

There will be a sense of both pride and hope as I enter the operating room, where the transplantation surgeon will have placed the patient on the heart–lung machine. The equipment that has kept her alive for the past week will be in the hallway, being cleaned. Everyone will be focused on installing the new heart into a person who will now have a future. I will assist the surgeon in sewing in the organ. He will unclamp the aorta, fresh blood will run into the coronary arteries, and the gray tissue will turn pink. Will the heart start? Will it work? Within a minute or two, the muscle will jump to life and start beating.

Soon, the job of the 1250-lb heart–lung machine will be taken over by this little muscle. The surgeon will tell the anxious family that all is well so far. It will have been a good day in the recipient zone.

Of course, it won't be over yet in the intensive care unit — a good outcome is not guaranteed. Although the heart's recovery is likely, other organs have been damaged, and how the liver, kidneys,

and brain will function has yet to be seen. Ultimate success will require meticulous attention to hundreds of details over the next weeks and months. And how will the whole patient herself fare? There will be much to think about and little time to reflect.

But at the moment, I am in the transition zone. I sit here, in a jet quietly cruising at 500 miles per hour, 40,000 ft above a sleeping country. It is the middle of the night. Unlike the other zones, this zone does not require me to do anything, to work out any details. I can now reflect.

This is a bizarre and surreal space. I envision the piece of flesh sterily wrapped and packed in ice in the cooler at my feet. We are both in transition. I am in the middle of a major mood swing. I think of the intense sadness in the donor zone and the joy, anticipation, and hope in the recipient zone. The people in each zone are aware of and understand one another, but they are, quite rightly, concentrating on their respective jobs. All this activity requires speedy air travel, with pilots to transport the organ

and us safely from zone to zone in a time frame that will allow the heart to recover without damage. The transition zone represents the interface of medical science, medical technology, aeronautical engineering, aviation, and medical professionalism.

I glance out the window at the dark, moonless night. The density of the stars in the sky and the lights on the ground below are about the same. In the absence of a horizon, the stars and the lights blend, and it looks as if we are suspended in space. From this strange perspective, it dawns on me that although I understand scientifically how each part of this process happens, the process as a whole still fills me with awe and wonder. The way it can change a life, a family, a community remains a mystery.

In the meantime, at the center of it all, in the transition zone, the pound of muscle lies cool, totally relaxed, between jobs. If I were wise, I would do the same.

Dr. Davis is an emeritus professor of clinical surgery at the Ohio State University and a surgeon at the Heart Center, Columbus Children's Hospital — both in Columbus, Ohio.

## Causes of Chronic Diarrhea

Henry J. Binder, M.D.

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Diarrhea can be classified in several ways. It is both a symptom and a sign. As a symptom, it is whatever the patient says it is: a decrease in consistency, an increase in the number or volume of bowel movements, or any combination thereof. As a sign, diarrhea is an increase in stool weight (or volume) of more than 200 g

(or ml) per 24 hours in a person on a Western diet. The distinction between chronic and acute diarrhea is arbitrary: it is determined by duration. Diarrhea is generally considered acute when it lasts less than two or three weeks. Such diarrhea is frequently caused by an infectious agent, is usually self-limiting, and often resolves with-

out treatment. Diarrhea is categorized as chronic when it lasts more than two or three weeks. Chronic diarrhea has multiple causes. During the past three decades, studies have delineated several ion-transport mechanisms that may be disturbed in one or more diarrheal disorders. The identification of five specific con-

genital diarrheal disorders (see table) has confirmed the importance of certain ion-transport mechanisms in health and disease. The report by Wang et al. in this issue of the *Journal* (pages 270–280) implicates a new cause of congenital diarrheal disorders: the absence of enteric hormones.

Diarrhea is often classified as osmotic or secretory.<sup>1</sup> It is considered osmotic if luminal substances are responsible for the induction of the fluid secretion, and it is considered secretory if endogenous substances (often referred to as “secretagogues”) induce fluid secretion that persists even when the patient is fasting. Textbooks frequently state that one can distinguish osmotic from secretory diarrhea by determining the electrolyte concentration in the stool: if there is an osmotic gap — that is, a substantial difference between the stool osmolality and twice the concentrations of sodium and potassium in the stool — the diarrhea is osmotic, and if not, it is secretory. The assessment of stool electrolytes, however, is more useful for teaching purposes than at the bedside, because data on what constitutes a substantial osmotic gap are scant. Moreover, many diarrheal disorders, such as celiac sprue, have more than one pathogenic mechanism, some of which may be secretory and others of which may be osmotic. I find it more helpful to assess the effect of a fast on stool output: when diarrhea ceases with fasting, a dietary nutrient is likely to be the cause; if diarrhea persists unabatedly with fasting, a dietary nutrient is not likely to be the cause.

In the former case, malabsorption of carbohydrates, fats, or both is probably to blame. The most

Congenital Diarrheal Disorders.		
Syndrome	Defective Transport Mechanism	Mutated Gene
Congenital chloride diarrhea	Chloride–bicarbonate exchange	<i>DRA</i>
Glucose–galactose malabsorption	Glucose-stimulated sodium absorption	<i>SGLT1</i>
Congenital sodium diarrhea	Sodium–hydrogen exchange	<i>NHE3</i>
Congenital bile-acid diarrhea	Sodium-dependent bile-acid absorption	<i>ABAT</i>
Congenital lactase deficiency	Lactase–phlorizin hydrolase	<i>LCT</i>

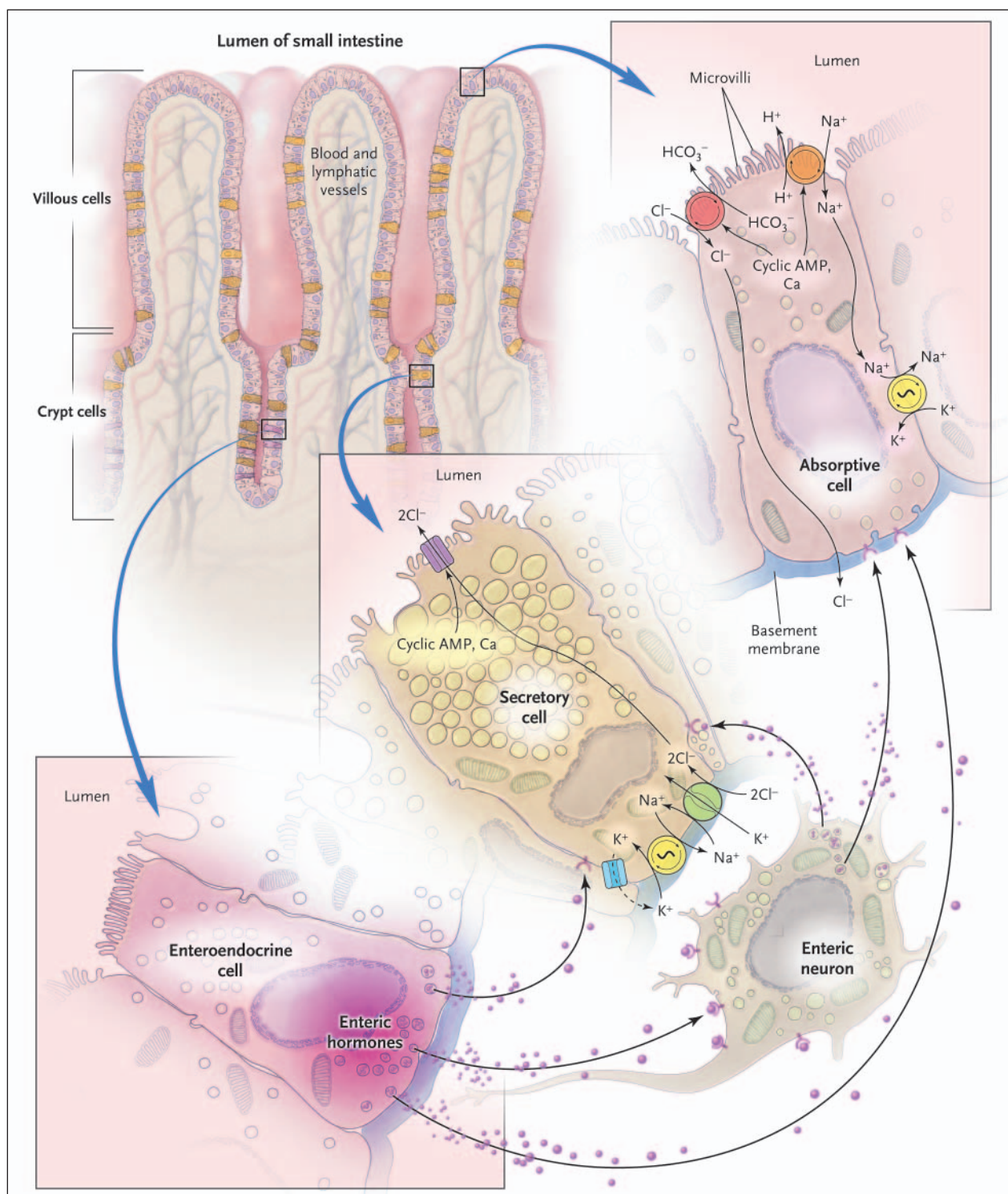
common cause of carbohydrate malabsorption is lactose intolerance, secondary to primary lactase deficiency or lactase nonpersistence. In the absence of lactase deficiency, there are several uncommon defects in carbohydrate absorption — including sucrase–isomaltase deficiency — that may be responsible. In the absence of carbohydrate malabsorption in a patient with osmotic diarrhea, it is essential to determine whether steatorrhea is present. Although diarrhea alone may be responsible for an increase in fat excretion of up to 11 g per day (normally, less than 7 g of fat per day is excreted by persons consuming 100 g of fat per day), greater rates of fat malabsorption can be explained only by one or more defects in fat digestion and absorption, which consists of five well-characterized steps.<sup>2</sup> Successful therapy will depend on the identification of the specific defect or defects in fat digestion and absorption. For example, the administration of pancreatic enzymes will reduce steatorrhea in patients with chronic pancreatitis or cystic fibrosis whose steatorrhea results from the reduced hydrolysis of dietary lipids by pancreatic lipase.

Central to almost all diarrheal disorders is the induction of fluid and electrolyte secretion in one

or more segments of the small intestine, the large intestine, or both. In secretory diarrhea, secretagogues affect ion transport in the intestine both by stimulating chloride secretion through the activation of the cystic fibrosis transmembrane regulator and by inhibiting sodium and chloride absorption. In steatorrhea, diarrhea is caused by the induction of fluid and electrolyte secretion in the colon by nonabsorbed fatty acids.

What are the mechanisms underlying the diarrhea of the patients described by Wang et al.? These patients have mutant neurogenin-3, a transcription factor that is pivotal to the development of the pancreatic beta cell and, it would now seem, the enteroendocrine cell. The salient observations include the facts that diarrhea ceased when the patients fasted and was induced when anything other than water was ingested; that the mucosa of the small intestine was essentially normal, except for the absence of enteroendocrine cells; and that there was no inflammatory component. Although diarrhea was induced by orally administered glucose, it is not known whether a glucose-tolerance test would have disclosed normal glucose absorption.

The absence of intestinal endocrine cells and enteric hormones



#### Regulation of Absorptive and Secretory Processes in the Intestine.

Epithelial cells in the small intestine originate in the crypt, have a spatial distribution along the crypt–villous axis, and then migrate to the tip of the villus, where they slough into the lumen. Secretory processes generally occur in crypt cells, whereas absorptive processes are located in villous cells. Enterioendocrine cells are sparse but are present in the crypt. Almost all diarrheal disorders are associated with net fluid secretion. This secretion is most often secondary to the stimulation of active chloride secretion and to the inhibition of active absorption of sodium and chloride (by messengers such as cyclic AMP) which involves the coupling of sodium–hydrogen exchange and chloride–bicarbonate exchange. Absorptive and secretory processes are regulated by both the enteric nervous system and enteric hormones, although little is known about the role of enteric hormones in vivo.

is likely to be central to the diarrhea in these patients; enteric hormones may increase sodium and chloride absorption or induce anion secretion. Hitherto, there has been little to implicate enteric hormones in causing diarrhea: a single patient with autoimmune polyglandular syndrome type I had a defect in cholecystokinin that presumably led to reduced pancreatic-enzyme secretion and steatorrhea.<sup>3</sup> A similar mechanism, however, could not explain the diarrhea of the patients described by Wang et al., which persisted even in the absence of dietary fat.

Overall intestinal function in-

volves the coordinated interaction of intestinal ion transport and motor activity, which are functionally linked through the enteric nervous system. Enteric hormones would presumably affect ion transport through a paracrine mechanism, either directly — by regulating absorptive processes, secretory processes, or both in intestinal epithelial cells (see figure) — or indirectly, through the enteric nervous system, which is regulated by several enteric peptides and neurotransmitters. The mechanisms that are responsible for diarrhea in patients with mutant neurogenin-3 remain unclear; their delineation should shed welcome

light on the physiology of enteric hormones.

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Dr. Binder is a professor of medicine and cellular and molecular physiology at Yale University School of Medicine, New Haven, Conn.

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