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ORIGINAL ARTICLES

Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study

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A randomised double-blind prevention trial with a factorial design was conducted at 33 centres in seven countries to determine whether supplementation with folic acid (one of the vitamins in the B group) or a mixture of seven other vitamins (A, D, B₁, B₂, B₆, C, and nicotinamide) around the time of conception can prevent neural tube defects (anencephaly, spina bifida, encephalocele). A total of 1817 women at high risk of having a pregnancy with a neural tube defect, because of a previous affected pregnancy, were allocated at random to one of four groupsnamely, folic acid, other vitamins, both, or neither. 1195 had a completed pregnancy in which the fetus or infant was known to have or not have'a neural tube defect; 27 of these had a known neural tube defect, 6 in the folic acid groups and 21 in the two other groups, a 72% protective effect (relative risk 0.28, 95% confidence interval 0.12-0.71). The other vitamins showed no significant protective effect (relative risk 0.80, 95% CI 0.32-1.72). There was no demonstrable harm from the folic acid supplementation, though the ability of the study to detect rare or slight adverse effects was limited. Folic acid supplementation starting before pregnancy can. now be firmly recommended for all women who have had an affected pregnancy, and public health measures should be taken to ensure that the diet of all women who may bear children contains an adequate amount of folic acid.

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Introduction

It has long been suspected that diet has a role in the causation of neural tube defects, which are among the most common severe congenital malformations. The possibility that folic acid (a vitamin in the B group) might be involved was raised in 1964.¹² In 1980 and 1981 the results of two intervention studies were published in which vitamin supplementation around the time of conception was given to women who had had a pregnancy with a neural tube defect.³⁴ These suggested that folic acid or other vitamin

supplementation might reduce the risk of a recurrence. In the first study,³ which was not randomised, participating women were given a mixture of eight vitamins which included folic acid (0.36 mg/day), and women who were already pregnant or had declined to take part in the study served as controls. The risk of a recurrence in supplemented women was about one-seventh that in the unsupplemented women.

The second study was a small randomised trial of folic acid supplementation alone (4 mg/day).⁴ It yielded inconclusive results when analysed according to randomly allocated treatment group (so avoiding bias), but when analysed after the transfer of women in the folic acid group who did not take their capsules to the control group (ie, ignoring the randomisation and so introducing the possibility of bias) the supplemented women had a significantly lower recurrence rate.

The lower recurrence rate in the supplemented women in these two studies is unlikely to have arisen purely by chance. Two explanations were possible. One is that folic acid or possibly the other vitamins can prevent some cases of neural tube defects. A second plausible explanation is that women who chose to take the vitamins represented a selected group, perhaps with a more affluent or health-conscious diet, who were therefore at low risk of having a further affected pregnancy. Indeed, it is likely that such selection was operating; however, it was not known whether there was also a genuine preventive effect, and, if so, its magnitude and whether the responsible component was folic acid or one of the other vitamins.

Neither further statistical analysis of the results of these studies nor the accumulation of further results without appropriate controls would have solved the problem.⁵ The issue could be resolved only by performing a large trial in which, to avoid bias, women at risk would be randomly allocated to various groups, including a control group that

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TABLE I—NUMBER OF WOMEN RANDOMISED AND NUMBER WITH INFORMATIVE PREGNANCIES ACCORDING TO CENTRE

	No of women	Informative
Centre	randomised	pregnancies*
UK		
Glasgow	383	287
Cardiff	64	40
St Bartholomew's Hospital	61	46
Newcastle	54	28
Oxford	49	38
Edinburgh	32	19
Queen Charlotte's	25	21
Sheffield	15	7
Dundee	13	8
East Birmingham	11	9
The London Hospital	10	9
Southampton	5	5
St George's Hospital	5	3
University College Hospital	3	3
Aberdeen	3	0
Ashton-under-Lyne	1	0
Leicester	1	0
Total UK	735	523
Hungary		
Budapest	284	201
Debrecen	149	86
Miskolc	111	65
Pecs	88	56
Szombathely	62	47
Szeged	54	33
Gyor	21	2
Israel	140	107
Australia		
Adelaide	31	19
Melbourne	24	8
Sydney	20	14
Canada		
Hamilton	23	19
Halifax	10	2
Vancouver	8	8
USSR, Moscow	53	5
France, Lyon	4	0
Total non-UK	1082	672
Grand total	1817	1195

*An informative pregnancy was one in which the fetus or infant was known to have or not have a neural tube defect by the time the trial was stopped.

did not receive the extra vitamins. Furthermore, such a study would also permit the unbiased detection of any major adverse effects. A trial was launched in July, 1983, with the aim of recruiting women known to be at high risk through having had a previous affected pregnancy. It was the intention to obtain information on the outcome of at least 2000 pregnancies unless a sufficiently clear result emerged sooner. By April, 1991, sufficiently conclusive results had emerged to warrant ending the trial. The results at that time are the subject of this paper.

Methods

The study was an international, multicentre, double-blind randomised trial involving 33 centres (17 in the UK and 16 in six

other countries). Women with a previous pregnancy affected by a neural tube defect, not associated with the autosomal recessive disorder Meckel's syndrome, were eligible for the study if they were planning another pregnancy and were not already taking vitamin supplements. Women with epilepsy were excluded in case the folic acid supplementation adversely affected their treatment. Antenatal diagnosis of neural tube defects was available at all centres in the study. The effect of supplementation both with folic acid and with a selection of other vitamins was investigated by use of a factorial study design. Women were allocated at random to one of four supplementation groups, the supplements containing folic acid, other vitamins, both, or neither, in the following way:

Group	Folic acid	Other vitamins
А	Yes	No
В	Yes	Yes
С	No	No
D	No	Yes

Comparison of the outcomes in groups A and B with those in groups C and D tested the effect of folic acid supplementation; comparison of the outcomes in groups B and D with those in groups A and C tested the effect of the other vitamins. Separate sets of random allocations were used for each centre to ensure that there would be approximately equal numbers of women in each supplementation group at each centre.

The capsules used in the study were prepared by the Boots Company and packaged in 2-week calendar "blister" packs. Women in the trial were asked to take a single capsule each day from the date of randomisation until 12 weeks of pregnancy (estimated from the first day of the last menstrual period). Capsules for those in the folic acid groups contained 4 mg of folic acid-the larger of the two doses used in the previous studies being chosen because a negative result with the lower dose would have left the matter open. Capsules for those in the multivitamin groups contained vitamin A 4000 U, D 400 U, B₁ 1.5 mg, B₂ 1.5 mg, B₆ 1.0 mg, C 40 mg, and nicotinamide 15 mg. The control substance in the capsules was dried ferrous sulphate 120 mg and di-calcium phosphate 240 mg. The potency of the capsules was independently checked every three months by Hoffmann La Roche in Basel, Switzerland. The trial was double-blind, in that neither the doctor nor the patient knew which regimen had been allocated. It was agreed that the groups to which patients were allocated would normally be revealed only at the end of the trial. The randomisation was carried out through the Clinical Trials Service Unit in Oxford.

Women invited to join the trial were given a week to decide if they wished to take part, so that they could consider the matter at leisure and discuss the matter further with others if they wished. All patients were given a printed information leaflet about the trial.

No special advice was specified regarding diet. On entry into the trial, samples of blood and urine were collected and sent to the central trial office in the Department of Environmental and Preventive Medicine at St Bartholomew's Hospital for folic acid radioimmunoassav6 analysis. performed by (Amersham International). Patients were then given capsules and requested to attend every three months so that a note could be made of their general health and how many capsules they had taken. Blood and urine samples were collected at each visit for despatch to the trial office laboratory and a further supply of capsules was given. The last visit took place in the 12th week of pregnancy. The outcomes of all completed pregnancies were recorded, including details of any fetal malformation, sex, birthweight, and head circumference. In the

TABLE II-MEAN AGE, MEAN NUMBER OF PREVIOUS BIRTHS, AND MEAN NUMBER OF PREVIOUS NEURAL TUBE DEFECT PREGNANCIES AMONG ALL WOMEN RANDOMISED ACCORDING TO RANDOMISATION GROUP

Ra	ndomisa	ation group				In previous pregnancies, mean no of				
	Folic acid	Other vitamins	No. of women	Mean age (yr)	Total births	Livebirths	Miscarriages and other intrauterine deaths*	Terminations of pregnancy	Mean no of previous NTD pregnancies	
A	+	_	449	27.0	2.05	0.88	0.43	0.74	1.03	
в	+	+	461	27.4	2.12	0.94	0.48	0.70	1.04	
С	-	-	454	26.8	2.05	0.91	0.43	0.71	1.01	
D	-	+	453	26.5	1.88	0.81	0.39	0.68	1.01	

*Including ectopic pregnancies

						WAS INFORM						
						Number	of comp	pleted pregr	nancies			
Randomisation group		No of	Not informative				Informative					
	Folic acid	Other vitamıns	women randomised	Miscarriage	Ectopic pregnancy	Termination of pregnancy	Total	Livebirth	Miscarriage	Stillbirth	Termination of pregnancy	Total
Ā	+	-	449	39	1	0	40	290	3	2	3	298
В	+	+	461	41	3	0	44	285	4	2	4	295
С	—	-	454	41	4	1	46	283	3	3	11	300
D	-	+	453	33	2	2	37	287	6	0	9	302
Total			1817	154	10	3	167	1145	16	7	27	1195

TABLE III—OUTCOME OF ALL PREGNANCIES ACCORDING TO RANDOMISATION GROUP AND WHETHER THE PREGNANCY WAS INFORMATIVE

event of a termination of pregnancy or miscarriage the fetus was examined if possible. A woman remained in the trial until she had had a pregnancy in which the fetus could be classified as having a neural tube defect or not ("informative pregnancy"). If, for example, she had a miscarriage and the fetus was not examined, she remained in the study in the same randomisation group until the end of the trial or until she had an informative pregnancy. In this way each woman contributed no more than one informative event to the study. The final results are based on the outcome of all informative pregnancies. Whenever a neural tube defect (anencephaly, spina bifida cystica, or encephalocele) was reported, independent corroboration was sought, with a necropsy report if one was performed, or a description of the lesion for independent review at the trial centre in London (done without knowledge of the allocated group). To monitor possible toxicity associated with the supplementation, forms were provided for the notification of any medical event arising among the women in the trial irrespective of whether this was thought to be associated with the capsules. The health of each child born into the study was ascertained annually by sending a questionnaire to the mother on the infant's first, second, and third birthday. This part of the study is continuing. The results of the study, available only to the principal investigator, the study administrator, and the data monitoring committee, were reviewed every six months to enable the study to be stopped early if, as indeed occurred, a clear result emerged.

Results

Table I shows the numbers of women randomised and the numbers of informative pregnancies according to centre. Just over half were from outside the UK. All four groups were similar with respect to age and the outcome of previous pregnancies; thus randomisation had ensured that like was being compared with like (table II). Women in the UK centres were also categorised according to social class as defined by the Registrar General; the proportions in social class distributions were similar in the four groups—for example, the proportions in classes IV and V combined were 25%, 29%, 29%, and 28% in groups A, B, C, and D, respectively. Table III gives the outcome of all pregnancies according to randomisation group and whether or not the pregnancy was informative. The miscarriage rate was similar in the four groups. Most (23/30) of the terminations were performed on account of antenatal diagnosis of a neural tube defect.

Table IV shows the prevalence of neural tube defects in each of the four groups. Among women allocated to the groups receiving folic acid the rate was 1.0% and among those allocated to the other groups it was 3.5%, yielding a relative risk of 0.28 (95% confidence interval 0.12 to 0.71). The relative risk among women allocated to the "other vitamin" groups compared with the remaining groups was 0.80, a result that was not statistically significant (95% CI 0.37-1.72). Table IV also provides data after exclusion of the 164 women who may have been pregnant at the time of randomisation (ie, the first day of the last menstrual period occurred less than 14 days after the date of randomisation). The results of these analyses are virtually identical. In table v we give the results after excluding women who reported that they had stopped taking the capsules before their last scheduled visit (an "on-treatment" analysis). The recurrence rate among such women in the folic acid groups of the trial was 0.7% and in the groups without folic acid the recurrence rate was 3.4%, yielding a relative risk of 0.21 (95% CI 0.07-0.62). The relative risk among women allocated to the "other vitamin" groups, excluding those who stopped taking capsules, was 0.93 (95% CI 0.41-2.12). There is no indication that the vitamins other than folic acid conferred any preventive effect nor that they enhanced the effect of folic acid, although the power of the study to detect an interaction is limited. The effect of folic acid on the risk of anencephaly was not significantly different from that on spina bifida/encephalocele (the relative risks were 0.44 [3/593 vs 7/602] and 0.22 [3/332 vs 14/602], respectively), nor did it differ significantly between the UK centres and the other centres (the relative risks were 0.38 [3/261 vs 8/262] and 0.24 [3/332 vs 13/340], respectively).

The trial results were regularly reviewed. The figure shows the results of a sequential analysis up to April 12, 1991, when the data monitoring committee recommended that the trial be stopped—a decision that was endorsed by the steering committee. The difference between the number of neural tube defects in the non-folic-acid groups and in the

TABLE IV---PREVALENCE OF NEURAL TUBE DEFECTS (NTD) ACCORDING TO RANDOMISATION GROUP: MAIN ANALYSIS BASED ON ALL WOMEN RANDOMISED WHO HAD AN INFORMATIVE PREGNANCY CLASSIFIED ACCORDING TO RANDOMISATION GROUP (INTENTION-TO-TREAT ANALYSIS)

		,	Women not already pregnant at randomisation*			
Randomisation group		Relative risk: folic acid <i>vs</i>			Relative risk: folic acid vs	
Folic acıd	: Other vitamins	NTD/all	non-folic acid (95% CI)	NTD/all	non-folic acid (95% CI)	
+	_	2/298		2/258	1.00())	
+	+	4/295	1.0%)	3/256	1.0%)	
	-	13/300 21/602	3.5%)	11/260	3.5%)	
-	+	8/302 521/002 (<u>(</u> (<u></u>), <u>(</u>), (), <u>(</u>),	7/257	5.278)	

*First day of last menstrual period was 14 days or more after date of randomisation

TABLE V---PREVALENCE OF NEURAL TUBE DEFECTS ACCORDING TO RANDOMISATION GROUP AMONG WOMEN WITH INFORMATIVE PREGNANCIES: SUBORDINATE ANALYSIS EXCLUDING WOMEN WHO STOPPED TAKING CAPSULES (ON-TREATMENT ANALYSIS)

				All women	Women not already pregnant at randomisation*			
Randomisation group		ation group		Relative risk: folic acid vs		Relative risk: folic acid vs		
	Folic acid	Other vitamins	NTD/all	non-folic acid (95% CI)	NTD/all	non-folic acid (95% CI)		
A B C D	+ + -	- + - +	$\begin{array}{c c}1/280\\3/278\\11/281\\8/277\end{array}4/558($	$\begin{array}{c} 0.7\%) \\ 3.4\%) \end{array} \right\} 0.21 (0.07-0.62)$	$\begin{array}{c} 1/242\\ 2/241\\ 10/243\\ 7/234\\ \end{array} \begin{array}{c} 3/483 \ (0)\\ 17/477 \ (3)\\ \end{array}$	0.6%) 0.17 (0.05–0.59) 0.6%)		

*First day of last menstrual period was 14 days or more after admission.

TABLE VI—INFORMATIVE PREGNANCIES: ABNORMALITIES OTHER THAN NEURAL TUBE DEFECTS ACCORDING TO RANDOMISATION GROUP

Randomisation		misation		No with abnormal			
	Folic acid	Other vitamins	Total non-NTD	outcomes other than NTD	All reported abnormalities as notified (T = termination of pregnancy; M = miscarriage)		
A	+	_	296	7	Agenesis of corpus callosum and hydrocephalus (T); Down's syndrome; tetralogy of Fallot; severe asphyxia with low birthweight and cleft palate; pes varus; intrauterine growth retardation; polydactyly		
В	+	+	291	12	Lethal multiple pterygium syndrome (M); trisomy 15 (M); Adams-Oliver syndrome; Turner's syndrome (T); talipes; hypospadias; pyloric stenosis; dislocatable hips; persistent fetal circulation; pectus excavatum; purple birthmark/lump between eyes; unexplained neutropenia		
C	-	_	287	5	Partial deletion chromosome 18 (M); Down's syndrome; bilateral talipes (2); cardiac murmur		
D	-	+	294	8	Hydropic fetus with cervical cystic lymphangioma, complex cardiac malformation, and ganglioneuroblastic hamartoma of adrenals; hydropic fetus and cervical hygroma (T); Klinefelter's syndrome (T); congenital nystagmus and dilated ventricles; arthrogryposis; pes equinovarus; mongolian blue spot; skin tag at base of spine		
Total			1168	32	_		

folic-acid groups is plotted sequentially against the total number of neural tube defects in the trial. The boundaries define the limits for stopping the trial early at values calculated to give 75% power to detect a halving in the relative risk (at p = 0.05). It can be seen that the boundary was crossed after the 27th case. This sequential analysis was used as a guide, in the decision whether to terminate the trial, rather than as an absolute indication.

The observed relative risk estimate of the effect of folic acid supplementation will tend to be exaggerated, since the trial was stopped early because of the results. An estimate of the relative risk allowing for early stopping,⁷ itself an approximation that is influenced by the exact choice of the boundaries in the figure, was 0.33 (p=0.013, 95% CI 0.06-0.80)—close to the directly observed estimate of 0.28. The use of alternative reasonable boundaries yields similar results. Early stopping has not, therefore, distorted our measure of effect to any material extent.

Possible adverse effects of folic acid to the fetus and the mother were examined. Table VI shows the number of reported congenital abnormalities other than neural tube defects (together with any reported details) according to randomisation group. The details of the abnormalities are as notified, irrespective of severity. There were more reports in the vitamin groups, but this excess could readily have arisen by chance. In addition two of the disorders in the vitamin groups were inherited single gene defects-Adams-Oliver syndrome (autosomal dominant) and lethal multiple pterygium syndrome (autosomal recessive). Examination of the individual disorders did not reveal any excess that provides grounds for concern. The mean birthweights and head circumferences of infants with notified abnormalities born in the study were similar in all four randomisation groups (3387, 3376, 3344, and 3382 g and 34.2, 34.1, 34.1, and 34.1 cm, respectively in groups A, B, C, and D). Among all women randomised the mean number of women

reporting a medical disorder (typically non-specific ailments such as infertility, irregular menses, vomiting in pregnancy, upper respiratory illness) was similar in all four groups (16, 15, 11, and 19% respectively) with no single medical problem giving rise to particular concern.

7% of women who had informative pregnancies stopped taking their capsules before they became pregnant, usually because they lost interest in participating in the trial; among the remaining women, 95.4% took 80% or more of their assigned capsules, 3.8% took 50-79%, and 0.8% took less



Sequential analysis, showing cumulative difference between number of neural tube defects (NTDs) in the folic acid and non-folic-acid groups plotted against total number of NTDs.

The boundaries of the diagram define the stopping points of the study. Upper and lower boundaries of the figure were constructed by use of approximation that number of events in the folic acid groups minus number in the groups without folic acid follows a gaussian distribution with mean N(1-r)/(1+r) and variance N, where r is the relative risk and N is the total number of neural tube defects in the study.²² By taking the parameters of this gaussian distribution, equations given by Armitage²³ can be used to specify the upper and lower boundaries of the figure.

TABLE VII—SERUM FOLIC ACID CONCENTRATIONS AT LAST VISIT BEFORE BECOMING PREGNANT ACCORDING TO RANDOMISATION GROUP AMONG WOMEN WITH INFORMATIVE PREGNANCIES

R	andomi	sation		Serum	folic acid (I	ng/ml)
	Folic acid	Other vitamins	No*	10th centile	50th centile	90th centile
A B C D	+ + -	 + - +	$\begin{array}{c} 277\\ 261\\ 267\\ 274\\ \end{array}\right\} 538\\ 541$	$ \begin{array}{c} 21 \\ 25 \\ 3 \\ 3 \end{array} $ 3	$\begin{array}{c} 44 \\ 46 \\ 5 \\ 5 \\ 5 \end{array} \right\} 5$	

*Number tested was less than number of informative pregnancies because women became pregnant before the first three-monthly visit (64) or because a blood sample was not taken at the last visit before becoming pregnant (52).

than 50%, as judged by capsule counts at their quarterly visits. Table VII shows the 10th, 50th, and 90th percentile of serum folate concentrations according to randomisation group. The samples were taken at the visit immediately before they became pregnant (median interval between this visit and the first day of the last menstrual period was 7 days). The concentrations were substantially higher in the women allocated to folic acid than in those who were not (even at the 10th centile) while those in the groups without folic acid were not materially different from the baseline concentrations at the time of randomisation. The red cell folate results were similar. Compliance, therefore, was good.

Discussion

Our results show that folic acid supplementation can prevent neural tube defects. The relative risk estimate for the women allocated to take folic acid was 0.28 compared with the control groups—that is, 72% of neural tube defects were prevented (95% CI 29% to 88%). The result is unlikely to be due to chance and the randomised doubleblind design excludes bias as an explanation. The results also demonstrate that it is folic acid, rather than any of the other vitamins, that is responsible for the preventive effect.

We can be confident about the reliability of the diagnoses of neural tube defects in the trial. In the 27 cases recorded, 23 of the women had a termination of pregnancy and 4 had live births. Of these 4, in 2 cases the mothers were known to have declined termination and in 2 the reason was not known; 2 of the 4 survived. 18 of the 25 dead cases were confirmed by necropsy reports and in the remaining 7 descriptions confirmed the diagnosis. The diagnosis was unbiased with respect to randomisation group, since this was not known to the local participants.

6 women allocated to folic acid had neural tube defect pregnancies. Their serum folic acid concentrations (22, 36, 38, 118, 186, 194 ng/ml) were not unusually low for supplemented women. Lack of compliance with the regimen, or failure of folic acid absorption, is unlikely to be an explanation for these failures of prevention.

Results have been reported from two other randomised trials—the South Wales trial⁴ referred to earlier, and more recently an interim analysis from a study performed in Budapest in which a multivitamin capsule containing 0.8 mg of folic acid was given daily to unselected women instead of women with a previous neural tube defect pregnancy.⁸ In the first the recurrence rate was 2/60 in the folic acid group compared with 4/51 in the controls, and in the second the occurrence rates were 0/599 and 3/703, respectively. Both results suggested an effect but were inconclusive. Six observational studies of dietary folate or the use of folic acid and other vitamin supplements and neural tube defects have been published⁹⁻¹⁴ and one recent non-randomised folic acid

supplementation study.¹⁵ All but one showed an association but all may have suffered from the selection bias outlined above, and none could specifically identify folic acid as the responsible vitamin.

The non-randomised intervention study reported by Smithells and his colleagues yielded a sevenfold ratio in risk between supplemented and unsupplemented women,^{3,16} compared with our threefold ratio. A likely explanation for this difference is that the result from the non-randomised study reflects a combination of vitamin prophylaxis and selection bias, while our randomised trial reflects the prophylactic effect alone. However, the size of the studies is too small to exclude chance as a possible explanation.

Our trial was conducted among women who had had one or more neural tube defect pregnancies because of their higher risk of a recurrence, about ten times the general risk. There is, however, no reason to believe that the preventive effect of folic acid is restricted to this group. If additional folic acid can prevent a second neural tube defect pregnancy it is also likely to prevent a first one. It is implausible that serial occurrences of the same event have separate causes. Each woman who has had a recurrent neural tube defect pregnancy must have had a first; it is extremely unlikely that a method of preventing the second will not also tend to prevent the first, though the quantitative effect may be different in women having recurrences from that in women in general. If women who have already had an affected infant were genetically more susceptible to having affected pregnancies than women in general, the relative effect of an environmental cause such as a lack of folic acid would, in expectation, be the same in causing first cases as in causing subsequent ones if the effects of the environmental and genetic factors combine as the product of the two alone. It would be an underestimate if they combined additively. Insofar as the former is the more likely model, our result will be an unbiased estimate of the effect in the general population; if it were the latter, it would be conservative. If the genetic factor relied exclusively on a relative lack of folic acid to express the defect but otherwise folic acid had no role in the causation of neural tube defects, the effect would be greater in preventing recurrences than in preventing first cases. It is, however, a less likely model and one that does not explain the results of observational studies of folic acid intake and neural tube defects among women in the general population.^{10,11,13,14} Prophylaxis may, in practice, be lower in general because a smaller proportion of women who have not had an affected pregnancy may take folic acid supplements than women seeking to avoid a recurrence.

Women at high risk, having already experienced an affected pregnancy, have more to gain from supplementation than women at low risk, so a risk of toxicity that is acceptable in the former may be less acceptable in the latter. We recognise that a trial such as our own that has sufficient statistical power to demonstrate efficacy usually has insuffcient power to answer the question of safety for public health purposes. A judgment on safety needs to be taken on wider grounds. Folic acid is water soluble and readily excreted, and is not known to be toxic. Over 95% of pregnancies with neural tube defects occur in women without a previous affected pregnancy and this, taken with the fact that there is now a proven benefit, argues for increasing the intake of folic acid among all women who wish to become pregnant, not only those at high risk.

There remains the question of the dose of folic acid. If a 4 mg per day supplement is effective, a lower dose (for example, 0.36 mg per day as used by Smithells and his

colleagues³) is also likely to be effective, though possibly less so. A very large trial would be needed to estimate the relative efficacy of the two doses.

One reason for questioning the view that a relative lack of folic acid is a major cause of neural tube defects has been the observation that the United Kingdom has had one of the highest rates of neural tube defects in the world but was unlikely to be unusually deficient in folic acid. Either the UK does, in fact, have a lower folic acid intake than other countries, perhaps partly through losses in cooking, or the conjugates of folic acid in foods typically eaten in the UK may be relatively poorly absorbed, or there are other dietary factors that interfere with its absorption or metabolism, or there is an interaction with a genetically controlled disturbance of folic acid metabolism.

Another reason to question the efficacy of folic acid is the fact that individual studies have not shown a significant difference in the serum folic acid concentrations of women with affected and unaffected pregnancies; differences in red cell folate levels have been found but they have not been very large.¹⁷⁻²¹ It is possible that the range of values of blood folic acid levels among women in most populations is too narrow for such differencies (if present) to be readily demonstrable. The position would then be analogous to examining the mean difference in number of cigarettes between lung cancer cases and controls in a study of smoking and lung cancer among individuals who all smoke between 15 and 20 cigarettes a day. The mean difference would be extremely small, and not discernible except in very large studies. The lack of a clear association between serum folate levels and neural tube defects and only a modest difference in red cell folate levels is not, therefore, inconsistent with the protective effect of folic acid supplementation.

Folic acid supplementation can now be recommended for all women who have had a previously affected pregnancy, and public health measures should be taken to ensure that all women of childbearing age receive adequate dietary folic acid. The demonstration that folic acid is the effective agent avoids the need to use a mixture of vitamins with the associated extra costs and concern over possible toxicity (eg, from vitamin A). It is less clear whether all women planning a pregnancy should take folic acid supplements. The case rests upon questions of safety and cost. In any event, community-wide prevention may be difficult to achieve by providing supplements to everyone and consideration should be given to extending the fortification of staple foods with folic acid.

This study has established the specific role of folic acid in the prevention of neural tube defects. It has produced a clear answer to an important medical question on which opinion and practice have been divided. The trial has resolved the uncertainty and has provided a basis for concerted preventive practice.

Steering committee

John Burn, Malcolm Ferguson-Smith, Edmund Hey, Paul Polani, Charles Rodeck, Geoffrey Rose (chairman), Nicholas Wald (study coordinator and principal investigator), and J. Modle and M. Hennigan (departments of health observers).

Data monitoring committee

Eva Alberman, Peter Armitage (chairman), and Geoffrey Chamberlain.

Trial office

Administration: Joan Sneddon, Karen Fordham (formerly Alison Bickmore and Patricia Collins). Computing: James Densem. Statistics: Chris

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Participating centres

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Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis

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A few patients remain severely affected by atopic dermatitis into adult life despite treatment with steroids. azathioprine. systemic and photochemotherapy. 33 patients took part in a double-blind, placebo-controlled, crossover study to assess the efficacy and safety of cyclosporin (5 mg/kg per day) in adults with severe refractory atopic dermatitis. Treatments were given for eight weeks each with one group (n=16) receiving placebo followed by cyclosporin and another (n=17) receiving cyclosporin and then placebo. Disease activity, extent of disease, sleep and itch, topical steroid use, and adverse events were assessed every two weeks. Both extent and activity of dermatitis were significantly improved (p < 0.001) as were subjective measures of disease. 20 patients receiving cyclosporin reported adverse events compared with 8 taking placebo, although no patient required withdrawal from the study. Cyclosporin therapy led to an increase in the mean serum urea, creatinine, and bilirubin concentrations, although only the rise in bilirubin was significant (p = 0.001). Our results confirm that cyclosporin is a safe and effective short-term treatment for severe, refractory atopic dermatitis.

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Introduction

The dermatitis associated with atopic disease is an intensely pruritic condition with a typical morphology and distribution. Although the cause of this dermatitis remains unknown, immunological mechanisms are thought to be important.¹ In most patients the disease begins in infancy and steadily improves throughout childhood; symptoms can be controlled with emollients and topical steroids. Some patients remain severely affected into teenage years and adult life, and may require treatment with systemic steroids, azathioprine, or photochemotherapy. Despite these measures, control is often poor, but there have been recent case reports and open studies suggesting that cyclosporin may be an effective alternative treatment for these patients.²⁻⁸ We have completed the first double-blind,

placebo-controlled, crossover study to assess the efficacy and safety of cyclosporin in a group of adults with severe refractory atopic dermatitis.

Patients and methods

Protocol

Each patient was randomly allocated to receive either cyclosporin, formulated as soft gelatine capsules, at a dose of 5 mg/kg per day for eight weeks followed immediately by identical-looking placebo for eight weeks or placebo followed by cyclosporin. After these treatment sequences there was a follow-up period of four weeks. Approval for the study was obtained from the ethical committees of each of the four participating centres and, after giving informed consent, 33 patients aged 17–56 years with severe long-standing atopic dermatitis resistant to conventional therapy were recruited from clinic. 18 patients also had a history of asthma. No formal assessments of pulmonary function were made and no changes took place in their asthma treatment.

The diagnosis of atopic dermatitis was made according to the clinical and morphological criteria defined by Hanifin and Rajka.⁹ Treatment with systemic steroids, cytotoxic drugs, or photochemotherapy was stopped two weeks before the study. Topical steroid preparations were continued and their frequency of application monitored. Patients were excluded if they had abnormal renal or hepatic function, treated or untreated hypertension, a history of malignant disease, acute uncontrolled infection, or were taking nephrotoxic drugs or agents likely to interfere with the pharmacokinetics of cyclosporin. Appropriate contraceptive precautions were necessary for women of child-bearing age; pregnant or lactating mothers were excluded.

Clinical assessment

Patients were assessed every two weeks by measuring the following variables:

Disease activity—Six clinical features (erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring, and

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