

## Niacin Revisited

### A Randomized, Controlled Trial of Wax-Matrix Sustained-Release Niacin in Hypercholesterolemia

Joseph M. Keenan, MD; Patricia L. Fontaine, MD; Joyce B. Wenz, RDMS; Shepherd Myers, MA; Zhiquan Huang, MD; Cynthia M. Ripsin, MS

• Two hundred one male and female subjects, aged 20 to 70 years, with elevated low-density lipoprotein cholesterol values (in the 75th to 95th percentiles), participated in a randomized, controlled, double-blind study using a new form of niacin (Endur-acin), which employs a wax-matrix vehicle for sustained release. Four niacin treatment groups (daily doses of 2000, 1500, 1250, and 1000 mg) were compared with placebo- and diet-treated controls to determine side-effect profile and optimal range of efficacy. The groups given 2000 and 1500 mg demonstrated significant reductions in values of low-density lipoprotein cholesterol (-26% and -19.3%, respectively), total cholesterol (-18.4% and -13.3%), and total cholesterol-high-density lipoprotein cholesterol ratio (-20.4% and -19.4%) when compared with diet- and placebo-treated controls. Smaller improvements were seen in high-density lipoprotein cholesterol and triglyceride levels. Blood chemistry monitoring indicated that reduction in low-density lipoprotein cholesterol level strongly correlated with an increase in baseline levels of some enzymes for niacin-treated subjects. The improved side-effect profile of the wax-matrix form of niacin was particularly notable. The dropout rate due to side effects was only 3.4% and was coupled with good medication compliance.

(Arch Intern Med. 1991;151:1424-1432)

Coronary artery disease is the leading cause of death in the United States.<sup>1</sup> About 1.5 million myocardial infarctions occur annually and are associated with considerable cardiovascular morbidity and related expense.<sup>1,2</sup> Elevated blood cholesterol level is one of the principal modifiable risk factors for cardiovascular disease.

Niacin is the oldest of today's commonly used hypocholesterolemic agents. First prescribed for the treatment of elevated cholesterol level in 1955, it has since maintained a good

record for safety and efficacy<sup>3</sup> and has been shown to reduce both cardiovascular risk and overall mortality.<sup>4</sup> Despite these benefits and the recommendation that it be used as a first-choice drug for hypercholesterolemia,<sup>5</sup> niacin's frequent cutaneous and gastrointestinal side effects have greatly restricted its use.<sup>6,6</sup> Sustained-release niacin preparations have been developed in an attempt to lessen side effects, but to date they have not offered much improvement over unmodified niacin. Knopp et al,<sup>7</sup> comparing effects of unmodified niacin with a widely prescribed capsule form of time-release niacin (Nicobid), found no significant difference between the two forms of niacin in terms of dropout rates (unmodified, 25%; Nicobid, 18%), while adherence was better for subjects taking unmodified niacin (90% of prescribed doses) when compared with time-release niacin (64% of prescribed doses).<sup>7</sup> More recently, Luria<sup>8</sup> noted a 40% dropout rate due to niacin side effects among subjects using only 1000 mg of a capsule form of sustained-release niacin.

A new formulation of niacin, a wax-matrix sustained-release preparation, has been demonstrated to have superior bioavailability when compared with the capsule form of time-release niacin.<sup>9</sup> Anecdotal reports and at least one uncontrolled study suggest that wax-matrix sustained-release niacin has good efficacy, with a much-reduced incidence of medication dropouts (4%) and side effects.<sup>10</sup>

We report the results of a controlled clinical trial specifically designed to assess the efficacy of wax-matrix sustained-release niacin (Endur-acin) over a range of dosage schedules as an intervention for hypercholesterolemia. Equally important clinically, this study sought to evaluate the claims that wax-matrix sustained-release niacin is an exceptionally well-tolerated formulation of niacin.

#### SUBJECTS AND METHODS

##### Recruitment

Potential subjects were initially identified by two methods: chart review at two family practice training clinics and review of results

Accepted for publication November 14, 1990.

From the Department of Family Practice and Community Health, University of Minnesota, Minneapolis.

Reprint requests to Department of Family Practice, 825 Washington Ave SE, Box 25, Minneapolis, MN 55414 (Dr Keenan).

Table 1.—Baseline Characteristics of Niacin, Diet, and Placebo Groups\*

Characteristic	Total Group (N=158)	Niacin, mg				Placebo			Significance
		2000 (N=22)	1500 (N=25)	1250 (N=25)	1000 (N=27)	Group 1 (N=17)	Group 2 (N=21)	Diet (N=21)	
Age, y	50 ± 11	51 ± 11	47 ± 11	49 ± 13	49 ± 10	53 ± 9	50 ± 11	54 ± 12	F = 1.17, NS
Body mass index, kg/m <sup>2</sup>	27.0	26.6	28.5	26.4	25.7	26.8	27.1	28.2	F = 1.3, NS
Cholesterol, mmol/L (mg/dL)									
Total	6.82 ± .65 (264 ± 25)	6.95 ± .60 (269 ± 23)	6.81 ± .53 (263 ± 20)	6.82 ± .76 (264 ± 29)	6.92 ± .78 (268 ± 30)	6.75 ± .62 (261 ± 24)	6.71 ± .64 (259 ± 25)	6.72 ± .60 (260 ± 23)	NS
HDL	1.30 ± .37 (50 ± 14)	1.28 ± .31 (49 ± 12)	1.20 ± .25 (46 ± 10)	1.25 ± .39 (48 ± 15)	1.43 ± .43 (55 ± 17)	1.37 ± .38 (53 ± 15)	1.28 ± .40 (49 ± 15)	1.31 ± .39 (51 ± 15)	P < .05
LDL	4.76 ± .56 (184 ± 22)	4.82 ± .52 (186 ± 20)	4.77 ± .43 (184 ± 17)	4.82 ± .61 (186 ± 24)	4.79 ± .75 (185 ± 29)	4.67 ± .45 (181 ± 17)	4.70 ± .49 (182 ± 19)	4.71 ± .60 (182 ± 23)	NS
Triglycerides, mmol/L (mg/dL)	1.63 ± .71 (144 ± 63)	1.86 ± .57 (165 ± 50)	1.81 ± .83 (160 ± 74)	1.57 ± .91 (139 ± 81)	1.51 ± .66 (134 ± 58)	1.55 ± .56 (137 ± 50)	1.56 ± .65 (138 ± 58)	1.52 ± .68 (135 ± 60)	NS
% nonsmokers	53.2	7.8	9.1	9.1	10.4	4.5	7.1	5.2	
% smokers	7.1	.6	2.6	2.6	0.0	1.3	0.0	0.0	χ <sup>2</sup> = 17.2, NS
% exsmokers	39.6	5.8	4.5	4.5	6.5	4.5	5.2	8.4	
% do not drink alcohol	19.0	.7	2.0	4.6	5.2	5.2	3.3	.7	
% do drink alcohol	81.0	13.7	14.4	11.8	11.8	9.8	8.5	11.1	χ <sup>2</sup> = 10.0, NS
Physical activity score									
Work	1.8	1.8	1.7	1.8	1.8	2.0	2.2	1.7	F = 1.39, NS
Leisure	2.0	1.7	2.0	2.1	2.3	2.1	2.0	2.2	F = 2.02, P = .07

\*Values unless otherwise indicated are mean ± SD. NS indicates not significant; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

from community-based cholesterol screening programs. Individuals were invited by letter to be screened for the study if they were between 20 and 70 years of age and had a previously recorded serum cholesterol value between the 75th and 95th percentiles for age and sex by Lipid Research Clinics standards.<sup>11</sup> Exclusionary conditions were the following: fasting triglyceride level greater than 4.52 mmol/L; fasting serum glucose value greater than 8.3 mmol/L; hyperuricemia or history of gout; history of peptic ulcer disease; active liver disease; history of drug or alcohol abuse; concurrent use of drugs known to affect lipid levels; previous surgical treatment to lower lipid levels; and pregnancy or a reasonable chance of becoming pregnant during the study. Subjects who qualified for the study on the basis of initial cholesterol and chemistry screening results were further evaluated with two additional complete lipid profiles (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides). Subjects whose LDL-C values were between the 75th and 95th percentiles for age and sex, based on the average of the baseline measurements, were then invited to participate in the study. Subjects gave written informed consent for this study, which was approved by the Human Subjects Committee of the University of Minnesota, Minneapolis. Table 1 gives baseline characteristics of study subjects.

#### Laboratory Methods

All serum for lipid determinations was obtained using a standardized protocol for phlebotomy technique and specimen handling. All plasma specimens were frozen until they could be analyzed by the Clinical Chemistry Laboratory of the University of Minnesota Hospital, a Centers for Disease Control-certified facility. Total cholesterol and HDL-C levels were measured with the cholesterol oxidase method (Roche Diagnostic Systems reagent and Roche COBAS FARA analyzer; Roche Diagnostics Systems, Nutley, NJ). Triglyceride values were assayed with an enzymatic method (Triglyceride GPO, Boehringer Mannheim Diagnostics, Indianapolis, Ind) and the same analyzer (Roche COBAS FARA). Low-density lipoprotein cholesterol values were calculated using the standard Friedewald formula.

#### Study Protocol

All subjects underwent a complete health history and physical examination at the beginning of the study to note baseline physical findings and cardiovascular risk factors. An end-of-study physical examination was optional.

After initial enrollment, all participants received instruction in the American Heart Association Step I (AHA-I) diet. Instruction consisted of a 2-hour small-group lecture given by a registered dietitian. Participants were advised to continue with the AHA-I diet for the duration of the study. They were informed that dietary compliance would be monitored by unscheduled telephone calls from certified interviewers near the end of each study phase.<sup>12</sup>

After a minimum of 6 weeks of dietary intervention, participants were randomized into treatment groups for the experimental phase of the study. Subjects were stratified by age, sex, and LDL-C level to ensure proportional distribution of these variables among seven treatment groups: diet alone, placebo (two groups), and niacin (four groups). A diet-alone control group was included to compare eating behavior and dietary adherence in groups taking medication vs not, as well as consequences in blood lipid levels. Likewise, one placebo-treated group (placebo group 2) had a scheduled reduction in the number of pills taken in the final phase to observe changes, if any, in medication compliance, dietary adherence, and blood lipid values. A more complete analysis of the behavioral aspects of the study will be reported in another article.

Niacin dosage varied among treatment groups and over time, as depicted in Table 2. Niacin and placebo tablets were distributed at large-group meetings conducted by us. These meetings also served as patient education sessions. Niacin side effects were discussed, and means of handling common side effects were described (eg, taking niacin with food or preceded by an aspirin tablet to reduce the incidence of flushing). The importance of continuing the AHA-I diet was stressed.

Three fasting lipid profiles were obtained from every subject at the end of the diet phase and at the end of each treatment phase. Three lipid determinations were made at each interval to enhance accuracy, and average values were used in analysis.<sup>13</sup> To monitor for asymptomatic side effects, fasting chemistry profiles (including glucose, uric acid, and liver enzymes) were obtained at entry and at the end of intermediate- and full-dose phases.

The Innovite Corporation (Tigard, Ore) was responsible for manufacture of both niacin and placebo tablets, which were identical in appearance and taste. Innovite also packaged the tablets according to a double-blind scheme in which niacin- and placebo-treated groups were known to investigators and participants only by group number and color of label. The identity of treatment groups was kept in a locked safe until the completion of the study. No medical complications occurred to require breaking the code.

Group	Phase 1, Low Dose, 4 wk	Phase 2, Intermediate Dose, 8 wk	Phase 3, Full Dose, 8 wk
Niacin, 1000 mg	250	500	1000
Niacin, 1250 mg	250	750	1250
Niacin, 1500 mg	250	1000	1500
Niacin, 2000 mg	250	1500	2000
Placebo group 1	1	2	4
Placebo group 2	1	4	2
Diet alone	...	...	...

\*All groups began with a 6-week phase of diet alone. Values are milligrams of niacin or tablets of placebo.

### Monitoring for Dietary and Drug Adherence

Baseline dietary behavior was assessed by a self-administered semiquantitative food frequency questionnaire.<sup>14</sup> To assess dietary adherence after initial group instruction by the registered dietitian, subjects were contacted by certified interviewers near the end of each study phase and asked to recall everything they had eaten in the preceding 24 hours. Food portion visual charts had been given to each patient so that portion size could be accurately assessed. Information obtained from telephone interviews was analyzed using the University of Minnesota Nutrition Coordinating Center's computerized diet analysis. Dietary behavior with respect to intake of cholesterol and saturated and polyunsaturated fats was further analyzed using the formulas of Keys et al<sup>15-18</sup> to determine the impact of diet on blood lipid levels.

Compliance with drug regimens was estimated with pill counts. Subjects were informed that each pill bottle contained more pills than were actually required for each study phase; remaining pills were expected to be turned in at the end of each phase for counting.

### Monitoring for Side Effects

Side effects were evaluated by questionnaire at the end of appropriate study phases. Niacin's common side effects (flushing, gastrointestinal upset, pruritis) and less-common side effects (dizziness, diarrhea, palpitations, visual changes) were listed, and participants were asked to report incidence and severity of these and any other symptoms experienced. Frequency of side effects was estimated, and severity of side effects was rated on five-point Likert scales. In addition, because side effects could be an important factor affecting dropout rate, any participants who failed to complete the study were contacted by telephone and asked to give their reasons for discontinuing.

### Statistical Analysis

The statistical analysis utilized a 7 × 5 (group × phase) repeated-measures analysis of variance (ANOVA) to compare treatment groups with respect to changes in lipid profiles and nutritional variables. A 7 × 3 (group × phase) repeated-measures ANOVA was used to investigate differences in blood chemistry results. For significant group × phase interactions, post hoc analyses were accomplished using Tukey's Honestly Significant Difference Test to investigate group differences at specific phases. The  $\chi^2$  test was used to analyze baseline characteristics that might have an effect on cholesterol levels.

## RESULTS

### Success of Randomization Scheme

Two hundred one subjects were randomized into treatment and control groups. There were no significant differences among groups with regard to lipid values at study entry, with the exception of a higher mean HDL-C level in the group given 1000 mg of niacin. Likewise, mean age, body mass index, and subjects' habits with respect to cigarette smoking,

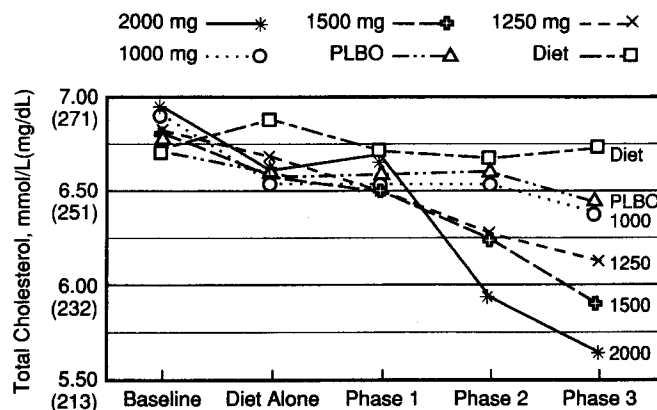


Fig 1.—Group changes in total cholesterol values in five phases of the study of wax-matrix sustained-release niacin, with doses indicated. PLBO indicates placebo.

alcohol consumption, and physical activity showed no significant differences among groups. Only subjects who completed the entire study are included in the analysis.

### Dropout Rate

One hundred fifty-eight subjects (79%) completed the entire study protocol. Of the 43 who did not complete the protocol, 24 (56%) cited logistical problems such as work and clinic scheduling difficulties, transportation problems, and child care conflicts. Most of these dropouts (70%) were from the diet- or placebo-treated groups or had dropped out during the diet phase before any niacin treatment had begun. In an additional seven subjects (16%), unrelated medical problems developed that caused them to terminate involvement. Uncommon reasons for discontinuing (two or fewer subjects each) included lack of continuing interest in study participation, dissatisfaction with assignment to the diet control group, moving away, fear of niacin side effects before treatment, and unavailability for follow-up.

Of the 117 subjects in niacin treatment groups, four dropped out owing to presumed niacin side effects. This translates into a 3.4% niacin-related dropout rate.

### Changes in Lipid and Lipoprotein Values

Group means were obtained at the end of each study phase for TC, LDL-C, HDL-C, triglycerides, and TC/HDL-C ratio. Figures 1 through 5 show the results of blood lipid values by study phase. Table 3 is a reference chart of the actual lipid values by group and phase of study.

At the end of the diet phase of the study (ie, after subjects in all groups had observed the AHA-I diet for a minimum of 6 weeks), the entire study population demonstrated little change in lipid values. They averaged a 2.7% decrease in TC value, a 3.3% decrease in LDL-C value, a 2% decrease in TC/HDL-C ratio, and no changes in HDL-C and triglyceride values. By the end of the third study phase, the higher-dose groups (1500 and 2000 mg) experienced significant ( $P < .05$ ) reductions in TC, LDL-C, and TC/HDL-C ratio compared with placebo-treated and control groups. The group given 1500 mg of niacin had a reduction of the TC/HDL-C ratio of 19.4%, which was essentially comparable with the 20.4% TC/HDL-C ratio reduction for the group given 2000 mg of niacin.

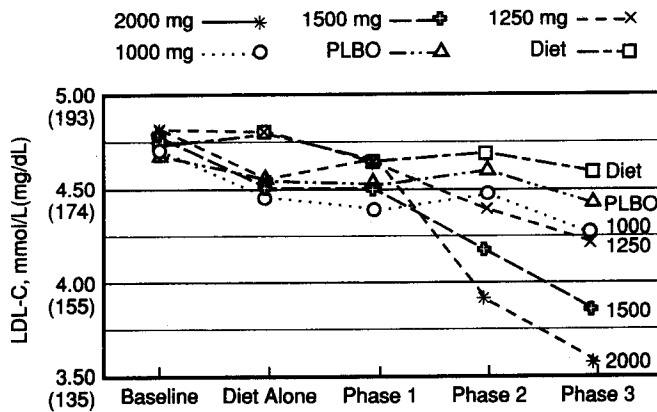


Fig 2.—Group changes in low-density lipoprotein cholesterol (LDL-C) values in five phases of the study of wax-matrix sustained-release niacin, with doses indicated. PLBO indicates placebo.

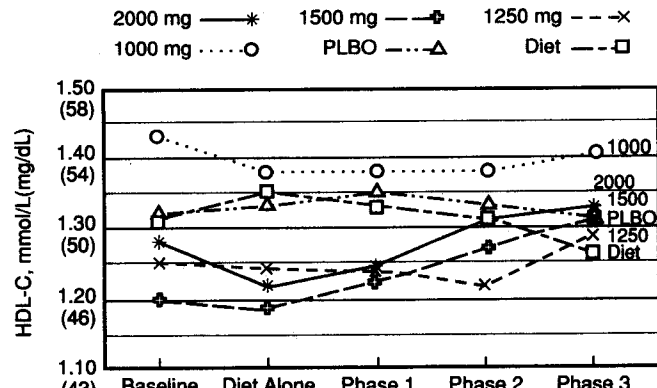


Fig 3.—Group changes in high-density lipoprotein cholesterol (HDL-C) values in five phases of the study of wax-matrix sustained-release niacin, with doses indicated. PLBO indicates placebo.

High-density lipoprotein cholesterol level increased in the third study phase compared with mean preliminary values in the three groups given the highest doses of niacin (1250, 1500, and 2000 mg). However, only in the group given 1500 mg of niacin was the increase in HDL-C level statistically significant ( $P < .05$ ). Triglyceride levels showed modest but not statistically significant improvement with the groups given higher niacin doses.

#### Adherence to AHA-I Diet

Analysis of subjects' baseline diets indicated that they were consuming an average of 33% of total energy as fat, with 11% as saturated, 12% as monounsaturated, and 7% as polyunsaturated fat. The baseline cholesterol consumption averaged 263 mg/d. Analysis of the 24-hour recall surveys during the final phase of the study revealed means for the entire study population that approximate the guidelines suggested for the AHA-I diet: 31.3% of total energy as fat, 10% saturated, 12% monounsaturated, and 7% polyunsaturated, with a mean cholesterol intake of 225 mg/d.

Analysis of group dietary behavior revealed no significant differences between groups at the beginning of the study or during any subsequent phase of the study. Intake of fats and dietary cholesterol by group and phase when evaluated by the formulas of Keys et al predicted minimal differences in change

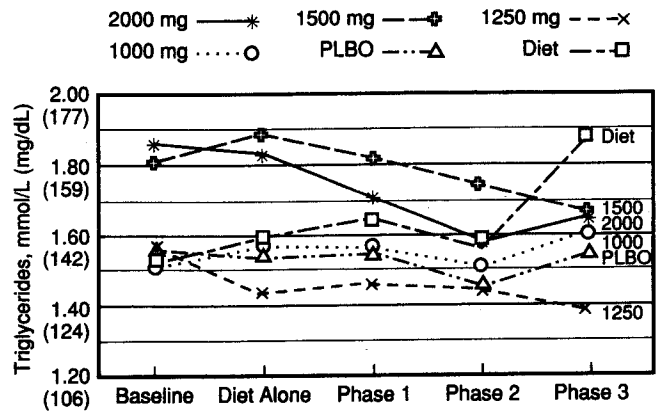


Fig 4.—Group changes in triglyceride values in five phases of the study of wax-matrix sustained-release niacin, with doses indicated. PLBO indicates placebo.

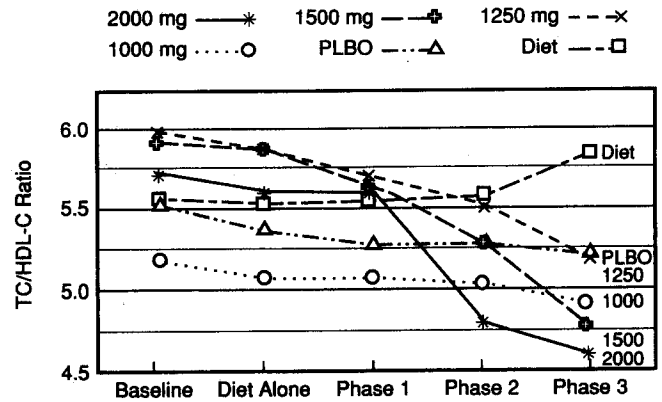


Fig 5.—Group changes in total cholesterol–high-density lipoprotein cholesterol (TC/HDL-C) ratios in five phases of the study of wax-matrix sustained-release niacin, with doses indicated. PLBO indicates placebo.

in plasma cholesterol levels (<3%) due to the diet portion of the intervention.

#### Adherence to Niacin Regimens

Overall, adherence to the niacin regimens for the entire study revealed only minor intergroup differences. Percentage of doses taken ranged from a high 95% in the group given 1500 mg of niacin to 88% in the group given 2000 mg of niacin. Intermediate levels of adherence were demonstrated by the placebo-treated group (93%), the group given 1000 mg of niacin (92%), and the group given 1250 mg of niacin (89%). There was a tendency for adherence to wane slightly over the course of the study, with 94.4% of doses taken by all groups in the first study phase, 91% of doses taken in the second phase, and 89.6% of doses taken in the third phase. At the highest doses (third phase), adherence for the group given 2000 mg of niacin dropped slightly, to 84%, while the other groups maintained percentages similar to their overall means.

#### Side Effects

While the majority of subjects receiving niacin experienced some symptoms due to the drug, the symptoms were largely infrequent, tolerable, or easily managed. To reflect clearly the clinical importance of side effects, a subset of clinically significant symptoms was identified for analysis. Side effects

Table 3.— Summary of Lipid Results by Study Phase and Percent Change From Baseline to Phase 3\*

Treatment	Baseline	Diet	Phase 1	Phase 2	Phase 3	% Change Baseline to Phase 3
<b>TC, mmol/L (mg/dL)</b>						
<b>Niacin, mg</b>						
2000	6.95 ± 0.60 (269 ± 23)	6.61 ± 0.69 (256 ± 27)	6.70 ± 0.69 (259 ± 27)	5.93 ± 1.01 (229 ± 39)	5.65 ± 1.15 (218 ± 44)	-19
1500	6.81 ± 0.53 (263 ± 20)	6.58 ± 0.91 (254 ± 35)	6.49 ± 0.66 (251 ± 26)	6.24 ± 0.74 (241 ± 29)	5.89 ± 0.75 (228 ± 29)	-13
1250	6.83 ± 0.76 (264 ± 29)	6.70 ± 0.89 (259 ± 34)	6.52 ± 0.87 (252 ± 34)	6.27 ± 0.85 (242 ± 33)	6.12 ± 0.79 (237 ± 31)	-10
1000	6.92 ± 0.78 (268 ± 30)	6.56 ± 0.93 (254 ± 36)	6.49 ± 0.96 (251 ± 37)	6.54 ± 1.02 (253 ± 39)	6.38 ± 0.86 (247 ± 33)	-8
Placebo	6.73 ± 0.63 (260 ± 24)	6.59 ± 0.89 (255 ± 34)	6.58 ± 0.83 (254 ± 32)	6.60 ± 0.84 (255 ± 32)	6.43 ± 0.80 (249 ± 31)	-4
Diet alone	6.72 ± 0.60 (260 ± 23)	6.88 ± 0.76 (266 ± 29)	6.71 ± 0.74 (259 ± 29)	6.68 ± 0.45 (258 ± 17)	6.73 ± 0.74 (260 ± 29)	+0.07
<b>LDL-C, mmol/L (mg/dL)</b>						
<b>Niacin, mg</b>						
2000	4.82 ± 0.53 (186 ± 20)	4.55 ± 0.63 (176 ± 24)	4.66 ± 0.64 (180 ± 25)	3.89 ± 0.79 (150 ± 31)	3.57 ± 1.11 (138 ± 43)	-26
1500	4.77 ± 0.43 (184 ± 17)	4.52 ± 0.75 (175 ± 29)	4.48 ± 0.57 (173 ± 22)	4.19 ± 0.60 (162 ± 23)	3.84 ± 0.64 (148 ± 25)	-20
1250	4.82 ± 0.61 (186 ± 24)	4.80 ± 0.84 (186 ± 32)	4.63 ± 0.86 (179 ± 33)	4.38 ± 0.80 (169 ± 31)	4.20 ± 0.91 (162 ± 35)	-13
1000	4.79 ± 0.75 (185 ± 29)	4.46 ± 0.89 (172 ± 34)	4.39 ± 0.96 (168 ± 37)	4.47 ± 1.00 (173 ± 39)	4.24 ± 0.86 (164 ± 33)	-11
Placebo	4.69 ± 0.47 (181 ± 18)	4.55 ± 0.74 (176 ± 29)	4.52 ± 0.67 (175 ± 26)	4.60 ± 0.71 (178 ± 27)	4.41 ± 0.66 (171 ± 26)	-6
Diet alone	4.71 ± 0.60 (182 ± 23)	4.80 ± 0.70 (186 ± 27)	4.64 ± 0.59 (179 ± 23)	4.68 ± 0.48 (181 ± 19)	4.58 ± 0.74 (177 ± 29)	-3
<b>HDL-C, mmol/L (mg/dL)</b>						
<b>Niacin, mg</b>						
2000	1.28 ± 0.31 (49 ± 12)	1.22 ± 0.26 (47 ± 10)	1.25 ± 0.29 (48 ± 11)	1.32 ± 0.39 (51 ± 15)	1.33 ± 0.37 (51 ± 14)	+4
1500	1.20 ± 0.26 (46 ± 10)	1.20 ± 0.34 (46 ± 13)	1.22 ± 0.29 (47 ± 11)	1.27 ± 0.34 (49 ± 13)	1.32 ± 0.32 (51 ± 12)	+9
1250	1.25 ± 0.39 (48 ± 15)	1.24 ± 0.34 (48 ± 13)	1.24 ± 0.33 (48 ± 13)	1.22 ± 0.32 (47 ± 12)	1.29 ± 0.35 (50 ± 14)	+3
1000	1.44 ± 0.43 (56 ± 17)	1.38 ± 0.41 (53 ± 16)	1.38 ± 0.42 (53 ± 16)	1.38 ± 0.37 (53 ± 14)	1.40 ± 0.40 (54 ± 15)	-2
Placebo	1.32 ± 0.40 (51 ± 15)	1.33 ± 0.41 (51 ± 16)	1.35 ± 0.41 (52 ± 16)	1.34 ± 0.37 (52 ± 14)	1.32 ± 0.38 (51 ± 15)	-0.4
Diet alone	1.31 ± 0.39 (51 ± 15)	1.35 ± 0.41 (52 ± 16)	1.33 ± 0.45 (51 ± 17)	1.31 ± 0.43 (51 ± 17)	1.26 ± 0.41 (49 ± 16)	-4
<b>Triglycerides, mmol/L (mg/dL)</b>						
<b>Niacin, mg</b>						
2000	1.86 ± 0.57 (165 ± 50)	1.83 ± 0.55 (162 ± 49)	1.72 ± 0.54 (152 ± 48)	1.59 ± 0.72 (141 ± 64)	1.65 ± 0.68 (146 ± 60)	-11
1500	1.82 ± 0.83 (161 ± 74)	1.89 ± 1.00 (167 ± 89)	1.82 ± 1.25 (161 ± 111)	1.75 ± 1.06 (155 ± 94)	1.66 ± 1.06 (147 ± 94)	-9
1250	1.57 ± 0.91 (139 ± 81)	1.43 ± 0.56 (127 ± 50)	1.46 ± 0.76 (129 ± 67)	1.44 ± 0.57 (128 ± 50)	1.37 ± 0.50 (121 ± 44)	-13
1000	1.51 ± 0.66 (134 ± 58)	1.57 ± 0.64 (139 ± 57)	1.56 ± 0.71 (138 ± 63)	1.50 ± 0.55 (133 ± 49)	1.60 ± 0.67 (142 ± 59)	+7
Placebo	1.56 ± 0.61 (138 ± 54)	1.53 ± 0.63 (136 ± 56)	1.55 ± 0.66 (137 ± 58)	1.44 ± 0.53 (128 ± 47)	1.54 ± 0.60 (136 ± 53)	-1
Diet alone	1.52 ± 0.68 (135 ± 60)	1.59 ± 0.74 (141 ± 66)	1.64 ± 1.01 (145 ± 89)	1.56 ± 0.63 (138 ± 56)	1.88 ± 1.13 (167 ± 100)	+24
<b>TC/HDL-C ratio</b>						
<b>Niacin, mg</b>						
2000	5.73 ± 1.36	5.61 ± 1.10	5.60 ± 1.27	4.80 ± 1.35	4.57 ± 1.64	-20
1500	5.92 ± 1.37	5.88 ± 1.62	5.64 ± 1.46	5.27 ± 1.57	4.76 ± 1.42	-20
1250	5.98 ± 1.92	5.85 ± 1.87	5.69 ± 1.77	5.51 ± 1.79	5.18 ± 1.82	-13
1000	5.18 ± 1.33	5.07 ± 1.30	5.07 ± 1.48	5.03 ± 1.34	4.90 ± 1.39	-5
Placebo	5.54 ± 1.61	5.36 ± 1.57	5.26 ± 1.43	5.28 ± 1.41	5.20 ± 1.20	-6
Diet alone	5.56 ± 1.67	5.52 ± 1.69	5.54 ± 1.22	5.58 ± 1.66	5.83 ± 1.79	+5

\*TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol. Values are mean ± SD.

were defined as clinically significant, even if they occurred only once or twice in the entire study, when subjects rated them as moderate to severe in intensity. Moderate to severe symptoms were specifically defined as any requiring reduction or discontinuation of niacin treatment, modification of daily routine, or use of an over-the-counter or physician-prescribed remedy to alleviate the symptom. Thus, any subject experiencing flushing severe enough to warrant taking

aspirin, or heartburn requiring the use of an antacid, was characterized as having clinically significant symptoms.

The side effects most commonly experienced by niacin-treated subjects are given in Table 4. Although subjects in placebo treatment groups did experience side effects, no episodes fulfilled the criteria for clinically significant symptoms. Statistically significant differences between the combined niacin-treated and the combined placebo-treated

Table 4.—Incidence of Clinically Significant Symptoms in Niacin-Treated Subjects	
Symptoms	Niacin-Treated Groups, No. (%)
Flushing	14 (10.2)*
Itching	10 (7.3)*
Tingling	5 (3.6)
Upper gastrointestinal tract symptoms	7 (5.1)
Constipation	2 (1.5)
Diarrhea	6 (4.4)
Dizziness	1 (0.7)
Palpitations	2 (1.5)
Blurred vision	2 (1.5)

\*Significantly greater incidence than in placebo-treated groups ( $P < .05$ ).

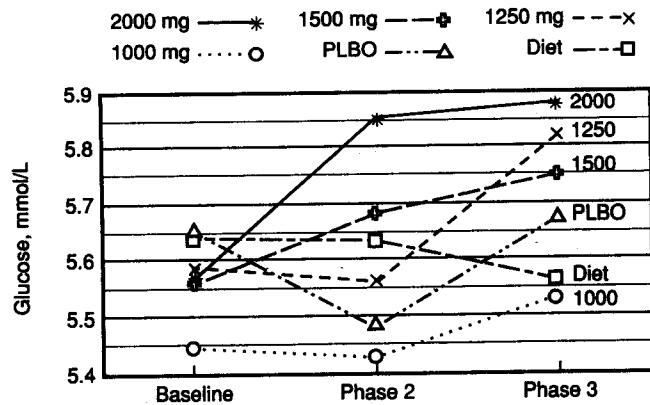


Fig 6.—Group changes in blood glucose values at baseline, intermediate, and full-dose phases, with doses indicated. PLBO indicates placebo.

groups were present only for incidence of flushing (10.2% of niacin-treated subjects;  $\chi^2 = 5.98$ ,  $P = .01$ ) and itching skin (7.3% of niacin-treated subjects;  $\chi^2 = 4.14$ ,  $P = .04$ ).

#### Abnormalities in Blood Chemistry Values

Interval monitoring of blood chemistry values, including blood glucose, uric acid, and liver enzymes, appeared to reveal a pattern of chance abnormalities seen in multiple testings of large groups of subjects. Less than 3% of the chemistry test results were out of the normal range, and these were mostly borderline abnormalities scattered with similar incidence throughout all groups (control and treatment). Analysis of group means for each blood chemistry test by phase did show significant differences between baseline levels for some groups as well as significant intergroup differences in treatment phases. The three groups given higher doses of niacin (1250, 1500, or 2000 mg) all showed significant increases ( $P < .01$  to  $P < .05$ ) in the alkaline phosphatase level from baseline to the third phase. However, only the group given 2000 mg showed a significant increase ( $P < .01$ ) in mean glucose levels from baseline to the final study phase. Furthermore, when comparing intergroup differences within the third phase, the group given 2000 mg demonstrated significantly higher levels ( $P < .01$ ) of alkaline phosphatase than all other groups except the group given 1250 mg. Of note, the reduction in the LDL-C level correlated strongly ( $r = -.49$ ,  $P < .001$ ) with an increase in the aspartate aminotransferase (AST) level for the niacin treatment groups ( $n = 96$ ), and there was no similar correlation for control groups. Figures 6

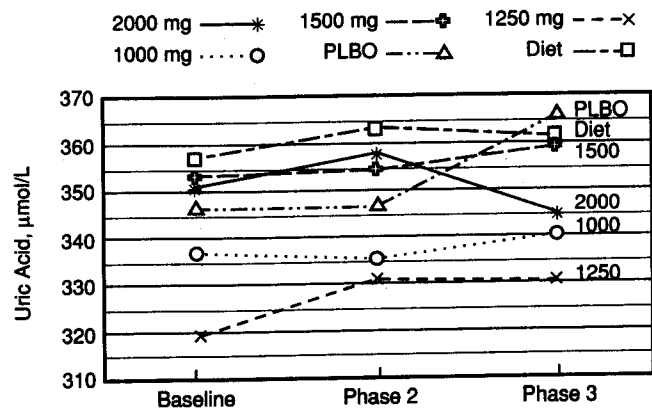


Fig 7.—Group changes in blood uric acid values at baseline, intermediate, and full-dose phases, with doses indicated. PLBO indicates placebo.

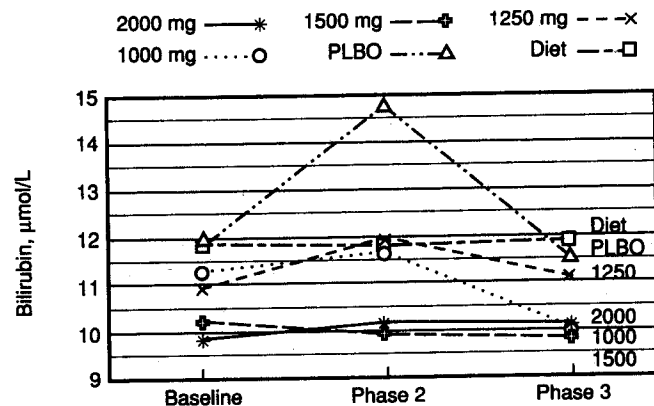


Fig 8.—Group changes in blood bilirubin values at baseline, intermediate, and full-dose phases, with doses indicated. PLBO indicates placebo.

through 11 summarize these data for blood glucose, uric acid, and liver function tests (bilirubin, alkaline phosphatase, AST, and lactate dehydrogenase).

In one subject taking 2000 mg/d of niacin, marked gastrointestinal symptoms and a hepatitislike syndrome developed, with several days of nausea and vomiting and associated elevation of AST value. Her symptoms abated promptly after discontinuing use of niacin, and her liver function test results returned to normal over the following 4 weeks. Results of other tests for viral hepatitis were normal.

In three niacin-treated subjects (2.6%), asymptomatic elevation of AST values developed, as it did in 4.8% of subjects in groups given placebo and diet alone. Mean elevation of AST values was 75 U/L for niacin-treated subjects and 57 U/L for controls.

#### COMMENT

The mechanism of niacin's action of lipoprotein metabolism is not fully understood, but investigators have demonstrated that niacin reduces very low-density lipoprotein cholesterol values and in turn decreases hepatic synthesis of LDL-C.<sup>19</sup> Knopp et al<sup>7</sup> have suggested that time-release niacin may directly reduce LDL-C levels without an attendant reduction in very low-density lipoprotein or triglyceride values. Sterol balance studies of the intake and elimination of cholesterol

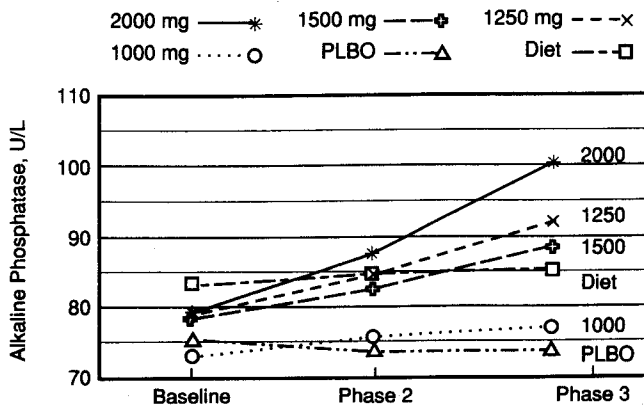


Fig 9.—Group changes in blood alkaline phosphatase values at baseline, intermediate, and full-dose phases, with doses indicated. PLBO indicates placebo.

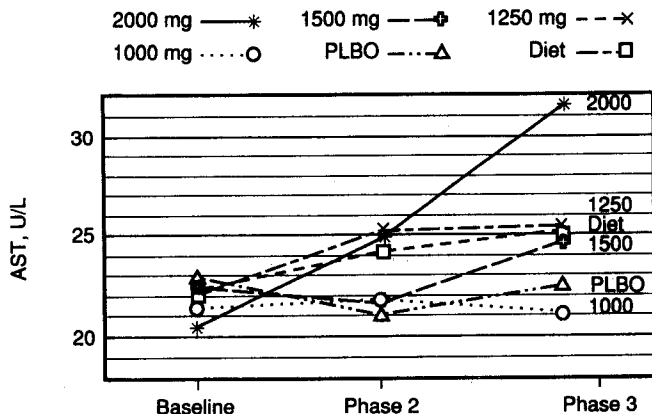


Fig 10.—Group changes in aspartate aminotransferase (AST) values at baseline, intermediate, and full-dose phases, with doses indicated. PLBO indicates placebo.

with niacin are essentially neutral, so it does not appear to reduce cholesterol by increased excretion.<sup>19</sup>

In this study, the changes in blood lipid values were measured to assess the efficacy of the AHA-I diet and the various dosage schedules of wax-matrix niacin in conjunction with the AHA-I diet. The lipid values measured (TC, LDL-C, HDL-C, triglycerides, and TC/HDL-C ratio) were limited to those typically used in the routine clinical treatment of hypercholesterolemic patients. The diet-alone intervention resulted in very little change in blood lipid values. This appears to be explained, in part, by the relatively healthful diet behavior of these subjects before entry (33% of energy from fat and 263 mg/d average cholesterol intake). It was evident during the study that some of the diet-treated control subjects were disappointed that they were not selected into one of the treatment groups. Perhaps this adversely affected their motivation for dietary compliance. However, analysis of nutritional monitoring failed to show significant intergroup differences in diet behavior. Even though there were significant individual successes with the diet intervention, the overall impact on group lipid changes was not impressive.

Several other recent studies involving groups of subjects on fat- and cholesterol-modified diets have reported relatively healthful prestudy baseline eating behavior.<sup>20,21</sup> This may reflect the improved eating habits of our society or may

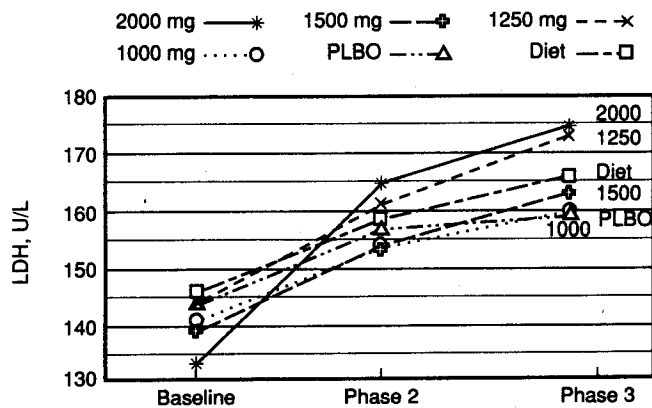


Fig 11.—Group changes in lactate dehydrogenase (LDH) values in baseline, intermediate, and full-dose phases, with doses indicated. PLBO indicates placebo.

simply be characteristic of subjects who volunteer for such studies. A large dietary intervention study, the Multiple Risk Factor Intervention Trial, demonstrated a sustained 7.5% reduction in cholesterol level over a 6-year period (1979 to 1985).<sup>22</sup> The investigators also reported that this reduction was less than expected, and they accounted for the difference by noting that baseline fat and cholesterol consumption of their subjects was less than hypothesized using the National Diet Heart Study information from 1968. If the baseline dietary habits of study subjects are indicative of patterns in the overall population, then the eating behavior of our society appears to be getting more healthful and prudent.

The blood lipid results of this study demonstrate the efficacy of relatively modest doses of wax-matrix sustained-release niacin in reducing LDL-C levels. In contrast, the changes in HDL-C and triglyceride values were less impressive, and they did not follow a typical dose-response curve as seen with LDL-C values. Luria<sup>8</sup> reported a significant increase in HDL-C levels (+31%) with a 1-g dose of sustained-release niacin but no significant change in triglyceride or LDL-C values. Knopp et al<sup>7</sup> showed a significant response in HDL-C (+26%) and triglyceride (-27%) values with 3 g of unmodified niacin but insignificant changes in HDL-C and triglyceride values using 3 g of time-release niacin.<sup>7</sup> These disparate lipid results with similar doses of a pharmacological agent are confusing and suggest that the pharmacokinetics associated with the various formulations may indeed change the specific lipid effect. The accumulated literature on niacin suggests that it is useful for lowering TC, LDL-C, and triglyceride values and for increasing the HDL-C level. This may be true for unmodified niacin, but the effect on blood lipid values appears far more variable with sustained-release preparations.

This study was designed to assess a range of dosage schedules to determine, if possible, an optimal dose for clinical use. It was noted that the group given 2000 mg of niacin showed some drop in medication adherence (84%) in the third, full-dose phase, as compared with the group given 1500 mg of niacin (95% adherence in the third study phase). The 1500-mg dose seemed to offer the best combination of efficacy and tolerance. Although niacin therapy must be individualized, it appears that, at least initially, 1500 mg of the wax-matrix form of niacin would be a desirable total dose for most patients.

The asymptomatic abnormalities in liver function test results seen in some of the study subjects and the transient hepatitislike syndrome in one case strongly support the monitoring of liver function during niacin therapy. As noted in this study, abnormal elevations of values of blood glucose, uric acid, and liver enzymes (transaminases) can occur with niacin use, yet our experience supports the literature that indicates these abnormalities are easily reversible with lowering the dose or discontinuing use of the medication.<sup>6</sup> Also, borderline abnormalities of liver function tests occurred as often in the control groups as in those treated with niacin, suggesting that clinicians should recheck such results before discontinuing niacin therapy. The most severe reaction to niacin treatment is a fulminant toxic hepatitis, which can require liver transplantation. A recently reported case of profound liver failure associated with high doses (6000 mg/d) of sustained-release (not wax-matrix) niacin<sup>28</sup> underscores the need for physician management of niacin therapy.

One of the most interesting and, perhaps, important findings of this study is an observation resulting from the blood chemistry monitoring. An increase in the enzyme levels of AST, lactate dehydrogenase, and alkaline phosphatase correlated strongly and significantly with the reduction in LDL-C level in all niacin treatment groups, whereas the control groups failed to demonstrate such a correlation. These findings suggest a hepatic site of action for niacin's lipid-lowering effect. Analysis of the predictive value of these enzyme changes may offer a more sensitive method of monitoring both toxic and therapeutic effects. To date, clinicians have followed the blood chemistry values of patients receiving niacin therapy to monitor for abnormalities in liver function and glucose and uric acid metabolism, but they have failed to appreciate the subtler changes that occur within the normal range of values. More information on the relationship between the change in baseline values of liver function tests (AST, alkaline phosphatase) and niacin effects may prove useful in the clinical management of niacin therapy. A long-term follow-up study with approximately 100 of these subjects is currently under way and will offer an opportunity to evaluate these findings further.

Physicians should be aware that quality and bioavailability of various over-the-counter vitamin preparations can be extremely variable. The Food and Drug Administration requires that products designated "generally regarded as safe" assay within 10% of the quantity of drug or vitamin the manufacturer claims it contains. There are no standards, most notably for controlled-release products, that specify solubility in the gastrointestinal tract, rate of release of medication, or bioavailability. Thus, physicians and patients alike should be cautioned that not all niacin preparations are alike or equivalent, despite similar milligram strengths. Figge et al<sup>19</sup> demonstrated almost twice the bioavailability of the wax-matrix sustained-release niacin when compared milligram for milligram with capsule time-release niacin. This is consistent with the clinical findings of Knopp et al,<sup>7</sup> who demonstrated lipoprotein changes with 3000 mg of time-release niacin (LDL-C, -13%; HDL-C, +8%) that were almost comparable with those seen in this study with the 1500-mg dose of wax-matrix niacin (LDL-C, -19.3%; HDL-C, +9.5%).

The types of side effects seen in this study are similar to those reported in sustained-release niacin studies by Luria<sup>8</sup>

and Knopp et al.<sup>7</sup> However, the dropout rates due to niacin intolerance for those studies (40% and 14%, respectively) were notably higher than in this study (3.4%) and suggest that wax-matrix niacin has milder and less-frequent side effects than the capsule form of time-release niacin. Superior tolerance is further supported by favorable adherence to medication schedules in this study (range, 84% to 95% of doses). By contrast, Knopp et al<sup>7</sup> reported that adherence in their study (64%) was hampered by side effects.

The major cutaneous side effects of niacin—flushing, tingling, and itching—appear to be related to the rate of gastrointestinal absorption. For example, taking niacin with food slows absorption and decreases flushing. Surprisingly, in view of the better side-effect profile of wax-matrix niacin, the findings of a bioavailability study indicate that the wax-matrix niacin is twice as well absorbed over 24 hours as the capsule form of controlled-release niacin.<sup>9</sup> With greater absorption, increased side effects would be expected. Since this is not the case, one could speculate that the wax-matrix vehicle must effectively provide a smooth rate of sustained release to help minimize side effects.

An additional and significant advantage of wax-matrix sustained-release niacin is the cost of the medication. At approximately \$0.25/d for a 1500-mg regimen, it is far less expensive than most other medications available for the treatment of hyperlipidemia, including capsule time-release niacin.

#### CONCLUSION

Three separate, well-designed clinical trials have demonstrated that pharmacological reduction of cholesterol levels in asymptomatic hypercholesterolemic men results in lowered cardiac morbidity and mortality.<sup>24-26</sup> The National Cholesterol Education Program (NCEP) guidelines have established new national standards for the diagnosis and treatment of hypercholesterolemia.<sup>5</sup> Using NCEP standards, it is estimated that 36% of all adults aged 20 to 74 years, or over 60 million Americans, are in need of medical advice and intervention for high blood cholesterol levels.<sup>27</sup> Although diet and life-style adjustments are advised as the first level of intervention, it is likely that many of these patients will still require the addition of drug therapy to manage their cholesterol levels adequately. Thus, a safe, effective, well-tolerated, and affordable pharmacological intervention is needed for the growing numbers of persons who are identified as hypercholesterolemic and who fail the first level of intervention.

This study has demonstrated that relatively low doses of wax-matrix sustained-release niacin can provide effective therapy for hypercholesterolemia. More importantly, this form of sustained-release has greatly improved the side-effects profile of one of the oldest and safest cholesterol-lowering agents. This and its low cost make wax-matrix sustained-release niacin an attractive first choice when drug therapy is indicated.

This study was relatively short, only 8 weeks at full dose. Thus, additional research is needed with larger subject groups for longer periods to assess the potential for additional improvements in lipoprotein values and to confirm these results and their maintenance over time. Also, further study is warranted of the bioavailability of various niacin preparations as well as of the toxic vs therapeutic effects of niacin on liver function.

## References

1. National Center for Health Statistics. Advance report of final mortality statistics, 1985. *Monthly Vital Statistics Report [Suppl]*. 1988;37. Hyattsville, Md: Public Health Service publication 88-1120.
2. American Heart Association. *1989 Heart Facts*. Dallas, Tex: American Heart Association; 1988.
3. Altschul R, Hoffer A, Stephen JD. Influence of nicotinic acid on serum cholesterol in man. *Arch Biochem Biophys*. 1955;54:558-559.
4. Canner PL, Berge KG, Wenger NK, et al. Fifteen-year mortality in coronary drug project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245-1255.
5. The Expert Panel. *Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults*. Bethesda, Md: Public Health Service; 1989. US Dept of Health and Human Services publication NIH 89-2925.
6. Blum CB, Levy RI. Current therapy for hypercholesterolemia. *JAMA*. 1989;261:3582-3587.
7. Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues of mechanism of action of niacin. *Metabolism*. 1985;34:642-650.
8. Luria MH. Effect of low-dose niacin on high-density lipoprotein cholesterol and total cholesterol/high-density lipoprotein cholesterol ratio. *Arch Intern Med*. 1988;148:2493-2496.
9. Figge HL, Figge J, Souney PF, et al. Comparison of excretion of nicotinic acid after ingestion of two controlled release nicotinic acid preparations in man. *J Clin Pharmacol*. 1988;28:1136-1140.
10. Alderman JD, Pasternak RC, Sacks FM, Smith HS, Monrad ES, Grossman W. Effect of a modified, well-tolerated niacin regimen on serum total cholesterol, high density lipoprotein cholesterol and the cholesterol to high density lipoprotein ratio. *Am J Cardiol*. 1989;64:725-729.
11. Rifkind BM, Segal P. Lipid Research Clinics Program reference values for hyperlipidemia and hypolipidemia. *JAMA*. 1983;250:1869-1872.
12. Morgan KJ, Johnson SR, Rizek RL, Reese R, Stampley GL. Collection of food intake data: an evaluation of methods. *J Am Diet Assoc*. 1987;87:888-896.
13. Jacobs DR, Barrett-Connor E. Retest reliability of plasma cholesterol and triglyceride: the lipid research clinics prevalence study. *Am J Epidemiology*. 1982;116:878-885.
14. Willett WC, Reynolds RD, Cottrell-Hoehner S, Sampson L, Browne ML. Validation of a semi-quantitative food frequency questionnaire: comparison with a 1-year diet record. *J Am Diet Assoc*. 1987;87:43-47.
15. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet, I: iodine value of dietary fat versus 2S-P. *Metabolism*. 1965;14:747-758.
16. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet, II: the effect of cholesterol in the diet. *Metabolism*. 1965;14:759-765.
17. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet, III: differences among individuals. *Metabolism*. 1965;14:766-775.
18. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet, IV: particular saturated fatty acids in the diet. *Metabolism*. 1965;14:776-787.
19. Grundy SM, Mok HYI, Zech L, Berman M. Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. *J Lipid Res*. 1981;22:24-36.
20. Demark-Wahnefried W, Bowering J, Cohen PS. Reduced serum cholesterol with dietary change using fat-modified and oat bran supplemented diets. *J Am Diet Assoc*. 1990;90:223-229.
21. Van Horn LV, Liu K, Parker D, et al. Serum lipid response to oat product intake with a fat-modified diet. *J Am Diet Assoc*. 1986;86:759-764.
22. Dolecek TA, Milas NC, Van Horn LV, et al. A long-term nutrition intervention experience: lipid responses and dietary adherence patterns in the multiple risk factor intervention trial. *J Am Diet Assoc*. 1986;86:752-758.
23. Mullin GE, Greenon JK, Mitchell MC. Fulminant hepatic failure after ingestion of sustained-release nicotinic acid. *Ann Intern Med*. 1989;111:253-255.
24. Committee of Principal Investigators, World Health Organization. W.H.O. cooperative trial on primary prevention of ischaemic heart disease with clofibrate to lower serum cholesterol: mortality follow-up. *Lancet*. 1984;2:600-604.
25. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med*. 1987;317:1237-1245.
26. The Lipid Research Clinics Coronary Primary Prevention Trial results, II: the relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984;251:365-374.
27. Sempos C, Fulwood R, Haines C, et al. The prevalence of high blood cholesterol levels among adults in the United States. *JAMA*. 1989;262:45-52.