Growth Faltering in Rural Gambian Infants Is Associated with Impaired Small Intestinal Barrier Function, Leading to Endotoxemia and Systemic Inflammation

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ABSTRACT Growth faltering of rural Gambian infants is associated with a chronic inflammatory enteropathy of the mucosa of the small intestine that may impair both digestive/absorptive and barrier functions. The aim of this study was to determine whether the enteropathy was associated with a compromised barrier function that allowed translocation of antigenic macromolecules from the gut lumen into the body, with subsequent systemic immunostimulation, resulting in growth retardation. Rural Gambian infants were studied longitudinally at regular intervals between 8 and 64 wk of age. On each study day, each child was medically examined, anthropometric measurements were made, a blood sample was taken and an intestinal permeability test performed. Evidence of chronic immunostimulation was provided by abnormally elevated white blood cell, lymphocyte and platelet counts, and frequently raised plasma concentration of C-reactive protein. Intestinal permeability was abnormal and associated with impaired growth \( r = -0.41, P < 0.001 \). Plasma concentrations of endotoxin and immunoglobulin (Ig)G-endotoxin core antibody were also elevated and related to both growth \( r = -0.30, P < 0.02; r = -0.64, P < 0.0001, \) respectively) and measures of mucosal enteropathy. Plasma IgG, IgA and IgM levels increased rapidly with age toward adult concentrations. Raised values were related to poor growth but also to measures of mucosal enteropathy and the endotoxin antibody titer. The interrelationships among these variables and growth suggested that they were all part of the same growth-retarding mechanism. These data are consistent with the hypothesis of translocation of immunogenic lumenal macromolecules across a compromised gut mucosa, leading to stimulation of systemic immune/inflammatory processes and subsequent growth impairment. J. Nutr. 133: 1332–1338, 2003.

KEY WORDS: infant growth • intestinal permeability • endotoxin • inflammation • enteropathy

Poor growth of children during the first 2 y of life is commonly seen in most developing countries including The Gambia, where the present study was undertaken (1). Early assumptions that such poor growth could be explained entirely on the basis of inadequate nutrition from diets deficient in one or more nutrients have not generally been substantiated (2), and dietary supplementation schemes have invariably failed to raise growth performance to expected levels (3–5). An alternative explanation of the poor growth of infants in developing countries is that faltering occurs as a consequence of chronic or recurrent exposure to infection brought about by living in an unhygienic and unsanitary environment (2). Many common respiratory and gastrointestinal diseases are known to be associated with poor growth, and it is likely that these illnesses retard growth by stimulation of the body’s immune and inflammatory systems (6,7). Moreover, it is now clear that such immunostimulation can occur in the absence of overt clinical symptoms of disease (8).

Data from The Gambia are consistent with this view.

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breakdown of the mucosal barrier function allows translocation of macromolecules from the intestinal lumen into the body where they activate both local and systemic immune and inflammatory responses. Such immunostimulation would be expected to contribute to growth faltering.

SUBJECTS AND METHODS

Seventy-three infants (36 boys and 37 girls) from the rural Gambian village of Keneba were studied longitudinally, at 8, 12, 16, 24, 30, 36, 44, 52 and 64 wk of age between January 1996 and August 1997. All infants in the village aged between 8 and 48 wk when the study commenced were recruited, after which further infants entered the study as they reached 8 wk of age, and others left as they exceeded age 64 wk. Children were followed for an average of 10.7 ± 3.8 (sd) mo.

At each study visit, height and weight were measured, a blood sample was drawn and an intestinal permeability test performed. Two children dropped out of the study early on due to their mothers leaving Keneba, and they were excluded from the analysis. Overall, 483 height and weight measurements were recorded, 454 blood samples obtained and 435 successful intestinal permeability tests were performed. At each visit, children also received a full medical examination and were given appropriate treatment as required. Each blood sample was also checked for the presence of malaria parasites; however, these were found on only six occasions. Severe malaria is rarely seen in children of this age; in all six cases, only mild symptoms were present and the children responded well to treatment.

Finger-prick blood samples (300–400 µL) were collected into heparinized tubes at all clinic visits except 8, 44 and 64 wk and centrifuged at 1,500 × g for 10 min to separate cells from plasma. At 8, 44 and 64 wk of age, blood (1–2 mL, drawn by venipuncture) was collected into endotoxin free tubes (Quadratech, Epsom, UK), centrifuged at 1,500 × g for 10 min and used for estimates of plasma endotoxin. On each occasion, a blood film was also made and examined for malaria parasites (a frequent cause of systemic inflammation in the tropics). Plasma was stored at −40°C until transported back to the UK on dry ice. Hematological measurements were made on 2 or 3 occasions on 37 randomly selected infants.

Plasma albumin and immunoglobulins (IgA, IgG and IgM) were measured by immunoturbidimetric techniques using a Cobas Bio centrifugal analyzer (Roche Diagnostics, Welwyn Garden City, UK). C-reactive protein (CRP) was estimated by an ELISA technique. All assays used Dako (Ely, UK) antibodies and standards. Commercially available ELISA assay kits were used to measure plasma concentrations of endotoxin (Coatest chromo-LAL) and endotoxin core antibody (Coastet endoCAB), (Chromogenix products, Quadratech Diagnostics, Epsom, UK). For the endotoxin assays, endotoxin-free pipettes and ELISA plates were required, and only blood collected into endotoxin-free tubes was used. Endotoxin concentrations were standardized against U.S. reference endotoxin EC-6 and are reported into endotoxin units (EU)/L. Plasma albumin and immunoglobulins were measured by automated enzymatic assays (14,15).

RESULTS

Growth and intestinal permeability. At 8 wk of age, mean weight and height of children (Table 1) were close to UK normal values (16). However, after this time, children grew more slowly and by 64 wk of age, mean weight had increased to only 8.14 ± 0.94 kg and height to 73.0 ± 2.0 cm. This poor growth rate was reflected in a progressive deterioration in both weight- and height-for-age Z-scores throughout the study period (Fig. 1). Weight-for-height Z-scores at 8 and 64 wk were −0.09 ± 1.04 and −1.28 ± 1.10, respectively. In contrast, intestinal permeability increased beyond 12 wk of age to more than double by the end of yr 1 of life (r = 0.44, P < 0.001) (Fig. 2). This rise occurred as a result of both increasing lactulose (r = 0.18, P < 0.001) and decreasing mannitol excretion with age (r = −0.14, P < 0.01). The age-related increase in intestinal permeability differs from the situation in UK infants in which values at 8 wk (Table 1) are similar, but then fall toward adult levels during yr 1 of life (9,17). Age corrected growth in both weight and height over the whole period of the study was negatively related to intestinal permeability, (r = −0.41, P < 0.001), i.e., growth was poorer with higher (more abnormal) permeability values. Lactulose excretion was similarly inversely related to growth, (r = −0.39, P < 0.001).

Immunostimulation and growth. Infants showed evidence of chronic low level immunostimulation, (Table 2) with 39% of white blood cell counts >11.5 × 10⁶/L (upper limit of normal in UK), mean lymphocyte count almost double the upper limit of normality and 50% of platelet counts > 500 × 10⁴/L [upper limit of normal in UK (18)]. The mean geometric concentration of plasma CRP, was within the normal range of values, but 25% of all CRP measurements were > 5 mg/L (the upper limit of normal) and 17% were > 10 mg/L. Plasma CRP concentration was markedly elevated in 6 children with malaria parasitemia, (mean 24.3 mg/L, P < 0.05), but no association with malaria was seen for other variables.

Mean plasma concentrations of IgG, IgA and IgM were near normal at 8 wk of age (Table 1), but increased rapidly with age (Fig. 3a–c), and all three were elevated above expected values in all other age groups (19). Close negative associations were found between plasma immunoglobulin levels and age corrected growth rates, (r = −0.63, −0.64 and −0.33 for IgG, (P < 0.001), IgA, (P < 0.001) and IgM (P < 0.005) respectively. However there was no association between plasma CRP concentrations and growth. Plasma concentrations of all three immunoglobulins were also related to intestinal permeability, r = 0.41 and 0.41 (P < 0.001) for IgG who explained that her child could be withdrawn from the study at any time.

Statistics. Multiple regression analysis was used to test the significance of associations between continuous variables, using the Statistical Package for Social Sciences (SPSS, Chicago, IL) version 9.0. Growth of each child was calculated from the change in height and weight from recruitment to final clinic visit, divided by the number of days in the study and expressed as height and weight gain per month. In the statistical models, growth data were always corrected for age-related changes. Summary data for all other variables were calculated as the means of all measurements made on each child during participation in the study. These summary data were used in all analyses. Nonnormally distributed variables such as the lactulose:mannitol (L/M) ratio and plasma concentrations of CRP, endotoxin and IgG antibody to endotoxin were normalized by log transformation. The interrelationships among the several variables affecting growth were examined using partial and semipartial correlations. Anthropometric Z-scores were calculated using 1990 UK standard values (16).
and IgA, respectively and \( r = 0.28, P < 0.02 \) for IgM. IgG and IgA concentrations were also related to lactulose recovery, \( r = 0.26 \) and 0.25, \( P < 0.02 \), respectively.

**Endotoxin and endotoxin-core antibodies.** The mean (free) plasma endotoxin concentration (calculated as the geometric mean) was 202 EU/L (95% confidence interval 160–257 EU/L), which is twice the upper limit of normal, 100 EU/L (20). Of the measurements, 24% gave values \( < 500 \) EU/L and 11% were \( > 1000 \) EU/L. Concentrations were already high at 8 wk (Table 1), but increased further with age, \( r = 0.204, P < 0.05 \). High mean plasma endotoxin concentrations were associated with poorer age-corrected growth in height and weight, \( r = 0.30, P < 0.02 \) and elevated plasma IgG concentrations \( r = 0.31, P < 0.02 \). They were also associated with raised lactulose recovery \( r = 0.36, P < 0.02 \) in the intestinal permeability test.

IgG endotoxin-core antibody concentrations in plasma increased more dramatically with age than endotoxin itself (Fig. 4). The rather high value observed at 8 wk of age (Table 1) was probably due to maternally derived IgG antibody. Concentrations then fell close to the expected UK value of \( 40 \times 10^3 \) MU/L (20,21) up to 16 wk after which they rose sharply with age, with the highest values seen in the oldest children. Mean plasma endotoxin concentrations and IgG endotoxin core antibody titers were related \( r = 0.30, P < 0.02 \).

High plasma concentrations of IgG endotoxin core antibody were related to poor height and weight growth, \( r = -0.64, P < 0.0001 \) (Fig. 5) and to raised intestinal permeability and lactulose recovery, \( r = 0.35, P < 0.005 \) for both (Fig. 6). There were also strong associations with plasma immunoglobulin concentrations, \( r = 0.68, 0.51 \) and 0.47 for IgG, IgA and IgM, respectively, \( P < 0.001 \) for all.

**Interrelationships with growth.** Intestinal permeability, plasma immunoglobulin concentrations and IgG endotoxin core antibody titers were all related to infant growth in both

### TABLE 1

<table>
<thead>
<tr>
<th>Anthropometric, plasma and intestinal permeability variables in Keneba infants at 8 wk of age</th>
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<tbody>
<tr>
<td><strong>Anthropometry</strong></td>
</tr>
<tr>
<td>Age, mo</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>Height, cm</td>
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<td>Weight-for-age Z-score</td>
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<td>Height-for-age Z-score</td>
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<tr>
<td>Weight-for-height Z-score</td>
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<tr>
<td><strong>Plasma concentrations</strong></td>
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<tr>
<td>Albumin, g/L</td>
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<td>IgA, g/L</td>
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<td>IgG, g/L</td>
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<tr>
<td>IgM, g/L</td>
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<tr>
<td>C-reactive protein, ( 1 ) mg/L</td>
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<tr>
<td>Endotoxin, ( 1 ) EU/L</td>
</tr>
<tr>
<td>IgG endotoxin-core antibody, ( 1 ) MU ( \times 10^3 )/L</td>
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<tr>
<td><strong>Permeability data</strong></td>
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<tr>
<td>Lactulose:mannitol ratio ( 1 )</td>
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<tr>
<td>Lactulose recovery, %</td>
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<td>Mannitol recovery, %</td>
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</tbody>
</table>

\( 1 \) Values are geometric means (95% confidence interval). Abbreviations: Ig, immunoglobulin; EU, endotoxin units; MU, median units.
height and weight but were also all interrelated. These interrelationships have been examined using semipartial correlations estimated by linear regression analysis. This analysis allows the independent and shared contribution of each variable to growth and the degree of overlap of variables in their relationship to growth to be assessed.

For univariate relationships between plasma IgG and intestinal permeability with height growth, $r^2$ values were 0.43 and 0.22, respectively, but when combined, $r^2$ rose to only 0.48, indicating that 77% of the observed relationship between permeability and growth was accounted for by the relationship between plasma IgG and growth. Similarly, the association of endotoxin antibody titer with growth gave an $r^2$ of 0.46 individually, which rose to 0.51 when combined with intestinal permeability, also indicating an overlap of 77% of the association between permeability and growth. Repeating the calculations for plasma IgG and IgG endotoxin core antibody titer gave a combined $r^2$ of 0.51, with 86% of the IgG relationship being explained by the IgG endotoxin core antibody association with growth. Combining all three parameters, i.e., intestinal permeability, plasma IgG concentration and IgG endotoxin core antibody titer, gave a total $r^2$ of 0.56 for their association with growth, with overlaps as shown in the Venn diagram (Fig. 7).

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### TABLE 2

**Hematological variables and plasma protein concentrations in Keneba infants**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Keneba infants</th>
<th>Expected UK values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/L</td>
<td>104 ± 11</td>
<td>115–155</td>
</tr>
<tr>
<td>Total white cell count, $10^9$/L</td>
<td>10.9 ± 3.5</td>
<td>6.0–11.5</td>
</tr>
<tr>
<td>Granulocytes, %</td>
<td>32.3 ± 14.5</td>
<td>54–62</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>60.0 ± 16.2</td>
<td>25–33</td>
</tr>
<tr>
<td>Platelet count, $10^9$/L</td>
<td>507 ± 155</td>
<td>150–400</td>
</tr>
<tr>
<td>Plasma albumin, g/L</td>
<td>35.2 ± 2.01</td>
<td>39–42</td>
</tr>
<tr>
<td>Plasma C-reactive protein, mg/L</td>
<td>1.92 (1.65–2.24)</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

1 Values are means ± SD.
2 From (18).
3 Hematological values are means for 37 subjects measured a mean of 2.5 times.
4 Plasma protein concentrations are means for 73 subjects measured a mean of 6.2 times.
5 Geometric mean (95% confidence interval).

#### FIGURE 3

**Increases in plasma concentrations of immunoglobulin (Ig)G (panel a), IgA (panel b) and IgM (panel c) with age in Gambian infants.** Values are means ± SEM for all of the children in the study ($n = 71$).

#### FIGURE 4

**Variation in plasma immunoglobulin (Ig)G endotoxin-core antibody titer with age in Gambian infants.** Values are geometric means and 95% confidence intervals for all of the children in the study ($n = 71$). The horizontal line represents the mean expected titer in normal UK children (20,21).

#### FIGURE 5

**Scatterplot showing the relationship between plasma immunoglobulin (Ig)G endotoxin-core antibody titer and age corrected height growth of Gambian infants.** Each point represents the mean antibody titer and mean monthly growth rate for each child in the study ($n = 71$).
DISCUSSION

Growth in both height and weight of rural Gambian infants in this study is characteristic of children living in developing countries (9). At 8 wk of age, height- and weight-for-age Z-scores of Keneba infants were not far below UK standards, but by 64 wk, the infants were stunted although less severely wasted. The deterioration in growth occurred despite all infants being breast-fed throughout the study period and data showing breast-milk intake to be substantial up to 21–24 mo of age (22). Moreover, dietary supplementation with a highly nutritious, energy dense porridge, containing the recommended levels of vitamins and minerals had previously been shown to have no effect on child growth in this village (5). No overt food shortages occurred during the study period and none of the subjects suffered any severe illness during the investigation. Six mild cases of malaria were identified during the study but all responded well to treatment. Malaria parasitemia was associated with raised plasma CRP concentrations but was without effect on other variables.

The elevated lymphocyte, platelet and total white counts in the blood, coupled with the raised plasma concentration of CRP, nevertheless provided clear evidence of a chronic stimulation of the infants’ immune and inflammatory systems. Plasma concentrations of the three major immunoglobulins, IgG, IgA and IgM, were also raised in these children at all ages, but the divergence from expected values increased with age such that by 1 y of age, mean values for IgG and IgA were 1.6- and 1.9-fold higher, respectively, than age-matched controls (19).

Although a systemic inflammatory response can arise in response to many diseases, this study suggests that the small intestine may be a particularly important source of inflammation in these children. Evidence that the intestine is linked to growth failure comes from three sets of observations. First, intestinal permeability was found to account for 22% of the variability in growth failure; this was as high as 43% from this time and were related to intestinal permeability values. The semipartial correlations showed that as much as 77% of the variability in growth failure explained by intestinal permeability measurements was shared by IgG (or IgG endotoxin antibody), suggesting that all of these abnormalities are part of a common underlying disease process involving the gut. Second, the magnitude of the abnormalities of introduction of weaning foods and the onset of growth faltering. This increase in intestinal permeability is also in complete contrast to the pattern seen in UK infants who show a progressive reduction during y 1 of life (23). Second, inflammatory indices, such as plasma concentrations of immunoglobulins, endotoxin and endotoxin antibodies also increased from this time and were related to intestinal permeability values. The semipartial correlations showed that as much as 77% of the variability in growth failure explained by intestinal permeability measurements was shared by IgG (or IgG endotoxin antibody), suggesting that all of these abnormalities are part of a common underlying disease process involving the gut. Third, the raised plasma concentrations of endotoxin and endotoxin antibody directly implicate intestinal involvement.

Endotoxin is a component of the cell wall of many gram-negative bacteria; in children, the most likely source of endotoxin in the body is from bacteria in the gastrointestinal or urinary systems. Because none of the children in the study presented with a urinary tract infection, it is highly probable that the circulating endotoxin originated from luminal gastrointestinal tract bacteria and/or their breakdown products that translocated across a “leaky” mucosa (24). The association of increased plasma endotoxin with increased lactulose recovery is in keeping with this premise. Within the body, endotoxin elicits an immune response resulting in the production of anti-endotoxin antibodies (including IgG anti-endotoxin core antibody), which facilitate its rapid removal. Because the endotoxin antibodies persist in the blood for much longer than the endotoxin itself, their measurement allows a better estimate of the overall level of endotoxin exposure than measurement of the antigen itself (25). Although an association was observed between plasma levels of endotoxin and growth, \( r = -0.31 \), the relationship between plasma IgG anti-endotoxin antibody titer and growth was much stronger, \( r = -0.64 \). In fact, this single measurement could predict > 40% of the infants’ growth faltering. Moreover, elevated endotoxin core antibody concentrations were closely associated with raised intestinal permeability and lactulose uptake, adding further evidence for the premise of a “leaky” gut barrier. High plasma IgG anti-endotoxin core antibody titers were also closely related to total plasma IgG, IgA and IgM \( r^2 = 0.46 \), of intestinal permeability ratio and mean plasma IgG concentration for each child in the study \( n = 71 \).
0.26 and 0.22, respectively), raising the possibility that endotoxin antibodies made up a major part of the raised total immunoglobulin levels. However, it is probable that part of this association could be explained by a polyclonal immune response to many different macromolecules entering the body through the damaged intestinal mucosa (26).

All three of the major variables measured, i.e., intestinal permeability, plasma immunoglobulin concentrations and IgG anti-endotoxin titers, were related to infant growth in both height and weight. However, the semipartial regression analysis allowed a clearer understanding of how they were interrelated. The very substantial degree of overlap of all three measurements in their relationship with growth strongly suggests that they are all part of a single mechanism that overall predicted up to 55% of the growth retardation observed in these children.

Previous studies of Gambian infants demonstrated that their small intestinal mucosal enteropathy is also associated with decreased ability to digest lactose and that this effect could explain up to 25% of observed growth faltering (13). However, because there was some overlap between the malabsorption and the leaky barrier system in their associations with growth, a combination of both mechanisms indicated that the mucosal enteropathy could account for up to 64% of the growth deficit of these infants.

These data demonstrate a very strong association between intestinal disease and growth faltering of infants living in unhygienic surroundings but unfortunately, are only able to show associations and not cause and effect relationships. Attempts to define cause and effect relationships by time-series analysis were not successful with this dataset. It appears that the sequence of mucosal damage, inflammatory and immune response, and growth retardation occurs over a short period of time, well within the 4–6 wk sampling frequency used in this investigation. The findings, however, are clearly in keeping with the proposed hypothesis. The mucosa of the small intestine is a major interface between the body and its environment, and these results suggest that damage to this tissue can result in breaches of the barrier function that allow hazardous material to enter the body and cause growth faltering by the metabolic sequelae after immunostimulation. The alternative hypothesis, that the poor growth and mucosal damage are the result of a nutritional deficit, is less tenable. For example, it can be suggested that a process that causes growth failure also happens to cause an enteropathy, and that the translocated material from the gut and malabsorption of nutrients resulting from the enteropathy are incidental to growth. Although this is possible, it is difficult to entirely exclude the intestine as being involved in a causal chain of events because both endotoxemia and malabsorption/malassorption can independently cause growth failure. Moreover, growth faltering and mucosal damage first appear at ~3 mo of age when breast milk intake in Keneba is known to be nutritionally adequate for normal growth (22). Indeed, carefully supervised dietary supplementation of infants in the village over many years has totally failed to prevent growth retardation (5).

The results provide a demonstration of the view expressed by Solomons et al. (2) that disease rather than diet may be the major cause of growth impairment of children in underprivileged communities. In the case of The Gambia, it appears that child growth is impaired by a chronic, asymptomatic mucosal enteropathy. It is also important to note that the presence of the enteropathy did not equate with diarrheal disease; infants had diarrhea for <10% of the time they had an enteropathy, and there was no long-term relationship between diarrhea prevalence and either intestinal permeability or overall infant growth (9). It is clear that the lack of association between diarrheal disease and long-term growth as described by Briend et al. (27) does not preclude the possibility of the presence of a growth-retarding gastrointestinal enteropathy.

The etiology of the enteropathy remains unknown, although it seems to be associated with the introduction of unhygienically prepared weaning foods (9). However once initiated, it appears to be largely self-perpetuating (11), with persistent translocation of antigen through the mucosa causing further local immunostimulation and consequent further damage to the tissue. In this way, episodes of enteropathy can last for many months with prolonged effects on growth (9). Small bowel mucosal enteropathy has often been described in severely malnourished children in many parts of the world, but was generally believed to occur as a result of malnutrition. The current results suggest that the opposite view may be the case, i.e., that the mucosal damage is the cause of the malnutrition rather than the consequence. Moreover, increasing number of reports of abnormalities of intestinal permeability in all parts of the developing world (9) suggest that asymptomatic small intestinal enteropathy is both common and widely spread and therefore may be a major contributor to growth impairment and malnutrition worldwide. However, its full effect on growth will not be fully established until effective therapeutic or preventative measures can be found and implemented.

For commentary on this article, see the article by Solomons in this issue (28).

LITERATURE CITED


