

2.5 Other, though weaker, risk factors include the age of the mother (where there may be slightly increased rates in the youngest and the oldest) and lower socio-economic status.

2.6 In considering the prevention of NTD a distinction must be made between primary and secondary prevention. Primary prevention is effected by measures which prevent the development of NTD in the embryo. Secondary prevention is brought about through screening and the option of selective termination of pregnancy, and has been available for nearly twenty years. The opportunity to introduce primary preventive measures following the recent MRC trial is a major medical and social advance.

2.7 The prevalence of NTD at birth is influenced by background variation in incidence which is of unknown causation. Prevalence is influenced also, probably to a greater degree, by the effectiveness of preventive measures. Primary prevention influences the prevalence of NTD before selective termination of pregnancy. If programmes of primary and secondary prevention are concurrent, both can influence the prevalence of NTD at birth and it is important to distinguish their separate contributions to any observed trends.

3. Folate status, folic acid supplementation and neural tube defect

3.1 Since 1964, it has been recognised that her folate status might affect a woman's risk of having a baby with an NTD [6,7]. The evidence was, however, non specific and inconclusive. Women with affected pregnancies had significantly lower red cell folate levels than those with unaffected pregnancies [8] and ate diets which had lower amounts of folate [9].

3.2 In the early 1980s, two studies involving women who had already had an affected infant suggested that the taking of folic acid with or without other vitamins, from before conception and during the first weeks of pregnancy, had a preventive effect. One study was randomised and used supplements of folic acid alone (4 milligrams (4000 micrograms)) but was too few in numbers to provide a definitive answer [3]. The other used a multivitamin preparation containing a mixture of eight vitamins including 0.36 milligrams (360 micrograms) per day folic acid; because of the design of the study, bias may have been introduced into the results[2]. The MRC Vitamin Study, which was large and randomised, has now confirmed the findings in respect of folic acid (para 1.1).

3.3 Over 95 per cent of pregnancies resulting in a baby with NTD are first occurrences. Trials currently in progress should show whether folic acid supplementation would also prevent these first occurrences (para 7.3). *A priori* it seems likely that it would, and case-control [10,11,12] and prospective observational studies [13] also indicate that it may.

3.4 It is not known how the oral administration of folic acid prevents NTD [14,15]. There are several theories, the simplest being that folic acid, which is known to be efficiently absorbed and then

incompletely converted into metabolically active folates, corrects a folate deficiency. It has also been suggested that there may be a metabolic block not as yet clearly identified, which can be overcome, either by increased levels of folate, or by unaltered folic acid. Another explanation focuses on the process of neural tube closure. It is postulated that either the mother's, or the embryo's genetic make-up influences the efficiency of closure and that in either circumstance extra folic acid or folate may reduce the risk of failure of the normal process of closure of the neural tube. There is clearly a need for more research on the mechanisms by which folic acid prevents NTD. Once these are defined it may become apparent that folic acid interacts with other compounds which could also be important in primary prevention.

4. Folates in the diet

4.1 Foods and tissues do not naturally contain folic acid but products known as folates which are in the B vitamin group. There are several different folates which vary in the extent to which they are absorbed from foods and only one-half to two-thirds of the total folate from normal mixed diets may be available [16].

4.2 Foods which are rich in folates include green leafy vegetables and liver. Any diet that is rich in other B vitamins and vitamin C is usually also rich in folate. The analysis of folate in food is difficult and no present day method is entirely satisfactory. Table 1 indicates the main food sources of folate and Appendix 1 details current estimated folate content of various foods. Folates are vulnerable to heat and they dissolve in water so that cooking may cause a considerable reduction in the folate contents of food and there may also be gradual loss with prolonged storage. It is clear, therefore, that the measured folate content of food can only provide an approximate indication of the dietary intake.

4.3 The Ministry of Agriculture, Fisheries and Food has conducted a survey of household food consumption in Great Britain continuously since 1940 [17]. The intakes recorded refer to food as purchased per household and, until 1992, excluded foods eaten outside the home and dietary supplements. Folate values have been determined routinely since the late 1970s and in 1990 the average daily intake of folates was a little over 200 micrograms per person. All income groups have increased their intakes to a small extent over the past 10 years and this trend has been most marked in Scotland so that regional differences have diminished substantially (Table 2).

4.4 The average daily folate intake recorded from a representative sample of non pregnant 16-49 year old women, who weighed their

food for one week in 1986/7, was 218 micrograms; the 2.5 and 97.5 percentiles were 96 and 376 micrograms respectively. Vegetables and fruit contributed 39 per cent, cereals 22 per cent (breakfast cereals 4 per cent)*, milk and milk products 9 per cent, and meat and meat products 10 per cent of the total. In this age group, older women ate more folate than younger women, and intakes were greater in non manual social classes [18].

4.5 Requirements for all nutrients for population groups in the United Kingdom were reviewed in 1991, and the report from the Committee on Medical Aspects of Food Policy summarises the available data about the absorption and metabolism of dietary folates and indicates the dietary requirements [19]. For women of reproductive age the Estimated Average Requirement is given as 150 micrograms (0.15 milligrams) of folate per day; the Reference Nutrient Intake, which is the intake which will meet the needs of almost all women in this group, is 200 micrograms (0.2 milligrams) per day. The Committee advised on general nutritional grounds an increment for pregnancy of 100 micrograms (0.1 milligrams) per day but made no specific recommendations for the pre-conceptual period.

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*Many more breakfast cereals and some breads are now fortified with folic acid than in 1986/7 when the survey was done.

Table 1: Food sources of folate/folic acid

Rich sources (more than 100 micrograms (0.1 milligrams) per serving*)

Fresh, raw, or cooked** Brussels sprouts, asparagus, spinach, kale, cooked black eye beans.
Breakfast cereals (fortified with folic acid).
Liver ***

Good sources (50 - 100 micrograms (0.05 - 0.1 milligrams) per serving*)

Fresh, raw, frozen and cooked** broccoli, spring greens, cabbage, green beans, cauliflower, peas, beansprouts, okra, cooked soya beans, iceberg lettuce, parsnips, chick peas. (Larger (150-200 grams) portions of broccoli, cauliflower and spring greens will supply more than 100 micrograms.)
Kidneys, yeast and beef extracts.

Moderate sources (15 - 50 micrograms (0.015 - 0.05 milligrams) per serving)

Potatoes, most other fresh and cooked vegetables, most fruits, most nuts, tahini.
Bread (100 grams), brown rice, wholegrain pasta, oats, bran,
Weetaflakes,
Weetabix.
Cheese, yoghurt, milk (pint), eggs, salmon, beef, game.

Poor sources (less than 15 micrograms (less than 0.015 milligrams) per serving)
White rice, white pasta, alcoholic drinks, soft drinks, sugar, most pastries, cakes, most other meats and fish.
Most other breakfast cereals (not fortified with folic acid).

* Minimum recommended portion sizes 100 grams of these vegetables. All other portions as published [20].

** Based on vegetables boiled for 10 to 20 minutes [21]. Steamed, stir fried and microwaved vegetables cooked for a shorter time will lose less.

*** Pregnant women and those intending to become pregnant are advised not to eat liver or liver products because of the risk of possible adverse effects from consuming excess vitamin A [22].

Table 2: Average folate/folic acid intakes per head in Great Britain based on household food purchases 1980-1990

Average folate intake: micrograms per day

Year	All households	England	Wales	Scotland
1980	213	214	222	197
1981	213	214	219	195
1982	208	210	207	184
1983	200	203	189	178
1984	200	203	197	176
1985	222	225	212	198
1986	231	232	239	215
1987	236	236	243	234
1988	230	230	223	228
1989	244	245	237	242
1990	244	243	246	247

Source: National Food Survey - MAFF

5. Supplemental folic acid

5.1 The dose of folic acid given in the MRC Vitamin Study was 4 milligrams (4000 micrograms) and this was specially prepared for the research protocol (Para 1.1). There are several multivitamin preparations which provide much less folic acid, about 0.3 to 0.5 milligrams (300 to 500 micrograms), per recommended daily dose. One such preparation was used in an earlier intervention study (para 3.2).

5.2 Folic acid is available as a medicinal product either as a single constituent or in combination with other active ingredients such as iron compounds or vitamins. Preparations which have a medicinal product licence are subject to control under the Medicines Act 1968, and only these may make medicinal claims, for instance that they can be used to treat or prevent disease. All other formulations of folic acid are categorised as foods, and are subject to the provisions of the Food Safety Act 1990, whether they are presented in a pharmaceutical form (eg capsules, tablets) or as an added ingredient to conventional foods (eg fortified breakfast cereals).

5.3 For medicinal products there are three categories of availability. They may be limited to sale on prescription by a doctor, for sale in pharmacies only, or may be allowed on general sale. Preparations of folic acid containing up to 0.2 milligrams (200 micrograms) as a daily dose may be on general sale. Products containing a daily dose between 0.2 and 0.5 milligrams (200 and 500 micrograms) may be bought over the counter at pharmacies but may not be on general sale. Products containing a daily dose in excess of 0.5 milligrams (500 micrograms) may only be supplied on prescription. The dose currently advised by the Chief Medical Officer for the prevention of recurrence of NTD is 5 milligrams (5000 micrograms) because no 4 milligram (4000 microgram) tablets

are currently available [4]. These tablets are only available on prescription.

5.4 All preparations of folic acid without a medicinal product licence are controlled under the Food Safety Act 1990 even if they are presented in a pharmaceutical form, either as pure folic acid or, more usually, as part of a multivitamin preparation. They may not make medicinal claims. There are no statutory limits on their content of folic acid, although the Health Food Manufacturers' Association (HFMA) guidelines recommend an upper limit of 0.5 milligrams (500 micrograms) per daily dose. However, not all manufacturers are members of HFMA, and there are no restrictions on the folic acid content of imported products.

5.5 Conventional foods may also contain folic acid which is added during manufacture. Some food manufacturers have chosen to fortify some breakfast cereals with folic acid. As an example, fortified cornflakes contain 0.25 milligrams (250 micrograms) of folic acid per 100 gram, while their unfortified content of folates is 0.07 milligrams (70 micrograms). A brand of bread is also fortified so that 1 slice contains approximately 0.05 milligrams (50 micrograms) of folic acid. The folic acid/folates contents of a selection of foods are given in Appendix 1.

6. Preventing recurrence of neural tube defect

6.1 Women or men with spina bifida themselves, or with a history of a previous child with NTD, should be counselled about the increased risk of a future offspring being affected. Folic acid supplements should be advised for all those who may become pregnant; only women who have been sterilised or who are using a reliable means of contraception can be excluded. Folic acid supplements should be continued until the twelfth week of pregnancy.

6.2 The daily dose of folic acid which was advised by the Chief Medical Officer was 5 milligrams (5000 micrograms) [4] although if a 4 milligram folic acid tablet becomes licensed, this dose should be used as it would then match the amount given in the MRC Vitamin Study. This dose may however need to be revised if new information shows that a lower dose would be as effective in preventing NTD recurrences.

6.3 Folic acid tablets are cheap and they should be available on prescription for the prevention of NTD both before and during pregnancy. Folic acid-only tablets are preferable to multivitamin preparations, as the MRC Study showed no benefit from taking vitamins other than folic acid. Excessive intakes of other nutrients could result if the dose of folic acid was achieved by consuming several multivitamin pills.

6.4 There are rare but potentially serious hazards of folic acid therapy in particular groups of people. Sub-acute combined degeneration of the spinal cord may be precipitated by giving folic acid at doses of 5 milligrams (5000 micrograms) to people who are vitamin B_{12} deficient. This complication usually occurs in older people and no case of neurological damage has been observed among 17,000 women of reproductive age given folic acid supplements for

the treatment of anaemia [23]. Epileptic women on anticonvulsant therapy need individual counselling by their doctor before starting folic acid. There is a theoretical risk that folic acid may affect drug control of epilepsy adversely although this complication has not been seen in practice.

7. Preventing first neural tube defects

7.1 First occurrences of NTD in women who have not previously had a baby with this malformation account for 95 per cent of cases. It is therefore important to consider whether folic acid, which is effective in preventing a major proportion of recurrences, will also prevent first occurrences. The evidence which shows that folic acid reduces the risk of the first occurrence of NTD is inadequate to assess the magnitude of the effect, nor does it allow firm conclusions about what dose is most effective (para 3.3).

7.2 Observational studies have shown that women in the general population who take vitamin supplements, usually including folic acid, have a lower risk of having a baby with NTD [10,11]. One of these studies suggested that the effect was related to folic acid alone and that the size of the effect was similar to that in the MRC Study [11]. Studies of dietary folate intake also give support to the role of increased folic acid/folate in reducing the risk of NTD [11,12].

7.3 Two prospective intervention trials are now in progress to assess the effect of folic acid supplements in preventing first occurrences. A randomized trial in Hungary using 0.8 milligrams (800 micrograms) daily gives preliminary support to the efficacy of folic acid in preventing first occurrences as well as recurrences but the numbers are too small to be conclusive on their own [13]. The second trial, in China, is in its early stages and has not yielded any results.

7.4 The choice of a recommended amount of folic acid, however, can only be interim, and it may need to be revised in the light of new data. Because the same aetiological factors probably operate in preventing a first occurrence as operate in preventing recurrences, it is likely that the efficacy of folic acid will be similar. Side effects from the administration of 4 milligrams (4000 micrograms) folic acid

to women trying to get pregnant have not been recorded, nevertheless the possibility of such effects cannot be excluded. Although a slight chance of side effects may be acceptable to women who have had an affected pregnancy because of their high risk of a recurrence, it might not be acceptable to women in general because of their much lower risk. To reduce the likelihood of adverse effects, a lower dose than that used in the MRC Vitamin Study may be used in the general population. The balance of evidence suggests that a dose of 0.4 milligrams (400 micrograms) is likely to be protective, although whether to the same extent as a higher dose is unknown. For these reasons it is suggested that, as a general recommendation, all women should take an extra 0.4 milligrams (400 micrograms) folic acid prior to conception and during the early months of pregnancy.

7.5 It has already been emphasised that this recommendation for folic acid supplementation is based on limited data. Furthermore, it is at present unknown whether folate from the diet and folic acid from supplements are metabolically complementary and whether they have equivalent effects. If, however, they are regarded as complementary and, assuming that dietary folate intake now is on average about 0.2 milligrams (200 micrograms) per day, the addition of 0.4 milligrams (400 micrograms) of folic acid per day would bring the average intake to about 0.6 milligrams (600 micrograms) folate/folic acid per day. There are three possible ways of achieving this intake: eating more foods containing natural folate, eating more foods fortified with folic acid, and taking supplementary folic acid either as a medicinal preparation or as a food supplement. These strategies are, of course, not mutually exclusive and most women will adopt more than one.

7.6 Eating more folate-rich foods and avoiding over-cooking are already part of advice for healthy eating for the general population. It is current advice that, on average, UK consumption of vegetables and fruit needs to double. Women who are planning a pregnancy would benefit particularly from such a change of diet. Some women may be able to select a diet with 0.6 milligrams (600 micrograms) folate/folic acid by increasing their consumption of folate-rich foods, but it is very unlikely that in the short term this measure alone will

ensure sufficient intake for the majority who need it.

7.7 Some breakfast cereals and at least one brand of bread are now fortified with folic acid (Appendix 1) and the possibility of increasing the amount of fortification and including a wider range of foods has been considered. For this to be an effective way of ensuring an increased intake for all women becoming pregnant, it would also mean that the majority of the entire population consumed considerably more than the current average intake of folate/folic acid. The possible hazards of excessive indiscriminate fortification particularly for some segments of the population, especially elderly people, are unknown. Those with vitamin B_{12} deficiency, epileptics and patients on treatment with folic acid antagonists are potentially vulnerable groups. We accept that the present levels of folic acid fortification in those breakfast cereals and breads that are fortified are reasonable and most unlikely to cause any problems but we would not wish to see these levels greatly exceeded. To avoid the potential risks of indiscriminate fortification we recommend that fortification be restricted to breakfast cereals and bread. The range of fortified bread and breakfast cereals could, with advantage, be increased (including wholemeal breads) so that there is a greater variety of such foods but we do not recommend universal fortification of bread or breakfast cereals. It is important that a choice of unfortified bread and breakfast cereals remains available. For those who want to increase their consumption, foods which have folic acid added should, where practicable, indicate the level of fortification so as to permit a free dietary selection.

7.8 Because many women who may become pregnant may not achieve sufficient folate/folic acid intake by dietary measures alone (increased consumption of naturally containing foods (para 7.6) and/or increasing consumption of fortified foods (para 7.7)), we recommend that all women who are planning a pregnancy should be advised to take 0.4 milligrams (400 micrograms) folic acid as a daily medicinal or food supplement from when they plan to have a baby until the twelfth week of pregnancy. Some doctors may choose to prescribe a higher dose on account of the possibility of a quantitatively greater

protection. We recommend that consideration be given to making folic acid available free of charge.

7.9 Many pregnancies are unplanned and these women, although they may have increased their folate intake from food, are therefore unlikely to be taking folic acid supplements when they conceive. Nevertheless, supplementation should still be started as soon as a woman suspects she may be pregnant or if she recognises the risk of pregnancy following unprotected sexual intercourse. Teenage pregnancies present a particular challenge.

7.10 The strategies recommended will require a major programme of education for professionals and general population alike.

7.11 It is most important that the process should be monitored both to provide early warning of hazards and to determine any changes in the prevalence of NTD. Monitoring must of course also include the prevalence of NTD before pregnancies are terminated and we recommend that a central co-ordinating facility be established to ensure that all events are recorded. We recommend that the efficacy of our recommendations are formally reviewed.

7.12 The advice given in this report should be introduced without delay. Future trials may identify different amounts of folic acid which offer an improvement on the current guidance. Research should also be undertaken on the mechanisms of action of folic acid and of folates in preventing NTD and this may lead to other forms of primary prevention.

8. Recommendations

The Expert Advisory Group on Folic Acid and Neural Tube Defects made the following recommendations.

To prevent recurrence of neural tube defect in the offspring of women or men with spina bifida themselves, or with a history of a previous child with neural tube defect

8.1 all such women and men should be counselled about the increased risk of a future offspring being affected;

8.2 folic acid supplements at a daily dose of 5 milligrams (5000 micrograms) should be advised for all those women who wish to become pregnant or who are at risk of becoming pregnant; the daily dose should be reduced to 4 milligrams (4000 micrograms) if this preparation becomes available as a licensed product;

8.3 prescriptions of folic acid, when given for the prevention of NTD, should be free of charge;

8.4 folic acid supplementation should continue until the twelfth week of pregnancy;

8.5 folic acid-only preparations are preferable to multivitamin preparations;

8.6 women in this group who are also receiving anticonvulsant therapy need individual counselling by their doctor before starting folic acid supplementation.

To prevent first occurrence of neural tube defect

8.7 extra folate/folic acid is recommended for all women prior to conception and during the first twelve weeks of pregnancy (see para 7.4);

8.8 the three possible ways of achieving an extra intake of folate/folic acid (eating more folate rich foods, eating foods fortified with folic acid, taking folic acid as a medicinal/food supplement) are not mutually exclusive;

8.9 women who are planning a pregnancy should eat more folate-rich foods and avoid over-cooking them;

8.10 the range of breads and breakfast cereals fortified with folic acid should be increased (including wholemeal breads);

8.11 fortification of foods with folic acid should be restricted to breads and breakfast cereals;

8.12 the present levels of folic acid fortification in breads and breakfast cereals should not be greatly exceeded;

8.13 foods which have folic acid added should where practicable indicate the level of fortification;

8.14 there should continue to be a choice of unfortified breads and breakfast cereals;

8.15 all women who are planning a pregnancy should be advised to take 0.4 milligrams (400 micrograms) folic acid as a daily medicinal or food supplement from when they begin trying to conceive until the twelfth week of pregnancy;

8.16 women who have not been supplementing their folate/folic acid intakes and who suspect they may be pregnant should start supplementation at once and continue until the twelfth week of

pregnancy;

8.17 consideration should be given to making folic acid tablets or capsules available free of charge as a pre-pregnancy supplement.

Concerning education, monitoring and review of these recommendations

8.18 there should be major programmes of education for professionals and for the general population;

8.19 there should be a central co-ordination facility to monitor the prevalence of neural tube defects both before antenatal diagnosis and at birth, to determine changes in prevalence and to monitor for early warnings of hazard;

8.20 research should be undertaken on the mechanisms by which folate/folic acid prevents neural tube defects;

8.21 the efficacy of the recommendations in this report should be reviewed formally taking note of the outcomes of future prevention trials.

9. References

1. The MRC Vitamin Study Group. Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study. *Lancet* 1991; **238**: 131-137.

2. Smithells RW, Nevin NC, Seller MJ, Sheppard S, Harris R, Read AP, Fielding DW, Walker S, Schorah CJ, Wild J. Further experience of vitamin supplementation for prevention of neural tube defect recurrences. *Lancet* 1983; **1**: 1027-1031.

3. Laurence KM, James N, Miller MH, Tennant GB, Campbell H. Double-blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects. *BMJ* 1981; **282**: 1509-1511.

4. Department of Health. *Folic acid in the prevention of neural tube defects.* Letter from the Chief Medical and Nursing Officers PL/CMO(91)11, PL/CNO(91)6. London, 12 August 1991.

5. Wald N, Cuckle H. Some practical issues in the antenatal detection of neural tube defects and Down's syndrome. In: Drife J et al, eds. *Antenatal Diagnosis of Fetal Abnormalities*. London: Springer-Verlag, 1991; 45-54.

6. Hibbard BM. The role of folic acid in pregnancy. *J Obstet Gynaecol Brit Commwlth* 1964; **71**: 529-542.

7. Hibbard ED, Smithells RW. Folic acid metabolism and human embryopathy. *Lancet* 1965; **1**: 1254.

8. Smithells RW, Sheppard S, Schorah CJ. Vitamin deficiencies and neural tube defects. *Arch Dis Child* 1976; **51**: 944-949.

9. Laurence KM, James N, Miller M, Campbell H. Increased risk of recurrence of pregnancies complicated by fetal neural tube defects in mothers receiving poor diets and possible benefits of dietary counselling. *BMJ* 1980; **281**: 1592-1594.

10. Mulinare J, Cordero JF, Erickson D, Berry RJ. Periconceptional use of multivitamins and the occurrence of neural tube defects. *J Am Med Ass* 1988; **260**: 3141-3145.

11. Milunsky A, Jick H, Jick SS, Bruell CL, MacLaughlin DS, Rothman KJ, Willet W. Multivitamin folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. *J Am Med Ass* 1989; **262**: 2847-2852.

12. Bower C, Stanley FJ. Dietary folate as a risk factor for neural-tube defects: evidence from a case-control study in Western Australia. *Med J Aust* 1989; **150**: 613-618.

13. Czeizel A, Fritz G. Ethics of a randomized trial of periconceptional vitamins. *J Am Med Ass* 1989; **262**: 1633-1634.

14. Molloy AM, Kirke P, Hillary I, Weir DG, Scott JM. Maternal serum folate and vitamin B concentrations in pregnancies associated with neural tube defects. *Arch Dis Child* 1985; **60**: 660-665.

15. Yates JRW, Ferguson-Smith MA, Shenkin A, Guzman-Rodriguez R, White M, Clark BJ. Is disordered folate metabolism the basis for the genetic predisposition to neural tube defects? *Clin Genet* 1987; **31**: 279-287.

16. Herbert V. RDI of folate in humans. *Am J Clin Nutr* 1987; **45**: 661-670.

17. Ministry of Agriculture, Fisheries and Food. *Household Food Consumption and Expenditure 1990*. London: HMSO, 1991.

18. Gregory J, Foster K, Tyler H, Wiseman M. *The Dietary and Nutritional Survey of British Adults*. London: HMSO, 1990.

19. Department of Health. *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom*. London: HMSO, 1991. (Report on Health and Social Subjects; 41).

20. Crawley H. *Food Portion Sizes*. London: HMSO, 1988.

21. Holland B, Welch AA, Unwin ID, Buss D, Paul AA, Southgate DAT. *McCance and Widdowson's The Composition of Foods 5th Ed.* Cambridge: Royal Society of Chemistry, 1991.

22. Department of Health and Social Security. *Vitamin A and pregnancy.* Letter from the Chief Medical and Nursing Officers PL/CMO(90)11, PL/CNO(90)10. London, 25 October 1990.

23. Hibbard ED, Spencer W J. Low serum B12 levels and latent Addisonian anaemia in pregnancy. *J Obstet Gynaecol Brit Commwlth* 1970; **77**: 52-57.

Appendix 1

Folate/folic acid content of selected foods

Food	Folate/ folic acid (microgram per 100 gram)	Portion size (gram)	Folate/ folic acid per serving (microgram)
Vegetables (boiled* unless stated)			
Broccoli	65	45	30
Brussels sprouts	110	90	100
Cabbage	30	90	25
Carrots	15	60	10
Cauliflower	50	90	45
Green beans	55	90	50
Peas	45	65	30
Potatoes old	25	180	45
Potatoes new	20	180	40
Spinach	90	90	80
Sweet corn	35	30	10
Lettuce, raw	55	30	15
Tomatoes, raw	15	85	15
Cucumber, raw	9	25	2
Fruit			
Bananas	15	100	15
Grapefruit	25	80	20
Oranges	30	160	50
Orange juice	20	200	40

Folate/folic acid content of selected foods (cont)

Food	Folate/ folic acid (microgram per 100 gram)	Portion size (gram)	Folate/ folic acid per serving (microgram)
Cereals and cereal products			
Rice, white, boiled	4	150	5
Spaghetti, boiled	4	230	9
White bread, average	30	90	25
Wholemeal bread, average	40	105	40
Soft grain bread (fortified with folic acid)	120	90	105
Cornflakes (unfortified)	7	40	3
Cornflakes (fortified with folic acid)	250	40	100
Branflakes (unfortified)	100	40	40
Branflakes (fortified with folic acid)	250	40	100
Other foods			
Bovril	1040	9	95
Yeast extract	1010	4	40
Liver, lambs', fried **	240	40	95
Milk, whole/semi-skimmed	6	568 mls (1pt)	35

*There are slight variations in folate content depending on whether vegetables were fresh or frozen and on how long they were boiled.

**Pregnant women and those intending to become pregnant are advised not to eat liver or liver products because of the risk of possible adverse effects from consuming excess vitamin A[22].

Appendix 2

Register of members' commercial interests

		Nature of interests
Professor Dame June Lloyd (Chairman)		
Personal interests: None		
Non-personal interests:		
Milupa	)	
Nutritional Consultative Panel	)	Research grants
Scientific Hospital Supplies	)	
Dr J Ball		
Personal interests: None		
Non-personal interests: None		
Dr S Bingham		
Personal interests: None		
Non-personal interests: None		
Professor B M Hibbard		
Personal interests: None		
Non-personal interests: None		

Professor R Himsworth

Personal interests: None

Non-personal interests:

Nutritional Consultative Panel	)	Funding PhD student
National Dairy Council	)	

Professor A A Jackson

Personal interests: None

Non-personal interests:

Nestle	)	
Servier	)	
BASF/KNOLL AG	)	Research support
Seven Seas Health Care	)	
Milk Marketing Board	)	
Duphar	)	
Viggo-Spectramed	)	
Kabi Pharmacia	)	Training support
Scientific Hospital Supplies	)	

Professor A Tomkins

Personal interests: None

Non-personal interests: None

Professor N Wald

Personal interests:

Logical Medical Systems	Director Consultant in
Roussel Laboratories	Mifepristone Post Marketing Surveillance Study

Non-personal interests:

Amerlite Diagnostics	Grant

Prepared by Department of Health
Printed in the UK 1992

Dd. DH004880, 11/93, M50, GP 3396/6 CCN 16268.

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