Adaptation of cholesterol absorption after proximal resection of porcine small intestine

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Abstract  Cholesterol absorption occurs primarily in the upper small intestine. Our aim was to assess absorption of cholesterol during ileal adaptation after proximal small intestinal resection. In vivo absorption and elimination of cholesterol, plasma cholesterol, cholesterol precursors, and plant sterols were related to intestinal morphology and transit. Fractional cholesterol absorption, the daily amount of cholesterol absorbed, plasma cholesterol, and plant sterol to cholesterol proportions were significantly reduced, whereas fecal loss of cholesterol as neutral steroids, less bile acids, plasma cholesterol precursor proportions, and ileal mass and villus height were significantly increased after 8 weeks of the resection. Cholesterol absorption efficiency, decreased by the resection, was gradually increased from 5.4 ± 2.2 to 26.9 ± 3.9% during the 14 postoperative weeks (P < 0.0001) simultaneously with a 46% increase in villus height compared with transection (P < 0.0001), but absorption remained still below control levels (80.4 ± 2.5%, P < 0.0001). In resected and control animals, villus height correlated positively with cholesterol absorption efficiency (r = 0.85, P < 0.0001; r = 0.76, P = 0.01) and plasma plant sterol proportions (r = 0.94 ± 0.05, P < 0.0001; r = 0.78 ± 0.05, P < 0.008), respectively. In conclusion, after massive proximal small bowel resection, adaptation of intestinal cholesterol absorption efficiency occurs in the distal ileum closely paralleling villus hypertrophy. —Pakarinen, M., T. A. Miettinen, J. Lauronen, P. Kuusanmäki, P. Raivio, T. Kivistö, and J. Halttunen. Adaptation of cholesterol absorption after proximal resection of porcine small intestine. J. Lipid Res. 1996. 37: 1766–1775.

Supplementary key words  cholesterol precursors • plant sterols

Cholesterol is absorbed predominantly in the upper small intestine through apical villus cells from an aqueous monomer phase being essentially dependent on micellar solubilization and transported exclusively by the lymphatic system mainly as esterified cholesterol (1–3). Low rate of passive bile salt uptake in the proximal small intestine allows reutilization of bile acids in the formation of mixed micelles, which together with effective lipolysis, prevents expansion of oil phase and enables effective mucosal uptake of luminal cholesterol (2–4). On the other hand, impaired ileal bile acid absorption, despite compensatory increase in hepatic bile acid synthesis, may reduce intraluminal bile salt level below the critical micellar concentration and this, in turn, may lead to malabsorption of cholesterol (5, 6). Reduced jejunal absorptive surface due to gut resections or villous atrophy in untreated celiac disease and accelerated intestinal transit decrease fractional cholesterol absorption (2, 7–9). Displacement of cholesterol from bile salt micelles by plant sterols may further impair cholesterol absorption (10). In general, increased fecal elimination of cholesterol as neutral steroids or bile acids lowers the plasma cholesterol level which, in turn, results in enhanced cholesterol synthesis (11).

After proximal small bowel resection, gut absorptive area is reduced, intestinal transit time is shortened, and bulk absorption of nutrients occurs in the remaining ileum. Shorter villi, lower activities of mucosal lipid reesterifying enzymes, and concentration of fatty acid-binding protein, and less efficient chylomicron production in the distal ileum compared to jejunum may contribute to less efficient ileal mucosal uptake and transport of dietary lipids in intact small intestine (3, 12–14). Remaining small intestine undergoes structural and functional adaptation to resection. Crypt cell production rate, crypt and villus cellularity, crypt depth, villus height, and the intestinal remnant diameter and length are increased contributing to increased absorption of different nutrients per unit small intestinal length (15, 16).

Abbreviations: GLC, gas-liquid chromatography.
*To whom correspondence should be addressed.
To study cholesterol metabolism in the growing pig, to show whether adaptation of cholesterol absorption occurs after massive proximal small bowel resection, and to evaluate the factors contributing to cholesterol absorption during normal growth and ileal adaptation, we concentrated on in vivo absorption and fecal elimination of cholesterol in pigs at varying time intervals after 75% proximal small bowel resection or transection, and related the results to plasma cholesterol levels, small bowel morphology, and intestinal transit. In addition to fecal excretion studies, cholesterol metabolism was also evaluated determining plasma cholesterol precursor (squalene, methylsterols, \(\Delta^5\)-cholestenol, lathosterol, and desmosterol) and plant sterol (\(\beta\)-sitosterol and campesterol) to cholesterol proportions, two variables reflecting the synthesis and absorption of cholesterol, respectively (17, 18).

MATERIALS AND METHODS

Animals and diet

Twenty female pigs weighing 20.9 (range 16.0–25.0) kg, purchased from a commercial supplier were used. The animals were housed individually in a light- and temperature-controlled environment, fed twice a day at standardized times, and offered water ad libitum. During acclimation of at least 5 days and the experimental period the pigs were fed with standard pig chow (Suomen Rehu OY, Turku, Finland) containing 61.7% (wt/wt) carbohydrate, 17.0% protein, 9.5% fat, 4.7% crude fiber, and 12.0% aqueous substance. Gas-liquid chromatographic (GLC) measurements using a 50-meter long SE-30 capillary column (Hewlett-Packard, Palo Alto, CA) revealed that the diet contained 76.7 µg cholesterol, 133.7 µg campesterol, and 341.3 µg \(\beta\)-sitosterol per 1000 mg of chow.

The animals used in this study were cared for according to the principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH publication no. 86-23, revised 1985), and authorization no. 154613 in accordance with Finnish legislation.

Operations

Animals were randomly assigned into control and resection groups and underwent surgery after an overnight fast, under general anesthesia with endotracheal intubation. They received perioperatively 500–1000 ml Ringer's lactate intravenously and 500 mg ceftriaxone intramuscularly (i.m.) as a single dose. After a midline abdominal incision, proximal 75% of small intestine was resected (n = 15) from 10 cm distal to the ligament of Treitz after transection of ileum 5 cm proximal to the ileocecal junction. Distal 25% of small bowel remained functioning. Small intestine was transected at three respective sites in the transected control animals (n = 5) as shown in Fig. 1. The pigs described here served as control animals in a separate ileum autotransplantation.

![Fig. 1. A schematic diagram of the experimental animals. In the study group proximal 75% of the small intestine was resected. Intestinal sampling sites: (A) proximal jejunum; (B) mid-ileum; (C) distal ileum.](image)
study, and, for this reason, distal ileal transection was performed. Bowel continuity was restored by end-to-end anastomoses using one layer seromuscular running stitch of 5-0 polyglyconate monofilament after the transection sites were marked with nonabsorbable sutures for subsequent identification. Phenytoin (100 mg) was given i.m. for postoperative analgesia and the animals were kept on a liquid diet for the first postoperative day, whereafter the standard chow was introduced.

Study protocol
Preoperatively, 4, 8, and 14 weeks after the small bowel resection and 14 weeks after the transection, intestinal transit time was measured before a 3-day stool collection at the end of an 8-day marker feeding period. Then, fasting venous blood and intestinal samples were obtained, and the animals were killed with a lethal injection of thiopental. Thus, five resected animals were killed 4 and 8 weeks after the operation and five resected and five transected animals were killed 14 weeks after the operation. Five pigs subjected to small bowel resection were studied twice; preoperatively and 4 weeks after the resection. In the two groups, one transected control group (n = 5) and one resected group (n = 5) that were followed for 14 weeks, additional blood samples were drawn under light ketamine sedation 4 and 8 weeks after the operation for serial determinations of plasma cholesterol precursors and plant sterols.

Fractional cholesterol absorption was measured using a double-isotope feeding method (19). For this and determinations of fecal steroids of cholesterol origin, the pigs were fed capsules containing [14C]cholesterol (0.09 µCi), [3H]stigmastanol (0.25 µCi), and chromic oxide (200 mg) two times a day with each meal for 8 days under strict supervision. To measure intestinal transit time the animals ingested 1–2 g of carmine red powder with the first capsules, and the time when the stools turned red was recorded. A 3-day stool collection was performed at the end of the 8-day period. Fasting venous blood samples were drawn for analyses of plasma lipids, cholesterol precursors, and plant sterols. The animals were weighed weekly, and checked daily for chow intake and stool consistency.

Laboratory determinations
Fecal neutral sterols and bile acids were quantitated by GLC on the 50-meter long SE-30 capillary column (Hewlett-Packard) and calculated in relation to chromic oxide (20–22). Fecal chromic oxide was determined from the 3-day fecal samples according to the method of Bolin, King, and Klosterman (23). Total plasma cholesterol, cholesterol precursors (squalene, lanosterol, Δ8-dimethylsterol, Δ8-methostenol, methystenol, Δ5-cholestenol, lathosterol, and desmosterol), plant sterols (campesterol and β-sitosterol), and amounts of cholesterol and plant sterols in the diet were determined by GLC on the 50-m cross-linked methyl silicone SE-30 capillary column (Hewlett-Packard) (17, 18). A 500-µL plasma sample or 2000 mg of chow was saponified by a mixture of 10 N KOH in 99.5% ethanol (1:9) after addition of internal standard 5α-cholestanol. The nonvolatile lipids were extracted with n-hexane for subsequent trimethylsilylation (37°C for 1 h) and quantitation. Identification of noncholesterol sterols and squalene was based on retention times of reference sterols or of mass spectrometrically analyzed peaks derived from human plasma samples. The peaks were measured using computerized HP 3396A Integrator (Hewlett-Packard). In order to eliminate the effects of variation in lipoprotein concentrations transporting squalene and noncholesterol sterols, results are expressed in terms of 102 × µg/mg of cholesterol which expresses squalene and noncholesterol sterol concentrations in the plasma sterol mixture (24).

Calculations
The percentage absorption of cholesterol was calculated by dividing the fecal [14C]cholesterol to [3H]stigmastanol ratio by the dietary 14C to 3H ratio in the capsules (19). Total intestinal cholesterol influx, including biliary, dietary, and mucosal cholesterol, was calculated using an indirect method based on the presumption that exogenous and endogenous cholesterol are absorbed equally as follows: intestinal cholesterol influx = fecal neutral steroids/(1 - fractional cholesterol absorption) (25, 26). The difference between intestinal cholesterol influx and dietary cholesterol was considered as biliary cholesterol, although it includes some cholesterol derived from intestinal mucosa. Intestinal cholesterol influx multiplied by fractional cholesterol absorption equaled the absorbed daily amount of cholesterol. Net cholesterol elimination was calculated as the difference between the sum of fecal neutral steroids and bile acids and dietary cholesterol.

Tissue sampling
During the first operation and at the time of killing, the small intestinal length was measured along the antimesenterial border and small intestinal tissue samples were obtained from proximal jejunum, mid-ileum, and distal ileum (Fig. 1). Portions of intestine immediately on either side of the anastomosis were discarded to avoid transection-induced hyperplasia. Samples were carefully freed from mesentery after division into 15-cm length and cut open along the mesenteric border, cleaned from visible mucus and debris with a sterile gauze, measured for length and circumference, and weighed. Separate full thickness biopsies were fixed in
formalin, embedded in paraffin, and cut to 2–3 μm sections. Villus height was measured from the villus–crypt junction to the tip of the villus from Periodic Acid Schiff-stained slides by a single blinded pathologist. In every specimen an average of four well-oriented randomly chosen villi from opposite sites were measured.

Analysis of data

Analysis of variance with Fisher’s protected least significant difference test and unpaired Student’s t test, when appropriate, were used for comparisons among the groups. Correlations were calculated by linear regression analysis. The results are expressed as mean ± SEM.

RESULTS

At start, the three groups were similar in body weight: 20.6 ± 1.2 kg for preoperative, 18.6 ± 1.1 kg for transection, and 21.6 ± 0.8 kg for resection, and in small bowel length: 1208 ± 54 cm, 1286 ± 60 cm, and 1279 ± 40 cm, respectively.

All animals were operated without complications. The resected animals excreted semiformal stools for 1–6 weeks after the surgery. The 14-week weight gain was reduced markedly by resection (38.6 ± 0.9 kg) when compared with transection (65.0 ± 1.3 kg, P < 0.0001), despite a significant increase in daily chow intake when normalized to body weight (resection, 33.7 ± 2.7 g · kg⁻¹ · day⁻¹; transection, 25.7 ± 1.0 g · kg⁻¹ · day⁻¹; P < 0.05). Intestinal transit time increased with time in the controls and it was markedly decreased by the resection followed by an increase with time (Table 1).

Plasma cholesterol, cholesterol precursors and plant sterols

Plasma total cholesterol increased slightly with increasing age in the controls and it decreased significantly by up to 28% during 4 to 14 weeks after resection (Table 2).

In general, the plasma cholesterol precursor to cholesterol proportions decreased and those of plant sterols increased gradually after the transection (Table 2). After the resection the respective values were higher and lower than in the transected animals. The changes were more consistent for the demethylated than methyl precursors. In relative terms, the increase was most striking for Δ⁴-cholestenol and, in absolute terms, for lathosterol. Both absolute and relative decreases in the plasma campesterol proportions clearly exceeded those of β-sitosterol. In both operated groups the plant sterols increased after the fourth follow-up week so that campesterol/β-sitosterol proportions were markedly higher in the control than in the resection group and the ratios increased respectively from 2.65 ± 0.05 and 1.10 ± 0.05 at 4 weeks to 3.30 ± 0.10 and 1.39 ± 0.06 at 14 weeks after the operation.

Absorption and elimination of cholesterol

In general, dietary cholesterol intake was low and that of plant sterols was actually high in this series of growing pigs (27). Fractional cholesterol absorption was increased significantly in the transection group from the preoperative values (Table 3). The amount of total cholesterol absorbed per kg of body weight remained unchanged because dietary intake and biliary secretion of cholesterol were reduced with advancing age. The resection group showed a substantial decrease (up to 89.4%) in cholesterol absorption efficiency which was still, despite a fourfold increase, 66.5% lower than in the control group at the end of the study. Dietary intake and biliary secretion of cholesterol tended to be increased

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**TABLE 1.** Body weight, intestinal transit and small bowel morphology during ileal adaptation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative</th>
<th>Transection</th>
<th>Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative week</td>
<td></td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>23.2 ± 1.3</td>
<td>28.9 ± 0.2</td>
<td>52.1 ± 31</td>
</tr>
<tr>
<td>Small bowel length, cm</td>
<td>1208 ± 54</td>
<td>1490 ± 116</td>
<td>16.9 ± 0.3</td>
</tr>
<tr>
<td>Terminal (50%) ileum</td>
<td>304 ± 12</td>
<td>369 ± 30</td>
<td>544 ± 56</td>
</tr>
<tr>
<td>Small intestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumference, cm</td>
<td>3.70 ± 0.17</td>
<td>4.44 ± 0.08*</td>
<td>5.93 ± 0.15*</td>
</tr>
<tr>
<td>Wet weight, g/cm</td>
<td>0.84 ± 0.04</td>
<td>1.45 ± 0.04*</td>
<td>2.03 ± 0.07*</td>
</tr>
<tr>
<td>Villus height, μm</td>
<td>425 ± 11</td>
<td>569 ± 36*</td>
<td>497 ± 24</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM.

*P < 0.05 or less compared with preoperative.

**TABLE 2.** Plasma cholesterol precursor and plant sterols

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative</th>
<th>Transection</th>
<th>Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absorption</td>
<td>0.84 ± 0.04</td>
<td>1.45 ± 0.04*</td>
<td>2.03 ± 0.07*</td>
</tr>
<tr>
<td>Elimination</td>
<td>0.84 ± 0.04</td>
<td>1.45 ± 0.04*</td>
<td>2.03 ± 0.07*</td>
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**TABLE 3.** Plasma cholesterol precursor and plant sterols

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<th>Variable</th>
<th>Preoperative</th>
<th>Transection</th>
<th>Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>0.84 ± 0.04</td>
<td>1.45 ± 0.04*</td>
<td>2.03 ± 0.07*</td>
</tr>
<tr>
<td>Elimination</td>
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in the resection group. Overall and net elimination of cholesterol in feces were markedly decreased in the control group mainly as cholesterol itself, less so as bile acids, during the follow-up of 14 weeks. In the resected pigs the respective values, especially the neutral steroid output, were markedly increased after resection but decreased gradually with improving fractional absorption of cholesterol.

### Intestinal adaptation

The transection group underwent an expected age-related increase of small intestinal mass and villus height (Table 1). During the 14-week study proximal resection increased the ileal remnant length, circumference, wet weight, and villus height significantly by 162%, 147%, 169%, and 146% (P < 0.003 for all) of the respective transection values.

### Correlations

In the unresected (preoperative and 14 weeks after the transection) animals, fractional cholesterol absorption correlated positively with intestinal transit time and villus height, and negatively with the fecal excretion of neutral steroids and plant sterols and net elimination of cholesterol. In the resection group, villus height was positively and fecal neutral steroids negatively related to fractional absorption of cholesterol (Table 4 and Fig. 2). The correlations between the fractional cholesterol absorption and fecal plant sterols (r = -0.47), intestinal transit time (r = 0.50) or net cholesterol elimination (r = -0.51) did not quite reach statistical significance (P = 0.05).
TABLE 4. Correlation of fractional cholesterol absorption with dietary variables, plasma cholesterol, small bowel morphology and transit time, and steroid excretion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unresected (n = 10)</th>
<th>Resected (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary cholesterol, mg·kg⁻¹·day⁻¹</td>
<td>-0.53</td>
<td>-0.30</td>
</tr>
<tr>
<td>Dietary plant sterols, mg·kg⁻¹·day⁻¹</td>
<td>-0.66*</td>
<td>-0.47</td>
</tr>
<tr>
<td>Plasma cholesterol, mg/dL</td>
<td>0.03</td>
<td>-0.05</td>
</tr>
<tr>
<td>Intestinal transit time, h</td>
<td>0.92*</td>
<td>0.50</td>
</tr>
<tr>
<td>Small bowel length, cm</td>
<td>0.46</td>
<td>-0.23</td>
</tr>
<tr>
<td>Villus height, µm</td>
<td>0.76*</td>
<td>0.85*</td>
</tr>
<tr>
<td>Biliary cholesterol secretion, mg·kg⁻¹·day⁻¹</td>
<td>-0.45</td>
<td>-0.37</td>
</tr>
<tr>
<td>Fecal neutral steroids, mg·kg⁻¹·day⁻¹</td>
<td>-0.85*</td>
<td>-0.64*</td>
</tr>
<tr>
<td>Fecal bile acids, mg·kg⁻¹·day⁻¹</td>
<td>-0.65</td>
<td>-0.30</td>
</tr>
<tr>
<td>Net cholesterol elimination, mg·kg⁻¹·day⁻¹</td>
<td>-0.77*</td>
<td>-0.51</td>
</tr>
</tbody>
</table>

Dietary plant sterols equal fecal plant sterols in Table 3.

*P < 0.05.

**P < 0.01.

***P < 0.001.

0.075, P = 0.055, and P = 0.053, respectively) in the pigs with massive proximal resection.

When all animals were included, the plasma cholesterol level was positively related to cholesterol absorption efficiency (r = 0.56; P < 0.01) and negatively to fecal neutral steroids (r = -0.65; P < 0.001), but was unrelated to fecal bile acids (r = -0.24; P = 0.24). The two lathosterols, Δβ-cholestenol and lathosterol, and desmosterol correlated negatively with fractional cholesterol absorption (r = -0.55, r = -0.54, and r = -0.55, respectively; P < 0.01 for all) and positively with fecal bile acid excretion (r = 0.42; P < 0.05, r = 0.40; P < 0.05, and r = 0.54; P < 0.01, respectively), while desmosterol had, in addition, a positive correlation with fecal neutral steroids (r = 0.53; P < 0.01). The sum of methylsterols studied was positively related to fecal bile acids (r = 0.50; P < 0.01). The plant sterol proportions had high positive correlation with fractional cholesterol absorption (Fig. 3) and negative with fecal neutral steroids (r = -0.82 for campesterol and r = -0.85 for β-sitosterol; P < 0.0001 for both), and bile acids (r = -0.56 and r = -0.58, respectively; P < 0.01 for both). Furthermore, both campesterol and β-sitosterol were strongly positively related to intestinal villus height (r = 0.94 and r = 0.95, respectively; P < 0.0001 for both; Fig. 4) the regression coefficient being markedly different between the control and the resected animals not only for plant sterols but also for fractional cholesterol absorption (Fig. 2).

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[Fig. 2. Correlation between small intestinal villus height and fractional cholesterol absorption in unresected, preoperative and transected, control animals (y = 4.22x + 220) and in pigs with 75% proximal small bowel resection (y = 12.9x + 452).]

[Fig. 3. Correlation between fractional cholesterol absorption and plasma β-sitosterol to cholesterol proportion. A regression line combining preoperative and transected control animals and pigs with 75% proximal small bowel resection is shown (y = 0.19x - 2.25).]
of cholesterol. Reduced return of intestinal cholesterol to the liver activated cholesterol synthesis as assessed by elevated plasma cholesterol precursors and net elimination of cholesterol into feces (Tables 2 and 3). Up-regulation of apolipoprotein B receptor activity and decreased secretion of very low density lipoprotein, caused by cholesterol and fat malabsorption, may have, in turn, reduced plasma cholesterol. Biliary secretion of cholesterol appeared to be little affected by the resection and it was normalized by increasing age similarly in both groups. The sterol findings resemble closely those seen in celiac disease during a gluten-free diet regimen when damaged jejunal mucosa recovers and improves its absorptive function (8, 28). However, villus hypertrophy-induced improvement in absorption only partly corrected cholesterol and bile acid malabsorption, so that net fecal elimination and synthesis of cholesterol were still increased and plasma cholesterol levels failed to improve after the resection (Table 2). It can be expected that these non-steady state growing animals transported cholesterol into peripheral tissues for formation of expanding organs, suggesting that activated cholesterol synthesis was, in fact, higher than indicated by net cholesterol elimination. Accordingly, at the end of the follow-up, net elimination was 2.4 times higher in the resected than control pigs while the respective value was 4.8 for Δ8-cholesterol. Thus, despite expressing the data per kg of body weight, the effects of body weight differences on cholesterol synthesis and secretion cannot be ruled out.

**Absorption of cholesterol**

Cholesterol absorption occurs essentially in the proximal jejunum and is completed along the length of the proximal 75% of the small intestine (1, 29). In humans, approximately 50% of ingested cholesterol is absorbed during its passage through the gastrointestinal tract; consequently, substantial amounts of intraluminal cholesterol enter the distal ileum, but remain unabsorbed (2, 29). In agreement with this, after 75% proximal small bowel resection, fractional cholesterol absorption decreased by 90% to the mean level of control animals absorbed cholesterol with efficiency of 51–80% at different ages. The observed decrease in cholesterol absorption efficiency and the plasma plant sterol proportions were essentially due to proximal resection, because the controls underwent identical operation without removal of the proximal small intestine. However, a significant increase in in vivo absorption of cholesterol during the 14 weeks after proximal resection was based on three separate lines of evidence. First, the fractional absorption of cholesterol increased; second, fecal cholesterol excretion as neutral steroids decreased; and third, the plasma proportions of plant sterols in-
creased (Tables 2 and 3). The plasma plant sterol proportions reflect cholesterol absorption efficiency in normal population and in patients with intestinal resections (18, 30). The present study shows this association for the first time for pigs both in the unresected control group and after massive proximal small bowel resection when sterol absorption exceptionally occurs in the ileum (Fig. 3).

Fecal excretion of bile acids increased modestly after resection, probably reflecting the loss of passive absorption of bile acids known to take place in the proximal small intestine (31, 32). The significant temporal decrease in fecal elimination of bile acids after resection suggests effective reabsorption of bile acids by adapting ileum, which has also been shown to occur in patients with celiac disease and after proximal 50% small bowel resection in the rat, presumably due to increased number of active transport sites (8, 33).

Adaptation to small intestinal resection involves mucosal hyperplasia, dilation, and lengthening of the intestinal remnant leading to increased absorption of nutrients per unit small bowel length (15, 16). Despite slightly earlier improvement in bile acid absorption, villus hypertrophy and adaptation of cholesterol absorption were not observed until 14 weeks postoperatively. Then the compensatory increase in the remnant circumference and length appeared to be completed, suggesting that the remaining ileum was too short to compensate for the reduced intestinal absorptive area simply by macroscopic enlargement. The close relationships between villus height and fractional cholesterol absorption supported this conclusion. To absorb cholesterol with comparable efficiency, the resected animals required substantially, over twofold, higher villi (Fig. 2). Similar associations between intestinal villus height and the plasma plant sterol proportions further imply the importance of villus size in sterol absorption in general, even in intact small intestine (Fig. 4). This is understandable because cholesterol and sitosterol are similarly, and predominantly, taken up by the apical halves of the villi (1).

It is of particular interest that the average whole small intestinal serosal surface calculated by bowel diameter and length was reduced only by 50% at 14 weeks after resection, whereas villus height was increased by 46% (Table 1), and still the cholesterol absorption efficiency was only 33% of that of the transected animals (Table 3). Thus, after massive proximal small bowel resection, cholesterol absorption efficiency was reduced clearly more than would be expected simply due to the decreased amount of absorptive area. This may reflect intrinsic regional differences in intestinal cholesterol esterification and chylomicron production capacity which are lower in the ileum than the jejunum (3, 14), because cholesterol is transported in large part in esterified form by the chylomicrons (3). Decreased absorptive capacity of individual enterocytes due to rapid enterocyte turnover, bulky intestinal contents, expansion of the intraluminal oilphase and, especially, rapid transit may further reduce cholesterol absorption after massive resection (9, 34, 35). Late compensation in individual enterocyte transport capacity seems to occur (36, 37), and further improvement in cholesterol absorption efficiency may have taken place with longer postoperative follow-up. In fact, in patients with ileal bypass, adaptation of cholesterol absorption proceeds even 8 years after operation (38).

A stepwise multiple regression analysis suggested that cholesterol absorption efficiency was determined by intestinal transit time ($r = 0.92$), dietary plant sterols ($r = -0.79$), and villus height ($r = 0.76$) in the control animals, but after the resection only ileal villus height was a significant factor ($r = 0.85$), plant steroids and intestinal transit time being somewhat less significant contributors. It should be noted, however, that the inverse associations between dietary plant sterols and percentage cholesterol absorption may also reflect a higher overall dietary intake during a lower absorption, because the diet contained a fixed amount of plant sterols in relation to cholesterol. Yet the interfering effects of dietary plant sterols and accelerated intestinal transit on cholesterol absorption are well characterized in various clinical conditions (9, 27, 30, 39), while the positive correlation between jejunal villus height and fractional cholesterol absorption has been reported previously in celiacs (28). Intestinal transit section slightly delays transit shortly after operation (40), which may have contributed to the observed age-dependent improvement of cholesterol absorption efficiency in the controls. The higher the fecal elimination of bile acids, the lower were the plasma proportions of plant sterols and the higher was fecal neutral steroid excretion (~0.6 1; $r = -0.76$). Thus, decreased intraluminal bile acid concentration may have impaired micellar solubilization of cholesterol and plant sterols contributing to malabsorption of these sterols, even though cholesterol absorption efficiency was not related to fecal bile acids. However, reduced intestinal absorptive surface and rapid transit after proximal resection allow shortened time for mucosal uptake and sterol delivery from the luminal bile salt micelle to the ileal mucosa. The brush border membrane possesses greater uptake of cholesterol than sitosterol and the former is delivered at a greater rate from the intraluminal bile salt micelle to the membrane (41).

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