Effect in Man of Large Doses of Pyridoxine on Serum Cholesterol

By Robert B. Failey, Jr., M.D.

Pyridoxine (400 mg./day) was given to 21 individuals for periods up to a maximum of 36 days. A slight but significant fall in serum cholesterol levels was observed, the effect being more marked in diabetic than in nondiabetic subjects.

Atherosclerotic plaques observed in man and several species of animals characteristically contain large amounts of cholesterol, and numerous experimental and epidemiologic studies have demonstrated a relationship between serum cholesterol levels and the incidence of atherosclerosis. Pyridoxine (vitamin B₆) has been among the several agents considered effective in inhibiting the development of atherosclerosis. Rinehart and Greenberg reported the finding of atherosclerotic lesions in pyridoxine-deficient monkeys. Witten and Holman presented evidence indicating that pyridoxine in the rat enhanced the conversion of linoleic to arachidonic acid. Their work indicated that pyridoxine and linoleic acid together were more effective in controlling the deficiency manifestations of these two substances in rats than either did separately. Kinsell et al. showed that linoleic acid, as a constituent of dietary fat, had a marked effect in lowering serum cholesterol levels. At the present time the substitution of vegetable fats high in linoleic acid content for the highly saturated animal fats of many human diets represents the most effective if not necessarily the most practical means of lowering serum cholesterol levels. Pyridoxine has been shown necessary for the conversion of tryptophane to niacin, and nicotinic acid (although not the amide) has been shown to lower the serum cholesterol level of man and animals.

METHOD

The purpose of the present study was to assay the effect of large doses of pyridoxine upon the human serum cholesterol level. Pyridoxine hydrochloride up to 400 mg./day was administered orally. Twenty-one patients hospitalized at the Indiana University Medical Center and at the Indianapolis Veterans Hospital were studied. Five were female diabetics ranging in age from 50 to 71 years, who were hospitalized for periods of from 21 to 36 days because of occlusive arterial disease of the toes and feet. Some of these subjects had undergone surgical removal of small areas of gangrene during their hospitalizations; none showed signs of acidosis, coma, febrile disease, or any marked variation in insulin requirement while in the hospital. None required more than 50 units of insulin per day to control their diabetes. The remaining 16 patients were hospitalized essentially for domiciliary care. These were males, ranging in age from 41 to 80 years, who were hospitalized for a variety of chronic pulmonary and cardiac diseases. None of these subjects showed any evidence of nutritional impairment, and there were no significant fluctuations in weight during the period of the study. No special dietary program was employed beyond that used routinely for the diabetics. Cholesterol determinations were done by the method of Zak et al. as modified by Herrmann.

RESULTS

Results of the study are presented in table 1. In this table the diabetic patients are presented as two groups. Although 5 diabetics were studied initially, 3 left the hospital before follow-up controls could be obtained. Similarly, the results for the combined group of diabetic and nondiabetic patients are presented twice because of lack of follow-up con-
TABLE 1.—Serum Cholesterol Levels Before, During and After Oral Administration of Pyridoxine

<table>
<thead>
<tr>
<th></th>
<th>Controls (mg. %)</th>
<th>Pyridoxine (200 mg. dose)</th>
<th>Pyridoxine (400 mg. dose)</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 diabetic subjects</td>
<td>20—5 days 253.2</td>
<td>—</td>
<td>28—7 days 234.0 mg. %</td>
<td>—</td>
</tr>
<tr>
<td>2 diabetic subjects</td>
<td>8—5 days 264.0</td>
<td>—</td>
<td>9—5 days 259.5 mg. %</td>
<td>10—5 days 275.5 mg. %</td>
</tr>
<tr>
<td>6 nondiabetic subjects</td>
<td>24—10 days 256.7</td>
<td>24—20 days 247.0 mg. %</td>
<td>24—16 days 235.8 mg. %</td>
<td>24—19 days 242.2 mg. %</td>
</tr>
<tr>
<td>10 nondiabetic subjects</td>
<td>50—7 days 221.8</td>
<td>—</td>
<td>50—7 days 225.9 mg. %</td>
<td>50—7 days 228.4 mg. %</td>
</tr>
<tr>
<td>21 subjects, combined group</td>
<td>94—5—10 days 239.2</td>
<td>—</td>
<td>102—5—10 days 230.7 mg. %</td>
<td>—</td>
</tr>
<tr>
<td>18 subjects, combined group</td>
<td>82—5—10 days 238.1</td>
<td>—</td>
<td>83—5—16 days 232.9 mg. %</td>
<td>84—5—19 days 238.2 mg. %</td>
</tr>
</tbody>
</table>

* The figures above each serum cholesterol level indicate the number of determinations and the period of observation.

trols in the three above-mentioned individuals. The two groups of nondiabetics are composed of different individuals and do not represent any duplication. Figures for serum cholesterol are group averages obtained by combining the mean figures obtained for each individual, so that in obtaining the group averages each individual rather than each separate determination is weighed as one unit. Four of the 5 diabetic patients exhibited a fall in mean serum cholesterol levels while on the medication. In this group the highest single individual value obtained was 310 mg. per cent, the lowest 200 mg. per cent. In the long term study of nondiabetic patients, 5 of 6 individuals exhibited a fall in mean serum cholesterol levels. In this group the highest single individual value was 339 mg. per cent, the lowest 170. In the short-term nondiabetic group, 6 of 10 individuals showed lower cholesterol levels. In this group the highest single individual value was 300 mg. per cent, the lowest 150.

Statistical analysis of data obtained from the 6 nondiabetic patients in the long term study (line 3, table 1) showed that the control levels prior to medication were significantly higher than the follow-up controls after cessation of medication. The first control period values were significantly higher than those from any of the other groups. The mean control values of both control periods were significantly higher than the mean of the periods of medication, but there was not a significant difference between follow-up controls and either of the periods of medication.

Probability values of less than 0.05 are considered as significant.

Data from the short term study of nondiabetic patients (line 4, table 1) revealed no fall in mean cholesterol values either during medication or in the follow-up control period. In terms of the planned experiment, these values are obviously without significance.

Because of difference in the numbers of tests, two methods of analysis were used to determine significance of results obtained from the diabetic patients (lines 1 and 2, table 1). By the first method, the t values for the difference among the means during the control period and during medication were determined for each patient. Values of p were then determined, and then combined according to the method of Fisher. Significant difference (p < .05) between values from control periods and medication periods was ob-
served. By the second method of analysis, the mean serum levels for each patient were determined for the control and medication periods and were subjected to analysis of variance. Again a significant difference was noted.

In this study no placebo medication was employed during the control periods; however, the individuals serving as subjects for the study were not informed as to its purpose, and none inquired as to the results.

**DISCUSSION**

The average human requirement of pyridoxine sufficient to prevent deficiency signs has been stated to be 2 to 3 mg./day, and the dosage used in the present study was grossly in excess of this amount. It was also much larger than that employed in any of the presently recommended programs by which pyridoxine alone or in combination is administered in an attempt to lower serum cholesterol levels or inhibit formation of arterial atherosclerosis. Results do not indicate that these large doses of pyridoxine had any striking effect on serum cholesterol levels. The evidence does suggest that prolongation of the experiment over several more weeks' time might have led to a greater effect. The reduction in serum cholesterol is, however, not nearly as great as could be anticipated from starvation, dietary substitution of unsaturated fat, nicotinic acid, sitosterol, or certain of the substituted butyric acids. The combination of pyridoxine in small doses with linoleic acid has been proposed as an agent to lower serum cholesterol levels, and it is entirely possible that pyridoxine in combination with other agents may be even more effective. The reaction by which pyridoxine enhances the conversion of tryptophane to niacin could possibly be accelerated by excess pyridoxine. In the present study diets appeared to be normal, adequate, and essentially unvarying throughout the experiment. Again the possibility exists that variations in quantity and composition of protein as well as fat in the diet might, in combination with the pyridoxine, prove more effective than would either the drug or the diet separately. The significant and early fall in cholesterol levels seen in the diabetic patients in the present study when compared with that of the nondiabetic patients suggests that pyridoxine in large doses may be more effective in this group than among others. The mean serum cholesterol levels of the controls in this study approximated those given as normal for the present day population of the United States. Of this entire group only two individuals had control levels that were consistently over 300 mg. per cent, and it is possible that had the mean values of the controls been greater, the observed fall under medication would have been greater. We have observed that serum cholesterol levels of ambulatory people seem to be higher than those of hospitalized patients, even in instances in which debility and disease do not seem significant. It may well be that repetition of this study on ambulatory individuals would lead to a different result. Data reporting the effect of nicotinic acid upon serum cholesterol levels typically show a fall to around 250 mg. per cent, at which point values tend to stabilize in spite of increase in dosage of the drug. If, as has been suggested, pyridoxine acts somewhat in the manner of nicotinic acid, greater effect would be observed at higher initial cholesterol levels, and cholesterol levels would not be expected to go much below the 250 mg. per cent range. The failure to observe any fall in mean serum cholesterol levels in the short term, nondiabetic group may be attributable to the low (221.8 mg. per cent) mean control level, and it seems quite possible that a higher control level would have been followed by a fall during the period of medication. By contrast, the long term study of the nondiabetic patients does show a significant fall in serum cholesterol levels during the period of medication. In this group the failure of follow-up controls to attain the levels of the initial controls suggests a prolonged and cumulative effect of the drug.

**SUMMARY**

Pyridoxine in the amount of 400 mg./day
was administered orally to 21 individuals for periods of observation ranging from 5 to 36 days. Five diabetics who received medication for a maximum of 7 days showed a significant ($p < .05$) fall in serum cholesterol levels. Ten nondiabetics who received medication for a maximum of 7 days did not show a significant fall in serum cholesterol levels. Six nondiabetics who received medication for a maximum of 36 days showed a significant fall in serum cholesterol levels with a delayed rise during a follow-up control period.

**Acknowledgment**

The author is indebted to Miss Sally Ann Gordon for technical assistance in chemical determinations.

**Summario in Interlingua**

Pyridoxina in quantitates de 400 mg per di esseva administrate per via oral a 21 individuos durante periodos de observation de inter 5 e 36 dies. Cinque diabeticos, qui recipieva le medication durante 7 dies o minus, monstrava un reduction significative del nivellos de cholesterol seral ($p < 0.05$). Dece non-diabeticos, qui etiam recipieva le medication durante 7 dies o minus, non mostrava un reduction significative del nivellos de cholesterol in lor seros. Sex non-diabeticos, qui recipieva le medication durante 36 dies o minus, monstrava un reduction significative in le nivellos del cholesterol seral sequite per un retardo del re-ascendita durante le periodo de observation consecutori.

**References**

Effect in Man of Large Doses of Pyridoxine on Serum Cholesterol
ROBERT B. FAILEY, JR.

Circ Res. 1958;6:203-206
doi: 10.1161/01.RES.6.2.203

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1958 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/6/2/203