A preliminary report

A Cholesterol-Rich Diet Accelerates Bacteriologic Sterilization in Pulmonary Tuberculosis*

Carlos Pérez-Guzmán, MD, MS; Mario H. Vargas, MD, MS, FCCP; Francisco Quinonez, MD, MS; Norma Bazavilvakoz, CCN; Adriana Aguilar, RD; and the Instituto Nacional de Enfermedades Respiratorias Tuberculosis Outpatient Service Team†

Background: Hypocholesterolemia is common among tuberculous patients and is associated with mortality in miliary cases. Some in vitro studies have shown that cholesterol is necessary for the good functioning of macrophages and lymphocytes.

Study objectives: To determine whether a cholesterol-rich diet could accelerate sputum sterilization in patients with pulmonary tuberculosis.

Design: An 8-week follow-up, randomized, controlled trial carried out from March 2001 to January 2002.

Setting: A third-level hospital for respiratory diseases in Mexico City.

Patients and interventions: Adult patients with newly diagnosed pulmonary tuberculosis were hospitalized for 8 weeks and randomly assigned to receive a cholesterol-rich diet (800 mg/d cholesterol [experimental group]) or a normal diet (250 mg/d cholesterol [control group]). All patients received the same four-drug antitubercular regimen (ie, isoniazid, rifampin, pyrazinamide, and ethambutol).

Measurements and results: Every week, a quantitative sputum culture and laboratory tests were done and respiratory symptoms were recorded. Patients in the experimental group (10 patients) and the control group (11 subjects) were HIV-negative and harbored Mycobacterium tuberculosis that was fully sensitive to antitubercular drugs. Sterilization of the sputum culture was achieved faster in the experimental group, as demonstrated either by the percentage of negative culture findings in week 2 (80%; control group, 9%; p = 0.0019) or by the Gehan-Breslow test for Kaplan-Meier curves (p = 0.0037). Likewise, the bacillary population decreased faster (p = 0.0002) in the experimental group. Respiratory symptoms improved in both groups, but sputum production decreased faster in the experimental group (p < 0.05). Laboratory test results did not differ between the groups.

Conclusions: A cholesterol-rich diet accelerated the sterilization rate of sputum cultures in pulmonary tuberculosis patients, suggesting that cholesterol should be used as a complementary measure in antitubercular treatment.

CHEST 2005; 127:643–651

Key words: colony count; diet; microbial; Mycobacterium tuberculosis

Abbreviations: AFB = acid-fast bacilli; HDL = high-density lipoproteins; LDL = low-density lipoproteins

Pulmonary tuberculosis is one of the oldest diseases, afflicting the human race since ancient times. A milestone in therapy was the discovery of drugs with antimycobacterial activity, beginning in 1944 with the isolation of streptomycin. With the currently available drugs, > 90% of pulmonary tuberculosis cases can be cured. However, the success of the treatment depends on the use of appropriate antitubercular drugs, the adherence of the patient to treatment, the sensitivity of mycobacteria to antitubercular drugs, and the control of associated diseases. An additional factor that could negatively affect the efficacy of the antitubercular treatment is a deficiency in cellular immunity, which in turn can be influenced by nutritional status.

www.chestjournal.org CHEST / 127/2/ FEBRUARY, 2005 643

Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22021/ on 06/19/2017
Some years ago, we found that most patients with pulmonary tuberculosis had low total serum cholesterol levels, and that values of < 90 mg/dL were strongly associated with mortality in those patients with miliary disease. Although very scantily investigated, these associations have been already mentioned by others. For example, Taylor and Bangboye found low cholesterol levels in Nigerian tuberculous patients, and Harris et al and Kozarevic et al noticed that the mean cholesterol levels of patients who died of noncardiovascular diseases, such as cancer, tuberculosis, and *cor pulmonale*, were significantly lower in comparison with those who survived.

Cholesterol constitutes up to 30% of the total lipid content in the cell membrane, and participates in the fluidity of this structure. Consequently, cholesterol is involved in the activity of membrane-bound enzymes and membrane functions such as phagocytosis and cell growth. In this context, Drabowsky et al demonstrated that cholesterol content in the cell membrane of human lymphocytes is important for their cytotoxic function. Heiniger and Marshall demonstrated that cholesterol content in the cell membrane of activated lymphocyte subsets, such as CD4+ and CD8+ T cells, recruit macrophages and release molecules, such as interferon-γ and tumor necrosis factor-α, that render them more efficient in killing mycobacteria. In addition, cytotoxic lymphocytes (either CD4+ or CD8+) undergo phagocytosis of macrophages that have already internalized mycobacteria.

In the last few decades, cholesterol has received huge attention, mainly because of its deleterious effect on the cardiovascular system, and current recommendations are all directed to achieving low serum levels. However, taking into account the above-mentioned clinical observations and *in vitro* studies, it was evident for us that in the case of pulmonary tuberculosis, a low-cholesterol level might have a detrimental effect. Thus, we decided to investigate whether a cholesterol-rich diet could have a beneficial effect on the bacteriologic sterilization of sputum cultures in newly diagnosed cases of pulmonary tuberculosis in patients receiving the best antitubercular drug regimen. Some of the results of these studies have been reported previously.

**Patients and Methods**

A randomized and controlled clinical trial was carried out at the Instituto Nacional de Enfermedades Respiratorias, in Mexico City, from March 2001 to January 2002. During this period, all outpatients with class 3, category I21,22 pulmonary tuberculosis (ie, never treated, newly diagnosed patients with bacteriologic confirmation of the disease) were invited to enter the study, excluding those with a history of diabetes mellitus, an HIV-positive test result, or clinical or ECG data suggestive of coronary heart disease. Patients who accepted entry were randomly assigned to the experimental group (ie, cholesterol-rich diet) or the control group (ie, the normal diet) and were hospitalized for 8 weeks. If during the hospital stay an enzyme-linked immunosorbent assay result positive for HIV or a diagnosis of diabetes mellitus (hyperglycemia of > 126 mg/dL on 2 separate days) were disclosed, the patient was eliminated from the study.

Every day, all patients received a 2,500-calorie diet, distributed in three meals (at approximately 9 AM, 2 PM, and 7 PM), that fulfilled the minimum recommended dietary allowances for the major nutrients, including 250 mg/d cholesterol (control group) or 800 mg/d cholesterol (experimental group). Patients were unaware the group to which they had been assigned. The daily calorie intake was derived from proteins (16%), carbohydrates (54%), and lipids (30%). The extra amount of cholesterol in the experimental group was introduced into the diet by adding cholesterol-rich food such as butter, beef liver, egg yolk, and milk derivatives. All ingredients necessary to obtain the desired allowances were corroborated by one of the two nutritionists participating in the study (N.B. and A.A.), who were blinded to the bacteriologic and laboratory results.

During the entire study (8 weeks), all patients received a short-course regimen with four antitubercular drugs, which were administered daily at standard doses (isoniazid, 300 mg; rifampin, 600 mg; pyrazinamide, 1.6 g; and ethambutol, 1.2 g), under the directly observed therapy strategy, as proposed by the World Health Organization. Drugs were administered in the morning, approximately 30 to 60 min before breakfast. After the termina-
tion of the study, the patients completed the treatment on an outpatient basis. All patients were hospitalized in individual rooms in order to avoid the possibility of superinfection with mycobacteria from other patients.

At the beginning of the study, and every week thereafter, patients were evaluated through sputum culture, a sputum smear for acid-fast bacilli (AFB), WBC count, hemoglobin level measurement, hematocrit, and measurement of the levels of total serum cholesterol, high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), triglycerides, glucose, albumin, and globulins. Respiratory symptoms (ie, cough, sputum production, and dyspnea) were rated by the patient on a visual analog scale with a range of 0 to 10, with the assistance of one of the investigators (C.P.G.). Monitoring of the potential side effects of antitubercular drugs was performed using the usual clinical evaluation and laboratory tests recommended by the International Union Against Tuberculosis and Lung Diseases.1 Thus, besides the weekly measurement of liver enzyme levels, symptoms suggestive of drug toxicity, such as jaundice, hepatomegaly, abdominal pain, fever, anorexia, nausea, vomit, impaired vision, paresthesia, myalgias, muscle weakness, ataxia, pruritus, rash, anemia, and osteoarticular pain, were evaluated daily. The susceptibility of mycobacteria to antitubercular drugs was also tested at the beginning of the study, with the first sputum culture. Body mass index calculation, tuberculin skin test (purified protein derivative, 2 IU), and chest radiography (posteroanterior and left lateral views) were performed at the beginning and the end of the study. A percentage of radiologic improvement, primarily based on the extension of lesions, was independently calculated by two of the authors (C.P.G. and H.V.V.), who were blinded to any identifying information that was present on the chest radiograph.

For sputum culture and mycobacterial drug-susceptibility testing, sputum samples were homogenized with N-acetyl-L-cysteine, decontaminated with 1% NaOH, and cultured (ESP-culture system II; AccuMed International; Westlake, OH). The identification of the Mycobacterium tuberculosis strain was done using a confirmation kit (Accuprobe Culture confirmation kit; Gen-Probe; San Diego, CA) and through biochemical methods. For the quantitative determination of colony-forming units of M tuberculosis, 100 μL decontaminated sputum, nondiluted and diluted (ie, 1:10, 1:100, and 1:1000 in distilled water) was added to media (Middlebrook 7H-10 medium; DSMZ, Becton Dickinson; Cockeysville, MD) supplemented with oleic acid, albumin, and catalase. Samples were incubated at 37°C for >3 weeks. The colony count was analyzed as log of the colony forming units per milliliter in the 1:100 dilution. The protocol was approved by the Scientific and Ethics Committees of the Instituto Nacional de Enfermedades Respiratorias, and informed written consent was voluntarily obtained from each patient before entering the study.

Statistical Analysis

Most differences between the control group and the experimental groups were assessed by using the Fisher exact test for categoric variables, and the nonpaired Student t test was used for interval variables. The Mann-Whitney U test was applied for nonnormally distributed or ordinal variables. Agreement between the two chest radiograph reviewers was assessed by the intraclass correlation coefficient. The difference in the rapidity of sputum culture conversion between groups during the 8-week study also was assessed by the Gehan-Breslow test for Kaplan-Meier survival curves. Most statistical analyses were performed using a statistical software package (Prophet, version 5.0; BBN Technologies; Cambridge, MA). Statistical significance was set at p < 0.05 (two-tailed test). Data in the text and figures are expressed as frequencies or as the mean ± SEM.

Results

From among the 24 patients who initially entered the study, 3 were eliminated. One patient from the control group was eliminated from the study because sputum culture findings were always negative despite the first sputum smear being positive for AFB. Two patients were eliminated from the experimental group, one of them because diabetes mellitus was detected after his admission to the hospital, and the other because treatment was suspended due to intolerance to antitubercular drugs (ie, nausea and vomiting with a more than fivefold increase in serum levels of aspartate aminotransferase and alanine aminotransferase in the second week of treatment). Thus, 21 patients completed the study, all of them were HIV negative and harbored M tuberculosis that was fully sensitive to isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin.

The experimental group consisted of 10 subjects (8 women), who were 19 to 60 years old with a body weight range of 38.5 to 59.5 kg, whereas the control group included 11 patients (6 women), who were 17 to 60 years old with a body weight range of 38.0 to 55.5 kg. There were no significant differences between the groups regarding doses of antitubercular drugs received by patients (p = 0.42). At the beginning of the study, the groups were similar in almost all variables (Table 1). The only exception occurred in the radiologic appearance of tuberculous lesions, since there was a higher proportion of patients with cavitary lesions in the lungs in the experimental group (36%; p = 0.02). In the other radiologic variables that were analyzed, there was a tendency for the control group to include more patients with multilobar involvement (82% vs 40%, respectively; p = 0.08) and bilateral involvement (64% vs 30%, respectively; p = 0.20).

As can be seen in Figure 1, top, A, the rate of sputum culture conversion in the group that received a cholesterol-rich diet was faster (20%, 80%, 90%, and 90%, respectively, in the first 4 weeks of treatment) than in the control group (0%, 9%, 45%, and 73%, respectively). Thus, the proportion of patients in the experimental group whose sputum culture findings became negative at the end of the second week (8 of 10 patients) was much greater than that in the control group (1 of 11 patients; p = 0.0019), and this difference was close to statistical significance in the third week (9 of 10 patients vs 5 of 11 patients, respectively; p = 0.063). Moreover, the Gehan-Breslow test yielded a p value of 0.0037, thus corroborating the fact that the sterilization rate was significantly different between the groups. Using a different approach for the assessment, the control...
group needed a median duration of 28 days (range, 14 to 35 days) for the sputum culture conversion, whereas patients receiving a cholesterol-rich diet required 14 days (range, 7 to 49 days; p < 0.006).

Although the number of colony forming units cultured from the sputum rapidly decreased in both groups after the initiation of treatment, this decline was faster in the experimental group, reaching statistical significance at the second week (p = 0.00018) [Fig 1, middle, B]. Likewise, in the sputum smear the number of AFB decreased faster in the experimental group, although the difference did not reach statistical significance (Fig 1, bottom, C).

As can be seen in Figure 2, cough and dyspnea improved at the same rate in both groups, while sputum production decreased faster among patients eating a cholesterol-rich diet. This difference reached statistical significance at the end of the seventh week (p < 0.05).

Daily dietary intake during the 8-week study was almost the same for both groups for elements other than cholesterol (Fig 3). Thus, comparisons of calories and carbohydrates were devoid of statistical significance and, although proteins and noncholesterol lipids yielded a statistically significant difference, the absolute variation was negligible, and the daily intake was above the recommended dietary allowance. As planned, daily cholesterol intake was notably higher in the experimental group. Diets were well-tolerated in both groups.

At the beginning of the study, laboratory test results for blood or serum lacked statistically significant differences in both groups. Modifications of these variables during the study, if any, were similar in the two groups. The changes in selected variables throughout the 8-week study are shown in Figure 4. In both groups, levels of total cholesterol, LDL, and HDL had an initial increment during the first 2 weeks, followed by a plateau thereafter. Albumin also displayed this pattern, but the plateau was not reached until week 5. There were no apparent modifications in triglyceride levels during the study. The total number of leukocytes progressively decreased after treatment was initiated. Finally, in order to assess the coronary heart disease risk factors posed by cholesterol, the total cholesterol/HDL and the LDL/HDL ratios also were analyzed. These two indexes decreased similarly in both groups during

---

**Table 1—Baseline Features of the Tuberculous Patients Included in the Study**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cholesterol-Rich Diet (n = 10)</th>
<th>Normal Diet (n = 11)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>5</td>
<td>0.36</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>37.9 ± 5.2</td>
<td>43.2 ± 4.4</td>
<td>0.44</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>50.2 ± 2.0</td>
<td>47.9 ± 1.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Height, cm</td>
<td>159.8 ± 3.2</td>
<td>158.3 ± 2.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Body mass index</td>
<td>19.9 ± 1.2</td>
<td>19.2 ± 0.8</td>
<td>0.65</td>
</tr>
<tr>
<td>Patients with cavitary lesions, No.</td>
<td>9</td>
<td>4</td>
<td>0.02</td>
</tr>
<tr>
<td>Patients with multilobar lesions, No.</td>
<td>4</td>
<td>9</td>
<td>0.08</td>
</tr>
<tr>
<td>Patients with bilateral lesions, No.</td>
<td>3</td>
<td>7</td>
<td>0.20</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.7 ± 0.2</td>
<td>3.4 ± 0.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Globulins, g/dL</td>
<td>4.4 ± 0.2</td>
<td>4.5 ± 0.2</td>
<td>0.62</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>37.5 ± 2</td>
<td>38 ± 1.4</td>
<td>0.85</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.8 ± 0.7</td>
<td>13 ± 0.5</td>
<td>0.74</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>90.4 ± 3.9</td>
<td>92.9 ± 4</td>
<td>0.52</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>136.7 ± 10</td>
<td>157.9 ± 11.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>100.2 ± 7</td>
<td>115.1 ± 15.5</td>
<td>0.41</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>39.3 ± 3.1</td>
<td>41.7 ± 4.1</td>
<td>0.66</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>86.2 ± 9.1</td>
<td>94.4 ± 11.9</td>
<td>0.60</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio</td>
<td>3.58 ± 0.24</td>
<td>4.28 ± 0.27</td>
<td>0.07</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>2.19 ± 0.14</td>
<td>2.48 ± 0.23</td>
<td>0.32</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>20.7 ± 3.3</td>
<td>21.5 ± 4.7</td>
<td>0.90</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>17.1 ± 2.4</td>
<td>20.2 ± 2.4</td>
<td>0.38</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.23</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>9.110 ± 973.8</td>
<td>8,900 ± 1456.6</td>
<td>0.91</td>
</tr>
<tr>
<td>Lymphocytes, cells/μL</td>
<td>2.043.7 ± 225.4</td>
<td>1,478.5 ± 207.4</td>
<td>0.08</td>
</tr>
<tr>
<td>Leukocytes, cells/μL</td>
<td>0.9 ± 0</td>
<td>1 ± 0.1</td>
<td>0.19</td>
</tr>
<tr>
<td>RUN, mg/dL</td>
<td>26.8 ± 2</td>
<td>29 ± 3.2</td>
<td>0.57</td>
</tr>
<tr>
<td>PPD skin test, mm induration</td>
<td>15.9 ± 2.8</td>
<td>12.5 ± 2.6</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*Values given as mean ± SEM, unless otherwise indicated. ALT = alanine aminotransferase; AST = aspartate aminotransferase; PPD = purified protein derivative.
the first 3 weeks, and were largely unchanged (between 2.7 and 3.3, and between 1.5 and 1.8, respectively) during the rest of the study. The baseline mean total cholesterol levels were below the reported median values for the Mexican population (ie, approximately 190 mg/dL) in both the experimental group (136.7 ± 10.0 mg/dL) and the control group (157.9 ± 11.6 mg/dL).

Finally, the values derived from the result of the tuberculin skin test did not change at the end of the study, compared with initial values, in either group. The comparison between initial and final radiographs showed a similar improvement in the two groups, and were not statistically different (p = 0.32). The intraclass correlation coefficient between the chest radiograph reviewers showed an acceptable agreement of 0.82.

**DISCUSSION**

Pulmonary tuberculosis therapy requires the prolonged administration of relatively expensive drugs, with frequent side effects and difficulties in compliance. Thus, the search for new drugs that improve the current antitubercular regimens is a continuous need.29

A combination of up to four antitubercular drugs is currently the recommended therapeutic regimen for most new cases of pulmonary tuberculosis.21,22 This treatment has already been proven to decrease the bacillary population in just a few weeks, and to achieve a cure rate of > 90% at the end of a 6-month period.2 Therefore, any new improvement to this regimen has to be faced with the limitation of a narrow margin available to demonstrate its efficacy. Despite this, in our study we found that a cholesterol-rich diet accomplished this goal, inasmuch as it accelerated the sterilization rate of the sputum cul-

**Figure 1.** Weekly bacteriologic status, evaluated as the percentage of patients with mycobacteria in the sputum culture (top, A), the amount (mean ± SEM) of colony forming units (CFU) per milliliter sputum (middle, B), and the number (median) of AFB in the sputum smear (bottom, C). *p = 0.0019; **p = 0.00018.

**Figure 2.** Respiratory symptoms, rated by the patient on a scale of 0 to 10. Circles represent the median value from pulmonary tuberculous patients receiving a cholesterol-rich diet (○) or a normal diet (●). *p < 0.05.
ture. This beneficial effect of the cholesterol-rich diet can be demonstrated by several statistical approaches. Interestingly enough, this favorable effect was evident even when the experimental group had a higher proportion of patients with cavitary lesions and a trend to have more AFM in their initial sputum smear, two conditions that have been described to be associated with a prolonged time for sputum culture conversion.30

Patients in the control group followed a clinical and bacteriologic evolution that was similar or better than the course already described in a number of studies. Thus, in our study the median time to obtain the first negative sputum culture result was 28 days, which was very similar to the 26 days found by Telzak et al.30 Likewise, the sputum culture result became negative in 73% of our patients after the first month of treatment, which was comparable to the 69% found by the British Medical Research Council.31 Therefore, we can reasonably affirm that differences in the outcome between the groups were not due to a less-than-expected responsiveness of the control group.

Although we did not make attempts to investigate the mechanisms by which a cholesterol-rich diet affected the sterilization rate of a sputum culture, published data allowed us to speculate that an enhanced ability of immune cells to deal with mycobacteria might be the key factor. Among the few in vitro studies that have investigated the role of cholesterol in immune cells,11–14 perhaps the work that is more relevant to our findings is the one published by Catfield and Pieters.14 In that study, they found that the capacity of murine macrophages to phagocytose M. tuberculosis decreased by > 85% when they were depleted of cholesterol. Interestingly, this effect was clearly specific against mycobacteria and did not occur for other microorganisms such as Escherichia, Yersinia, Salmonella, and Lactobacillus. Moreover, it is known that the cholesterol/phospholipid ratio in the macrophage membrane is an important factor in determining the fluidity of the membrane, which in turn influences the ability of these cells to undergo phagocytosis of foreign material.10 Thus, membrane cholesterol levels must be maintained within a narrow range to permit normal membrane-dependent cellular functions.10 Therefore, an enhanced capability of macrophages to internalize mycobacteria is a possible explanation for the effect of the cholesterol-rich diet observed in our study. This speculation is reasonably justified because it is evident that macrophages, even when activated and able to kill mycobacteria, would not accomplish this task if they were incapable of uptaking them.

There is scarce information about the abnormalities of phagocytosis in pulmonary tuberculous patients. Antonaci et al32 found that neither polymorphonuclear cells nor monocytes had abnormal phagocytosis activity in their study. Preliminary Reports

![Figure 3. Average daily intake in pulmonary tuberculosis patients. *p < 0.05; **p < 10⁻²⁰.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22021/ on 06/19/2017)
Thus, according to the results observed by Gatfield and Pieters, abnormal phagocytosis in macrophages cannot be excluded.

A recent study by Schaible et al described a novel mechanism by which mycobacterial antigens can be presented to CD8+ T cells. They found that mycobacteria that have undergone phagocytosis by macrophages induce apoptosis in these cells, causing the release of apoptotic vesicles that carry mycobacterial antigens. These vesicles are engulfed by dendritic cells, which then present the antigens to CD8+ T cells, causing their activation. These cells, in turn, release interferon-γ, which promotes antimycobacterial effector mechanisms in uninfected bystander macrophages. Thus, according to this mechanism, even if nonactivated macrophages were unable to kill mycobacteria and die in the process, the final result would be favorable for the immune system.

Finally, although the exact mechanisms by which a cholesterol-rich diet accelerated the sputum conversion in pulmonary tuberculosis patients are yet unclear, our results seem to confirm that a cholesterol-rich diet enhances the bacteriologic improvement during the intensive phase of short-course therapy for pulmonary tuberculosis. The possibility that the faster rate of sputum sterilization in the experimental group might be due to a cholesterol-induced en-

![Figure 4. Time course of some selected serum or blood laboratory tests. Circles represent the mean ± SEM in pulmonary tuberculous patients receiving a cholesterol-rich diet (●) or a normal diet (○).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22021/)
hanced antitubercular drug absorption does not seem plausible. Pyrazinamide and ethambutol absorption is not influenced greatly by food intake, while serum concentrations of rifampin and isoniazid are reduced by ingesting fatty meals.1

At the entry of the study total serum cholesterol levels in both groups were below the median value reported by three Mexican population surveys that sampled approximately 50,000 subjects26–28 a finding that agrees with our previous observation related to the high prevalence of hypocholesterolemia in tuberculous patients.5 It is interesting to note that total serum cholesterol levels in patients eating the cholesterol-rich diet rose at the same rate as that in the control group, despite the approximately 3.6-fold higher dietary intake of this element. A somewhat similar trend also was observed for LDL and HDL. The fact that in both groups the initial increment of total cholesterol levels during the first 2 weeks was followed by a plateau during the remaining 6 weeks suggests that factors other than diet itself are efficiently regulating the total serum cholesterol levels. This is in agreement with advances in cholesterol homeostasis research showing that the enzymatic conversion of cholesterol to bile acids is regulated through feed-forward activation by oxysterols and feedback repression by bile acids.34,35 In our patients, dietary cholesterol might have been used to replenish metabolic pools (eg, cell membranes), transformed into other products such as hormones and vitamins A and D, or catabolized through bile salts. Thus, it is reasonable to speculate that the replenishment of metabolic pools occurred faster in those patients eating a cholesterol-rich diet than in control subjects, even when no differences in serum cholesterol levels were observed between the groups due to the catabolism of cholesterol into bile acids.

According to current guidelines,19 LDL did not reach levels at which a patient would be considered to be at risk for coronary heart disease. By contrast, HDL reached levels at which it would be considered to be a “negative” risk factor (ie, would become a protective factor).19 On the other hand, the total cholesterol/HDL and the LDL/HDL ratios (two putative atherogenic indexes36,37) progressively improved (ie, declined) in both groups throughout the study. Thus, the concern that a cholesterol-rich diet could promote a higher cardiovascular risk in tuberculous patients, at least during the first 8 weeks of therapy, is not supported by our study.

A potential limitation of our study is that micronutrients and trace elements, which might potentially differ among diets, were not estimated. Although our study clearly demonstrates that a cholesterol-rich diet increases the sputum conversion rate, the role of such elements, if any, should be addressed in further experiments.

In conclusion, our results showed that a cholesterol-rich diet accelerated the bacteriologic sterilization of the sputum culture in patients with newly diagnosed pulmonary tuberculosis during the intensive phase with four antitubercular drugs. These preliminary findings suggest that cholesterol should be used as a complementary measure in antitubercular treatment, a proposal that must be validated by further research in larger sample of patients. Our finding is important because the reduction of the infectious period for tuberculous patients decreases the risk of the dissemination of bacilli to others. More important, however, is that these results are in line with the hypothesis that low cholesterol levels have a detrimental influence in patients with pulmonary tuberculosis, and thus more studies about additional applications of cholesterol in the management of tuberculosis patients are needed.

Appendix

Members of the Instituto Nacional de Enfermedades Respiratorias Tuberculosis Outpatient Service Team include the following: Carlos Pérez-Guzmán, MD, MS; Joel Loesa-Irigoyen, MD; Héctor Villarreal-Velarde, MD; Andrea García-Cruz, MD; and Alfredo Torres-Cruz, MD.

References

1 Rieder HL. Interventions for tuberculosis control and elimination. Paris, France: International Union Against Tuberculosis and Lung Diseases, 2002; 15–93
10 Devlin TM. Biological membranes: structure and membrane transport. In: Devlin TM, ed. Textbook of biochemistry with
29 O’Brien R, Nunn PP. The need for new drugs against tuberculosis: obstacles, opportunities, and next steps. Am J Respir Crit Care Med 2001; 162:1055–1058