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M2 GI Sequence

Diarrhea and Malabsorption

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Winter 2012

University of Michigan
Medical School

Learning Objectives

- At the end of this lecture on diarrhea, students should be able to:
-
- 1. Identify and characterize the major pathophysiologic causes of diarrhea.
- 2. Discuss mechanisms responsible for secretory and osmotic diarrheas and be able to differentiate between them.
- 3. Construct a differential diagnosis for a patient with diarrhea in order of likelihood.
- 4. Identify a sequence of tests to determine the cause of diarrhea depending on the presenting symptoms.

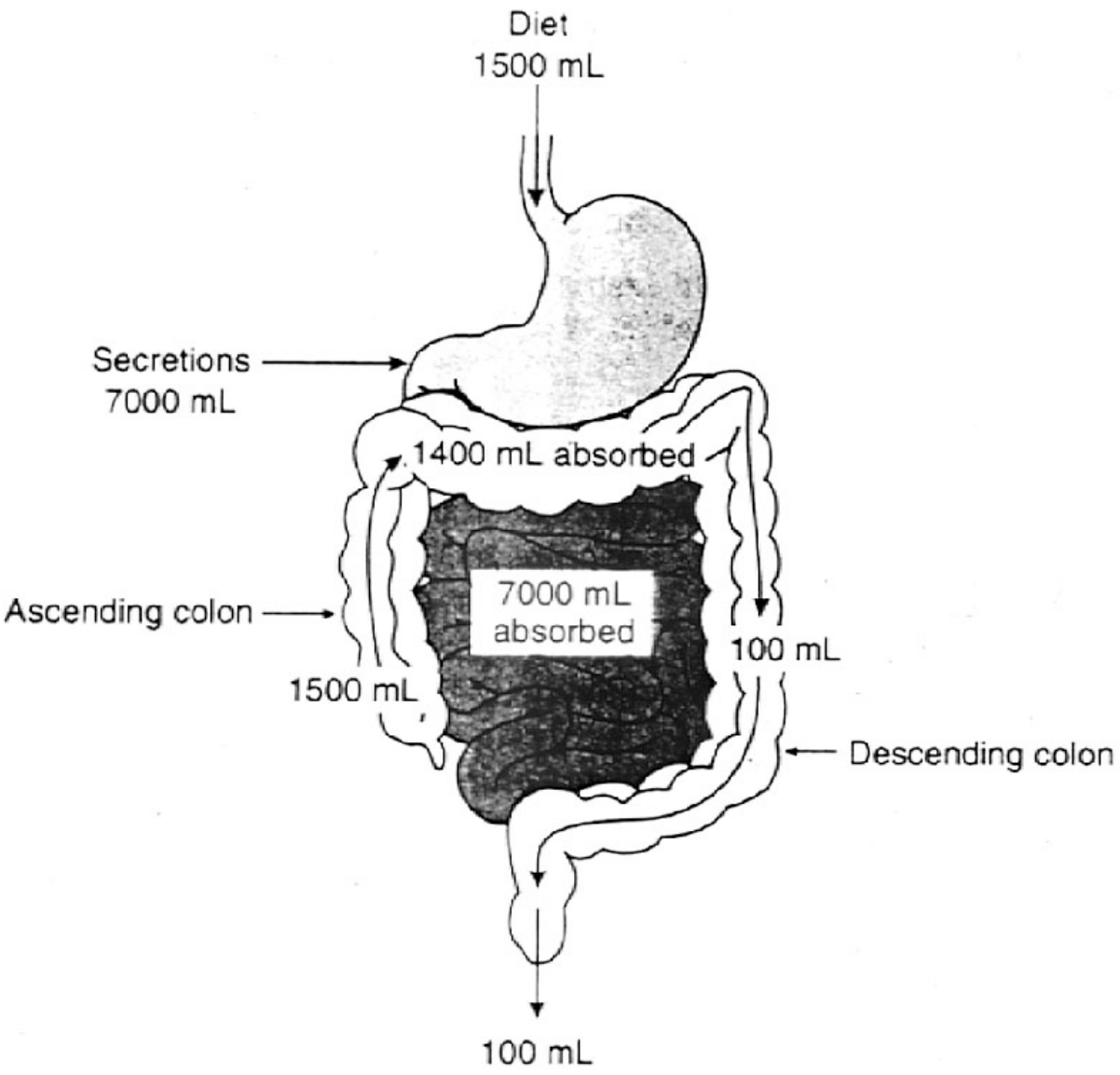
Industry Relationship Disclosures
Industry Supported Research and Outside Relationships

- None

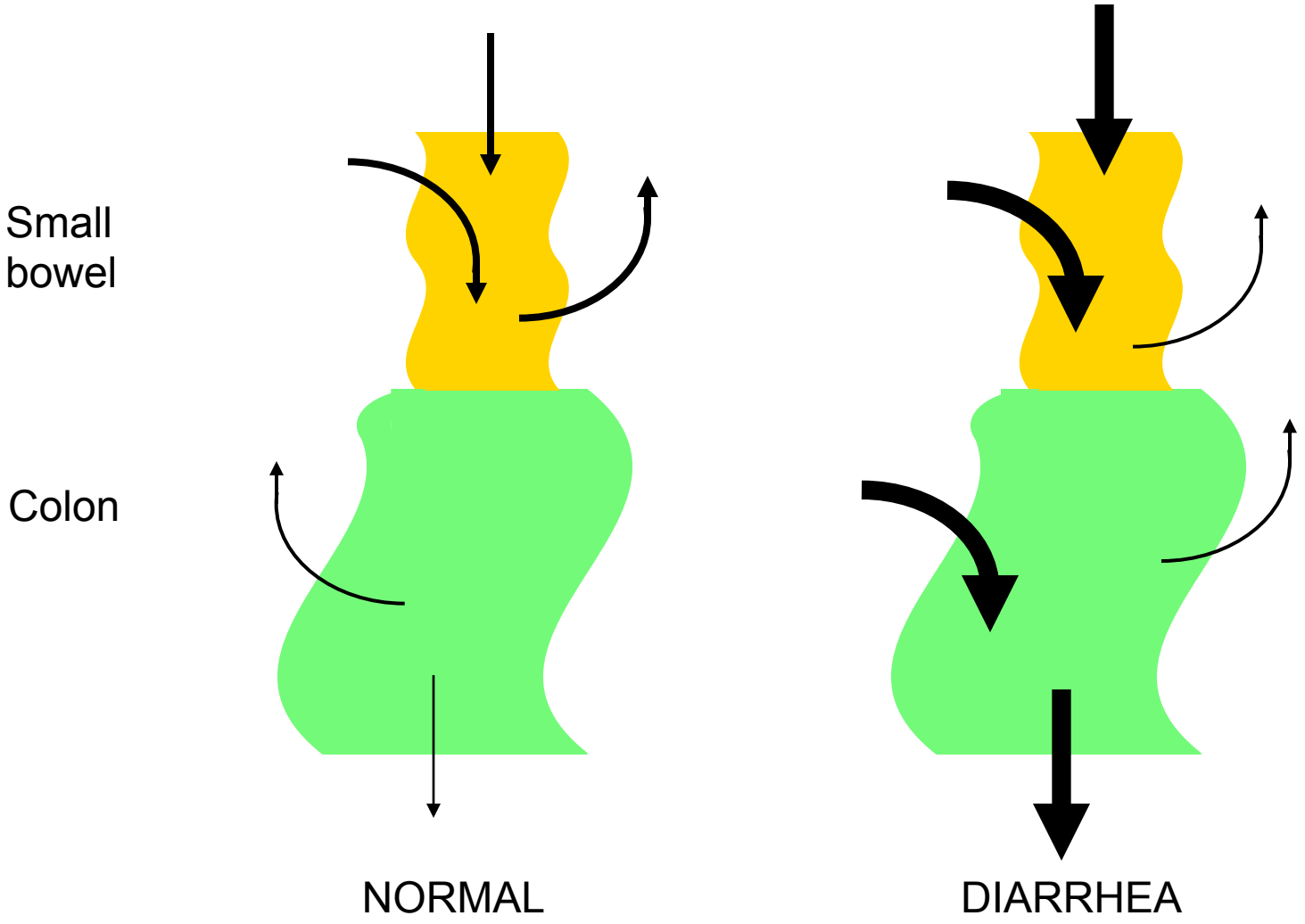
DIARRHEA

- Familiar to all of us
- Increased stool volume
  - Usually to >> 200 ml/24 hours
- Altered stool consistency
  - Increased liquidity
- Increased number of stools (not always)

Intestinal Fluid Movement (water follows solutes)



Diarrhea occurs when SB/colon solute loads exceed their absorptive capacities.



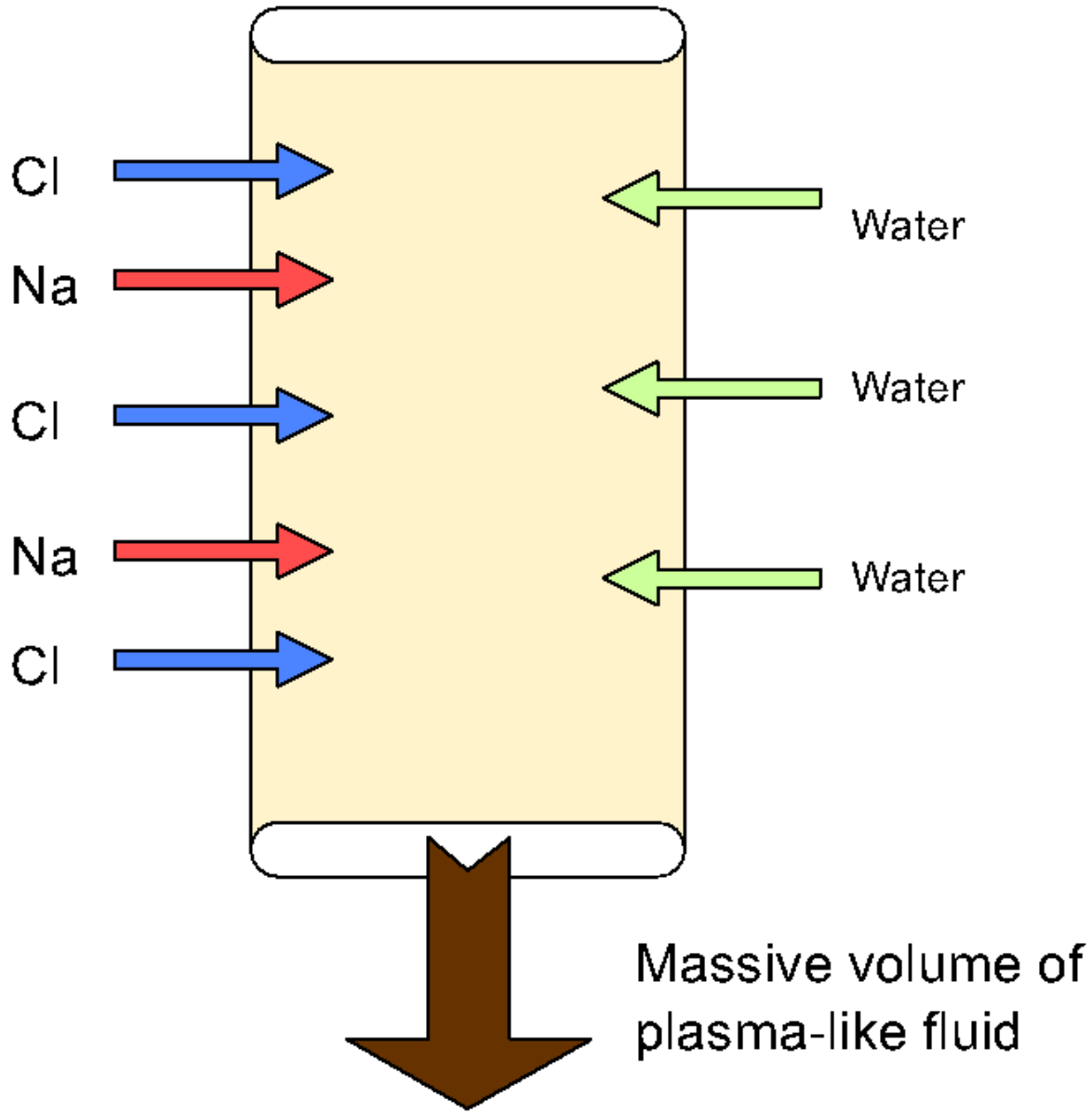
DIARRHEA - Mechanisms

- Too much input
- Not enough absorption
- Combination of both

Mechanisms of Diarrhea

- Secretory Diarrhea
- Osmotic diarrhea/malabsorption
- Increased bowel motility
- Decreased bowel surface area
- Inflammation

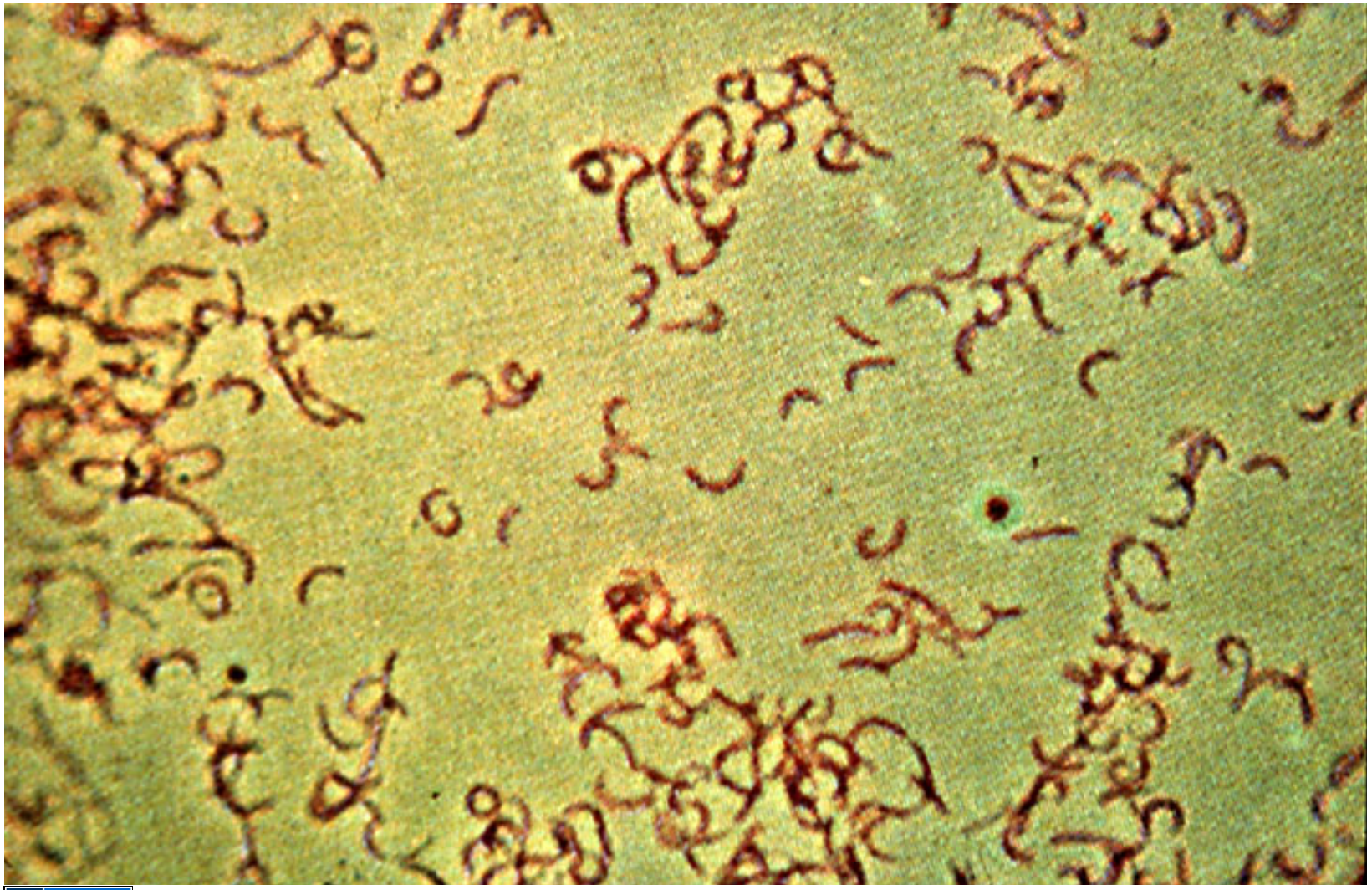
Secretory Diarrhea - A problem of excess input of electrolytes (NaCl) with water following.

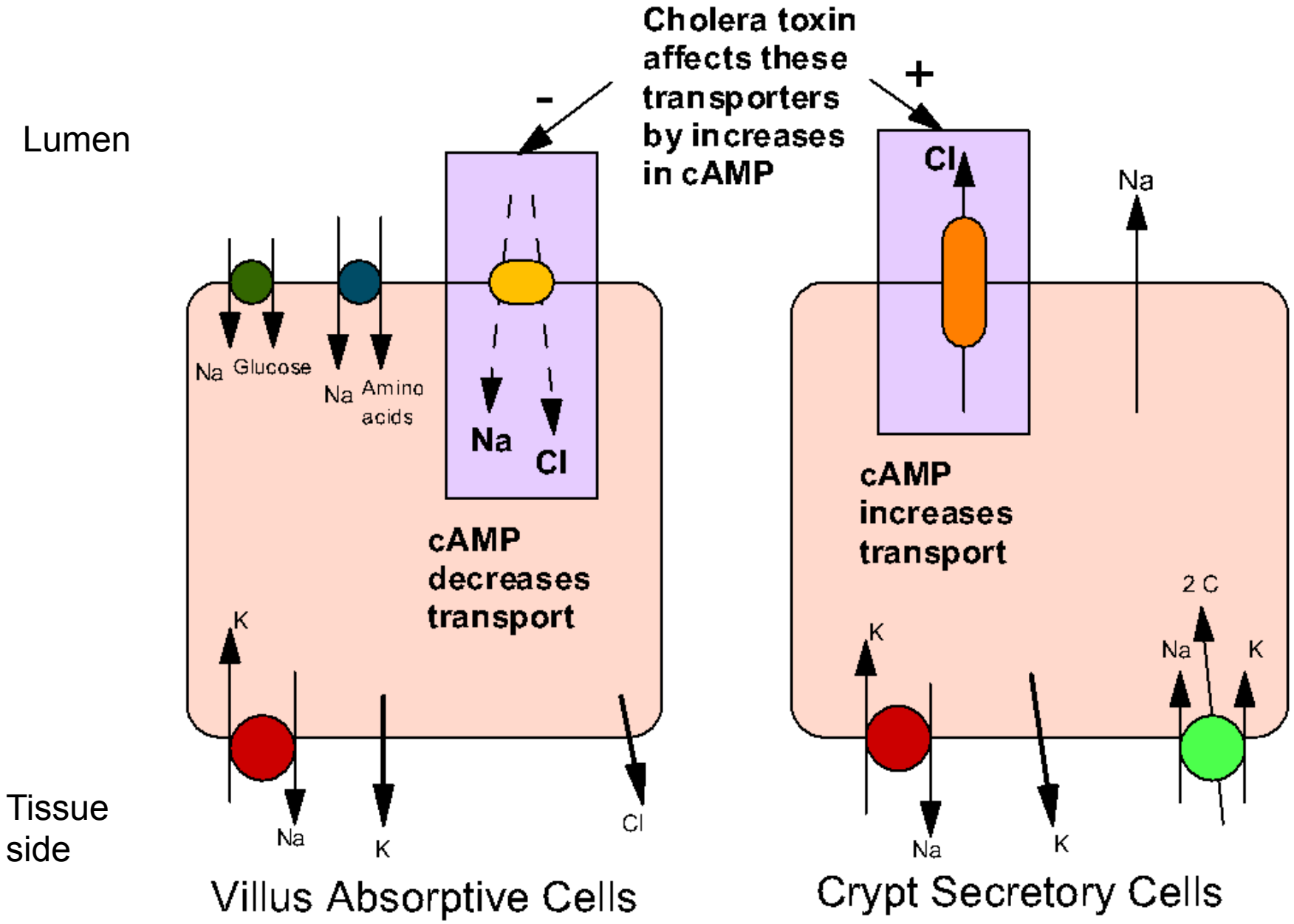


Clinical Manifestations of Secretory Diarrhea

- Large volume, watery diarrhea
- Little response to fasting
- Stool compositon is similar to plasma
  - (high NaCl)
- Dehydration and plasma electrolyte imbalance are common
- No WBC or RBC in stool

Cholera Vibrios




Lumen
Cholera toxin affects these transporters by increases in cAMP
-
+
Cl
Na
Na
Glucose
Na
Amino acids
Na
Cl
cAMP decreases transport
cAMP increases transport
K
2 C
Na
K
K
Na
K
Cl
Na
K
Tissue side
Villus Absorptive Cells
Crypt Secretory Cells

Clues to Secretory Diarrhea from Clinical Lab Studies: Fecal Electrolytes High Na in stool, blood hypokalemia

	Normal	Secretory Diarrhea
Na^+ (mEq/l)	~20-40	~80-110
K^+	~90	~40
Cl^-	~15	~60
HCO_3^-	~30	~50
Anions (SO_4^{-2}, PO_4^{-3}, fatty acids)	~85	~30
Other (Mg^{+2})	<15-20	<10
Volume (liters/day)	<1	5-10

Consequences of Large Volume Diarrhea/Secretory Diarrhea

- Dehydration due to massive loss of fluid overwhelming homeostatic mechanisms
- Electrolyte abnormalities
  - Hypokalemia (loss of K in stools)
  - Acidosis (loss of bicarbonate in stools)
  - Hyponatremia (loss of Na in stools and oral intake of free water)
- Mild malabsorption due to rapid transit and dilution of digestive enzymes

Origin of Electrolyte Abnormalities

- Dehydration: loss of 1-7 liters per day of liquid containing 80-100 mEq/liter Na
- Hyponatremia: loss of sodium and replacement orally with hypotonic fluids (water, sodas, fruit juices) in the presence of ADH (anti-diuretic hormone)
- Hypokalemia: stool K is high – may reach 40-80 mEq/liter. 2 liters of stool with 45 mEq/liter K in it is a daily loss of 90 mEq which is difficult to replace. (1 medium banana has 19 mEq)

Patient with cholera surrounded by bottles representing intestinal fluid loss.

Causes of Intestinal Secretion – I
stimulation of NaCl secreation

- Bacterial toxins
  - Cholera, E. coli, Shigella, etc.
- Inflammatory mediators
  - prostaglandins
- Circulating hormones
  - Gastrin (Z-E syndrome), Vasoactive intestinal polypeptide (VIP)

Causes of Intestinal Secretion - II

- Malabsorbed compounds that reach the colon and stimulate secretion
  - Bile acids
  - Fatty acids
- Laxatives (“natural” from plants) that stimulate secretion
  - Ricinoleic acid
  - Senokot
- Lack of mature villus/surface absorptive cells reducing absorption
  - viral gastroenteritis/celiac sprue

Osmotic Diarrhea is caused by the presence of poorly absorbed luminal osmols

Carbohydrates:

- Lactose (lactase deficiency)
- Sorbitol (chewing gum)

Minerals:

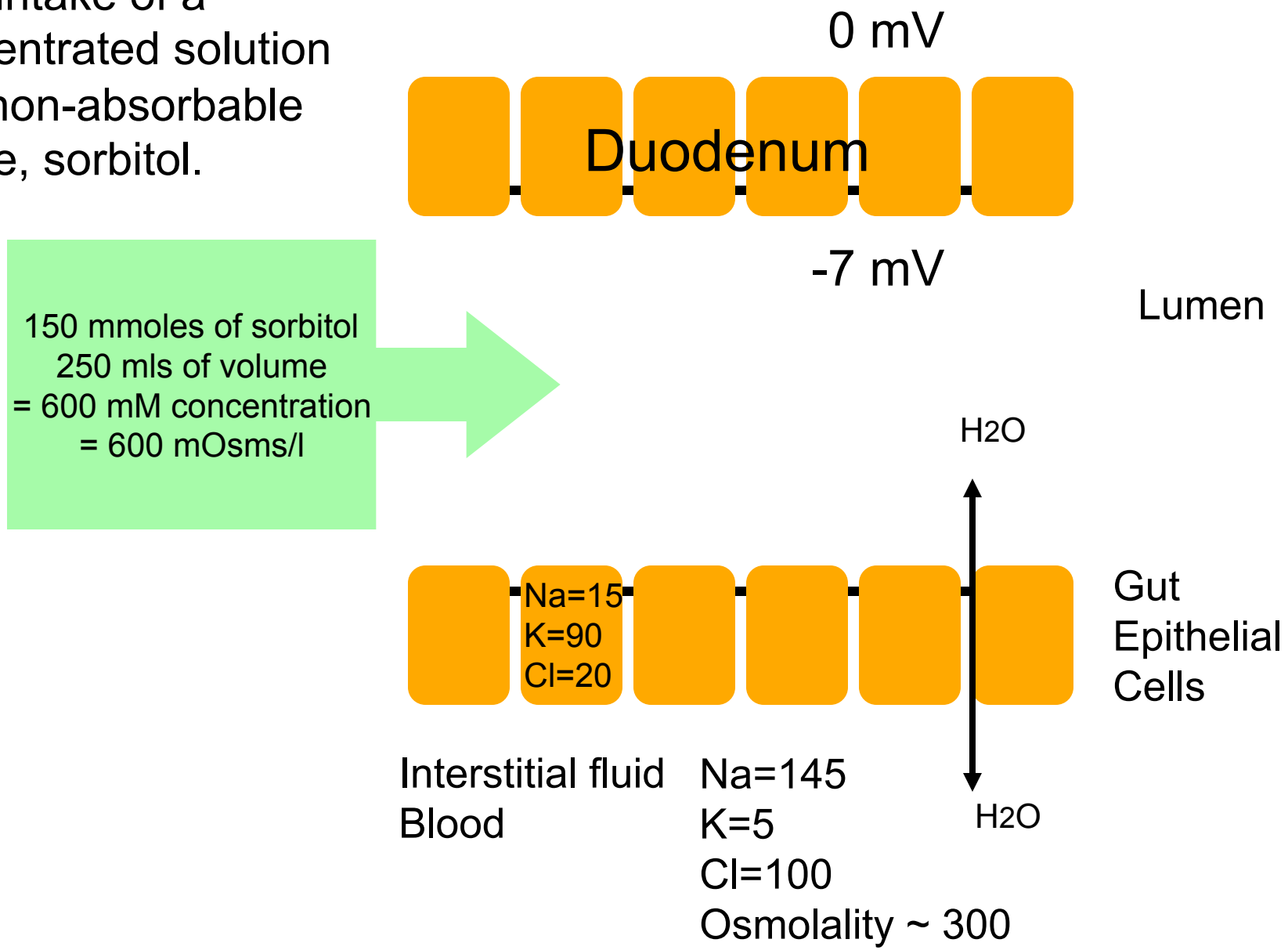
- Magnesium salts (MOM, Mg citrate)

Osmotic Principles

- The driving force of fluid movement is ion or solute transport
  - Solutes may be actively transported through cell membranes
  - Solute may move passively through cells following concentration and/or electrical gradients
- Water movement follows solute movement by osmosis
- Water may move between cells (tight junctions) or through cell membrane channels (aquaporins)

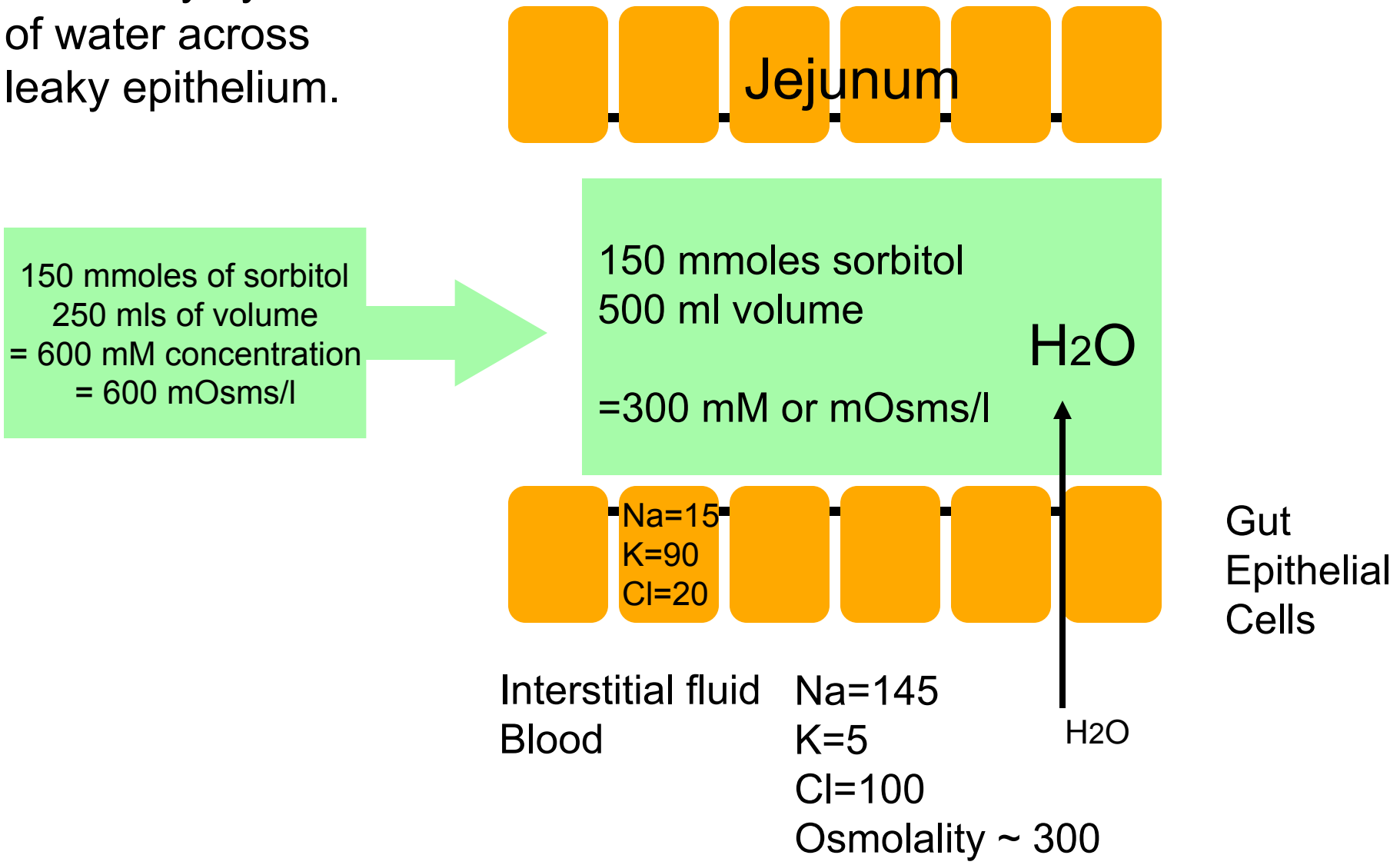
Pathophysiology of Osmotic Diarrhea

Step 1:
Oral intake of a concentrated solution of a non-absorbable solute, sorbitol.



Pathophysiology of Osmotic Diarrhea

Step 2:
Sorbitol diluted to isotonicity by flow of water across leaky epithelium.



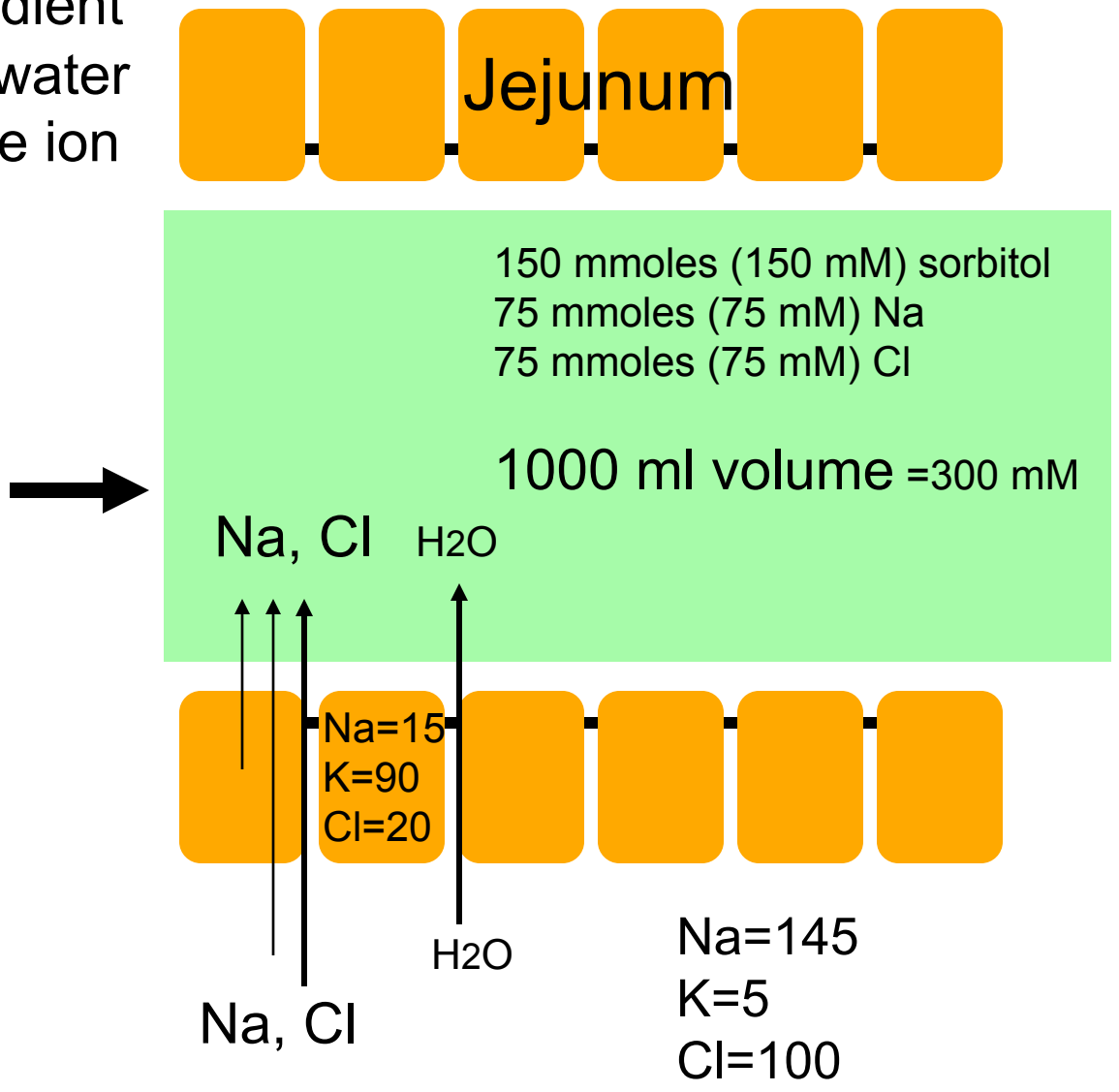
Pathophysiology of Osmotic Diarrhea

Step 3:
Salts move down concentration gradient accompanied by water to try to equilibrate ion concentrations.

150 mmoles sorbitol

500 ml volume

=300 mM

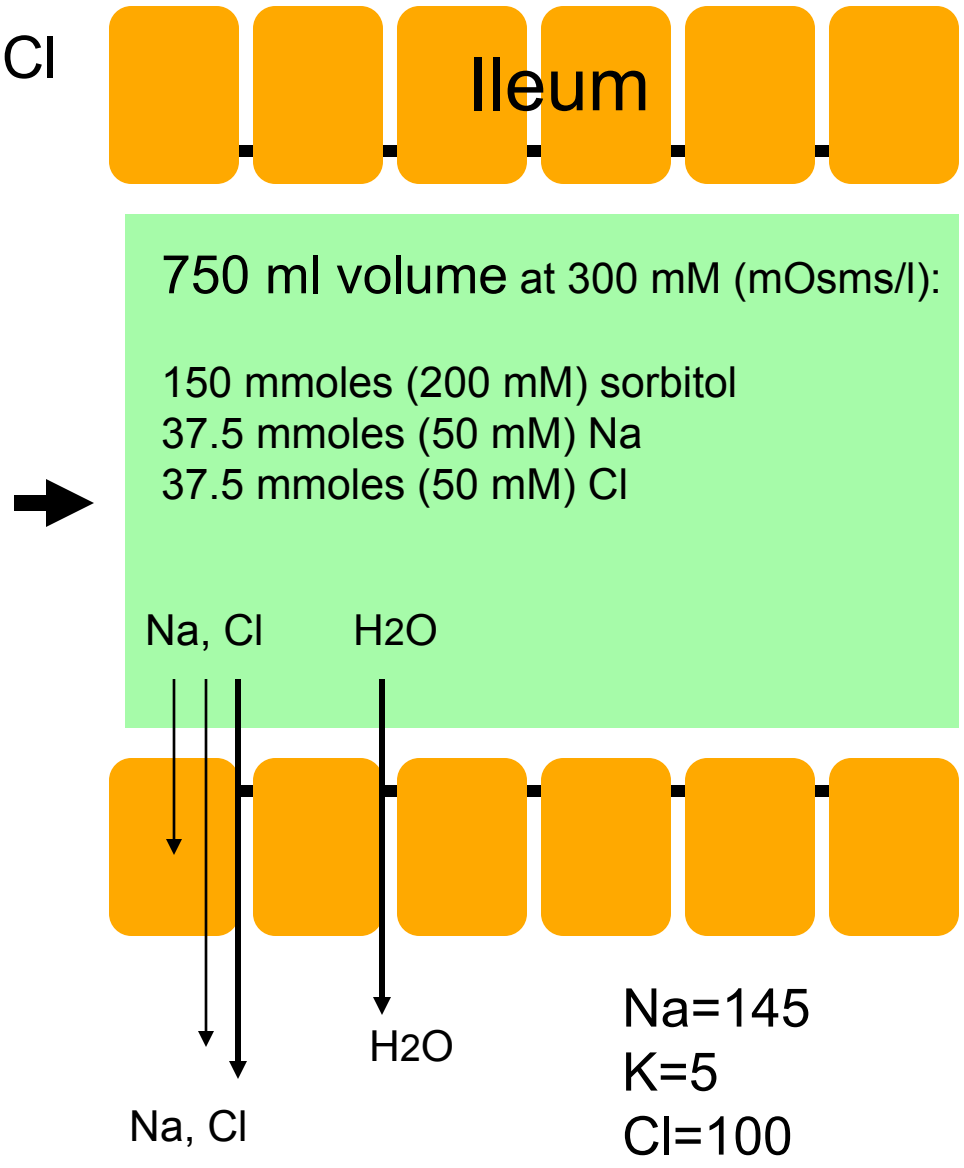


Pathophysiology of Osmotic Diarrhea

Step 4:
Ileum (less leaky, better able to maintain Na gradient) reduces NaCl concentration and volume .

150 mmoles sorbitol
75 mmoles Na
75 mmoles Cl

1000 ml volume
=300 mM

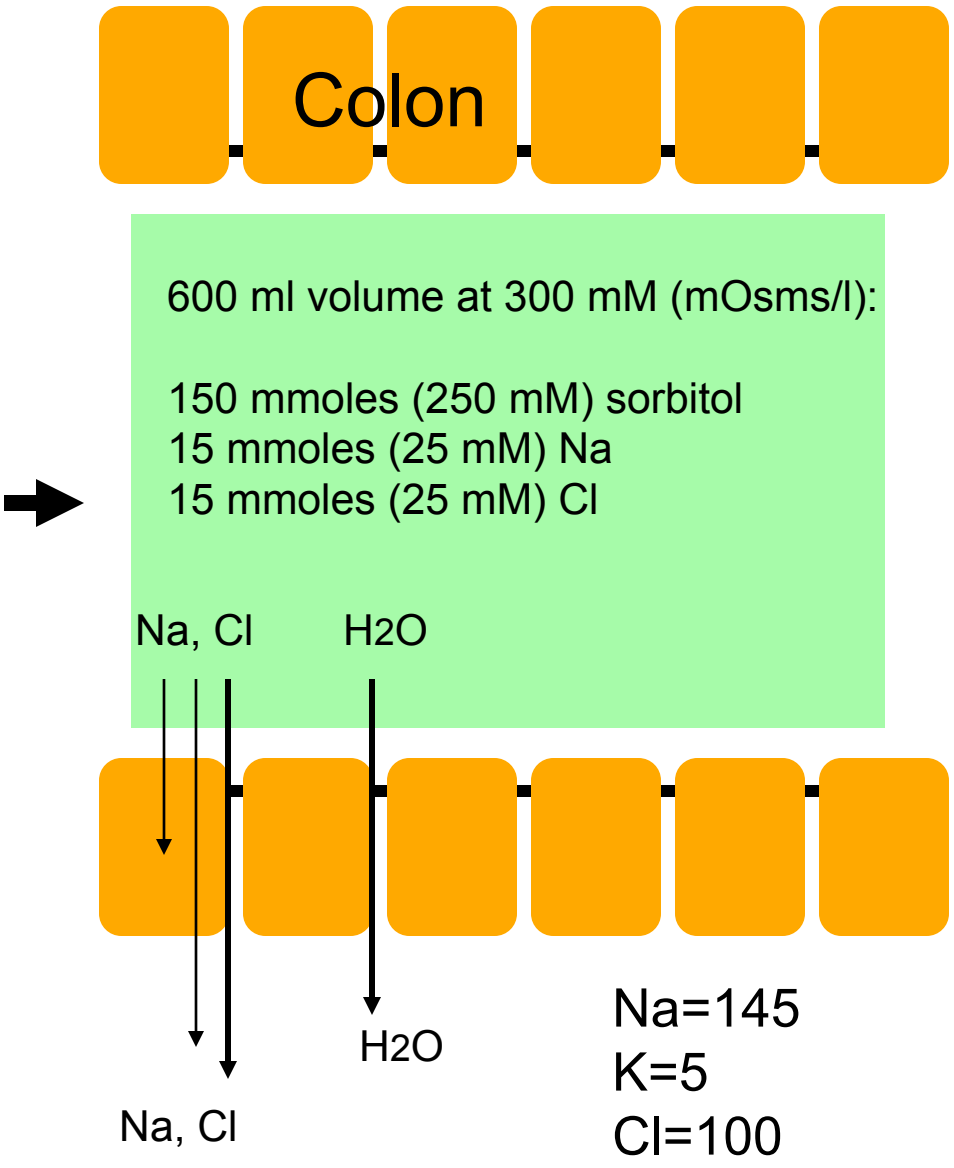


Pathophysiology of Osmotic Diarrhea

Step 5:
Colon (fairly “tight” and able to maintain higher Na gradient) further reduces NaCl concentration and volume .

750 ml volume at 300 mM (mOsms/l):

150 mmoles (200 mM) sorbitol
37.5 mmoles (50 mM) Na
37.5 mmoles (50 mM) Cl



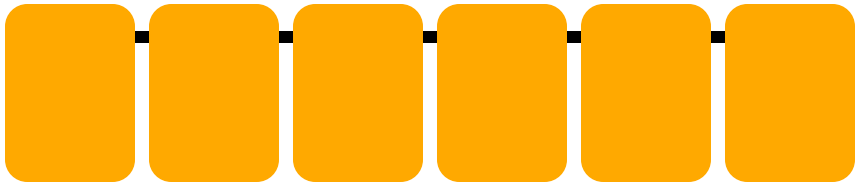
Pathophysiology of Osmotic Diarrhea

Step 6:
Overall Result

Oral Input:

150 mmoles of sorbitol
250 mls of volume
= 600 mM concentration

Stool Output:
600 ml volume
150 mmoles sorbitol
15 mmoles Na
15 mmoles Cl



Pathophysiology of Osmotic Diarrhea

- GI epithelia cannot maintain an osmotic gradient and cannot generate as high a Na or other ion gradient as the kidney can.

- Thus osmotic diarrhea is due to three factors
  - Amount of ingested material containing non-absorbed solute.
  - Volume of extra water needed to dilute the ingested material to isotonicity
  - Volume of water accompanying the Na, Cl and other ions that equilibrate across the gut epithelia.

Clinical Manifestations of Osmotic Diarrhea

- Moderate volume of stool
- Improves/disappears when oral intake stops
- Moderately watery/soft stool
- Often associated with increased flatus if due to carbohydrate malabsorption (see malabsorption lecture)
- No WBC or RBC in stool

Examples of Osmotic Diarrhea

- Ingestion of non-absorbable compounds
  - Magnesium salts
    - Antacids (Maalox, Mylanta)
    - Laxatives (Milk of Magnesia)
  - Sugars
    - Lactulose, sorbitol, mannitol, fructose, lactose
- Malabsorption of specific carbohydrates
  - Disaccharidase deficiency
- Generalized malabsorption of nutrients

Therapeutic agents that cause osmotic diarrhea: lactulose (used medically) and magnesium salts

Causes of Osmotic Diarrhea

Poorly absorbed sugars such as:

Sorbitol
Fructose

Sources of Sorbitol Leading to Osmotic Diarrhea

Nutrition Facts	Amount Per Serving	% DV*
Serving Size 1 stick (1.8g)	**Total Fat** 0g	0%
Servings Per Package 40	**Sodium** 0mg	0%
Calories <5	**Total Carbohydrate** 1g	<1%
	Sugars 0g	
	Sugar Alcohol 1g	
	Protein 0g	

*Percent Daily Values (DV) are based on a 2,000 calorie diet.

Not a significant source of other nutrients.

Original Flavor

SORBITOL, GUM BASE, MANNITOL, GLYCERIN, XYLITOL, ARTIFICIAL AND NATURAL FLAVORING, SOFTENERS, ACESULFAME POTASSIUM AND ASPARTAME.

Clues to Osmotic Diarrhea from Clinical Lab Tests

- Fecal electrolytes
- Fecal osmotic gap

Fecal Electrolytes

Solute (mEq/l)	Normal	Secretory	Malabsorption (Carbohydrate)	Osmotic (Mg salt)
Na^+	~40	**~90**	~40	~20
K^+	~90	~40	~40	~20
Cl^-	~15	**~60**	~10	**~60**
HCO_3^-	~30	~50	~10	~20
Anions (SO_4^{-2}, PO_4^{-2}, fatty acids)	~85	**~30**	~80	**~100**
Other (Mg^{+2})	<15-20	<10	10	**~70**
Sugars (mM)	0	0	**~100**	0
Volume (liters/day)	<1	5-10	1-2 *	1-2
Osmolality (mOsm/l)	~290	~290	~290	~290
2 (Na+K)	~260	~260	~160	~80
Fecal osmotic gap	~30 (range ~10-50)	~30	**~100**	**~200**

*

Measured osmolality of stool can be greater than plasma osmolality if unabsorbed carbohydrates are present and stool sits at room termperature for hours, allowing bacterial fermentation.

OSMOTIC GAP

Question: Are there osmotically active molecules in stool that should not be there?

Cations + anions + neutral molecules = 300 mM

Cations = anions (electroneutrality)

Na and K are the usual stool cations and are easily measured.

Anions are a mixed bag (Cl, bicarbonate, sulfate, phosphate, fatty acids) and are NOT easily measured.

Neutral molecules and unmeasured cations are also a mixed bag but usually constitute < 30mM.

Equation for measurable ions/molecules in stool: 2(Na+K) ~ 270-290 mM (plasma osmolality)

Thus the osmotic gap (osmotically active molecules that cannot be accounted for) can be calculated as:

Osmotic gap ~ 300 œ2(Na+K) ~10-50 mM for normal stool

An osmotic gap of >> 50 is quite abnormal and suggests osmotic diarrhea

Fecal Electrolytes

Solute (mEq/l)	Normal	Secretory	Malabsorption (Carbohydrate)	Osmotic (Mg salt)
Na^+	~40	**~90**	~40	~20
K^+	~90	~40	~40	~20
Cl^-	~15	**~60**	~10	**~60**
HCO_3^-	~30	~50	~10	~20
Anions (SO_4^{-2}, PO_4^{-2}, fatty acids)	~85	**~30**	~80	**~100**
Other (Mg^{+2})	<15-20	<10	10	**~70**
Sugars (mM)	0	0	**~100**	0
Volume (liters/day)	<1	5-10	1-2	1-2
Osmolality (mOsm/l)	~290	~290	~290	~290
2 (Na+K)	~260	~260	~160	~80
Fecal osmotic gap	~30 (10-50)	~30	**~100**	**~200**

Consequences of Osmotic Diarrhea

- Major: Diarrhea due to osmotic effects of non-absorbed solutes

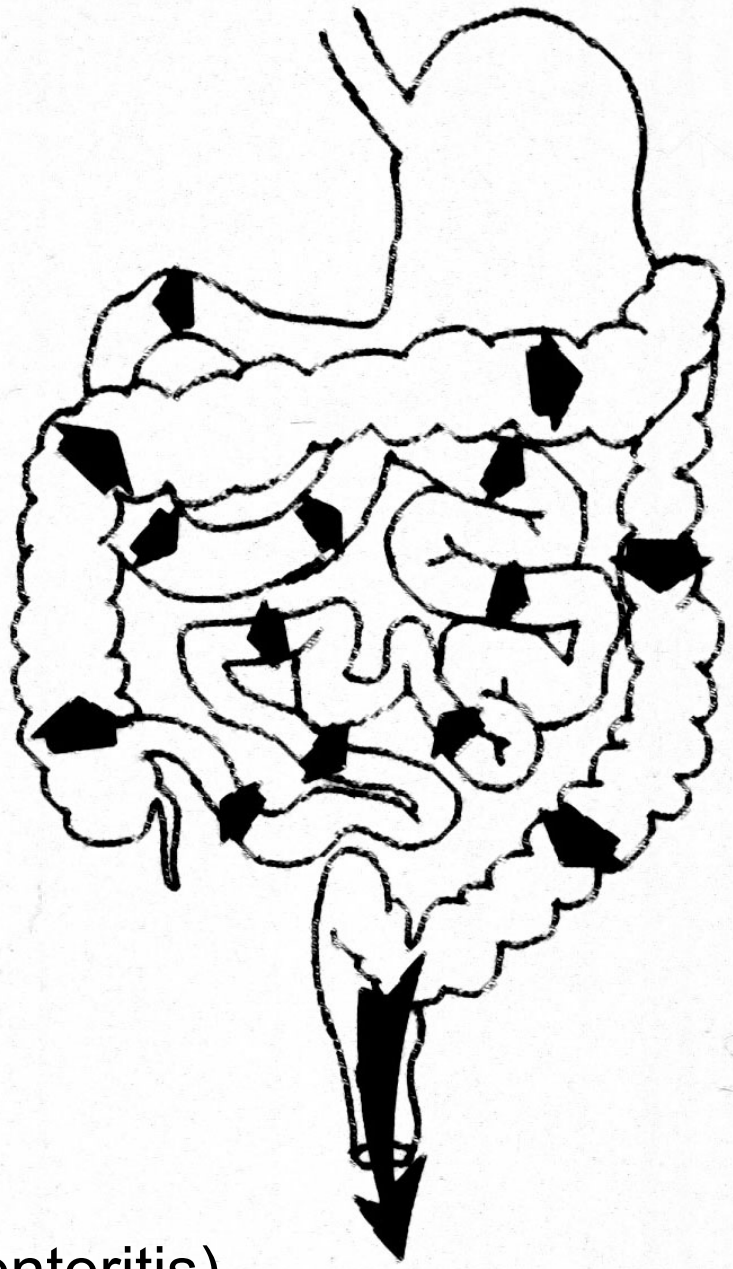
- Other: Nutritional deficiencies if generalized malabsorption is the cause

Diarrhea Due to Increased Bowel Motility

Rapid intestinal motility may result in diarrhea due to reduced contact time between luminal contents and bowel mucosa.

Examples include:

- Anxiety
- Hyperthyroidism
- Irritable bowel syndrome
- Postvagotomy diarrhea (dumping syndrome)
- Bowel infection (viral gastroenteritis)



Clues to Increased Bowel Motility

- Moderate diarrhea - usually watery
- Often occurs after meals - accentuated gastro-colic reflex
- No WBC, RBC in stool
- Recently eaten food visable in stools
- Louder bowel sounds often apparent
- No diagnostic tests- often must rule-out secretory/osmotic/inflammatory causes

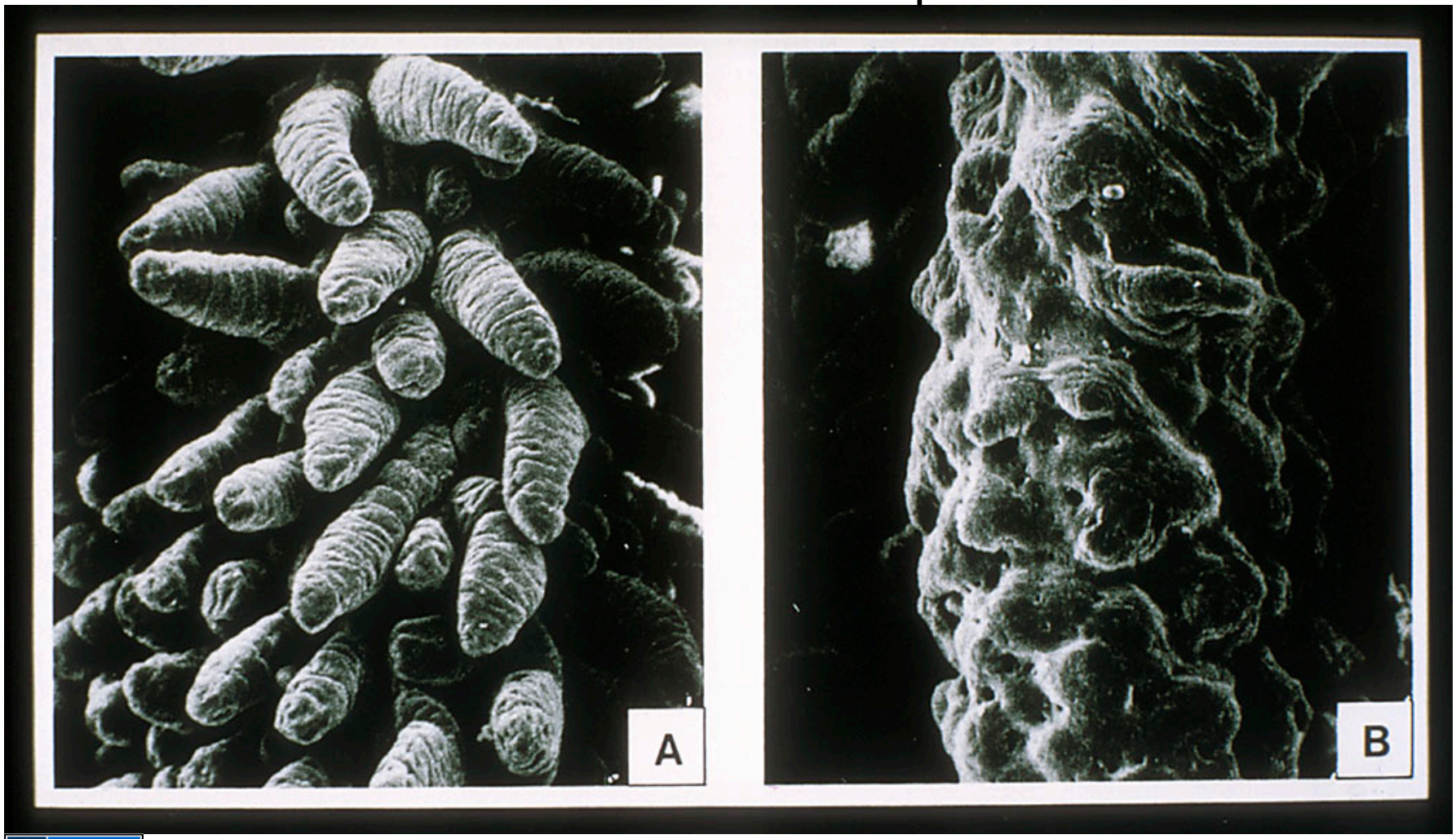
Consequences of Increased Bowel Motility

- Malabsorption
  - Nutrients (if small bowel is involved)
- Diarrhea and urgency
- Increased bowel sounds (if severe)
- Crampy abdominal pain (if severe)

Loss of Bowel Surface Area

- Functionally equivalent to increased bowel motility
- Underlying process causing loss of surface area may produce additional symptoms/signs
- Causes include surgical resection, mucosal disease, fistulas

Pig small intestinal villi before (A) and after (B) viral gastroenteritis.
Viral infection temporarily destroys mature villus enterocytes and can cause some malabsorption/secretion.



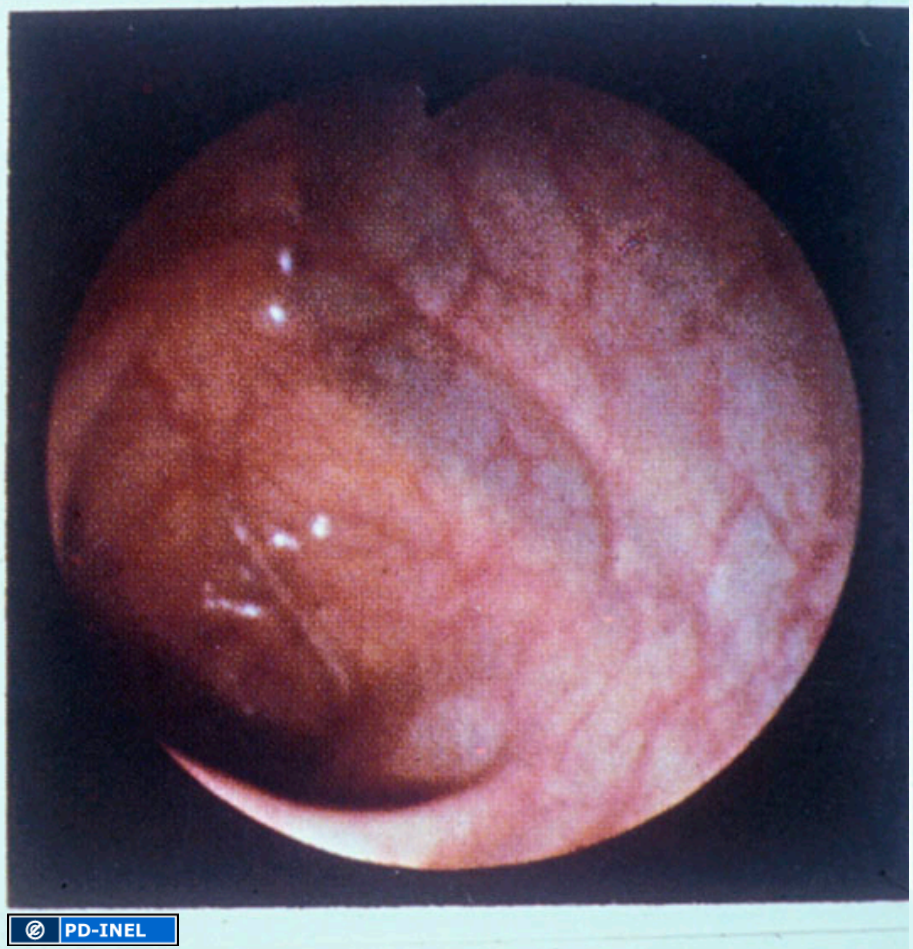
Small bowel x-ray of Crohn's disease showing fistula (arrow) between loops of bowel.

This fistula allows lumenal contents to bypass considerable small bowel mucosa.

Inflammation and Diarrhea

Normal Colon

Shigella dysentery



Ulcerative Colitis/

Inflammation-induced diarrhea
Results from several 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 malabsorption

Clinical Manifestations of Inflammatory Diarrhea

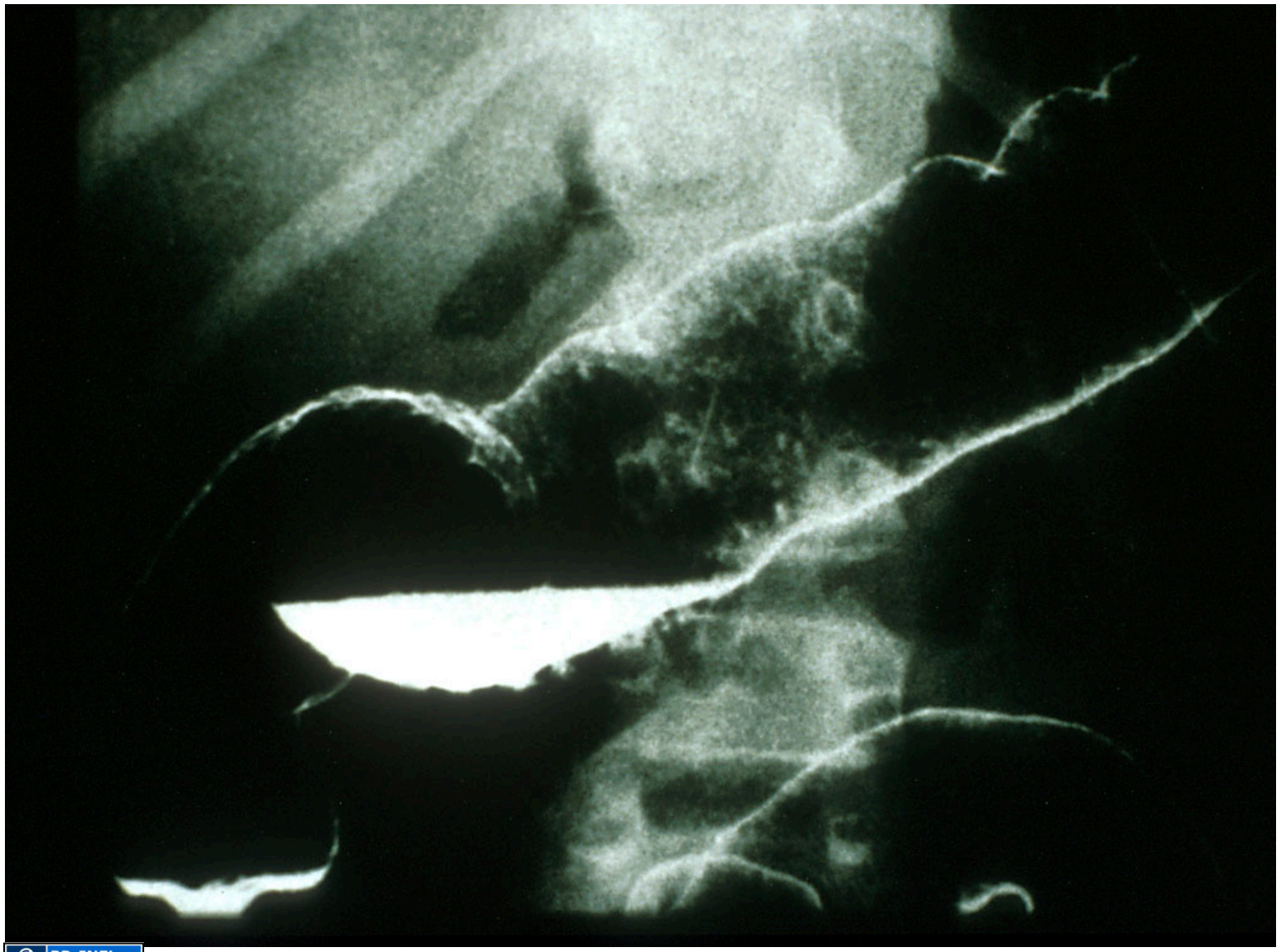
- Fever and systemic signs of inflammation (if severe/invasive organism)
- Small to moderate volume of diarrhea
- Bloody diarrhea and/or WBC/RBC in stool
  - except in mild inflammation like viral/microscopic colitis
- Often accompanied by rapid motility/ abdominal cramps
- Urgency/tenesmus if rectum is involved

Differential Diagnosis of Inflammatory Diarrhea

- Infectious diarrhea
  - viral, bacterial, parasitic
- Idiopathic inflammatory bowel disease
  - Crohn's disease, Ulcerative colitis
  - microscopic colitis
- Response to ischemia/injury

Normal
air-contrast
barium enema

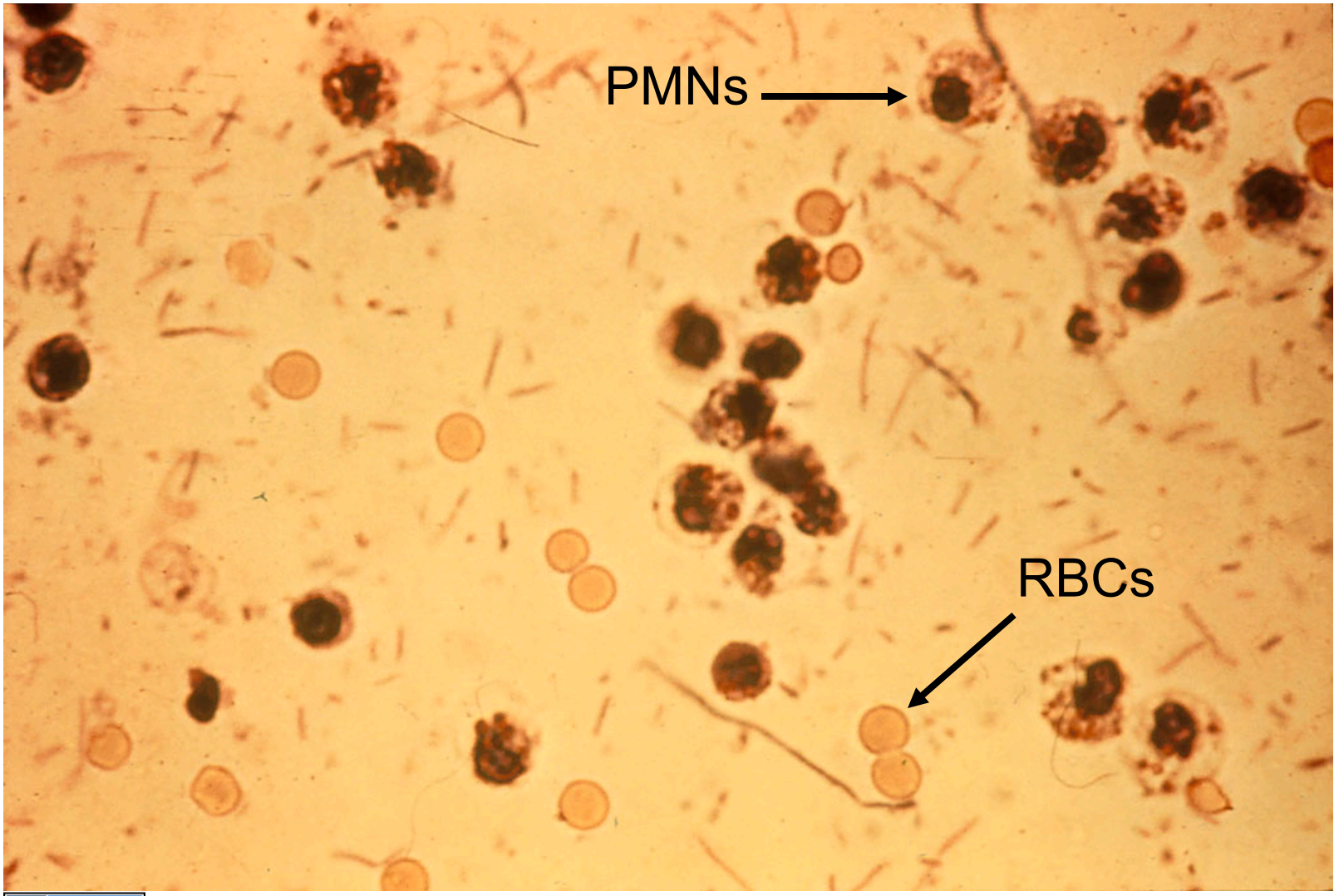
Air-contrast barium enema showing mucosal ulcerations and inflammation in ulcerative colitis.
This reduces absorptive surface area.



Crohn's Disease of the Terminal Ileum

Inflammation damages the mucosa, reducing the surface area for absorption.

Clues to Inflammatory Diarrhea on Gram Stain: Presence of WBC/RBC; Monotonic Bacterial Population



Overview: Differential Diagnosis of Diarrhea - I

- Secretory: bacterial toxins, hormones
  bile acids, fatty acids,
  idiopathic
- Osmotic malabsorption
  laxative
  abuse intake
  of non-
  absorbable solutes

Differential Diagnosis of Diarrhea - II

- Inflammatory: infections

  inflammatory bowel disease
  microscopic colitis
  lymphoma/ischemia

- Increased motility: hyperthyroidism
  irritable bowel syndrome

- Decreased surface area: fistulas

Diagnostic Approach to Diarrhea

- Use clinical clues from history, PE and basic laboratory studies to determine the most likely mechanism present.
- Utilize specific tests to confirm the type of diarrhea that is present (secretory, osmotic etc.)
- Construct a differential diagnosis and select diagnostic tests
- Algorithms are included in textbook and syllabus

Treatment of Diarrhea

- Specific
  - Logical approach is to identify and treat the underlying disease
- Symptomatic
  - In practice, symptomatic therapy may be critical to patient survival and the only available approach

Non-specific Treatment Of Diarrhea

- Rehydration
  - Often life-saving in severe diarrhea, especially in the very young (children) and the elderly
  - IV electrolytes and water - high tech, expensive
  - Oral rehydration solutions - high concept, low tech and very cheap.

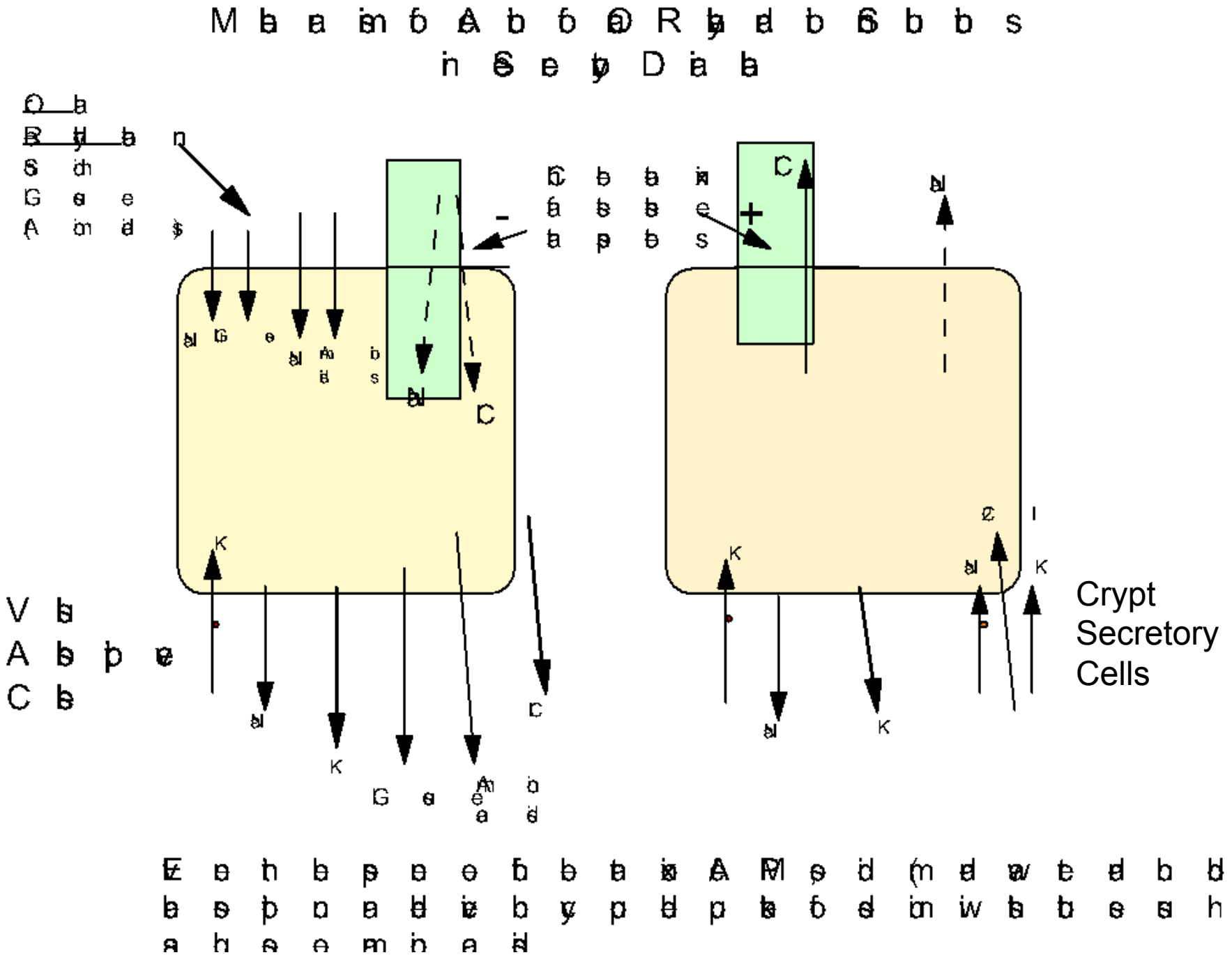
- Anti-motility drugs

Options available for management of diarrhea especially severe secretory diarrhea

- Oral rehydration therapy
- Measurement of stool output
- Antibiotics
- IV fluids and electrolytes

World Health Organization Oral Rehydration Solution

	Rehydration Solution	Fecal Electrolytes (mEq/l)
Glucose	110mM	--
Na^+	90 mEq/l	75
K^+	20 mEq/l	20
HCO_3^-/citrate	30 mEq/l	50
Cl^-	80 mEq/l	45


Crypt
Secretory
Cells

Anti-motility Agents (opiates)

- Increase capacitance of gut and thus time for reabsorption
- Useful in many types of diarrhea if specific therapy is not available or adequate
- Often need to use large doses and/or potent drugs and administer on a regular (rather than PRN) basis.
- Do not use in acute bloody diarrhea (infectious or inflammatory)

Additional Source Information

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