Supplementation with Folic Acid during Methotrexate Therapy for Rheumatoid Arthritis

A Double-Blind, Placebo-controlled Trial

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■ *Objective:* To determine the effect of two different weekly doses of folic acid on the toxicity and efficacy of low-dose methotrexate therapy for rheumatoid arthritis.
■ *Design:* Randomized, double-blind, placebo-controlled study.
■ *Patients:* 79 persons between 19 and 78 years of age who fulfilled the American Rheumatism Association's criteria for rheumatoid arthritis.
■ *Intervention:* Participants were randomly assigned to visually identical placebo or to 5 mg or 27.5 mg of folic acid each week.
■ *Measurements:* Duration, intensity, and clinical severity of toxic events; efficacy (indices of joint tenderness and swelling and grip strength); plasma and erythrocyte folate levels; and other laboratory variables.
■ *Results:* Folic acid supplementation at either dose did not affect the efficacy of methotrexate therapy as judged by joint indices and patient and physician assessments of disease. Patients given folic acid supplements had lower toxicity scores than did participants given placebo ($P \leq 0.001$). Low blood folate levels and increased mean corpuscular volumes were associated with substantial methotrexate toxicity, whereas daily dietary intakes of more than 900 nmol (400 μg) of folic acid were associated with little methotrexate toxicity.
■ *Conclusions:* Folic acid, an inexpensive vitamin, is safe in a broad range of doses and protects patients with rheumatoid arthritis who are taking methotrexate from toxicity while preserving the efficacy of methotrexate.

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The folic acid antagonist methotrexate (N-10-methyl-aminopterin) is useful in low doses (2.5 to 20 mg/wk) for treating chronic inflammatory diseases (1–7). Many trials have established the efficacy of methotrexate in rheumatoid arthritis (7–13). Compared with other disease-modifying drugs, methotrexate has the highest probability of drug continuation at 10 years. Dose response–related toxic effects have been reported in 30% to 90% of patients given methotrexate (13). Toxic effects include gastrointestinal intolerance, hematologic abnormalities, alopecia, hepatotoxicity, and pulmonary toxicity (14–22).

Some side effects of methotrexate administration, such as gastrointestinal intolerance, mimic complicated folate deficiency (23). Folate deficiency occurs frequently in patients with rheumatoid arthritis; further, folate stores are decreased in patients with rheumatoid arthritis who take methotrexate, suggesting that impaired folate status is related to toxicity (24–26).

Folic acid supplementation has been reported anecdotally to lessen toxicity in patients receiving methotrexate treatment (27, 28). In a 6-month, double-blind, placebo-controlled trial, 7 mg of folic acid weekly (1 mg/d or 2265 nmol/d) decreased methotrexate toxicity without affecting efficacy (29). This was confirmed by Stewart and colleagues (30) in a retrospective chart review.

Folinic acid (leucovorin, citrovorum factor) is a one-carbon–substituted, fully reduced folate that has also been administered during methotrexate therapy (31–36). Low doses of the vitamin (1 to 7 mg/wk) have decreased methotrexate toxicity (35, 36). Higher doses negate efficacy and lessen toxicity (31, 32). Thus, the folinic acid dose may critically affect the efficacy of methotrexate therapy.

The influence of the folic acid dose on methotrexate toxicity and efficacy remains controversial, and the effects of different doses of folic acid are not known (37, 38). Some investigators argue that if toxic effects occur, the most rational approach is to reduce the dose of methotrexate rather than to provide folic acid supplements (37). We designed a larger and longer study to evaluate different doses of folic acid, assuming that toxicity could be reduced without changing the efficacy of methotrexate.

Methods

Participants

Patients aged 19 to 78 years who fulfilled the American College of Rheumatology's revised criteria for rheumatoid arthritis

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consented to participate in the trial (39). Enrollment criteria included rheumatoid arthritis diagnosed more than 6 months previously, onset after the age of 16 years, and at least three of the following signs or symptoms: 3 or more swollen joints, 6 or more tender joints, at least 45 minutes of morning stiffness, and a Westergren erythrocyte sedimentation rate greater than or equal to 28 mm/h.

Referring rheumatologists and the principal investigator did the screening. Exclusion criteria included serious concomitant medical illnesses, liver enzyme levels twice the upper limit of normal, leukocyte counts less than 3.5×10^9/L or platelet counts less than 150×10^9/L, and use of methotrexate within the past 6 months. Gold salts were stopped for at least 10 days before the trial. This short washout period mirrors actual rheumatology practice. Patients remained under the care of their rheumatologists, abstained from alcohol use, did not become pregnant, and received stable doses of aspirin and nonsteroidal anti-inflammatory drugs. If prednisone was taken at entry, the dose could not exceed 10 mg/d. Hydroxychloroquine therapy was allowed during the study.

Study Design

Figure 1 shows the trial design. To maintain the double-blind status of the trial, the statistician carried out the randomization using a computer program in which the algorithm was transparent and a coded vial number represented the treatment assignment. Patients were assigned to treatment groups by a sequential treatment assignment process designed to balance the sample with respect to baseline features, including age, sex, folate-containing vitamin use, rheumatoid factor status, and prednisone use (40). Patients agreed to discontinue therapy with folate-containing vitamins during the trial. Rheumatoid factor was considered positive if the level was more than 30 IU/mL or if the titer was more than 1:160. Patients received either visually identical placebo or 5 mg (low-dose folic acid group) or 27.5 mg folic acid (high-dose folic acid group) each week, prepared by the Hospital Investigational Drug Service. Spectrophotometric analysis indicated that the mean ± SD folic acid content was 1 ± 0.15 mg (2.3 ± 0.3 μmol) and 5.5 ± 0.3 mg (12.5 ± 0.7 μmol) per capsule in the low-dose and high-dose folic acid groups, respectively. Lederle Laboratories provided the methotrexate (Rheumatrex; Pearl River, New York), which was started in a median oral dose of 16.5 μmol (7.5 mg) per week and increased in 5.5-μmol (2.5 mg) increments at the rheumatologist's discretion. Methotrexate was taken either in an undivided or a divided dose (that is, every 12 hours for three doses). The methotrexate dosing regimens were identical among the study groups. Folic acid supplements were given 5 days per week when methotrexate was not ingested. Compliance with the regimen was reinforced using a digital reminder cap (Counter Cap; Senetics, Boulder, Colorado). All participants and investigators were blinded to vitamin capsule content until the study was complete.

Clinical Assessment

Patients were evaluated immediately before methotrexate initiation at a mean of 13, 26, 39, and 53 weeks (Figure 1). Each patient was assessed by the same physician–nutritionist (SLM). Two research assistants (JSA or WHV) did the joint evaluations. In most cases, patients were examined by the same observer throughout the study. The joint counts for tenderness and swelling were not significantly different between the two observers ($P = 0.6$ for tenderness; $P = 0.9$ for swelling). The following variables were evaluated at each visit: 1) number of the 58 diarthrodial joints with swelling; 2) number of the 60 joints with tenderness on pressure or with pain on passive motion (or both); 3) joint swelling and tenderness indices, expressed as a sum, with each joint graded for swelling as 0 (none), 1 (mild), 2 (moderate), or 3 (severe); 4) mean grip strength (three measurements) for both hands expressed in mm Hg; 5) duration of morning stiffness expressed in hours; 6) patient's and physician's global assessments of disease activity graded as 0 (asymptomatic), 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe); 7) current medications and doses; 8) a 1-day dietary recall using the Minnesota Nutrition Data System software, Food Database version 6A, Nutrient Database version F21 (41); 9) eight activities of daily living assessed and averaged at baseline and at 12 months using the modified Health Assessment Questionnaire and scored on a scale of 1 (no difficulty) to 4 (unable to perform) (42); and 10) presence, duration, intensity, and severity of toxic effects at every follow-up visit and every 3 weeks by telephone interview (done by SLM).

Laboratory Assessments

At the initial visit, complete blood cell count, Westergren erythrocyte sedimentation rate, liver enzyme (aspartate amino transferase and alkaline phosphatase), rheumatoid factor by nephelometry, and serum creatinine values were obtained. The complete blood cell count, creatinine, and liver function tests were repeated at all visits. If laboratory values were obtained more frequently than stipulated in the protocol, they were recorded and became part of the toxicity score.

Blood for plasma and erythrocyte folate levels, using a methotrexate-resistant *Lactobacillus casei* microbiological assay, was drawn at all visits (43). At baseline, blood was drawn for a vitamin panel (plasma and erythrocyte folate, vitamins B_{12}, A, C, and E, carotene, riboflavin, thiamin, pyridoxine) (44–51). If patients had abnormal values for any of the vitamins, other than folate, the abnormality was treated with single vitamin supplements.

Radiographic Assessment

Hand and wrist radiographs taken within 6 months of entering the trial were assessed by one of the rheumatologists (GSA) without knowledge of study status. Joint erosions and space narrowing were determined by the modified method of Sharp (52). Results were expressed as the mean raw scores for joint erosion and joint space narrowing.

Toxicity: Frequency and Severity

Toxic effects and discontinuation of therapy with study medications due to toxicity were considered primary outcomes. We determined a toxicity score, modified from the one previously used, for each patient at each visit or until methotrexate therapy was discontinued (29) (Appendix).

Efficacy

We determined patient response to treatment using a modification of the criteria used in our previous folic acid supplementation trial and by others (8, 29, 53). We defined marked improvement in the joint swelling index and the joint tenderness and pain index as a net decrease of 50% or more in value at any

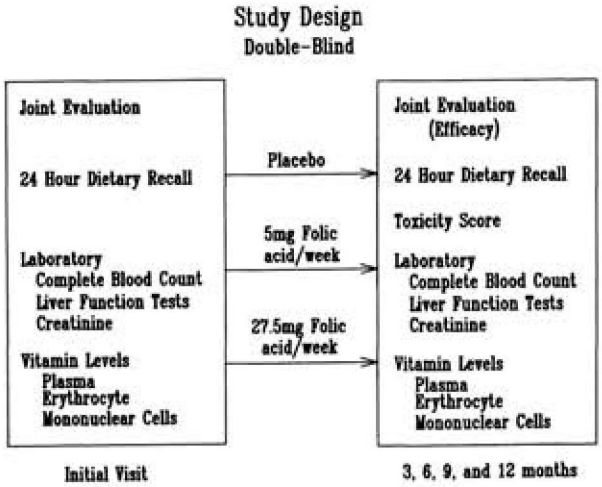

Figure 1. Study design for the double-blind, placebo-controlled trial. The randomization was done by the statistician using a sequential treatment assignment program in which the algorithm was transparent and a coded vial number was used as the treatment assignment.

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follow-up visit compared with visit 1. We defined moderate improvement as a 30% to 49% net decrease in the index, and no change as the index value remaining within 30% of the original value. We defined worsening as an increase in the index value of 30% or more.

We examined the effects of folic acid supplementation on changes in physician and patient global assessments, grip strength, morning stiffness, erythrocyte sedimentation rate, findings of the modified Health Assessment Questionnaire, complete blood cell counts, blood folate levels, and dietary folate and vitamin B_{12} intake.

Statistical Analysis

Sample Size and Analysis

In our previous study, the mean toxicity scores for patients receiving low-dose folic acid and placebo recipients were 0.21 and 1.06, respectively, for a difference of 0.85. The sample size tested the null hypothesis for no difference between placebo and low- and high-dose folic acid treatments, with respect to the mean toxicity score. The alternative hypothesis was that the difference in the score between at least one pair of treatments (placebo compared with low-dose folic acid, placebo compared with high-dose folic acid, or low-dose folic acid compared with high-dose folic acid) was greater than or equal to the difference observed previously. As described by Cohen (54) and implemented by Borenstein and Cohen (55), 25 patients per group was a sufficient number to detect a difference in the mean toxicity score of 0.85 between any pair of treatments at a significance level of 0.05 and a power of 0.80.

An underlying assumption in sample size estimates was that the scores are normally distributed. To address the potential non-normal character of the toxicity scores, we increased the sample size estimates by 4% to maintain the significance level and power if nonparametric analyses were used. To allow for a 20% attrition rate, the enrollment goal was 31 patients per group.

Patients were withdrawn if more than 3 weeks of methotrexate treatment was missed for any reason or if noncompliance was documented. Patients who withdrew from the trial because of toxic effects did so after consulting their rheumatologists. Patients contributed to data analyses until therapy with methotrexate was discontinued. For patients who withdrew before receiving 12 months of therapy, we computed toxicity and efficacy data based on data collected until drug therapy was discontinued.

Comparison of Data among Groups

We tested the baseline values of all outcome measures for normality using the Shepin-Wilk statistic. For normally distributed data, we used chi-square analyses to compare proportions and analysis of variance to evaluate the effects of treatment, time, and their interaction.

Non-normal distributions occurred in joint indices for pain and tenderness, physician and patient assessment of disease, grip strength, answers to the modified Health Assessment Questionnaire, and plasma and erythrocyte folate levels. We used the Wilcoxon rank-sum test to compare the three groups and Wilcoxon rank-sum tests for pair-wise comparison, if appropriate.

Comparison of Toxicity Scores

We used the Fisher exact test to compare the incidence of toxic effects in the folic acid and placebo groups. Because the primary outcome measure was the toxicity score, we included data until the study was complete or the participant withdrew. To evaluate the effects of time, treatment group, and their interaction on the toxicity score, we used analysis of variance on the rank of the toxicity scores. We did two-way analyses of variance (or on the ranks for data that were non-normally distributed) to evaluate the effects of time, treatment, and their interaction.

Results

Patients

We enrolled 94 patients (age range, 19 to 78 years) into the trial. Subsequently, we withdrew 15 patients because of noncompliance (numbers were equally distributed among the study groups). Our results are from 79 patients who completed the trial: 25 in the low-dose folic acid group, 26 in the high-dose folic acid group, and 28 in the placebo group. The demographic and selected clinical features of the patients in the three study groups were similar (Table 1). No patients were taking sulfasalazine before enrollment. We found no statistical difference among the groups in previous use of gold salts ($P = 0.92$). Four patients in the placebo group (23%), 4 in the low-dose folic acid group (14.3%), and 6 in the high-dose folic acid group (23%) previously had therapy with methotrexate discontinued because of toxic effects ($P = 0.76$). Patients who previously discontinued methotrexate therapy because of toxic effects were randomly distributed in the three groups. Other initial variables such as hemoglobin level, hematocrit, leukocyte count, mean corpuscular volume, creatinine level, aspartate aminotransferase value,

Table 1. Demographic and Selected Clinical Characteristics of 79 Patients with Rheumatoid Arthritis*

Characteristics	Study Group		
	Placebo ($n = 28$)	Low-Dose Folic Acid ($n = 25$)	High-Dose Folic Acid ($n = 26$)
Mean age, *y*	52.2 ± 13.0	54.4 ± 14.0	53.2 ± 14.3
Sex, *% women*	82	76	65
Race, *% white*	85.7	68	73
Mean disease duration, *y*	8.5 ± 8.2	7.4 ± 10	11.6 ± 9.5
Previous use of folate-containing vitamins, %	32	28	19
IgM rheumatoid factor positivity (>30 IU/mL or 1:160 titer), %	71	80	85
Concurrent use of aspirin or nonsteroidal anti-inflammatory drugs, %	86	80	88
Concurrent prednisone use, %	79	80	88
Concurrent hydroxychloroquine use, *n*	1	1	4
Patients previously receiving gold salts, *n*	16	17	17
Patients previously receiving methotrexate, *n*	4	6	4
Previous disease-modifying antirheumatic drug use, %	64	68	77
Mean joint erosion score	9.2 ± 9.5	15 ± 16.7	17.7 ± 17.8
Mean joint space narrowing	20.2 ± 20.1	29.1 ± 25.1	35.3 ± 31.1

* All comparisons between groups, $P > 0.05$. Means are expressed ± SD.

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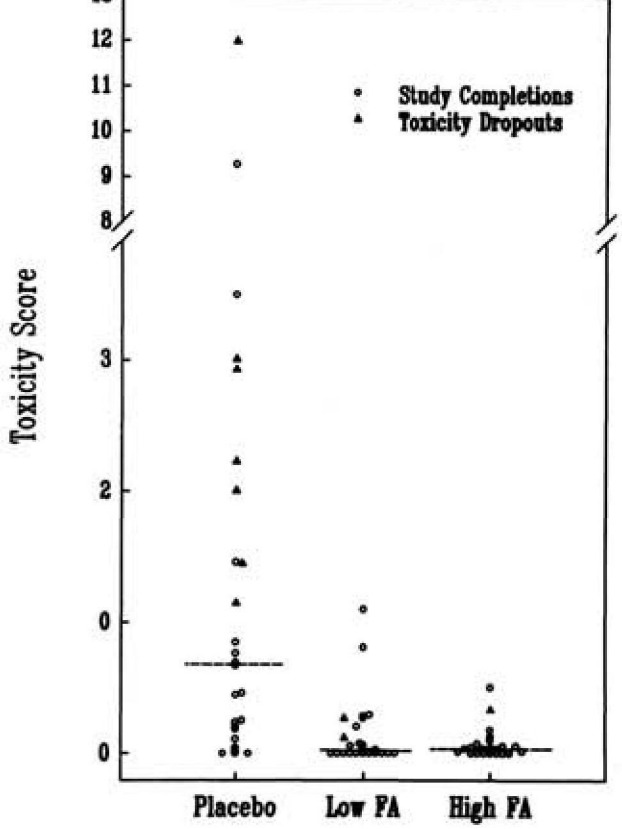

Figure 2. Median toxicity scores in the three study groups. The placebo group had a statistically higher toxicity score ($P = 0.001$) than the folic acid supplementation groups. The toxicity score was not significantly different between the low-dose folic acid and high-dose folic acid groups ($P = 0.71$). ▲ = patients withdrawn from the trial because of toxic effects; ○ = patients who completed the trial.

alkaline phosphatase level, and erythrocyte sedimentation rate were also similar among the groups. The erosion and joint space narrowing scores were similar at baseline among the three groups ($P = 0.16$ for joint space narrowing and $P = 0.17$ for erosions; Table 1).

We found no statistical differences in mean cumulative methotrexate dose among the three groups. The mean cumulative methotrexate doses at 53 weeks in the placebo, low-dose folic acid, and high-dose folic acid groups were 206 ± 88 mg, 217 ± 113 mg, and 284 ± 187 mg, respectively ($P = 0.24$). The average weekly methotrexate dose was 8.5 ± 1.5 mg, 9.4 ± 2.4 mg, and 9.6 ± 2.6 mg in the placebo, low-dose folic acid, and high-dose folic acid groups, respectively ($P = 0.27$).

The mean dietary folate and vitamin B_{12} intakes among the groups were never statistically different. Median dietary folate intakes were 204 μg/d in the placebo group, 195 μg/d in the low-dose folic acid group, and 230 μg/d in the high-dose folic acid group ($P = 0.37$ for all comparisons). The median daily intakes in all study groups did not substantially differ from the median values of 150 to 250 μg/d reported in the Second National Health and Nutrition Examination series (56).

Primary Outcome: Toxic Effects

Fifty-four patients (68%) experienced some form of toxicity: 25 (89%) in the placebo group, 12 (48%) in the low-dose folic acid group ($P < 0.002$ compared with placebo), and 17 (65%) in the high-dose folic acid group. Figure 2 shows the median toxicity score for the three groups (0.685, 0.016, and 0.031 in the placebo, low-dose folic acid, and high-dose folic acid groups, respectively). The toxicity score for the placebo group was greater than those for the two folic acid–supplemented groups ($P = 0.001$ for both comparisons for low-dose folic acid and high-dose folic acid compared with placebo; $P = 0.71$ for low-dose folic acid compared with high-dose folic acid). The most frequently reported toxicities were nausea and indigestion (31 patients), diarrhea (11 patients), stomatitis (9 patients), and rash (9 patients). When the patients receiving hydroxychloroquine were omitted from the analyses, the results were identical.

Other Outcomes

Efficacy

As noted in Table 2, the percentages of patients who

Table 2. Joint Swelling and Tenderness at 6 and 12 Months in the Three Treatment Groups

Outcome	6 Months			12 Months		
	Placebo ($n = 23$)	Low-Dose Folic Acid ($n = 24$)	High-Dose Folic Acid ($n = 23$)	Placebo ($n = 19$)	Low-Dose Folic Acid ($n = 23$)	High-Dose Folic Acid ($n = 18$)
	← % →					
Marked improvement						
Swelling	35	38	61	68	78	78
Tenderness	30	29	39	53	43	61
Moderate improvement						
Swelling	26	29	26	16	13	5
Tenderness	35	8	18	16	13	16
No change						
Swelling	35	33	9	11	5	17
Tenderness	26	55	39	21	35	17
Worsening						
Swelling	4	0	4	5	4	0
Tenderness	9	8	4	10	9	6

* $P > 0.5$ (chi-square) for comparisons among groups at 6 months and 12 months.

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Table 3. Data for Efficacy and Other Outcomes at Baseline, 6 Months, and 12 Months*

Outcome	Placebo Group			Low-Dose Folic Acid Group			High-Dose Folic Acid Group		
	Baseline	6 Months	12 months	Baseline	6 Months	12 months	Baseline	6 Months	12 months
Joint indices for tenderness†	34 (2, 99)	21 (0, 61)	18 (4, 62)	32 (6, 112)	20 (2, 99)	21 (0, 90)	34 (2, 105)	26 (0, 66)	14 (2, 41)
Joint indices for swelling†	45 (6, 85)	25 (3, 51)	12 (0, 51)	51 (14, 85)	28 (2, 48)	14 (2, 40)	43 (18, 103)	20 (4, 62)	13 (1, 58)
Patient assessment of disease activity†	3 (2, 5)	2 (1, 4)	2 (2, 4)	3 (2, 5)	2 (1, 5)	2 (1, 5)	3 (2, 5)	2 (1, 4)	2 (1, 4)
Physician assessment of disease activity†	4 (2, 4)	3 (2, 4)	2 (2, 4)	4 (2, 5)	3 (2, 4)	2 (2, 3)	4 (2, 5)	3 (2, 5)	2 (2, 4)
Grip strength in right hand, *mm Hg*†	56.5 (5, 100)	66.7 (10, 205)	61.7 (9.3, 167)	40.5 (0, 173)	45 (13, 127)	48.3 (18.3, 133)	35 (5, 132)	53.3 (5, 180)	46.7 (8.3, 118)
Grip strength in left hand, *mm Hg*†	46.7 (4.3, 208)	56.7 (10, 223)	56.7 (10.7, 150)	40 (5, 243)	34.2 (5, 115)	48.3 (10, 152)	32.5 (1.3, 183)	30 (6.7, 190)	48.3 (10, 157)
Modified Health Assessment Questionnaire	1.8 (1, 3.4)		1.5 (1, 2.8)	2 (1, 3.8)		1.2 (1, 2.8)	2 (1.1, 3.4)		1.2 (1, 2.6)

* Median (minimum, maximum).
† $P < 0.05$ for time effects for the three treatment groups.

had marked improvement, moderate improvement, no improvement, or worsening were similar among the three groups ($P > 0.5$). We observed marked improvement in the pain and tenderness index after 12 months in 53%, 43%, and 61% of patients receiving placebo, low doses of folic acid, and high doses of folic acid, respectively. We found marked improvement in the swelling index in 68%, 78%, and 78% of patients receiving placebo, low doses of folic acid, and high doses of folic acid, respectively.

Patient Withdrawal and Dropout

We withdrew 13 patients because of noncompliance. One patient was withdrawn for taking additional folate supplements and one because diagnosis was reconsidered. Seven patients in the placebo group, 2 in the low-dose folic acid group, and 2 in the high-dose folic acid group discontinued methotrexate treatment because of toxic effects. More dropouts occurred in the placebo group (25%) than in the folic acid groups (8%) ($P = 0.08$).

Other Indices

As noted in Table 3, patient and physician assessment, joint indices for swelling and tenderness, and grip strength improved with time. We found significant time effects with respect to joint tenderness indices ($P = 0.025$), joint swelling indices ($P = 0.027$), physician assessment of disease ($P = 0.011$), patient assessment of disease ($P = 0.008$), right-hand grip strength ($P = 0.032$), and left-hand grip strength ($P = 0.047$). We observed no significant time–treatment interactions.

At the follow-up visits, changes in the median or mean values for the following variables were not statistically different among the groups: modified Health Assessment Questionnaire, erythrocyte sedimentation rate, hemoglobin level, hematocrit, leukocyte count, mean corpuscular volume, creatinine concentration, and aspartate aminotransferase or alkaline phosphatase levels. However, six of the patients in the placebo group had a mean corpuscular volume of 100 fL or more at one or more follow-up visits compared with only one and none in the low-dose or high-dose folic acid groups, respectively ($P = 0.02$).

Mean baseline plasma folate levels were 15, 10, and 13.5 nmol/mL ($P > 0.1$), and mean baseline erythrocyte folate levels were 662, 591, and 624 nmol ($P > 0.1$) in the placebo, low-dose folic acid, and high-dose folic acid groups, respectively. After 1 year, mean plasma folate levels in the placebo group decreased to 4.8 nmol/mL ($P < 0.01$) and mean plasma folate levels increased four to five times from baseline values in the folic acid groups ($P < 0.001$). In contrast, mean erythrocyte folate levels in the low-dose and high-dose folic acid groups were little changed (± 5%) from baseline values after 1 year, whereas levels in the placebo group decreased by approximately 50% (349 nmol/mL; $P < 0.001$ for baseline values compared with values at 1 year). Twelve (43%), 5 (20%), and 4 (15%) patients in the placebo, low-dose folic acid,

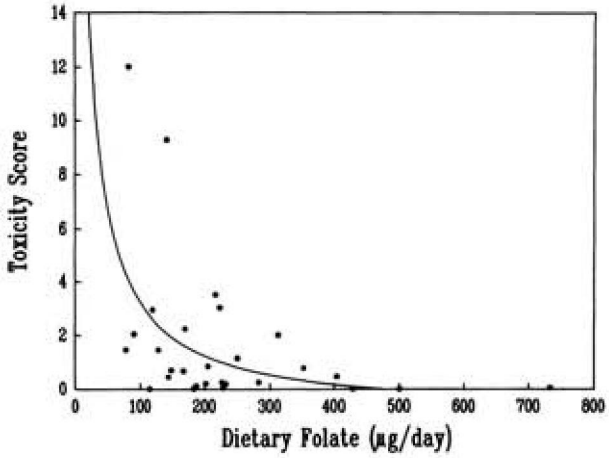

Figure 3. Toxicity score as a function of dietary folate intake in the placebo group. An exponential decay curve was fitted to the data. To convert micrograms to nanomoles, divide micrograms by 0.441 (the formula weight of folic acid is 441.4).

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