The Role of Hormones in the Pathophysiology of Acute and Chronic Diarrhea

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It has been estimated that between 5 and 20 million children die each year as a result of acute and chronic diarrhea. The investigation of the pathogenesis and treatment of this major clinical problem is, therefore, of special importance, representing one of the most important challenges to medicine in the last decades of this century. Aspects of the pathophysiology of the clinical problem that have not yet been well defined are the role of hormones in the etiology of the diarrhea and the effects of diarrhea itself on the secretion and function of hormones. This chapter surveys the reasons why an understanding of hormone release in these contexts may be of particular relevance and documents current knowledge as well as indicating areas for future research.

THE ROLE OF HORMONES IN THE REGULATION OF FOOD UTILIZATION

The efficient utilization of food depends on the integrated activities of several physiological systems, beginning with the propulsion of food through the gut. The motor activities of the stomach, small gut, and large intestine are normally coordinated to ensure proper postprandial expulsion of the acidified contents of the stomach into the small gut for complete mixing with digestive juices and for storage of feces until elimination. The secretion of acid, alkali, digestive enzymes, and fluid is coordinated with the motility of the gut so that the appropriate digestive juices are secreted in relation to the presence of food in different parts of the alimentary tract. The absorption of nutrients stimulates the release of metabolic hormones that control the disposal of the substrates.

Although several mechanisms may be responsible for the coordination of these activities, there is now convincing evidence that all of the above processes are affected by regulatory peptides secreted by the gut and pancreas, with additional influences from hormones of the pituitary, thyroid, and adrenal glands. The peptides can exert their effects either systemically (endocrine effect), as neurotransmitters (neurocrine activity), or locally on surrounding cells (paracrine...
The peptides that are known to affect the regulation of food utilization are listed in Table 1, together with a resume of their actions. The distribution of the peptides acting as circulating hormones throughout the primate gut is shown in Fig. 1. For more detailed accounts of current knowledge the reader is referred to recent reviews (1,2).

We have shown previously that the circulating concentrations of these peptides change dramatically within hours of birth in the human neonate, and we have suggested that they play a key role in regulating the adaptation of the infant to enteral nutrition through stimulating gut growth, influencing acid and enzyme secretion, and modulating pancreatic endocrine development (3). At present, there is no evidence to suggest that once the infant has fully adapted to enteral feeding these peptides have a role in the child other than that in the adult, although this remains to be proved, particularly since the infant is more susceptible than the adult to the development of persistent gastrointestinal dysfunction.

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Diarrhea is defined clinically as the frequent passage of loose stools, usually with a water content greater than 10 ml/kg of body weight per day. In most cases in childhood diarrhea is an acute self-limiting disorder caused by infection, but it can also progress to a chronic and serious disorder leading to malnutrition with additional secondary effects on the gut. A vicious and often fatal cycle of self-perpetuating diarrhea is thus initiated. Intractable diarrhea of infancy encompasses a heterogeneous group of disorders, as listed in Table 2, ranging from conditions causing villous atrophy to anatomical and inflammatory lesions. It follows from the above that the symptom of diarrhea can be the result of several pathogenetic mechanisms.

**TABLE 1. Regulatory peptides and hormones involved in food utilization**

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrin</td>
<td>Gastric acid secretion, growth of the gut</td>
</tr>
<tr>
<td>Secretin</td>
<td>Pancreatic exocrine secretion</td>
</tr>
<tr>
<td>Cholecystokinin</td>
<td>Gallbladder contractility</td>
</tr>
<tr>
<td>GIP</td>
<td>Modulation of insulin secretion</td>
</tr>
<tr>
<td>VIP</td>
<td>Intestinal secretions, blood flow</td>
</tr>
<tr>
<td>Motilin</td>
<td>Intestinal transit</td>
</tr>
<tr>
<td>Neuropeptide</td>
<td>Gastric motility</td>
</tr>
<tr>
<td>Enteroendocrine</td>
<td>Gut growth, gut transit time</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Glucose homeostasis</td>
</tr>
<tr>
<td>Insulin</td>
<td>Pancreatic growth, exocrine function, intestinal absorption</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Insular hormone release, intestinal absorption</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Fuel utilization</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Gut enzyme activity</td>
</tr>
<tr>
<td>Thyroxine/T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Gut development, hormone receptor activity, metabolic rate</td>
</tr>
</tbody>
</table>
From this discussion it could be hypothesized that the normal interrelations of regulatory peptides and hormones could be disturbed by diarrhea in various ways. Thus, for example, in acute infectious diarrhea, changes in hormone release might be responsible for, or contribute to, the looseness of the stools through increasing either the motor activity of the gut or intestinal secretions. Conversely, gut damage might alter the secretion of hormones, depending on the anatomical localization of the damage, with secondary effects elsewhere in the gut. Similar considerations apply to the causes of chronic diarrhea.

These aspects have not been studied in detail, and there is, as yet, little information as to how the various causes of diarrhea alter the release of peptides and their endocrine, paracrine, and neurocrine effects in adults or in childhood. Nonetheless, changes in plasma concentrations of hormones have been studied under three circumstances, namely, acute infective diarrhea, malabsorption secondary to celiac disease, tropical sprue, and cystic fibrosis, and the watery diarrhea syndrome associated with VIPomas and ganglioneuromas. The changes in circulating hormones induced by these disorders support the above hypothesis and
TABLE 2. Disorders identified with intractable diarrhea of infancy (listed by groups according to pathophysiology)

<table>
<thead>
<tr>
<th>Disorders associated with villous atrophy</th>
<th>Anatomical problems associated with IDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral gastroenteritis</td>
<td>Short bowel syndrome</td>
</tr>
<tr>
<td>Cow's milk protein enteropathy</td>
<td>Hirschsprung's disease</td>
</tr>
<tr>
<td>Soy protein enteropathy</td>
<td>Gastrochisis</td>
</tr>
<tr>
<td>Eosinophilic gastroenteropathy</td>
<td>Malrotation</td>
</tr>
<tr>
<td>Sprue</td>
<td>Ileal atresia</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Intestinal lymphangiectasia</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Metabolic entities associated with IDI</td>
</tr>
<tr>
<td>Immunodeficiency syndromes</td>
<td>Acrodermatitis enteropatica</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td>Abetalipoproteinemia</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>Wolman's disease</td>
</tr>
<tr>
<td>Hirschsprung's disease</td>
<td>Hypoparathyroidism</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Disorders associated with secretory diarrhea</td>
<td>Pancreatic insufficiency</td>
</tr>
<tr>
<td>Familial chloride diarrhea</td>
<td>Glucose–galactose malabsorption</td>
</tr>
<tr>
<td>Bacterial toxins: <em>Escherichia coli</em></td>
<td>Sucrase–isomaltase deficiency</td>
</tr>
<tr>
<td><em>Vibrio cholera</em></td>
<td></td>
</tr>
<tr>
<td>Hormones elaborated by tumors: VIPoma,</td>
<td></td>
</tr>
<tr>
<td>Zollinger–Ellison syndrome, medullary</td>
<td></td>
</tr>
<tr>
<td>carcinoma of the thyroid, basophilic</td>
<td></td>
</tr>
<tr>
<td>leukemia, systemic mastocytosis</td>
<td></td>
</tr>
<tr>
<td>Inflammatory lesions of the colon</td>
<td></td>
</tr>
<tr>
<td>Bile-acid-induced secretory diarrhea</td>
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</tbody>
</table>

Indicate that further study may improve knowledge of the pathophysiology of the various causes of diarrhea.

**ACUTE INFECTIOUS DIARRHEA**

During the last decade, considerable advances have been made in understanding the pathogenesis of acute infectious diarrhea. It is now apparent that several mechanisms are responsible for the interaction of the infecting organism and the gut leading to the clinical symptom of diarrhea. With some organisms, for example, cholera, there is a chemical effect on gut mucosal cells as a result of bacterial endotoxin affecting cyclic AMP activity and increasing fluid secretion (4,5), and the mucosal structure is left relatively unaffected. Other organisms, for example, enteroviruses, attack the cell surface causing either structural change or destruction of the whole enterocyte (6,7). Finally, some organisms, for example, *E. coli*, cause symptoms both by invasion leading to destruction and by release of endotoxins (8,9). It should also be noted that different organisms affect different parts of the gut, *Shigella*, for example, affecting primarily the colon, and cholera affecting the small gut.

Although it has been a subject of intense controversy there is now good evidence that there are changes in the motility of gut during acute infectious diarrhea (11), but whether these are primary phenomena caused by toxins acting directly on gut muscle or through effects on mucosal nerves or peptides remains
an uncertain issue. It follows from these points that it is possible that different organisms causing infectious diarrhea might have different effects of gut hormone release. There is, unfortunately, no evidence to date to support this.

The only comprehensive study that has considered hormonal changes in the context of acute diarrhea is that of Besterman et al. (12). In this study the effects on circulating hormone concentrations of a standard test breakfast were measured in 12 adult patients with acute and presumed infectious diarrhea, compared with normal controls. In only four patients, however, was a pathogenic organism positively identified. Plasma hormone concentrations were measured before and after the meal in the patients and controls and after recovery from diarrhea.

From this study, the fasting levels, peak postprandial rises, and total integrated responses after the breakfast for blood glucose and plasma insulin, gastrin, GIP, pancreatic polypeptide (PP), glucagon, motilin, enteroglucagon, and VIP are shown in Table 3. Patients with diarrhea had significantly reduced fasting levels of blood glucose with a decreased postprandial rise; fasting plasma insulin concentrations were, however, higher in the patients, although the postprandial rise was similar. It can also be seen that the patients had markedly increased fasting levels of PP, motilin, and enteroglucagon with differences in postprandial response. Plasma VIP concentrations were significantly greater both before and after the meal in the patients with diarrhea. No differences were seen in plasma gastrin, GIP, or glucagon levels (Table 3). Figure 2 shows the progression of concentrations of six hormones from the time of admission to discharge compared with controls. At presentation, fasting levels of PP, motilin, enteroglucagon, and VIP are elevated; motilin and enteroglucagon concentrations fall with recovery, but PP and VIP remain elevated. It is not known for how long these abnormalities persist.

These results demonstrate profound abnormalities in both the preprandial and postprandial concentrations of gut and pancreatic hormones in acute diarrhea in adults with changes during recovery. The potential significance of these data is discussed below.

One further study in the context of acute infectious diarrhea is noteworthy, and this is the observation that cholera toxin introduced into the feline small intestine caused a marked increase in intestinal venous VIP concentrations (13). These results support a previous preliminary report that the stool water of choleraic patients contained a high concentration of VIP (14). The release of VIP from the feline gut could be prevented by tetrodotoxin, a nerve conduction blocking agent. It is likely, therefore, that the local activity of VIP in the gut wall is involved somehow in the pathogenesis of choleraic secretion. Other mechanisms, however, including release of prostaglandins may be of equal or greater importance (15).

It must be emphasized that at present it is not known whether the hormone response to infectious diarrhea is influenced or altered by the stage of maturity of the gut, i.e., neonatal, infantile, or adult, and this is an obvious area for further investigation.
<table>
<thead>
<tr>
<th></th>
<th>Gastrin (pm)</th>
<th>Blood glucose (mm)</th>
<th>Insulin (pm)</th>
<th>GIP (pm)</th>
<th>HPP (pm)</th>
<th>Pancreatic glucagon (pm)</th>
<th>Motilin (pm)</th>
<th>Entero-glucagon (pm)</th>
<th>VIP (pm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 13)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Basal</td>
<td>5.0 ± 1.0</td>
<td>4.6 ± 0.2</td>
<td>19.0 ± 1.0</td>
<td>17.0 ± 4.0</td>
<td>22.0 ± 5.0</td>
<td>4.2 ± 0.8</td>
<td>41.0 ± 8.0</td>
<td>19.0 ± 2.0</td>
<td>5.5 ± 0.9</td>
</tr>
<tr>
<td>Peak rise</td>
<td>17.0 ± 5.0</td>
<td>2.1 ± 0.2</td>
<td>125.0 ± 11.0</td>
<td>43.0 ± 5.0</td>
<td>181.0 ± 31.0</td>
<td>3.4 ± 0.7</td>
<td>25.0 ± 6.0</td>
<td>21.0 ± 4.0</td>
<td>3.2 ± 1.2</td>
</tr>
<tr>
<td>TIR*</td>
<td>2.9 ± 0.7</td>
<td>895.0 ± 39.0</td>
<td>13.0 ± 1.5</td>
<td>8.3 ± 1.1</td>
<td>23.1 ± 3.4</td>
<td>0.8 ± 0.1</td>
<td>7.9 ± 1.7</td>
<td>5.2 ± 0.5</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Acute diarrhea patients (n = 12)</td>
<td></td>
<td></td>
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<tr>
<td>Basal</td>
<td>10.0 ± 3.0</td>
<td>3.5 ± 0.1** b</td>
<td>25.0 ± 2.0††</td>
<td>20.0 ± 4.0</td>
<td>41.3 ± 6.0††</td>
<td>4.1 ± 0.5</td>
<td>138.0 ± 26.0**</td>
<td>64.5 ± 12.0**</td>
<td>16.5 ± 1.6**</td>
</tr>
<tr>
<td>Peak rise</td>
<td>24.0 ± 6.0</td>
<td>1.2 ± 0.2*</td>
<td>105.0 ± 18.0</td>
<td>40.0 ± 5.0</td>
<td>250.0 ± 47.0</td>
<td>2.2 ± 0.6</td>
<td>63.0 ± 13.0††</td>
<td>41.0 ± 16.0</td>
<td>9.3 ± 2.3††</td>
</tr>
<tr>
<td>TIR*</td>
<td>4.6 ± 1.3</td>
<td>722.0 ± 38.0*</td>
<td>13.6 ± 1.9</td>
<td>8.5 ± 0.7</td>
<td>26.2 ± 3.6</td>
<td>0.8 ± 0.1</td>
<td>27.9 ± 5.5**</td>
<td>15.5 ± 3.0**</td>
<td>3.2 ± 0.4**</td>
</tr>
</tbody>
</table>

* Total integrated responses (TIR) for peptides in nM/180 min and for blood glucose in mM/180 min.

b Significance versus controls: p < 0.05†, 0.02‡, 0.01††, 0.005**, 0.001**.
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Several reports have now appeared on the circulating concentrations of hormones in celiac disease, a condition localized to the small intestine (16–22). Although there are minor differences in the results (which may reflect differences in the ages and the severity of the disease in the patient groups investigated), the studies report profiles that are consistent and suggest a pathognomonic pattern.

Basal and postprandial plasma insulin concentrations are reduced; plasma secretin concentrations after citric acid and GIP levels after a meal are both diminished in children with celiac disease (Fig. 3). It is of interest that the latter hormone response did not return to normal soon after institution of a gluten-free diet (18). In contrast, plasma enteroglucagon concentrations arising from an unaffected part of the gut showed a massive postprandial increase (Fig. 3) with a decrease in response to treatment. Plasma motilin levels were only marginally elevated above control postprandial values. Gastrin from the stomach and PP from the pancreas were relatively unchanged, thus showing that the gut

**FIG. 2.** Plasma hormone concentrations in controls and in patients with acute diarrhea on admission and discharge from hospital (data compiled from ref. 12).

HORMONE PROFILES IN CHRONIC DIARRHEA AND MALABSORPTION
hormone profile in untreated celiac disease accurately reflects the anatomical distribution of the disease; normalization of the endocrine response reflects improvement in the mucosa with treatment. The status of cholecystokinin in celiac disease is rather more controversial in view of methodological difficulties, but it has been reported that its secretion is also impaired in celiac disease (21).

In contrast to celiac disease, tropical malabsorption affects the entire length of the gut, often causing profuse diarrhea. The available evidence suggests that this is caused by intestinal bacterial colonization. Some aspects of the hormone profile before and after feeding are similar in adult subjects with sprue and with celiac disease (23). Thus, there is normal gastrin, PP, and neurotensin release but impaired insulin and GIP secretion (Figs. 4, 5). On the other hand, although motilin and enteroglucagon are both elevated in basal samples, they do not change markedly after a meal (23) (Figs. 6, 7). The lack of change in postprandial enteroglucagon and motilin levels is different from that noted above in patients with celiac disease. Restudy of these patients 4 years after successful treatment

![FIG. 3. Blood glucose and plasma hormone concentrations in celiac disease and in control subjects. Basal samples were drawn before and after a meal for all substances except secretin, where the stimulus was citric acid ingestion (data compiled from ref. 18).]
HORMONES AND DIARRHEA

Fig. 4. Plasma insulin concentrations (mean ± SEM) before and after a test meal in patients with tropical sprue (open circles and solid line) compared with controls (closed circles, broken line). (From Besterman et al., ref. 23, with permission.)

showed entirely normal pre- and postprandial hormone profiles (S. R. Bloom, unpublished data). Moreover, the changes in plasma enteroglucagon levels closely correlated with breath hydrogen content (23).

It might be predicted that the severity of the underlying mucosal damage in disorders affecting the small bowel might alter the circulating hormonal profile, and there is evidence that this is so. Thus, Arnold et al. (16) have presented data on basal and integrated hormone responses to meals in relation to severity of mucosal damage in a heterogeneous group of children with malabsorption caused by celiac disease, disaccharide intolerance, infectious diarrhea, and lambliiasis (Fig. 8). It can be seen that there is a progressive and highly significant fall in the integrated response of four hormones to the standard meal with increasing severity of the mucosal atrophy.

In contrast to patients with celiac disease and tropical malabsorption, children with cystic fibrosis have markedly decreased fasting plasma PP concentrations (24), with complete abolition of the postprandial increase (Fig. 9). Fasting plasma enteroglucagon concentrations were grossly elevated and remained so after a
FIG. 5. Plasma GIP concentrations (mean ± SEM) before and after a test meal in patients with tropical sprue (open circles, continuous line) and controls (closed circles, broken line). (From Besterman et al., ref. 23, with permission.)

FIG. 6. Plasma motilin concentrations (mean ± SEM) before and after a test meal in tropical sprue compared with normal controls (From Besterman et al., ref. 23, with permission.)
FIG. 7. Plasma enteroglucagon concentrations (mean ± SEM) before and after a test meal in patients with tropical sprue (open circles, continuous line) compared with normal controls (closed circles, broken line). (From Besterman et al., ref. 23, with permission.)

FIG. 8. Integrated 2-hr hormonal response to a mixed test meal in children with malabsorption and with increasing degrees of mucosal atrophy. (From Arnold et al., ref. 16, with permission.)
meal (Fig. 10); no differences were seen, however, in basal or postprandial responses of plasma glucagon, gastrin, secretin, VIP, or motilin in cystic fibrosis. Thus, yet another chronic malabsorptive disorder appears to have a specific hormonal profile.

It can be concluded from these studies that the endocrine milieu reflects not only the nature of the underlying disease in chronic diarrhea but also the degree of mucosal damage and the response to treatment.

HORMONE PROFILES IN THE WATERY DIARRHEA SYNDROME

The role of VIP in the pathogenesis of choleraic diarrhea has been mentioned above. This peptide has now also been shown to be the cause of the watery diarrhea syndrome. This condition is characterized by profuse watery diarrhea,
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FIG. 10. Plasma enteroglucagon concentrations (mean ± SEM) before and after a test meal in children with cystic fibrosis and controls. (From Adrian et al., ref. 24, with permission.)

hypokalemia, and non-β islet-cell tumors (25). The syndrome also occurs in children with ganglioneuromas and neuroblastomas (26).

There is now conclusive evidence that excess release of VIP is responsible for all the clinical features of the disease (25), the evidence being based not only on measurements of plasma and tissue VIP levels in affected subjects (1) (Fig. 11) but also on the fact that infusion of VIP in pigs causes profuse diarrhea (27) similar to that in the affected human patient. It is probable that the mechanism of the effect is the action of VIP in stimulating intestinal epithelial cyclic AMP production and hence increased intestinal secretion.

DISCUSSION

The above brief review confirms that changes in circulating concentrations of hormones occur in patients with acute infectious diarrhea and chronic malabsorption and in the watery diarrhea syndrome. It is obvious, however, that such measurements only poorly reflect the events occurring in the gut itself. Nonetheless, it is possible to speculate on the role of each of the hormonal changes documented; the endocrine differences are summarized in Table 4.

In the context of acute infectious diarrhea, the changes in motilin levels are of particular interest in view of the effects of this hormone on gut motility. In
vitro studies have shown that motilin causes dose-dependent contractions of isolated rabbit and human intestinal segments (10). In vivo infusions of the hormone in adults cause an increase in electrical and pressure activities in the descending colon with reduction of small intestinal transit time, strong contractions of the stomach are also induced (28). Thus, the finding of substantially elevated plasma motilin concentrations in patients with acute diarrhea may have relevance to the motility changes that are known to occur (11). Further support for this contention lies in the observation that the levels of the hormone fall with resolution of the disease. It is not clear, however, what the mechanism of the stimulation of motilin secretion is under these circumstances, and it would be of interest to determine whether different infecting organisms affect motilin release in different ways.

In chronic diarrheal states such as after intestinal resection (29), ulcerative colitis (30), and Crohn's disease (30), motilin levels are also elevated as they are in tropical malabsorption and to a lesser extent in untreated celiac disease. Since normal motilin levels are found in patients with the irritable bowel syndrome without demonstrable organic pathology (31), these observations suggest...
that in chronic diarrhea there is also a disturbance in motilin secretion. It is not clear whether this is primarily or partially responsible for the pathogenesis of the diarrhea or whether it is caused by secondary or adaptive changes in the gut mucosa. Further study of motilin secretion in chronic functional and organic diarrhea in childhood is needed to determine whether the above findings are also evident in early life. Similarly, the effects of specific antimotility therapy on levels of the hormone need to be documented.

The plasma gut hormone profile in chronic diarrhea corresponds to the anatomical localization of the disease. Thus, in celiac disease, localized to the small bowel, the hormones produced in this affected region show abnormal plasma concentrations; gastric secretion of gastrin is normal, but secretin and GIP are particularly affected. The hormones from the unaffected distal small bowel and colon, neurotensin and enteroglucagon, are elevated. It is unexpected to find an increase in secretin and GIP cell numbers in small bowel biopsies of children with celiac disease (22,32), and this suggests that decreased numbers of hormone-secreting cells are not responsible for the attenuated plasma concentrations, but rather that adequate absorption of the stimulus is necessary for the hormone release (20).

Whatever the mechanism is of the failure of secretin and GIP release, the abnormality may be responsible for some important functional changes in celiac disease. Thus, such patients have a failure of pancreatic exocrine function (33,34), which is likely to be secondary to impaired secretin release. Others have demonstrated impaired cholecystokinin secretion in celiac disease (35). If substan-
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tiated, this may explain the impaired gallbladder contractility found in these patients.

Patients with celiac disease also have impaired glucose tolerance as a result of inadequate insulin secretion. Since GIP has been suggested to be the main effector, or "incretin," of the enteroinsular axis (36), it is tempting to suggest that it is the failure of GIP that is responsible for the abnormal pancreatic insular function.

It is possible that deranged gut "signals" are also responsible for the abnormal PP response to feeding reported by Arnold et al. in patients with chronic diarrhea (16). On the other hand, plasma levels of this hormone are elevated in acute diarrhea for reasons that are not understood. These findings lead to the possibility that changes in PP levels might be markers of the progression from acute to an intractable chronic diarrhea, and this requires further study. At present, the role of the hormone in digestive physiology is uncertain, although in addition to effects on pancreatic exocrine secretion and gallbladder contraction (37), it may have an effect on stimulating fluid absorption from the distal ileum (38).

Plasma enteroglucagon levels are elevated in both acute and chronic diarrhea and return to normal with resolution of the disease, indicating an important role for measurement of this hormone as an indicator of response to therapy. The physiological role of the hormone is more difficult to assess. Indirect evidence suggests that it may stimulate villous growth and slow intestinal transit (39). Recent clinical evidence further supports its action as a trophic hormone in that a partially purified form of enteroglucagon stimulates the rate of mucosal DNA synthesis in rodents (40). Enteroglucagon may therefore be acting as a key trophic agent to the gut and stimulating its response to injury (29).

The importance of VIP has been alluded to above in discussion of the watery diarrhea syndrome. However, its vasodilator effects and influence on inhibiting absorption and stimulating water and ion secretion and adenylate cyclase activity as well as relaxing colonic smooth muscle make it potentially an important hormone in the pathological mechanisms of diarrhea other than in this rare syndrome. Further studies are clearly needed to substantiate its role under these circumstances.

It is of interest, although hardly surprising in view of the anatomical distribution of the above diseases, that gastrin secretion is remarkably unaffected. Although gastrin is a contender as a trophic hormone in regulating gut growth (41), a more important role for the hormone may be the maintenance of gastric acid release to prevent reinfection.

Changes in intermediary metabolism, as reflected by disturbances in glucose tolerance, occur in both acute and chronic diarrhea. These changes are likely to be multifactorial in origin, including abnormal absorption of nutrients and impaired insulin release. Other metabolic hormones may also be involved in this process, including cortisol and growth hormone, particularly since the secretion of the latter has been shown to be impaired in children with celiac disease (20).
Malnutrition itself may have an important role on the structure and function of the gut and pancreas. Although it is unlikely that this could be implicated in the changes described in previously healthy adults with acute diarrhea, it assumes increasing theoretical importance in children with chronic diarrhea, and the role of preexisting and concurrent malnutrition on the hormonal responses in diarrheal states is unknown. Finally, it has also been shown that fasting and meal-stimulated hormone levels are not affected substantially in adults by prolonged periods of total parenteral nutrition (42). It is not known whether this is also true in infancy or childhood, and the whole question of the effects of specific therapy for diarrhea, including drug therapy and prolonged intravenous feeding, on hormone release in childhood remains to be determined. We have shown that deprivation of enteral feeding in neonates prevents the appearance of postnatal surges in hormones to which we have assigned a key role in the adaptation to enteral feeding after birth (3). Whether these changes are modified by diarrhea in early postnatal life also requires further clarification.

CONCLUSIONS

There is little doubt that changes in plasma hormone concentrations and profiles can be defined in patients with diarrhea resulting from different diseases. Some of the implications of these changes have been considered above. It will now be important to measure these hormones in children in relation to specific infectious and parasitic organisms in order to determine, first, whether the effects are the same as in adults and, second, whether the different actions of these infectious agents in causing acute diarrhea are reflected in different endocrine profiles.

Information on the immunohistology of regulatory peptides in these diseases is likely to be a most fruitful area of research (1), and this information is needed urgently since circulating levels of hormones poorly reflect the events in the gut itself. Studies in experimental diarrhea in relation to specific antidiarrheal therapy might lead to drugs that interfere with the action of the hormones.

Perhaps some hormones themselves, for example, enteroglucagon, could conceivably be used in the future as therapeutic agents. Of greater practical importance now, however, is the need to follow longitudinally hormone measurements in children who progress into chronic intractable diarrhea. There might well be a hormone or group of hormones whose measurements are of diagnostic or prognostic importance. Changes in hormone profile might also be used to monitor specific therapy. These aspects are certainly worthy of further investigation.

Finally, it must be remembered that other active substances, including enkephalins, endorphins, and prostaglandins (1) are also found in the gut mucosae, and some of the features of diarrhea can be attributed to their actions. The interaction of these substances with hormones and regulatory peptides within the gut represents a major area of future work.
REFERENCES