Use of Combined Diet and Colestipol in Long-Term (7–7½ Years) Treatment of Patients with Type II Hyperlipoproteinemia

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SUMMARY  Long-term effects of diet and colestipol (a bile acid sequestrant) were studied in 25 patients with familial type II hyperlipoproteinemia. Serum lipids and body weights of an initial group of 30 patients were stabilized by low cholesterol-saturated fat-refined carbohydrate diet and the patients were then randomized into placebo and drug-treatment groups. After explaining that the drug is nontoxic and effective in lowering serum lipids, total cholesterol (C) and low-density lipoprotein cholesterol (LDL-C), colestipol (30 g/day) and diet were given to the 25 patients who remained in the long-term follow-up program. The treatment resulted in highly significant lowering of serum lipids (mg/dl, mean ± SEM): C and LDL-C from 412.7 ± 24.4 and 331.1 ± 22.8 to 270 ± 11.0 and 188.1 ± 13.8, respectively (p < 0.001 in each instance) over 7–7½ years. Although we observed no absolute increase in high density lipoprotein (HDL), the HDL/LDL ratio was elevated. Long-term colestipol and diet treatment reduced the xanthoma size and stabilized angiographically visualized atherosclerotic lesions in 21 of the 25 patients who showed a satisfactory hypolipemic response. It did not cause nutritional or metabolic disturbances.

COLESTIPOL, a tetraethylene-pentamine and epichlorhydrin copolymer, is a synthetic anionic bile acid-binding resin which sequestrates bile acids in the intestinal tract to reduce their reabsorption.

This stimulates an increased rate of hepatic sterol synthesis. However, if increased hepatic cholesterol biosynthesis is insufficient to compensate for the exaggerated cholesterol degradation into bile acids, hepatic cholesterol pool may be reduced, and will result in lowering of plasma cholesterol concentration.

Several colestipol studies of different durations in man have reported serum cholesterol reductions of 14–20% from the pretreatment or placebo treatment levels. Since hypercholesterolemia in patients with familial type II hyperlipoproteinemia is caused at least partially by a decrease in cholesterol-rich low density lipoprotein (LDL) catabolism, a preparation which acts to facilitate cholesterol removal should be a rational pharmacologic approach to complement dietary therapy.

We report observations in a series of atherosclerotic patients with type II hyperlipoproteinemia who were encouraged to maintain satisfactory long-term compliance (7–7½ years) to a combined diet-colestipol treatment program.

Patients and Methods

Patient Selection

Eighteen male and 12 female atherosclerotic patients, aged 38–65 years with type II hyperlipoproteinemia, were selected for the trial. Diagnosis of the abnormality was made on: 1) a consistently elevated serum lipid level-total serum cholesterol > 260 mg%, LDL cholesterol (LDL-C) ≥ 190 mg% and triglycerides < 180%, 2) demonstration of similar lipoprotein abnormality in first-degree family members in 24 of the 30 patients, and 3) lack of significant response to a standard low saturated fat-low cholesterol diet in six patients who had either no living or hypercholesterolemic family members. Each patient received a detailed description of the drug, was explained the purpose of the study, and then signed an informed consent form approved by the Institutional Review Board.
Review Committee. Women of childbearing age, patients maintained on long-term steroid or hormonal therapy, and those with hyperlipidemias secondary to hepatic, hormonal, metabolic and renal disease were excluded from the study.

Diet

To prepare patients for the trial, all antilipemic drug and dietary therapy was discontinued for 4 weeks to obtain three "baseline" plasma lipid levels at 2-week intervals. The subjects were given detailed instructions to go on a low cholesterol, low saturated fat and limited simple-carbohydrate ("therapeutic") diet (estimated to contain about 20% protein, 40% fat, 40% carbohydrate; ≤ 300 mg cholesterol and p/s ratio of 1.2) for 6 weeks. We reviewed 24-hour dietary records periodically during the preparatory period and at intervals throughout the colestipol treatment to emphasize and encourage adherence.

Methods

Patients were randomized into drug and placebo groups by the central coordinating center. "Medications" were drug in 5-g packages and placebo (2 g of Avicel — microcrystalline cellulose powder). In the first 2 months, the dosages prescribed were four packages of either drug (20 mg) or placebo per day, to be taken before meals.

Serum lipid-lipoprotein studies were made at 6, 4 and 2 weeks and just before the patient began to take either placebo or drug, while still on the therapeutic diet. The week the study began, each patient also underwent complete physical and ophthalmologic examinations and ECG, chest x-ray, urinalysis, and biochemical (fasting blood sugar, creatinine, serum glutamic oxaloacetic transaminase, total serum bilirubin, alkaline phosphatase, uric acid, triiodothyronine, calcium, phosphorus) and hematological (hematocrit, hemoglobin, red, white and differential blood counts, and prothrombin time) studies. Brief physical examinations and plasma lipid-lipoprotein analyses were made at monthly intervals; hematological and biochemical studies were repeated every 3 months throughout the treatment. Serum cholesterol and triglyceride concentrations were measured with automated procedures and standardized by the Center for Disease Control, US Public Health Service. LDL-C was calculated as the difference between total serum cholesterol value and that in the high-density (HDL-C) fraction plus very low-density cholesterol (VLDL-C). Statistical analysis of the differences between plasma lipid levels before and at various intervals of intervention was made by paired t test. Average frequency of angina pectoris and the number of nitroglycerin tablets used were estimated during each clinic visit. Exercise stress tests on treadmill were performed every 4–6 months.

After establishing the hypcholesterolemic efficacy of colesitop and its relative safety in an 8-week trial, we prescribed 10 g of the drug three times a day for all 30 patients. Twenty-five cooperative patients (15 males and 10 females) who kept a consistent clinic attendance and a good diet-drug or placebo adherence record were maintained in the study. Their compliance to the long-term diet-drug treatment was repeatedly reinforced by monthly follow-up, close physician-patient relationship, sharing of laboratory findings, package count and periodic dietary recall and review as mentioned previously. Five patients were dropped.

Table 1. Design of Colesitop Study

<table>
<thead>
<tr>
<th>Treatment Period (Pt no.)</th>
<th>Regular diet (30) Baseline</th>
<th>Therapeutic diet (30)</th>
<th>Diet + colesitop or placebo (15) Double-blind</th>
<th>Diet + colesitop (long-term) (25 Unblind)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−) before drug or placebo</td>
<td>0, 2, 4</td>
<td>−6, −4, −2, 0</td>
<td>2, 4, 6, 8</td>
<td>84–90</td>
</tr>
<tr>
<td>Clinic visit</td>
<td>1, 2, 3</td>
<td>4, 5, 6, 7</td>
<td>8, 9, 10, 11</td>
<td></td>
</tr>
<tr>
<td>Physicians visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examination, dietary review and/or modification</td>
<td>X X X X</td>
<td>X X X X</td>
<td>X X</td>
<td>X</td>
</tr>
<tr>
<td>Visit and package count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-lipoprotein analysis</td>
<td>X X X</td>
<td>X X X X</td>
<td>X X X X</td>
<td>X X</td>
</tr>
<tr>
<td>Ophthalmologic and battery of laboratory studies (detailed in text)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Every 3 mos</td>
</tr>
</tbody>
</table>
from the study (three moved away, two could not attend the clinic regularly). The experimental design of the study is outlined in table 1.

Coronary, brachiocephalic and peripheral arteriograms were performed in 12 (figs. 1-12), three (figs. 13-15) and four patients, respectively, before and 3-4 years after institution of the treatment program to evaluate the state of atherosclerotic lesions and the efficacy of intervention in modifying the anatomical abnormalities. Cine coronary arteriograms were performed by the selective technique of Sones. Brachiocephalic and peripheral arteriograms were made by catheterization of femoral arteries. Each coronary arteriogram and angiogram was reviewed by three observers at the same time to reach a consensus. Previous studies have verified the accuracy of high-quality arteriograms capable of detecting a 10-20% decrease in cross-sectional area of the lumen.17, 18

Clinical Status

Twenty-one of the 25 patients had cutaneous, corneal, tendinous cholesterol deposits or combined findings. Seventeen had angina pectoris, and nine had one or more myocardial infarctions (documented by history, ECG and coronary arteriogram). Ten had brachiocephalic or peripheral vascular diseases or both, and five of them also had coronary artery disease (CAD).

Results

Pertinent clinical manifestations of these patients are shown in table 2. Long-term hypolipemid therapy had no effect on corneal arcus, but it did induce slow resolution of xanthelasma and tendinous xanthoma.

Four patients with severe hypercholesterolemia (total cholesterol ranged consistently above 500 mg/dl before treatment) were resistant to therapy (average < 12% decrease in total serum cholesterol). Throughout treatment and observation two developed two episodes of nonfatal myocardial infarction and congestive heart failure. One patient had three attacks of coronary insufficiency, and the other had two episodes of transient cerebral ischemia without residual neurological damage during the early stage of the 7-7½-year follow-up. All of the acute complications responded well to intensive medical management.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Incidences before treatment</th>
<th>Incidences on long-term treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendinous xanthoma</td>
<td>11</td>
<td>9 improved; 2 subsided</td>
</tr>
<tr>
<td>Xanthelasma</td>
<td>4</td>
<td>2 improved; 2 subsided</td>
</tr>
<tr>
<td>Corneal arcus</td>
<td>11</td>
<td>Persisted</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>17</td>
<td>12 improved; 5 stabilized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*(3 episodes of coronary insufficiency)</td>
</tr>
<tr>
<td>Myocardial infarction (MI)</td>
<td>9</td>
<td>*2 recurrences of MI; *2 heart failure (controlled)</td>
</tr>
<tr>
<td>Brachiocephalic and/or Peripheral vascular occlusive disease</td>
<td>10</td>
<td>8 stable; *2 transient ischemia</td>
</tr>
</tbody>
</table>

*Nine cardiovascular complications occurred in four patients who were resistant to treatment; serum cholesterol mean ± sd = 518 ± 21 and 458 ± 49 before and after drug treatment, respectively, an average decrease of only 11.6%.
These episodes encouraged improved adherence to the diet-drug regimen. Package count and diet analyses, made in all patients, indicated an average consistent adherence rate of about 90%. At the time of this report, the cardiovascular signs and symptoms and other clinical manifestation of all patients had improved or stabilized, as estimated by subjective and objective criteria. A comparison of their pertinent pretreatment clinical findings and the changes of their signs and symptoms after prolonged antilipemic therapy are summarized in table 2.

Effect of Diet and Drug Treatment on Plasma Lipids

The “therapeutic diet” was effective in lowering the total serum cholesterol, triglyceride and LDL-C concentrations of 30 type II patients significantly, by averages of 6.7, 47 and 3.8%, respectively (table 3).

As the diet was being maintained, the patients were randomized into drug and placebo groups. A comparative study of the two groups after an 8-week trial showed that the drug had caused significant reduc-
tions in total serum cholesterol and LDL-C, but had little effect on the serum HDL-C and triglyceride of treated patients (table 4).

Table 5 compares the short- and long-term effects of colestipol in 25 patients in whom the dietary factor remained relatively constant. Total serum cholesterol and LDL-C of these patients continued to decrease over the 7-7½ years of combined diet and drug treatment after the initial short-term response. These reductions were highly significant compared with the lipid levels during the preparatory dietary treatment period. There was no associated increase in serum triglyceride, but HDL-C tended to increase slightly but insignificantly. Due to a large reduction in LDL-C, the HDL-C/LDL-C ratio was significantly elevated with treatment.

Figure 16 is presentation of total serum cholesterol and triglyceride over the period of study.

Coronary arteriograms were obtained before and after 3-4 years of treatment in 12 patients. A comparative study did not show a significant regression of the original lesions. In eight patients (figs. 1-8) the pre-existing lesions had remained stable. Variable degrees of progression were discernible in the other four (figs. 9-12) who had marked hypercholesterolemia which was not amenable to satisfactory control.

**Figure 4.** A) Advanced left coronary artery lesions of JB. B) Lesions show no significant atherosclerotic progression in 47 months.

**Figure 5.** A) Diffusely scattered left coronary artery lesions of WM. B) Lesions show no significant change in 37 months.
Brachiocephalic or peripheral arteriograms were repeated in three and five patients, respectively, after 3–4 years of medical therapy. None developed new lesions or showed significant progression of the basic arterial disease. The brachiocephalic angiograms before and after treatment are shown in figures 13–15.

**Side Effects**

Constipation was the most common early unpleasant side effect.\(^4\)\(^6\) Seven of the 25 patients complained of constipation during the initial drug administration period. However, four patients on placebo also experienced these symptoms. Other side effects of colestipol included nausea, bloating, gritty taste,\(^4\)\(^7\) and skin dryness, which has been reported by one investigator.\(^7\) Constipation was controlled by administration of mild hydroscopic laxatives and an increased fluid intake. Skin dryness responded to lotion or cream containing lanolin. After a period of adjust-

**Table 3.** Effects of “Therapeutic” Diet on Serum Lipids of 30 Patients with Type II Hyperlipoproteinemia

<table>
<thead>
<tr>
<th>Serum lipids (mg/dl)</th>
<th>Values observed in periods of study</th>
<th>Baseline (mean ± SEM)</th>
<th>On diet (mean ± SEM)</th>
<th>Δ and (P)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(4 wks)*</td>
<td>(6 wks)†</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td>437.4 ± 22.4</td>
<td>408.2 ± 21.5</td>
<td>-29.2 (P&lt;0.005)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td></td>
<td>172.0 ± 17.5</td>
<td>91.0 ± 12.2</td>
<td>-81 (P&lt;0.001)</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td></td>
<td>350.0 ± 23.6</td>
<td>336.6 ± 23.0</td>
<td>-13.4 (P&lt;0.05)</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td></td>
<td>53.9 ± 2.0</td>
<td>56.6 ± 2.2</td>
<td>+2.7 NS</td>
</tr>
</tbody>
</table>

*Value represents mean of the average of three readings obtained in each patient.
†Value represents mean of the average of three readings obtained in each patient at the end of 6 weeks.
‡Paired \(t\) test.
Figure 8. A) Multiple lesions in right coronary artery of RM. B) Lesions show no significant change in 46 months.

Figure 9. Left anterior oblique view of right coronary artery of CB. A) Multiple areas of disease. Arrow indicates segment of severe narrowing. B) Follow-up study 42 months later shows complete occlusion of the artery. No significant change was noted in his left coronary arteries.

Table 4. Effects of Colestid (20 g/day) vs Placebo on Serum Lipids of Patients with Type II Hyperlipoproteinemia (15 in Each Group)

<table>
<thead>
<tr>
<th>Serum lipids (mg/dl)</th>
<th>Placebo group on diet only*</th>
<th>Placebo and diet (8 weeks)†</th>
<th>Δ and p*</th>
<th>Colestid group on diet only*</th>
<th>Drug and diet (8 weeks)†</th>
<th>Δ and p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>397.9 ± 22.1</td>
<td>403.4 ± 22.6</td>
<td>+ 5.5</td>
<td>416.9 ± 24.4</td>
<td>308.5 ± 19.8</td>
<td>- 108.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
<td>p &lt;0.005</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>96.8 ± 12.1</td>
<td>104.6 ± 13.1</td>
<td>+ 7.8</td>
<td>89.4 ± 11.2</td>
<td>101.1 ± 13.7</td>
<td>+ 11.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>325.5 ± 23.4</td>
<td>321.7 ± 23.1</td>
<td>- 2.8</td>
<td>337.9 ± 23.0</td>
<td>239.1 ± 18.9</td>
<td>- 98.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
<td>p &lt;0.001</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>52.8 ± 2.4</td>
<td>53.2 ± 2.1</td>
<td>+ 0.4</td>
<td>53.4 ± 2.4</td>
<td>56.6 ± 2.3</td>
<td>+ 3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

*Value represents mean of reading obtained in each patient at the end of 6 weeks.
†Value represents mean of reading obtained in each patient at the end of 8 weeks.
‡Paired t test.
Figure 10. A) Initial right coronary artery angiogram of SW shows multiple lesions. B) Subsequent study 37 months later shows it was completely occluded. C) Left coronary artery showed multiple lesions initially. D) Progression has occurred in the left main stem and left anterior descending in the follow-up study.

Table 5. Short- and Long-Term Effect of Diet-Colestid (90 g/day) on Serum Lipids of 25 Patients with Type II Hyperlipoproteinemia

<table>
<thead>
<tr>
<th>Serum lipids (mg/dl) (mean ± SEM)</th>
<th>Values observed in period of study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On diet only</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>412.7 ± 24.4</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>88.0 ± 11.1</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>331.1 ± 22.8</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>53.9 ± 2.0</td>
</tr>
<tr>
<td>HDL/LDL</td>
<td>0.19 ± 0.03</td>
</tr>
</tbody>
</table>

*Value represents mean of the average of 3 last readings obtained in each patient.
†Value represents mean of reading obtained in each patient at the end of 8 weeks.
‡Paired t test.
FIGURE 11. A) Initial left coronary arteriogram of PO showed narrowing of circumflex at point of bifurcation. B) Subsequent study 39 months later revealed severe degree of stenosis at this site. Patient became symptomatic. The right coronary artery was patent.

FIGURE 12. A) Initial right coronary artery arteriogram of AC. Arrow indicates area of significant stenosis. B) Forty-nine months later, right coronary artery was occluded. C) Initial arrow points to minor narrowing of circumflex artery. D) They were significantly stenosed in a follow-up study.
Figure 13. A) Brachiocephalic angiograms of EH. B) Angiogram 41 months later. Arrows indicate sites of right and left carotid arterial stenosis. No significant changes are apparent.
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FIGURE 15. A) Brachiocephalic angiogram of AR. B) Angiogram 63 months later. Arrows in A indicate sites of severely diseased lesions at the bifurcation of right and left carotids. In B, white arrow points to surgical repair of left carotid; black arrow points to the right carotid lesion which has remained unchanged under observation. No new lesion has appeared in the meantime.

ment of variable duration, all patients were able to continue taking 30 g/day of this odorless and tasteless drug for 7–7½ years with few or no untoward side effects. Repeated clinical and laboratory studies did not reveal evidence of gastrointestinal, hematologic, biochemical or urinary abnormality caused by the drug. Although we did not measure plasma levels of fat soluble vitamins, B₉, and folate, none of the patients experienced symptoms or signs of cholelithiasis, hypoprothrombinemia due to vitamin K deficiency, or hematologic and neurologic abnormalities while taking colestipol without interruption for an extended period. None of the patients developed gastrointestinal bleeding, obstruction or cancer during the course of treatment.

Discussion

Our study differs from others in the duration of follow-up observation and in the emphasis on patient adherence to both diet and drug treatment. The close long-term follow-up studies have helped to establish the safety and effectiveness of colestipol in lowering the plasma LDL-C of patients with type II hyperlipoproteinemia when administered in conjunction with diet. None of the patients in our series developed either a reduced response to the hypolipemic effect or any persistent undesirable side reaction to the drug during prolonged regular administration.

To obtain a valid evaluation of the hypcholesterolemic action of colestipol, all patients in our study have been encouraged to maintain a standardized dietary intake to minimize the well-known dietary influence on plasma lipid concentrations (table 3), despite the possibility that some patients might have partially modified their diet before the institution of therapeutic diet. When holding the dietary factors relatively constant, we have observed a wide variation
in response to the same drug dosage between patients. In contrast to other reports, our data show that patients with extensive manifestations of type II abnormality with marked hypercholesterolemia are most resistant to therapy. Differences in experimental design and patient selection\(^9\), \(^{10}\) would account for the report that hypocholesterolemic response is generally more pronounced among patients with high serum cholesterol levels than in those with more modest elevations.\(^{21}\)

A number of investigators have reported variable degrees of serum triglyceride and VLDL elevation with colestipol treatment;\(^4\), \(^5\), \(^{21}\), \(^{22}\) some of them have noted that the drug-induced hypertriglyceridemia is mild and inconsistent.\(^4\), \(^5\), \(^{20}\), \(^{23}\) In our study, we observed neither early nor late hypertriglyceridemia secondary to the drug administration, mostly because patients in this series have adhered rather closely to a therapeutic diet relatively low in saturated fat, and in total and simple carbohydrate calories. The importance of dietary therapy has been emphasized for successful management of hyperlipidemia by investigators in the field of lipid metabolism and atherosclerosis.\(^4\), \(^{12}\), \(^{13}\), \(^{24}\), \(^{25}\)

Our data indicate that colestipol treatment lowers the total serum cholesterol concentration by selectively decreasing its LDL-C component without altering the HDL-C concentration. Although there is no significant absolute HDL-cholesterol increase with long-term drug administration, the HDL-C/LDL-C ratio is increased as the result of LDL-C reduction. We do not know whether the altered relationship between HDL-C and LDL-C could influence the atherosclerotic process.

Bemis and his associates reported significant progression of CAD in 52% of 73 patients at an
average interval of 23.8 months. These investigators noted significant correlation of hyperlipidemia (with preponderance of type IV hyperlipoproteinemic patients) with progression of CAD.26 Kimbiris et al. studied 35 patients with advanced CAD at an average interval of 26.2 months, and observed significant progression in 68.5%.27 Conflicting serial angiographic findings were reported by Knight and coworkers28 and by Henderson and Rowe29 on the use of ileal bypass to lower serum lipids. Sanmarco et al., however, reported angiographic improvement, stabilization and progression in six, 16, and 16 patients, respectively, after a systematic attempt to control risk factors for 15 ± 3 months.30 Apparently, in these studies, changes in CAD could be related to an interplay of several CAD risk factors. We have no information on the prior use of serial angiographic study to evaluate the effect of long-term effective control of type II hyperlipoproteinemia on coronary atherosclerosis.

Although no definitive conclusion can be drawn from the observed correlation between satisfactory control of type II hyperlipoproteinemia and reduction of xanthoma size and apparent stabilization of atherosclerotic lesions in 21 of 25 patients, our observations are encouraging and support the reported regression or lack of progression of atherosclerosis in animals and man after successful control of hyperlipidemia.31-34

Acknowledgment

We thank Dr. M.E. Sanmarco and Dr. David H. Blankenhorn, University of Southern California Medical School, Los Angeles, California, for their help in securing pertinent references on the use of serial coronary angiography to evaluate progression and regression of atherosclerosis.

References

Use of combined diet and colestipol in long-term (7--7 1/2 years) treatment of patients with type II hyperlipoproteinemia.

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