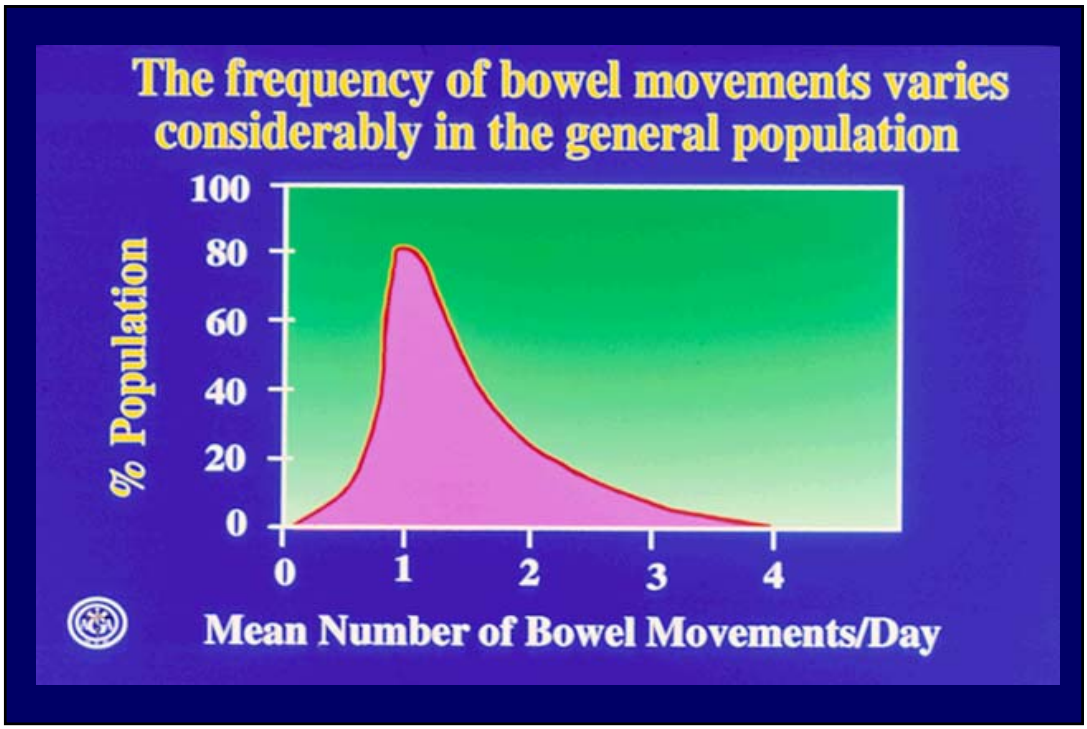
Diarrhea

Donald P. Kotler, MD



Diarrhea is a major cause of worldwide morbidity and mortality

- 3-5 Billion Episodes per Year
- 5 Million Deaths per Year, 80% under One Year of Age
- A Major Cause of Work Absenteeism
- A Major Economic Burden, Particularly in Developing Nations

Diarrhea is both a sign and symptom

A. As a symptom:

1. ↑ Frequency
2. ↑ Volume
3. ↓ Consistency

B. As a sign:

Stool weight > 150 to 200 g per 24 hr.
(stool water > 150 to 200 ml per 24 hr.)

Daily intake and endogenous secretions are efficiently absorbed by the gastrointestinal tract

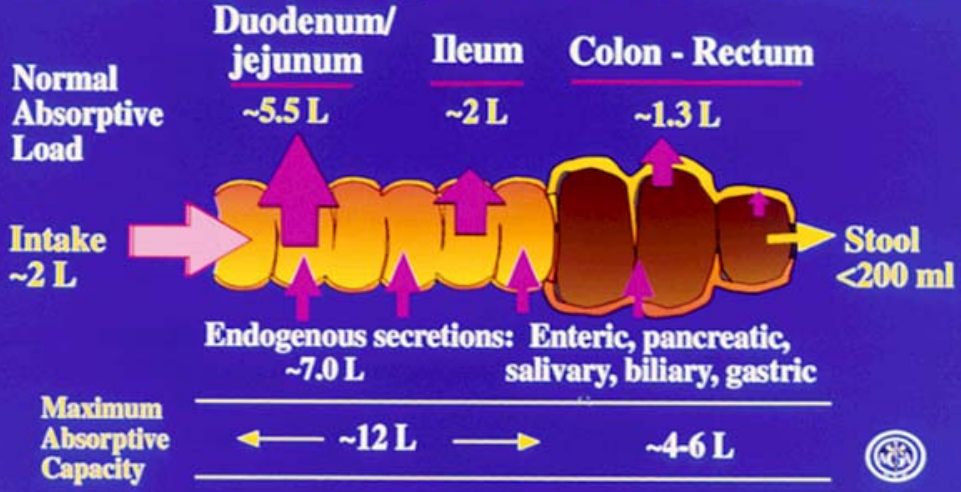
Oral intake	2000
Salivary Glands	1500
Stomach	2500
Bile	500
Pancreas	1500
Intestine	1000
	9000 Total presented to intestine
-	8800 Absorbed
Stool	200

Endogenous Secretions 7000

Net Balance 2000 - 200 = 1800

% Absorbed $\frac{8800}{9000}$ = 98%

The amount of fluid absorbed differs throughout the intestine



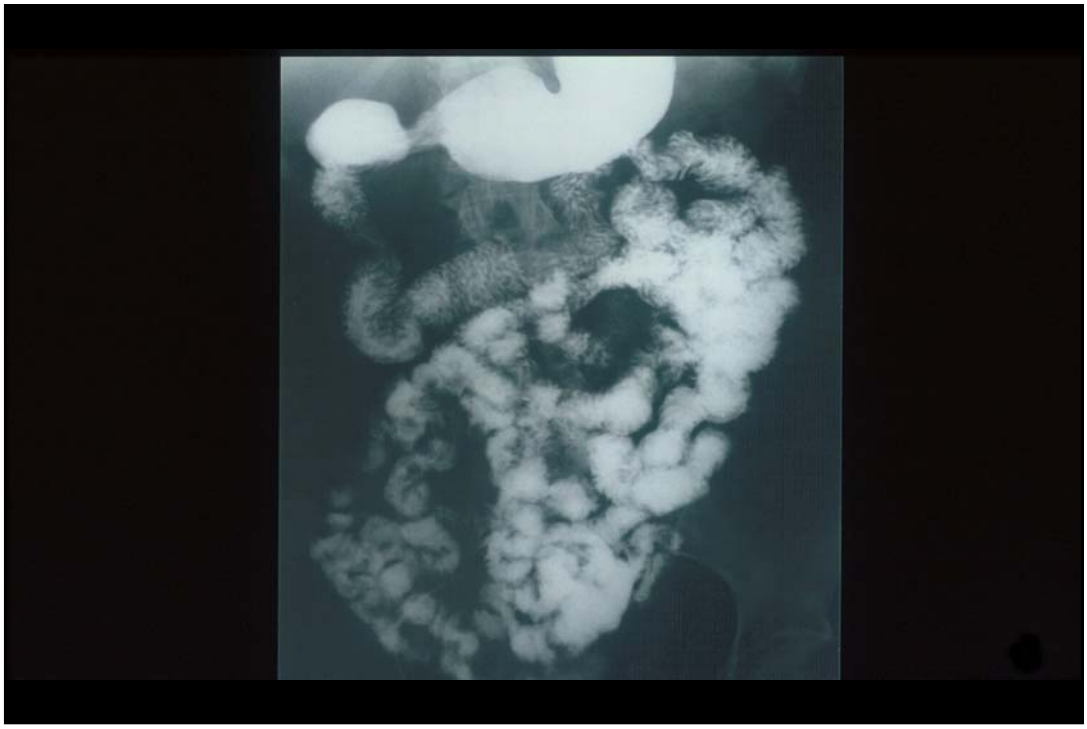
Intestinal mucosa

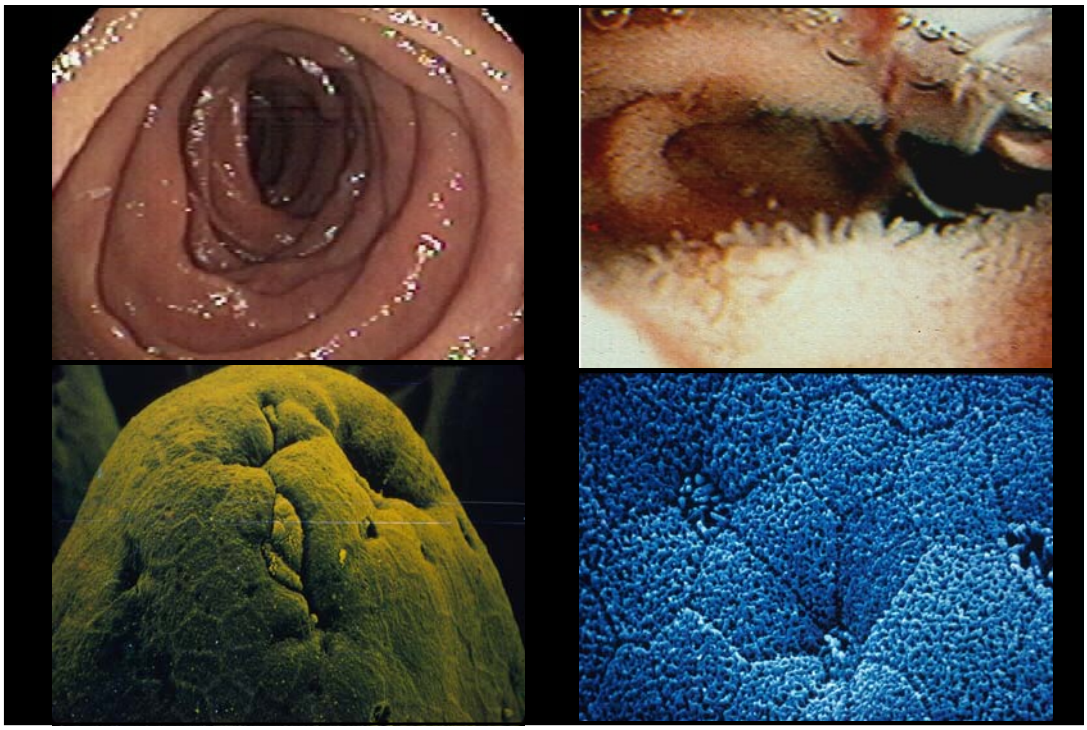
- Large surface area
- Stable ionic microenvironment
- Epithelial cell turnover
- Epithelial cell maturation
- Structural and functional adaptations
- Epithelial cell polarity

The intestine has a very large surface area for absorption

Type of Surface	Amplification Factor	Surface Area (cm^2)
Mucosal cylinder	1	3,300
Fold of Kerkring	3	10,000
Villi	10	100,000
Microvilli	20	2,000,000

Total surface area = 200 m^2
Double Tennis Court = 175 m^2





Intestinal epithelial cells are continually renewed

Villus Region

Crypt Region

Cell death and sloughing

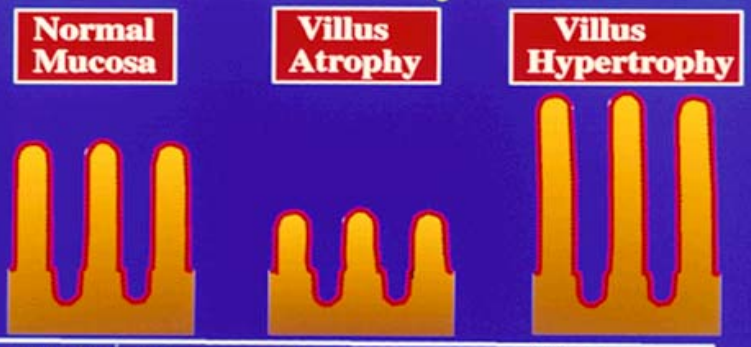
Turnover time ~ 48-72 hr

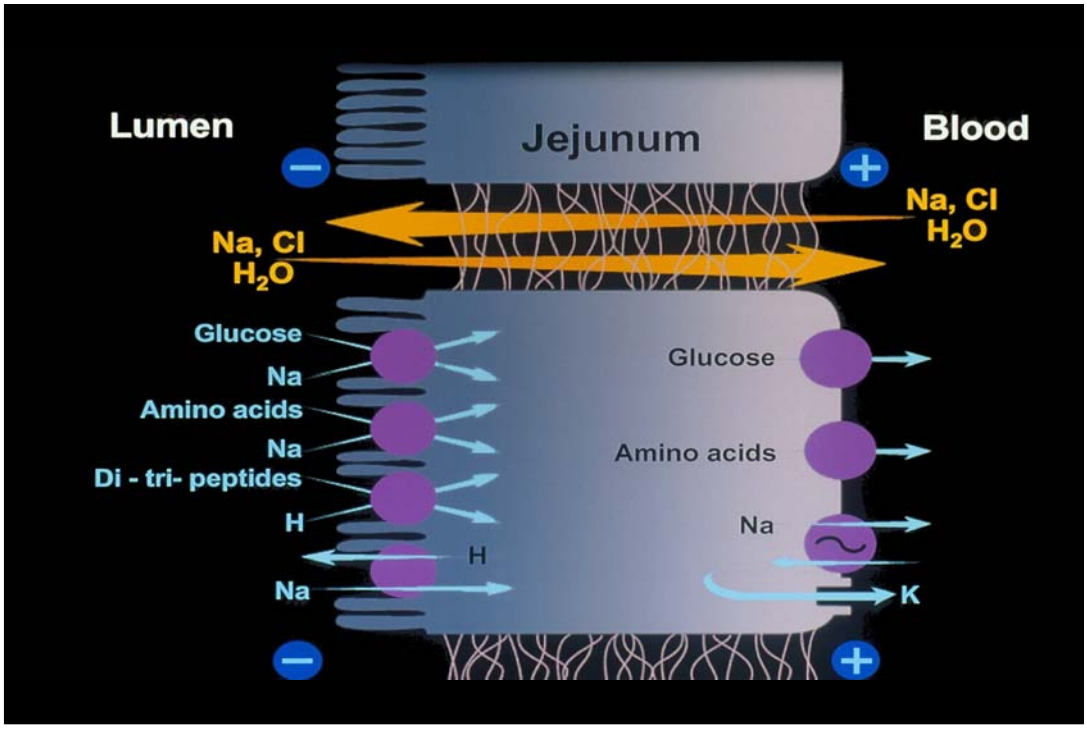
Dividing Cells

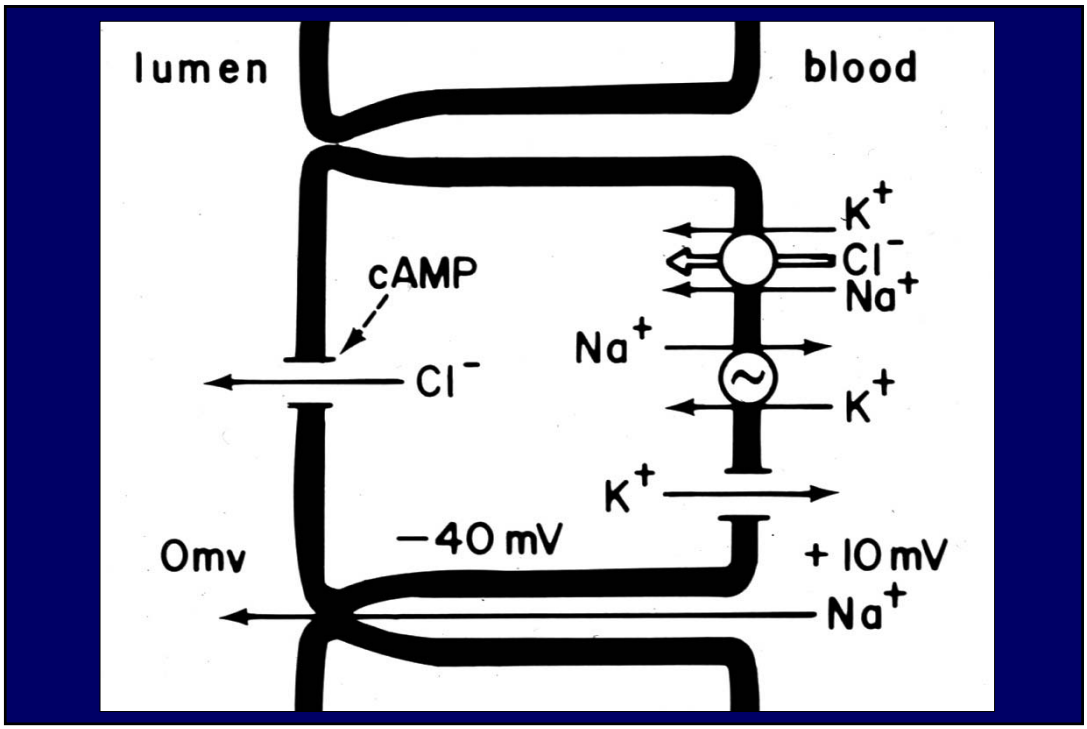
Paneth Cells

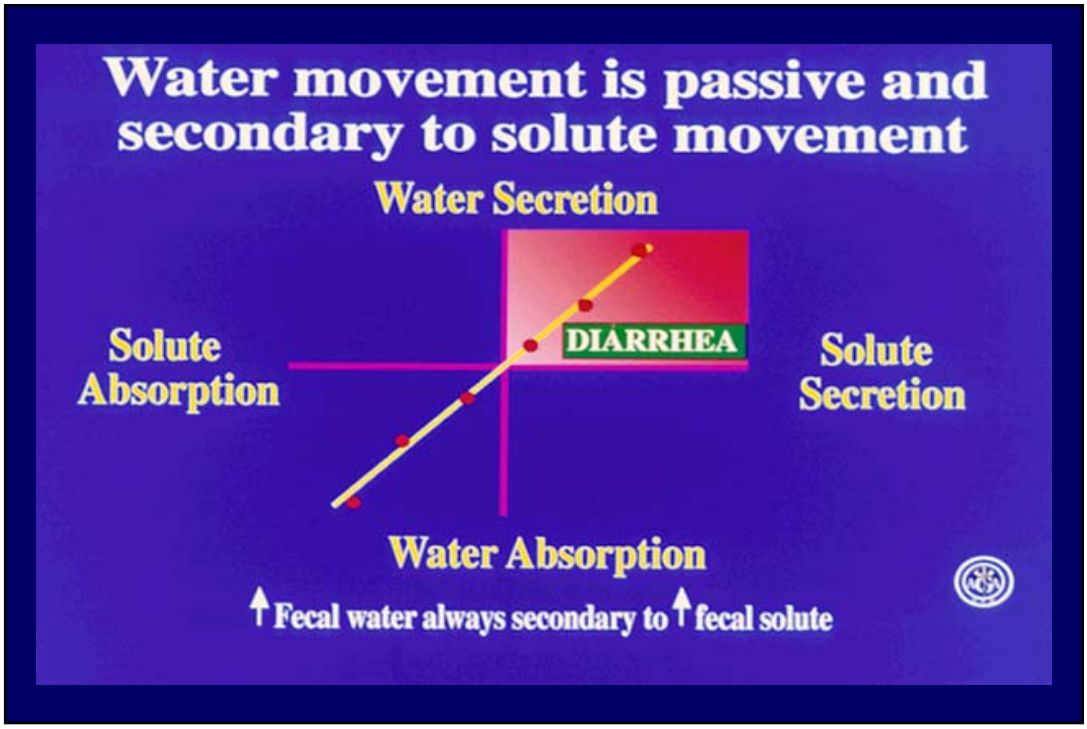
Normally: # Cells entering villus = # Cells dying

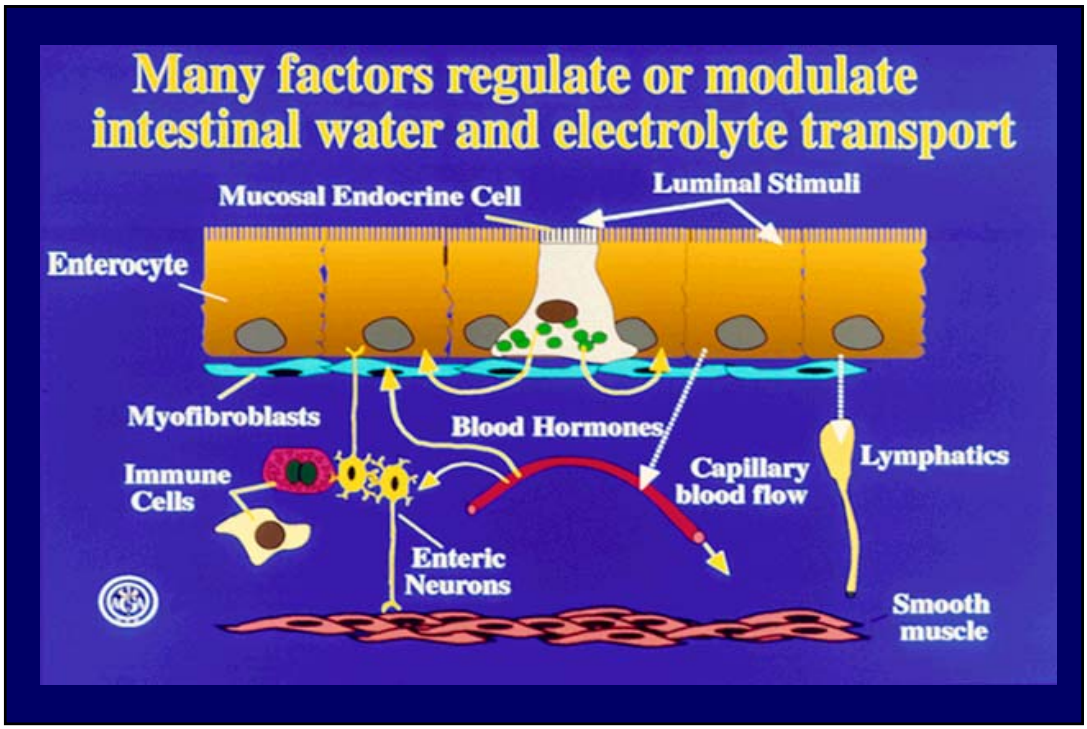
The intestinal mucosa changes with nutrient availability and disease




Lumen
Jejunum
Blood
Na, Cl
H_2O
Na, Cl
H_2O
Glucose
Na
Amino acids
Na
Di - tri- peptides
H
Na
H
Glucose
Amino acids
Na
K

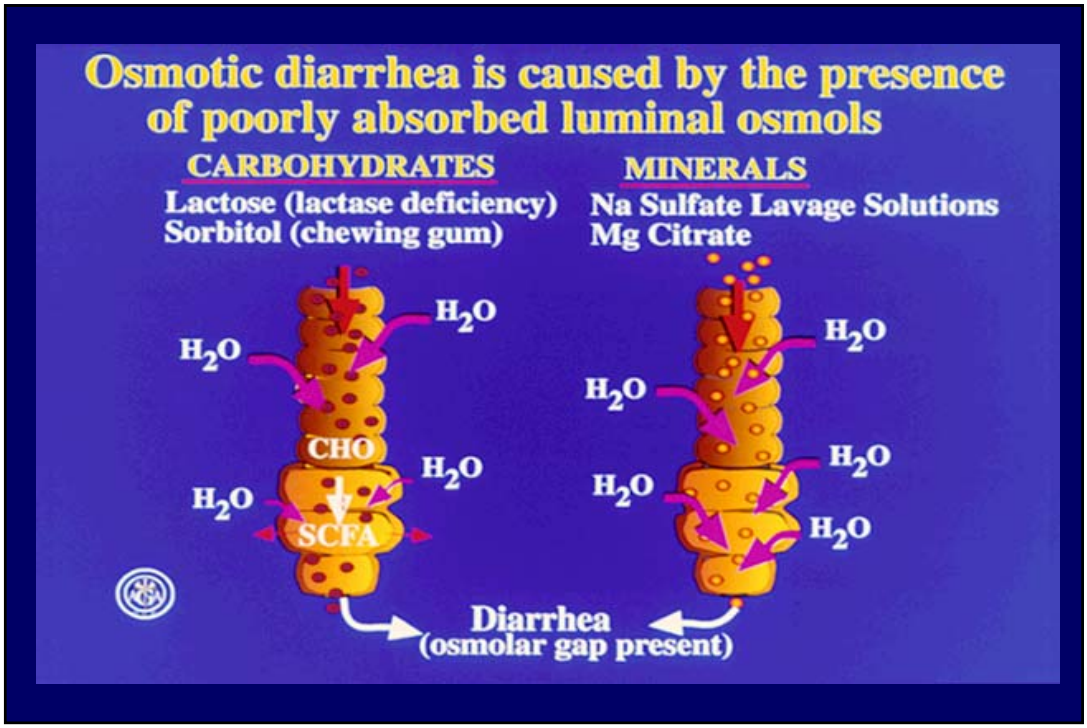

lumen
blood
cAMP
Cl^-
K^+
Cl^-
Na^+
Na^+
K^+
K^+
Omv
−40 mV
+ 10 mV
Na^+


Water movement is passive and secondary to solute movement
Water Secretion
Solute Absorption
DIARRHEA
Solute Secretion
Water Absorption
Fecal water always secondary to fecal solute


Many factors regulate or modulate intestinal water and electrolyte transport
Mucosal Endocrine Cell
Luminal Stimuli
Enterocyte
Myofibroblasts
Blood Hormones
Immune Cells
Capillary blood flow
Lymphatics
Enteric Neurons
Smooth muscle

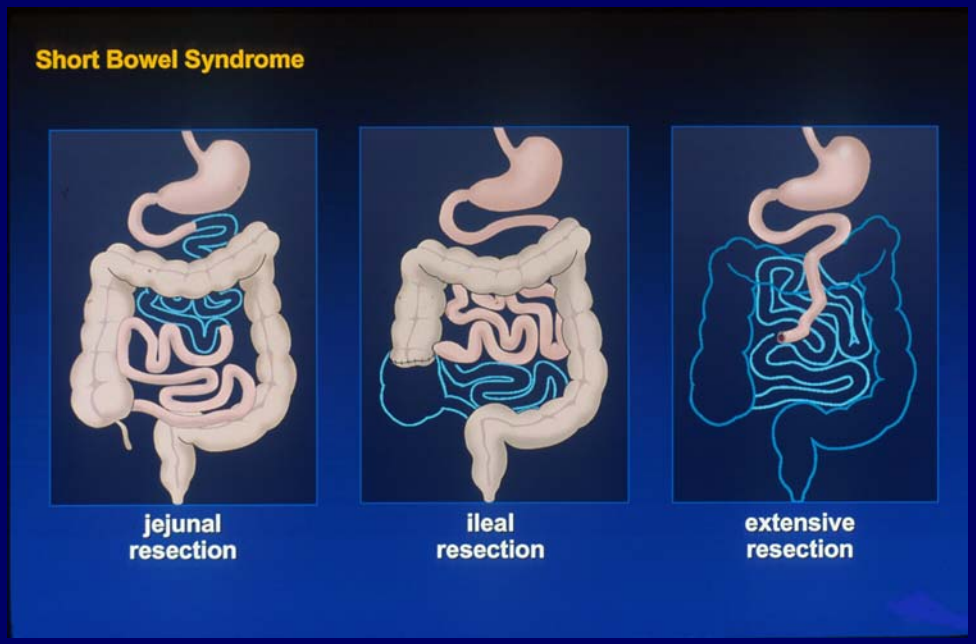
Pathophysiology of diarrhea

- Osmotic
  - decreased surface area
  - unabsorbable solute
- Secretory
  - nutrient
  - toxin
  - other mediator
- Mixed mechanisms



Pathogenic mechanisms

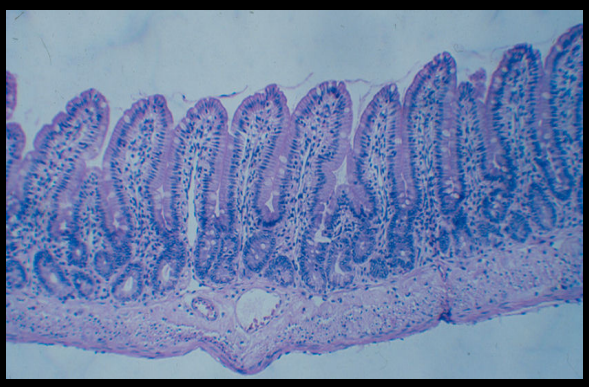
- Decreased mucosal surface area
- Ileal dysfunction
- Exudative enteropathy
- Inflammatory or tumor-associated secretagogues
- Altered motility
  - Slow transit/bacterial overgrowth
  - Rapid transit



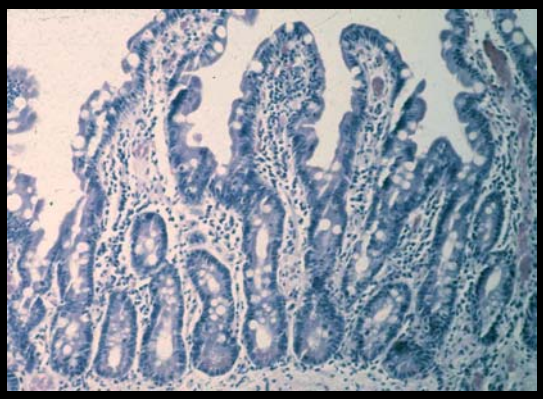
Consequences of intestinal resection

	Jejunal resection	Ileal resection
Total nutrient absorption	Normal (if <75%)	Normal
B12, bile salt absorption	Normal	Decreased
Adaptation	Normal	Decreased
Transit	Normal	Rapid

Normal mucosa



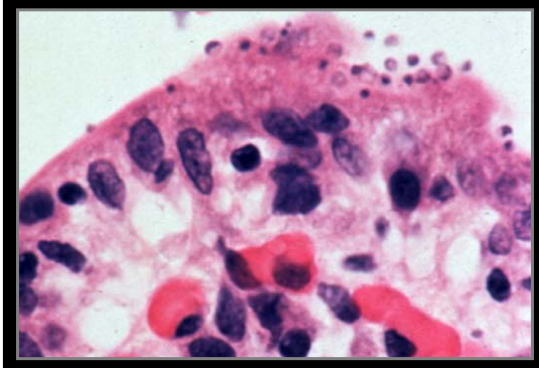
Partial villus atrophy

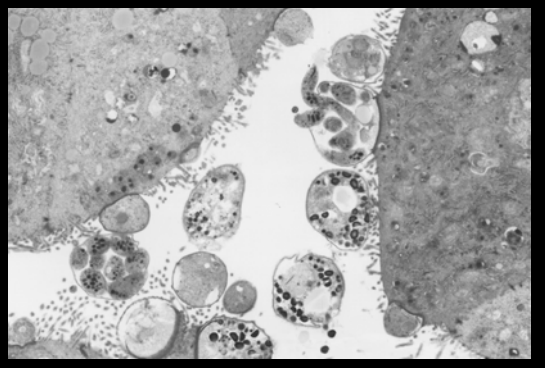


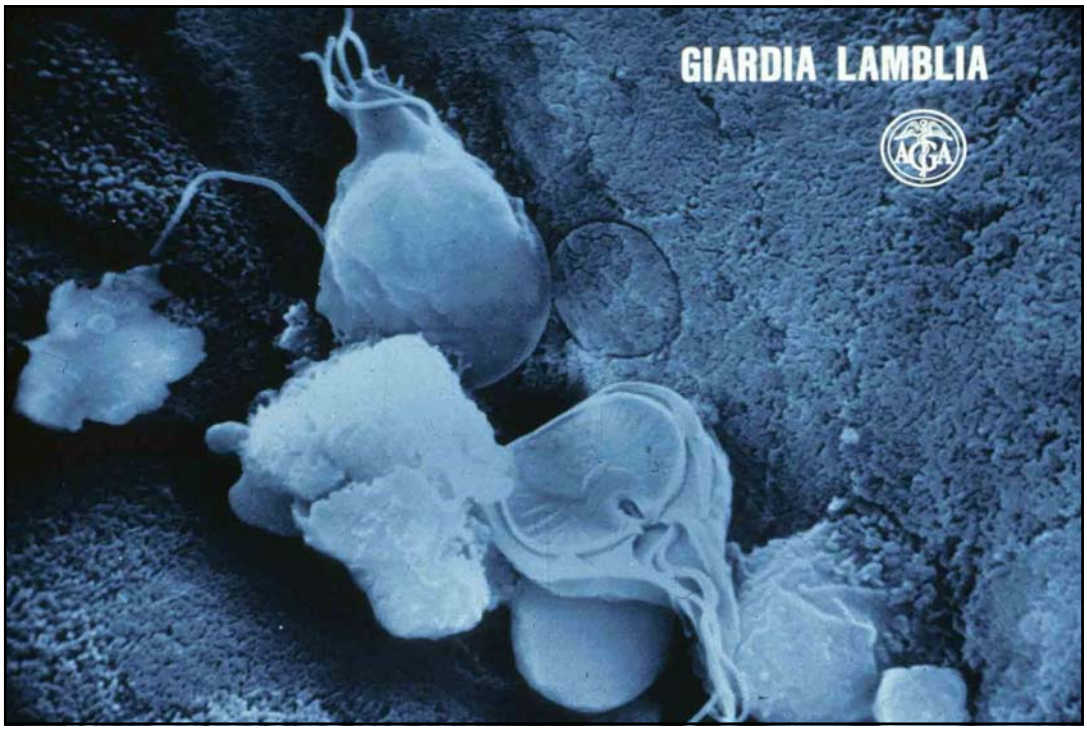
Viruses associated with gastroenteritis

- Rotaviruses
- Adenoviruses
- Caliciviruses
- Norwalk like viruses or SRSV (Small Round Structured Viruses)
- Astroviruses
- SRV (Small Round Viruses)
- Coronaviruses
- Toroviruses

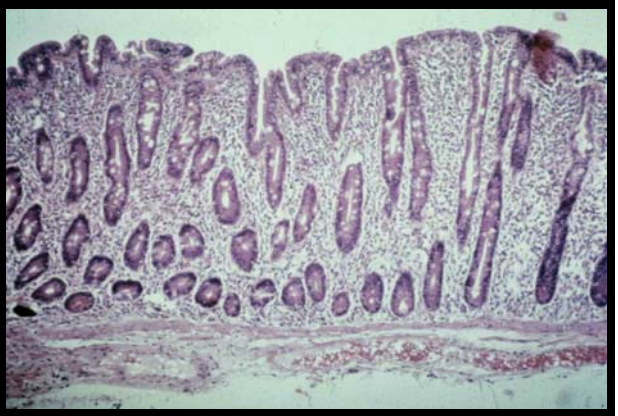
Cryptosporidiosis



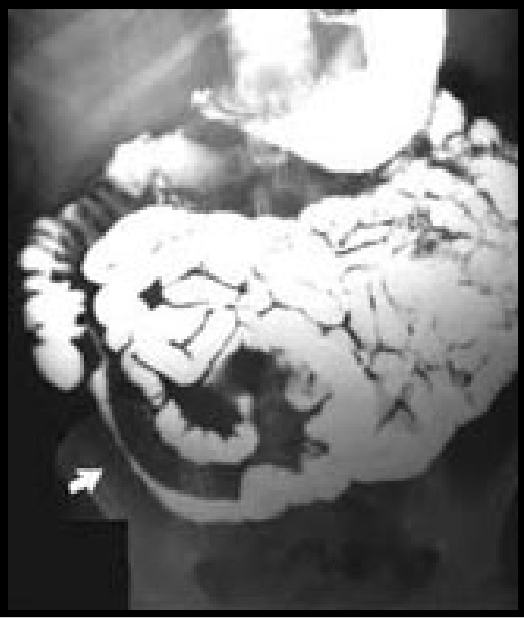




Celiac disease



Crohn's ileitis



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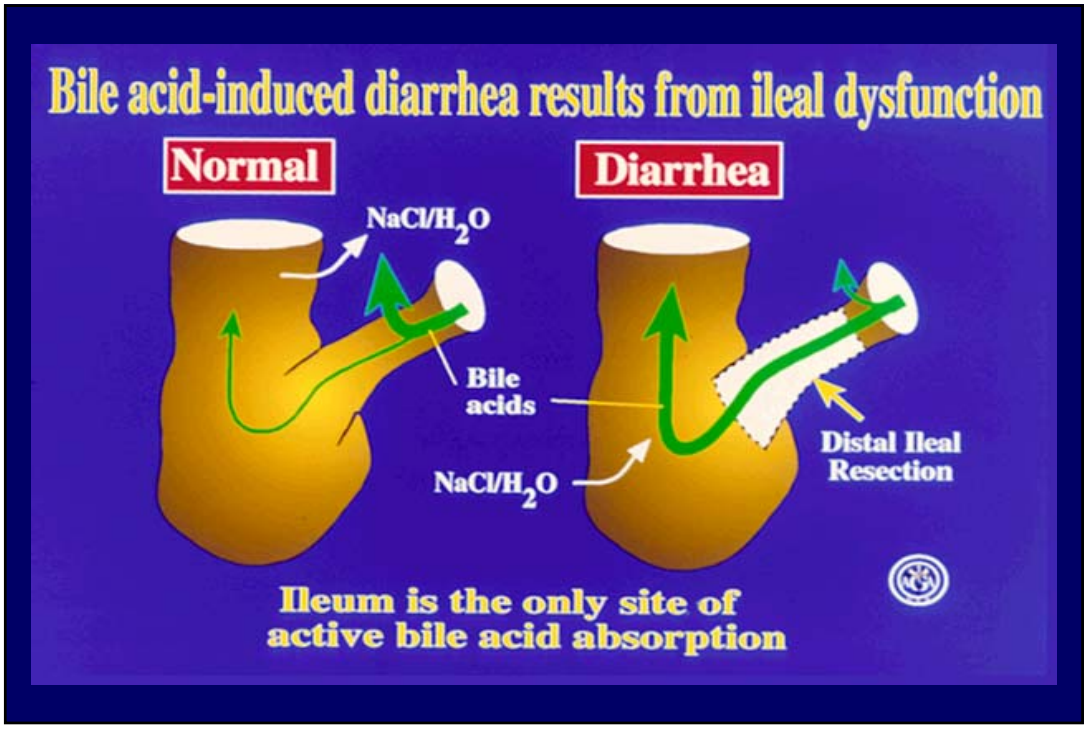
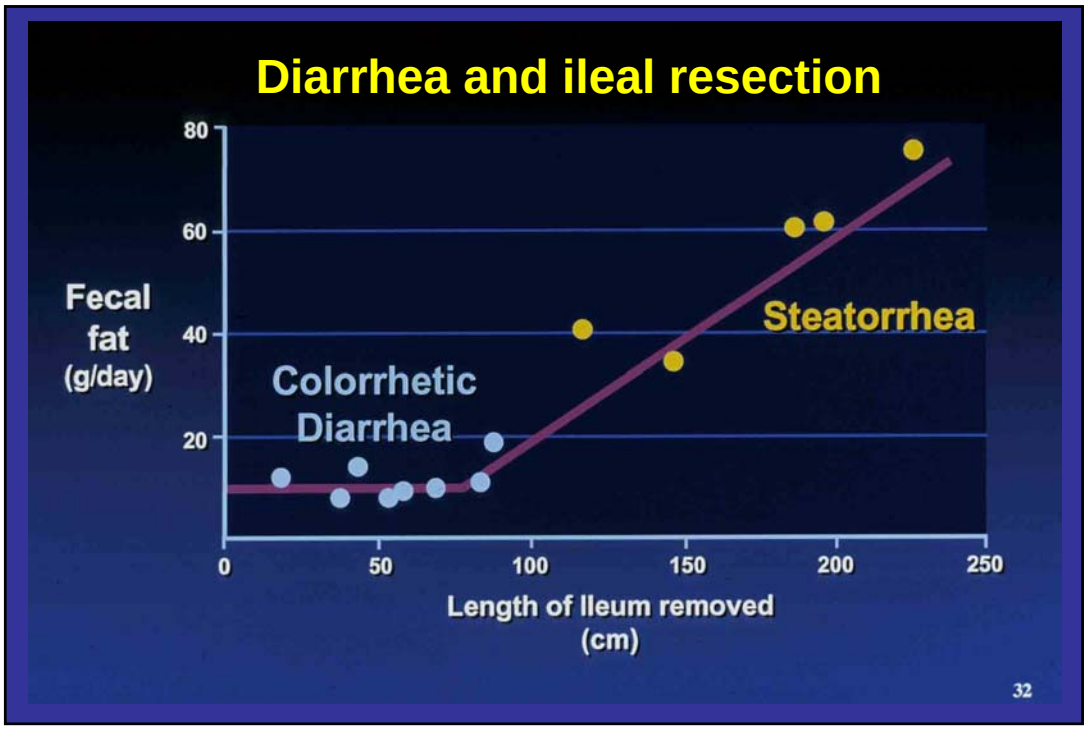

Bile acid-induced diarrhea results from ileal dysfunction
Normal
Diarrhea
NaCl/H2O
Bile acids
NaCl/H2O
Distal Ileal Resection
Ileum is the only site of active bile acid absorption


Diarrhea and ileal resection
Fecal fat (g/day)
80
60
40
20
Steatorrhea
Colorrhetic Diarrhea
0
50
100
150
200
250
Length of Ileum removed (cm)
32

Hydroxy fatty acids (OHFA) are produced from dietary lipids by enzymes of enteric bacteria

Oleic Acid $CH_3 - (CH_2)_7 - CH = CH - (CH_2)_7 - COOH$

(Dietary lipids do not contain OHFA)

↓ *Hydroxylation by Enteric Bacteria*

Hydroxy Stearic Acid $CH_3 - (CH_2)_7 - CH(OH) - CH_2 - (CH_2)_7 - COOH$

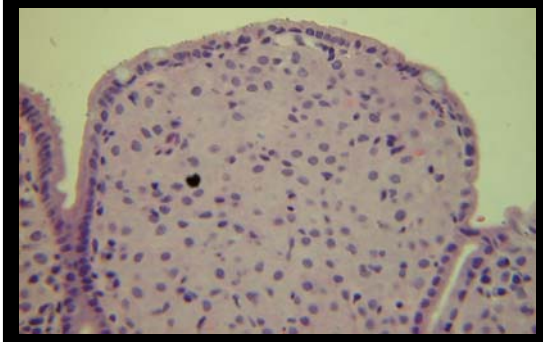
Ricinoleic acid, the active ingredient of castor oil, is an OHFA

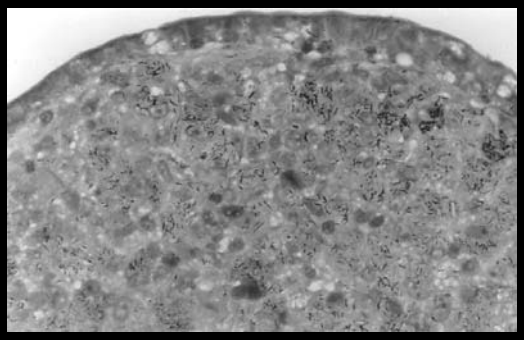
Laxatives are exogenous compounds that act similar to endogenous secretagogues

Endogenous	Exogenous
Bile Acids	Phenolphthalein
Fatty Acids	Bisacodyl
Hydroxy Stearate	Dioctyl Sodium Sulfosuccinate
	Ricinoleate (in castor oil)

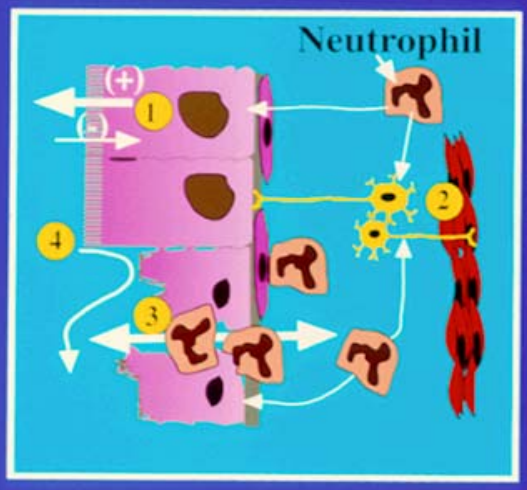
Mycobacterium avium

Mycobacterium avium





Inflammation-induced diarrhea results from several mechanisms

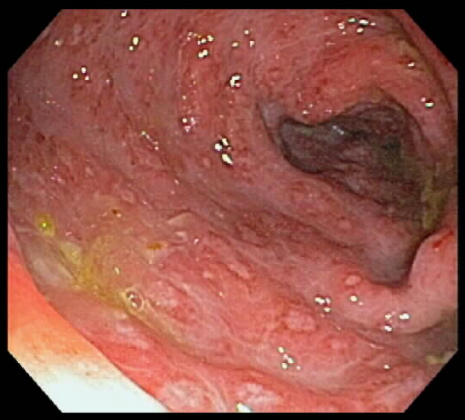


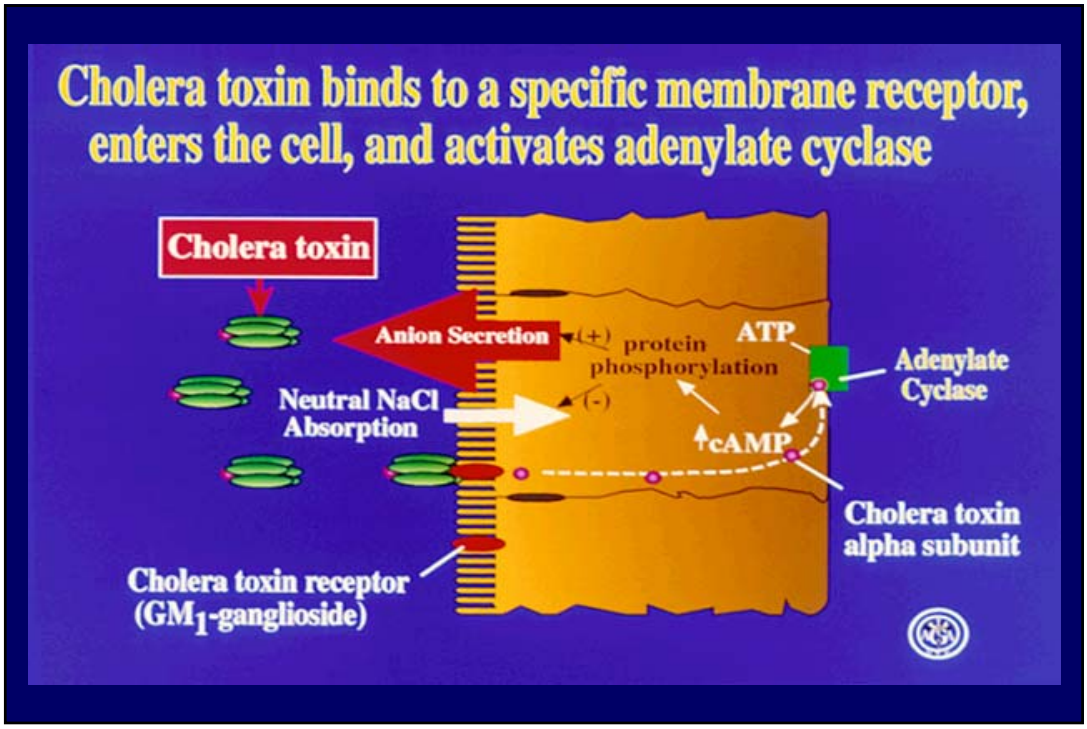
MECHANISMS

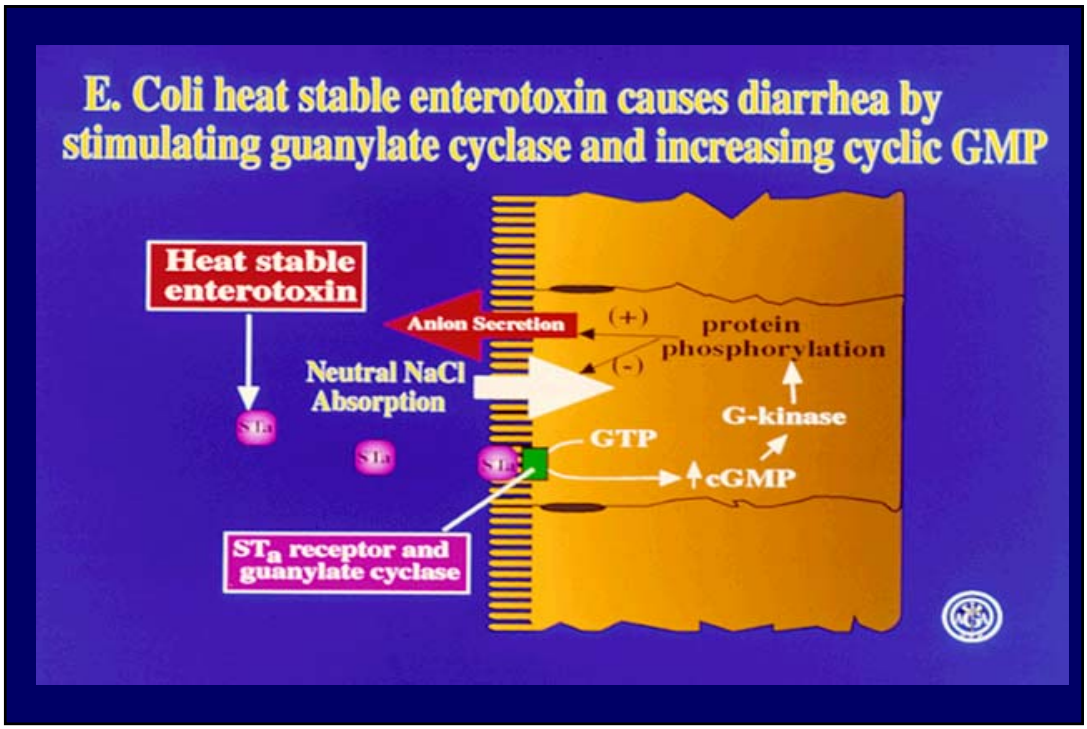
1. Stimulated secretion and inhibited absorption
2. Stimulation of enteric nerves causing propulsive contractions and stimulated secretion
3. Mucosal destruction and increased permeability
4. Nutrient maldigestion and malabsorption

Ulcerative colitis

Cytomegalovirus colitis




Cholera toxin binds to a specific membrane receptor, enters the cell, and activates adenylate cyclase
Cholera toxin
Anion Secretion
(+)
protein phosphorylation
(-)
ATP
Adenylate Cyclase
Neutral NaCl Absorption
cAMP
Cholera toxin alpha subunit
Cholera toxin receptor (GM_1-ganglioside)


E. Coli heat stable enterotoxin causes diarrhea by stimulating guanylate cyclase and increasing cyclic GMP
Heat stable enterotoxin
STa
Anion Secretion
(+)
protein phosphorylation
(-)
Neutral NaCl Absorption
G-kinase
GTP
cGMP
ST_a receptor and guanylate cyclase

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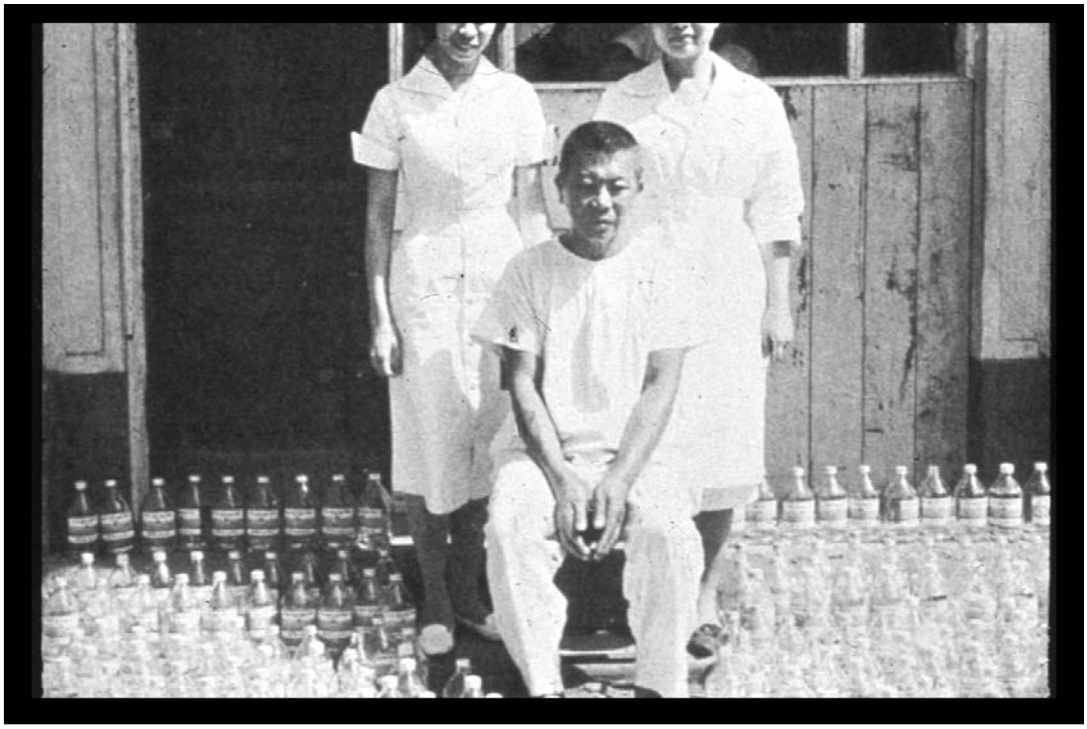
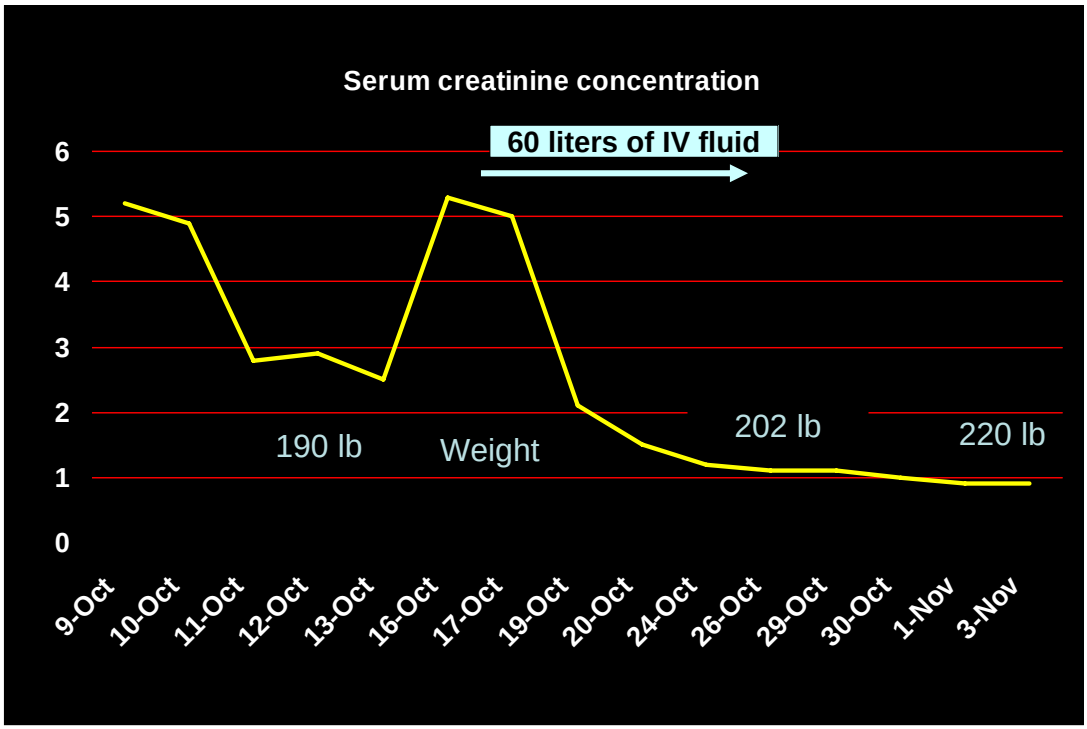
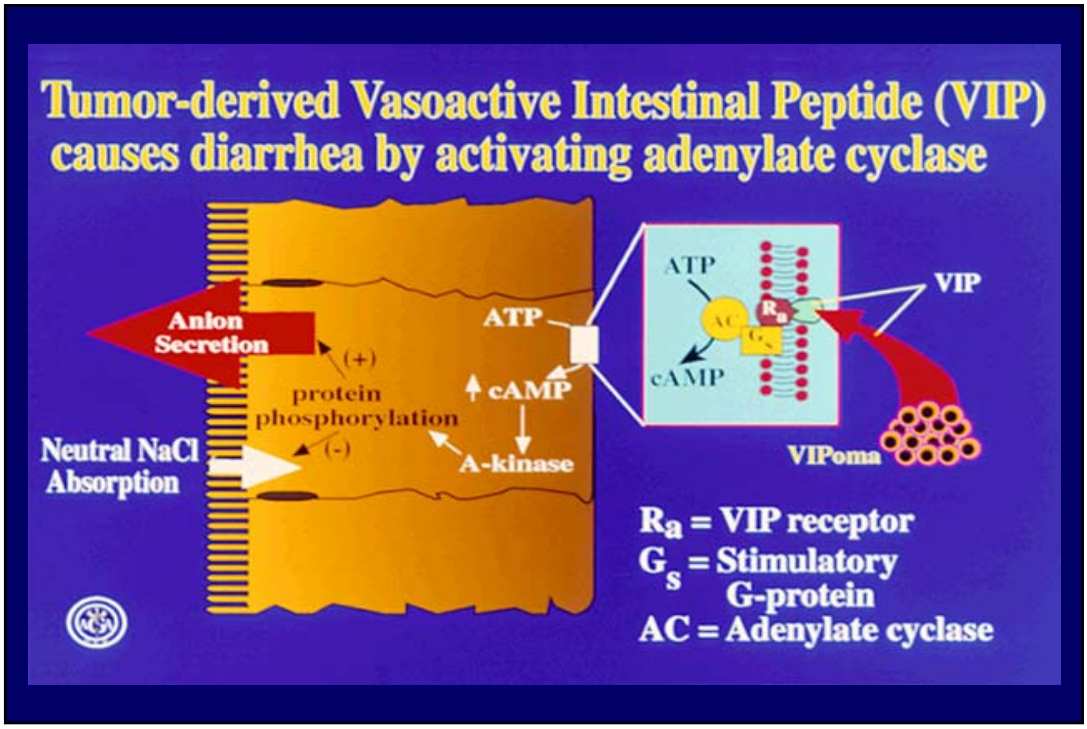
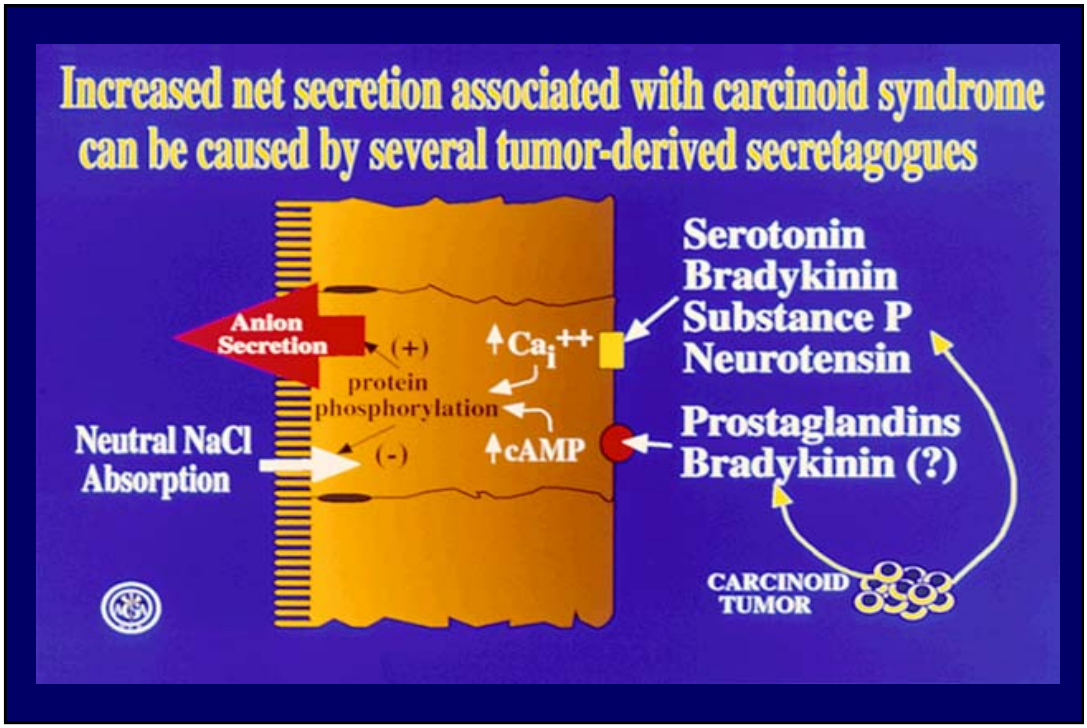



Serum creatinine concentration
60 liters of IV fluid
6
5
4
3
2
1
0
190 lb
Weight
202 lb
220 lb
9-Oct
10-Oct
11-Oct
12-Oct
13-Oct
16-Oct
17-Oct
19-Oct
20-Oct
24-Oct
26-Oct
29-Oct
30-Oct
1-Nov
3-Nov

20


Tumor-derived Vasoactive Intestinal Peptide (VIP) causes diarrhea by activating adenylate cyclase
Anion Secretion
(+)
protein phosphorylation
(-)
Neutral NaCl Absorption
ATP
cAMP
A-kinase
ATP
cAMP
VIP
VIPoma
R_a = VIP receptor
G_s = Stimulatory G-protein
AC = Adenylate cyclase


Increased net secretion associated with carcinoid syndrome can be caused by several tumor-derived secretagogues
Anion Secretion
(+)
protein phosphorylation
(-)
Neutral NaCl Absorption
Ca_i^{++}
cAMP
Serotonin
Bradykinin
Substance P
Neurotensin
Prostaglandins
Bradykinin (?)
CARCINOID TUMOR

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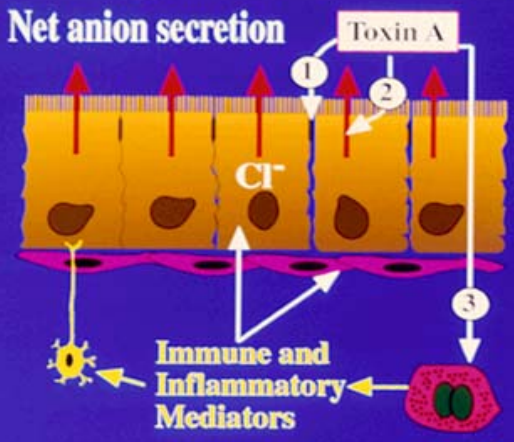
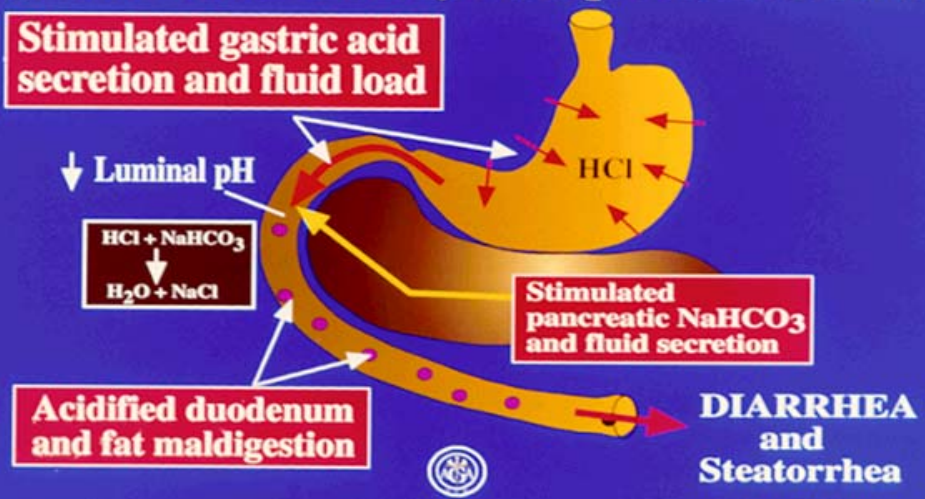
C. difficile toxin A stimulates net intestinal secretion and causes diarrhea through several mechanisms



Mechanisms of Action

1. Increased paracellular secretion
2. Stimulates anion secretion directly
3. Stimulates secretion through release of immune and inflammatory mediators

Diarrhea associated with Zollinger-Ellison Syndrome is caused by multiple mechanisms



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Practice guidelines for the management of infectious diarrhea

Guidelines - why?

- Response to need for cost effective approach to diagnosis and management
- Evidence-based approach
  - Identify uncertainties
  - Grades the quality of the evidence as much as the evidence itself
- Work in progress: needs periodic revision

Guidelines

Strength

- A - Good evidence to recommend
- B - Fair evidence to recommend
- C - Poor evidence to recommend for or against
- D - Fair evidence to recommend against
- E - Good evidence to recommend against

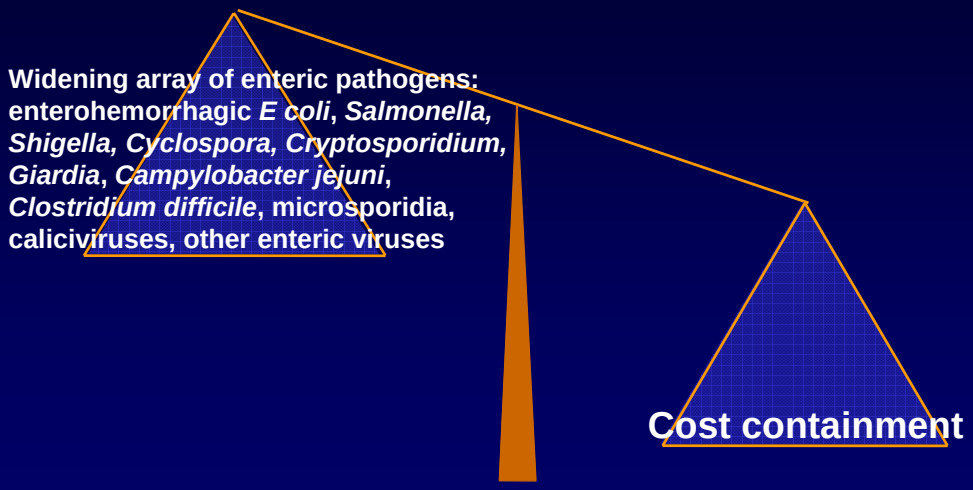
Quality

- I - At least 1 RCT
- II - At least 1 well-designed trial
  - not RCT
  - cohort, case control, dramatic uncontrolled studies
- III - Expert opinion

Diarrhea: magnitude of the problem

- Second leading cause of morbidity and mortality worldwide
- >200 million cases of diarrhea per year in the US
- 73 million physician consultations, 1.8 million hospitalizations, 3,100 deaths (mostly in the elderly)
- Other morbidities: HUS, Guillain-Barre, malnutrition
- Etiology hardly ever determined
- Etiologic diagnosis usually is too late to be of clinical use in outpatients
- Often untreated, even if diagnosis is made
- The large majority of cases are self-limited in otherwise healthy children and adults

The conflict



Etiologic diagnosis: who cares?

- Public health: passive surveillance for common source outbreaks or serious pathogens
- Bioterrorism
- Vulnerable populations
  - Extremes of life
  - Malnourished
  - Immune deficient

Other considerations

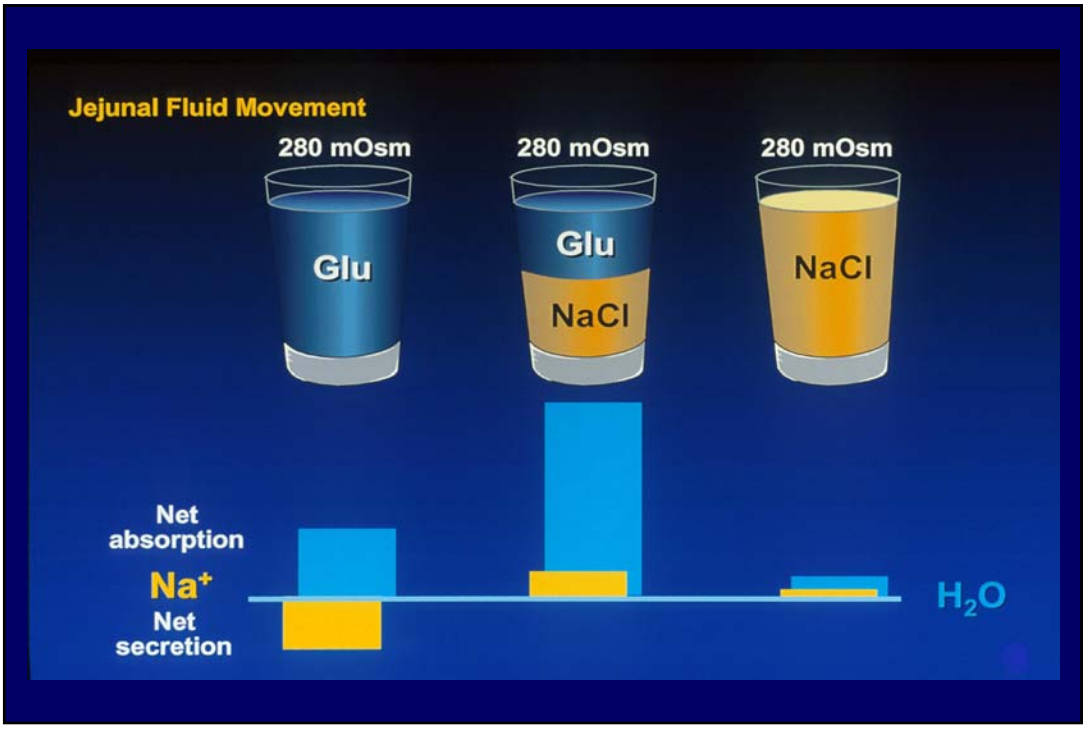
- Regional and seasonal variation in the US
- Globalization
- Infections promoted by crowding and uncertain hygeine
  - Child care
  - Schools
  - Cruise ships
- Decreased recovery with immune deficiency: HIV, immune suppressed, post-transplant, aging

Guidelines

- Oral rehydration
- Clinical and epidemiological evaluation
- Stool tests
- Antimicrobial therapy
- Antidiarrheals
- Available immunizations

Clinical recommendations

- **Initial rehydration: ORS A-I**
  - **available commercially**
  - **3.5 gm NaCl, 2.5 gm $NaHCO_3$, 1.5 gm KCl , and 20 gm glucose or glucose polymer per liter of water**
  - **glucose can be supplied as sucrose or cooked cereal flour**
  - **Na 90 mM, K 20 mM, Cl 80 mM, HCO_3 30 mM, glucose 111 mM**



Composition of oral solutions

	Na	Glucose	osmolality
WHO-ORS	90	111	310
Chicken soup	250	0	450
Sports drink	20	111	145
Ginger ale	3	500	540
Apple juice	3	690	730

Na and glucose as mM, osmolality in mosm