The Effect of Beta Sitosterol on the Serum Lipids of Young Men with Arteriosclerotic Heart Disease

By John W. Farquhar, M.D., Ralph E. Smith, M.D., and Mary E. Dempsey, M.S.

Previous studies in human beings on unrestricted diets have indicated that the plant sterols (beta or gamma sitosterol) cause decreases in serum cholesterol. In this study, 15 young men with previous myocardial infarction were given 12 to 18 Gm./day of beta sitosterol with resultant sustained reductions of serum cholesterol and beta lipoprotein lipid. Lipoprotein lipid fractionation was performed by paper electrophoresis. These changes occurred irrespective of initial serum cholesterol or content of diet. Control observations of the effects of diet, weight maintenance, and the inclusion of placebos brought about increased confidence that the changes were due to the administered sitosterol.

The search for agents capable of modifying the serum lipids of man was stimulated by the observation of Peterson in 1951 that the usual hypercholesterolemia of chicks fed cholesterol-enriched diets was prevented by the addition of plant sterols to the diet. In a similar study, Pollak2 described the same phenomenon in rabbits. Hernandez and Chaikoff3 found that the recovery of C14 labeled cholesterol from the thoracic duct of cholesterol-fed rats was substantially reduced by the addition of as little as 4 mg. of sitosterols to a meal containing 100 mg. of cholesterol. Subsequent investigators have reported decreases in serum cholesterol in normal and hypercholesterolemic human beings given varying doses of the plant sterols, gamma and beta sitosterols.4-6

More recently, Best and co-workers7 reported decreases in serum phospholipid, cholesterol, total lipid, and S3-100 lipoproteins after beta sitosterol administration. The reductions in phospholipid and lipoproteins were less consistent and less marked than the changes in serum cholesterol and total lipid. The only negative report to date is that of Wilkinson and co-workers8 who recently found that sitosterol was ineffective in lowering the serum cholesterol of man. Their observations were limited to 4 patients, 3 of whom had initial serum cholesterols of 200 mg./100 ml. or less. No placebo periods were included in their study.

This study was undertaken to evaluate the effects of β-sitosterol on the serum lipids in patients with arteriosclerotic heart disease, with careful attention to the control of diet, weight, and activity variables.

Methods and Materials

Fifteen normotensive, nondiabetic men between the ages of 26 and 45, who had sustained previous well documented myocardial infarction, were studied with serial serum lipid determinations during a 3-phase study: (1) a premedication period of 6 to 12 weeks, (2) a period of sitosterol administration of 12 to 24 weeks, (3) a period of placebo administration of 10 to 16 weeks.

The placebo preparation was similar in taste and appearance to the sitosterol and none of the patients were aware of the change.

Prior to the first phase of the study all patients were placed on diets designed to maintain constant weight. The per cent of calories from fat was from 23 to 28 per cent in 9 patients and from 40 to 48 per cent in 6 patients. With the exception of 1 patient who lost 8 pounds during the first phase, the weights of all the patients were maintained to within 3 pounds of their initial values.

Cholesterol intake was from 200 to 300 mg./day in the 9 patients on fat-restricted diets and 900 to 1000 mg./day in the 6 patients on diets “normal” in fat content. The original diets, and all revisions necessary to maintain constant weight, were made up by a member of the dietetic staff. No effort was made to measure the percentage of fat from animal
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Lipid

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f3-sitosterol*

were

given

or vegetable sources, but the proportions of these
types of fat did not vary much since all patients
followed their prescribed diets.

Three equal portions of β-sitosterol* were given

* Supplied by Eli Lilly and Company, Indianapolis, Ind.

orally immediately before meals in total amounts
of 12 to 18 Gm./day. During all phases of the study
the patients were ambulatory, and efforts were made
to achieve a "steady state" in respect to exercise,
diet, and body weight.

Fifteen apparently normal men matched for age
with the 15 study patients had serum lipid measure-
ments for comparative baseline studies.

Serum was obtained in the fasting state at weekly
or biweekly intervals during all phases. Serum was
analyzed for cholesterol by the method of Abell,9
total lipid by the method of Swahn,10 and lipoprotein
lipid calculated by protein and lipid staining of paper
strips separated by electrophoresis. The electropho-
resis was performed in an apparatus similar to
that described by Durrum and associates,11 using 6
35 cm. by 2.5 cm. Whatman 3 M.M.† strips run for
12 hours at 6 C. in barbitral buffer of pH 8.6 and ionic
strength 0.05. Alternate strips were stained for pro-
tein with bromphenol blue and for lipid with Sudan
black-B (fig. 1). The various lipid fractions of the
stained strips were assigned proportional values by
densitometric and planimetric measurement. The
mg./100 ml. of stainable lipid was computed by com-
parison with the total lipid value of each serum
sample. A technic was devised that we believed
allowed more precise measurement of β-lipoprotein
lipid by effecting its separation from the predomi-
antly neutral fat "origin" lipids (fig. 2). Refine-

† "Chromatography Grade."

<table>
<thead>
<tr>
<th>No. of Patients (all males)</th>
<th>Normal (15) Mean ± σ</th>
<th>Abnormal† (15) Mean ± σ</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Weight (lb.)</td>
<td>170</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>Total protein Gm./100 ml.</td>
<td>6.6 ± 0.4</td>
<td>7.0 ± 0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cholesterol mg./100 ml.</td>
<td>213 ± 34</td>
<td>291 ± 50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total lipid mg./100 ml.</td>
<td>965 ± 160</td>
<td>1204 ± 146</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>α Lipid mg./100 ml.</td>
<td>262 ± 65</td>
<td>224 ± 43</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>β Lipid mg./100 ml.</td>
<td>419 ± 96</td>
<td>557 ± 98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Origin lipid mg./100 ml.</td>
<td>248 ± 95</td>
<td>387 ± 90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>γ Lipid mg./100 ml.</td>
<td>36 ± 18</td>
<td>38 ± 15</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>β + Origin lipid mg./100 ml</td>
<td>667 ± 155</td>
<td>944 ± 140</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Standard deviation, σ = \sqrt{\frac{\sum (x - \bar{x})^2}{N - 1}}

† Measurements represent combined Means of pre-
médication and placebo periods.

‡ Probability that the differences between Means are
due to chance alone.
TABLE 2.—Mean Serum Cholesterol Changes in Patients with Arteriosclerotic Heart Disease During Beta Sitosterol Therapy

<table>
<thead>
<tr>
<th>Period</th>
<th>Cholesterol mg./100 ml.</th>
<th>p Value</th>
<th>Mean Diff. mg./100 ml.*</th>
<th>Mean % Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedication</td>
<td>293 ± 48</td>
<td>&lt;0.001</td>
<td>51</td>
<td>17 (drop)</td>
</tr>
<tr>
<td>Sitosterol</td>
<td>242 ± 30</td>
<td>&lt;0.001</td>
<td>46</td>
<td>16 (rise)</td>
</tr>
<tr>
<td>Placebo</td>
<td>288 ± 55</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Standard error of difference

\[ SE_{M_1-M_2} = \sqrt{\frac{s^2_1}{n_1} + \frac{s^2_2}{n_2}} \]

ments including low temperature control allowed satisfactory reproducibility of results.*

RESULTS

Comparison of the 15 study patients with 15 "normals" matched for age revealed significantly lower mean values in the normal group for \( \beta \)-lipoprotein and origin lipids, for total serum lipid, for protein, and for cholesterol (table 1).

A prompt fall in serum cholesterol occurred during the first 2 to 3 weeks of sitosterol. No tendency to return to pretreatment values was noted when sitosterol was taken for as long as 6 months. A similar prompt rise in serum cholesterol was noted within 3 weeks following substitution of placebo for sitosterol, the mean level of 288 mg./100 ml. during this phase being only 6 mg./100 ml. below the premedication mean of 293 mg./100 ml. The mean serum cholesterol values of the subjects during each phase of the study are summarized in tables 2 and 3.

Figure 3 expresses the changes in serum cholesterol in a different manner; the per cent deviation of each value from the mean of each patient is plotted on the ordinate, and the weeks of each phase of the study are plotted on the abcissa.

A lowering of \( \beta \)-lipoprotein lipid proportional in magnitude to that of cholesterol was observed during the sitosterol period; in contrast, there was no change in origin or \( \gamma \)-lipids. A slight rise in \( \alpha \)-lipoprotein lipid occurred during the sitosterol period, this change being statistically less significant than the change in \( \beta \)-lipoprotein lipid.

The 3 patients with control serum cholesterol levels below 250 mg./100 ml. had de-

TABLE 3.—Effect of Beta sitosterol on Serum Cholesterol of Fifteen Patients with Arteriosclerotic Heart Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>A* Premedication period</th>
<th>B Sitosterol period</th>
<th>C Placebo period</th>
<th>Change† A to B</th>
<th>Change† B to C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± s</td>
<td>Mean ± s</td>
<td>Mean ± s</td>
<td>mg./100 ml.</td>
<td>mg./100 ml.</td>
</tr>
<tr>
<td>1. L.D.</td>
<td>33</td>
<td>220 ± 2</td>
<td>187 ± 14</td>
<td>217 ± 4</td>
<td>-33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2. L.B.</td>
<td>35</td>
<td>220 ± 13</td>
<td>187 ± 13</td>
<td>220 ± 13</td>
<td>-33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3. R.T.</td>
<td>26</td>
<td>254 ± 16</td>
<td>186 ± 9</td>
<td>233 ± 15</td>
<td>-48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4. L.S.</td>
<td>43</td>
<td>260 ± 21</td>
<td>246 ± 15</td>
<td>280 ± 16</td>
<td>-14</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>5. D.L.</td>
<td>29</td>
<td>270 ± 21</td>
<td>224 ± 13</td>
<td>272 ± 11</td>
<td>-46</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>6. J.A.</td>
<td>38</td>
<td>271 ± 6</td>
<td>198 ± 11</td>
<td>216 ± 9</td>
<td>-73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7. J.E.</td>
<td>37</td>
<td>272 ± 6</td>
<td>243 ± 10</td>
<td>286 ± 33</td>
<td>-29</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>8. W.R.</td>
<td>42</td>
<td>284 ± 4</td>
<td>265 ± 13</td>
<td>318 ± 17</td>
<td>-19</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>9. M.M.</td>
<td>33</td>
<td>307 ± 10</td>
<td>240 ± 8</td>
<td>302 ± 7</td>
<td>-67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10. W.L.</td>
<td>33</td>
<td>307 ± 7</td>
<td>264 ± 18</td>
<td>298 ± 13</td>
<td>-43</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>11. J.L.</td>
<td>37</td>
<td>322 ± 21</td>
<td>270 ± 9</td>
<td>324 ± 20</td>
<td>-52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>12. A.S.</td>
<td>45</td>
<td>344 ± 0</td>
<td>210 ± 7</td>
<td>252 ± 12</td>
<td>-134</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>13. J.P.</td>
<td>43</td>
<td>353 ± 12</td>
<td>246 ± 6</td>
<td>353 ± 12</td>
<td>-107</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>14. W.L.</td>
<td>40</td>
<td>366 ± 12</td>
<td>356 ± 12</td>
<td>384 ± 17</td>
<td>-10</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>15. R.L.</td>
<td>29</td>
<td>367 ± 38</td>
<td>320 ± 20</td>
<td>365 ± 25</td>
<td>-47</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

* Mean number of determinations per patient: period A, 4.8; period B, 10.1; period C, 8.2.
† See note table 2.
Fig. 3. Serum cholesterol changes during the sitosterol and placebo periods. Each patient's cholesterol values are plotted as per cent deviation from their own control Mean cholesterol. Each dot represents 1 cholesterol value (for patients on a biweekly schedule) or the Mean of 2 cholesterol values (for patients on a weekly schedule). This graph best portrays the prompt and sustained cholesterol reduction occurring after sitosterol administration and the prompt rise on substitution of placebo.

Table 4.—Summary of Mean Changes in Total Lipid and Lipoprotein Lipid Fractions

<table>
<thead>
<tr>
<th>Lipoprotein lipid</th>
<th>Control period*</th>
<th>Sitosterol period</th>
<th>Difference mg./100 ml.</th>
<th>Mean ± S.D.</th>
<th>Mean ± S.D.</th>
<th>Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg./100 ml.</td>
<td>mg./100 ml.</td>
<td>mg./100 ml.</td>
<td>X±</td>
<td>X±</td>
<td>X±</td>
</tr>
<tr>
<td>α</td>
<td>224 ± 43</td>
<td>258 ± 46</td>
<td>+34</td>
<td>&lt;0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β</td>
<td>557 ± 98</td>
<td>438 ± 113</td>
<td>-99</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Origin</td>
<td>387 ± 90</td>
<td>393 ± 79</td>
<td>+6</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ</td>
<td>36 ± 15</td>
<td>38 ± 16</td>
<td>+2</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β + Origin</td>
<td>944 ± 140</td>
<td>850 ± 157</td>
<td>-94</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Lipid</td>
<td>1204 ± 146</td>
<td>1146 ± 152</td>
<td>-58</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Premedication and placebo periods are combined as “control period.”

Increases of similar magnitude to those with control cholesterol levels above 250 mg./100 ml.

No significant difference in response was noted in the 2 dietary groups.

A slight but statistically significant drop occurred in total lipid during the period of sitosterol administration. Table 4 summarizes the mean changes in total lipids and lipoprotein lipid fractions. All values are included save for the 2-week period immediately following substitution of the placebo for sitosterol. In Tables 4 and 5 the premedication and placebo periods are combined as the “control” period.

No untoward effects of sitosterol were observed during the period of observation; the preparation was palatable and well tolerated by all patients.

Table 5.—Summary of Individual Changes in Total Lipid and Lipoprotein Lipid Fractions after Beta Sitosterol Administration

Values in mg./100 ml. of stainable lipid.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total lipid mg./100 ml.</th>
<th>α-lipoprotein lipid mg./100 ml.</th>
<th>β-lipoprotein lipid mg./100 ml.</th>
<th>Origin lipid mg./100 ml.</th>
<th>γ-lipoprotein lipid mg./100 ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.D.</td>
<td>1034</td>
<td>1048</td>
<td>165 250</td>
<td>448 345 374 406 47 38</td>
<td></td>
</tr>
<tr>
<td>B.C.</td>
<td>1081</td>
<td>1053</td>
<td>280 202</td>
<td>400 391 363 444 38 16</td>
<td></td>
</tr>
<tr>
<td>R.T.</td>
<td>1021</td>
<td>900</td>
<td>248 299</td>
<td>578 326 173 235 22 40</td>
<td></td>
</tr>
<tr>
<td>L.S.</td>
<td>1342</td>
<td>1337</td>
<td>239 296</td>
<td>532 511 486 504 35 26</td>
<td></td>
</tr>
<tr>
<td>D.L.</td>
<td>1149</td>
<td>1166</td>
<td>176 268</td>
<td>528 497 416 330 29 71</td>
<td></td>
</tr>
<tr>
<td>J.A.</td>
<td>1008</td>
<td>894</td>
<td>212 240</td>
<td>454 335 310 293 32 26</td>
<td></td>
</tr>
<tr>
<td>J.E.</td>
<td>1340</td>
<td>1305</td>
<td>251 231</td>
<td>562 505 504 455 23 24</td>
<td></td>
</tr>
<tr>
<td>W.R.</td>
<td>1170</td>
<td>1140</td>
<td>236 301</td>
<td>551 426 340 366 43 47</td>
<td></td>
</tr>
<tr>
<td>M.M.</td>
<td>1280</td>
<td>1103</td>
<td>282 243</td>
<td>580 413 345 329 73 17</td>
<td></td>
</tr>
<tr>
<td>W.L.</td>
<td>1148</td>
<td>1094</td>
<td>176 188</td>
<td>504 465 442 395 26 46</td>
<td></td>
</tr>
<tr>
<td>J.L.</td>
<td>1367</td>
<td>1290</td>
<td>194 208</td>
<td>602 532 518 409 53 52</td>
<td></td>
</tr>
<tr>
<td>A.S.</td>
<td>1169</td>
<td>1106</td>
<td>181 292</td>
<td>628 310 337 481 23 26</td>
<td></td>
</tr>
<tr>
<td>W.R.</td>
<td>1487</td>
<td>1402</td>
<td>243 279</td>
<td>802 669 427 395 15 59</td>
<td></td>
</tr>
<tr>
<td>R.L.</td>
<td>1247</td>
<td>1215</td>
<td>203 208</td>
<td>625 594 376 366 44 47</td>
<td></td>
</tr>
</tbody>
</table>

| Mean     | 1204                  | 1146                            | 224 258                        | 557 458 387 393 36 38   |                                  |
| p        | <0.001                | <0.02                           | <0.001                         | <0.8                    | <0.8                            |

Discussion

The known variability of serum cholesterol and β-lipoprotein makes it advisable to include a number of measurements of these values. Use of placebos and control of diet and body weight add further confidence that observed changes are due to the medication given. Under these circumstances β-sitosterol effects prompt and sustained reductions of serum cholesterol, total lipid, and β-lipoprotein lipid of a moderate degree, with small increases occurring in α-lipoprotein lipid. These changes occur in patients with serum cholesterol not in the range usually considered as hypercholesterolemic and occur despite previous moderate fat and cholesterol limitation.

It has been adequately proved that sitosterols lower the serum cholesterol of man, and prevent increases in liver and plasma cholesterol of laboratory animals fed diets high in cholesterol. However, the mechanisms of these actions are unknown.
An attractive postulate is that sitosterol competes with cholesterol for available fatty acids, bile salts, and the enzyme used in cholesterol esterification, thereby interfering with cholesterol absorption.\textsuperscript{7-14} Swell and co-workers\textsuperscript{14} have shown that soy sterols are esterified in vitro in the presence of pancreatic cholesterol esterase, the rate of esterification being only slightly less than that of cholesterol. In contrast to the action of free sitosterol, Best, Duncan, and Wathen\textsuperscript{16} have found that sitosterol esters do not prevent increases in tissue lipids in myxedematous rats. This latter finding furnishes indirect support for the hypothesis that sitosterol acts by interfering with esterification of cholesterol.

A second postulate of the action of sitosterol is that it combines with cholesterol in the gut to form a more stable, less absorbable complex.\textsuperscript{5} This union may be similar to that complex formed in the Liebemann-Burchard reaction between cholesterol and digitonin, another sterol.

Either postulate assumes inhibition of absorption of both dietary cholesterol and that portion of endogenous cholesterol excreted in the bile. Since both dietary and biliary cholesterol are predominantly in the free form, there is no reason to believe sitosterol would differentiate between them.

Although studies to date would indicate that sitosterol acts on cholesterol absorption, further work is needed to determine its relationship to the transport, metabolism, and excretion of cholesterol and lipoproteins.

The possible role of sitosterol in the treatment of human atherosclerosis has not been established, nonetheless the lack of known side effects and the observed modification of serum lipids would indicate potential benefit from its use.

**Summary**

Baseline serum lipid values of 15 normotensive nondiabetic young men with arteriosclerotic heart disease are reported and compared with an apparently normal group matched for age. The abnormal group was characterized by significantly increased cholesterol, beta lipoprotein lipid, and total lipid.

In this abnormal group, $\beta$-sitosterol administration resulted in highly significant reductions in serum cholesterol and $\beta$-lipoprotein lipid, with a lesser reduction in total lipid and a slight rise in $\alpha$-lipoprotein lipid.

The apparent lack of deleterious effects, coupled with the observed changes, suggests potential benefits of sitosterol administration. Its role as a therapeutic agent in clinical medicine has not yet been established.

**Summario in Interlingua**

Es reportate valores de base pro lipido seral, observate in 15 normotensive e non-diabetic juvene adultos mascule con morbo cardiac arteriosclerotic. Le valores es comparate con illos obtenite ab un secunde e apparentemente normal grupp de individuos de etas correspondent. Le grupp anormal eseva characterisate per augmentos significative de cholesterol, lipido beta-lipoproteinic, e lipido total.

In iste grupp anormal, le administration de beta-sitosterol resultava in significativissime reductiones del cholesterol seral e del lipido beta-lipoproteinic, accompaniate de minus marcate reductiones de lipido total e un leve augmento del lipido alpha-lipoproteinic.

Le apparente absentia de effectos nocive, insimul con le supra-mentionate alterationes, indica possibilemente que le administration de sitosterol resulta in effectos benefic. Le rolo de sitosterol como agente therapeutic in le medicine clinic es non ancora establite.

**Acknowledgment**

The authors wish to express their appreciation to Miss Ardelle Mead and Mr. Thomas Jenny for technical assistance, and to Mrs. Janet Wesselman for preparing the diets.

**References**


The authors have previously reported a series of 300 American soldiers killed in Korea, in 77.3 per cent of whom, some gross evidence of coronary disease was demonstrated. The paper discusses all available clinical data and reviews the histopathology of the lesions. Complete records were available on 200 men. The average age was noted to be 22.1 years, average height 5 ft. 7\(\frac{3}{4}\) in. and average weight 145.8 lb. The gross and microscopic studies indicate that the coronary lesions are due in part to intravascular stress caused by the hemodynamics of the coronary circulation, as modified by anatomic factors. The stress results in subendothelial fibroblastic proliferation, deposition of a mucoid ground substance, and fragmentation of the internal elastic membrane. It is of interest to compare the lesions found in the American soldiers with the lesions found in a small series of Japanese natives now being studied. Thirty Japanese men, approximating the age group of the American soldiers, were found in material from 114 cases studied in Japan. The amount and distribution of the lipids on the elastica and within the parenchyma of the plaques found in the Americans, as compared to the Japanese, indicate that certain plasma lipids, as modified by diet, are another important agent in the development of coronary disease in young males.

Kitchell
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