The Starved Colon—Diminished Mucosal Nutrition, Diminished Absorption, and Colitis

W. E. W. ROEDIGER

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Nutrition of colonic epithelial cells is mainly from short chain fatty acids (SCFAs) produced by bacterial fermentation in the colonic lumen. n-Butyrate contributes more carbon of oxidation to epithelial cells than glucose or glutamine from the vasculature. Incomplete starvation of colonic epithelial cells through lack of luminal SCFAs leads, in the short term, to mucosal hypoplasia with either diminished absorption or diarrhea. A chronic lack of SCFAs or complete organ starvation in conjunction with other factors leads to nutritional colitis, either "diversion colitis" or "starvation colitis." Whether predominantly diarrhea or colitis develops in mucosal malnutrition appears to depend upon the severity and duration of starvation. Ulcerative colitis may be classified as a nutritional colitis in that colonic epithelial cells are unable to utilize SCFAs reflecting epithelial starvation despite abundant SCFAs. [Key words: Short chain fatty acids; Nutritional colitis; Diversion colitis; Starvation colitis; Ulcerative colitis]

"The problem of which metabolic pathway provides energy for a particular mechanism (of intestinal absorption) has interested many but remains largely unsolved"

P. A. Sanford—1970[1]

THE MUCOSA OF the intestinal tract is unique in that it draws nutrition from both the lumen and vasculature. The manner in which contramembranal delivery and utilization of fuel is coordinated under conditions of maximal and minimal function is unclear. Regulation of cellular metabolism, in the tradition of biochemistry, is studied by rates of fuel utilization under fed and fasted conditions: such data are now available for the colonic and small intestinal mucosa. This overview highlights the numerous ramifications of colonic mucosal starvation in disease processes which hitherto have remained unexplained yet seem to have an answer in physiologic experiments.

From the Department of Surgery, Queen Elizabeth Hospital, and University of Adelaide, Woodville, Australia

Address reprint requests to Dr. Roediger: Department of Surgery, The Queen Elizabeth Hospital, Woodville, S.A. 5011, Australia.

Intestinal Epithelial Cell Nutrition

Biochemical studies have confirmed that glutamine gained from the intestinal lumen or vasculature is the main substrate sustaining small intestinal epithelial cells (enterocytes).[2,3] When luminal nutrition fails endogenous supply of glutamine from muscle catabolism or hepatic ketogenesis meet all fuel requirements of enterocytes. The colonic epithelial cells (colonocytes) are differently fueled: short chain fatty acids derived from bacterial fermentation of starch and proteins are the main source of fuel totaling about 70 percent of requirements,[4,5] which cannot be easily replaced when the lumenal supply of fuel fails except from the less efficient and less abundant ketone bodies in the vasculature.[4,6] The points to be made are that starvational fuel supply to colonocytes and enterocytes are different and that lumenal depravation will exert the greatest toll from cellular efficiency of coloncytes rather than enterocytes.[7] These points derived from observations made with isolated epithelial cells have been confirmed *in vivo* in the intact mucosa

of the colon of starved animals[8] and after parenteral nutrition.[9]

Short Chain Fatty Acids and Colonic Absorption

Short chain fatty acids have received scientific scrutiny according to their perceived biological advantage or disadvantage to humans. They were first observed in human stool in 1878[10] and considered by pediatricians as early as 1912[11,12] to enhance bowel motility and secretion, a view now being revived.[13] By 1929 diet was known to influence levels of short chain fatty acids in the colon[14] and the absorption from the animal colon established in 1944.[15] Only in the last 10 years was their absorption in humans and metabolism by the mucosa of the human colon shown.[16–18] Most of the CO_2 generated by colonocytes of humans is from n-butyrate, which also acts as the major nonendocrine regulator of sodium absorption in the colon[19] (Fig. 1). Agents that either decrease or increase CO_2 production from n-butyrate to a similar degree increase or decrease sodium absorption in the colon[6,19] (Table 1). CO_2 in colonic epithelial cells has been shown to be a major regulator of sodium absorption at the membrane level.[21] In almost all experimental animals studied *in vivo* do short chain fatty acids have a stimulatory effect on absorption of sodium though not all *in vitro* experiments have confirmed this finding.[5]

Types of Colonic Starvation and Diarrhea

Mucosal starvation in the colon can be complete or incomplete, the former reflecting deprivation from the lumen and vasculature and the latter depravation from one side only but usually luminal starvation occurs more readily. Several conditions that produce either type of mucosal starvation are associated with a diminished capacity to absorb ions or even with diarrhea[22–28] (Table 2). The first objective correlation of diminished levels of luminal short chain fatty acids and diarrhea was reported in 1974 by Leegwater *et al.* who observed that a five-fold reduction of cecal short chain fatty acids was associated with diarrhea.[29] Starving rats for 48 hours reduces the level of fecal short chain fatty acids from 209 mM to 50 mM[30] and starvation of 72 hour renders the colonic mucosa of the rat into a secretory epithelium.[22] Rigorously excluding short chain fatty acids from the colon fashioned into Thiry-Vella loops converts the colonic mucosa from an absorptive to a secretory epithelium.[26] Diminished absorption in Thiry-Vella loops is associated with a diminished capacity to oxidize short chain fatty acids.[6,31] Older studies of colonic Thiry fistula in which short chain fatty acids were not excluded did not show diminished absorption from the colon.[32] In general, however, colonocytes from starved rats have a reduced capacity to oxidize short chain fatty acids and other fuels[31] to CO_2, a factor that controls absorption (Table 1) (Fig. 1).

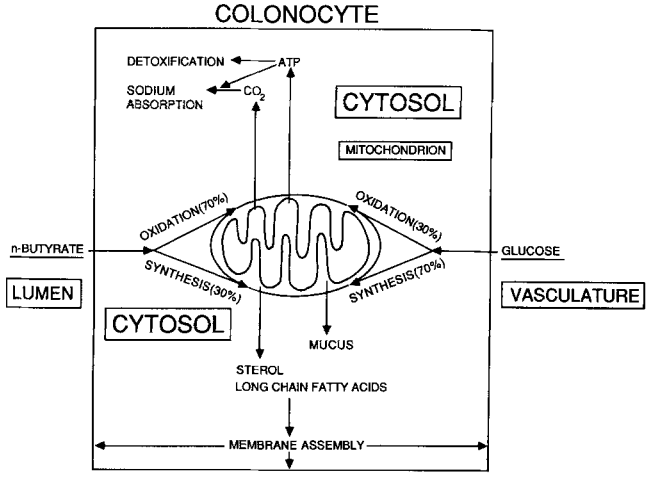

FIG. 1. Oxidative and synthetic contribution of n-butyrate/glucose to nutrition of colonocytes related to functions of sodium absorption, detoxification, and lipogenesis.

TABLE 1. *Selective Alteration of CO^2 Production from Short Chain Fatty Acid in Isolated Colonic Epithelial Cells by Nitrite and Sulfite Ions. Oxidation of Glucose Remained Unaltered*

Addition of Ions	Metabolic Effect on Fatty Acid Oxidation in Isolated Colonocytes	Absorptive Changes in Colonic Loops
Sodium nitrite (5mM)	Increased CO_2 production by 50 percent[6]	Increased sodium absorption by 50 percent[6]
Sodium sulfite (5mM)	Diminish CO_2 production by 70 percent[20]	Diminished sodium absorption by 88 percent[19]

TABLE 2. *Diminished Luminal and Vascular Nutrition of the Colonic Mucosa and Functional Effect on Absorption*

Type of Starvation	Species	Condition	Functional Effect
Complete Luminal	Animal	72h Starvation Malnutrition	Diarrhea[22] Absorption decreased[24]
Vascular	Human	Famine/malnutrition	Diarrhea[23]
Incomplete Luminal only	Animal	Germ free	Diarrhea[25]
		Thiry-Vella loops	Absorption decreased/ secretion[26]
	Human	Diverted colon	Absorption[27] decreased
		Gut sterilization	Diarrhea[28]

Famine Diarrhea

The severest form of starvation in humans occurs during famines caused by gross social upheaval.[33] All famines recorded have been associated with severe diarrhea[23] (Table 3). Medical observations are rarely made during famines but the Danish prisoners of war[23] and soldiers during the siege of Kut,[34] which included doctors, had diarrhea that could not be attributed to cholera. A lack of mucosal nutrition may have been a cause for the diarrhea. A feature of famine diarrhea, pointed out by Thaysen and Thaysen,[23] is that rapid refeeding worsens the diarrhea no doubt as the absorptive capacity of the grossly malnourished mucosa is impaired.[35] Once the initial worsening of famine diarrhea is overcome further diarrhea is stemmed by intake of food.

Insufficient Colonic Mucosa or Insufficient Short Chain Fatty Acids?

The generation of short chain fatty acids in the colon requires a reservoir capacity for adequate fermentation to proceed. A length of 10 to 15 cm of colon is inadequate for sufficient levels of short chain fatty acids to be reached,[36] while continent ileostomy pouches of that length of ileum permit generation of short chain fatty acids.[37] A negative relationship between the length of colon and lumenal short chain fatty acids was shown by Cummings *et al.*[38]: the shorter the colon the less short chain fatty acids were generated. There is no doubt that much of the salvage capacity of the colon depends on absorption of sodium stimulated by short chain fatty acids provided that sufficient surface area of colon and sufficient short chain fatty acids are present in the colon.

Diversion Colitis and Famine Colitis

Diversion colitis was first described by Glotzer *et al.*[39] in 1981 as a form of colitis observed in the defunctioned distal colon: the colitis cleared when the fecal stream was reinstated. The etiology is unknown but current hypotheses are that either mucosal nutrition is diminished[40] or that the bacterial flora in the defunctioned colon may change to cause colitis.[41] Studies by Harig *et al.*[40] showed that this type of colitis was reversed by perfusion with short chain fatty acids but not sodium chloride, which lends support to the view that mucosal nutrition plays a part in diversion colitis.[42] It is noteworthy that famine colitis associated with diarrhea and ulceration was described for the first time in 1872.[23] In the siege of Kut those patients that died from starvation had "mild catarrhal inflammation (of the colon) or widespread destruction of the mucosa."[34] Colitis was also observed during starvation in World War II.[23] Colitis of starvation in experimental animals was described in 1901,[43] but does not appear to have been studied further in any detail.

TABLE 3. *Recorded Episodes of Famine or "Hunger" Diarrhea Between 1846–1946**

Irish "Potatoe Famine"	1846–1851
Famine in Finland	1868
Siege of Paris	1870–1871
Turkish siege of Kut	1915–1916
Famine: Central Europe during World War I	
Famine in Russia	1917–1922
Finnish war of liberation	1918
Famine in Morogoro, Tanzania	1940
World War II	1940–1945

*Collated from reference.[23] Other famines such as the Boer War (1899–1902) and the Sino-Japanese War (1937–1939) are not recorded but also manifested with hunger diarrhea.

Mucosal Nutrition in Ulcerative Colitis

Colonocytes in ulcerative colitis are marked by an inability to use short chain fatty acids despite their abundance in the colonic lumen—"a famine in the sea of plenty."[44] The block in metabolism, which is incomplete in early colitis but more complete in established colitis, is unknown. Of note is that defunctioned segments of colon involved with ulcerative colitis have been perfused with steroids but did not improve.[45,46] Short chain fatty acids were not included in these perfusions so that an element of "diversion colitis" may have clouded the therapeutic interpretations of these trials. Perfusion of the colon *in situ* having bacteria capable of generating short chain fatty acids[47] has proven of benefit in one case of ulcerative colitis. A retrial with perfusions of defunctioned colitic segments but with steroids, 5-ASA, and short chain fatty acids may possibly prove worthwhile but until the cause of the block of fatty acid metabolism is found, treatment of ulcerative colitis with short chain fatty acids remains empirical.

From Luminal Starvation to Diarrhea and Colitis—A Communal Disease Pathway?

The thesis developed in this review is that mild, moderate, or severe malnutrition of the colonic mucosa, either luminal or systemic, underlies several clinical conditions.

Short chain fatty acids[48] and fermentation of fiber[49] in health stimulate colonic epithelial cell turnover and removing short chain fatty acids from the colon leads to loss of mucosal weight[8,50] and mucosal hypoplasia.[51] Short chain fatty acids act as a differentiating agent for neoplastic colonic epithelial cells[52] and may have a similar role in the healthy mucosa as they provide acetyl-CoA and acetoacetate[53] for long

chain fatty acid synthesis (unpublished personal observation), a process essential for structural components and membranes of colonic epithelial cells (Fig. 1). No doubt starvation abrogates such synthetic function and partially accounts for loss in mucosal weight[49,50] and morphologic changes.[8]

The current proposals are that mild malnutrition leads to functional changes such as diarrhea while moderate or prolonged malnutrition leads to morphologic changes as well. The factors that convert functional changes to morphologic changes of the malnourished mucosa are not known. One explanation might be that both oxidative and synthetic functions attributed to short chain fatty acids (Fig. 1) are impaired in colonocytes afflicted with severe starvation and colitis whereas only the oxidative functions of colonocytes might be affected in the early stages of starvation where diarrhea is more common. Also unanswered is why diversion colitis is rare in the defunctioned colon and why some absorptive capacity is retained in certain cases of defunctioned colon.[32] Possible explanations are that generation of short chain fatty acids by bacteria from shed mucus and cells may be sufficient to maintain integrity of epithelial cells. Possibly the vascular nutrition in well-nourished patients is adequate to furnish the needs of a resting mucosa (Fig. 1) but not the needs of a mucosa assailed by a bacterial flora altered in the defunctioned colon.[41]

The treatment of nutritional diarrhea and nutritional colitis is to provide adequate short chain fatty acids or substrates for bacteria to generate short chain fatty acids.[7,40] Collateral evidence that provision of oral food during infective diarrhea diminishes volume of stool and fluid output[54–57] indirectly supports the view that mucosal nutrition is an important factor in the control of other malabsorptive conditions associated with inflammation in the colon. Provision of food has adequately been shown to resolve starvation diarrhea.[7,35]

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