

## **Normalization of plasma lipoprotein concentrations in patients with type II hyperlipoproteinemia by combined use of neomycin and niacin**

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**ABSTRACT** The oral administration of neomycin or niacin as single-drug therapy can significantly lower total and low-density lipoprotein cholesterol concentrations in patients with type II hyperlipoproteinemia. However, in the majority of patients treated with one of these drugs as sole therapy plasma lipid and lipoprotein concentrations do not normalize. The effect of combined neomycin (2 g/day) and niacin (3 g/day) treatment on the plasma lipoprotein concentrations was determined in 25 type II hyperlipoproteinemic patients in a double-blind, randomized, placebo-controlled, crossover clinical trial. Treatment with neomycin was well tolerated by all 25 study patients and significantly reduced total and low-density lipoprotein cholesterol concentrations by 23% and 29%, respectively ( $p < .05$ ). In contrast to the well-tolerated neomycin regimen, 11 patients (44%) were unable to continue niacin treatment because of adverse side effects. In the 14 patients treated with both neomycin and niacin, niacin further lowered the concentrations of total and low-density lipoprotein cholesterol by 18% and 25%, respectively, and increased high-density lipoprotein cholesterol by 32% ( $p < .05$ ) compared with that in the patients receiving neomycin plus niacin placebo. Compared with diet-only therapy, combined treatment with neomycin plus niacin reduced the total plasma cholesterol concentration by 36%, low-density lipoprotein cholesterol by 45%, and the low-density lipoprotein/high-density lipoprotein ratio by 46% and it increased plasma high-density lipoprotein concentrations by 24% ( $p < .001$ ). During the study, 80% of all the study patients and 92% of the patients who complied with the combined regimen normalized their total and low-density lipoprotein concentrations. No serious or irreversible adverse side effects were detected during combination neomycin/niacin treatment. These results indicate that the lipoprotein concentrations in a majority of type II hyperlipoproteinemic patients can be safely normalized by either therapy with neomycin only or by combined treatment with neomycin/niacin.

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EPIDEMIOLOGIC, METABOLIC, AND GENETIC studies in man have long demonstrated an association between the plasma lipoproteins and coronary heart disease (CHD).<sup>1</sup> The issue of a possible cause and effect relationship between lipoproteins and atherogenesis as well as the possibility of interfering with the development of CHD by lowering total and low-density lipoprotein cholesterol concentrations have been evaluated by the Lipid Research Clinics (LRC) program.<sup>1,2</sup> Using a double-blind, randomized, placebo-

controlled clinical trial, the LRC investigators determined that lowering the total and low-density lipoprotein plasma cholesterol concentrations by diet and drug treatment significantly reduced the incidence of CHD.<sup>1</sup> In addition, a dose-response relationship was noted.<sup>2</sup> Therefore, lowering total and low-density lipoprotein cholesterol concentrations by pharmacologic means has been conclusively demonstrated to prevent CHD.

Currently the bile acid sequestrants cholestyramine and colestipol and the B-complex vitamin niacin are considered the hypocholesterolemic drugs of choice for patients with type II hyperlipoproteinemia. However, up to 30% of patients cannot tolerate cholestyramine because of unpalatability and gastrointestinal side effects.<sup>3,4</sup> Up to 68% of patients treated with cho-

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lestyramine suffer at least one adverse side effect of the drug<sup>2</sup> and the cost of the drug limits its widespread use. At 24 g/day, the cost to the patient for 1 month of cholestyramine treatment in the Washington, D.C., area approaches \$170. Therefore, despite the efficacy of therapy with bile acid sequestrants in reducing CHD risk, the search for a well-tolerated, palatable, inexpensive, and effective hypocholesterolemic drug regimen continues.

Neomycin, when given in low doses orally (2 g/day), is not absorbed into the circulation,<sup>5</sup> but it can reduce total<sup>4,6,7</sup> and low-density lipoprotein cholesterol concentrations<sup>8</sup> to a degree comparable to that seen with bile acid sequestrants. However, unlike cholestyramine, neomycin is well tolerated. In addition, a 1 month supply of neomycin (taken in doses of 2 g/day) is one-fifth the cost of cholestyramine. Since neomycin appears to reduce low-density lipoprotein cholesterol concentrations by either a reduction in very low-density lipoprotein synthesis or a decreased conversion of very low-density lipoprotein to low-density lipoprotein,<sup>9</sup> neomycin is a reasonable alternative to colestipol or cholestyramine treatment for patients with type II hyperlipoproteinemia.

Combined treatment with colestipol and niacin has been found to result in an even more striking decrease in total and low-density lipoprotein cholesterol concentrations.<sup>10</sup> We therefore assessed the effect of combined neomycin and niacin therapy in 25 patients with type II hyperlipoproteinemia who were enrolled in a double-blind, randomized, placebo-controlled, crossover clinical trial.

## Methods

**Patients.** Patients with diagnosis of type II hyperlipoproteinemia who were followed as outpatients in either the Lipid Metabolism Clinic or the Cardiology Clinic at the National Institutes of Health in Bethesda were invited to participate after the study protocol had been approved by the NHLBI Human Experimentation Committee. Of the 154 type II patients initially identified, 25 lived in the Washington, D.C., area and were willing to participate in the study. After patients had given their consent to participate, they discontinued use of any hypolipidemic medications for 3 months, after which three fasting blood samples for lipoprotein characterization were obtained at monthly intervals. All study patients had low-density lipoprotein cholesterol concentrations in the top tenth percentile for their ages and sexes, as outlined by the LRC.<sup>11</sup> This group included 16 men and nine women who were 25 to 65 years old (mean 49). Patients with secondary hyperlipidemia were excluded through evaluations for levels of total thyroxine, free thyroxine, triiodothyronine, thyroid-stimulating hormone, serum transaminases, alkaline phosphatase, creatinine, BUN, bilirubin, serum protein electrophoresis, fasting glucose, albumin, and total protein in serum and by urinalysis. Eight patients were heterozygous for familial hypercholesterolemia, as determined by family history and the presence of tendon xanthomas.

Nine subjects were hypertensive and were receiving a thiazide diuretic (n = 8) or propranolol (n = 1). No changes in the antihypertensive regimens were made after the beginning of the study. No other drugs known to affect lipid metabolism were taken by the study subjects.

**Laboratory determinations.** After a 12 to 14 hr fast, study patients in the sitting position had blood drawn in glass tubes with a final EDTA concentration of 0.01%. Blood samples were immediately placed on ice and plasma was isolated by centrifugation at 4°C. Cholesterol and triglyceride concentrations were determined in whole plasma and lipoprotein subfractions by enzymic assays with a Gilford 3500.<sup>12,13</sup> Plasma aliquots (d = 1.006 g/ml) were subjected to 18 to 24 hr, 39,000 rpm ultracentrifugation at 4°C with a 40.3 Ti Beckman rotor. The cholesterol concentration in the 1.006 infranate was subtracted from the total plasma cholesterol level to determine the very low-density lipoprotein cholesterol concentration. High-density lipoprotein cholesterol level was determined by quantitating the cholesterol content in the supernatant of plasma after dextran-sulfate precipitation (mol wt 50,000; Sochibo, France).<sup>14</sup> The low-density lipoprotein cholesterol concentration was calculated as the difference in cholesterol concentration between the 1.006 g/ml infranate and the level of high-density lipoprotein cholesterol.

**Study design.** Three months after all hypolipidemic therapy had been stopped, study patients were instructed about the study diet. Three monthly visits later, patients were started on 1 g of neomycin sulfate (Eli Lilly, Indianapolis) twice daily. During the 3 months of treatment with neomycin only, all study subjects returned for monthly visits. Each patient was then randomly assigned by pharmacy personnel to receive, in addition to neomycin, either niacin or an identical niacin placebo formulated at NIH. The final regimen of 1 g three times daily niacin/niacin placebo was achieved over a 3 week period using either 100 mg niacin tablets or an identical placebo. Patients were instructed to take the medication with meals and avoid hot drinks during the institution of niacin or niacin placebo therapy in order to decrease facial flushing. After taking one of the preparations for 3 months, each patient received the alternate preparation. Neither the patient nor clinic personnel were aware of which preparation the patient was taking. Each month, in addition to measuring fasting lipoprotein concentrations, renal, hepatic, and auditory functions were assessed. Compliance with therapy was assessed by pill counts at the end of each 3 month treatment interval.

Major objectives in dietary counselling and control during the study included weight maintenance to within 5% of initial body weight, cholesterol intake limited to 90 mg/1000 kcal, a polyunsaturated-to-saturated fatty acid ratio of 2:1, and total caloric intake of 15% to 20% protein, 35% to 40% fat, and 40% to 50% carbohydrates. The group of total carbohydrates included starches and sugars in the form of fructose, lactose, and other sugars. Sucrose in table sugar or sugar products and/or ethanol, based on subject preference, were limited to 10% of the total calories. The proposed ethanol allowance ranged from ⅓ to 1½ oz/day pure ethanol, depending on total caloric requirements. The calorie level established for each subject was based on his or her age, sex, height, weight, and activity level. Diet plans were adjusted as needed throughout the study to reach the dietary objectives.<sup>15</sup> A meal-planning guide in which a food exchange system was used was developed to teach individual diet plans to subjects. A teaching program dealing with topics related to the control of intake of various nutrients was developed and these topics were discussed with each subject during his monthly visit. Every 3 months a 3 day diet record consisting of 2 weekdays and 1 weekend day was kept by each subject before their clinic visit.<sup>16</sup> Records were reviewed with the subject to clarify and augment descriptive information. With use of the

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Minnesota Coding Center format, these dietary recalls were computerized and analyzed for their nutrient composition.<sup>17</sup>

All patients accepted into the study were given a complete baseline audiologic assessment before dietary or medical management was undertaken. Patients were evaluated in an IAC double-walled diagnostic sound suite with a Grason-Stadler 1701 dual-channel audiometer and TDH-49 headphones. Electrophysiologic measurements of middle ear and acoustic reflex function were made with the Amplaid 702 impedance meter and 703 x-y recorder. The audiologic test battery included threshold puretone and speech measurements as well as suprathreshold tests of speech recognition under conditions of quiet and ipsilateral noise. Standardized taped speech-recognition material (Auditec NU6 lists) was used and delivered at +30 dB above speech-reception threshold under both quiet and ipsilateral noise (signal-to-noise ratio = +5 dB) conditions.<sup>18</sup> Tympanometry was performed to assess the function of the middle ear. No patient with handicapping peripheral hearing loss or active middle ear disease was included in the study. In addition, acoustic reflex threshold and decay measures were obtained in the contralateral mode at 500, 1000, 2000, and 4000 Hz. The audiologic test battery described above was performed initially and at 3 month intervals by all patients. A shorter "monitoring" battery to assess speech and puretone thresholds and speech recognition in ipsilateral noise was performed once a month.

**Statistical methods.** To enhance the precision of the lipid and lipoprotein concentration values within each treatment period, the three values obtained during each treatment period for each subject were averaged and then the pairwise differences were computed as follows: neomycin and niacin placebo vs neomycin only, neomycin only vs neomycin and niacin, neomycin and niacin placebo vs neomycin and niacin, and each of these treatments vs diet only. The null hypothesis was tested by comparing the mean differences to their SEs in a paired sample t test. The differences were also examined separately according to compliance to niacin treatment. Differences for the niacin-compliant group were compared with those for patients during the diet-only, neomycin-only, and neomycin and niacin treatment periods by two-sample t test. To control for possible effects of dietary changes during treatment, an analysis of covariance was performed with dietary variables as covariates and neomycin treatment as the primary variable.

## Results

The plasma lipid and lipoprotein concentrations for the entire study group during each treatment period are listed in table 1. The elevated concentrations of total

cholesterol and low-density lipoprotein cholesterol concentrations during the diet-only phase of the study were significantly reduced with neomycin treatment (by 23% and 29%, respectively). Although no additional changes in the plasma lipoprotein concentrations were observed after combination therapy with neomycin and niacin placebo, the addition of niacin to neomycin treatment had a significant impact. The 9% and 12% declines in total and low-density lipoprotein cholesterol concentrations were paralleled by a significant 17% increase in the high-density cholesterol concentration. Therefore, for the entire study group the addition of niacin to the neomycin regimen led to additional significant reductions in total and low-density lipoprotein cholesterol concentrations and an increased high-density lipoprotein cholesterol level.

Since 11 of the 25 study subjects did not tolerate the addition of niacin to the neomycin regimen, the results given for the entire group underestimate the impact of the addition of niacin to the regimen. A more impressive niacin-induced reduction in total and low-density lipoprotein cholesterol concentrations was apparent when patients were grouped as compliers and noncompliers (table 2). This compliance classification was made at the conclusion of the study, but independently of the lipid data analysis and based on the niacin pill counts. "Compliers" consumed more than 85% of their prescribed niacin doses, whereas "noncompliers" ingested less than 50% of prescribed doses. Both groups ingested more than 85% of their prescribed neomycin doses. The separation of study subjects based on medication compliance is reflected in the differences in lipid concentrations during the niacin placebo and niacin treatment periods. No significant differences in total, low-density lipoprotein, or high-density lipoprotein cholesterol concentrations were observed between the niacin and niacin placebo treatment periods for the noncompliers. The compliers, on the

**TABLE 1**  
**Comparison of effects of placebo and niacin (given in combination with neomycin) in the entire group**

	Cholesterol concentration (mg/dl)				Triglyceride concentration (mg/dl)
	Total	VLDL	LDL	HDL	
Diet only	365 ± 89	30 ± 21	293 ± 87	42 ± 10	187 ± 107
Neomycin only	281 ± 79 <sup>A</sup>	33 ± 18	209 ± 71 <sup>A</sup>	39 ± 8 <sup>A</sup>	171 ± 93
Neomycin + placebo	275 ± 65 <sup>A</sup>	32 ± 13	202 ± 60 <sup>A</sup>	41 ± 12	166 ± 89
Neomycin + niacin	251 ± 74 <sup>ABC</sup>	26 ± 16 <sup>BC</sup>	178 ± 68 <sup>ABC</sup>	48 ± 11 <sup>ABC</sup>	137 ± 61 <sup>ABC</sup>

Values are mean ± SD.

VLDL = very low-density lipoprotein; LDL = low density lipoprotein; HDL = high density lipoprotein.

<sup>A</sup>Statistically significant difference from diet only ( $p < .05$ ).

<sup>B</sup>Statistically significant difference from neomycin only ( $p < .05$ ).

<sup>C</sup>Statistically significant difference between neomycin and niacin and neomycin + placebo treatment ( $p < .05$ ).

TABLE 2

Comparison of placebo and niacin given in combination with neomycin/niacin in compliers vs noncompliers

	Cholesterol concentration (mg/dl)				Triglyceride concentration (mg/dl)
	Total	VLDL	LDL	HDL	
Compliers (n = 14)					
Diet only	350 ± 34	30 ± 25	275 ± 75	45 ± 9	183 ± 112
Neomycin only	273 ± 80 <sup>A</sup>	35 ± 22	200 ± 73 <sup>A</sup>	38 ± 8	186 ± 110
Neomycin + placebo	270 ± 74 <sup>A</sup>	32 ± 14	197 ± 66 <sup>A</sup>	41 ± 11	166 ± 85
Neomycin + niacin	223 ± 60 <sup>ABC</sup>	21 ± 11 <sup>BC</sup>	151 ± 50 <sup>ABC</sup>	51 ± 10 <sup>ABC</sup>	122 ± 50 <sup>ABC</sup>
Noncompliers (n = 11)					
Diet only	383 ± 96	30 ± 16	316 ± 99	38 ± 8	192 ± 107
Neomycin only	291 ± 79 <sup>A</sup>	31 ± 18	220 ± 71 <sup>A</sup>	40 ± 8	152 ± 93
Neomycin + placebo	281 ± 54 <sup>A</sup>	31 ± 11	209 ± 52 <sup>A</sup>	41 ± 13	166 ± 97
Neomycin + niacin	286 ± 77 <sup>A</sup>	32 ± 19	211 ± 76 <sup>A</sup>	43 ± 12 <sup>A</sup>	144 ± 64

Values are mean ± SD.

Abbreviations are as in table 1.

<sup>A</sup>Statistically significant difference from diet only (p < .05).

<sup>B</sup>Statistically significant difference from neomycin only (p < .05).

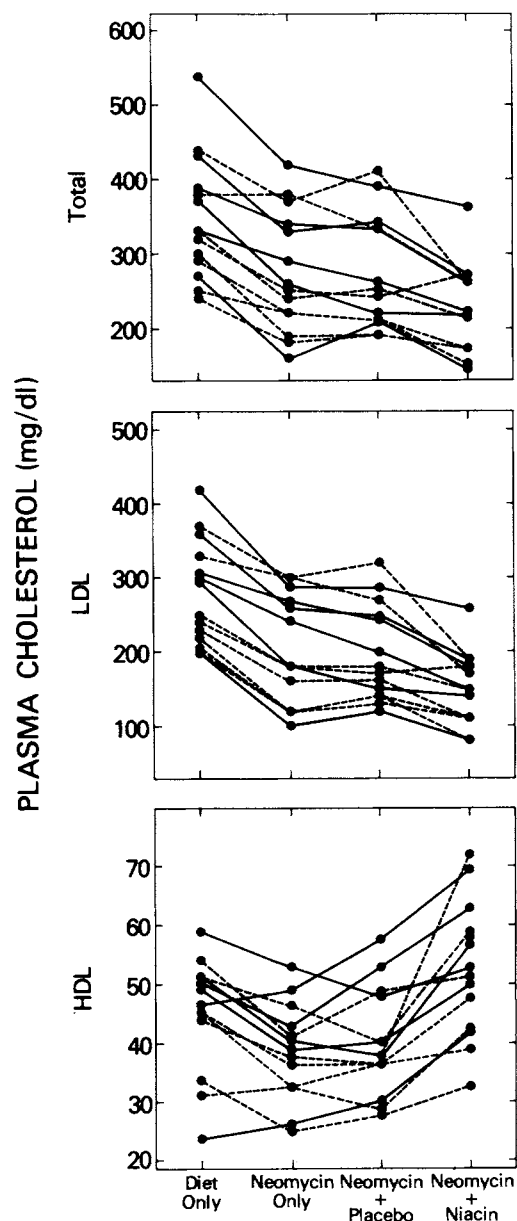
<sup>C</sup>Statistically significant difference from neomycin + placebo (p < .05).

other hand, experienced a further 17% reduction in total cholesterol concentration, a 23% decline in low-density lipoprotein cholesterol concentration, and a 24% increase in high-density lipoprotein cholesterol concentration during the niacin compared with the neomycin plus placebo treatment period. Combined treatment with neomycin plus niacin significantly reduced the diet-only total cholesterol concentration by 127 mg/dl (36%) and low-density lipoprotein cholesterol concentration 124 mg/dl (45%). Therefore, the beneficial effects of niacin treatment observed for the entire group reflect the more striking benefit to patients able to tolerate the neomycin/niacin combination.

The effects of the different treatment regimens on total, low-density lipoprotein, and high-density lipoprotein cholesterol concentrations for the individual patients based on compliance are shown in figures 1 and 2. Consistent and significant declines in total and low-density lipoprotein cholesterol concentrations were seen for all study subjects on neomycin treatment. Although niacin placebo had no added effect to neomycin treatment, niacin treatment in the compliers consistently induced a further decline in low-density lipoprotein and total cholesterol concentrations and an increase in high-density lipoprotein cholesterol concentration. In only six of the 11 noncompliers was low-density lipoprotein cholesterol concentration normalized during the study. Of the 14 compliers, eight had normalized low-density lipoprotein cholesterol concentrations on neomycin only, but in 13 this end point was normalized with combined neomycin/niacin treatment.

During the double-blind, placebo-controlled crossover study of neomycin conducted previously in these same patients,<sup>8</sup> a significant residual effect of neomycin on the plasma lipoproteins was observed in study subjects receiving neomycin first. The total and low-density lipoprotein cholesterol levels during the 3 month placebo period were still reduced 7% to 12% from baseline. The effect of order in which the two treatments were received (niacin and niacin placebo) was therefore assessed. Evaluation of the effect of treatment on the lipoprotein concentrations for the total group, the compliers, and the noncompliers indicated that no residual or carryover effect was present with niacin treatment. Therefore, unlike the previous neomycin study, there is no underestimation of these niacin-induced effects.

These additional lipid and lipoprotein changes with neomycin/niacin treatment could not be explained by dietary changes during the study. Daily total caloric intake, polyunsaturated-to-saturated fatty acid ratio, daily cholesterol intake and ethanol intake, and the percent of calories taken as protein, carbohydrate, and fat did not change between periods. Paired t tests comparing these variables between treatment periods disclosed no significant differences. Furthermore, an analysis of covariance carried out with the above variables plus neomycin treatment as a covariate demonstrated that neomycin/niacin treatment was independently correlated with these changes in total cholesterol (p = .0001), low-density lipoprotein cholesterol (p = .0019), and high-density lipoprotein cholesterol concentrations (p < .001).

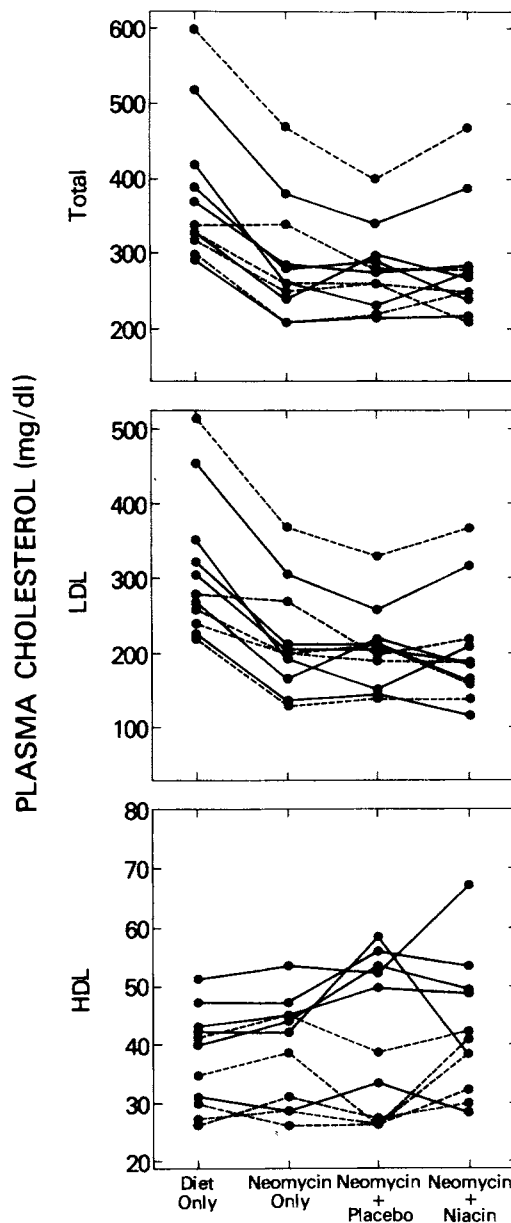


**FIGURE 1.** The effect of diet and drugs on the plasma lipoprotein concentrations in the compliant type II hyperlipoproteinemic study patients. The lipoprotein concentrations for each patient are shown for each treatment period for both women (---) and men (—). Compliant patients are those who ingested greater than 85% of prescribed doses of both neomycin and niacin.

Toxicity of this regimen was assessed with use of a standardized questionnaire as well as by monthly blood analyses. Results of most routine blood and urine studies were unaffected by either neomycin or niacin treatment. Statistically significant laboratory differences between treatment groups were observed (table 3). Neomycin-only treatment induced no consistent or significant differences from diet-only values. The addition of niacin to the regimen, however, resulted in statistically significant increases in the concentrations of the liver enzymes SGOT, SGPT, and alkaline

phosphatase. Compared with the placebo period, significant increases in glucose and uric acid as well as decreased BUN levels were observed. The changes in these serum chemistries reflect the more marked alterations that occurred in the compliant patients compared with those that were noncompliant (data not shown). Therefore, niacin treatment induced changes in serum chemistries that primarily reflect altered hepatic function.

These changes in serum biochemical markers were



**FIGURE 2.** The effect of diet and drug treatment on type II hyperlipoproteinemic study patients not compliant with niacin therapy. Patients ingesting more than 85% of prescribed neomycin doses but less than 50% of niacin doses were defined as noncompliers. Solid lines indicate men and dashed lines indicate women. Each data point represents the value for an individual patient.

TABLE 3

Selected serum chemistry concentrations for the entire study group during each treatment period

	SGOT	SGPT	Alk phos	Total bili	Glucose	Uric acid	Creatinine	BUN
Neomycin only	26 ± 6	35 ± 14	92 ± 35	0.4 ± 0.2	96 ± 8	6 ± 2	1.0 ± 0.2	15 ± 6
Neomycin + placebo	26 ± 7	39 ± 15 <sup>A</sup>	98 ± 38 <sup>A</sup>	0.5 ± 0.2	92 ± 9 <sup>A</sup>	6 ± 1	1.1 ± 0.2	15 ± 3
Neomycin + niacin	37 ± 23 <sup>AB</sup>	50 ± 30 <sup>AB</sup>	103 ± 40 <sup>A</sup>	0.5 ± 0.2	98 ± 12 <sup>B</sup>	7 ± 2 <sup>AB</sup>	1.1 ± 0.2	14 ± 4 <sup>B</sup>

Values are mean ± SD for the entire study group.

Alk phos = alkaline phosphatase; bili = bilirubin.

<sup>A</sup>Statistically significant difference from neomycin only ( $p < .05$ ).

<sup>B</sup>Statistically significant difference from neomycin + placebo ( $p < .05$ ).

paralleled by alterations in the clinical side effects experienced by our patients (table 4). As previously reported, neomycin induced mild nausea in 11% of treated patients, but this was relieved by taking the medication with meals. Niacin treatment, on the other hand, led to an increased incidence of abdominal pain, flushing, pruritus, rash, and dry eyes. These side effects were noted by both compliers and noncompliers. However, the noncompliers experienced significantly more headaches, nausea, and dry eyes during the niacin period than did compliers. The severity of skin flushing as well as nausea was the cause for discontinuing or limiting the niacin dose in the noncompliers. One patient developed signs and symptoms of hepatitis and another developed symptomatic hypotension during niacin therapy; niacin therapy was stopped in these patients. By 1 month after therapy was stopped, all these signs and symptoms had totally resolved. No glycosuria, frank diabetes, peptic ulcer disease, or acute gouty attacks developed over the course of the study. Although no serious or irreversible sequelae to niacin therapy developed, the annoying side effects contrasted sharply with the very well-tolerated neomycin.

Finally, no ototoxicity developed in any study subject. Puretone threshold, speech discrimination, speech-reception threshold, ipsilateral noise discrimination, and acoustic reflex threshold were unaffected during the study. All 25 of these patients have subsequently been maintained on 2 g/day neomycin for 12 to 30 months without any sign of ototoxicity. Therefore, sensitive, prospective evaluation indicates that prolonged use of neomycin has no adverse otologic effects at this dosage.

### Discussion

The recent results of the LRC Coronary Primary Prevention Trial,<sup>1,2</sup> as well as the NHLBI Intervention Study,<sup>19,20</sup> indicate that diet and drug intervention is useful in patients with increased concentrations of low-density lipoprotein cholesterol. Treatment not only retards the development of coronary atherosclerosis,<sup>19,20</sup> it also prevents myocardial infarction and death.<sup>1,2</sup> Therefore, the questions involved in clinical practice shift from "whether to treat" to "how best to treat."

A variety of medications including cholestyramine, colestipol, niacin, probucol, clofibrate, and gemfibro-

TABLE 4

Adverse side effects reported by patients during each treatment period

	Abdominal pain	Flushing	Pruritus	Rash	Dry eyes	Nausea
Total group (n = 25)						
Diet-only phase	6	3	12	8	4	1
Neomycin only	3	2	5	5	2	11 <sup>B</sup>
Neomycin + placebo	7	4	13	6	9	16 <sup>B</sup>
Neomycin + niacin	16	66 <sup>AB</sup>	52 <sup>AB</sup>	20 <sup>AB</sup>	20 <sup>AB</sup>	27 <sup>B</sup>
Compliers (n = 14)						
Neomycin + placebo	7	7	21	6	4	11
Neomycin + niacin	10 <sup>B</sup>	60 <sup>B</sup>	61 <sup>B</sup>	20 <sup>B</sup>	8	14
Noncompliers (n = 11)						
Neomycin + placebo	7	0	3		5	18
Neomycin + niacin	14	64 <sup>B</sup>	42 <sup>B</sup>		28 <sup>B</sup>	47 <sup>B</sup>

Values are percentages of responses that were positive.

<sup>A</sup>Statistically significant difference from diet only ( $p < .05$ ).

<sup>B</sup>Significant difference from neomycin + placebo period ( $p < .05$ ).

zils have been used in single-drug therapy in the treatment of patients with type II hyperlipoproteinemia.<sup>21</sup> Taken in conjunction with a controlled diet, these drugs induce a 9% to 35% reduction in the low-density lipoprotein cholesterol concentration in type II patients. However, in the vast majority of patients plasma lipoprotein concentrations do not normalize with a single-drug regimen. Since atherosclerosis as well as myocardial infarction and death are affected by low-density lipoprotein cholesterol reduction in a concentration-dependent manner, the goal of therapy should be to reduce the low-density lipoprotein cholesterol concentration to the lowest level possible.

Use of a combination of hypolipidemic drugs holds promise in normalizing plasma lipoprotein concentrations. Kane *et al.*<sup>10</sup> demonstrated that a combination of cholestyramine and niacin normalized the low-density lipoprotein cholesterol concentration in a majority of their type II hyperlipoproteinemic subjects. Combination of cholestyramine with the experimental inhibitor of cholesterol synthesis, Compactin, also induced near-normalization of plasma low-density lipoprotein cholesterol concentrations.<sup>22</sup> Therefore, the use of medications with complementary mechanisms of action have been more effective than single-drug therapy.

Neomycin is a nonabsorbable aminoglycoside antibiotic that has limited use in the treatment of infection. However, when taken in small doses orally, it lowers total and low-density lipoprotein cholesterol concentrations in type II hyperlipoproteinemic patients.<sup>4, 6, 8</sup> The effect of neomycin on the plasma lipoproteins is qualitatively and quantitatively similar to that achieved with the bile acid sequestrants cholestyramine and colestipol.<sup>8</sup> Since little, if any, ototoxicity or nephrotoxicity has been reported in patients free of underlying intestinal, renal, or hepatic disease when the low dose of 2 g/day is used, neomycin appears as a promising addition in the treatment of the hyperlipoproteinemias. The present findings of respective reductions of 23% and 29% in total and low-density lipoprotein cholesterol concentrations are similar to results of our previous study.<sup>8</sup> Moreover, all these patients have been treated with neomycin for at least a full year and some as long as 30 months without any evidence of toxicity. Therefore, neomycin is as safe and effective in the treatment of increased low-density lipoprotein cholesterol concentration as a variety of other drugs. Moreover, use of neomycin has the advantages that it may be given twice a day in tablet form, that there are no adverse side effects that compromise compliance, and that it is low cost (roughly 20% that of cholestyramine).

Since neomycin appears to act via inhibition of intestinal cholesterol absorption,<sup>9</sup> combination with niacin would be anticipated to provide complementary modes of action in the reduction of plasma lipid concentrations. In the patients compliant to both neomycin and niacin treatment, the reductions in total and low-density lipoprotein cholesterol concentrations were 36% and 45%, respectively. In addition, the high-density lipoprotein cholesterol concentration increased by 32%. In a total of 13 of 14 (92%) patients taking the neomycin/niacin combination plasma lipoprotein concentrations were normalized. Therefore, in patients able to tolerate niacin treatment, neomycin combined with niacin leads to normalization of the plasma lipoprotein concentrations.

A significant number of the study subjects (44%) could not tolerate niacin therapy. Although virtually all the patients experienced flushing and pruritus of the skin, only two discontinued the medication because of the cutaneous manifestations. The majority of niacin-noncompliant patients stopped taking the drug because of abdominal cramps, distension, or pain. Of interest is the fact that none of the patients unable to continue niacin therapy had difficulty in maintaining their neomycin treatment. Therefore, neomycin was tolerated much better than niacin by our patients.

In conclusion, the use of combined neomycin/niacin therapy leads to a normalization of the plasma lipoprotein concentrations in the majority of type II hyperlipoproteinemic patients. This regimen resulted in no serious toxicity and is considerably more inexpensive than conventional treatment. In addition, this study further substantiates the safety of prolonged neomycin therapy in patients without preexisting renal, hepatic, or intestinal disease. If longer term prospective studies confirm these findings in a larger number of patients, neomycin alone or in combination with other medications may emerge as the drug of choice in the life-long treatment patients with type II hyperlipoproteinemia.

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