Long-Term Reduction of Serum Cholesterol Levels of Patients with Atherosclerosis by Small Doses of Neomycin

By Paul Samuel, M.D., Charles M. Holtzman, M.D., and Jane Goldstein, B.S.

SUMMARY
The effect and tolerance of long-term oral administration of small doses of neomycin as a serum cholesterol reducing agent has been investigated. Sixteen patients were given neomycin sulfate orally for periods varying from 12 to 40.1 months, following control periods of 2.6 to 14.6 months. After an initial daily dose of 2 g of neomycin, the daily dose was varied between 0.5 and 2 g according to response. Average total serum cholesterol concentrations decreased in each of the 16 patients by 15 to 32%; the average decrease for the group was 22%. The difference was statistically significant in each patient at the 0.1% level. Serum cholesterol concentrations were maintained at the lower plateau as long as the drug was given. In an additional patient, after administration of neomycin for 2 months there was no change in serum cholesterol concentrations and the study was discontinued. Another developed severe diarrhea, nausea, and abdominal cramps during the first week of the study, so that medication was interrupted. No other serious side effects occurred. During the first 2 weeks of medication eight of the 16 patients experienced mild diarrhea or abdominal cramps or both which subsided spontaneously during continued medication. Physical examinations were carried out, kidney and liver functions remained normal, and pathogens were not grown from stool cultures.

Additional Indexing Words:
Serum lipids
Intestinal bacteria

Oral administration of neomycin in daily doses of 0.5 to 2 g reduces the serum cholesterol level in man. The average decline in serum cholesterol concentrations in this laboratory was 21% with daily administration of 1.5 to 2 g of neomycin, whereas smaller doses induced less marked changes. Neomycin was given for periods varying from 4 to 37 weeks in these studies, maintaining serum cholesterol levels at a lower plateau than usual for as long as the drug was given. Serum cholesterol returned to control values in each case after administration of neomycin was discontinued. The effect of neomycin on the level of human serum cholesterol has been studied in a number of other laboratories with essentially similar results. The aim of the present investigation was to study the long-term effectiveness and tolerance of small oral doses of neomycin as a serum cholesterol-reducing agent in a group of ambulatory patients who had normal everyday activities and diet.

Methods
Eighteen patients, 10 males and eight females, were studied. The age range was from 12 to 62 years at the beginning of the study. Clinical diagnoses are included in table 1. Serum lipid
### Table 1

**Effect of Long-Term Administration of Neomycin on the Average Total Serum Cholesterol Concentration in Seventeen Patients**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Length (mo)</th>
<th>Average total serum cholesterol</th>
<th>Daily dose (g)</th>
<th>Length (mo)</th>
<th>Average total serum cholesterol</th>
<th>Fall (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.K.</td>
<td>39 M</td>
<td>Familial hypercholesterolemia*</td>
<td>5.1</td>
<td>352 ± 23†</td>
<td>0.5 to 2</td>
<td>40.1</td>
<td>265 ± 21†</td>
<td>25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C.L.</td>
<td>43 M</td>
<td>Coronary artery disease</td>
<td>8.4</td>
<td>318 ± 14</td>
<td>1.5 to 2</td>
<td>29.0</td>
<td>261 ± 17</td>
<td>18</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C.S.</td>
<td>42 F</td>
<td>Familial hypercholesterolemia*</td>
<td>3.5</td>
<td>353 ± 11</td>
<td>1 to 2</td>
<td>21.2</td>
<td>241 ± 21</td>
<td>32</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A.F.</td>
<td>45 F</td>
<td>No clinical disease</td>
<td>8.0</td>
<td>254 ± 15</td>
<td>1.5 to 2</td>
<td>20.0</td>
<td>209 ± 17</td>
<td>18</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>H.F.</td>
<td>47 M</td>
<td>Coronary artery disease, CVA‡</td>
<td>8.8</td>
<td>312 ± 21</td>
<td>1.5 to 2</td>
<td>20.0</td>
<td>234 ± 17</td>
<td>25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A.K.</td>
<td>12 M</td>
<td>Familial hypercholesterolemia and xanthomatosis*</td>
<td>9.5</td>
<td>846 ± 80</td>
<td>1.5</td>
<td>16.7</td>
<td>646 ± 51</td>
<td>24</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>N.H.</td>
<td>39 M</td>
<td>Familial hypercholesterolemia*</td>
<td>12.2</td>
<td>310 ± 17</td>
<td>1 to 2</td>
<td>16.0</td>
<td>249 ± 21</td>
<td>20</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A.G.</td>
<td>43 M</td>
<td>Coronary artery disease</td>
<td>2.6</td>
<td>297 ± 8</td>
<td>1 to 2</td>
<td>13.6</td>
<td>253 ± 26</td>
<td>15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>M.R.</td>
<td>53 F</td>
<td>Peripheral vascular insufficiency</td>
<td>13.0</td>
<td>281 ± 17</td>
<td>2</td>
<td>13.3</td>
<td>218 ± 16</td>
<td>22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>S.S.</td>
<td>62 M</td>
<td>Coronary artery disease, diabetes mellitus</td>
<td>12.2</td>
<td>229 ± 17</td>
<td>2</td>
<td>12.5</td>
<td>168 ± 9</td>
<td>27</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>J.C.</td>
<td>40 M</td>
<td>Cerebral vascular insufficiency</td>
<td>9.8</td>
<td>291 ± 18</td>
<td>1.5 to 2</td>
<td>12.2</td>
<td>234 ± 14</td>
<td>20</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D.B.</td>
<td>47 F</td>
<td>Essential hypertension</td>
<td>12.8</td>
<td>224 ± 15</td>
<td>2</td>
<td>12.0</td>
<td>181 ± 14</td>
<td>19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C.K.</td>
<td>60 F</td>
<td>Coronary artery disease</td>
<td>3.0</td>
<td>383 ± 20</td>
<td>1.5</td>
<td>12.0</td>
<td>298 ± 14</td>
<td>22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E.D.</td>
<td>52 M</td>
<td>Coronary artery disease</td>
<td>14.4</td>
<td>250 ± 17</td>
<td>1.5 to 2</td>
<td>12.0</td>
<td>200 ± 11</td>
<td>20</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>S.P.</td>
<td>59 F</td>
<td>Essential hypertension</td>
<td>13.4</td>
<td>262 ± 18</td>
<td>2</td>
<td>12.0</td>
<td>219 ± 15</td>
<td>16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>J.L.</td>
<td>45 M</td>
<td>Coronary artery disease</td>
<td>14.6</td>
<td>319 ± 20</td>
<td>2</td>
<td>12.0</td>
<td>250 ± 20</td>
<td>22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A.G.</td>
<td>52 F</td>
<td>Peripheral vascular insufficiency</td>
<td>4.3</td>
<td>244 ± 17</td>
<td>2</td>
<td>2.2</td>
<td>230 ± 11</td>
<td>—</td>
<td>&gt; 0.01</td>
</tr>
</tbody>
</table>

*Control triglyceride level below 100 mg%.
†Standard deviation.
‡CVA = cerebrovascular accident.
studies were restricted to the long-term determination of total serum cholesterol concentrations. Detailed work-up and genetic differentiation of hyperlipemias on the participants of the present study has been published elsewhere. All patients were ambulatory, their respective diseases under good control, and 12 of the 18 patients were working at their regular jobs throughout the study. Medications, other than experimental were kept constant, and other substances known to influence serum cholesterol levels were not given. The diet was uncontrolled, but the patients were instructed to adhere to their customary diets. Ten of the 18 patients were seen weekly, five were seen every second week, and three every third week on a regular basis, with a few appointments missed (vacations, holidays, and family or job engagements). They were weighed and physical examinations, blood counts, tests of urine, blood urea nitrogen, blood sugar, serum bilirubin, serum transaminases, ceph- alin flocculation, thymol turbidity, and stool cultures for pathogens were carried out periodically, both during control and experimental periods. Patients with evidence of kidney or liver disease were not accepted in the group.

Total serum cholesterol concentrations were determined in the fasting state at each visit by the methods of Abell and associates. Control serum cholesterol levels, prior to the administration of neomycin, were observed for periods varying from 2.6 to 14.6 months. The average length of the control period was 9.2 months in the 18 patients. The average total number of serum cholesterol determinations during control periods was 36.1, or 3.9 per month. Neomycin sulfate was given orally at daily dose levels varying from 0.5 to 2 g. Five patients were given 2 g, and another was given 1.5 g of neomycin daily throughout the study. For the remaining patients, the usual initial daily dose was 2 g. The dose was subsequently decreased and was varied throughout the study according to response. Neomycin was given uninterruptedly for 12 to 40.1 months to 16 subjects. The average length of drug administration was 17.2 months. The average total number of serum cholesterol determinations was 51.5, or 3.8 per month during administration of neomycin.

Results

The results of the long-term administration of neomycin are summarized in table 1. Average total serum cholesterol concentrations were decreased in 16 patients by 15 to 32%. The average decrease for the group was 22%. The difference was statistically significant at the 0.1% level in each patient. Transitional values of serum cholesterol were included in the calculations of the averages. Serum cholesterol concentrations reached a lower plateau 1 to 5 weeks (average, 2 weeks) after the beginning of the administration of the drug, and remained at a lower level as long as the drug was given. The daily dose level of neomycin was varied in 10 patients from 0.5 to 2 g during the study. The daily dose was reduced or augmented according to the response of the individual. A specific dose level was given for at least 1 month before changing to another dose level. Figures 1 and 2 illustrate the variations of the daily doses of neomycin and the serum cholesterol levels. In the present study the least marked reduction of average serum cholesterol levels (15%) occurred in a patient who received initially

![Figure 1](image1)

**Figure 1**

*Effect of oral administration of neomycin at daily dose levels varying from 0.5 to 2 g for 40.1 months on the concentration of serum cholesterol of R.K., 39 M.*

![Figure 2](image2)

**Figure 2**

*Effect of the oral administration of neomycin at daily dose levels varying from 1 to 2 g for 16 months on the concentration of serum cholesterol of N.H., 39 M.*

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2 g, then 1 g of neomycin daily. However, the next least marked reduction (16%) occurred in a patient who was given 2 g of the drug throughout the study. For the three patients who had the most marked reduction of serum cholesterol levels (25 to 32%), daily doses varied from 0.5 to 2 g.

An additional patient (A.G., 52 F) was given 2 g of neomycin orally for 2.2 months without appreciable change in the level of serum cholesterol. At this point administration of the drug was discontinued, and it was concluded that neomycin had no effect on the serum cholesterol levels in this subject.

No severe side effects were noted during the administration of the drug. Eight of the 17 patients developed mild diarrhea, abdominal cramps, and mild nausea during the first or second week of the administration of neomycin, which was easily controlled with tincture of paregoric. The administration of neomycin was continued and the symptoms subsided by the end of the second week in each of these patients. They were then completely free of side effects during the remaining part of the study, for periods up to more than 3 years. The weight of all except two patients remained within two pounds variation throughout the study. The first exception was a 12-year-old boy (A.K., 12 M) with familial hypercholesterolemia and xanthomatosis. During 16.7 months of administration of neomycin he grew 2.6 inches and his weight increased by 21 pounds. Another patient (E.D., 52 M) lost nine pounds during the administration of neomycin, with no apparent influence on the effect of the drug on the level of serum cholesterol. Physical examinations and the monitoring laboratory tests remained unchanged during the administration of neomycin, except in one subject. This patient (R.K., 39 M) had a temporary increase in the level of serum transaminases and of thymol turbidity for 4 weeks during the second year of neomycin administration, without any other symptoms. It was felt that this may have been due to a mild form of anicteric hepatitis. His family had liver function tests done, and one child was found to have the same temporary abnormalities. It was then concluded that these abnormalities were not due to the experimental medication, and its administration was continued uninterruptedly. The laboratory values returned to normal spontaneously, and since then neomycin has been given to this patient for an additional year without evidence of clinical or laboratory side effects. This episode had no apparent effect on serum cholesterol levels during the study.

The eighteenth patient in this study, a 37-year-old woman with type II-familial hypercholesterolemia, was given 2 g of neomycin daily. During the first week of the administration of the drug she developed severe diarrhea and nausea. The study was interrupted, and no further attempts were made to give her the drug.

**Discussion**

It is generally accepted that the oral administration of neomycin consistently lowers the concentration of serum cholesterol in man. The results of the present study suggest that the drug is effective for relatively extended periods and that the concentration of serum cholesterol will not return to control levels during medication, even after as long as 3 years. Furthermore, the administration of the drug on a long-term basis in a group of patients with normal activities seems feasible without significant side effects. Serum cholesterol values were abnormally high in 11 patients during control periods. Following the administration of neomycin, the level of serum cholesterol was reduced to values regarded as normal for age and sex in eight of the patients.

A review of the literature on the oral use of neomycin as a serum cholesterol reducing agent is presented in table 2. Including the present study, the effect of the drug on blood cholesterol has been reported to the best of our knowledge in a total of 180 patients. The daily dose of neomycin in these studies varied from 200 mg to 12 g. The medication was continued for 6 days to 40.1 months. When daily oral doses varying from 0.5 to
## Table 2

*Review of the Literature of the Oral Administration of Neomycin as a Serum Cholesterol-Reducing Agent in Man*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Daily dose of neomycin</th>
<th>Length of administration</th>
<th>Number of patients</th>
<th>Number of patients responding</th>
<th>Average fall (%)</th>
<th>Number of patients</th>
<th>Side effects</th>
<th>Nature of side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samuel and Steiner (1959)1</td>
<td>0.5 to 2 g</td>
<td>3 to 10 wk</td>
<td>10</td>
<td>10</td>
<td>11 to 29</td>
<td>4</td>
<td>Mild, transitory diarrhea</td>
<td></td>
</tr>
<tr>
<td>Goldsmith et al. (1959)4</td>
<td>2 g</td>
<td>Circa 70 days</td>
<td>2</td>
<td>2</td>
<td>&quot;Significant&quot;</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Samuel (1959)2</td>
<td>1.5 to 2 g</td>
<td>4 to 20 wk</td>
<td>18</td>
<td>18</td>
<td>21</td>
<td>6</td>
<td>Transitory diarrhea</td>
<td></td>
</tr>
<tr>
<td>Jacobson et al. (1960)15</td>
<td>12 g</td>
<td>6 days</td>
<td>9</td>
<td>7</td>
<td>10 to 36</td>
<td>9</td>
<td>Diarrhea, malabsorption syndrome</td>
<td></td>
</tr>
<tr>
<td>Kalliomaki et al. (1960)5</td>
<td>1.05 to 2 g</td>
<td>9 to 27 days</td>
<td>33</td>
<td>27</td>
<td>8 to 27</td>
<td>16</td>
<td>Decreased vitamin A absorption</td>
<td></td>
</tr>
<tr>
<td>Samuel and Waithe (1961)3</td>
<td>1.5 to 2 g</td>
<td>4 to 37 wk</td>
<td>30</td>
<td>30</td>
<td>21</td>
<td>10</td>
<td>Temporary diarrhea</td>
<td></td>
</tr>
<tr>
<td>Steiner et al. (1961)6</td>
<td>0.5 to 4 g</td>
<td>4 to 36 wk</td>
<td>20</td>
<td>20</td>
<td>10 to 30</td>
<td>3</td>
<td>Loose stools for short periods</td>
<td></td>
</tr>
<tr>
<td>Powell et al. (1962)7</td>
<td>2 g</td>
<td>24 days</td>
<td>5</td>
<td>5</td>
<td>25</td>
<td>5</td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Samuel et al. (1962)16</td>
<td>2 g</td>
<td>5 to 15 wk</td>
<td>4</td>
<td>4</td>
<td>23</td>
<td>1</td>
<td>Mild diarrhea</td>
<td></td>
</tr>
<tr>
<td>Hamilton (1963)8</td>
<td>2 g</td>
<td>3 wk</td>
<td>1</td>
<td>1</td>
<td>25</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Leveille et al. (1963)9</td>
<td>200 mg</td>
<td>12 days</td>
<td>4</td>
<td>0</td>
<td>—</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Hvidt and Kjeldsen (1963)10</td>
<td>3 mg</td>
<td>10 days</td>
<td>10</td>
<td>8</td>
<td>11 to 19</td>
<td>6</td>
<td>Diarrhea, mild steatorrhea</td>
<td></td>
</tr>
<tr>
<td>Nunn et al. (1963)17</td>
<td>4 g</td>
<td>1 wk</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Best and Duncan (1964)11</td>
<td>12 g</td>
<td>1 wk</td>
<td>5</td>
<td>5</td>
<td>35</td>
<td>5</td>
<td>Severe diarrhea</td>
<td></td>
</tr>
<tr>
<td>Samuel et al. (1965)18</td>
<td>2 g</td>
<td>12 to 26 wk</td>
<td>4</td>
<td>4</td>
<td>20 to 29</td>
<td>1</td>
<td>Mild diarrhea</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>0.5 to 2 g</td>
<td>12 to 40.1 mo</td>
<td>17</td>
<td>16</td>
<td>22</td>
<td>8</td>
<td>Mild transitory diarrhea and abdominal cramps*</td>
<td></td>
</tr>
</tbody>
</table>

*In one additional patient administration of neomycin was interrupted for severe diarrhea and nausea.
12 g of neomycin were given, the level of serum cholesterol decreased in 169 of 180 patients (94%). Average falls of total serum cholesterol concentrations varied from 10 to 36%. Analysis of side effects were included in 11 papers, representing a total of 165 patients. In four publications there were no data reported on side effects. Daily oral doses of 12 g of neomycin induced severe diarrhea and malabsorption syndrome in 14 patients. The remaining 151 subjects were given daily doses varying from 0.5 to 4 g. At this dose level 60 patients (40%) were reported to have mild transitory diarrhea or abdominal cramps or both, which subsided spontaneously 1 to 2 weeks after the beginning of medication, with continued administration of the drug. In the present study, one patient is reported in whom the administration of the drug (2 g daily) had to be discontinued because of severe diarrhea and nausea. No major or organic side effects during the administration of neomycin for cholesterol-lowering purposes were reported in the literature, and all authors agreed that daily dose levels of 2 g or less were tolerated without noteworthy side effects after the initial 2 weeks of medication.

A previous report from this laboratory showed that smaller doses of neomycin induced less marked changes of serum cholesterol than the daily administration of 2 g.1 One group of investigators gave 200 mg of neomycin per day orally to patients and reported that this dose had no effect on serum cholesterol.9

Studies on a variety of serum lipids were reported from a number of laboratories during the administration of neomycin. The esterified fraction of serum cholesterol,1-3, 6 serum phospholipids,1, 2, 6, 7, 9 and total serum lipids1, 6 decreased in proportion to total serum cholesterol. The alpha and beta-lipoprotein ratios were not altered by neomycin.3, 6 The variation of serum glycerides was inconsistent in one laboratory7, 9; marked reductions of serum triglycerides were reported from another.11 The concentration of free fatty acids was reduced during the administration of the drug.7

The fall in serum cholesterol due to fat free or low fat diets is augmented by administration of neomycin. The addition of neomycin to a regimen of a fat free diet in four patients10 or to a regimen of a low fat diet in three patients6 resulted in further serum cholesterol reductions of from 14 to 26%, after the dietary regimens had reduced the level of serum cholesterol by 10 to 23% from initial control periods.

The potential toxicity of parenterally administered neomycin has been pointed out repeatedly.19-22 It is, however, generally accepted that neomycin is poorly absorbed from the gastrointestinal tract. The oral administration of the drug was reported to be well tolerated even in relatively high doses for prolonged periods in patients without kidney disease, and reports on toxic side effects during the oral administration of the drug are scarce. Kunin and associates23 pointed out that patients with renal insufficiency accumulated neomycin in the serum due to decreased renal excretion of the small amounts of drug absorbed which led to serious side effects. Ototoxicity was reported in three adults24-26 and in one infant27 during the oral administration of neomycin. However, the prolonged use of neomycin administered orally in a group of premature infants was well tolerated.28 Dawson and associates29 reported that the daily oral administration of a large dose, 4 to 10 g, of neomycin to 20 patients with liver disease was well tolerated for periods up to 10 months. In a subsequent study Last and Sherlock24 gave similar large doses of the drug orally to 27 patients with liver disease for periods up to 140 days. One patient developed ototoxicity during the study. Monilia overgrowth was reported in surprisingly few cases during the administration of neomycin. Permanent audiotoxicity and temporary nephrotoxicity, due to oral administration of the drug, was reported in one patient by Greenberg and Momary.25 Conversely, Stormont and associates30 concluded that no evidence of neomycin toxicity was
encountered in a group of 56 patients with severe liver disease, who were given 4 to 8 g of oral neomycin daily for the treatment of hepatic coma.

It should be emphasized that in the present study the maximum dose given was 2 g of neomycin daily. On this program the patients had no significant change in weight or in fecal fat excretion. It should also be made clear that the lowering of serum cholesterol by neomycin is an experimental procedure and should be handled as such.

The mechanism by which neomycin lowers the level of serum cholesterol is unknown. One of the working theories in this laboratory is that the action of the drug may be mediated through its effect upon the intestinal bacterial flora. This possibility has been discussed, in detail, in previous papers.

References


Clinical Research:
Method, Support, and Ethic

Those of us who are engaged in medical education and research fear the treason of the clerks, who wish to have everything tidy and circumscribed and who forget that the oak sheds ten thousand acorns to produce another tree and the fish spawns a million eggs to maintain the race of fishes. Research requires a spirit, not of prodigality but of magnificence, using that word as it was used by the Greeks, who thought that three virtues are essential if a democracy is to remain great—proper ambition, magnificence, and greatness of spirit...

There is at present a good deal of uninspired clinical research, research of which we may say, in Lord Macaulay's words, "The inquiry may amuse us but the decision leaves us no wiser." Apart from ethical problems, therefore, it is a good thing that clinical science and human experiment should recently have come under sharp scrutiny. There is need to bring together in frank cooperation the people who do the experiments and those who submit to them. If only those things are done which can be explained and agreed to by an intelligent patient, clinical research as a whole will greatly gain. Not only what is unreasonable but what is jejune and trivial will not be tolerated. A voluntary hospital used to mean a hospital in which the doctors gave their services voluntarily; it may come to mean one in which the patients voluntarily cooperate in research.

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