Diarrhea as a *symptom* (i.e., when the term is used by patients to describe their bowel movement pattern) may reflect a decrease in stool consistency, an increase in stool volume, an increase in number of bowel movements, or any combination of these three changes. In contrast, diarrhea as a *sign* is a quantitative increase in stool water or weight of >200–225 mL or g per 24 h when a Western-type diet is consumed. Individuals consuming a diet with higher fiber content may normally have a stool weight of up to 400 g/24 h. Thus, the clinician must clarify what an individual patient means by diarrhea. Some 10% of patients referred to gastroenterologists for further evaluation of unexplained diarrhea do not have an increase in stool water when this variable is determined quantitatively. Such patients may have small, frequent, somewhat loose bowel movements with stool urgency that is indicative of proctitis but do not have an increase in stool weight or volume.

It is also critical to establish whether a patient's diarrhea is secondary to diminished absorption of one or more dietary nutrients rather than being due to small- and/or large-intestinal fluid and electrolyte secretion. The former has often been termed *osmotic diarrhea*, while the latter has been referred to as *secretory diarrhea*. Unfortunately, both secretory and osmotic elements can be present simultaneously in the same disorder; thus, this distinction is not always precise. Nonetheless, two studies—determination of stool electrolytes and observation of the effect of a fast on stool output—can help make this distinction.

The demonstration of the effect of prolonged (>24 h) fasting on stool output can suggest that a *dietary nutrient* is responsible for the individual's diarrhea. Secretory diarrhea associated with enterotoxin-induced traveler's diarrhea would not be affected by prolonged fasting, as enterotoxin-induced stimulation of intestinal fluid and electrolyte secretion is not altered by eating. In contrast, diarrhea secondary to lactose malabsorption in primary lactase deficiency would undoubtedly cease during a prolonged fast. Thus, a substantial decrease in stool output by a fasting patient during quantitative stool collection lasting at least 24 h is presumptive evidence that the diarrhea is related to malabsorption of a dietary nutrient. The persistence of stool output during fasting indicates that the diarrhea is likely secretory and that its cause is *not* a dietary nutrient. Either a luminal (e.g., *E. coli* enterotoxin) or a circulating (e.g., vasoactive intestinal peptide) secretagogue could be responsible for unaltered persistence of a patient's diarrhea during a prolonged fast. The observed effects of fasting can be compared and correlated with stool electrolyte and osmolality determinations.

Measurement of stool electrolytes and osmolality requires comparison of Na^+ and K^+ concentrations in liquid stool with the osmolality of the stool in order to determine the presence or absence of a so-called stool osmotic gap. The following formula is used:

$$2 \times (\text{stool } [Na^+] + \text{stool } [K^+]) \leq \text{stool osmolality}$$

The cation concentrations are doubled to estimate stool anion concentrations. The presence of a significant osmotic gap suggests the presence in stool water of a substance (or substances) other than Na/K/anions that is presumably responsible for the patient's diarrhea. Originally, stool osmolality was measured, but it is almost invariably greater than the required 290–300 mosmol/kg H_2O, reflecting bacterial degradation of nonabsorbed carbohydrate either immediately before defecation or in the stool jar while specimen awaits chemical analysis, even when the stool is refrigerated. As a result, the stool osmolality should be assumed to be 300 mosmol/kg H_2O. A low stool osmolality (<290 mosmol/kg H_2O) reflects the addition of either dilute urine or water, indicating either collection of urine and stool together or so-called factitious diarrhea, a form of Münchausen's syndrome. When the calculated difference in the formula above is >50, an osmotic gap exists; its presence suggests that the diarrhea is due to a nonabsorbed dietary nutrient—e.g., a fatty acid and/or a carbohydrate. When this difference is <25, it is presumed that a dietary nutrient is not responsible for the diarrhea. Since elements of both osmotic diarrhea (i.e., due to malabsorption of a dietary nutrient) and secretory diarrhea may be present, this distinction at times is less clear-cut at the bedside than when used as a teaching example. Ideally, the presence of an osmotic gap will be associated with a marked decrease in stool output during a prolonged fast, while an osmotic gap will likely be absent in an individual whose stool output is not reduced substantially during a period of fasting.

NUTRIENT DIGESTION AND ABSORPTION

The lengths of the small intestine and the colon are ~300 cm and ~80 cm, respectively. However, the effective functional surface area is ~600-fold greater than that of a hollow tube as a result of folds, villi (in the small intestine), and microvilli. The functional surface area of the small intestine is somewhat greater than that of a doubles tennis court. In addition to nutrient digestion and absorption, the intestinal epithelia have several other functions:

1. *Barrier and immune defense.* The intestine is exposed to a large number of potential antigens and enteric and invasive microorganisms, and it is extremely effective at preventing the entry of almost all of these agents. The intestinal mucosa also synthesizes and secretes secretory IgA.
2. *Fluid and electrolyte absorption and secretion.* The intestine absorbs ~7–8 L of fluid daily, a volume comprising dietary fluid intake (1–2 L/d) and salivary, gastric, pancreatic, biliary, and intestinal fluid (6–7 L/d). Several stimuli, especially bacteria and bacterial enterotoxins, induce fluid and electrolyte secretion that may lead to diarrhea (Chap. 160).
3. *Synthesis and secretion of several proteins.* The intestinal mucosa is a major site for the production of proteins, including apolipoproteins.
4. *Production of several bioactive amines and peptides.* The intestine is one of the largest endocrine organs in the body and produces several amines (e.g., 5-hydroxytryptophan) and peptides that serve as paracrine and hormonal mediators of intestinal function.

The small and large intestines are distinct anatomically (villi are present in the small intestine but are absent in the colon) and functionally (nutrient digestion and absorption take place in the small intestine but not in the colon). No precise anatomic characteristics separate duodenum, jejunum, and ileum, although certain nutrients are absorbed exclusively in specific areas of the small intestine. However, villous cells in the small intestine (surface epithelial cells in the colon) and crypt cells have distinct anatomic and functional characteristics. Intestinal epithelial cells are continuously renewed; new proliferating epithelial cells at the base of the crypt migrate over 48–72 h to the tip of the villus (or surface of the colon), where they exist as well-developed epithelial cells with digestive and absorptive function. This high rate of cell turnover explains the relatively rapid resolution of diarrhea and other digestive-tract side effects during chemotherapy as new cells not exposed to these toxic agents are produced. Equally important is the paradigm of separation of villous/surface cell and crypt cell functions. Digestive hydrolytic enzymes are present primarily in the brush border of villous epithelial cells. Absorptive and secretory functions are also separate: villous/surface cells are primarily, but not exclusively, the site for absorptive function, while secretory function is located in crypts of both the small and large intestines.

Nutrients, minerals, and vitamins are absorbed by one or more active-transport mechanisms. These mechanisms are energy dependent and are mediated by membrane transport proteins. These processes will result in the *net* movement of a substance against or in the absence of an electrochemical concentration gradient. Intestinal absorption of amino acids and monosaccharides (e.g., glucose) is also a specialized form of active transport—*secondary active transport*. The movement of actively transported nutrients against a concentration gradient is Na^+ dependent and is due to a Na^+ gradient across the apical membrane. The Na^+ gradient is maintained by Na^+,K^+-adenosine triphosphatase (ATPase), the so-called Na^+ pump located on the basolateral membrane, which extrudes Na^+ and maintains low intracellular [Na] as well as the Na^+ gradient across the apical membrane. As a result, active glucose absorption and glucose-stimulated Na^+ absorption require both the apical membrane transport protein SGLT1 and the basolateral Na^+,K^+-ATPase. In addition to exhibiting Na^+ for its absorption, glucose stimulates Na^+ and fluid absorption; this effect is