Effects of Nicotinic Acid on Serum and Tissue Cholesterol in Rabbits

By JOSEPH M. MERRILL, M.D. AND JANET LEMLEY-STONE, PH.D.

Studies reported in this communication showed that under the experimental conditions, nicotinic acid partially prevented a rise in serum cholesterol but effectively prevented cholesterol deposition in the aorta and, to a lesser extent, cholesterol storage in the liver.

SERUM cholesterol is lowered by oral nicotinic acid in the human and in the rabbit. The fall in serum cholesterol is roughly proportional to the initial elevation and the amount of nicotinic acid required to produce striking changes in the serum is rather large. These observations pertaining to serum cholesterol assume more importance if they are accompanied by changes in tissue cholesterol. The purpose of this study was to determine: (1) if the lowered serum cholesterol was accompanied by lowered tissue cholesterol in the aorta and (2) if the nicotinic acid lowered serum cholesterol by causing deposition of cholesterol in the liver.

METHODS

Seventeen male rabbits (aged 10 months) were divided into three groups. Group I (6 animals) was fed a stock rabbit chow* for 8 weeks and served as a control. Group II (6 animals) consumed the same stock diet to which 2 per cent cholesterol had been added. Group III (5 animals) ate the stock diet with the addition of 2 per cent cholesterol and 0.4 per cent nicotinic acid. These diets were continued for 8 weeks. Body weight and serum cholesterol were determined at weekly intervals. The method of Pearson, Stern, and McCavack3 was used for determination of total serum cholesterol. At the end of 8 weeks the animals were killed and the liver, kidney, adrenal glands, aorta and pulmonary artery inspected for gross evidence of atherosclerosis or adventitious lipid deposits. Samples of the liver and a 1.5 cm. portion of the aorta just distal to the aortic valve were taken for cholesterol analysis. The tissues were homogenized, extracted with chloroform and total cholesterol estimated by the Kingsley and Schaffert procedure.4

RESULTS

The average serum cholesterol values for the 3 groups of animals is shown in figure 1. The differences in serum cholesterol confirmed the earlier observation of Altshul that oral nicotinic acid inhibited the rise which occurs when a high cholesterol diet is fed to rabbits.

The final average weight of the 3 groups of animals with per cent change during the study are shown in table 1. It will be noted that although groups II and III lost weight during the course of the experiment, there was no difference between these 2 groups in the amount of weight lost.

The results of the tissue analysis of the rabbit aorta for total cholesterol are shown in table 1. The difference in the cholesterol content of the aorta between groups II and III was significant (p < 0.001). There was no significant difference between the cholesterol content of the aorta of the control group and that of the group fed cholesterol plus nicotinic acid.

The figures for the cholesterol content of the liver are shown in table 1. Although the addition of cholesterol to the diets of rabbits appreciably increased the cholesterol content of the liver, the addition of nicotinic acid to the diet substantially reduced the amount of cholesterol which was found in the liver. The difference in the cholesterol content of the liver of groups II and III was significant (p < 0.02). Figure 2 illustrates the difference which was observed by inspection of a representative liver from each dietary group. There was a good correlation between these gross pathological changes and the chemically determined cholesterol content.

DISCUSSION

From these studies it is evident that nicotinic acid when added to a diet high in cholesterol prevented the expected increase in the cholesterol content of both serum and aorta. The low serum cholesterol level was not a result of deposition of the substance in the liver.
NICOTINE ACID EFFECTS ON SERUM AND TISSUE CHOLESTEROL

Fig. 1. Average weekly serum cholesterol determinations in the three experimental groups.

Aorta and liver are considered representative tissues of the body, these results suggest that the low serum cholesterol reflects low total tissue cholesterol.

The mechanism whereby nicotinic acid lowers serum and tissue cholesterol is unknown. Contradictory evidence has been presented concerning the metabolic end products of nicotinic acid in rabbits. It has recently been reported that the major portion of administered nicotinic acid is excreted as a methylated derivative (1-methyl-3-carboxyamide-6-pyridone). The large number of methyl groups which would be required for the excretion of large amounts of nicotinic acid might produce a relative deficiency of methyl groups. A reduction of methyl groups may influence the rate of cholesterol synthesis from acetate groups.

SUMMARY

These studies confirm the earlier observation that oral nicotinic acid prevents the anticipated rise in serum cholesterol. The present data indicate that nicotinic acid is effective not only

Table 1.—Effects of Oral Cholesterol and Nicotinic Acid on Serum and Tissue Cholesterol

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of animals</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Av. final wt. (% change in wt. during experiment)</td>
<td>9.4 lbs. (+12%)</td>
<td>8.2 lbs. (-7%)</td>
<td>8.2 lbs. (-7%)</td>
<td></td>
</tr>
<tr>
<td>Av. final serum cholesterol</td>
<td>49.1 (SE ± 10.7)</td>
<td>1262.4 (SE ± 156.5)</td>
<td>500.4 (SE ± 174.4)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Av. aorta cholesterol (mg./100 Gm. fresh tissue)</td>
<td>133 (SE ± 9.8)</td>
<td>331 (SE ± 30.5)</td>
<td>138 (SE ± 23.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Av. liver cholesterol (mg./100 Gm. fresh tissue)</td>
<td>282 (SE ± 102)</td>
<td>6553 (SE ± 1460)</td>
<td>1506 (SE ± 474)</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

*p, value of difference between groups II and III.

Fig. 2. Representative livers from groups I, II and III respectively. 1, 319 mg. cholesterol/100 Gm. fresh tissue; 2, 7194 mg. per cent; 3, 1510 mg. per cent.
in lowering the serum cholesterol but under these experimental conditions effectively prevents cholesterol deposition in the aorta and, to a lesser extent, cholesterol storage in the liver.

**SUMMARY IN INTERLINGUA**

Le hie reportate studios supporta le previe observation que oral acido nicotinic preveni expectate augmentos del cholesterol serai. Le datos indica que acido nicotinic es efficace non solmente in reducer le cholesterol serai sed etiam—sub iste conditiones experimental—in prevenir le deposition de cholesterol in le aorta e, a grados minus marcate, le immagasinage de cholesterol in le hepate.

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