Reproducing Abnormal Cholesterol Biosynthesis as Seen in the Smith-Lemli-Opitz Syndrome by Inhibiting the Conversion of 7-Dehydrocholesterol to Cholesterol in Rats

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Abstract

The Smith-Lemli-Opitz syndrome is a recessive inherited disorder characterized by neurologic developmental defects and dysmorphic features in many organs. Recently, abnormal cholesterol biosynthesis with impaired conversion of 7-dehydrocholesterol to cholesterol has been discovered in homozygotes. To reproduce the biochemical abnormality, BM 15.766, a competitive inhibitor of 7-dehydrocholesterol-Δ7-reductase, the enzyme that catalyzes the conversion of 7-dehydrocholesterol into cholesterol was fed by gavage to rats. After 14 d, plasma cholesterol concentrations declined from 48 mg/dl to 16 mg/dl and 7-dehydro-cholesterol levels rose from trace to 17 mg/dl. Hepatocytes surrounding the central vein developed balloon necrosis. Stimulating cholesterol synthesis with cholesterylamine followed by BM 15.766 produced an additional 40% decline (P < 0.05) in plasma cholesterol and 34% increase in 7-dehydrocholesterol levels compared to the inhibitor alone. Adding 2% cholesterol to the diet during the second week of BM 15.766 treatment increased plasma cholesterol threefold and decreased 7-dehydrocholesterol concentrations 55%. Hepatic 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase activity increased 73% with a 3.9-fold rise in mRNA levels but cholesterol 7α-hydroxylase activity decreased slightly though mRNA levels increased 1.4 times with BM 15.766 treatment. These results demonstrate that BM 15.766 is a potent inhibitor of 7-dehydrocholesterol-Δ7-reductase. The model reproduces abnormal cholesterol biosynthesis as seen in the Smith-Lemli-Opitz syndrome and is useful to test different treatment strategies. Stimulating early steps of cholesterol synthesis worsens the biochemical abnormalities while feeding cholesterol inhibits abnormal synthesis, improves the biochemical abnormalities and prevents liver damage. (J. Clin. Invest. 1995. 95:76-81.) Key words: Disease model, animal • fetal growth retardation • lipid metabolism, inborn errors • HMG-CoA reductase • Cholesterol 7α-hydroxylase

Introduction

The Smith-Lemli-Opitz syndrome is an autosomal recessive disorder characterized by severe mental retardation with neurologic dysfunction, failure to thrive, and distinctive dysmorphic features, that was first described in 1964 (1). The most prominent clinical manifestations include microcephaly, micrognathia, wide spread eyes, cataracts, flat nares, low set posteriorly rotated ears, and syndactyly. The prevalence of homozygotes is about 1 in 20,000 births (2) with an estimated carrier frequency of 1 to 2% (3).

Recently, we reported that homozygotes with the Smith-Lemli-Opitz syndrome show abnormal cholesterol biosynthesis with extremely low cholesterol levels and the accumulation of the cholesterol precursor, 7-dehydrocholesterol, and two related dehydrocholesterol isomers in plasma and tissues (4). The biochemical abnormalities probably result from incomplete conversion of the cholesterol precursor, 7-dehydrocholesterol to cholesterol suggesting that the microsomal enzyme which catalyzes this reaction, 7-dehydrocholesterol-Δ7-reductase is abnormal (Fig. 1).

In 1986, Pill and colleagues reported that BM 15.766, a synthetic piperazine derivative, inhibited the conversion of 7-dehydrocholesterol to cholesterol in cultured rat hepatocytes (5) and in rats (6). Other inhibitors of cholesterol synthesis such as AY-9944, trans-1,4-bis-(2-dichlorobenzylaminomethyl) cyclohexane dihydrochloride (7) which also blocks 7-dehydrocholesterol-Δ7-reductase and triparanol, 1-[p-(2-diethylaminoethoxy)-phenyl]-1-(p-tolyl)-2-(p-chlorophenyl) ethanol, an inhibitor of desmosterol-24-reductase (8), when fed to pregnant animals, may produce severe congenital abnormalities in their offspring. (9–11). Some of the congenital defects resemble those found in homozygotes with the Smith-Lemli-Opitz syndrome and suggest that defects in cholesterol synthesis are capable of producing congenital abnormalities common to the phenotype. In this paper, we describe the effects of BM 15.766 on cholesterol and bile acid metabolism in rats and demonstrate that inhibition of 7-dehydrocholesterol-Δ7-reductase reproduces the biochemical abnormalities found in homozygotes with the Smith-Lemli-Opitz syndrome. The effect of cholesterol feeding and bile acid malabsorption was also evaluated in the BM 15.766-treated rats.

Methods

Chemicals

BM 15.766, 4-[(2-[1-(4-chlorocinnamyl)piperazin-4-yl]ethyl)-benzoic acid was a gift from Boehringer Mannheim GmbH (Mannheim, Germany). 7-Dehydrocholesterol (5,7-cholesten-3β-ol) was purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI) and cholesterol (5-cholesten-3β-ol) was obtained from Sigma Chemical Co. (St. Louis, MO).

Experimental plan

28 male Sprague-Dawley rats from Charles River Laboratories (Wilmington, MA) weighing 300–350 g were housed individually, and were
Neutral sterols were extracted with hexane from 1 ml plasma or 0.5 ml bile after saponification in 1N ethanolic NaOH. Trimethylsilyl ether derivatives were prepared and quantitated by capillary gas-liquid chromatography as described previously (13). The retention times of the sterol trimethylsilyl ethers relative to the internal standard, 5α-cholestan (retention time 15.21 min) were: cholesterol, 1.41 and 7-dehydrocholesterol, 1.48.

**Assays for hepatic microsomal total 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and cholesterol 7α-hydroxylase activities.** Hepatic microsomes were prepared by differential ultracentrifugation (14), and the protein determined according to Lowry et al. (15). The assay for HMG-CoA reductase activity was based on the methods by George et al. (16) and Nguyen et al. (17). Briefly, 50–200 μg of microsomal protein was preincubated at 37°C for 5 min in a final volume of 150 μl buffer (50 mM K2HPO4, 30 mM EDTA, 10 mM DTT, 70 mM KCl, pH 7.4) containing a NADPH generating system (34 mM NADP+; 30 mM glucose-6-phosphate, 0.3 U glucose-6-phosphate dehydrogenase) and [3H]mevalonolactone (40,000 dpm) as internal recovery standard. The reaction was started with the addition of 30 nmol [3-3H]HMG-CoA (Amersham Corp., Arlington Heights, IL; specific activity, 30 nmol/mmol) and stopped after 15 min at 37°C with the addition of 20 μl 6N HCl. Zero-time controls were run with each experiment. After lactonization at 37°C for 30 min, the products were separated by thin-layer chromatography, and mevalonolactone quantitated by liquid scintillation counting (17).

Cholesterol 7α-hydroxylase activity was measured in hepatic microsomes by the isotope incorporation method of Shefer et al. (14).

**Isolation and quantitation of mRNA.** Total RNA from samples of frozen liver was isolated by the acid guanidinium thiocyanate-phenol-chloroform extraction method (18). Portions of frozen liver, 0.2 g, were homogenized in 2 ml of room temperature TRI Reagent purchased from Molecular Research Center, Cincinnati, Ohio, using a Polytron Tissue Disruptor at full speed for 5–10 s. After 5 min, 0.4 ml of chloroform was added, the sample mixed vigorously and centrifuged at 12,000 g for 15 min at 4°C. The aqueous phase was removed and 1 ml of isopropanol was added. The samples were mixed and allowed to stand at room temperature for 5–10 min, then centrifuged at 12,000 g for 10 min at 4°C. The pellet RNA was then washed in 75% ethanol. The total RNA pellet was dissolved in 100 μl of diethylyrocarbonate treated water. Poly(A)⁺ RNA was isolated by oligo (dT) cellulose chromatography (19). The relative levels of HMG-CoA reductase and cholesterol 7α-hydroxylase mRNA were quantitated by Northern blotting analysis as previously described (20) except that a Red Roller hybridization oven from Hoefer Scientific Instruments was used. β-Actin was served as the internal standard. The cDNAs for hamster HMG-CoA reductase, pRED 227 and human β-actin, HHCl 89 were purchased from American Type Culture collection (Rockville, MD). The cDNA for rat liver cholesterol 7α-hydroxylase, 7α6β, was a gift from Dr. J. Y. L. Chiang (Northeastern Ohio University, Rootstown, OH).

**Statistical study**

Data were analyzed statistically using the unpaired Student's t test.

**Results**

Measurements of plasma cholesterol and 7-dehydrocholesterol levels in rats treated with BM 15.766 are given in Table I. After 3 d of BM 15.766 feeding, plasma cholesterol concentrations declined 40% (P < 0.05) and 7-dehydrocholesterol levels which were barely detected in untreated controls, increased markedly. Continuing the treatment for 2 wk resulted in a 67% decline for plasma cholesterol (P < 0.0001) and a further rise (+60%) in 7-dehydrocholesterol levels. Discontinuation of the inhibitor for 2 wk allowed plasma cholesterol concentrations to

Inhibition of 7-Dehydrocholesterol-Δ7-Reductase in Rats
recover to the pretreatment level at which time 7-dehydrocholesterol disappeared from the plasma. The changes in biliary sterol and bile acid outputs during these treatment periods are listed in Table II. After 2 wk of feeding BM 15.766, biliary cholesterol secretion was reduced 53% (P < 0.0001) with a marked increase of 7-dehydrocholesterol, so that the precursor was 1.8 times more abundant than cholesterol in the bile. Discontinuing the inhibitor for 2 wk, restored biliary cholesterol outputs to normal levels and eliminated 7-dehydrocholesterol from the bile.

Total biliary bile acid outputs which represent the hepatic bile acid flux declined 18% (P < 0.05) after 2 wk of BM 15.766. After the inhibitor was stopped for 2 wk, the biliary bile acid output rebounded 68% (P < 0.0005) which was 37% greater (P < 0.05) than the bile acid output in the untreated rats (Table II). Cholic acid was the major biliary bile acid and accounted for 77±5% of the total bile acids. The proportion rose to 88±4% after 2 wk treatment with BM 15.766 and returned to pretreatment value after discontinuation of the inhibitor.

Figs. 2 and 3 show the changes in plasma cholesterol and 7-dehydrocholesterol concentrations in rats when either 2.5% cholestyramine or 2% cholesterol was added to the diet in combination with BM 15.766. When cholestyramine was given together with BM 15.766 (Fig. 2), plasma cholesterol levels declined an additional 40% (P < 0.05) and 7-dehydrocholesterol rose 34%, as compared with levels after BM 15.766 feeding for 3 d. In contrast, when 2% cholesterol was added to the diet during the second week of BM 15.766 feeding (Fig. 3), plasma cholesterol concentrations increased threefold (P < 0.0001), which was 20% above the control level while 7-dehydrocholesterol levels were reduced 50% (P < 0.005) as compared with 2 wk of BM 15.766 feeding alone.

Activities for hepatic HMG-CoA reductase and cholesterol 7a-hydroxylase, the respective rate-controlling enzymes for cholesterol and bile acid synthesis are reported in Table III. After 2 wk of BM 15.766 treatment, HMG-CoA reductase activity rose 73% (P < 0.05) and remained elevated even after the inhibitor was discontinued for the following 2 wk. However, the administration of 2% cholesterol in chow during the second week of BM 15.766 treatment inhibited HMG-CoA reductase activity 75% (P < 0.005) compared to BM 15.766 alone. In contrast, cholestyramine treatment for 7 d combined with BM 15.766 treatment for the final 3 d increased the activity 8.8 times (P < 0.0001).

Cholesterol 7a-hydroxylase activity declined 13% (NS)

### Table I. The Effect of BM 15.766 on Plasma Sterols

<table>
<thead>
<tr>
<th></th>
<th>Cholesterol</th>
<th>7-dehydrocholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dl</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Controls (n = 6)</td>
<td>48.1±6.0</td>
<td>Trace</td>
</tr>
<tr>
<td>BM 15.766 3 d (n = 3)</td>
<td>28.9±4.8</td>
<td>10.7±1.7</td>
</tr>
<tr>
<td>BM 15.766 2 wk (n = 9)</td>
<td>15.7±4.7</td>
<td>17.0±3.4</td>
</tr>
<tr>
<td>BM 15.766 2 wk + 2 wk no treatment* (n = 8)</td>
<td>52.4±6.2</td>
<td>Trace</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. * After 2 wk of BM 15.766 feeding, the treatment was discontinued for the following 2 wk. † Trace amounts of 7-dehydrocholesterol, < 0.005 mg/dl.

### Table II. The Effect of BM 15.766 on Biliary Sterols and Bile Acid Output

<table>
<thead>
<tr>
<th></th>
<th>Biliary sterols</th>
<th>Biliary bile acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cholesterol</td>
<td>7-dehydrocholesterol</td>
</tr>
<tr>
<td>Controls (n = 6)</td>
<td>193±45</td>
<td>trace†</td>
</tr>
<tr>
<td>BM 15.766 2 wk (n = 9)</td>
<td>90±26</td>
<td>249±69</td>
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<tr>
<td>BM 15.766 2 wk + 2 wk no treatment* (n = 4)</td>
<td>199±59</td>
<td>trace†</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. * After 2 wk of BM 15.766 feeding, the treatment was discontinued for the following 2 wk. † Trace amounts of 7-dehydrocholesterol, < 0.005 mg/dl.
Table III. The Effect of BM 15.766 on the Hepatic Total HMG-CoA Reductase and Cholesterol 7α-Hydroxylase Activities

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HMG-CoA reductase (pmol/mg/min)</th>
<th>Cholesterol 7α-hydroxylase (pmol/mg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 6)</td>
<td>53.4 ± 9.4</td>
<td>19.7 ± 6.0</td>
</tr>
<tr>
<td>BM 15.766 2 wk (n = 9)</td>
<td>92.4 ± 33.5</td>
<td>17.2 ± 6.0</td>
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<tr>
<td>BM 15.766 2 wk + 2 wks no treatment* (n = 4)</td>
<td>100.5 ± 35.7</td>
<td>24.5 ± 8.9</td>
</tr>
<tr>
<td>BM 15.766 2 wk + 1 wk</td>
<td>24.0 ± 9.4</td>
<td>22.9 ± 3.1</td>
</tr>
<tr>
<td>Cholesterol† (n = 5)</td>
<td>33.5 ± 8.4</td>
<td>13.3 ± 5.6</td>
</tr>
<tr>
<td>BM 15.766 3 d (n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine + BM 15.766 3 d§ (n = 3)</td>
<td>294.5 ± 4.6</td>
<td>30.7 ± 8.9</td>
</tr>
</tbody>
</table>

* After 2 wk of BM 15.766 feeding, the treatment was discontinued for the following 2 wk. † 2% cholesterol was added to the diet during the second week of the 2 wk BM 15.766 treatment. § 2.5% cholestyramine was fed for 7 d combined with BM 15.766 feeding in the last 3 d.

After 2 wk of BM 15.766 treatment but increased 42% after the inhibitor was discontinued for 2 wk. Adding 2% cholesterol to the diet during the second week of BM 15.766 treatment increased the activity 33% (NS). When the inhibitor was combined with cholestyramine, cholesterol 7α-hydroxylase activity rose 2.3 times compared with 3 d of inhibitor treatment alone (P < 0.05).

Figs. 4 and 5 and Table-IV show the effect of BM 15.766 on relative steady state mRNA levels of hepatic HMG-CoA reductase and cholesterol 7α-hydroxylase respectively, as determined by Northern blot analysis and densitometric scanning and corrected for the recovery of β-actin mRNA. Relative steady state mRNA levels of both HMG-CoA reductase (P < 0.005) and cholesterol 7α-hydroxylase (P < 0.001) were increased in rats treated with BM 15.766 for 2 wk compared to the control rats and remained high 2 wk after BM 15.766 was withdrawn.

Fig. 6 shows the effect of 2 wk treatment of BM 15.766 on hepatic histology. Under light microscopy, the general architecture of the hepatic lobule was preserved, but hepatocytes around the central vein showed balloon degeneration. Electron microscopy revealed increased mitochondria and proliferation of the rough endoplasmic reticulum. Discontinuing the inhibitor for 2 wk restored normal liver histology although increased mitochondria and rough endoplasmic reticulum persisted (not shown).

Discussion

These results confirm that BM 15.766 is a potent inhibitor of cholesterol biosynthesis. By blocking 7-dehydrocholesterol-Δ7-reductase (Fig. 1), BM 15.766 caused a marked reduction in plasma cholesterol levels associated with an enormous increase in the concentration of the cholesterol precursor, 7-dehydrocholesterol. Biliary cholesterol outputs also declined markedly with the excretion of 7-dehydrocholesterol enhanced so that the ratio of the precursor to cholesterol was 1.7 times greater in bile than in plasma. The elevated enrichment of 7-dehydrocholesterol relative to cholesterol in bile not only reflects the enzymatic block and inability of 7-dehydrocholesterol to be transformed to cholesterol but also suggests that 1.8 times more 7-dehydrocholesterol than cholesterol is produced since biliarysterol outputs probably mirror endogenous hepatic sterol synthesis. 2 wk after the inhibitor (BM 15.766) was discontinued, the cholesterolsynthetic pathway had normalized: plasma cholesterol concentrations and biliary cholesterol outputs were restored and 7-dehydrocholesterol was eliminated from plasma and bile. This suggests that the inhibition of cholesterol biosynthesis by BM 15.766 is reversible and that newly formed 7-

Table IV. The Effect of BM 15.766 on the Relative Hepatic HMG-CoA Reductase and Cholesterol 7α-hydroxylase mRNA Levels

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HMG-CoA reductase mRNA*</th>
<th>Cholesterol 7α-hydroxylase mRNA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 6)</td>
<td>0.08 ± 0.03</td>
<td>0.46 ± 0.26</td>
</tr>
<tr>
<td>BM 15.766 2 wk (n = 6)</td>
<td>0.21 ± 0.07</td>
<td>1.03 ± 0.05</td>
</tr>
<tr>
<td>BM 15.766 2 wk + 2 wks no treatment§ (n = 6)</td>
<td>0.18 ± 0.03</td>
<td>0.75 ± 0.05</td>
</tr>
</tbody>
</table>

* Corrected for the recovery of β-actin mRNA. † After 2 wk of BM 15.766 feeding, the treatment was discontinued for the following 2 wk. § P < 0.005 as compared with the relevant control value. ‡ P < 0.001 as compared with the relevant control value.
dehydrocholesterol-$\Delta^7$-reductase in the absence of the inhibitor is capable of transforming the accumulated 7-dehydrocholesterol to cholesterol. Interestingly, HMG-CoA reductase activity and mRNA levels remained stimulated probably by the need to replenish depleted tissue cholesterol pools. Similarly, when cholesterol is fed during treatment with BM 15.766, plasma cholesterol rose to pretreatment levels and 7-dehydrocholesterol concentrations declined substantially. Not only is dietary cholesterol absorbed to replace depleted plasma and tissue compartments, but the expanded cholesterol pool exerts negative feedback control on HMG-CoA reductase (Table III) reducing abnormal endogenous synthesis as evinced by the decrease in 7-dehydrocholesterol levels. Conversely, when HMG-CoA reductase was stimulated by pretreatment with cholestyramine, the biochemical abnormalities caused by BM 15.766 were worsened with further decreased cholesterol and increased 7-dehydrocholesterol levels in plasma (Fig. 2). The increased formation of the early precursor, mevalonic acid, which is the product of HMG-CoA and almost totally committed to the cholesterol biosynthetic pathway, mostly ended as 7-dehydrocholesterol in the BM 15.766 treated rats because of the inhibition of 7-dehydrocholesterol-$\Delta^7$-reductase.

After 2 wk of BM 15.766 treatment, HMG-CoA reductase activities and steady state mRNA levels were increased indicating up-regulation of early steps of the cholesterol biosynthetic pathway probably stimulated by the marked reduction in circulating plasma cholesterol and biliary bile acid pools. Clearly, the accumulated 7-dehydrocholesterol does not exert negative feedback regulation of HMG-CoA reductase.

The bile acid pool decreased as evidenced by the reduced hepatic bile acid flux during treatment with BM 15.766. The reduction in cholesterol 7a-hydroxylase activity in combination with increased steady state mRNA levels suggests that the decreased cholesterol substrate supply and/or competitive inhibition of cholesterol 7a-hydroxylase by the large microsomal pool of 7-dehydrocholesterol account for diminished formation of bile acids. 2 wk after BM 15.766 was discontinued, the hepatic bile acid flux was 30% higher than the pretreatment level (Table II) suggesting increased bile acid synthesis that was supported by the increased cholesterol supply, elimination of 7-dehydrocholesterol, higher levels of hepatic microsomal cholesterol 7a-hydroxylase activity and abundance of hepatic cholesterol 7a-hydroxylase mRNA.

Together these findings confirm the location of the biochemical abnormality in the Smith-Lemli-Opitz syndrome. Homozygotes with this syndrome show reduced plasma and tissue cholesterol concentrations associated with high levels of 7-dehydrocholesterol (4), precisely the biochemical findings produced by BM 15.766 in the rats. Clearly, 7-dehydrocholesterol-$\Delta^7$-reductase is abnormal in Smith-Lemli-Opitz homogygotes. Also the rat experiments where cholesterol was given with BM 15.766 suggest that cholesterol treatment of the homozygotes with Smith-Lemli-Opitz syndrome might be beneficial. The added absorbed cholesterol can replenish tissue pools and in-

Figure 6. Photomicrograph of hepatic histology (hematoxylin and eosin stain) in rat treated with BM 15.766 for 2 wk. Hepatocytes around the central vein show balloon degeneration (×200).
hibit HMG-CoA reductase to suppress the rate-controlling step of the abnormal pathway. Stimulating HMG-CoA reductase by feeding cholestyramine is counterproductive and would be expected to worsen the biochemical abnormalities by reducing cholesterol levels further and increasing the precursor concentrations, since the conversion of 7-dehydrocholesterol to cholesterol was blocked. Because bile acid synthesis is also compromised, treatment should also include bile acid replacement to expand the pool and facilitate cholesterol absorption and exert additional feedback inhibition of cholesterol synthesis (21).

In a preliminary report, Shefer et al. (22) showed that 7-dehydrocholesterol-Δ7-reductase activity in the liver of rats treated with BM 15.766 and of a homozygote with the Smith-Lemli-Opitz syndrome was reduced, as compared with the control values. Thus, reduced 7-dehydrocholesterol-Δ7-reductase activity, which was competitively blocked in rats treated with BM 15.766 and is inherently abnormal in the Smith-Lemli-Opitz syndrome, is responsible for the biochemical abnormalities in this disease.

The absence of desmosterol (5,24-cholestadien-3β-ol) or other C-24 unsaturated sterols in the plasma and bile of the BM 15.766 treated rats indicated that the function of Δ24 reductase is not affected by inhibition of 7-dehydrocholesterol-Δ7-reductase. The double bond in the side chain at C-24 can be reduced easily and all desmosterol intermediates transferred to the 7-dehydrocholesterol pathway. In addition, the deficiency of cholesterol in BM 15.766–treated animals and patients with the Smith-Lemli-Opitz syndrome strongly indicates that the desmosterol pathway is not separate from the pathway through which 7-dehydrocholesterol is used and can not produce cholesterol independently when the Δ7 reductase is blocked. (Fig. 1)

In summary, BM 15.766 is a powerful inhibitor of 7-dehydrocholesterol-Δ7-reductase reproducing the biochemical defects of low plasma cholesterol with high 7-dehydrocholesterol levels, found in homozygotes with the Smith-Lemli-Opitz syndrome. Stimulating cholesterol synthesis with cholestyramine worsens the biochemical abnormalities while feeding cholesterol shuts down abnormal cholesterol synthesis and restores cholesterol in the plasma and tissues.

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