

Before the
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

In re: Food Labeling; Health Claims and)
Label Statements; Request for) Docket No. 91N-100H
Scientific Data and Information)
) (Comparative Folic Acid/NTD)
)

ORIGINAL

SUPPLEMENTAL COMMENTS OF
JULIAN M. WHITAKER, M.D.;
PURE ENCAPSULATIONS, INC.;
WEIDER NUTRITION INTERNATIONAL, INC.;
XCEL MEDICAL PHARMACY, LTD.;
THE AMERICAN PREVENTIVE MEDICAL ASSOCIATION; AND
DURK PEARSON AND SANDY SHAW.

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Julian M. Whitaker, M.D.; Pure Encapsulations, Inc.; Weider Nutrition International, Inc.; XCEL Medical Pharmacy, Ltd.; the American Preventive Medical Association; and Durk Pearson and Sandy Shaw (collectively "Joint Commenters"), by counsel and in response to the notice seeking scientific data and information ("Notice") published in the Federal Register, 64 Fed. Reg. 48841-48842 (September 8, 1999) and 65 Fed. Reg. 4252-4253 (January 26, 2000), hereby submit these comments.

I. BACKGROUND OF THE JOINT COMMENTERS

Julian M. Whitaker, M.D. Julian M. Whitaker, M.D. is a physician licensed to practice medicine in the states of California and Washington. He graduated from Dartmouth College in 1966 with a B.S. degree and from Emory University in 1970 with an M.D. degree. He received additional training in surgery as a resident at the University of California Medical School. From 1975 to 1976 he worked as a physician at the

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Pritikin Institute in California. Since that time he has been the Clinical Director of the Whitaker Wellness Institute in Newport Beach, California. He is the author of five books: *Reversing Heart Disease* (1985), *Reversing Diabetes* (1987), *Reversing Health Risk* (1989), *Natural Healing* (1994), and *What Your Doctor Won't Tell You About Bypass* (1995). Since August of 1991 he has been the editor of *Health & Healing*, currently the nation's largest single editor health newsletter. In 1998, *Health & Healing* had over 500,000 subscribers. He receives royalties from the distribution and sale of several dietary supplements based on formulas he develops and licenses. Among the supplements which Dr. Whitaker has formulated (and from which he receives royalty payments) are two containing folic acid, each with 0.8mg of the acid per daily serving. He wants to place the proposed health claim on the labels and in the labeling of his folic acid dietary supplements and, but for FDA's extant bar on labeling use of the claim, he would do so. Accordingly, he seeks FDA approval of the claim.

Durk Pearson and Sandy Shaw. Pearson and Shaw are scientists residing in Nevada. They design dietary supplement formulations and license them to manufacturing and retailing companies. They are authors of four books on aging and age-related diseases, including the #1, million plus copy best seller *Life Extension: A Practical Scientific Approach* (1982). They have also published three other health books, two of which were best sellers: *The Life Extension Companion* (1984); *The Life Extension Weight Loss Program* (1986); and *Freedom of Informed Choice—FDA Versus Nutrient Supplements* (1993). Durk Pearson and Sandy Shaw were plaintiffs in the Pearson v. Shalala case. The agency identifies this proceeding as one to aid FDA in implementing Pearson's mandate. Pearson and Shaw license two dietary supplements

that contain 0.8mg of folic acid per daily serving. Pearson and Shaw wish to communicate the nutrient/disease relationship that is the subject of these comments on their folic acid dietary supplement labels and in the labeling associated with those products.

American Preventive Medical Association. The American Preventive Medical Association (APMA) is a non-profit organization located in Virginia. APMA was founded in October of 1992 and is dedicated to ensuring consumer access to preventive therapies and the rights of health care providers to offer those therapies. APMA was a plaintiff in the Pearson v. Shalala case. The agency identifies this proceeding as one to aid FDA in implementing Pearson's mandate. Several APMA physicians sell dietary supplements that contain 0.8mg of folic acid per daily serving. APMA and its practitioner members, and their hundreds of thousands of patients, would benefit from approval of the health claim that is the subject of this proceeding because it would enable the practitioner members to communicate and their patients to receive nonmisleading health information on labels and in labeling concerning the effects of folic acid on reducing the risk of neural tube defects (NTD). APMA and its member physicians therefore seek agency approval of the claim.

Pure Encapsulations, Inc. Pure Encapsulations, Inc. (Pure) is a Massachusetts corporation engaged in the business of manufacturing, distributing, and selling over 250 pharmaceutical grade dietary supplements for human and companion animal consumption. Eight of the dietary supplements manufactured and sold by Pure each contain 0.8mg of folic acid per daily serving. Pure would like to place the proposed

health claim that is the subject of this proceeding on the labels and in the labeling of those folic acid products.

Weider Nutrition International, Inc. Weider Nutrition International, Inc. (Weider) is a Utah corporation engaged in the business of manufacturing, distributing, and selling over 2,000 pharmaceutical grade dietary supplements for human and companion animal consumption. Weider has been a health, fitness and sports nutrition leader for nearly fifty years since its founding in 1939. Seven of the supplements manufactured and sold by Weider each contain 0.8mg of folic acid per daily serving. Weider would like to place the proposed health claim that is the subject of this proceeding on the labels and in the labeling of those folic acid products.

XCEL Medical Pharmacy, LTD d/b/a XCEL Health Care. XCEL Medical Pharmacy, Ltd. d/b/a XCEL Health Care (XCEL) is a California corporation engaged in the business of manufacturing, distributing, and selling pharmaceutical grade dietary supplements for human consumption. One of the supplements manufactured and sold by XCEL contains 0.8mg of folic acid per daily serving. XCEL would like to use the proposed health claim that is the subject of this proceeding on the labels and in the labeling of that folic acid product.

II. SUMMARY OF THE NOTICE

The Department of Health and Human Services (HHS), Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN), has published a Notice in the September 8, 1999 Federal Register, 64 Fed. Reg. 48841-48842, requesting scientific data, research study results, and other related information concerning four substance-disease relationships. On January 26, 2000, FDA announced in

the Federal Register that it was reopening the comment period and would accept scientific data and written comments that are submitted on or before April 3, 2000. 65 Fed. Reg. 4252. In *Pearson v. Shalala*, 164 F. 3d 650 (D.C. Cir. 1999) *reh'g denied en banc*, 172 F.3d 72 (D.C. Cir. 1999), the U.S. Court of Appeals for the D.C. Circuit held four FDA sub-regulations (prohibiting each of the four substances-disease relationships) invalid under the First Amendment (21 C.F.R. §§ 101.71(a), (c), (e); 101.79 (c)(2)(i)(G)). One of the invalid regulations is the subject of this comment. That regulation, 21 C.F.R. §101.79 (c)(2)(i)(G), prohibits the following claim: “.8 mg of folic acid in a dietary supplement is more effective in reducing neural tube defects than a lower amount in foods in common form.” 21 C.F.R. §101.79 (c)(2)(i)(G) reads in pertinent part: “The claim shall not state that a specified amount of folate per serving from one source is more effective in reducing the risk of neural tube defects than a lower amount per serving from another source.” The FDA Notice states that the agency will determine if an “appropriate scientific basis exists to support the issuance of a propose rule to authorize a health claim for the relationship between folic acid and NTD based on the data and information it receives.” 64 Fed. Reg. 48841. FDA requests that interested parties submit scientific data and information published between 1992 and the present concerning the relationship.

III. THE PROPER LEGAL ISSUE BEFORE THIS AGENCY IS NOT WHETHER THE CLAIM WILL BE AUTHORIZED BUT, RATHER, WHAT KIND OF DISCLAIMER SHOULD BE USED

Under *Pearson*, this agency must authorize the folic acid health claim. The Court rejected FDA’s argument that the claim was inherently misleading. *Pearson*, 164 F.3d at 656. Indeed, the Court found “that credible evidence did support this claim.” *Pearson*, 164 F.3d at 657, n.7. The Court determined that the claim was, at worst, potentially

misleading. *Pearson*, 164 F.3d at 657. In accordance with Supreme Court commercial speech precedent, only inherently misleading claims may be suppressed outright. 44 *Liquormart v. Rhode Island*, 517 U.S. 484, 503 (1996). Claims that are, at worst, potentially misleading must be authorized with corrective disclaimers. *Pearson*, 164 F.3d at 657-658. Thus, because the First Amendment – and not the agency’s own rules and policy preferences – is the Supreme law of the land, this agency must authorize the folic acid claim. The only legal question confronting the agency is precisely how to disclaim the claim to avoid a misleading connotation. In the first instance, the Court of Appeals has made that decision for the agency. *Pearson*, 164 F.3d at 658.

IV. FDA MUST IMMEDIATELY AUTHORIZE THE CLAIM ON AN INTERIM BASIS WITH THE DISCLAIMER SPECIFIED BY THE PEARSON COURT

The *Pearson* Court held the agency’s suppression of the folic acid claim invalid under the First Amendment to the United States Constitution. *Pearson*, 164 F. 3d at 657-9. It did so upon a complete record including all scientific evidence then before FDA. Having reviewed that evidence and the agency’s arguments against claim authorization, it held the claim not inherently misleading but, at worst, only potentially misleading. *Pearson*, 164 F. 3d at 657. Consistent with Supreme Court precedent, a potentially misleading claim must be authorized with disclaimers and may not be suppressed outright. 44 *Liquormart v. Rhode Island*, 517 U.S. 484, 503 (1996). Relying on that precedent, the Court of Appeals gave this agency a disclaimer it deemed sufficient to address the agency’s concerns about misleadingness. That disclaimer reads: “The evidence in support of this claim is inconclusive.” *Pearson*, 164 F. 3d at 658.

Because the rule FDA now enforces to prevent the claim from appearing on labels and in labeling is invalid, and because the Court has held the claim, at worst, only potentially misleading, FDA must no longer enforce the invalidated rule and must act immediately to allow the claim. Prudence dictates, and law necessitates, that this agency allow the claim on an interim basis with the disclaimer the Court crafted to cure potential misleadingness. That will ensure that the First Amendment rights of the Joint Commenters are not violated during the period of agency consideration of alternative disclaimers.

This agency has violated the *Pearson* Court's order by continuing to enforce the invalidated rule on the folic acid claim from the time of the issuance of the Court's mandate (April 20, 1999) until the present, approximately one year as of the date of these comments. The agency's enforcement of the invalidated rule is an unlawful act that cannot stand. The federal courts have held that violations of constitutional rights, including First Amendment rights, must be rectified with haste and cannot be allowed to stand for years while the Government contemplates its next move. Indeed, the Supreme Court has held that violation of a First Amendment right, even for a very short period of time, constitutes irreparable injury without proof of more. See *Elrod v. Burns*, 427 U.S. 347, 373 (1976) (plurality opinion) ("The loss of First Amendment freedoms, for even minimal periods of time, unquestionably constitutes irreparable injury") quoted in *Jackson v. City of Columbus*, 194 F.3d 737, 747 (6th Cir. 1999); *Iowa Right to Life Comm., Inc. v. Williams*, 187 F.3d 963, 969 (8th Cir. 1999); *Brownsburg Area Patrons Affecting Change v. Baldwin*, 137 F.3d 503, 507 (7th Cir. 1998); *New York Magazine v. Metropolitan Transportation Authority*, 136 F.3d 123, 127 (2nd Cir. 1998); see also *City*

of Lakewood v. Plain Dealer Publishing Co., 486 U.S. 750, 758 (1988); *Washington Free Community v. Wilson*, 426 F.2d 1213, 1218 (D.C. Cir. 1969). When Government violates First Amendment rights, the Supreme Court has held delay in eliminating the rights violation intolerable: “Speakers . . . cannot be made to wait for years before being able to speak with a measure of security.” *Riley v. National Federation of the Blind*, 784 U.S. 781, 793-94 (1988) (internal quotes omitted).

The Supremacy Clause of the Constitution establishes beyond peradventure of doubt that the Constitution and the laws in pursuance of it are supreme to contrary laws. U.S. Const. Art. VI, *Marbury v. Madison*, 5 U.S. 137, 178-180 (1803). Accordingly, this agency should not have continued to enforce the invalid rules beyond April 20, 1999 and clearly must immediately authorize the folic acid claim on an interim basis with the disclaimer specified by the Court of Appeals. At the conclusion of its rulemaking on the folic acid claim, FDA may then craft an alternative, final disclaimer, if deemed necessary, to cure any misleadingness the agency perceives based on the supplemental submissions it has solicited.

IV. RECENT SCIENTIFIC RESEARCH ADDS FURTHER EVIDENCE CONFIRMING THE SUPERIORITY OF .8 MG OF FOLIC ACID IN SUPPLEMENT FORM OVER LESSER AMOUNTS IN FOODS IN COMMON FORM

The evidence in support of the folic acid claim is overwhelming. Recent studies confirm that conclusion. Since the Joint Commenters’ initial submission in response to the agency’s public notice, additional research has appeared in the peer-reviewed literature germane to the claim, all militating in favor of the claim. The studies indicate that women are not likely to change eating behaviors in an effort to obtain the .4 mg they

need, at minimum, to increase the probability of a meaningful population wide reduction in NTD births. The studies establish that the level of folate in foods in common form, even when fortified, is not enough to provide effective protection for most women of childbearing age. The campaign to raise periconceptual levels of folic acid needs to be unequivocal in informing women in their childbearing years that they need dietary supplement folic acid to reliably reduce their risks of NTD births. The current FDA rules on the folic acid claim mislead consumers into believing that foods in common form can be trusted to reliably provide them with .4 mg or more of folic acid daily—a fact thoroughly refuted by the scientific evidence confirming that food folate is perishable due to food preparation, cooking, and shelf-life. The bioavailability of food folate is only about one-half of synthetic folic acid. FNB, IOM, NAS, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline* (IOM), Washington DC: National Academy Press, 1998: 32; Neuhauser ML, et al., “Absorption of dietary and supplemental folate in women with prior pregnancies with neural tube defects and controls,” *J Am Coll Nutr*, 1998, 17: 624-630). By contrast, folic acid in a dietary supplement remains the only reliable source of a consistent supply of .4 mg or more of folic acid daily. Moreover, the evidence confirms clearly now that .8 mg of folic acid in a dietary supplement provides superior NTD risk reduction to lesser amounts and is superior to folate found in foods in common form. Based on the superior bioavailability and dose response properties of synthetic folic acid for preventing NTDs, the Institute of Medicine (IOM) Food and Nutrition Board (FNB) recommends that pregnant women consume at least 600 ug of folate daily and emphasizes that more than 400 ug of that amount should come from synthetic folic acid.

See Exhibit 2 citing FNB, IOM, NAS, *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline* (IOM), Washington DC: National Academy Press, 1998: 32.

Among the recent studies germane to the claim are the ten described below and appended hereto as Exhibits 2 – 10. Based on the overwhelming body of publicly available scientific evidence, this agency should reverse its earlier decision and authorize the claim.

As explained below, even if the agency erroneously fails to approve the claim under its health claims review standard, it must nevertheless authorize it with a reasonable disclaimer because that authorization is required to avoid violation of the First Amendment to the United States Constitution.

In Exhibit 2 hereto (“Folic acid for the prevention of neural tube defects,” American Academy of Pediatrics, Committee on Genetics, *Pediatrics*, 1999, 104(2 Pt 1): 325-7), the American Academy of Pediatrics endorses the U.S. Public Health Service recommendation that all women capable of becoming pregnant consume 400 micrograms of folic acid daily to prevent neural tube defects (NTDs). Studies have demonstrated that adequate periconceptional folic acid supplementation can prevent 50% or more of NTDs. For women who have previously had an NTD-affected pregnancy, the United States Centers for Disease Control and Prevention (CDC) recommends increasing the intake of folic acid to 4,000 micrograms per day beginning at least 1 month before conception and continuing through the first trimester.¹ Implementation of these recommendations is

¹ The CDC recommendation illustrates CDC’s belief that there is a dose response relationship and that CDC expects the larger amount of folic acid to be more protective than the lower amount.

essential for the primary prevention of these serious and disabling birth defects. Because fewer than 1 in 3 women consume the amount of folic acid recommended by the USPHS, the Academy notes that the prevention of NTDs depends on an urgent and effective campaign to close this prevention gap. That campaign should be aimed at increasing folic acid intake through the use of supplements, fortified foods, or a combination of both. The Academy has concluded that the current FDA mandated US food fortification program inadequately addresses folic acid requirements and it would be nearly impossible to obtain enough folic acid from diet alone. The Academy recommends that all women of childbearing age consume 400 ug of folic acid in supplement form in addition to eating a folate rich diet.

In Exhibit 3 hereto (DeRose DJ, Crutcher JM, DePersio SR, "Improving the health of Oklahomans through clinical prevention. Part 1: Counseling to decrease major risk factors," *J. Okla. State Med. Assoc.* 2000 Feb; 93(2): 52-60), the authors note that research has shown that many patients will modify unhealthy behaviors as a result of services provided by physicians or staff in their offices, often with briefly delivered messages. The research indicates that physicians should make maximum use of their ability to promote healthy behaviors by their patients, with emphasis on the risk factors associated with significant morbidity in the state. The most effective means of reducing risk of NTDs is daily intake of supplemental folic acid. The authors conclude that physicians and health professionals should recommend that all women of childbearing age who are capable of becoming pregnant take a daily multivitamin containing 400 ug of folic acid.

In Exhibit 4 hereto (Iqbal MM, "Prevention of neural tube defects by periconceptional use of folic acid," *Pediatr Rev.* 2000 Feb; 21(2): 58-66), the author concludes that the possibility of "reducing the number of NTDs in the US by 70% with the consumption of 3 cents worth of folic acid per day presents an important opportunity... Efforts should be made to assure that all women capable of becoming pregnant consume 0.4mg of folic acid daily to achieve this goal... it is difficult, if not impossible, to achieve a daily intake of 0.4mg of folate through diet alone."

In Exhibit 5 hereto (Komaromy-Hiller G, Nuttall KL, "Folic acid fortification," *Lancet* 1999 354(9196): 2167-8), the authors demonstrate that current folic acid fortification programs have had a minor effect on plasma homocysteine levels and do not appear to adequately raise plasma folate levels to affect NTD risk.

In Exhibit 6 hereto (McDonnell RJ, Johnson Z, Delaney V, Dack P, "East Ireland 1980-1994: epidemiology of neural tube defects," *J Epidemiol Community Health* 1999 Dec; 53(12): 782-8), the authors identify the great need for increased supplemental folic acid intake among all women of child bearing age. The researchers noted that in 1997 only 16% of all pregnant women took supplements periconceptually. The study indicates that diets of women under 25 years old were significantly lower in folate than that of older women and that efforts aimed at increasing supplementation would be more effective than those aimed at modification of dietary habits in reducing risk of an NTD birth.

In Exhibit 7 hereto (Meyer RE, Oakley GP Jr., "Folic acid fortification," *Lancet.* 1999 Dec 18-25;354(9196):2168), the authors examine NTD trends after initiation of folic acid food fortification in January 1998. At best, the food fortification program

increases a woman's consumption of folic acid by only 100 ug per day "or a quarter of the amount recommended for birth-defect prevention." The data indicates that fortification has not affected NTD trends. The authors conclude that until implementation of American food fortification programs that increase daily folic acid consumption by at least 400 ug, women of reproductive age should be taught that they should "consume daily vitamin supplements containing 400 ug of synthetic folic acid."

In Exhibit 8 hereto (Michie CA, Narang I, Rogers J, Robinson A, "Folate supplementation and neural-tube defects" *Lancet* 2000 Jan 8; 355(9198):147), the authors conclude that language and associated cultural barriers may explain study results that indicate periconceptual use of folic acid by child bearing women is not widespread. The authors indicate that more information and education is needed to increase daily folic acid supplement intake by all women of childbearing age. The information must be clear that daily supplements are needed and that diet alone is not sufficient.

In Exhibit 9 hereto (Rosano A, Smithells D, Cacciani L, Botting B, Castilla E, Cornel M, Erickson D, Goujard J, Irgens L, Merlob P, Robert E, Siffel C, Stoll C, Sumiyoshi Y, "Time trends in neural tube defects prevalence in relation to preventive strategies: an international study," *J Epidemiol Community Health* 1999 Oct; 53(10):630-5), the authors examine the international prevalence of NTD births. The research results indicate that the prevention strategy of food fortification has not affected NTD rates. The data indicates, however, that fully implemented folic acid supplementation programs result in a decreased rate of NTD births. The authors point out the difficulty and expense of such and that in Western countries having the resources for a supplement program 50% of pregnancies are unplanned.

In Exhibit 10 hereto (Schader I, Corwin P, "How many pregnant women in Christchurch are using folic acid supplements in early pregnancy?" *N Z Med J.* 1999 Dec 10; 112(1101):463-5), the authors conclude that implementation of a folic acid supplementation program is critical to reducing NTD risk. The programs must be designed to not only increase knowledge of the benefits of folic acid, but cause behavior changes so that all women of reproductive age have access to and take a daily supplement of 400 ug of folic acid.

V. **FDA MUST NOT ASSESS "SIGNIFICANT SCIENTIFIC AGREEMENT" BASED ON ITS PROPOSED "GUIDANCE" BECAUSE THE GUIDANCE VIOLATES PEARSON, THE INTENT OF CONGRESS, AND THE PLAIN LANGUAGE OF THE NLEA**

On December 22, 1999, the FDA published a proposed "Guidance" in a failed attempt to comply with the *Pearson* Court's mandate that it define a standard for "significant scientific agreement." As explained in comments filed by the Joint Commenters in response to that guidance (attached hereto as Exhibit 12 and incorporated herein by reference), FDA may not require near conclusive proof as a condition precedent to approval of a dietary supplement health claim. Rather, Congress expects this agency to approve claims backed by "significant scientific agreement" without requiring them to satisfy the standard established by law for FDA approval of drugs (the "substantial evidence" standard in 21 U.S.C. § 355(e)). The bi-partisan Senate Committee on Labor and Human Resources explained in its Committee Report reviewing FDA's application of the health claims standard:

The committee notes that the significant scientific agreement standard is, by design, more flexible than the standard established by law for FDA to review and approve drugs, which requires a demonstration of safety and effectiveness based on "adequate and well-controlled clinical investigations." While the intake of a

nutrient on which a health claim is based must be safe, there is no requirement that health claims be derived from clinical trials, and, by its terms, the standard recognizes that significant scientific agreement on the validity of the claim does not have to be complete. Evidence from a broad range of reliable scientific sources should be considered in determining the adequacy of scientific support.

Senate Report 103-410, at 24.

In its Guidance, the FDA fails to fulfill the *Pearson* Court's order by explaining what "significant scientific agreement" means and what it does not mean. The Guidance does not provide information necessary for regulatees to perceive FDA's guiding principles. While, from the Guidance, the regulated class can understand that FDA views interventional studies involving well designed randomized, controlled clinical trials as its "gold standard," it is entirely impossible from the Guidance to perceive whether FDA will ever accept studies other than interventional or other than those involving randomized, controlled clinical trials, as sufficient for claim authorization. Moreover, FDA requires proof of direct causality (that a substance *will* result in a change in a disease endpoint) as a condition precedent to claim approval. A large body of evidence strongly supporting, but not conclusively proving, a substance-disease relationship appears unlikely to satisfy FDA. Thus, the only principle that regulatees can perceive with clarity from FDA's Guidance is that FDA will accept the same kind of near conclusive proof expected as a condition precedent for drug approval as its basis for dietary supplement claim approval. That principle, however, violates congressional intent as the excerpted passage above makes clear.

Congress plainly expects this agency to approve health claims for dietary supplements without requiring that those claims be backed by the same kind of near conclusive proof required for the grant of applications for new drugs. Accordingly, to the

extent that FDA's Guidance reveals a principle to the regulated class, that principle is one calling for a level of evidence that Congress has unequivocally rejected in the context of health claims for dietary supplements. Consistent with the dictates of Congress, this agency should hold that significant scientific agreement exists when

a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are *reasonably likely* to obtain the claimed health benefit.

Senate Report 103-410, at 24. Congress has determined that the above-quoted definition which it supplied in committee is "consistent with the NLEA's goal of assuring that consumers have access on food and dietary supplement labels to health claims that are scientifically supported, without having to wait until the degree of scientific certainty contemplated by the drug standard has been achieved." *Id.*

Based on the hundreds of studies submitted to the FDA in this docket and the docket reviewed by the *Pearson* Court, there can be no doubt that "a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are *reasonably likely* to obtain the claimed health benefit." Indeed, the evidence appears to surpass that expected by Congress for claim approval and to approach the near conclusive degree that FDA erroneously expects as a condition precedent for health claim approval. Accordingly, FDA should, indeed it must, approve the claim under 21 U.S.C. § 343(r)(5)(D) and its rules as backed by "significant scientific agreement."

VI. ASSUMING ARGUENDO THAT FDA FAILS TO FIND “SIGNIFICANT SCIENTIFIC AGREEMENT,” IT MUST NEVERTHELESS AUTHORIZE THE CLAIM WITH DISCLAIMERS CONSISTENT WITH PEARSON

Assuming *arguendo* that this agency decides that the folic acid claim is not backed by “significant scientific agreement” and, thus, decides not to *approve* it, it may not deny the claim but must nevertheless *authorize* it with a corrective disclaimer. *Pearson*, 164 F. 3d at 658. Indeed, as explained above, FDA has a constitutional obligation to authorize the claim at the earliest possible moment. In light of the fact that the *Pearson* Court has already determined that the claim is not inherently misleading (164 F. 3d at 656) and is, at worst, only potentially misleading, under applicable First Amendment precedent this agency has an incontrovertible duty to authorize the claim. That duty to authorize the claim trumps any contrary agency preference or rule and necessitates authorization with a disclaimer. U.S. Const. Art. VI, *Marbury*, 5 U.S. 178-180 (1803). That duty does not compel FDA to *approve* the claim, as the *Pearson* Court explained. *Pearson*, 164 F. 3d at 658. Indeed, if FDA finds “significant scientific agreement” lacking, it may choose not to place its imprimatur of approval upon the claim; nevertheless, even without claim approval under significant scientific agreement, the First Amendment compels FDA to authorize unapproved claims so long as the claims can be rendered nonmisleading through the addition of a disclaimer. *Pearson*, 164 F. 3d at 659. In this case, the Court of Appeals took the extraordinary step of fashioning disclaimers for the agency’s use. That action, coupled with the First Amendment burden upon government to rectify wrongful acts of suppression with haste, compels FDA to issue immediately an interim rule authorizing the claim with the final disclaimer specified by the Court. FDA may then arrest its unlawful enforcement of the constitutionally invalid

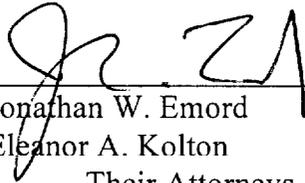
rule and proceed with rulemaking to define precisely the content of the disclaimer it desires to require for use with the claim.

VII. CONCLUSION

For the foregoing reasons, FDA must act immediately to authorize the folic acid claim on an interim basis requiring use of the disclaimer crafted by the *Pearson* Court, as explained above. That action is warranted because the *Pearson* decision invalidated the rule FDA now enforces unlawfully to prevent use of the folic acid claim. That action is also warranted because First Amendment precedent, cited above, requires immediate elimination of a civil rights violation, including a First Amendment right violation, by this government. Accordingly, FDA should immediately authorize the folic acid claim with the corrective disclaimer specified by the *Pearson* Court. If, upon completion of its rulemaking, it fails to approve the claim under “significant scientific agreement,” it must nevertheless authorize it with a disclaimer tailored to satisfy any other reasonable concerns the agency may have. In fact, based on the additional science adduced, FDA should approve the claim without disclaimers in light of the fact that the claim is amply supported by “significant scientific agreement.” To avoid a violation of the Administrative Procedure Act’s prohibition on arbitrary and capricious agency action, FDA should interpret “significant scientific agreement” as Congress intended. Under the congressionally intended definition, the folic acid claim should be *approved* by the agency. Nevertheless, if it is not *approved*, it should nevertheless be *authorized* with disclaimers, as required by the First Amendment.

Respectfully submitted,

JULIAN M. WHITAKER, M.D.;
PURE ENCAPSULATIONS, INC.;
WEIDER NUTRITION INTERNATIONAL, INC.;
XCEL MEDICAL PHARMACY LTD;
THE AMERICAN PREVENTIVE MEDICAL
ASSOCIATION; AND
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Date: April 3, 2000

EXHIBIT 1

Before the
FOOD AND DRUG ADMINISTRATION
Rockville, MD

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In re: Guidance for Industry:)
Significant Scientific Agreement)
In the Review of Health Claims) Docket No. 99D-5424
For Conventional Foods and)
Dietary Supplements; Availability)

COMMENTS OF
JULIAN M. WHITAKER, M.D.;
PURE ENCAPSULATIONS, INC.;
XCEL MEDICAL PHARMACY, LTD.;
MYCOLOGY RESEARCH LABORATORIES, LTD.;
DURK PEARSON and SANDY SHAW; and
AMERICAN PREVENTIVE MEDICAL ASSOCIATION

Julian M. Whitaker, M.D.; Pure Encapsulations, Inc.; XCEL Medical Pharmacy, Ltd.; Mycology Research Laboratories, Ltd.; Durk Pearson and Sandy Shaw; and the American Preventive Medical Association (collectively, "Joint Commenters"), hereby submit their comments in response to the agency's solicitation for comments in the above-referenced docket. See 64 Fed. Reg. 71794 (1999).

BACKGROUND OF JOINT COMMENTERS

Julian M. Whitaker, M.D. Julian M. Whitaker, M.D. ("Dr. Whitaker") is a physician licensed to practice medicine in the states of California and Washington. He graduated from Dartmouth College in 1966 with a B.S. degree and from Emory University in 1970 with an M.D. degree. He received additional training in surgery as a resident at the University of California Medical School. From 1975 to 1976 he worked as a physician at the Pritikin Institute in California. Since that time he has been the clinical director of the Whitaker Wellness Institute in Newport Beach, California. He is the author of five books: *Reversing Heart Disease* (1985), *Reversing Diabetes* (1987),

Reversing Health Risk (1989), *Natural Healing* (1994), and *What Your Doctor Won't Tell You About Bypass* (1995). Since August of 1991 he has been the editor of *Health & Healing*, currently the nation's largest single editor health newsletter. In 1996, *Health & Healing* had over 500,000 subscribers. He receives royalties from the distribution and sale of several dietary supplements. Dr. Whitaker has filed with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements. He therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA's insistence on a standard more rigorous than that intended by Congress.

Durk Pearson and Sandy Shaw. Durk Pearson and Sandy Shaw ("Pearson and Shaw") are scientists residing in Nevada. They design dietary supplement formulations and license them to manufacturing and retailing companies. They are authors of four books on aging and age-related diseases, including the #1, million plus copy best seller *Life Extension: A Practical Scientific Approach* (1982). They have also published three other health books, two of which were best sellers: *The Life Extension Companion* (1984); *The Life Extension Weight Loss Program* (1986); and *Freedom of Informed Choice—FDA Versus Nutrient Supplements* (1993). Durk Pearson and Sandy Shaw were plaintiffs in the *Pearson v. Shalala* case that is the subject of these comments. Pearson and Shaw license dietary supplements. They have filed with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements. They therefore have a keen interest in how FDA interprets its health claim standard and are adversely affected by FDA's insistence on a standard more rigorous than that intended by Congress.

American Preventive Medical Association. The American Preventive Medical Association (“APMA”) is a non-profit organization in Virginia. APMA was founded in October of 1992 and is dedicated to ensuring consumer access to preventive therapies and the rights of health care providers to offer those therapies. APMA was a plaintiff in the *Pearson v. Shalala* case that sought FDA approval of four health claims. Several APMA practitioner members sell dietary supplements and would like to use the health claims on the labels and in the labeling of those supplements. APMA practitioner members are desirous of filing additional health claim petitions with FDA. In addition, APMA and its practitioner members and their hundreds of thousands of patients would benefit from an effective and meaningful health claim approval process as described herein because it would enable them to communicate and receive nonmisleading health information on labels and in labeling of dietary supplements. APMA and its members therefore have a keen interest in how FDA interprets its health claim standard and are adversely affected by FDA’s insistence on a standard more rigorous than that intended by Congress.

Mycology Research Labs Ltd. Mycology Research Labs Ltd. (“Mycology”) is a corporation organized in Great Britain and engaged in the business of manufacturing, distributing, and selling multiple pharmaceutical grade dietary supplements for human consumption around the world, including in the United States. Mycology is desirous of filing with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements that it manufactures, distributes, and sells in the United States. It therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA’s insistence on a standard more rigorous than that intended by Congress.

Pure Encapsulations, Inc. Pure Encapsulations, Inc. (“Pure”) is a Massachusetts corporation engaged in the business of manufacturing, distributing, and selling pharmaceutical grade dietary supplements for human and companion animal consumption. Pure has filed with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements. It therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA’s insistence on a standard more rigorous than that intended by Congress.

XCEL Medical Pharmacy, LTD d/b/a XCEL Health Care. XCEL Medical Pharmacy, LTD d/b/a XCEL Health Care (“XCEL”) is a California corporation engaged in the business of manufacturing, distributing, and selling pharmaceutical grade dietary supplements for human consumption. XCEL is desirous of filing with FDA health claim petitions and would like to use health claims on the labels and in the labeling of dietary supplements that it manufactures, distributes, and sells. It therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA’s insistence on a standard more rigorous than that intended by Congress.

BACKGROUND OF AGENCY NOTICE

In 21 U.S.C. § 343(r)(5(D), Congress assigned the Food and Drug Administration the task of establishing a “procedure and standard respecting the validity of [the health] claim.” The FDA, however, did not provide regulatees with a defined standard for review of health claims. On January 15, 1999, the United States District Court for the District of Columbia held the FDA’s failure to define a standard for dietary supplement health claims a violation of the Administrative Procedure Act (APA). *Pearson v.*

Shalala, 164 F.3d 650, 659-661 (D.C. Cir.1999), *reh'g denied en banc*, 172 F.3d 72 (D.C. Cir. 1999).

In particular, the Court held FDA's failure to give definitional content to the phrase "significant scientific agreement" (its lode stone in reviewing dietary supplement health claims) a violation of the APA's prohibition on arbitrary and capricious agency action. *Pearson*, 164 F.3d at 660-661. The Court reasoned that "[i]t simply will not do for a government agency to declare—without explanation—that a proposed course of private action is not approved." It further reasoned that "[t]o refuse to define the criteria [the agency] is applying is equivalent to simply saying no without explanation." *Id.*

The Court held that FDA was required either case by case or sub-regulation by sub-regulation to define the standard, to "explain what [FDA] means by significant scientific agreement or, at minimum, what it does not mean." *Pearson*, 164 F.3d at 661. The Court required FDA to define the standard in a manner that would make it "possible for the regulated class to perceive the principles which are guiding agency action." *Id.*

The Court explained that it could be possible for FDA to define a standard with sufficient particularity that would satisfy the Administrative Procedure Act but yet not define it with that degree of particularity required to satisfy the First or Fifth Amendments to the United States Constitution. *Pearson*, 164 F.3d at 660 n.12.

On December 22, 1999, the FDA responded to the APA holding in the *Pearson* Court's remand not by promulgating a new rule but by issuing a notice of a guidance. 64 Fed. Reg. 71794 (Dec. 22, 1999). In its Guidance, FDA explains that it reviews "all relevant studies" concerning the nutrient/disease relationship and does so under a hierarchy that deems interventional studies involving randomized, controlled clinical

trials as the “gold standard.” Guidance at 4-5. Next down from the randomized, controlled clinical trials are observational studies, with greater preference accorded prospective than retrospective studies. Observational studies are, themselves, given a hierarchy: (1) cohort (longitudinal) studies; (2) case-control studies; (3) cross-sectional studies; (4) uncontrolled case series or cohort studies; (5) time-series studies; (6) ecological or cross-population studies; (7) descriptive epidemiology; and (8) case reports. Below observational studies are the following in their order of relative weight and significance: (1) research synthesis studies and (2) animal and in vitro studies. Guidance at 5.

The agency next discusses its method for ascertaining whether the studies include reliable measures of the substance and the disease or health-related condition. Guidance at 7. FDA states that it must identify “biomarkers (immediate or surrogate endpoint markers) for the presence or risk of disease.” Guidance at 7. FDA states that it must be able to identify and measure the substance in a food and determine the impact of that measured substance on the disease or health-related condition exclusive of other dietary components or the food itself. Guidance at 8-9.

In evaluating scientific studies, FDA will assess the susceptibility of the study to bias and confounders; quality assessment criteria (including adequacy and clarity of design; population studied; analytical methodology and quality control procedures); and the statistical methods used. Guidance at 10-13.

In evaluating the totality of the scientific evidence, FDA requires proof that “a change in the dietary intake of the substance *will* result in a change in a disease endpoint.” Guidance at 13 (emphasis added). Moreover, it requires proof of causation,

demanding strong evidence of a causal relationship. Guidance at 14-15. The agency depends primarily on use of interventional studies (randomized, controlled clinical trials) as a condition precedent to proof of causation, writing:

Causality can be best established by interventional data, particularly from randomized, controlled clinical trials, that show that altering the intake of an appropriately identified and measured substance results in a change in a valid measure of a disease or health-related condition. In the absence of such data, a causal relationship may be inferred based on observational and mechanistic data through strength of association, consistency of association, independence of association, dose-response relationship, temporal relationship, effect of dechallenge, specificity, and explanation of a pathogenic mechanism or a protective effect against such a mechanism (biological plausibility). Although these features strengthen the claim that a substance contributes to a certain health outcome, they do not prove that eating more or less of the substance will produce a clinically meaningful outcome. In many cases (for example, if the intake of the substance has not been or cannot be assessed adequately in available observational studies because it has not been commonly consumed or its intake cannot be assessed independently of other substances), controlled clinical trials are necessary to establish the validity of a substance/disease relationship.

Guidance at 15.

In determining the weight of the scientific evidence, FDA requires that two questions be answered in the affirmative: (1) whether the evidence in support of the substance/disease relationship outweighs that against it and (2) whether the evidence corroborates “that a change in the dietary intake of the substance *will* result in a change in the disease endpoint.” Guidance at 16 (emphasis added).

In the all-important matter of defining “significant scientific agreement,” FDA states that “[i]n the process of scientific discovery, significant scientific agreement occurs well after the state of emerging science, where data and information permit an inference, but before the point of unanimous agreement within the relevant scientific community that the inference is valid.” Guidance at 16. The agency states that “significant scientific agreement is not consensus in the sense of unanimity, it represents considerably more

than an initial body of emerging evidence.” Guidance at 16-17. In assessing whether significant scientific agreement exists, FDA states that it will “take[] into account the viewpoints of qualified experts outside the agency. . .” Guidance at 18. It states that it will “take into account:

- *review publications that critically summarize data and information in the secondary scientific literature;*
- *documentation of the opinion of an “expert panel” that is specifically convened for this purpose by a credible, independent body;*
- *the opinion or recommendation of a federal government scientific body such as the National Institutes of Health (NIH) or the Centers for Disease Control and Prevention (CDC); or the National Academy of Sciences (NAS); or an independent, expert body such as the Committee on Nutrition of the American Academy of Pediatrics (AAP), the American Heart Association (AHA), American Cancer Society (ACS), or task forces or other groups assembled by the National Institutes of Health (NIH).*

Guidance at 18.

SUMMARY

The United States Court of Appeals’ mandate to FDA is to “explain what [FDA] means by significant scientific agreement or, at minimum, what [FDA] does not mean.” *Pearson*, 164 F.3d at 661. The Guidance fails to comply with the mandate. While in the Guidance FDA has listed the rank it accords to varying types of scientific evidence (without specifying the comparative or cumulative weight of the different kinds of evidence) and has indicated that it expects near conclusive proof of causality as a condition precedent to claim approval, it has avoided explaining what it means by significant scientific agreement; it has also avoided explaining what it does not mean.

The Court’s mandate asks FDA to provide the regulated class sufficient information “to perceive the principles which are guiding agency action.” The Guidance does not provide information necessary for regulatees to perceive FDA’s guiding

principles. It does not explain the meaning of significant scientific agreement. While, from the Guidance, the regulated class can understand that FDA views interventional studies involving well designed randomized, controlled clinical trials as its “gold standard,” it is entirely impossible from the Guidance to perceive whether FDA will ever accept studies other than interventional or other than those involving randomized, controlled clinical trials as sufficient for claim authorization. It appears unlikely that FDA ever will because it requires proof of direct causality. Given FDA’s insistence on proof of direct causality (that a substance *will* result in a change in a disease endpoint) as a condition precedent to claim approval, it appears that only claims backed by well designed randomized, controlled clinical trials coupled with proof of direct causality will cause FDA to permit claim authorization. A large body of evidence strongly supporting, but not conclusively proving, a substance-disease relationship appears unlikely to satisfy the FDA.

Thus, the only principle that regulatees can perceive with clarity from FDA’s Guidance is that FDA will accept the same kind of near conclusive proof expected as a condition precedent for drug approval as a condition precedent for dietary supplement claim approval. That principle violates Congressional intent, however. Congress plainly expects this agency to authorize health claims for dietary supplements without requiring that those claims be backed by the same kind of near conclusive proof required for the grant of applications for new drugs. Accordingly, to the extent that FDA’s Guidance reveals a principle to the regulated class, that principle is one calling for a level of evidence that Congress has unequivocally rejected in the context of health claims for dietary supplements.

In addition, FDA's Guidance includes an unscientific bias and favoritism for certain non-governmental organizations, namely the Committee on Nutrition of the American Academy of Pediatrics, the American Heart Association, and the American Cancer Society. The agency places special emphasis upon the opinions and recommendations of these private organizations equating the value of those with the opinions and recommendations of federal government scientific bodies. It omits from specific reference the opinions and recommendations of other private bodies, such as universities, professional and scientific associations, and other scientific authorities. The action reveals an unscientific bias in favor of the private organizations listed and an arbitrary and capricious grant of privilege to the named private organizations to the exclusion of all others.

Finally, FDA's Guidance omits reference to the constitutional mandate in *Pearson*. The Guidance misleads the public and the regulated class to the extent that it suggests that a dietary supplement health claim not approved by FDA under its "significant scientific agreement" standard is prohibited on labels and in labeling. Under *Pearson's* constitutional mandate, even if claims fail the "significant scientific agreement" test, FDA must nevertheless authorize all that are, at worst, potentially misleading with corrective disclaimers. *Pearson*, 164 F.3d at 659-660. Because the constitutional mandate interprets the First Amendment to the United States Constitution and the First Amendment is the higher law against which contrary law cannot stand, FDA must make clear to the regulated class within the Guidance that a claim it deems not backed by "significant scientific agreement" will nevertheless be authorized when a disclaimer can render it nonmisleading.

For these reasons, explained in detail below, FDA should promptly revise its Guidance. It should comply with the mandate of the United States Court of Appeals for the D.C. Circuit by explaining what it means by significant scientific agreement or, at minimum, what it does not mean. In that regard, FDA cannot rest upon the highly inexact and largely vacuous and variable statement that significant scientific agreement occurs after emerging science but before unanimous agreement. The universe described is immense, so immense as to exceed any reasonable definitional boundary. Indeed, nearly all scientific evidence falls between the polar extremes of emerging science and consensus. Accordingly, FDA should define with as much specificity as possible where on the continuum of scientific evidence between emerging science and consensus “significant scientific agreement” lies. Does it occur when a significant minority or segment of scientists who study the relationship agree that the claimed relationship is supported by the scientific evidence? Does it occur when at least half of the scientists who study the relationship agree that the claimed relationship is supported by the scientific evidence? Does it occur when at least three quarters of the scientists who study the relationship agree that the claimed relationship is supported by the scientific evidence? When may it be said on the continuum of scientific evidence that significant scientific agreement has been reached? In that regard, consistent with the dictates of Congress, FDA should hold that significant scientific agreement exists when

a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are *reasonably likely* to obtain the claimed health benefit.

Senate Report 103-410, at 24.

Congress determined that the above-quoted definition it supplied in committee is “consistent with the NLEA’s goal of assuring that consumers have access on food and dietary supplement labels to health claims that are scientifically supported, without having to wait until the degree of scientific certainty contemplated by the drug standard has been achieved.” *Id.* FDA’s insistence on a higher standard, the equivalent of the drug certainty standard used as a condition precedent to grant of applications for new drugs, conflicts with Congress’s intentions and cannot stand.

ARGUMENT

A. FDA’S GUIDANCE VIOLATES PEARSON’S APA MANDATE BY FAILING TO DEFINE “SIGNIFICANT SCIENTIFIC AGREEMENT”

The *Pearson* Court ordered FDA to “explain what it means by significant scientific agreement or, at minimum, what it does not mean.” *Pearson*, 164 F.3d at 661. FDA’s Guidance fails to comply. Nowhere in the entire Guidance does FDA provide any reasonable explanation of what it means by significant scientific agreement (or what it does not mean). The only “definition” for the term that the agency offers in the Guidance is one so broad, so vacuous, and so inexact as to be entirely unusable by the regulated class. Indeed, the extraordinary breadth of the definition suggests that any meaning FDA imparts to the term on a case by case basis may be the product of political discretion (or anti-dietary supplement bias) as much, if not more, than rational scientific judgment. In the Guidance, the agency states that, “[i]n the process of scientific discovery, significant scientific agreement occurs well after the state of emerging science, where data and information permit an inference, but before the point of unanimous agreement within the relevant scientific community that the inference is valid.” Guidance at 16. That language embraces nearly the entire body of scientific evidence and does not afford the regulated

class sufficient information to discern where along the continuum of science between emerging data and consensus the point of significant scientific agreement exists. With the agency's definition, the regulated class certainly cannot discern the principles which guide FDA action (except that satisfaction of the drug certainty standard will probably suffice). Accordingly, the definition violates *Pearson's* APA mandate to the agency. To comply with the mandate, FDA must revise its Guidance promptly as explained below.

B. FDA'S GUIDANCE VIOLATES PEARSON'S APA MANDATE BY NOT REVEALING THE PRINCIPLES WHICH GUIDE AGENCY ACTION ON CLAIMS SUPPORTED BY EVIDENCE OTHER THAN INTERVENTIONAL STUDIES BEARING PROOF OF DIRECT CAUSALITY

From the Guidance, one may discern that FDA has adopted a hierarchy to evaluate scientific evidence, placing at its top well designed interventional studies (and at the top of such studies randomized, controlled clinical trials). Although FDA's preference for well designed interventional studies is reiterated throughout the document, the FDA does not explain whether studies other than the very lengthy and expensive randomized, controlled interventional ones will suffice and, if other studies would, what comparative and cumulative weight FDA affords evidence other than randomized, controlled interventional studies. For example, from the Guidance it is impossible to determine whether FDA would ever accept as a substitute for randomized, controlled interventional studies, a combination of observational and mechanistic studies, or—if so—what kind of such studies would suffice to substitute for randomized, controlled interventional studies.

From the Guidance, one may discern that FDA demands that the regulated class supply it with proof that “a change in the dietary intake of the substance *will* result in a

change in a disease endpoint.” FDA thus calls for conclusive proof of causality. FDA expects conclusive proof of causality regardless of the nature of the claim. Thus, a claim that a nutrient “may” reduce the risk of a disease or “may” reduce the symptoms of a disease is treated in the same manner as one that states a direct causal relationship (e.g., nutrient X will reduce the risk of disease Y, or nutrient X will reduce the symptoms of disease Y). Direct proof of causality is equal to that degree of proof required by this agency, pursuant to the “substantial evidence” standard, as a condition precedent to the grant of applications for new drugs. 21 U.S.C. § 355(e) (see generally *Weinberger v. Hynson Westcott & Dunning, Inc.*, 412 U.S. 609 (1973) and *E.R. Squibb & Sons, Inc. v. Bowen*, 870 F.2d 678, 679 (D.C. Cir. 1989).

FDA states that in evaluating the scientific evidence, it will require an affirmative answer to the following two questions: (1) whether the evidence in support of the substance/disease relationship outweighs that against it and (2) whether the evidence corroborates “that a change in the dietary intake of the substance *will* result in a change in the disease endpoint.” Thus, in light of FDA’s clear preference for randomized, controlled clinical trials and its insistence on direct evidence of causality, to the extent that a principle can be discerned from the Guidance, it is that FDA will authorize claims upon receipt of proof that they are corroborated by randomized, controlled clinical trials and upon receipt of proof of direct causality. That kind of near conclusive proof is the same as that required by FDA for approval of new drug applications. Accordingly, to the extent that FDA’s Guidance reveals a principle to the regulated class it is one calling for a level of evidence Congress has unequivocally rejected in the context of health claims for dietary supplements. FDA must revise its Guidance. It must replace it with one that

complies with *Pearson's* APA order and the dictates of Congress on interpreting "significant scientific agreement." The current Guidance fails on both accounts.

C. FDA'S GUIDANCE HARBORS AN UNSCIENTIFIC BIAS AND FAVORITISM FOR CERTAIN PRIVATE ORGANIZATIONS

In addition to its failure to explain what significant scientific agreement means (or, conversely, what it does not mean) in a manner that can enable the regulated class to discern the principles which guide agency action, the Guidance includes specific reference to a select group of private organizations. The reference gives equal weight to the opinions and recommendations of those organizations and the opinions and recommendations of federal government scientific bodies. Moreover, it fails to give equivalent weight to the opinions and recommendations of any other scientific body, e.g., any or all universities, other private scientific associations, and recognized authorities in the field of science. The agency offers no explanation for why the named private organizations (Committee on Nutrition of the American Academy of Pediatrics; the American Heart Association; and the American Cancer Society) should be given preferential treatment and status in the evaluation of health claims. For example, it does not explain (nor could it reasonably) why these private associations in particular are possessed of scientific insights, knowledge, and evidence superior to all others or why these private associations in particular should be viewed as equivalent to federal government scientific bodies. It is not at all unworthy of note that the American Heart Association and the American Cancer Society were amicus curiae in favor of the unsuccessful position articulated by the FDA in the *Pearson* case. Through that relationship, let alone all others between the FDA and those groups, FDA has engaged in legal and political battle against authorization of dietary supplement health claims. Thus,

far from serving as an unbiased source for opinion and recommendation, FDA has chosen precisely those entities that have a track record of partisan support for FDA's positions. For these many reasons, FDA's select listing of preferred private organizations in the Guidance constitutes arbitrary and capricious agency action and should be reversed in print as well as deed. The Joint Commenters do not object to agency acceptance of the opinion and recommendations of private scientific associations as sources of reputable information relevant to the evaluation of supplement-disease relationships, but the Joint Commenters strongly object to the arbitrary and capricious limited selection of three named associations made in the Guidance by FDA.

D. FDA'S GUIDANCE IS MISLEADING BECAUSE IT OMITTS REFERENCE TO *PEARSON'S* CONSTITUTIONAL STANDARD AS AN ALTERNATIVE GROUND FOR AUTHORIZATION

The Director of the Center for Food Safety and Applied Nutrition has made it clear that FDA understands *Pearson's* constitutional mandate to necessitate agency authorization of health claims even when those claims fail to satisfy its "significant scientific agreement" standard. Director Levitt wrote:

... [W]e agree that the court's decision requires FDA to reconsider not only whether each of the four claims meets the significant scientific agreement standard, but also, even if that standard is not met, whether the addition of a disclaimer to the claim could render it non-misleading. If the answer to either question is yes, we will authorize the claim.

See Exhibit A.

Indeed, the *Pearson* decision's constitutional mandate takes primacy over contrary agency rules and interpretations. It is, after all, the First Amendment which, under the Supremacy Clause, is the supreme law of the land. U.S.CONST. Art. VI. See also *Marbury v. Madison*, 5 U.S. 137, 180 (1803). Therefore, the complete omission of

the fact that a claim not authorized under significant scientific agreement may still have to be under the First Amendment is derelict of the agency. Indeed, the omission from the Guidance of reference to the *Pearson* Court's disclaimer requirement to protect First Amendment rights is a glaring one that renders the Guidance false and misleading. Its omission is material because regulatees may perceive that FDA's failure to authorize a claim under significant scientific agreement condemns the claim to indefinite suppression when, in fact, the constitutional duty of this agency is to authorize all, at worst, potentially misleading claims with corrective disclaimers. FDA must revise the Guidance to make clear to the regulated class that a claim it deems not backed by "significant scientific agreement" will nevertheless be authorized when a disclaimer can render it nonmisleading.

E. FDA'S GUIDANCE VIOLATES THE NLEA BY FAILING TO DEFINE "SIGNIFICANT SCIENTIFIC AGREEMENT" AS CONGRESS INTENDED

Congress has been severely critical of the way in which FDA has interpreted "significant scientific agreement." See Senate Report No. 103-410. In fact, Congress has documented the existence of an unscientific agency bias against dietary supplements and dietary supplement health claims that it has found wholly inconsistent with the intended meaning of "significant scientific agreement." The following are among Congress' findings on agency bias against claim approval:

In fact, the FDA has had a long history of bias against dietary supplements. S.Rep.No. 103-410, at 14 (1994).

Mindful of the persistent evidence of FDA bias against dietary supplements . . . S.Rep.No. 103-410, at 30 (1994).

Given the FDA's historical bias against dietary supplements. . . S.Rep.No. 103-410, at 31 (1994).

Despite a voluminous scientific record indicating the potential health benefits of dietary supplements, the Food and Drug Administration has pursued a heavy-handed enforcement agenda against dietary supplements for over 30 years. S.Rep.No. 103-410, at 14 (1994).

FDA's treatment of health claims on dietary supplements and its implementation of the health claims standard is hindering, rather than fostering, the dissemination of truthful and nonmisleading information about the nutrient/disease relationship. S.Rep.No. 103-410, at 23 (1994).

The committee has heard multiple complaints that the FDA has been overly slow and rigid in considering and approving health claims for dietary supplements. S.Rep.No. 103-410, at 30 (1994).

FDA has applied [its health claims review standard] in a way that limits consumer access to important information on diet and health. S.Rep.No. 103-410, at 23 (1994).

The FDA has acted to restrict the information that the public may receive about dietary supplements. S.Rep.No. 103-410, at 16 (1994).

Despite the fact that the scientific literature increasingly reveals the potential health benefits of dietary supplements, the Food and Drug Administration has pursued a regulatory agenda, which discourages their use by citizens seeking to improve their health through dietary supplementation. S.Rep.No. 103-410, at 14 (1994).

In December, 1991, FDA proposed rules implementing the NLEA, but rejected all but one claim for supplements (for calcium/osteoporosis in White and Asian Women). Only one other claim has been approved since that time, the claim for folic acid and neural tube defects, and that claim was only approved after intense public pressure on the FDA. S.Rep.No. 103-410, at 15-16 (1994).

The preceding examples show how the FDA has tried to "protect" the public against "unsafe" products for which there is no evidence that the product is unsafe. The FDA has also acted to restrict the information that the public may receive about dietary supplements. Folic acid is a clear example. S.Rep.No. 103-410, at 16 (1994).

Beholden as it must be to Congress for its statutory authority, FDA has acted in a most peculiar manner. Rather than comply with the dictates of Congress, it has defied them. It

has chosen (against the express congressional command that it not do so) to articulate clearly only one sure way to achieve health claim approval (i.e., establish to FDA's satisfaction that a claim is backed by randomized, controlled clinical trials and direct proof of causation, to wit, establish satisfaction of the drug certainty standard). Congress plainly and unequivocally rejected the drug certainty standard for dietary supplement health claims. It has implored this agency to adopt a definition for significant scientific agreement far less stringent, a definition that FDA does not adopt in the Guidance. In committee Congress has made its expectations clear:

The Committee notes that the significant scientific agreement standard is, by design, more flexible than the standard established by law for FDA to review and approve drugs, which requires a demonstration of safety and effectiveness based on “adequate and well-controlled clinical investigations.” While the intake of a nutrient on which a health claim is based must be safe, there is no requirement that health claims be derived from clinical trials, and, by its terms, the standard recognizes that scientific agreement on the validity of the claim does not have to be complete. Evidence from a broad range of reliable scientific sources should be considered in determining the adequacy of scientific support.

In implementing the significant scientific agreement standard, FDA will be expected to take full advantage of the flexibility of the standard to maximize the availability on food and dietary supplement labels and labeling of disease-related information consumers can prudently use to affect their risk of disease.

This includes recognizing that there will nearly always be some remaining scientific uncertainty about the validity of any diet-related health claim; that some individuals consuming or avoiding a nutrient in response to a health claim may benefit, while others may not; and that the benefits for any individual may consist not of absolutely avoiding a disease, but rather of reducing her or his risk of a disease.

The end point for evaluation of the adequacy of support for a claim should not be definitive proof that the nutrient has the stated effect for all populations, but that the nutrient will produce the stated effect in the majority of a target population the majority of the time. In addition, the scientific evidence supporting a claim should not be held to the same standard used in evaluating new drug applications.

Under the significant scientific agreement standard, the FDA should authorize claims when a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are reasonably likely to obtain the claimed health benefit. This is consistent with the NLEA's goal of assuring that consumers have access on food and dietary supplement labels to health claims that are scientifically supported, without having to wait until the degree of scientific certainty contemplated by the drug standard has been achieved.

S.Rep.No. 103-410, at 24.

Thus, FDA's Guidance has violated the intent of Congress by not defining significant scientific agreement as Congress ordered it to in Senate Report No. 103-410. FDA may not interpret significant scientific agreement to have a meaning contrary to that intended by Congress. Indeed, FDA's Guidance is wholly inconsistent with the intent of Congress on interpreting significant scientific agreement under the NLEA. Accordingly, that interpretation is invalid under *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984) because Congress has spoken to the precise matter in issue and the agency's interpretation is unreasonable in light of congressional intent.

F. JOINT COMMENTERS' RECOMMENDATIONS FOR REVISION TO THE GUIDANCE

The FDA must revise the Guidance if it is to survive judicial review. The Guidance fails to define "significant scientific agreement" as ordered by the *Pearson* Court. The Guidance indicates that a health claim is likely to be approved only if it is backed by randomized, controlled clinical trials and direct proof of causality. That benchmark is far higher than the one intended by Congress for dietary supplement health claims. Moreover, FDA has revealed an unscientific bias in favor of three private associations' opinions and recommendations. Finally, it has omitted from the Guidance the material fact that even if FDA deems a claim not backed by "significant scientific

agreement,” it has a constitutional duty nonetheless to authorize even a potentially misleading claim with a corrective disclaimer.

To cure the many defects in the Guidance, FDA should: (1) define “Significant Scientific Agreement” as Congress intended, to wit: **“when a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are reasonably likely to obtain the claimed health benefit;”** (2) should state where on the continuum of scientific evidence between emerging science and consensus “significant scientific agreement” exists consistent with Congressional intent; (3) should state clearly that it will not require the drug certainty standard of proof (i.e., randomized, controlled interventional studies and direct proof of causality) as a condition precedent to dietary supplement health claim approval; (4) should remove reference to the Committee on Nutrition of the American Academy of Pediatrics; the American Heart Association; and the American Cancer Society from the Guidance and make clear that it will not view those organization’s opinions or recommendations as in any way more significant than the views of any other private scientific body or private scientific authority; and (5) should include reference to *Pearson’s* constitutional mandate and make clear that if a claim fails to satisfy FDA’s “significant scientific agreement” standard it will be authorized nonetheless so long as the addition of a disclaimer can render it nonmisleading.

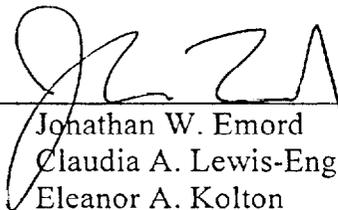
CONCLUSION

For the foregoing reasons, FDA should immediately discontinue reliance on the Guidance and revise it as recommended herein.

Respectfully submitted,

JULIAN M. WHITAKER, M.D.;
PURE ENCAPSULATIONS, INC.;
XCEL MEDICAL PHARMACY, LTD.;
MYCOLOGY RESEARCH LABORATORIES, LTD.;
DURK PEARSON and SANDY SHAW; and
AMERICAN PREVENTIVE MEDICAL ASSOCIATION,

By

A handwritten signature in black ink, appearing to read 'JW Emord', written over a horizontal line.

Jonathan W. Emord
Claudia A. Lewis-Eng
Eleanor A. Kolton
Counsel for Joint Commenters

Dated: February 22, 2000

Exhibit A



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

OCT 5 1999

Jonathan W. Emord
1050 Seventeenth Street, NW
Suite 600
Washington, DC 20036

Dear Mr. Emord:

This is in response to your letter of September 23, 1999. Your letter made several requests relating to FDA's Federal Register notice of September 8, 1999 (64 Fed. Reg. 48841), which solicited scientific data on the four health claims remanded to the agency in Pearson v. Shalala. Specifically, you requested that FDA (1) extend the time for submitting scientific data on the four claims until 75 days after the agency publishes its guidance on the significant scientific agreement standard; (2) confirm to you in writing and publish a correction notice in the Federal Register clarifying that FDA intends to consider whether the four claims may be authorized with a disclaimer even if the agency determines that they do not meet the significant scientific agreement standard.

With respect to your first request, we agree to extend or reopen the comment period on the September 8, 1999, notice for 75 days after the significant scientific agreement guidance is published. We agree that this is an example of when taking additional time is warranted. Be assured that the agency will give careful consideration to the data that it receives during the second 75 days.

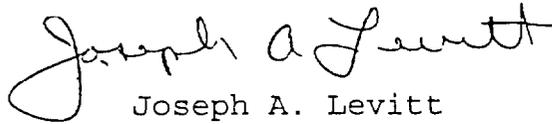
As to your second request, we agree that the court's decision requires FDA to reconsider not only whether each of the four claims meets the significant scientific agreement standard, but also, even if that standard is not met, whether the addition of a disclaimer to the claim could render it non-misleading. If the answer to either question is yes, we will authorize the claim. We do not believe that a Federal Register correction notice is necessary, however. The September 8 Federal Register notice was only intended to solicit scientific data on the four remanded claims, not to describe the procedure and standard the agency will use to evaluate them. The notice stated that FDA was planning to reevaluate the scientific evidence for the claims "as a first step in complying with the court's decision." 64 Fed. Reg. at 48842 (emphasis added). Given the fact that the notice contained no errors and was not intended to explain the court's decision or set forth the agency's plans for implementing the decision, we see no need for a correction notice.

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Your concerns about the notice and about statements in FDA's September 17, 1999, letter seem to stem at least in part from a misunderstanding about FDA's use of the word "authorize." By saying that the four claims must be "authorized" by FDA before they may be made in labeling, we meant only that the claims cannot be used unless and until FDA issues a regulation permitting them. We did not mean to imply that we would issue such a regulation only if the claims are found to meet the significant scientific agreement standard.

We hope that the above responds to your concerns.

Sincerely,

A handwritten signature in cursive script that reads "Joseph A. Levitt". The signature is written in dark ink and is positioned above the typed name and title.

Joseph A. Levitt
Director
Center for Food Safety
and Applied Nutrition

EXHIBIT 2

AMERICAN ACADEMY OF PEDIATRICS

Committee on Genetics

Folic Acid for the Prevention of Neural Tube Defects

ABSTRACT. The American Academy of Pediatrics endorses the US Public Health Service (USPHS) recommendation that all women capable of becoming pregnant consume 400 μg of folic acid daily to prevent neural tube defects (NTDs). Studies have demonstrated that periconceptional folic acid supplementation can prevent 50% or more of NTDs such as spina bifida and anencephaly. For women who have previously had an NTD-affected pregnancy, the Centers for Disease Control and Prevention (CDC) recommends increasing the intake of folic acid to 4000 μg per day beginning at least 1 month before conception and continuing through the first trimester. Implementation of these recommendations is essential for the primary prevention of these serious and disabling birth defects. Because fewer than 1 in 3 women consume the amount of folic acid recommended by the USPHS, the Academy notes that the prevention of NTDs depends on an urgent and effective campaign to close this prevention gap.

ABBREVIATIONS. NTDs, neural tube defects; USPHS, US Public Health Service; CDC, Centers for Disease Control and Prevention; MRC, Medical Research Council; IOM, Institute of Medicine; AAP, American Academy of Pediatrics.

BACKGROUND

Neural tube defects (NTDs) are among the most common birth defects contributing to infant mortality and serious disability. NTDs, which include anencephaly, spina bifida, and encephalocele, occur in approximately 1 of 1000 births in the United States.¹ An estimated 4000 pregnancies are affected with NTDs each year. More than one third of these pregnancies are spontaneously lost or electively terminated; thus, about 2500 infants per year are born with an NTD. The results of 2 randomized controlled trials and several observational studies showed that 50% or more of NTDs can be prevented if women consume a folic acid-containing supplement before and during the early weeks of pregnancy^{2,3} in addition to the folate in their diet. Based on a synthesis of these data, the US Public Health Service (USPHS) and Centers for Disease Control and Prevention (CDC) recommendations were developed.^{4,5} Because the evidence for folic acid prevention evolved over time, there are two separate recommendations: one for women who have no history of a previous NTD-affected pregnancy and one

for women who have had a previous NTD-affected pregnancy.

WOMEN WITH NO HISTORY OF A PREVIOUS NTD-AFFECTED PREGNANCY

Of children with an NTD, 95% are born to couples with no family history of these defects. Evidence to date suggests that supplementation with a multivitamin containing 400 (0.4 mg) μg of folic acid prevents the occurrence of >50% of NTDs when it is taken before conception and continued throughout the first trimester of pregnancy.⁵ The USPHS recommends that all women of childbearing age who are capable of becoming pregnant take 400 μg of folic acid daily.⁵ Implementing this recommendation may provide the opportunity for primary prevention of 50% or more of these serious disabling birth defects. Regular and ongoing ingestion of folic acid by women of childbearing age is necessary because approximately half of the pregnancies in the United States are unplanned,⁶ and neural tube closure occurs during the first 4 weeks of gestation.⁷ Despite the publication of the USPHS recommendation in September 1992, a 1998 poll showed that 70% of women aged 18 to 45 years still are not following the USPHS recommendation.⁸

WOMEN WHO HAVE HAD A PREVIOUS NTD-AFFECTED PREGNANCY

Among US couples who have had a child with an NTD, the recurrence risk is 2% to 3% in subsequent pregnancies.⁹ In 1991, the Medical Research Council (MRC) Vitamin Study Group reported the results of a well-designed, prospective, randomized trial of folic acid supplementation for the prevention of NTDs in pregnancies of women who had a previous child with an NTD, and the CDC published its recommendations for consumption of 4000 (4 mg) μg of folic acid.⁴ The results of the MRC study conclusively demonstrated that a daily dosage of 4000 μg of folic acid, in addition to folate in the diet, before and during early pregnancy resulted in a 71% reduction of recurrence of NTDs. The addition of other vitamins to the dosage of folic acid did not reduce the risk further. Use of multivitamins without folic acid did not result in a reduced risk for NTDs. The MRC study did not explore the possible benefit of a dosage lower than 4000 μg of folic acid. However, an earlier nonrandomized study conducted in the United Kingdom suggested that a lower dosage, 360 μg daily, resulted in a comparable reduction of recurrence of NTDs.¹⁰ Although adverse maternal or fetal effects of a daily 4000 μg dosage of folic acid were

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.
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not detected by the MRC study, the small size of the study groups precluded detection of uncommon adverse effects.

FOLATE AND FOLIC ACID

Folic acid, also known as pteroylmonoglutamic acid, is a synthetic compound used in dietary supplements and fortified foods. The term *folate* includes all compounds that have the vitamin properties of folic acid—including folic acid and naturally occurring compounds in food.¹¹ The average diet in the United States contains 200 μg of naturally occurring food folate, which is less bioavailable than folic acid.¹² Additional intake of foods rich in folate could raise the average intake, but it has not been demonstrated that increased consumption of food folate would prevent NTDs as effectively as a daily vitamin supplement containing 400 μg of folic acid. A small comparison study suggests that blood folate concentrations are increased much more by folic acid supplementation than by naturally occurring food folate in the diet.¹³ Economic and social circumstances may make an adequate increase in dietary folate difficult or unlikely, and the behavioral change required among a large fraction of women may take years to achieve.

Folic acid is a water-soluble vitamin that has no known toxicity. However, higher doses of folic acid can correct the anemia of vitamin B₁₂ deficiency (pernicious anemia), which might be an important clue to the presence of vitamin B₁₂ deficiency in some instances. Folic acid does not prevent the neurologic consequences of vitamin B₁₂ deficiency, and, for this reason, the USPHS recommendation cautioned that intake of folate should be not >1000 μg per day. However, the Institute of Medicine (IOM) Food and Nutrition Board recently set the tolerable upper intake limit of synthetic folic acid at 1000 μg , thus eliminating food folate from the calculation.¹⁴ Because pernicious anemia rarely occurs before the age of 50 years, it is likely to be rare among women consuming folic acid during the reproductive years. Folic acid has been consumed by about a quarter of all women for many years and extensively during later pregnancy without apparent adverse effects; however, studies that definitively address the question of maternal and fetal safety of folic acid are not available.

The IOM Food and Nutrition Board's recommended dietary allowance (RDA) for folate is 400 μg for adults and 600 μg for pregnant women.¹⁴ To reduce the risk for NTDs, the IOM recommended that women capable of becoming pregnant consume 400 μg of folic acid daily from fortified foods, vitamin supplements, or a combination of the two. This is in addition to the naturally occurring folate obtained from a varied diet.¹⁴ The majority of multivitamin preparations contain 400 μg of folic acid. These preparations are available over the counter and are already being taken by about 30% of non-pregnant women aged 18 to 45 years in the United States.⁸ Tablets containing folic acid alone are available over the counter in dosages up to 800 μg but the availability is very limited when compared with

multivitamin preparations. Folic acid tablets in a 1000 μg dose are available by prescription only. This preparation is most frequently utilized by women who are taking 4000 μg because of a previous NTD-affected pregnancy.

In March 1996, the Food and Drug Administration mandated that enriched cereal-grain products be fortified with 140 μg of folic acid per 100 g of flour.¹⁵ This measure increases the proportion of women who consume the USPHS-recommended daily dosage of 400 μg of folic acid only an additional 3%, because this fortification level will provide the average woman only an additional 100 μg of folic acid per day (unpublished data, 1992).

RECOMMENDATIONS

1. **Prevention for Women With No History of a Previous NTD-Affected Pregnancy.** The American Academy of Pediatrics (AAP) endorses the USPHS recommendation that all women of child-bearing age who are capable of becoming pregnant should consume 400 (0.4 mg) μg of folic acid daily. Because of the high rate of unplanned pregnancies in the United States, the AAP encourages efforts at devising a program of food fortification to provide all women a daily intake of 400 μg of folic acid. In the absence of optimal fortification, the AAP encourages women to consume 400 μg of folic acid daily in addition to eating a healthy diet. At present, the most convenient, inexpensive, and direct way to meet the recommended dosage is by taking a multivitamin containing 400 μg of folic acid, but efforts to increase the availability of folic acid-only supplements should be encouraged for women who prefer not to take multivitamins. Because the risk for NTDs is not totally eliminated by folic acid use, routine prenatal screening for NTDs is still advisable.
2. **Prevention for Women Who Have Had a Previous NTD-Affected Pregnancy.** Women with a history of a previous pregnancy resulting in a fetus with an NTD should be advised of the results of the MRC study. During times in which a pregnancy is not planned, these high-risk women should consume 4000 (4 mg) μg of folic acid per day. However, they should be offered treatment with 4000 μg of folic acid per day starting 1 month before the time they plan to become pregnant and throughout the first 3 months of pregnancy, unless contraindicated. Women should be advised not to attempt to achieve the 4000 μg daily dosage of folic acid by taking over-the-counter or prescription multivitamins containing folic acid because of the possibility of ingesting harmful levels of other vitamins, for example, Vitamin A.¹⁷ It should be noted that 4000 μg of folic acid did not prevent all NTDs in the MRC study. Therefore, high-risk patients should be cautioned that folic acid supplementation does not preclude the need for counseling or consideration of prenatal testing for NTDs.
3. **Prevention for Other High-Risk Persons.** No intervention or observational studies address prevention for other high-risk persons. Women with a close

relative (eg, sibling, niece, or nephew) who has an NTD (risk is approximately 0.3% to 1.0%), women with type 1 diabetes mellitus (risk is approximately 1%), women with seizure disorders being treated with valproic acid or carbamazepine (risk is approximately 1%), and women or their partners who have an NTD (risk may be 2% to 3%)¹⁸ and are planning a pregnancy should discuss with their physician the risk for an affected child and the advantages and disadvantages of increasing their daily periconceptional folic acid intake to 4000 μg .

4. **Public Health Programs: Supplementation, Surveillance, and Food Fortification.** The AAP recommends that the Department of Health and Human Services expeditiously devise and implement an educational program to prevent folic acid-preventable NTDs throughout the use of supplements, fortified foods, or a combination of both. The program should support surveillance of effectiveness and adverse outcomes to further refine the effective folate dose and mechanisms of actions. In light of the recent IOM recommendation, the AAP also encourages additional efforts at devising a program of food fortification with folic acid to provide all women capable of becoming pregnant a daily intake of 400 μg of folic acid.

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EXHIBIT 3

1: J Okla State Med Assoc 2000 Feb;93(2):52-60

Improving the health of Oklahomans through clinical prevention. Part 1:
Counseling to decrease major risk factors.

DeRose DJ, Crutcher JM, DePersio SR

Oklahoma State Department of Health, Oklahoma City 73117, USA.

Compared to other states, Oklahomans suffer higher levels of morbidity and mortality from several common conditions--coronary heart disease, chronic lung disease, stroke and injury. Unhealthy personal behaviors contribute significantly to each of these conditions, thus rendering them at least partially preventable by changing those behaviors. Research has shown that many patients will modify unhealthy behaviors as a result of services provided by physicians or staff in their offices, often with briefly delivered messages. In this report we will discuss the most common preventable illnesses suffered by Oklahomans and the risk factors associated with those illnesses. Physicians should make maximum use of their ability to promote healthy behaviors by their patients, with emphasis on the risk factors associated with significant morbidity in the state. They should also focus on those risk factors patients are likely to change following physician counseling, as determined by prevention research and described in the U.S. Preventive Services Task Force document Guide to Clinical Preventive Services. In general, physicians should consistently deliver messages that address tobacco products, alcohol and other drugs, the use of seat belts, and diet and exercise. Also, they should recommend that all women of childbearing age who are capable of becoming pregnant take a multivitamin containing folic acid daily.

PMID: 10692812, UI: 20157201

2: J Am Diet Assoc 2000 Feb;100(2):159

Folic acid and Down syndrome.

Trissler RJ

Publication Types:

News

PMID: 10691390, UI: 20149775

3: N Z Med J 1999 Dec 10;112(1101):463-5

How many pregnant women in Christchurch are using folic acid supplements in early pregnancy?

Schader I, Corwin P

Christchurch School of Medicine.

AIMS: To determine the proportion of pregnant women in Christchurch using folic acid supplements in early pregnancy. To evaluate the level of current knowledge

relating to folic acid amongst pregnant women. To determine the main sources from which this information was gained. METHODS: A short questionnaire was administered to 191 pregnant women in Christchurch during antenatal visits with their lead maternity carer. The survey contained questions relating to knowledge about folic acid and use together with sources of information regarding folic acid. Obstetric and demographic details were also collected. RESULTS: The response rate was 95.5%. Ninety-one per cent (174/191) of participants had heard of folic acid and, of these, 63% knew that folic acid reduces the risk of spina bifida. Of the 191 participants in the study, 118(62%) took folic acid supplements at some stage of their pregnancy, however, only 33(17%) had taken periconceptual folic acid supplements. Of the 44% of all women in the study with a planned pregnancy, only 35% had taken folic acid supplements periconceptually. Of those women with an unplanned pregnancy (55%), only 2.8% had taken a folic acid supplement periconceptually. The main sources of advice for women relating to folic acid were general practitioners (48%) or media advertising, either in the form of a magazine, or health pamphlet or television promotion (20%). CONCLUSIONS: The results of this study indicate that the level of knowledge amongst women of child-bearing age relating to folic acid is relatively high compared with other countries. Despite this high level of knowledge, only a small percentage of women are actually consuming a folic acid supplement during the recommended periconceptual period due in part to the high proportion of unplanned pregnancies. These results emphasize the need for an effective public health strategy to ensure that all women of child-bearing age have access to an adequate folic acid intake.

EXHIBIT 4

Prevention of Neural Tube Defects by Periconceptional Use of Folic Acid

Mohammad Masud Iqbal, MD, MPH, MSPH*

OBJECTIVES:

After completing this article, readers should be able to:

1. Identify today's most common vitamin deficiency in women.
2. List the etiology of neural tube defects (NTDs) and its relationship with folic acid.
3. Describe how up to 70% of NTDs can be prevented among women of child-bearing age.
4. Name the diagnostic methods used to detect NTDs.
5. Describe the relationship between increased intake of folic acid and vitamin B₁₂ deficiency.

Introduction

Birth defects are the leading cause of infant mortality and a major contributor to heightened morbidity in the United States. The basic definition of a birth defect is a structural abnormality present at birth. Infant mortality attributable to birth defects has not declined as rapidly as overall infant mortality; from 1968 to 1995, the proportion of infant mortality due to birth defects increased from 14.5% to 22.2%. It has been estimated that approximately 20% to 25% of all birth defects are due to gene mutations, 5% to 10% to chromosomal abnormalities, and another 5% to 10% to exposure to a known teratogenic agent (such as prescription drugs, chemicals, or radiation) or a maternal factor. Together, these percentages account for only 30% to 40% of birth defects, leaving the etiology of more than 50% unexplained. It has been speculated that environmental factors account for no more than 10% of all congenital anomalies. Genetic factors are responsible for 30% of pediatric hospital admissions.

Birth defects rank somewhere between second and fifth among causes of death in children younger than 1 year of age; 3% to 4% of infants in their first year of life are diagnosed as having major birth defects. Of the 120,000 to 150,000

infants born with serious birth defects each year, approximately 6,000 die during their first 28 days of life and another 2,000 die before reaching their first birthdays.

Economic Cost of Birth Defects

In an aggregate analysis of the expense of illness in the United States, congenital abnormalities as a group was estimated to cost \$6.3 billion in 1980 or 1.4% of the total cost of illness. This estimate did not include nonmedical direct costs, such as special education and developmental services. Although recent advances in medical technology have increased the chances of survival for children who have birth defects and disabilities, the quality of life for most of these children remains compromised. The economic cost of medical conditions such as birth defects often is discussed without a full understanding of how these conditions affect the lives of infants and families.

Because estimates of the cost per new case of birth defects represent the savings from preventing a case, an incidence-based approach enables assessment of the value of prevention strategies. This type of approach was used to estimate the cost of illness for some of the major, most clinically important structural birth defects in the United States. This report used data from a California birth defect monitoring program (adjusted to provide

national estimates) and national data to estimate the costs of major structural birth defects occurring in the United States during 1992 (Table 1). The birth defects were selected based on their clinical significance and broad representation of the organ system.

These findings are subject to at least four limitations. First, California data used to estimate incidence rates and treatment costs may not be representative of the United States; total costs per case may vary from state to state. Second, the contribution of time and effort by family members to the provision of care were not estimated and may be substantial for some cases. Third, the psychological costs of these types of illness, which may exceed traditional human capital costs, were not included. For these and other reasons, the use of the human capital approach underestimates what the public is willing to pay to prevent these conditions. Finally, excess medical and educational costs probably were underestimated for some conditions because they could not be ascertained completely. If all of the approximately 120,000 to 150,000 infants born each year in the United States who have serious birth defects had been included in this analysis, the economic costs would have been higher.

Neural Tube Defects (NTDs)

NTDs are among the most serious and common birth defects to cause infant mortality, morbidity, and disability in the United States. Each year, approximately 4,000 births that involve NTDs as well as other defects result in miscarriage or stillbirth. There are several forms of NTDs, and they vary widely in severity. The birth prevalence of these conditions has declined substantially over the past 60 years due to better medical care. NTDs are reported in 3.6 to 4.6/10,000 live births in the United States. These rates underestimate true incidence,

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TABLE 1. Estimated Total Economic Costs* of Selected Birth Defects

| CONDITION | INCIDENCE RATE/ 10,000 LIVE BIRTHS | DIRECT MEDICAL COST (MILLIONS) | DIRECT NONMEDICAL COST (MILLIONS) | INDIRECT COST (MILLIONS) | TOTAL ANNUAL COST (MILLIONS) | COST PER NEW CASE (THOUSANDS) |
|---------------------------|------------------------------------|--------------------------------|-----------------------------------|--------------------------|------------------------------|-------------------------------|
| Cerebral palsy | 12.3 | \$ 852 | \$445 | \$1,129 | \$2,428 | \$503 |
| Spina bifida | 4.2 | \$ 205 | \$ 43 | \$ 241 | \$ 489 | \$294 |
| Truncus arteriosus | 1.1 | \$ 108 | \$ <1 | \$ 101 | \$ 210 | \$505 |
| Tetralogy of Fallot | 3.5 | \$ 185 | \$ 4 | \$ 171 | \$ 360 | \$262 |
| Tracheoesophageal fistula | 2.9 | \$ 62 | — | \$ 103 | \$ 165 | \$145 |
| Cleft lip/palate | 17.7 | \$ 97 | \$ 20 | \$ 599 | \$ 697 | \$101 |
| Renal agenesis | 4.3 | \$ 25 | — | \$ 399 | \$ 424 | \$250 |
| Urinary obstruction | 10.4 | \$ 46 | — | \$ 297 | \$ 343 | \$ 84 |
| Down syndrome | 10.5 | \$ 279 | \$389 | \$1,180 | \$1,848 | \$451 |
| Diaphragmatic hernia | 3.7 | \$ 63 | — | \$ 302 | \$ 364 | \$250 |
| Omphalocele | 1.9 | \$ 28 | — | \$ 104 | \$ 132 | \$176 |
| Upper limb reduction | 4.4 | \$ 11 | \$ 24 | \$ 135 | \$ 170 | \$ 99 |
| Lower limb reduction | 2.2 | \$ 17 | \$ 12 | \$ 139 | \$ 167 | \$199 |
| Total [†] | 83.8 | \$2,104 | \$887 | \$5,039 | \$8,031 | \$244 |

*Costs (in 1992 dollars) are based on lifetime estimates for the 1988 birth cohort in California adjusted for differences in births and costs between California and the nation and for inflation during 1988 to 1992.

[†]Column totals are less than column sums because total cost estimates reflect a downward adjustment to avoid duplication when a child had more than one condition.

however, because affected pregnancies may be spontaneously or electively aborted and because not all cases are detected and reported at birth. Population-based active surveillance programs that include prenatal diagnosis have reported NTD rates of 7.2 to 15.6/10,000 liveborn and stillborn infants. Women in the United States who have had a pregnancy resulting in an infant or fetus who has an NTD have a 2% to 3% risk for having another pregnancy resulting in a similarly affected infant or fetus.

SPINA BIFIDA

Spina bifida is an inclusive name for various conditions characterized by incomplete fusion of the vertebral arches with a protruding sac that contains meninges, spinal cord, or nerve roots that cause permanent damage to the spinal cord and spinal nerves. It is a complicated and common birth defect that can affect pregnancy without warning. Results

of prenatal examinations suggest that affected fetuses exhibit leg movement until the third trimester but become paralyzed later in pregnancy, several months after the initial spinal cord defect occurs. The Centers for Disease Control and Prevention (CDC) estimates that 300,000 to 400,000 infants are born each year with spina bifida worldwide. In the United States, approximately 2,500 infants are born annually with spina bifida and anencephaly, and an estimated 1,500 fetuses affected by these birth defects are aborted.

Based on 1992 cohort data, the estimated lifetime cost of spinal bifida is \$294,000 per case. Spina bifida can range from mild (spina bifida occulta) to severe (myelomeningocele). Depending on the pattern and level of spinal cord involvement, the resultant deficit can include a lifelong handicap due to infectious complications, motor and sensory paraplegia, bladder and

bowel incontinence, Arnold-Chiari malformations, and hydrocephalous.

ANENCEPHALY

Unlike spina bifida, in which 80% to 90% of infants survive into adulthood, anencephaly is a lethal malformation characterized by the absence of the cranial vault and the cerebral hemisphere that usually results in stillbirth or death within hours or days. Fifty percent of anencephalic fetuses are aborted spontaneously, but if pregnancy goes to term, the infants quickly succumb, showing only slow, stereotyped movements and frequent decerebrate posturing. The incidence of anencephaly is 1/1,000 live births and is responsible for about 50% of all NTDs.

ENCEPHALOCELE

Encephalocele is a rare congenital defect of the skull that results in herniation of meninges and brain

tissue. It is seen most commonly in the occipital region, where it may be associated with other anomalies, such as brainstem and skull base deformities and hydrocephalous. The incidence of occipital encephalocele is 1/10,000 live births. Most encephaloceles are detected in children shortly after birth, and the outcome relates to the position of the defect and to the associated anomalies.

Development of NTDs

The primitive nervous system begins as a flat neural plate 2 weeks after conception, which becomes indented by a longitudinal groove at 20 days, with neural folds on the flanks. These folds begin to fuse in the midline, forming a cylinder in the middle of the plate. In a zipper fashion, this dorsal closure is promulgated rostrally and caudally, resulting in a tubular structure with an open anterior and posterior aperture. At 26 days, the anterior aperture closes, followed at 29 days by the posterior aperture. Factors necessary for formation of the neural tube are intrinsic in the neural ectoderm and adjacent mesoderm.

In September 1992, the USPHS issued the recommendation that all women of childbearing age who are capable of becoming pregnant should be offered treatment with 0.4 mg of folic acid daily . . .

A teratologic insult in embryogenesis timed to interfere with the closure of the anterior aperture will result in anencephalus. Failure of the posterior aperture to close results in an exposed spinal cord, which is recognized later as spina bifida. In broad terms, NTDs result from incomplete neurulation and refer to a wide spectrum of congenital malformations in which separations of the midline vertebral and cranial elements are the common feature, but they usually are taken to mean anencephalus, spina bifida, and encephalocele.

Etiology of NTDs

Despite considerable progress having been made in understanding

NTDs, they remain the most common serious birth defect, and the etiology of most cases still is unknown. It is accepted that there is a genetic-environmental interaction in the causation of NTDs. Genetic and epidemiologic studies have suggested high-risk groups: those who have a past history of NTDs; a maternal age of less than 20 or more than 35 years; parity (primipara and grand multipara); and low socioeconomic status with gross nutritional deficiency and inadequate antenatal care.

Several clinical and epidemiologic studies have reported various teratogens that produce NTDs in offspring, including radiation; maternal hyperthermia such as prolonged high fever; exposure to heat and hot-tub use; hypo- and hypervitaminosis A; maternal viral infections such as rubella, toxoplasma, and cytomegalovirus; and drugs such as aminopterin, pyrimethamine, trimethoprim, triamterane, sulfasalazine, methotrexate, anticonvulsants (eg, valproic acid and carbamazepine), aliphatic nitrites, phenothiazines, cyclophosphamide, and cyanide. Teratogens cause NTDs by acting as folic acid antagonists or by

being associated with inadequate folic acid availability to the embryo.

A number of environmental agents also have been hypothesized as etiologic, particularly dietary agents such as soft water, blighted potatoes, nitrite-cured corn beef, canned peas treated with magnesium salts, effluent from factories, and zinc deficiency. However, none of these factors has been proved scientifically to be linked with NTDs.

Certain occupations such as male painters, female agricultural workers, and male welders have been associated with an increased risk of NTDs in offspring. Also, several studies suggested that compared with women of normal weight, women who are extremely obese before pregnancy have a significantly increased risk of having an

infant who has NTDs and several other malformations, such as central nervous system, great vessel, ventral wall, or other intestinal defects.

Mildly elevated maternal plasma homocysteine (Hcy) levels recently have been observed in some pregnancies that resulted in NTDs and other birth defects. In the past 2 decades, research has shown mild hyperhomocysteinemia to be linked to an increased risk of premature atherosclerosis, pregnancies complicated by NTDs, early pregnancy loss, and venous thrombosis. Plasma Hcy is governed by both genetic and nutritional factors. A lack of B vitamins (folic acid), mutation of the 5,10-methylenetetrahydrofolate reductase genes, or a combination of the two can explain elevated Hcy levels in blood plasma. Genetic mutations were found on the first chromosome (677 C T and 1298 A-C) and can explain up to 50% of the protective effect of folic acid against NTDs.

A personal or family history of a pregnancy affected by an NTD is associated with an increased risk of having an affected pregnancy, as is maternal type 1 diabetes, but about 90% to 95% of cases occur in the absence of any positive history. Infants of women who have type 1 diabetes have a 1% to 2% risk of NTDs. NTDs are seen more frequently in certain racial/ethnic groups, particularly Hispanics and Caucasians of European extraction, and are less common among Ashkenazi Jews, most Asians, and African-Americans.

NTDs also appear to occur more frequently in association with fetal alcohol syndrome. Folic acid supplementation is not known to prevent NTDs or other teratogenic effects of alcohol on the embryo and fetuses of alcoholic women. The primary goal for such women is to avoid excessive alcohol ingestion during pregnancy. Women who have a folic acid deficiency because of intestinal disorders (such as celiac disease, small intestine malabsorption, or intestinal bypass) and those who have epilepsy and are using certain anticonvulsants may be at greater risk for having offspring who have NTDs. Infants of women treated with valproic acid and carbamaz-

epine during pregnancy have an estimated 1% to 2% and 1% risk for spina bifida in offspring, respectively. It seems prudent to determine whether women who have epilepsy and are planning a pregnancy have a folic acid deficiency. It is not known, however, whether folic acid supplementation would decrease the risk of NTDs in the offspring of these women.

NTDs and Folic Acid

Thirty years ago, it was suggested that maternal intake of certain vitamins during pregnancy affected the incidence of serious fetal malformations. Subsequent research has revealed that folate (folic acid), a B vitamin, plays a crucial role in the development of the central nervous system during the early weeks of gestation, which generally is before pregnancy is confirmed. In a significant number of embryos, an inadequate supply of folate at this time leads to failure of the primitive neural tube to close and differentiate normally, resulting in NTDs. Numerous studies have confirmed the importance of an adequate intake of folate during the weeks just before and after conception. Randomized placebo-controlled trials and nonrandomized controlled trials in pregnant women who had a prior pregnancy affected by an NTD have demonstrated that folic acid supplements substantially reduce the risk of recurrent NTDs.

CLINICAL INVESTIGATIONS

It has been suspected that diet has a role in the causation of NTDs. The possibility that folic acid might be involved was raised in 1964 by Hibbard. In 1980 and 1981, the results of two other interventional studies were published in which vitamin supplementation was instituted around the time of conception among women who already had had a child who had an NTD. In the first study, which was not randomized, participating women were given a mixture of eight vitamins that included folic acid (0.36 mg/d), with women who already were pregnant or who had declined to take part in the study serving as controls. The

risk of recurrence in the supplemented group was about one-seventh that of the group who received no supplements. The second study was a small randomized trial of folic acid supplementation alone (4 mg/d). It yielded inconclusive results when analyzed according to randomly allocated treatment group (so avoiding bias), but when analyzed after transferring to the control group those women in the folic acid group who did not take their capsules (ie, ignoring the randomization and so introducing the possibility of bias), the supplemented women had a significantly lower risk.

To avoid bias, an international multicenter, double-blind, randomized British Medical Research Council (MRC) prevention trial was initiated in July 1983. Conducted at 33 centers (17 in the United Kingdom and 16 in six other countries), it was designed to determine whether supplementation with 4 mg 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 could prevent NTDs. A total of 1,817 women who had previous pregnancies affected by an NTD that was not associated with the autosomal recessive disorder were eligible

1,817 women, 1,195 had a completed pregnancy in which the fetus or infant was known to have or not have an NTD. A total of 27 infants had known NTDs, with 6 in the folic acid groups and 21 in the two other groups. Sequential analysis showed a 72% protective effect (relative risk, 0.28; 95% confidence interval [CI], 0.12 to 0.71). The other vitamins showed no significant protective effect (relative risk, 0.80; 95% CI, 0.32 to 1.72). There was no demonstrable harm from the folic acid supplementation, although the ability of the study to detect rare or slight adverse effects was limited. The study result is unlikely to be due to chance, and the randomized double-blind design excluded bias as an explanation. The results also demonstrate that folic acid, rather than any other vitamins, is responsible for the preventive effect.

Another significant study was a randomized, double-blind, controlled trial from Hungary that enrolled 4,753 women planning pregnancy. Results documented that the first occurrences of NTDs could be prevented significantly by administering periconceptional multivitamin supplements daily that included 0.8 mg of folic acid. This study was extended to examine the effect of supplementation on other congenital

None of the trials of healthy pregnant women reported serious adverse effects associated with folic acid supplementation.

for the study if they were planning another pregnancy and were not already taking vitamin supplements. Women who had epilepsy were excluded in case the folic acid supplementation adversely affected their treatment. The effect of both forms of supplementation was investigated by use of a factorial study design.

The women were allocated randomly to one of four groups—folic acid, other vitamins, both, or neither. The four groups were similar with respect to age and the occurrence of previous pregnancies. Women were asked to take a single capsule each day from the date of randomization until 12 weeks of pregnancy (estimated from the first day of the last menstrual period). Of

abnormalities. Periconceptional administration of multivitamin supplements reduced NTDs by 50% and the incidence of other major genetic congenital abnormalities, such as cardiovascular anomalies, defects of the urinary tract, congenital hypertrophic pyloric stenosis, and congenital limb defects.

Six observational studies of dietary folate or the use of folic acid and other vitamin supplements and NTDs and one nonrandomized folic acid supplementation study have been published. All but one showed an association, but all may have suffered from selection bias, and none could identify folic acid specifically as the responsible vitamin.

Results of the British MRC ran-

domized, controlled trial proved that folic acid can prevent spina bifida and anencephaly and provided critical scientific data on which to base public health policy for preventing these birth defects. Within weeks of publication of this study, the CDC developed and issued guidelines for women who had had a pregnancy affected by spina bifida or anencephaly. In September 1992, the United States Public Health Service (USPHS) issued the recommendation that all women of child-bearing age who are capable of becoming pregnant should be offered treatment with 0.4 mg of folic acid daily to reduce their risk of having an NTD-affected pregnancy. For women who already have had an NTD-affected pregnancy, the USPHS also recommends administration of 4.0 mg (4,000 mcg) of folic acid every day starting 1 to 3 months prior to the planned conception and continuing throughout the first 3 months of pregnancy.

Research during the past 5 years makes it clear that people who do not take folic acid supplements are at increased risk for functional folate deficiency, which has been proven to cause spina bifida and anencephaly and has been associated with an increased risk for occlusive cardiovascular disease. The evidence that consumption of folic acid during the periconceptional period can reduce the number of NTDs has been accumulating for several years. Published data are available from randomized control trials, nonrandomized interventional trials, and observational studies (Table 2).

ADVERSE EFFECTS

Research on adverse effects from folic acid supplementation is limited. Evidence that folic acid supplements in daily doses of 1 to 5 mg can mask the hematologic manifestations of vitamin B₁₂ deficiency, possibly delaying its diagnosis and treatment and thereby leading to permanent neurologic consequences, is limited to uncontrolled interventional studies and case reports. Hematologic improvement in pernicious anemia also has been reported in some patients receiving folic acid doses of less than 1 mg, but the response is

not consistent, particularly at lower doses. Nevertheless, this has been advanced as one reason to avoid universal supplementation or food fortification with folic acid. However, it also has been argued that it is unreasonable to maintain anemia and ease the B₁₂ deficiency diagnosis at the risk of an avoidable NTD. Limited evidence supports independent associations of low-normal folate and B₁₂ levels and high Hcy levels with NTDs, suggesting that a causal mechanism for these defects may be an abnormality in methionine synthase, a folate- and B₁₂-dependent enzyme. If these results are confirmed, supplementation with both folic acid and B₁₂ may be appropriate to prevent NTDs. This could reduce the potential for adverse effects of folate supplementation in patients deficient in B₁₂.

None of the trials of healthy pregnant women reported serious adverse effects associated with folic acid supplementation. In the Hungarian trial, infants born to women who received a multivitamin, multi-mineral supplement with folic acid did not differ in mortality, somatic development, mental and behavioral development, and total serious or chronic disorders at 8 to 21 months (mean, 11 mo) of age from those born to women receiving only trace elements. The rate of atopic dermatitis, asthma, and wheezy bronchitis was significantly increased among those whose mothers received multivitamins (16 versus 5/1,000), but more affected infants in the supplemented group also had a family history of these disorders. This difference also may be a chance effect due to the large number of comparisons made. A group of 91 children born to women who had taken daily multivitamins containing 0.36 mg of folic acid to prevent NTD recurrences revealed no adverse effects on health, auditory, visual, growth, or developmental status at age 7 to 10 years compared with the general population. There were significant increases in neurotic traits, but whether this was attributable to folic acid or to other causes (eg, increased parental anxiety related to having had a previously affected pregnancy) is unknown.

FOLATE-RESISTANT NTDs

Most of the randomized and nonrandomized controlled trials showed that among women at high risk of having a child who had an NTD, those who received 4 mg/d of folic acid had approximately 70% fewer cases of NTD-affected offspring than those who received no supplements. Several interventional retrospective and case-control studies also support this conclusion, although the mechanism of this action is unclear. Approximately 30% of NTDs appear resistant to folic acid (as with the curly tail mutant mouse, a model of folate-resistant NTDs). The administration of inositol to the mouse can cure such defects, but this does not occur in humans. The molecular pathway by which this is achieved is thought to be by the upregulation of the retinoic acid receptor beta in the underlying hindgut endoderm, which corrects a proliferation defect.

EXPERIMENTAL ANIMAL INVESTIGATIONS

In mice, folate did not reduce NTDs, but methionine did. The curly tail mouse has been studied extensively to determine the agents that prevent NTDs in embryos. Prevention has been found with retinoic acid, inositol, hydroxyurea, mitomycin C, 5-fluorouracil, cytosine arabinoside, possibly riboflavin, vitamin C, and vitamin D₂. No prevention was seen with folic acid, folinic acid, vitamin B₆, vitamin B₁₂, zinc, methionine, or thymidine.

Mechanism of Action of Folic Acid

The mechanism of action of folic acid still is being investigated. Kirke et al suggested that there may be a metabolic block rather than a simple deficiency effect. Others have found that the Hcy level is significantly higher for mothers of infants who have NTDs during pregnancy than for vitamin B₁₂-matched controls. Methionine synthase is a folate-dependant enzyme, and a defect in it would lead to increased levels of Hcy. Overcoming an abnormality in Hcy metabolism, particularly an abnormality of methionine synthase

TABLE 2. Results From Various Studies on Folic Acid and Neural Tube Defects (NTDs)

| STUDY | DESIGN | SUBJECTS | RESULTS | RELATIVE RISK | COMMENTS |
|-------------------------------|--|--|---|----------------------|---------------------|
| Interventional Studies | | | | | |
| Laurence, et al | Randomized, controlled trial in Wales | <ul style="list-style-type: none"> • Pregnant women who had prior NTD-affected pregnancy • Supplemented mothers took 4 mg folic acid daily; unsupplemented mothers took placebo at least 1 month before conception through the first trimester | <ul style="list-style-type: none"> • 2 NTD pregnancies among 60 supplemented women • 4 NTD pregnancies among 51 unsupplemented women | 0.40* | 60% risk reduction |
| UK MRC Study | Randomized, controlled, multicenter trial | <ul style="list-style-type: none"> • Pregnant women with prior NTD-affected pregnancy • Supplemented mothers took 4 mg folic acid daily; unsupplemented mothers took placebo at least 1 month before conception through the first trimester | <ul style="list-style-type: none"> • 6 NTD pregnancies among 593 supplemented women • 21 NTD pregnancies among 602 unsupplemented women | 0.28 [†] | 72% risk reduction |
| Smithells et al | Nonrandomized, controlled, multicenter trial in UK | <ul style="list-style-type: none"> • Pregnant women with prior NTD-affected pregnancy • Supplemented mothers took 0.36 mg folic acid plus multivitamin daily; unsupplemented mothers took nothing at least 1 month before conception through the first trimester | <ul style="list-style-type: none"> • 3 NTD pregnancies among 454 supplemented women • 24 NTD pregnancies among 519 unsupplemented women | 0.14 [†] | 86% risk reduction |
| Vergel et al | Nonrandomized, controlled trial in Cuba | <ul style="list-style-type: none"> • Pregnant women with prior NTD-affected pregnancy • Supplemented mothers took 5 mg folic acid daily; unsupplemented mothers took nothing at least 1 month before conception through the first trimester | <ul style="list-style-type: none"> • 0 NTD pregnancies among 81 supplemented women • 4 NTD pregnancies among 114 unsupplemented women | Undetermined* | Complete protection |

(continued)

*Not statistically significant.

[†]Statistically significant.

TABLE 2. Studies on Folic Acid and NTDs (continued)

| STUDY | DESIGN | SUBJECTS | RESULTS | RELATIVE RISK | COMMENTS |
|------------------------------|---|---|---|-------------------|----------------------|
| Observational Studies | | | | | |
| Mulinare et al | Case-control study in Atlanta, Georgia | <ul style="list-style-type: none"> • NTD case babies and normal control babies • Pregnant women without a prior NTD-affected pregnancy • History of multi-vitamin supplement containing 0 to 0.8 mg of folic acid at least 1 month before conception through the first trimester | <ul style="list-style-type: none"> • 24 supplemented NTD cases • 157 unsupplemented NTD cases • 1,075 unsupplemented controls | 0.40 [†] | 60% risk reduction |
| Bower and Stanley | Case-control study in western Australia | <ul style="list-style-type: none"> • Spina bifida case babies and normal control babies • Pregnant women without a prior NTD-affected pregnancy • Highest folate quartile compared with the lowest • History of multi-vitamin supplement containing folic acid at least 1 month before conception through the first trimester | <ul style="list-style-type: none"> • 77 cases; 154 controls • Highest folate quartile compared with the lowest • Increasing protective effect observed from lowest to highest quartile | 0.25 [†] | 75% risk reduction |
| Mills et al | Case-control study in California and Illinois | <ul style="list-style-type: none"> • NTD case babies and normal control babies • Pregnant women without a prior NTD-affected pregnancy • History of multi-vitamin supplement containing 0.8 mg of folic acid at least 1 month before conception through the first trimester | <ul style="list-style-type: none"> • 89 supplemented NTD cases • 214 unsupplemented NTD cases • 90 supplemented controls • 196 unsupplemented controls | 0.9* | No protective effect |
| Milunsky et al | Prospective cohort study in New England | <ul style="list-style-type: none"> • NTD case babies and normal control babies • Pregnant women without a prior NTD-affected pregnancy • Multivitamin supplement with or without 0.1 to 1.0 mg of folic acid at least 1 month before conception through the first trimester | <ul style="list-style-type: none"> • 10 NTD pregnancies among 10,713 women who took multivitamin with folate • 39 NTD pregnancies among 11,944 women who took multivitamin without folate | 0.28 [†] | 72% risk reduction |

*Not statistically significant.

[†]Statistically significant.

by folic acid supplementation, presently is favored. Methionine synthase is pivotal in methylation reactions to produce myelin basic protein and make tetrahydrofolate for DNA synthesis, either of which may be the responsible pathway for producing NTDs.

Discussion

The incidence of NTDs is declining throughout the world following the introduction of ultrasonographic examination and measurement of maternal serum alpha fetoprotein (MSAFP), amniotic fluid alpha fetoprotein (AFAFP), and amniotic fluid acetylcholinesterase (AFAChE). The latter two measurements are employed primarily as confirmatory tests and should not be regarded as part of the routine screening of women at risk of NTDs. Ultrasonography is used both as a screening test and as a follow-up test after positive results on MSAFP screening. All cases of anencephaly and approximately 65% of cases of spinal bifida could be identified by measurement of MSAFP and ultrasonography.

The decline in the rates of NTDs in the United States began before the widespread availability of prenatal diagnostic services, suggesting the presence of a substantial environmental component in the etiology of these defects (eg, improved nutrition). Available data indicate that folic acid can help to avert NTDs when administered at doses of 4 mg/d to women who already have had an NTD-affected pregnancy. Results of the British MRC study suggest that the addition of other vitamins to the folic acid confers no added benefit in terms of NTDs. Based on the findings from several studies, folic acid supplementation at a dose of 4 mg/d beginning 1 to 3 months prior to conception and continuing through the first trimester is recommended for women planning pregnancy who have had a pregnancy previously affected by an NTD.

However, results of controlled trials indicate that folic acid supplementation will not prevent all NTDs. The protective effect demonstrated in studies of lower-dose folic acid,

measured by the reduction of NTD incidence, ranged from none to substantial. Therefore, it is reasonable to estimate that administration of low-dose (0.4 mg/d) folic acid supplementation to all women capable of pregnancy would reduce the incidence of NTDs in the United States.

The use of periconceptual folic acid supplements does not preclude offering screening for NTDs, although the cost-effectiveness of such screening is likely to be reduced if there is a lower risk of occurrence. The possibility of reducing the number of cases of NTDs in the United States by 70% with the consumption of 3 cents worth of folic acid per day presents an important opportunity in public health. Efforts should be made to assure that all women capable of becoming pregnant consume 0.4 mg of folic acid daily to achieve this goal.

Implementation of this recommendation presents a challenge because almost 50% of the pregnancies in the United States are unplanned. Furthermore, it is difficult, if not impossible, to achieve a daily intake of 0.4 mg of folate through diet alone. To derive the protective benefit of vitamin supplementation, women must begin to take supplements before conception occurs, a potentially less likely step if pregnancy occurs unexpectedly. Fortification of food is a "passive" public health intervention that can increase women's intake of folic acid during the critical period of embryonic development. In February 1996, the USPHS announced that folic acid fortification of enriched cereal grain products (flour, bread, pasta, rice, and corn meal) would become mandatory as of January 1, 1998. Fortification is expected to increase the daily intake of folic acid among women of reproductive age by about 100 mcg/d. Such fortification would prevent about 1,000 spina bifida and anencephaly birth defects each year and perhaps as many as 50,000 premature deaths each year from coronary heart disease.

The most commonly cited potential risk of food fortification is the previously noted masking of megaloblastic anemia that often is associated with vitamin B₁₂ deficiency,

which might complicate the diagnosis and treatment of this problem, thereby increasing the potential for irreversible neurologic damage. Physicians should be aware of this possibility and remember that vitamin B₁₂ deficiency, although occurring most commonly in the elderly, can occur at any age. Also, care should be taken to keep total folate consumption to less than 1 mg/d, except under the supervision of a physician.

The recommended intake of folate in the periconceptual period may be achieved by advising women who could become pregnant to supplement a healthy, folate-rich diet with a daily vitamin pill; fortifying foods with folic acid; or combining these measures.

Programs should be implemented to educate physicians, other health professionals, and the public about the value of folic acid supplementation in preventing NTDs. Ongoing surveillance programs should monitor the prevalence of NTDs in fetuses and newborns. Basic and clinical research into the mechanisms by which folic acid prevents NTDs should be encouraged. In addition, more clinical trials are needed to determine the effectiveness of folic acid in preventing the occurrence and recurrence of NTDs.

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PIR QUIZ

Quiz also available online at www.pedsinreview.org.

5. The combination of ultrasonography and measurement of alpha fetoprotein could detect approximately what percentage of cases of neural tube defects prenatally?
 - A. 10.
 - B. 30.
 - C. 50.
 - D. 70.
 - E. 90.
6. To help prevent neural tube defects in the fetus, women should begin taking folic acid supplementation:
 - A. 1 year prior to pregnancy.
 - B. 6 months prior to pregnancy.
 - C. 3 months prior to pregnancy.
 - D. During the first trimester.
 - E. During the second trimester.
7. Neural tube defects relate to a teratogenic effect on the embryo that occurs during the:
 - A. First week of pregnancy.
 - B. Third to fifth weeks of pregnancy.
 - C. Tenth to twelfth weeks of pregnancy.
 - D. Second trimester.
 - E. Third trimester.
8. Women at highest risk for a pregnancy complicated by a neural tube defect in the fetus:
 - A. Are of Ashkenazi Jewish heritage.
 - B. Have decreased levels of plasma homocysteine.
 - C. Have experienced a miscarriage.
 - D. Have given birth to an infant with anencephaly.
 - E. Took phenobarbital for febrile seizure prophylaxis during childhood.

EXHIBIT 5

Sir—There can be little doubt that Sheila Gore¹ highlights a flaw in current methods of defining and recording drug-related deaths in the UK. Such figures are vital in planning judicial policy, treatment services, and most importantly, prevention strategy. However, to achieve the degree of accuracy that Gore suggests would require regular surveys of drug users, which is difficult and cost prohibitive.

The National Programme on Substance Abuse Deaths (NPSAD) was established in 1997 to monitor drug-related deaths in the UK. Our response is to report the cause of death ratio, looking at the number of drug-related deaths in specific categories (ie, 15–24-year-olds) and the drugs implicated in these deaths. This allows quick surveillance of the pattern of deaths over time. NPSAD receives data on drug-related deaths from coroners in England and Wales. Cases must meet one or more of the following criteria: one or more psychoactive substances directly implicated in the death; history of dependence or abuse of psychoactive drugs; or presence of controlled drug at necropsy.

To facilitate comparison with national and international databases, cause of death is re-coded by International Classification of Diseases (tenth revision) categories. Cases are reported by demographic characteristics, drugs implicated in death, whether they were prescribed drugs, associated risk for age, sex, and history of drug use. The programme reports regional differences and trends over time.

The most recent report, which covered the period July to December, 1998, showed 695 drug-related deaths reported by 96 coroners in England and Wales (131 were aged 15–24 years). Heroin was implicated in 60 deaths (57 men, eight women) and ecstasy in four (all men).

A method to obtain an accurate death rate is to study a defined population, such as addicts notified to the Home Office Addicts Index. A 27-year study of notified addicts² recorded 1104 drug-related deaths in 15–24-year-olds, giving an average annual rate of 3.2 per 1000 person-years in the last 10 years. A 20-year study of notified addicts aged 15–19 years showed that teenage addicts are 12 times more likely to die before age 20 years than non-addicts of the same age.³

NPSAD does not distinguish between first-time, sporadic, and regular drug use, and we acknowledge that this information would be useful. However, it is very difficult to distinguish, record, and monitor this type of data.

The role of a central specialist

register, suggested by Gore, is currently fulfilled by our programme, with substantial collaboration from the Home Office and coroners in England and Wales. The data compiled by NPSAD is used by drug action teams in informing policy development in accord with national strategy.⁴ The programme is being extended to Northern Ireland and Scotland.

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Folic acid fortification

Sir—Jean Lawrence and colleagues' (Sept 11, p 915)¹ report that median serum folate has increased in the USA since the Food and Drug Administration (FDA) mandated the fortification of cereals and grains. We see a similar inverse trend in plasma homocysteine testing. Homocysteine is, in part, a functional marker of folate status²—as folate rises, homocysteine concentrations would be expected to decrease.

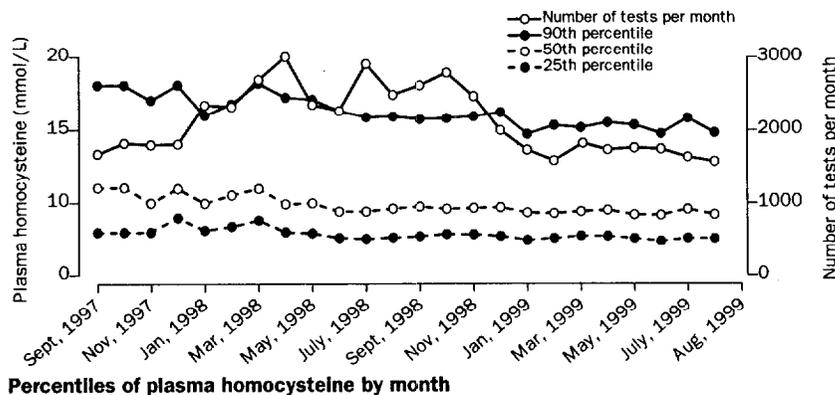
The clinical reference laboratory at our institution has tested between 1500 and 3000 plasma homocysteine specimens each month since September, 1997. Records before that time were difficult to collate because of software limitations in our laboratory information system. Specimens were received from throughout the USA. Plasma homocysteine was measured by high-

performance liquid chromatography with electrochemical detection.³

The figure shows all specimens tested between Sept 1, 1997, and Aug 31, 1999, in which sex was known and age was 30–59 years. A limited age distribution was selected because homocysteine tends to increase with age. Although the average value for women was lower, the same trend was seen when data were separated by sex (data not shown). The higher number of specimens in 1998 corresponds to the increased interest in homocysteine, and the decrease from 1998 is due to the availability of commercial kits suitable for hospital-based testing.

Over the 8-month period from September, 1997, to March, 1998, percentiles seem stable. From April, 1998, however, there was an apparent downward trend. As of August, 1999, the last month for which we have complete data, the trend seems to continue. This pattern follows a slightly different time course from that described for folate, namely an upward trend beginning in 1997.¹ There are several possible reasons for this apparent lag in homocysteine response. First, other factors that affect homocysteine, such as vitamins B₆ and B₁₂, and genetic influences, may confound the comparison. Second, the populations may be substantially different. Third, as a functional indicator of folate metabolism, homocysteine may simply require more time in which to register an effect. For whatever reason, our data suggests that plasma homocysteine concentrations are falling. Folate fortification of food is a likely explanation.

The specific goal of folate fortification is to decrease the rate of neural-tube defects (NTDs).² In the UK, supplementation has not decreased the NTD rate.⁴ Although the effect on NTD rates remains to be seen in the USA, fortification does seem to be having an effect on homocysteine. In terms of its effect on coronary heart disease, the benefits of decreasing homocysteine could be substantial. As Lawrence and



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colleagues' note, analysis of data from other laboratories could support or counter these findings.

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Sir—Jean Lawrence and colleagues¹ report that blood folate concentrations have increased in the USA after folic acid fortification of enriched grain products. Their findings are consistent with those recently reported by Jacques and colleagues.² Both groups attribute these trends to folic acid fortification, which is believed to have been implemented by mid-1997. Although these findings are encouraging, to date we have seen no studies that examine the potential effects of fortification on the prevalence of NTDs. We present here an early assessment of the birth prevalence of NTDs after fortification.

From the North Carolina Birth Defects Monitoring Program, a population-based surveillance programme that covers about 100 000 live births per year, we identified 361 liveborn and stillborn infants with NTDs who were delivered between Jan 1, 1995, and Dec 31, 1998. We matched case records with North Carolina vital statistics files and used the reported date of last menses to estimate the date of conception for each case. Rates of NTDs were calculated on the basis of the date of conception by dividing the number of cases conceived during a given period by the total number of liveborn infants whose conception occurred during that time. NTD rates for the 36 months immediately before fortification (July, 1994, to June, 1997) were used to predict the rates among conceptions occurring after fortification began (July, 1997, to March, 1998).

A slight downward trend in the rate of total NTDs (from 10.2 to 7.5 per 10 000 live births) and spina bifida (from 6.0 to 4.4 per 10 000 live births) was seen for conceptions occurring during the 36-month prefortification

period, whereas the rate for anencephaly remained constant (2.2 per 10 000 live births). Among fetuses conceived during the 9 months after fortification, we found very little difference between the observed and expected rates of total NTDs, anencephaly, and spina bifida. In fact, the rate for fetal NTDs increased to 7.9 per 10 000 live births after fortification.

Folic acid fortification in the USA was predicted to increase the average woman's consumption of folic acid by only 100 µg per day, or a quarter the amount recommended for birth-defect prevention.³ Our early findings, which show no evidence of a change in NTD trends after fortification, support the assertion that the current fortification concentration in the USA is too low for full prevention of birth defects. We continue to monitor these trends and will reassess the situation in the future. However, on the basis of our data, we cannot assume that the increased post-fortification blood folate concentrations reported in the studies by Lawrence et al,¹ and Jacques et al,² are any indication that fortification has led to a decline in NTD rates.

Seldom do we have an opportunity to implement a cheap, simple, and safe public-health programme that can present severe, life-altering conditions such as spina bifida and anencephaly. To improve the health of children, governments should immediately implement fortification programmes that will increase consumption of folic acid by at least 400 µg a day. Until such programmes are implemented, we should teach women of reproductive age to consume daily vitamin supplements containing 400 µg of synthetic folic acid.

The North Carolina Birth Defects Monitoring Program is funded by a grant from the North Carolina chapters of the March of Dimes Birth Defects Foundation and by a cooperative agreement (U50/CCU416075-01) with the Division of Birth Defects and Pediatric Genetics, Centers for Disease Control and Prevention.

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Shifts in mortality curves

Sir—L B Tan and R Murphy's review (Oct 16, p 1378)¹ on presentation of trial mortality data is both highly relevant and timely in the context of current medical practice. With the onslaught of evidence-based medicine derived from large randomised trials, the practice of medicine is becoming more dogmatic. As Tan and Murphy state, there is substantial public and peer pressure to prescribe drugs that are widely reported as being beneficial. For the practising clinician, it is difficult to distinguish between statistical benefit and clinical relevance of a specific therapeutic agent, as reported in trials. Thus, knowledge of the extra time gained with an improved quality of life will certainly help patients and clinicians to decide whether a drug should be taken daily for the rest of the patient's life. Further, drugs carry costs and may have adverse effects, including death.

Undertaking of a trial with wide entry criteria to show the benefits of a drug can only produce findings relevant to the specific trial population that are valid only for the duration of the trial. The "law of averages" is at work here. If a specific drug benefits more patients than it harms, then this drug would be of positive value, and its prescription is encouraged. The entry criteria for the trial then determine which patients get the new treatment, but these criteria may not identify whether a therapeutic agent would benefit a particular patient on an individual basis. In this traditional approach, a patient is told that if he or she takes a drug, and if there are x number of other patients doing the same for y length of time, then z number of lives would be saved within the timeframe. The drawback is that there is no way of telling whether this patient will be one of the z patients. This is a pressing issue when x and y are large, with a small z and the disease is chronic. We should be putting more effort into the classification of patients before drug initiation, and the development of more objective measures to assess and monitor both the beneficial and harmful effects of drugs.

This difficulty is especially acute in chronic heart failure in which each new therapy (angiotensin-converting enzyme inhibitor, β -blocker, angiotensin II antagonist, and so on) causes a further fall in the patient's already low blood pressure. This difficulty may force us into more tailoring of therapy to the individual. For example, we reported that angiotensin-converting enzyme inhibitors only enhance

EXHIBIT 6

EXHIBIT 6

East Ireland 1980-1994: epidemiology of neural tube defects

R J McDonnell, Z Johnson, V Delaney, P Dack

Abstract

Study objective—The objective of the study was to describe the epidemiology of neural tube defects (NTD) in the eastern region of Ireland using the EUROCAT register of congenital malformations.

Design, setting and patients—EUROCAT registries monitor the prevalence of congenital anomalies in defined populations using multiple sources for case ascertainment. All cases of NTD on the Dublin EUROCAT register born between 1980 and 1994 were extracted and analysed. The crude birth prevalence rate for all NTD, spina bifida, anencephaly and encephalocoele were calculated for each year. Parameters measured were: sex ratio, stillbirth rate, proportion of low birth-weight babies (<2500 g) and the proportion who were premature (<37 weeks gestation).

Main results—Of 821 NTD cases, 419 (51.0%) had spina bifida, 322 (39.2%) had anencephaly, 69 (8.4%) had encephalocoele and 11 (1.3%) were iniencephalic. The crude birth prevalence of NTD decreased fourfold from 46.9/10 000 births in 1980 to 11.6/10 000 in 1994. The downward trend ceased during the early 1990s. Younger mothers had significantly higher rates of NTD affected births. Twenty two per cent of NTD cases had additional non-central nervous system anomalies. In 40 cases, there was a previous family history of NTD in siblings. Seasonal effects in birth prevalence were observed. Birth notification was the most frequent mechanism of ascertainment.

Conclusion—There was a marked fall in the birth prevalence of NTD during the 15 year period. This change was real and not accounted for by pre-natal screening and diagnostic practises with termination of pregnancy, which is not legally permissible in Ireland. Dietary factors may have had an influence. Rates of NTD in this region are still higher than many other parts of Europe. Primary prevention strategies through increased folic acid intake are necessary to further reduce NTD affected births.

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Neural tube defects (NTD) are major congenital abnormalities of the nervous system that result from incomplete closure of the developing neural tube early in pregnancy. Anencephaly, spina bifida and encephalocoele account for almost all NTD. Ireland and other

Celtic countries of the British Isles are known to have high prevalence rates of NTD compared with other parts of Europe.¹ Since 1980, surveillance of NTD in various parts of Europe has been carried out through EUROCAT, which is a concerted action of the European Union for the surveillance of congenital anomalies.²⁻⁵ The Dublin EUROCAT Registry has monitored NTD in counties Dublin, Kildare and Wicklow in the eastern region of Ireland from 1980 onwards. Health care services in these counties are provided by the Eastern Health Board, whose total catchment population of 1.3 million is covered by the registry. This paper describes the epidemiology of NTD in the region during the 15 year period 1980-1994.

Method

EUROCAT registries use as many data sources as possible so as to achieve a high level of case ascertainment. The Dublin registry uses birth notification forms, death certificates for children under two years, the Hospital Inpatient Enquiry Scheme (HIPE; a computerised system containing diagnostic and other details for cases discharged from paediatric and acute hospitals), karyotyping records, neonatal paediatric listings and maternity hospital necropsy. The latter source is used to ascertain stillbirths with NTD, in addition to birth notification forms. Screening with termination of pregnancy is not undertaken in Ireland for legal reasons and therefore this study is based on live and stillbirths only.

All cases of NTD on the register with birth dates between 1 January 1980 and 31 December 1994 were extracted and analysed. The following items are routinely collected for each EUROCAT case: birth date, sex, single or multiple birth, birth weight, gestation, presence of additional congenital malformations, mother's county of residence, birth date and reproductive history. The proportion of all congenital anomalies on the register accounted for by NTD was calculated. Analysis was carried out by time, place (county of residence of mother) and person. Prevalence (birth) rates per 10 000 births were examined each year for the 15 year study period and by five year periods. The following factors were compared by type of NTD: prevalence, sex ratio, the proportion of cases with a birth weight less than 2500 g, the proportion of cases born before 37 weeks gestation, the proportion of mothers under the age of 35 years and the proportion of stillbirths. Comparisons involving marital status are based on five categories as legally defined in Ireland (married, single,

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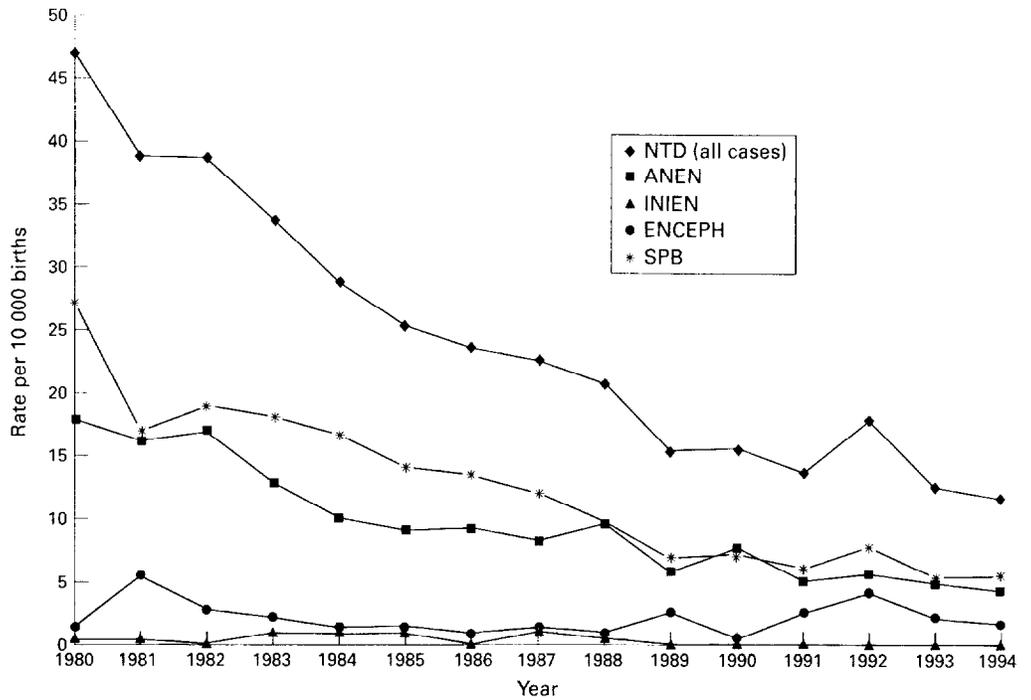


Figure 1 Trends by type of NTD 1980-1994.

widowed, separated, divorced). Information on cohabiting couples who are single according to this categorisation is not available. The effect of season of birth on prevalence and the prevalence of each type of NTD by the source of ascertainment were examined. The socioeconomic group (SEG) of NTD cases was examined; SEG is an 11 point non-ordinal scale⁶ and has been used by the Central Statistics Office (CSO) since 1951. The SEG of each NTD case was based on the occupation of the father of the affected child, using the coding classification of the CSO and we categorised cases as manual and non-manual based on SEG. Denominator birth data for the years 1980-

1994 were supplied by the CSO. The latter also provided denominator data on the occupations of fathers of children born in the Republic of Ireland from 1980-1994. Where the occupation was not stated (this frequently occurred when the mother was unmarried), the SEG was categorised as "unknown". Precurrence was defined as birth of siblings with NTD before the index case. Information on affected siblings born before the introduction of the EURO-CAT register was historical and had been recorded on the data collection form of index cases born in the early 1980s. Data on NTD affected siblings of index cases born more recently were available from the register also.

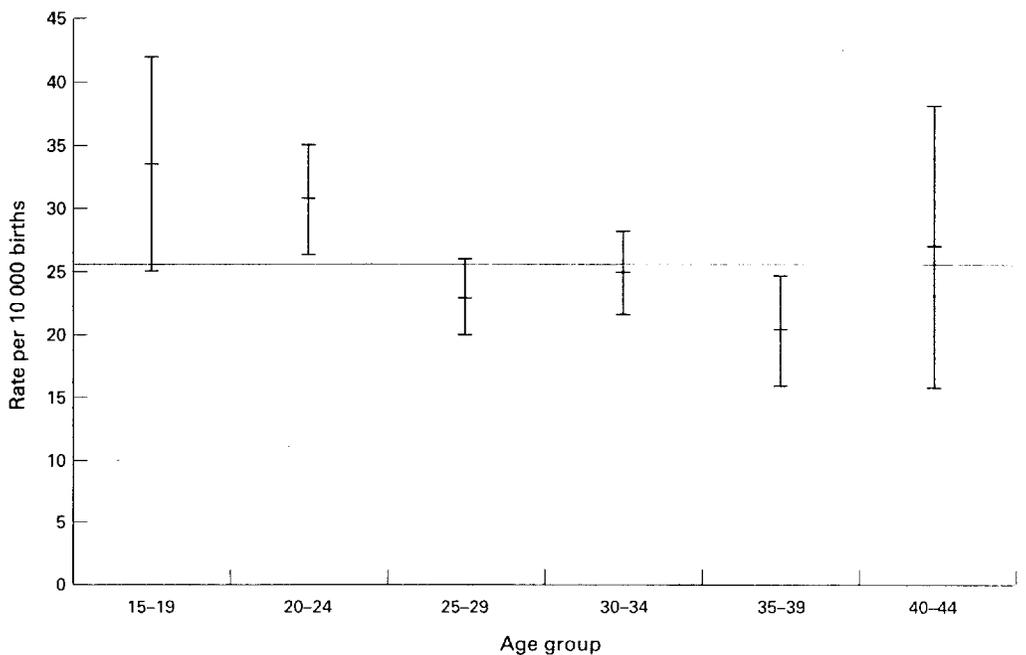


Figure 2 Age of mother at delivery and NTD rate per 10 000 births (95% CI). The reference line (25.6/10 000) refers to the overall rate of NTD for the period 1980-1994.

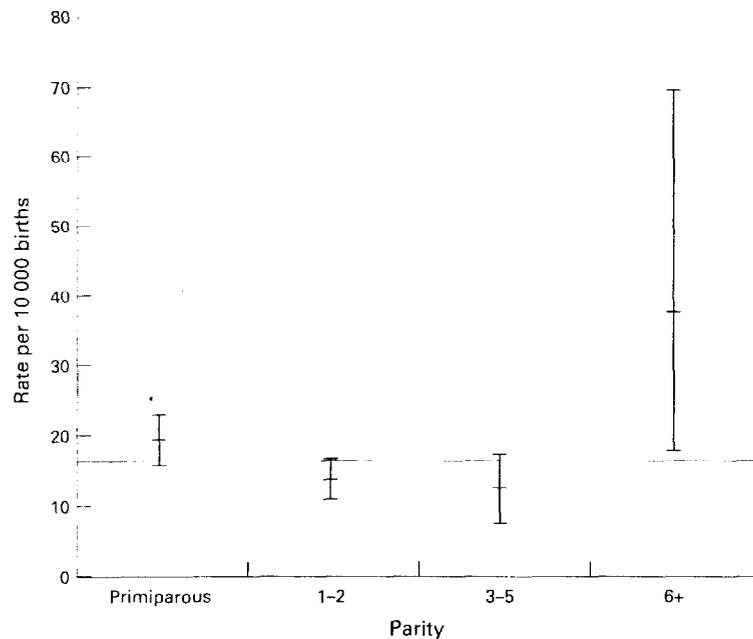


Figure 3 Rate of NTD per 10 000 births and parity 1987-1994 (95% CI). The reference line (16.3/10 000) refers to the overall rate of NTD for the period 1987-1994.

The data were analysed using SAS Version 6.07 (SAS is a registered trademark of SAS Institute Inc, Cary, NC, USA). The χ^2 test was used for comparison of proportions and as an approximation of the Poisson heterogeneity test for comparing rates using vital statistics denominators. The software package Confidence Interval Analysis program (CIA)⁷ was used in calculating 95% confidence intervals (CI) and χ^2 for trend using Epi Info 6.04a⁸ for mothers' age at delivery and SEG. Seasonality tests carried out were: Edwards' test⁹ for a simple harmonic curve, Freedman's test¹⁰ for deviation from uniform incidence and the Ratchet circular scan test.¹¹

Results

Between 1980-1994, there were 320 750 births in the Eastern Health Board region of Ireland; 9161 children were registered with major or minor congenital anomalies on the Dublin register. Of these, 821 (9.0%) had an NTD. The birth prevalence for NTD during the 15 year period was 25.6 per 10 000 births in the region overall.

Of the 821 NTD cases, 419 (51.0%) had spina bifida, 322 (39.2%) were anencephalic, 69 (8.4%) had encephalocoele and 11 (1.3%) were iniencephalic; the corresponding birth prevalence per 10 000 births was 13.1 for spina bifida, 10.0 for anencephaly, 2.2 for encephalocoele and 0.3 for iniencephaly. There were 330 (40.2%) males, 487 (59.3%) females and the sex of four cases was either unknown or

indeterminate. Figure 1 shows the trend in birth prevalence over the 15 years for all types of NTD. There were 124 NTD affected births in 1980, representing the largest number in the period and this had fallen to 21 NTD affected births in 1994. The birth prevalence rate for NTD fell from 46.9 to 11.6 per 10 000 births from 1980-1994 (χ^2 for linear trend = 119.3, df=1, $p < 0.001$) with a sharp fall during 1980/81, followed by a more gradual decline after this, and almost levelling off from 1989 although rising again in 1992. When the data were divided into five year periods the trend was significant for the periods 1980-1984 (χ^2 for linear trend=11.1, df=1, $p < 0.001$) and 1985-1989 (χ^2 for linear trend=4.8, df=1, $p < 0.05$) but not significant for the period 1990-1994.

The rates for spina bifida and anencephaly followed a similar pattern during the period. The birth prevalence of spina bifida declined from 27.2 per 10 000 births in 1980 to 5.5 in 1994 (χ^2 for linear trend = 86.4, df=1, $p < 0.0001$). Likewise, the birth prevalence of anencephaly fell from 17.8 per 10 000 births in 1980 to 4.4 in 1994 (χ^2 for linear trend = 55.1, df=1, $p < 0.0001$). In contrast, the trend had not significantly changed for encephalocoele during the 15 year period, at 1.5/10 000 births in 1980 and 1.65/10 000 births in 1994. The spina bifida/anencephaly ratio for the 15 year period was 1.3 (419/322), the ratio of encephalocoele to other NTDs was 0.09 (69/752).

Figure 2 shows the rate of NTD with 95% confidence intervals for mothers in a range of age groups. The risk of having an NTD affected child decreased with age (χ^2 for linear trend = 9.6, df=1, $p < 0.01$). The trends among the different types of NTD were similar; there was a decreasing prevalence of spina bifida as the mothers age at delivery increased (χ^2 for linear trend = 7.9, df=1, $p < 0.01$); the same trend was also evident for anencephaly, although it was not statistically significant. There was no association between the rate of NTD and marital status.

We examined the relation between the rate of NTD and parity of the mother for the eight year period 1987-1994 (data on parity before 1987 were incomplete). There was no significant trend for NTD and increasing parity. The birth prevalence rate of NTD during the period was 16.3/10 000. Figure 3 shows the rate for different categories of mother's parity.

Sixteen NTD cases were births from twin pregnancies. Using national data on twinning, the risk of a child of a twin birth having NTD was estimated at 1:441 (22.7/10 000) compared with 1:389 (25.6/10 000) for singleton births (NS). Of the NTD affected twins, 10 had spina bifida, four were anencephalic and two had encephalocoele. The sex of the non-NTD affected twin was available for 12 of the twin sets; all except one child was of the same sex as its sibling. One pair of twins (both female) was concordant for spina bifida. All twins except one (anencephalic) were live births.

Table 1 shows the characteristics of cohorts of the different types of NTD. The female to

Table 1 Characteristics of cohorts of the different types of NTD registered 1980-1994

| | Spina bifida (n=419) | Anencephaly (n=322) | Encephalocoele (n=69) | Iniencephaly (n=11) | p value |
|-------------------------|-------------------------|------------------------|--------------------------|------------------------|---------|
| Sex ratio (female/male) | 1.1 | 2.1 | 1.2 | 1.1 | <0.001 |
| % Birth weight <2500 g | 14.7 | 81.5 | 29.3 | 93.8 | <0.001 |
| % <37 weeks gestation | 14.0 | 55.0 | 36.0 | 71.0 | <0.01 |
| Maternal age: 35+ years | 9.0 | 9.0 | 12.0 | 19.0 | NS |
| % Stillbirths | 10.0 | 58.0 | 22.0 | 87.0 | <0.001 |

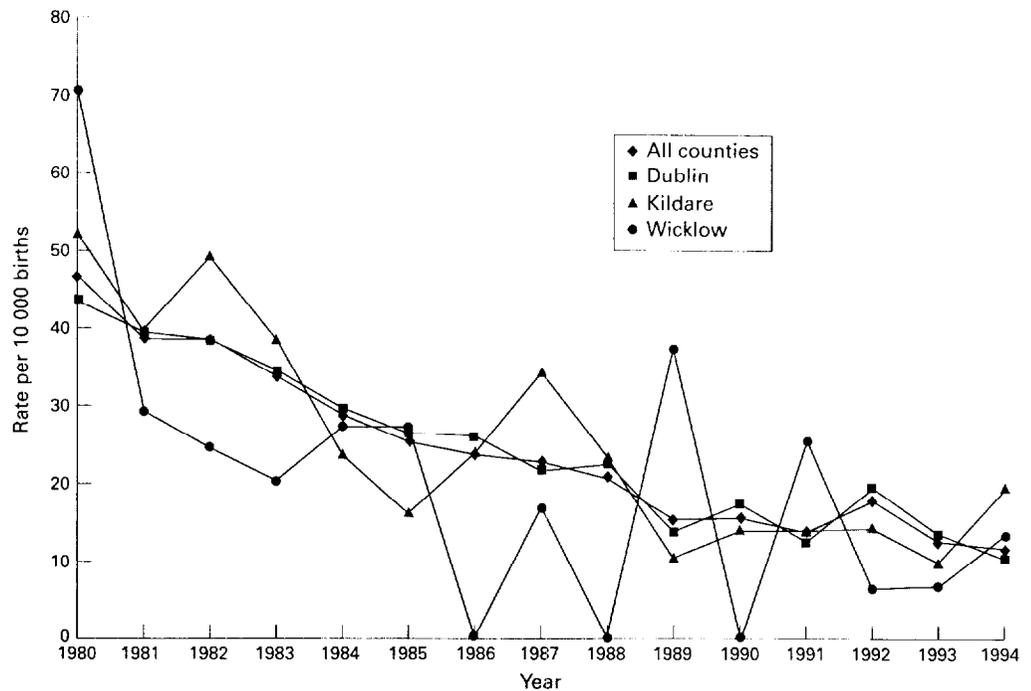


Figure 4 NTD in counties Dublin, Kildare and Wicklow 1980–1994.

male sex ratio was significantly higher for anencephalics and iniencephalics compared with spina bifida and encephalocele. There were also significant differences between the type of NTD with regard to the proportions who were stillborn, born before 37 weeks gestation and who had a birth weight less than 2500 g. There was little difference between the proportion of mothers aged over 35 years at delivery and the different types of NTD.

The NTD rate among mothers in manual SEGs (26.3/10 000, 95% CI 23.3, 29.3) did not differ significantly from that of the non-manual group (22.4/10 000, 95% CI 20.2, 24.8). Seasonal variation in the birth prevalence of NTD during the 15 year period was observed. Birth prevalence of NTD was higher in the January–June period at 28.0/10 000 compared with a rate of 23.2/10 000 during July–December. Although Freedman's test for any deviation from a uniform incidence was significant ($p < 0.05$), the Ratchet circular scan test and Edwards' test did not reach significance. The peak prevalence occurred in April. When the data were examined by five year periods, a seasonal effect was only observed during the period 1985–89; the Ratchet circular scan test and Edwards' test were significant ($p < 0.05$) with the peak prevalence in May, and Freedman's test was also significant ($p < 0.05$).

In 40 of the NTD cases, there was a previous family history of NTD in siblings. The total number of siblings of these cases was 1865 giving a precurrence rate for NTD of 2.1% (40/1865), corresponding to a rate of 214/10 000 siblings. In 57 of the NTD cases there were other siblings previously affected with a congenital anomaly (including NTD) giving a precurrence rate for all congenital anomaly of 3.1% (57/1865).

The number of NTD affected births in counties Dublin, Kildare and Wicklow during the period 1980–1994 were 668, 96 and 57 respectively with corresponding prevalences per 10 000 births of 25.8 (95% CI 23.9, 27.8) for Dublin, 27.0 (95% CI 21.6, 32.5) for Kildare, and 21.5 (95% CI 15.9, 27.1) for Wicklow. Figure 4 shows the trend in NTD birth prevalence in each county. The Wicklow rate showed considerable year to year variation, particularly from 1986–1991 but the overall rate did not differ significantly from counties Dublin and Kildare combined. There was a significant downward trend from 1980–1994 for Dublin (χ^2 for linear trend=104, $df=1$, $p < 0.001$) and Kildare (χ^2 for linear trend=17.8, $df=1$, $p < 0.001$) but not for Wicklow.

Of the 821 NTD cases in the study, there were 184 (22.4%) cases with additional non-central nervous system (non-CNS) anomalies recorded; 113 had one additional anomaly, 29 had two and 42 had three or more. The total number of anomalies for all cases was 326, table 2 shows the main categories of additional anomaly. Cystic anomalies (16/48) and renal agenesis/dysgenesis (14/48) were the most frequent kidney anomalies recorded and the most frequent cardiovascular anomaly was ventricular septal defect (9/35). Nineteen cases

Table 2 Most frequent non-CNS additional anomalies

| Additional anomaly | Number | % Of total anomalies |
|--|--------|----------------------|
| Anomalies of the kidneys/urinary tract | 48 | 14.7 |
| Anomalies of cardiovascular system | 35 | 10.7 |
| Abdominal wall anomalies | 19 | 5.8 |
| Lung anomalies | 18 | 5.5 |
| Anomalies of the diaphragm | 16 | 4.9 |
| Intestinal anomalies | 15 | 4.6 |
| Congenital dislocation of hip (unilateral) | 12 | 3.7 |

Table 3 Most frequent sole source of ascertainment for NTD types

| Ascertainment source | Spina bifida (n=73) | | Anencephaly (n=64) | | Encephalocele (n=27) | | All NTD (n=164) | |
|----------------------|---------------------------------|------------------------------|---------------------------------|------------------------------|---------------------------------|------------------------------|---------------------------------|------------------------------|
| | % Ascertained if source omitted | % Ascertained if only source | % Ascertained if source omitted | % Ascertained if only source | % Ascertained if source omitted | % Ascertained if only source | % Ascertained if source omitted | % Ascertained if only source |
| Birth notification | 94.5 | 68.5 | 78.1 | 79.7 | 92.6 | 74.1 | 87.8 | 73.8 |
| Acute hospitals | 95.9 | 60.3 | 100 | 0 | 81.5 | 48.2 | 95.1 | 34.8 |
| Pathology/laboratory | 94.5 | 37.0 | 90.6 | 56.3 | 100 | 29.6 | 93.9 | 43.3 |
| Neonatal units | 97.3 | 28.8 | 95.3 | 20.3 | 96.3 | 14.8 | 96.3 | 23.2 |

of NTD had abdominal wall anomalies, for example, omphalocele or gastroschisis. There was no significant difference between children born with NTD alone and those with additional anomalies with regard to sex, the proportion weighing under 2500 g, the proportion born before 37 weeks gestation or the proportion who were stillborn.

Information on source of ascertainment for each NTD case was available for the period 1989–1994 only. There were 164 cases of NTD during this six year period. In 26.8% (44/164) there was one sole source of ascertainment. Table 3 shows the percentage ascertainment from different sources. As a sole source of ascertainment, birth notification provided a higher percentage of cases than any of the other sources. No cases of anencephaly were ascertained through acute hospitals whereas 60.3% of spina bifida cases were ascertained through this source.

Discussion

Our study is population based and covers a 15 year period of NTD affected births in a defined geographical region in the east of Ireland with a combined population of 1.3 million (one third of the population of the state). Previous studies of the epidemiology of NTD in Ireland have primarily been hospital based on births in Dublin maternity hospitals using the total number of births in the hospitals as the denominator. A retrospective study of anencephaly and spina bifida¹² during the years 1953–54 and 1961–82 showed a decreasing trend in NTD from 85.4/10 000 in 1954 to 38.0 in 1982. Another study¹³ found an incidence of 65/10 000 in the period 1970–75. Although hospital based, these studies use similar definitions of NTD, and their findings generally concur with our study, reflecting a fall in the rate of NTD from the very high levels seen before 1980 to the lower rates of the early 1990s. Another Dublin hospital based study of spina bifida alone¹⁴ for the period 1966–77 showed an incidence of 39/10 000 for spina bifida, but included spina bifida occulta and isolated hydrocephalus in their definition of NTD. There is little information on rates of NTD in other parts of the country, apart from that available from the Galway EUROCAT register,² with an NTD rate of 19.3/10 000 births during the same study period as ours. A previous hospital based study¹⁵ in the same region showed an incidence of 29.6/10 000 births for the period 1974–85. A population based study¹⁶ of NTD covering the five year period 1979–84 using early EUROCAT data showed an NTD birth prevalence of 39/10 000

births; the data used are included in the 15 year period covered by our study.

The “Celtic” countries of the British Isles have had a much higher prevalence of NTD during the past 16 years compared with other European countries.² Although the birth prevalence of NTD has been falling in European and other developed countries^{2 17 18} since the early 1980s, partly attributable to prenatal diagnosis of NTD and selective termination, the total prevalence of NTD (including live births, stillbirths and terminations) has remained relatively stable. This has not been the case in the British Isles.² The dramatic fall in the birth prevalence of NTD shown in our study is likely to be real and not influenced by pre-natal diagnostic practises as termination of pregnancy in Ireland is not legally permissible. Residents may travel outside the state to obtain a termination, however, the numbers taking this route are very small (personal communication, National Statistics Office, London) and unlikely to have influenced the overall prevalence during the study period. The absence of pre-natal screening/termination of pregnancy in Ireland allows description of the epidemiology of NTD under “natural” conditions. Such a study would not be possible in other European countries where termination of pregnancy is legal. The decreasing trend in NTD prevalence observed was most dramatic before the introduction of campaigns in the early 1990s aimed at increasing folic acid intake among women of childbearing age. A similar fall in total prevalence of NTD has also been reported in other Celtic areas of the British Isles. It is unclear why there has been such a marked decline in NTD rates in Ireland since the early 1980s and what environmental factors, if any, may have been responsible or contributed to it. There are no reliable data available on the use of vitamin supplements by women in Ireland before 1995. Changes in patterns of dietary intake over the past 30 years associated with economic prosperity and all year round availability of foods such as vegetables (particularly those containing folic acid) may have had some influence. Overall vegetable consumption increased rapidly in the late 1970s and fell off in the early 1980s before rising again; however, Ireland is still one of the lowest vegetable and fruit consumers in the European Union.¹⁹ The major producer of breakfast cereals in Ireland began fortifying all their cereals with folic acid since 1987 (personal communication, Kellogg's, UK).

Our study also showed a higher risk of NTD among younger mothers as has been observed in other studies,^{20 21} this may in part be

attributable to a lower folic acid content in diets of younger women; a national nutrition survey²² in Ireland in 1990 showed a lower daily folate intake among women aged less than 25 years than those aged 25 to 40 years (the daily folate intake of women over 40 years of age was also lower).

The spina bifida to anencephalic ratio and the encephalocele to all NTD ratio are similar to those reported previously for the British Isles as a whole.²¹ The predominance of female anencephalic births over males in our study is similar to that seen in other countries and likewise the slight female predominance in spina bifida births. Not surprisingly, anencephalic and iniencephalic affected births had the worst outcome in terms of the proportions who were stillborn and low birthweight, consequent on the severe and lethal nature of the abnormality. Although the non-manual SEGs had a lower rate of NTD in our study, this was not significant. Studies elsewhere have shown lower rates among those where the father's work was non-manual.^{20 21 24}

We defined the index case as that which was ascertained and registered in the Dublin EUROCAT registry, although some of these had siblings born with NTD before the establishment of the registry. We therefore calculated precurrence rates rather than recurrence rates for NTD cases. The precurrence rate of NTD among family siblings at 2.1% was higher than that seen in a study of precurrence of congenital anomaly in southern Belgium²⁵; Elwood, Little and Elwood²⁴ cite a general precurrence rate in Europe of 4.6% and that precurrence and recurrence rates do not significantly differ.

Previous research has shown a predominance of NTD births in the winter months^{26 27} particularly in October to December and January to March in the British Isles. This contrasts with a peak in April/May in our study that seems to have been determined by the significant variation during the five year period 1985-89, without much seasonal variation during the other five year periods. However, these results should be interpreted with caution as there is an overall long term downward trend in the data. In a previous Irish study²⁸ an April peak was also observed.

There was substantial fluctuation in the rate of NTD in two of the three counties—that is, Kildare and Wicklow. In some years, no NTD births were recorded in Wicklow. However, each year Dublin has approximately four times the number of births of the other two counties combined and the NTD birth prevalence in Dublin therefore was the major determinant of the overall trend for the three counties combined.

The importance of using multiple sources of ascertainment is demonstrated by the finding that more than half of spina bifida cases were ascertained through acute hospitals; in contrast, no cases of anencephaly were ascertained from this source. This is likely to be a consequence of anencephaly being easily identifiable at birth with its associated high mortality, whereas cases of

spina bifida may be admitted to acute hospitals for care before ascertainment to the registry.

By the mid-1990s the birth prevalence of NTD in this region of Ireland seems to have levelled off at a rate that is still higher than that of many European regions. Our research team found in 1997 that 16% of pregnant women were taking peri-conceptual folic acid.²⁹ The protective effect of folic acid in the prevention of recurrence³⁰ and primary occurrence^{31 32} of NTD has been demonstrated previously. Therefore, if peri-conceptual folic acid use increased to 100%, we could expect a substantial fall in the number of NTD cases in Ireland. It is essential that all women are aware of the importance of peri-conceptual folic acid and are taking it. Fortification of staple foodstuffs in Ireland is under urgent consideration also, as an effective way of increasing folate intake.

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Conflicts of interest: none.

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EXHIBIT 7

colleagues' note, analysis of data from other laboratories could support or counter these findings.

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Sir—Jean Lawrence and colleagues' report that blood folate concentrations have increased in the USA after folic acid fortification of enriched grain products. Their findings are consistent with those recently reported by Jacques and colleagues.² Both groups attribute these trends to folic acid fortification, which is believed to have been implemented by mid-1997. Although these findings are encouraging, to date we have seen no studies that examine the potential effects of fortification on the prevalence of NTDs. We present here an early assessment of the birth prevalence of NTDs after fortification.

From the North Carolina Birth Defects Monitoring Program, a population-based surveillance programme that covers about 100 000 live births per year, we identified 361 liveborn and stillborn infants with NTDs who were delivered between Jan 1, 1995, and Dec 31, 1998. We matched case records with North Carolina vital statistics files and used the reported date of last menses to estimate the date of conception for each case. Rates of NTDs were calculated on the basis of the date of conception by dividing the number of cases conceived during a given period by the total number of liveborn infants whose conception occurred during that time. NTD rates for the 36 months immediately before fortification (July, 1994, to June, 1997) were used to predict the rates among conceptions occurring after fortification began (July, 1997, to March, 1998).

A slight downward trend in the rate of total NTDs (from 10.2 to 7.5 per 10 000 live births) and spina bifida (from 6.0 to 4.4 per 10 000 live births) was seen for conceptions occurring during the 36-month prefortification

period, whereas the rate for anencephaly remained constant (2.2 per 10 000 live births). Among fetuses conceived during the 9 months after fortification, we found very little difference between the observed and expected rates of total NTDs, anencephaly, and spina bifida. In fact, the rate for fetal NTDs increased to 7.9 per 10 000 live births after fortification.

Folic acid fortification in the USA was predicted to increase the average woman's consumption of folic acid by only 100 µg per day, or a quarter the amount recommended for birth-defect prevention.³ Our early findings, which show no evidence of a change in NTD trends after fortification, support the assertion that the current fortification concentration in the USA is too low for full prevention of birth defects. We continue to monitor these trends and will reassess the situation in the future. However, on the basis of our data, we cannot assume that the increased post-fortification blood folate concentrations reported in the studies by Lawrence et al,¹ and Jacques et al,² are any indication that fortification has led to a decline in NTD rates.

Seldom do we have an opportunity to implement a cheap, simple, and safe public-health programme that can present severe, life-altering conditions such as spina bifida and anencephaly. To improve the health of children, governments should immediately implement fortification programmes that will increase consumption of folic acid by at least 400 µg a day. Until such programmes are implemented, we should teach women of reproductive age to consume daily vitamin supplements containing 400 µg of synthetic folic acid.

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Shifts in mortality curves

Sir—L B Tan and R Murphy's review (Oct 16, p 1378)¹ on presentation of trial mortality data is both highly relevant and timely in the context of current medical practice. With the onslaught of evidence-based medicine derived from large randomised trials, the practice of medicine is becoming more dogmatic. As Tan and Murphy state, there is substantial public and peer pressure to prescribe drugs that are widely reported as being beneficial. For the practising clinician, it is difficult to distinguish between statistical benefit and clinical relevance of a specific therapeutic agent, as reported in trials. Thus, knowledge of the extra time gained with an improved quality of life will certainly help patients and clinicians to decide whether a drug should be taken daily for the rest of the patient's life. Further, drugs carry costs and may have adverse effects, including death.

Undertaking of a trial with wide entry criteria to show the benefits of a drug can only produce findings relevant to the specific trial population that are valid only for the duration of the trial. The "law of averages" is at work here. If a specific drug benefits more patients than it harms, then this drug would be of positive value, and its prescription is encouraged. The entry criteria for the trial then determine which patients get the new treatment, but these criteria may not identify whether a therapeutic agent would benefit a particular patient on an individual basis. In this traditional approach, a patient is told that if he or she takes a drug, and if there are x number of other patients doing the same for y length of time, then z number of lives would be saved within the timeframe. The drawback is that there is no way of telling whether this patient will be one of the z patients. This is a pressing issue when x and y are large, with a small z and the disease is chronic. We should be putting more effort into the classification of patients before drug initiation, and the development of more objective measures to assess and monitor both the beneficial and harmful effects of drugs.

This difficulty is especially acute in chronic heart failure in which each new therapy (angiotensin-converting enzyme inhibitor, β -blocker, angiotensin II antagonist, and so on) causes a further fall in the patient's already low blood pressure. This difficulty may force us into more tailoring of therapy to the individual. For example, we reported that angiotensin-converting enzyme inhibitors only enhance

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adenovirus during a fatal outbreak of enterovirus-71-associated hand, foot, and mouth disease in Sibul, Sarawak. *Lancet* 1999; 354: 987-91.

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Cluster headache and melatonin

Sir—J N Blau and H O Engel (Sept 18, p 1001)¹ describe a new cluster-headache precipitant—increased body heat, from the environment, a hot bath, or central heating in 52 (26%) of 200 patients, and from exercise in 23 (12%) patients (three by sexual intercourse).

The causes of cluster headache are still unknown; the temporal pattern of the cluster periods suggest the involvement of central structures in particular the hypothalamus, which regulates circadian rhythms. The pineal gland through melatonin secretion plays a central part in the circadian organisation of biological rhythms. Evidence obtained in animals suggests that the pineal gland and melatonin may be related to the regulation of core body temperature. Dependent on the species considered, melatonin has a part in the generation of seasonal rhythms of daily torpor and hibernation, in heat stress tolerance, and in setting the core body temperature set point. In human beings, the circadian rhythm of melatonin is closely associated with that of core body temperature, the nocturnal decline of this temperature being inversely related to the rise of melatonin.²

Chazot and colleagues³ reported lower melatonin concentrations in cluster-headache patients than in controls. Waldenlind and colleagues⁴ also show lower concentrations in the cluster period than remission.

Increased body heat might precipitate cluster-headache attacks by alteration of melatonin concentrations, leading to hypothalamic dysregulation and chronobiological dysfunction. These findings also support a therapeutic option of

melatonin in the prophylaxis of cluster headache.⁵

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Folate supplementation and neural-tube defects

Sir—L Abramsky and colleagues (Sept 18, p 998)¹ report a high rate of neural-tube defects (NTDs) in the UK population in 1996-98, despite a national campaign to encourage supplementation with folic acid in the prenatal period. Our data from a population at risk over the same period suggest that poor compliance with preconceptional or antenatal folate supplementation, in conjunction with a low folate intake, remains a major hurdle.

Mothers in the west of London have a high rate of NTDs, in particular those in the Indian or Pakistani population, in whom serum concentrations of folate are low.² A direct-questioning survey of 1357 women in a west London antenatal clinic from January to May, 1998, showed that 380 (28%) had not taken folic acid supplements before attendance at the clinic. 285 of these women were of Indian or Pakistani origin and 323 were primiparous. None of the women was aware of the benefits of the vitamin supplement. In 1998 there were no live deliveries of NTDs from the clinic, since all were diagnosed antenatally by ultrasonography. There were six terminations for NTDs; four from primiparous pregnancies, five in women of Indian or Pakistani origin (three with English as a second language). Only three women

who had a termination had taken some antenatal folic acid. This lack of compliance with antenatal folic acid is not surprising because a UK study has shown that if English is a mother's second language, the idea of antenatal care is not always understood.³

There are no other obvious factors other than folate deficiency that might increase the rate of NTDs in the west London population. None of the families with an NTD in 1998 was consanguineous. There was no indication of a poor zinc intake, and the rate of mutations in the methylenetetrahydrofolate reductase gene are thought to be similar to that in Caucasian populations. Folate concentrations have proved lower by other investigators in London in the Indian or Pakistani ethnic group, suggesting that this should be the main target for treatment.³

How might this situation be improved? Intervention with food fortification with folic acid was effective in raising serum folate and reducing serum homocysteine in an American study.⁴ This approach overcomes the complications of local dietary custom and periconceptional planning, but it may be difficult to ensure an adequate intake of folic acid in all mothers. We propose implementing a local strategy with both food supplementation of specific foods and an educational campaign. A lack of behavioural change after a recent folate promotion campaign has been documented in Virginia, USA, so the difficulties in London are not unique.⁵ The public-health approach to recent folate supplementation is important as a cardioprotective measure and a method to reduce NTDs; it merits careful consideration and more debate.

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EXHIBIT 9

Time trends in neural tube defects prevalence in relation to preventive strategies: an international study

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Abstract

Objective—To examine time trends in neural tube defects (NTD) prevalence from 1987 to 1996 in relation to the primary prevention policies for folic acid supplementation strategies in different countries.

Design—Retrospective time trends analysis of NTD prevalence.

Setting—11 birth defect registries of congenital malformations participating in the International Clearinghouse for Birth Defects Monitoring System, in the period from 1 July 1987 to 30 June 1996.

Subjects—8207 live births, stillbirths and terminated pregnancies affected by anencephaly or spina bifida registered by the 11 participating centres 1987–1996.

Outcome measures—Prevalence rate ratios based on the annual rates, using the Poisson regression model.

Results—During the study period a significant fall in prevalence rates for all NTD is present in Atlanta (USA), England and Wales, Hungary and Japan, and a significant rise in Norway and South America. After adjusting for the secular trends observed in the earlier years of the study, no significant trend can be attributed to preventive strategies. Data on NTD prevalence are supplemented with information on folate awareness among some of the populations studied.

Conclusion—There is no evidence that, up to the middle of 1996, any change in time trend was attributable to the introduction of national folate supplementation policies. The possible effectiveness of folate supplementation policies for the reduction of NTD clearly needs to be tried and studied for several more years. Considering that in the Western world about 50% of pregnancies are unplanned, a policy that rests on action taken before conception can only have limited success. Strategies based on food enrichment, such as was introduced in the USA from the beginning of 1998, may prove to be more successful.

(*J Epidemiol Community Health* 1999;53:630–635)

support to the hypothesis that folic acid supplements, either alone or in multivitamin preparations, could prevent a high proportion of NTD if taken before and during early pregnancy.^{2,3} The strongest support for the hypothesis came from two large, randomised studies. The UK Medical Research Council⁴ showed that folic acid, 4 mg daily, gave significant protection against recurrences of NTD. Czeizel and Dudas⁵ showed that a multivitamin preparation containing folic acid 0.8 mg protected against the first occurrence of NTD.

After these publications, government health departments in a number of countries began to consider how this new knowledge might be put to practical use by developing public health policies relating to folic acid supplementation.

The purpose of this study, which was carried out by the International Centre for Birth Defects (ICBD) in collaboration with the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS), was to examine time trends in NTD prevalence in relation to folic acid supplementation strategies in different countries.

Methods

Our inquiries into the extent of folic acid supplementation were related to three questions:

- 1 Is there a national policy on folate supplementation?
- 2 If so, how effectively is it being implemented?
- 3 Whether or not there is a national policy, what is actually happening? Are women being encouraged, by health personnel or the mass media, to increase their folic acid intake? How aware are women of folic acid and its relevance to fetal development?

Several of the countries represented by the programmes participating in this study promulgated national policies at different times during the course of this study. In some of these, studies have been undertaken to determine the extent to which their policies are being implemented. To augment this information, the directors of participating programmes were asked to undertake at least one, and preferably two, "folate awareness surveys" to determine what women of childbearing age knew about folic acid, and how many had taken steps to increase their folic acid intake, by taking vitamin pills, by changing their diet, or both, before starting a pregnancy.

Our study of time trends in NTD prevalence was based on birth registries in ICBDMS. This

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A possible link between folic acid deficiency and neural tube defects (NTD) in humans was first proposed by Hibbard and Smithells.¹ Throughout the 1980s, a number of observational and intervention studies gave strong

Table 1 Cases of NTD by registry and period

| Programme | Period covered | No of births monitored | NTD cases | | |
|----------------------|----------------|------------------------|---------------------------|-------------------|-------|
| | | | Live births + stillbirths | Induced abortions | Total |
| England and Wales | 1988-96 | 6 500 000 | 1042 | 3055 | 4097 |
| France, Central East | 1987-96 | 955 000 | 192 | 305 | 497 |
| France, Paris | 1987-96 | 380 000 | 53 | 275 | 328 |
| France, Strasbourg | 1987-95 | 120 000 | 15 | 80 | 95 |
| Hungary | 1987-96 | 1 150 000 | 412 | 51 | 463 |
| Israel | 1988-96 | 28 000 | 16 | 0 | 16 |
| Japan | 1988-96 | 1 110 000 | 752 | 0 | 752 |
| North Netherlands | 1988-96 | 169 000 | 122 | 35 | 157 |
| Norway | 1987-96 | 568 000 | 289 | 103 | 392 |
| South America | 1988-96 | 748 000 | 1208 | 0 | 1208 |
| USA, Atlanta | 1988-96 | 350 000 | 167 | 35 | 202 |
| Total | | 12 078 000 | 4268 | 3939 | 8207 |

was founded in 1974, and links a group of birth defects registries that have reliable records of the prevalence of all major congenital anomalies in the populations they cover. Some are based on defined geographical populations, others on births in one or more hospitals. Their methodologies are not identical but do not change over time, so year on year comparisons of prevalence rates are valid.

Monitoring programmes included in this study fall into two categories:

- 1 Those that have data on induced abortions for NTD.
- 2 Those in countries where induced abortion for birth defect is illegal.

Programmes in countries that permit induced abortions but that do not have access to the relevant data have been excluded. The aim of this was to limit the study to registries including all cases of NTD that would have been born if no legal induced abortions had taken place.

For the purposes of this study, NTD were defined as anencephaly and spina bifida. Cases in which the two conditions coexist are classified as anencephaly—that is, no infant or fetus is counted twice.

The time period covered was from 1 January 1988 to 30 June 1996 for live and still births. Induced abortions were recorded from 1 July 1987 to 31 December 1995 on the basis that, had they not been aborted, they would have been born, on average, about six months later. If the gestational age of an aborted fetus was known, a theoretical date of birth was calculated. Time trends were calculated from these data.

Annual time trends were analysed using a regression model. As we are interested in the relation between the number of cases per year over a period of time, allowing for possible confounding factors, the most suitable model is the Poisson regression model.⁶

Using different Poisson models, we estimated the average annual variation in prevalence rates 1988-96 (table 2) and the ratio between the prevalence rates in the two periods before and after 1994, when the folate policies might have begun to produce effects (table 3). However, such ratios do not distinguish the real effect of the policies from the general trend of NTD occurrence. For this purpose we estimated the ratios adjusted for the effect of long term tendency (table 4). The results are

expressed in terms of prevalence rate ratio (PRR). Values of PRR>1 indicate an increase, values of PRR<1 indicate a decrease. (For further statistical details, see appendix)

Results

INQUIRIES INTO FOLATE SUPPLEMENTATION

National policies on folate supplementation for prevention of NTD

Recommendations on folate supplementation for the prevention of NTD were first promulgated to the public and the health professions in the USA in September 1992, followed by England and Wales in December 1992. Similar recommendations were made in the Netherlands in November 1993. Hungary followed suit in September 1995. In Israel, a national policy was agreed but was thought not to have been implemented before the end of the study period. Up to that time, Japan, Norway, France and South America had not adopted any national policies on supplementation.

Folate awareness

The existence of a national policy on folate supplementation does not mean that it is necessarily being implemented, or to what extent. The absence of a national policy does not necessarily mean that the public and health professions are not informed about the use of folic acid to prevent NTD and are not using it for this purpose. An attempt was therefore made by most of the participating programmes to determine from representative samples of women of childbearing age (in many cases, women attending antenatal clinics) their knowledge and use of folic acid for NTD prevention.

England and Wales—A number of studies have been carried out by Sutcliffe,⁷ Clark and Fisk⁸ and Wild.⁹ These showed very low levels of awareness in the year after national recommendations had been promulgated, with a significant improvement thereafter. Three studies in the city of Leeds showed that in 1993, 11 (1.8%) of 613 women interviewed at their first antenatal clinic attendance had taken folic acid before conception. The following year this figure had risen to 110 (18.2%) of 603 comparable women. By 1996 the number had increased to 208 (30.6%) of 679 women. (Wild 1997, personal communication)

France—A study in Paris in 1995,¹⁰ showed that 68 (9.3%) of 733 women in maternity hospitals had taken folic acid before pregnancy or during the first month. In 58 of these cases (85%) the folic acid was prescribed by a doctor.

Hungary—Of 105 women interviewed in 1992, seven (6.7%) had taken multivitamins that included folic acid before conception.¹¹ None had taken folic acid alone. It should be mentioned, however, that Hungary contributed the largest number of women of any country participating in the UK Medical Research Council study¹ on prevention of NTD recurrence, and was the location of the only randomised study of prevention of first occurrence of NTD.² The preventive role of folic

Table 2 Time trend analysis: cases and rates by registry and by year—Anencephaly

| Registry | Year | | | | | | | | | | | | | | | | | | PRR† (95% CI) | | |
|---------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------------------|-------|----------------------|
| | 1988 | | 1989 | | 1990 | | 1991 | | 1992 | | 1993 | | 1994 | | 1995 | | 1996 | | | Total | |
| | cases | rates | | cases | rates |
| England and Wales | 298 | 4.28 | 248 | 3.59 | 258 | 3.64 | 241 | 3.43 | 231 | 3.34 | 221 | 3.26 | 209 | 3.13 | 203 | 3.12 | 79 | 2.42 | 1988 | 3.42 | 0.95 (0.94, 0.97) |
| France-Central East | 14 | 1.53 | 18 | 1.80 | 22 | 2.04 | 24 | 2.24 | 23 | 2.19 | 23 | 2.31 | 25 | 2.51 | 17 | 1.67 | 7 | 1.34 | 173 | 2.00 | 1.01 (0.95, 1.07) |
| France-Paris | 18 | 4.37 | 14 | 3.35 | 22 | 5.22 | 26 | 6.16 | 21 | 5.12 | 13 | 3.23 | 15 | 3.71 | 22 | 5.45 | 5 | 4.96 | 156 | 4.60 | 1.01 (0.94, 1.08) |
| France-Strasbourg | 5 | 3.68 | 6 | 4.47 | 8 | 5.81 | 8 | 5.81 | 11 | 8.01 | 7 | 5.32 | 5 | 3.86 | 6 | 4.62 | | | 56 | 5.21 | 1.01 (0.91, 1.13) |
| Hungary | 25 | 2.00 | 13 | 1.05 | 13 | 1.03 | 26 | 2.03 | 3 | 0.25 | 4 | 0.34 | 10 | 0.86 | 10 | 0.89 | 3 | 0.53 | 107 | 1.04 | 0.86 (0.80, 0.94) |
| Israel | 1 | 2.69 | 2 | 5.01 | 2 | 5.34 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 1 | 3.55 | 1 | 7.39 | 7 | 2.54 | 0.92 (0.68, 1.26) |
| Japan | 89 | 6.43 | 67 | 5.73 | 63 | 5.46 | 56 | 4.61 | 36 | 3.48 | 32 | 2.84 | 39 | 3.43 | 30 | 2.91 | 7 | 1.58 | 419 | 4.32 | 0.87 (0.84, 0.91) |
| North Netherlands | 9 | 7.75 | 3 | 1.57 | 4 | 2.04 | 5 | 2.52 | 3 | 1.57 | 6 | 3.09 | 3 | 1.55 | 6 | 3.13 | 2 | 2.09 | 41 | 2.61 | 0.92 (0.81, 1.05) |
| Norway | 16 | 2.76 | 16 | 2.67 | 12 | 1.95 | 15 | 2.45 | 20 | 3.31 | 14 | 2.33 | 24 | 3.97 | 21 | 3.46 | 6 | 1.93 | 144 | 2.80 | 1.03 (0.97, 1.10) |
| South America | 29 | 6.64 | 36 | 7.40 | 47 | 7.62 | 39 | 4.90 | 86 | 8.63 | 96 | 8.15 | 99 | 8.53 | 95 | 8.55 | 60 | 8.50 | 587 | 7.84 | 1.04 (1.00, 1.08) |
| USA-Atlanta | 12 | 3.27 | 7 | 1.84 | 9 | 2.32 | 9 | 2.35 | 8 | 2.09 | 11 | 2.81 | 3 | 0.75 | 9 | 2.26 | 6 | 2.98 | 74 | 2.25 | 0.96 (0.88, 1.06) |
| Total | 516 | | 430 | | 460 | | 449 | | 442 | | 427 | | 432 | | 420 | | 176 | | 3752 | | |

*Note: 71 terminated cases from England and Wales, 4 from France-Central East and 5 from France-Paris were excluded because their calculated date of birth was outside the considered period 1.1.88-30.6.96. †PRR = Prevalence rate ratio for annual change according to Poisson regression model.

acid was therefore very well known and had received a good deal of publicity through the media.

Netherlands—A survey of 485 women in their first pregnancies was carried out in 1994, the year after the publication of official advice, and showed that four (0.8%) had taken folic acid during the recommended period.¹² Further surveys were carried out in 1995 and 1996, before and after a national campaign publicising folic acid. In 1996, 96% of well educated women had heard of folic acid, 89% before conception. The corresponding figures for less well educated women were 80% and 64%. These figures were all higher than in the 1995

survey. Folic acid had been taken for the recommended period by 32% of well educated women and 17% of less well educated women. The corresponding figures in 1995 were 10% and 2% (De Walle 1997, personal communication).

South America—A survey of 491 women was carried out in 1996 and showed that about 1% had taken folic acid in the first month of pregnancy.¹³

United States—A survey carried out in South Carolina in 1992-1994¹⁴ showed that 6 (8%) of 71 women with a history of previous NTD affected pregnancy had taken folic acid in the periconceptional period. A 1995 study in

Table 3 Time trend analysis: cases and rates by registry and by year—Spina bifida

| Registry | Year | | | | | | | | | | | | | | | | | | PRR† (95% CI) | | |
|---------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------------------|-------|----------------------|
| | 1988 | | 1989 | | 1990 | | 1991 | | 1992 | | 1993 | | 1994 | | 1995 | | 1996 | | | Total | |
| | cases | rates | | cases | rates |
| England and Wales | 324 | 4.65 | 273 | 3.95 | 252 | 3.55 | 275 | 3.92 | 234 | 3.38 | 215 | 3.18 | 167 | 2.50 | 216 | 6.62 | 82 | 2.51 | 2038 | 3.51 | 0.94 (0.92, 0.96) |
| France-Central East | 38 | 4.17 | 20 | 2.00 | 36 | 3.34 | 38 | 3.54 | 37 | 3.53 | 44 | 4.42 | 41 | 4.11 | 47 | 4.61 | 19 | 3.62 | 320 | 3.70 | 1.04 (1.00, 1.09) |
| France-Paris | 11 | 2.67 | 28 | 6.71 | 24 | 5.69 | 12 | 2.84 | 17 | 4.15 | 22 | 5.47 | 23 | 5.70 | 19 | 4.71 | 11 | 10.91 | 167 | 4.92 | 1.05 (0.99, 1.12) |
| France-Strasbourg | 5 | 3.68 | 5 | 3.72 | 4 | 2.90 | 4 | 2.90 | 6 | 4.37 | 5 | 3.80 | 6 | 4.64 | 4 | 3.08 | | | 39 | 3.63 | 1.01 (0.88, 1.16) |
| Hungary | 85 | 6.79 | 61 | 4.92 | 51 | 4.04 | 52 | 4.07 | 25 | 2.05 | 26 | 2.21 | 24 | 2.07 | 18 | 1.60 | 14 | 2.49 | 356 | 3.46 | 0.83 (0.79, 0.87) |
| Israel | 2 | 5.39 | 1 | 2.50 | 1 | 2.67 | 1 | 3.24 | 0 | 0.00 | 1 | 3.37 | 1 | 3.55 | 2 | 7.11 | 0 | 0.00 | 9 | 3.26 | 1.06 (0.81, 1.38) |
| Japan | 41 | 2.96 | 35 | 2.99 | 40 | 3.47 | 39 | 3.21 | 37 | 3.58 | 44 | 3.90 | 36 | 3.17 | 42 | 4.07 | 19 | 4.30 | 333 | 3.44 | 1.04 (0.99, 1.09) |
| North Netherlands | 13 | 11.19 | 14 | 7.33 | 20 | 10.18 | 22 | 11.07 | 14 | 7.30 | 7 | 3.61 | 9 | 4.66 | 10 | 5.22 | 7 | 7.31 | 116 | 7.39 | 0.90 (0.83, 0.98) |
| Norway | 24 | 4.13 | 35 | 5.85 | 25 | 4.07 | 29 | 4.73 | 33 | 5.45 | 17 | 2.83 | 31 | 5.12 | 39 | 6.42 | 15 | 4.82 | 248 | 4.83 | 1.02 (0.97, 1.07) |
| South America | 31 | 7.10 | 31 | 6.37 | 54 | 8.75 | 53 | 6.66 | 69 | 6.93 | 99 | 8.40 | 109 | 9.39 | 122 | 10.98 | 53 | 7.51 | 621 | 8.29 | 1.05 (1.01, 1.09) |
| USA-Atlanta | 20 | 5.46 | 17 | 4.46 | 21 | 5.42 | 14 | 3.66 | 14 | 3.66 | 13 | 3.33 | 17 | 4.27 | 6 | 1.51 | 6 | 2.98 | 128 | 3.89 | 0.90 (0.84, 0.97) |
| Total | 594 | | 520 | | 528 | | 539 | | 486 | | 493 | | 464 | | 525 | | 226 | | 4375 | | |

*Note: 71 terminated cases from England and Wales, 4 from France-Central East and 5 from France-Paris were excluded because their calculated date of birth was outside the considered period 1.1.88-30.6.96. †PRR = Prevalence rate ratio for annual change according to Poisson regression model.

Table 4 Time trend analysis: cases and rates by registry and by year—Anencephaly and Spina bifida

| Registry | Year | | | | | | | | | | | | | | | | | | | | PRR† (95% CI) |
|---------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|----------------------|
| | 1988 | | 1989 | | 1990 | | 1991 | | 1992 | | 1993 | | 1994 | | 1995 | | 1996 | | Total | | |
| | cases | rates | |
| England and Wales | 622 | 8.93 | 521 | 7.54 | 510 | 7.19 | 516 | 7.35 | 465 | 6.72 | 436 | 6.44 | 376 | 5.63 | 419 | 6.43 | 161 | 4.93 | 4026 | 6.93 | 0.95 (0.93, 0.96) |
| France-Central East | 52 | 5.70 | 38 | 3.80 | 58 | 5.39 | 62 | 5.78 | 60 | 5.72 | 67 | 6.73 | 66 | 6.61 | 64 | 6.27 | 26 | 4.96 | 493 | 5.70 | 1.03 (1.00, 1.07) |
| France-Paris | 29 | 7.04 | 42 | 10.06 | 46 | 10.91 | 38 | 9.00 | 38 | 9.27 | 35 | 8.70 | 38 | 9.41 | 41 | 10.16 | 16 | 15.87 | 323 | 9.52 | 1.03 (0.98, 1.08) |
| France-Strasbourg | 10 | 7.36 | 11 | 8.19 | 12 | 8.71 | 12 | 8.71 | 17 | 12.38 | 12 | 9.13 | 11 | 8.50 | 10 | 7.69 | | | 95 | 8.85 | 1.01 (0.92, 1.10) |
| Hungary | 110 | 8.79 | 74 | 5.97 | 64 | 5.06 | 78 | 6.10 | 28 | 2.29 | 30 | 2.55 | 34 | 2.93 | 28 | 2.49 | 17 | 3.02 | 463 | 4.50 | 0.84 (0.80, 0.87) |
| Israel | 3 | 8.08 | 3 | 7.51 | 3 | 8.02 | 1 | 3.24 | 0 | 0.00 | 1 | 3.37 | 1 | 3.55 | 3 | 10.66 | 1 | 7.39 | 16 | 5.80 | 0.97 (0.78, 1.20) |
| Japan | 130 | 9.40 | 102 | 8.73 | 103 | 8.92 | 95 | 7.82 | 73 | 7.07 | 76 | 6.74 | 75 | 6.60 | 72 | 6.98 | 26 | 5.88 | 752 | 7.76 | 0.95 (0.92, 0.97) |
| North Netherlands | 22 | 18.94 | 17 | 8.90 | 24 | 12.21 | 27 | 13.58 | 17 | 8.87 | 13 | 6.70 | 12 | 6.21 | 16 | 8.36 | 9 | 9.40 | 157 | 10.01 | 0.91 (0.85, 0.97) |
| Norway | 40 | 6.89 | 51 | 8.52 | 37 | 6.03 | 44 | 7.18 | 53 | 8.76 | 31 | 5.16 | 55 | 9.09 | 60 | 9.88 | 21 | 6.75 | 392 | 7.63 | 1.02 (0.98, 1.07) |
| South America | 60 | 13.74 | 67 | 13.77 | 101 | 16.37 | 92 | 11.57 | 155 | 15.56 | 195 | 16.55 | 208 | 17.92 | 217 | 19.53 | 113 | 16.01 | 1208 | 16.14 | 1.04 (1.02, 1.07) |
| USA-Atlanta | 32 | 8.73 | 24 | 6.30 | 30 | 7.74 | 23 | 6.01 | 22 | 5.76 | 24 | 6.14 | 20 | 5.02 | 15 | 3.77 | 12 | 5.97 | 202 | 6.14 | 0.93 (0.88, 0.98) |
| Total | 1110 | | 950 | | 988 | | 988 | | 928 | | 920 | | 896 | | 945 | | 402 | | 8127 | | |

*Note: 71 terminated cases from England and Wales, 4 from France-Central East and 5 from France-Paris were excluded because their calculated date of birth was outside the considered period 1.1.88–30.6.96. †PRR = Prevalence rate ratio for annual change according to Poisson regression model.

Georgia¹⁵ showed a low level of awareness of the protective effect of folic acid against NTD. A national sample of American woman interviewed in 1995 also showed a low level of awareness of the preventive effect of folic acid.¹⁶

EXAMINATION OF NTD PREVALENCE

Table 1 shows the numbers of cases of NTD by programme. After adjusting the induced abortions to expected dates of birth, as explained above, the numbers of cases and rates are as

shown in tables 2, 3 and 4. Secular trends are evident in some programmes before the introduction of any folate supplementation policies. Over the whole study period, for anencephaly, three programmes (England and Wales, Hungary and Japan) showed a significant fall, while South America showed a significant rise. For spina bifida, a significant fall is seen in Atlanta (USA), England and Wales, Hungary and North Netherlands, while South America again showed a rise. For all NTD, Atlanta, England

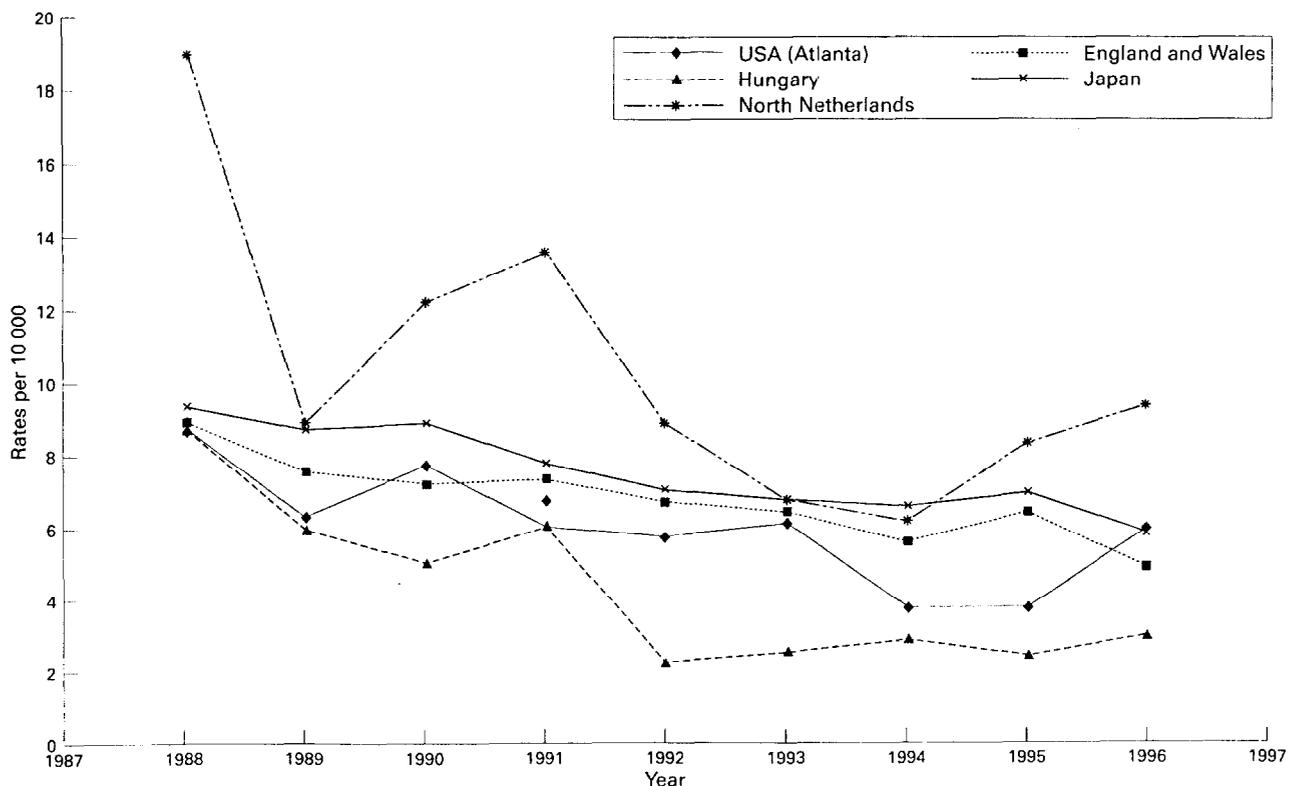


Figure 1 Significant downward trends—NTD rates 1988–96.

Table 5 Crude comparison between period before (88-93) and after (94-96) the initiation of strategies of prevention

| Registry | Period | Anencephaly PRR (95% CI) | Spina bifida PRR (95% CI) | Anenc and Spina bifida PRR (95% CI) |
|---------------------|--------|-----------------------------|------------------------------|--|
| England and Wales | 88-96 | 0.83 (0.75, 0.92) | 0.75 (0.67, 0.83) | 0.79 (0.73, 0.85) |
| France-Central East | 88-96 | 0.95 (0.68, 1.32) | 1.21 (0.96, 1.52) | 1.11 (0.92, 1.34) |
| France Paris | 88-96 | 1.01 (0.71, 1.44) | 1.27 (0.92, 1.76) | 1.14 (0.90, 1.45) |
| France Strasbourg | 88-92 | 0.76 (0.39, 1.46) | 1.06 (0.52, 2.19) | 0.88 (0.54, 1.43) |
| Hungary | 88-96 | 0.71 (0.45, 1.13) | 0.49 (0.36, 0.65) | 0.53 (0.42, 0.68) |
| Israel | 88-96 | 1.18 (0.22, 6.10) | 1.56 (0.38, 6.22) | 1.13 (0.36, 3.55) |
| Japan | 88-96 | 0.60 (0.47, 0.77) | 1.11 (0.88, 1.41) | 0.81 (0.68, 0.96) |
| North Netherlands | 88-96 | 0.83 (0.42, 1.66) | 0.65 (0.42, 1.01) | 0.69 (0.48, 1.01) |
| Norway | 88-96 | 1.30 (0.92, 1.83) | 1.24 (0.95, 1.61) | 1.25 (1.02, 1.55) |
| South America | 88-96 | 1.16 (0.98, 1.36) | 1.28 (1.09, 1.49) | 1.22 (1.08, 1.36) |
| USA-Atlanta | 88-96 | 0.73 (0.43, 1.24) | 0.67 (0.44, 1.01) | 0.69 (0.50, 0.96) |

PRR = Prevalence rate ratio for change between 1988-93 and 1994-96 according to Poisson regression model.

and Wales, Hungary, Japan and North Netherlands all show a significant fall, South America a significant rise. There are no other significant changes in prevalence.

Significant downward trends in five programmes are shown graphically in figure 1. In four of these programmes, the downward trend has no definable beginning or end. As is to be expected, the programmes with the largest numbers of cases (England and Wales and Japan) show the smoothest curves, and these two programmes are the only ones in which the lowest rate was recorded in the final year of the study (1996). In Hungary, there is a downward trend from 1988 to 1992 and very little change thereafter.

In tables 5 and 6, the years covered in the study have been arbitrarily divided into two periods, 1988-1993 and 1994-1996. These correspond very approximately to periods (1) when supplementation policies could not be expected to have had any significant influence, and (2) when an effect could have been seen in countries that were the first to promulgate policies. Table 5 is a crude comparison. It shows a significant fall in prevalence rates for all NTD from the first to the second period in Atlanta (USA), England and Wales, Hungary and Japan, and a significant rise in Norway and South America. In table 6, the figures have been adjusted to allow for the secular trends observed in the earlier years of the study. The significant trends seen in table 5 are no longer evident apart from the increase in Norway, attributable to an increase in spina bifida.

Table 6 Adjusted for secular trend comparison between period before (88-93) and after (94-96) the initiation of strategies of prevention

| Registry | Period | Anencephaly PRR (95% CI) | Spina bifida PRR (95% CI) | Anenc and Spina bifida PRR (95% CI) | Power* |
|---------------------|--------|-----------------------------|------------------------------|--|--------|
| England and Wales | 88-96 | 0.99 (0.85, 1.14) | 0.95 (0.82, 1.10) | 0.97 (0.88, 1.06) | 0.99 |
| France-Central East | 88-96 | 0.74 (0.46, 1.20) | 1.01 (0.71, 1.43) | 0.91 (0.71, 1.15) | 0.81 |
| France Paris | 88-96 | 0.99 (0.59, 1.66) | 1.18 (0.72, 1.95) | 1.09 (0.81, 1.47) | 0.37 |
| France Strasbourg | 88-92 | 0.54 (0.22, 1.28) | 0.99 (0.35, 2.79) | 0.70 (0.40, 1.21) | 0.10 |
| Hungary | 88-96 | 1.91 (0.92, 3.95) | 1.19 (0.79, 1.79) | 1.33 (0.99, 1.80) | 0.86 |
| Israel | 88-96 | 8.76 (0.26, 298.31) | 2.10 (0.17, 25.54) | 2.56 (0.43, 15.05) | 0.03 |
| Japan | 88-96 | 1.08 (0.75, 1.54) | 0.93 (0.65, 1.31) | 1.04 (0.85, 1.28) | 0.84 |
| North Netherlands | 88-96 | 1.45 (0.49, 4.27) | 1.02 (0.54, 1.94) | 1.21 (0.71, 1.77) | 0.22 |
| Norway | 88-96 | 1.28 (0.74, 2.20) | 1.45 (1.95, 2.21) | 1.39 (1.05, 1.83) | 0.58 |
| South America | 88-96 | 1.02 (0.80, 1.31) | 1.18 (0.93, 1.51) | 1.09 (0.95, 1.27) | 0.81 |
| USA-Atlanta | 88-96 | 0.77 (0.36, 1.65) | 0.96 (0.52, 1.74) | 0.88 (0.60, 1.31) | 0.39 |

PRR = Prevalence rate ratio for change between 1988-93 and 1994-96 according to Poisson regression model. *Power for detecting a 25% variation with a two tailed α value of 0.05.

KEY POINTS

- Many studies confirm that folic acid supplements could prevent most NTDs.
- Public health policies relating to folic acid supplementation have been adopted by health authorities in many countries.
- The existence of a national policy does not necessarily imply that it is being implemented.
- The frequency of NTD up to mid-1996 seems not to have been influenced by folate supplements.

However, there is no significant change in NTD rates in Norway over the whole study period. In 1994 and 1995 (both included in the second period) the rates for both anencephaly and spina bifida were rather higher than usual but fell again in 1996. The rise in rates between the two periods is probably a chance event. For a better evaluation of the results table 6 reports the statistical power for detecting a 25% variation between the two periods with a two tailed α of 0.05. The large sample size allows for a high level of statistical power, but for small registries.

Discussion

The statistically significant falls and rises in NTD prevalence rates from January 1988 to mid-1996 seem to represent continuing secular trends, decreasing in the USA (Atlanta), England and Wales, Hungary, Japan and the Netherlands, and increasing in South America. There is a rough association between significantly falling incidence rates and the early promulgation of recommendations, but it seems unlikely that the recommendations have caused the fall. It seems more probable that more affluent countries experience falling NTD rates and can afford to allocate resources to folate supplementation programmes, while the reverse is true in poor countries. At one time, the British Isles (United Kingdom and Republic of Ireland) had the unenviable reputation of having the highest NTD rates in the world. This distinction now belongs to South and Central America, where poverty coincides with the illegality of pregnancy termination.

There is no convincing evidence that, up to the middle of 1996, any change was attributable to the introduction of national folate supplementation policies. Even in England and Wales, the rate adjusted for secular trend did not decrease significantly between 1988-93 and 1994-96, although the power estimates in table 6 suggest that such a decrease might well have occurred if the uptake of folic acid before conception for the whole county had matched the Leeds figures (18%-31% for 1994-96). It is clear that, where supplementation policies have been promulgated, they take a very long time and a great deal of effort to implement. The possible effectiveness of folate supplementation for the reduction of NTD clearly needs to be tried and studied for several more years. However, recognising that, in the Western

world at least, approximately 50% of pregnancies are unplanned, a policy that rests on action taken before conception can only have limited success. The alternative of fortifying staple foods by adding folic acid to cereal flours, which was mandatory in the USA with effect from 1 January 1998, may prove to be a more successful strategy, provided that the level of enrichment is sufficient.

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Conflicts of interest: none.

Appendix

Application of the Poisson models

The Poisson regression is most appropriate for count data, it has only rarely been applied either in epidemiology or anywhere else. This appendix presents the way in which a time distribution of cases of birth defects can be analysed exploiting the potential of the Poisson regression.

In the Poisson regression model, the incidence rate for the j -th observation, say r_j , (the j -th year in our case) is assumed to be given by $r_j = \exp(\alpha + \beta_1 x_{1j} + \beta_2 x_{2j} + \dots + \beta_k x_{kj})$, where $x_{1j} + x_{2j} + \dots + x_{kj}$ are the values of k independent variables in the j -th year. However, dealing with birth defects, the incidence rate at which events occur is not calculable as we cannot know the total number of pregnancies at risk and the total number of NTD cases among them.¹⁷ This is not possible as a great number of early miscarried pregnancies are not registered, or even not recognised as such by the mother. Instead of the incidence rate, we have therefore considered a "corrected" prevalence rate at birth. This is not a perfect estimate of the natural birth prevalence. Some terminated pregnancies would miscarry rather than ending in affected births if they were not terminated, and a substantial proportion of pregnancies terminated for NTDs are probably not notified as such.¹⁸

We are interested in temporal changes that occurred around 1994, when the folate policies might have begun to produce effects. For this purpose the general model adopted in this study is the following: $r_j = \exp(\alpha + \beta_1 x_{1j} + \beta_2 x_{2j})$ where x_{1j} is the time variable (set at 0 for 1988, 1 for 1989 and so on) and x_{2j} is a dummy variable that is equal to 0 for years before 1994 and 1 from 1994 onwards. To compare rates, one can easily calculate the PRR, which is the exponential transformation of β , for the relevant variable. The PRR shows the variation of the prevalence rate corresponding to one unit change of

one independent variable, say x_i , holding constant all the other x s. The rates after and before this change are the ratio's numerator and denominator respectively, so that values of $PRR > 1$ indicate an increase and values of $PRR < 1$ indicate a decrease.

Three particular models have been estimated, including the general one:

- (1) For studying the general tendency of the prevalence rates during the study period, the model adopted is $r_j = \exp(\alpha + \beta_1 x_{1j})$ and the relevant PRRs estimate the average annual variation in prevalence rates during the period.
- (2) For studying initially the temporal changes occurring around 1994, when the folate policies might have begun to produce effects, the model used is $r_j = \exp(\alpha + \beta_2 x_{2j})$. Here, the PRR compares the prevalence rates before 1994 with the rates from 1994 onwards.
- (3) To distinguish the real effect of the policies from the general trend of the NTD occurrence (which (2) does not do), we must adjust the time series for the effect of long term trends, represented by the factor x_1 . Therefore the model adopted is $r_j = \exp(\alpha + \beta_1 x_{1j} + \beta_2 x_{2j})$. The relevant PRR, calculated as $\exp(\beta_2)$, indicates how much larger or smaller the prevalence rates are before and after 1994, given the secular trend.

Maximum likelihood estimates of the parameters are obtained using the Poisson function of the STATA software.¹⁹

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How many pregnant women in Christchurch are using folic acid supplements in early pregnancy?

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Abstract

Aims. To determine the proportion of pregnant women in Christchurch using folic acid supplements in early pregnancy. To evaluate the level of current knowledge relating to folic acid amongst pregnant women. To determine the main sources from which this information was gained.

Methods. A short questionnaire was administered to 191 pregnant women in Christchurch during antenatal visits with their lead maternity carer. The survey contained questions relating to knowledge about folic acid and use together with sources of information regarding folic acid. Obstetric and demographic details were also collected.

Results. The response rate was 95.5%. Ninety-one per cent (174/191) of participants had heard of folic acid and, of these, 63% knew that folic acid reduces the risk of spina bifida. Of the 191 participants in the study, 118(62%) took folic acid supplements at some stage of their pregnancy, however, only 33(17%) had taken periconceptual folic acid supplements. Of the 44% of all women in the study with a planned pregnancy, only 35% had taken folic acid supplements periconceptually. Of those women with an unplanned pregnancy (55%), only 2.8% had taken a folic acid supplement periconceptually. The main sources of advice for women relating to folic acid were general practitioners (48%) or media advertising, either in the form of a magazine, or health pamphlet or television promotion (20%).

Conclusions. The results of this study indicate that the level of knowledge amongst women of child-bearing age relating to folic acid is relatively high compared with other countries. Despite this high level of knowledge, only a small percentage of women are actually consuming a folic acid supplement during the recommended periconceptual period due in part to the high proportion of unplanned pregnancies. These results emphasize the need for an effective public health strategy to ensure that all women of child-bearing age have access to an adequate folic acid intake.

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defects.^{1,2} The New Zealand Ministry of Health therefore recommends that all women of child-bearing age take a daily folic acid supplement of 0.8 mg before conception and for the first 12 weeks of pregnancy.³ It is not known how many pregnant women actually know of, and follow, this recommendation. New Zealand relies on public education of women regarding folic acid supplementation and women have to pay for their folic acid supplements. It is not known how successful this strategy is. The main aim of this study was to determine how many women are using folic acid supplements in early pregnancy in order to judge the effectiveness of current neural tube defect prevention strategies.

According to the 1997 annual report of the International Clearinghouse for Birth Defects Monitoring Systems,⁴ the rate of neural tube defects in New Zealand is 3.12 per 10 000 live births. This translates to 17.5 neural tube defect cases per year in New Zealand (with a live birth rate of 56 353 for the year ending September 1998).⁵ Worldwide rates range from 1.76 in the UK, 2.95 in the USA, 5.45 in Australia to 27.3 in Ireland (all figures per 10 000).⁴ Over the past eight years public education campaigns to raise awareness regarding the value of folic acid supplementation have been carried out in these countries. In Western Australia the percentage of pregnant women consuming folic acid supplements periconceptually rose from 19.1% in 1993 to 43.1% in 1995 following a two and a half year public health promotion.⁶ In the UK, studies were conducted to ascertain changes in folic acid awareness before and after the British Health Education Authority's campaign in 1995. The percentage of women taking a folic acid supplement before conception rose from 1.8% in 1993 to 30.6% in 1996.⁷ There have been no published data to date in New Zealand concerning the level of folic acid consumption amongst women of child-bearing age.

Methods

A sample size of 200 participants was selected for the study. This figure was selected after consideration of the likely precision for a sample where 60% had heard of folic acid and 2-10% had taken periconceptual folic acid. These proportions represent a median derived from comparable overseas studies. All pregnant women attending public (Christchurch Women's Hospital and Burwood Hospital) and private (The Oxford Clinic, St Georges Pregnancy Centre) antenatal clinics were invited to participate. Participants were interviewed and questions relating to their knowledge and use of folic acid was obtained, as well as obstetric and demographic details.

It has been shown from randomized controlled trials over the past ten years that consumption of a daily folic acid supplement of 0.4 mg periconceptually (defined here as one month before conception through to 28 days post-ovulation) can significantly reduce the incidence of both recurrent (72% reduction) and first-time neural tube

Results

Two hundred pregnant women were approached for the study and 191 agreed to participate giving a response rate of 95.5%. The ages of participants ranged from 16 to 43 years. Time of gestation ranged from 2 to 42 weeks. The majority (81%, 156/191) of participants in this study were New Zealand European, with 10% Maori and 9% from various other ethnic backgrounds. Occupation and highest level of educational qualification were ascertained. Half of the sample group were involved in an occupation outside the home, approximately one-third (36%) of participants reported "homemaker" as their present occupation, 9.4% were unemployed and the remaining 3% were students. In terms of education, 53% of all participants had school certificate, sixth-form certificate or bursary qualifications, 24% attained a tertiary qualification and 21% reported no qualification. Slightly more than half (56%) of all participants held a community services card. Comparison of this sample with the latest census data for Christchurch and all of New Zealand, with regard to ethnicity and education, is summarized in Table 1. This indicates that the sample was very representative of the Christchurch population but would underrepresent Maori and Pacific Island women, compared to the New Zealand population.⁸

Obstetric details were elicited: 40.3% of all participants were nulliparous, 34.6% primiparous, 25% had more than one child and 24.1% responded that they had a previous miscarriage. One of the participants had a previous stillborn child and another participant reported having given birth to a child with a neural tube defect (anencephaly). Slightly less than half of all participants (44%) had planned their pregnancy. Of these, 37% had informed their doctor of their desire to conceive and 62% of these women reported that folic acid had been discussed with their doctor.

Knowledge about folic acid. In response to questions relating to folate awareness, 174 (91%) of participants had heard of folic acid. For these women who had heard of folic acid, 119 knew that it was important in preventing spina bifida or birth defects. Knowledge regarding the best time to start taking folic acid supplements was encouraging, with 107 women stating that its levels should be increased before conception and 97 knew to continue taking it through the first trimester of pregnancy.

For women who knew of the importance of folic acid, 46% knew that folate levels increase through diet; 84% of these

women quoted green vegetables as a main source and 17% knew fresh fruit also contained folic acid. The majority of women who had heard of folic acid (48%) learned about it through their general practitioner, 20% via media advertising either in the form of public health pamphlets, magazine or television advertising. Thirteen per cent had found out about folic acid from friends, 12% through midwives, and the rest from other sources.

Use of folic acid. Of the participants, 118 (62%) took a folic acid supplement (either a pure folic acid tablet or a multivitamin preparation containing folic acid) at some stage of their pregnancy. Eight (4%) of participants reported having made dietary changes involving an increase in folate-rich foods. Only 33 (17%) of the women took folic acid during the recommended periconceptual period, 54 (28%) women started folic acid supplements when they knew they were pregnant (this varied from 4-24 weeks gestation) and a further 22 (11.5%) women started folic acid later in their pregnancy. Nine (5%) women could not remember when they started their folic acid supplement.

Most pregnancies in this sample (106, 55%) were unplanned. Only three of the women with unplanned pregnancies used folic acid periconceptually. Thirty of the 85 women with planned pregnancies used folic acid periconceptually. (Table 2 shows a summary of these results together with results, from similar studies from overseas.)

There was a strong association between education and folic acid use, (Table 3). Parity did not influence folic acid use, with 60% of nulliparous women and 55% of primiparous and multiparous women using folic acid at some point in their pregnancy.

Discussion

The current New Zealand Ministry of Health recommendations advise all women of child-bearing age to consume a daily 0.8 mg folic acid supplement one month before and twelve weeks after conception in order to reduce the risk of a child being born with a neural tube defect. This study shows that a large proportion of pregnant women are aware of this recommendation compared with other countries (Table 2). However, few pregnant women actually take folic acid supplements during the periconceptual period. This can be partly explained by the high rate of unplanned pregnancies in this study.

An attempt was made to include as representative a sample as possible of pregnant women in the Christchurch area by sampling participants from a variety of antenatal clinics, both public and private. However, this study sampled only *pregnant* women. It could be expected that knowledge relating to folic acid would be higher in a group of pregnant women (who have been exposed to pregnancy/health literature at antenatal clinics), than to a random sample of women of child-bearing age. The results of this study may therefore overestimate the percentage of women who were aware of the folic acid recommendation. However, the percentage of women who reported taking a periconceptual folic acid supplement was low and it is this finding which re-emphasizes the need for effective strategies to be implemented.

The results pertaining to folic acid awareness and educational status mirror those from the studies conducted

Table 1. Ethnicity and education status of sample compared to Christchurch and New Zealand.¹

| | Sample (%) | Christchurch (%) | New Zealand (%) |
|------------------------------|------------|------------------|-----------------|
| Ethnicity¹ | | | |
| European | 86 | 86 | 74.8 |
| Maori | 10 | 7.2 | 15.1 |
| Pacific Island | 3 | 2 | 5 |
| Asian | 6 | 4 | 4.6 |
| Education | | | |
| None | 23 | 31.9 | 34.7 |
| School ² | 53 | 32 | 30 |
| Tertiary | 23 | 35.5 | 34.8 |

1: Total is greater than 100% as subjects could elect more than one ethnic group. 2: School includes school certificate, sixth-form certificate and bursary qualifications. Two overseas subjects were impossible to classify.

Table 2. Folic acid supplement knowledge of, and use by pregnant women in Christchurch compared to the United Kingdom, Western Australia, Ireland and the Netherlands.

| | Christchurch | Western Australia ⁶ | Ireland ⁹ | Netherlands ¹⁰ | United Kingdom ⁷ |
|--|--------------|--------------------------------|----------------------|---------------------------|-----------------------------|
| Percentage of women who took folic acid periconceptually | 17 | 30.6 | 7 | 35.5 | 30.6 |
| Percentage of women with planned pregnancies | 44 | 62 | | 85 | |
| Percentage of women with planned pregnancies taking periconceptual folic acid. | 35 | 43 | | 51 | |
| Percentage of women who had heard of folic acid | 91 | 67.5 | 63.6 | 74 | |

Table 3. Highest education level and folic acid use.

| Educational level | Using periconceptual folic acid ² (%) | Using folic acid at any time (%) |
|---------------------------------|--|----------------------------------|
| None | 7 | 43 |
| School ¹ | 16 | 54 |
| Tertiary | 32 | 77 |
| Significance level ³ | p=0.0027 | p=0.0016 |

1: School includes school certificate, sixth form certificate and bursary qualifications, tertiary includes university or polytechnic; 2: Percentages refer to the proportions of women in each education category; 3: p-values from logistic-based trend test.

in Western Australia and Dublin, Ireland, which found that greater knowledge and periconceptual use of folic acid is associated with higher educational level and socioeconomic status.^{6,9} Considering that there is an inverse social gradient associated with neural tube defects, these findings emphasize the value of designing an effective public health strategy which will ensure that all women of child bearing age, irrespective of educational or socioeconomic factors, are able to have access to adequate folic acid levels.⁹ Three main approaches to the problem have been explored: education with encouragement of women to consume folic acid supplements, education combined with a selective fortification strategy and the larger population strategy involving folate fortification of flour.

The education and supplementation strategy would require a targeted campaign involving the concerted efforts of health care providers in identifying opportunities for folic acid education of women, in addition to large-scale media advertising campaigns. This approach has provided encouraging results in Western Australia, where the percentage of women with planned pregnancies who had taken periconceptual folic acid rose from 19.1% to 43.1% after the Western Australia health promotion project.⁶ This approach preserves the right of choice and promotes individual responsibility for health care decisions. It has been argued however, that the education and supplementation strategy cannot be effective in targeting the problem of unplanned pregnancies. For this reason, the folate fortification strategy has been proposed.

A folate fortification strategy can be carried out in two ways, the first is a selective approach where folate can be added by the manufacturer independently to specific foods such as breads or cereals, with an associated health claim on the product package. This approach has been implemented in Britain in association with close monitoring of folate status on the target population and a large public health campaign to encourage increased folate intake amongst women of child-bearing age. It appears that selective fortification will soon be introduced in New Zealand.¹¹ The second approach is the larger population-based strategy where folate is added to a staple food item such as flour. The United States (since 1 January 1998) has

adopted this universal fortification strategy, by which 140 µg of folic acid is added to every 100 g of grain products.¹²

There is currently debate overseas for and against such a population-based approach, with proponents arguing that it is a cost-effective and simple approach to ensuring that all women have access to sufficient folate, regardless of socioeconomic status or lack of pregnancy planning. Conversely, there are arguments against such a strategy. Concerns have been raised regarding the possible masking of pernicious anaemia and the precipitation of its neurological complications in the elderly population and the, as yet unknown, long-term effects of high folate intakes on the greater population.^{13,14} Compulsory fortification can be considered a form of mass treatment of the population and this brings with it also the important issue of public choice in relation to dietary intake.

Evaluation of the successes of both strategies carried out in the UK and the USA seems prudent when considering a neural tube defect prevention programme for New Zealand. The results from this study suggest that the current approach in New Zealand has not been hugely effective and emphasize the need for an effective public health strategy, which will ensure that all women of child-bearing age have access to adequate intake of folic acid.

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IN PRACTICE

Outcomes of transrectal ultrasound scan of the prostate with sector biopsies for 323 New Zealand men with suspicion of prostate cancer

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Abstract

Aims. To assess the results and clinical outcomes of the first four years of transrectal ultrasound scanning (TRUS) with sector biopsies of the prostate, as the definitive

second-line investigation for men with suspicion of prostate cancer, including comparability with subsequent information from histology of surgical specimens.

Methods. Information was collated from the author's ongoing surgical audit. TRUS and sector biopsies were