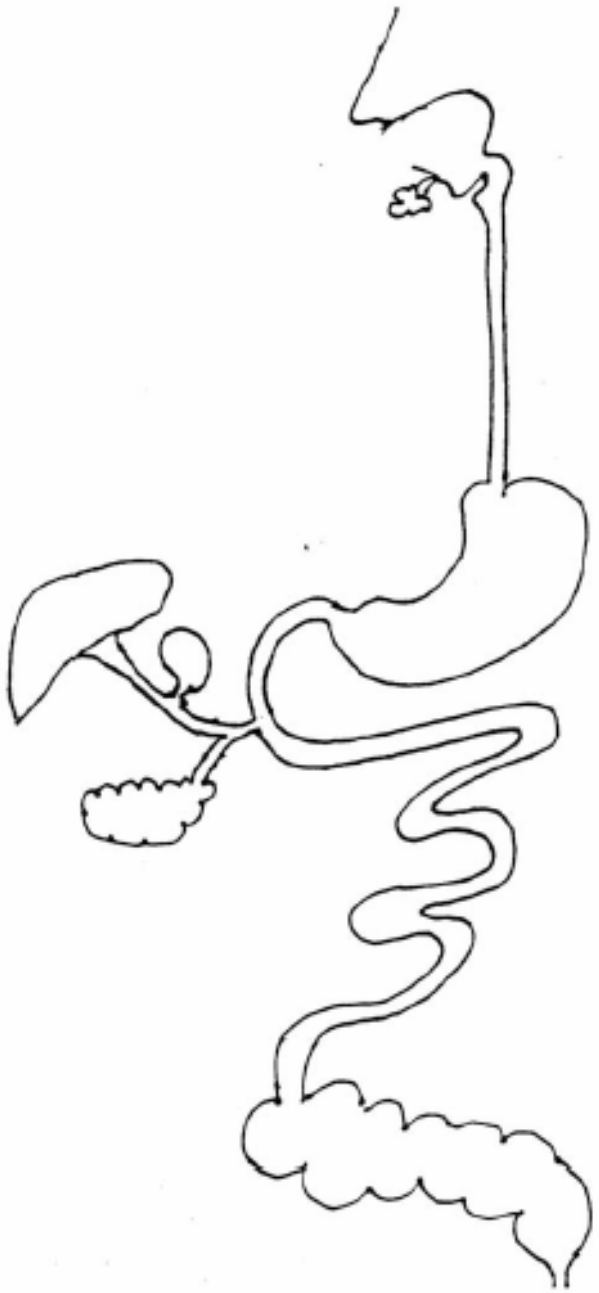
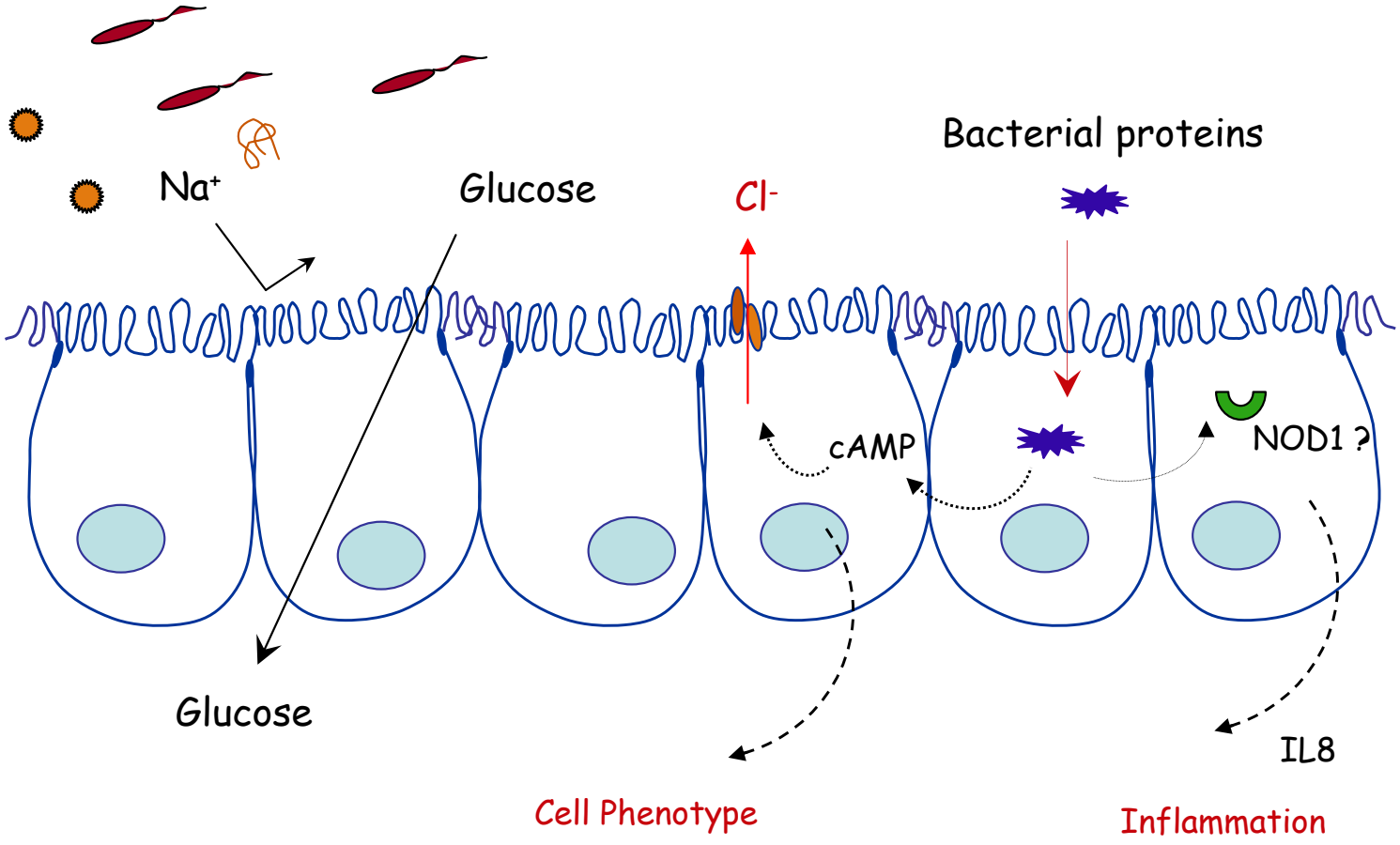
Anatomy, Physiology, & Biophysical Chemistry of Te Digestion

- Barrier Function
- Terminal Digestion
- Vectorial Transport
- Innate and Acquired Immunity

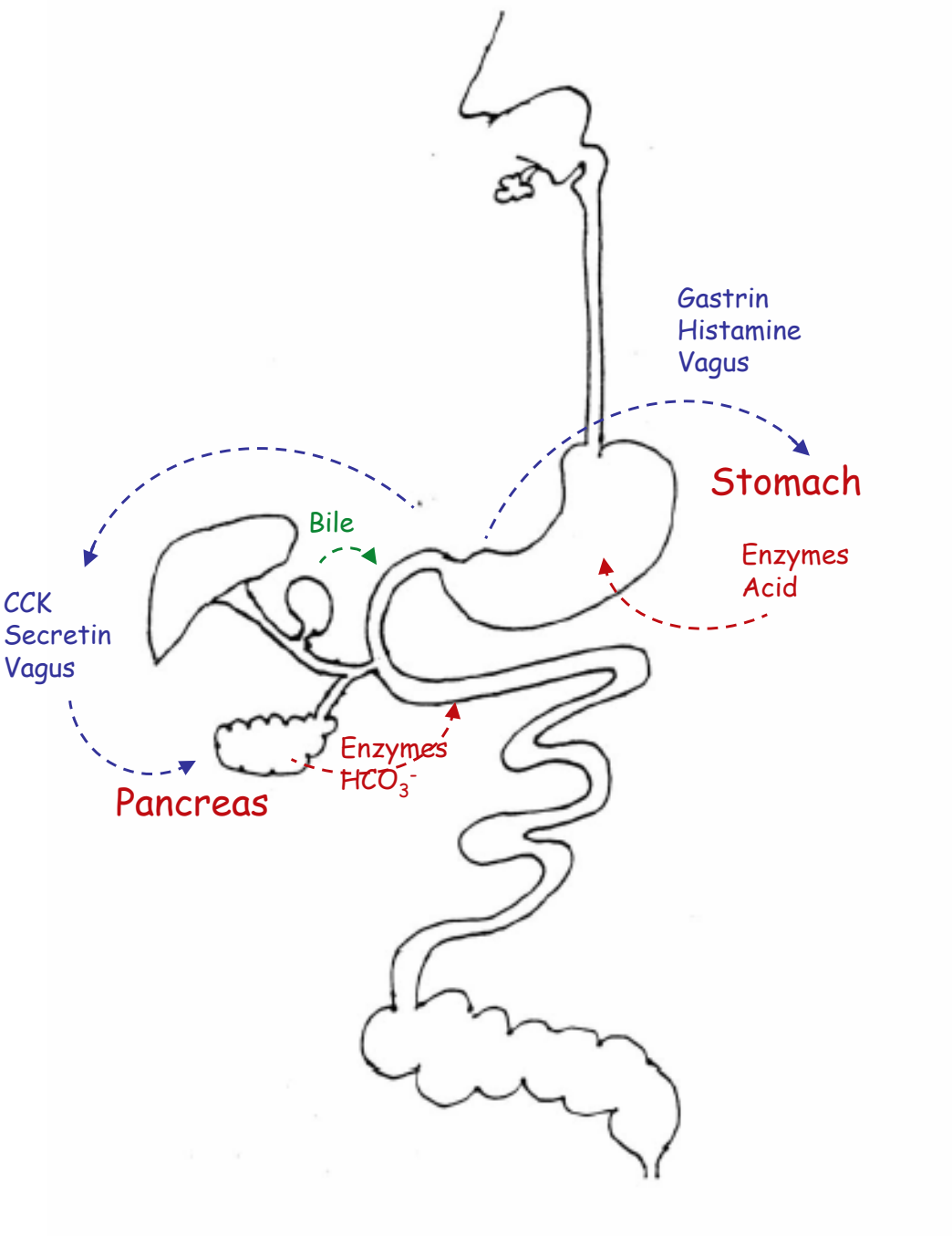


The Integrateed GI Mucosa



Intralumenal Digestion

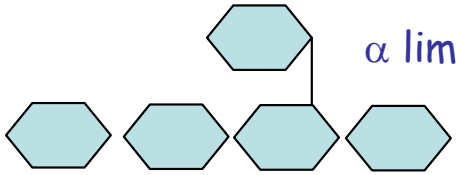
- **Proteins:** Trypsin, chymotrypsin, elastase, carboxypeptidase etc
- **Carbohydrates:** amylase
- **Fats:** lipase, co-lipase, bile salts
- **DNA, RNA:** DNase etc



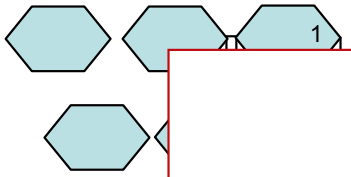
Enzyme Kinetics

Intralumenal Digestion: water soluble substrates

β1-4 linkage



α limit dextrans



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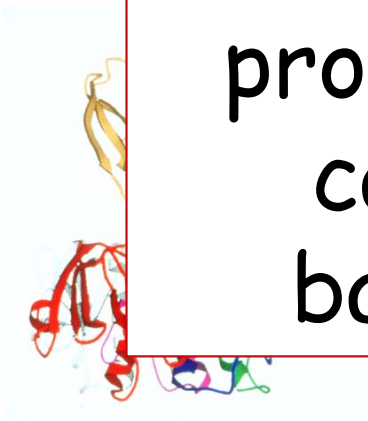
iose

CAUTION:

Danger! Minefield! Danger! Minefield! Danger! Minefield! Danger!

NONE of these enzymatic products are in a form that can cross the intestinal barrier and be absorbed



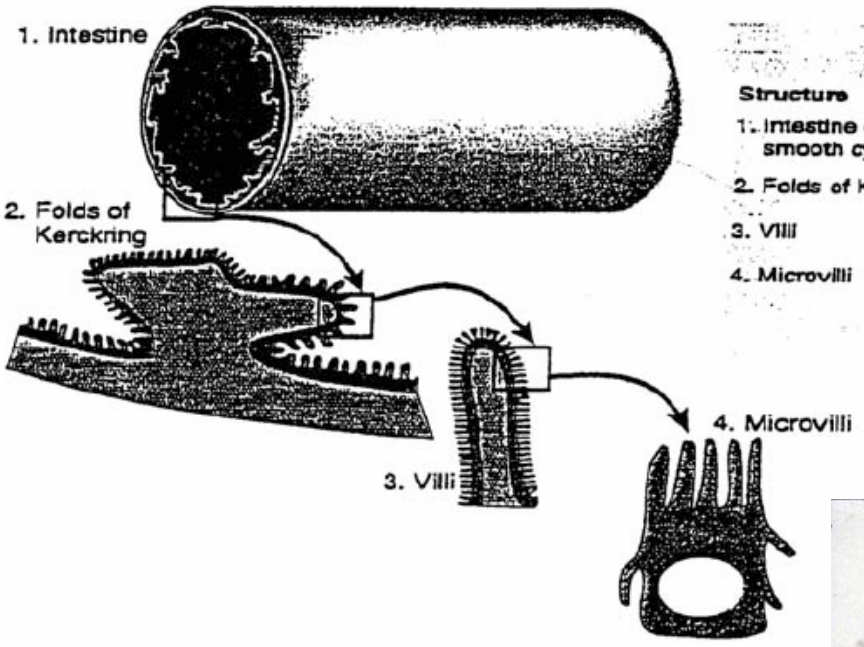
leu-phe-tyr-ala-ser-gly-asp-lys-ser-gly-

DNA/RNA → DNAase, RNAase → nucleotides

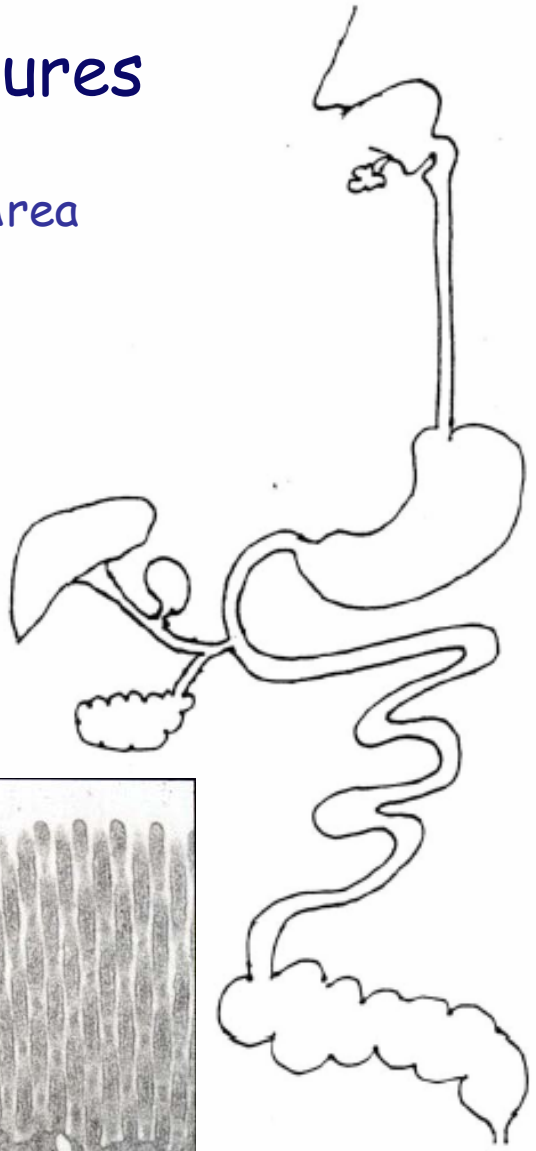

V

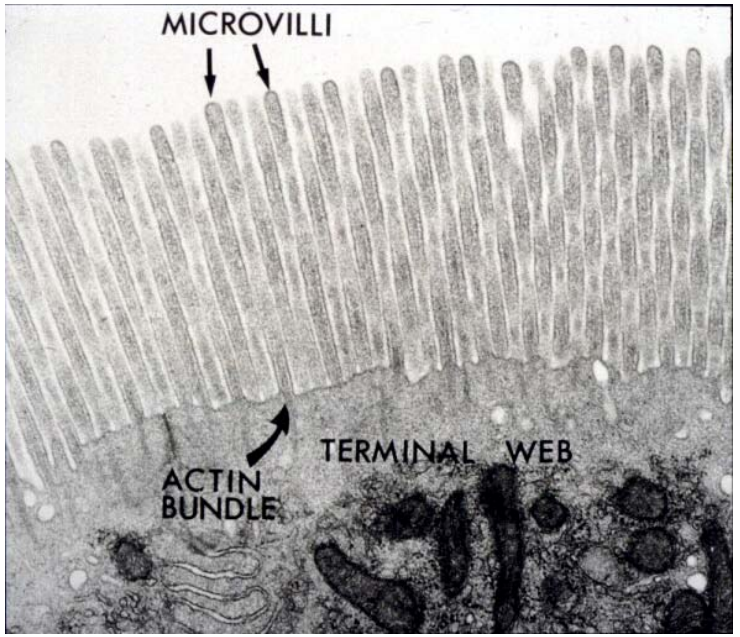
General Features

Surface Area

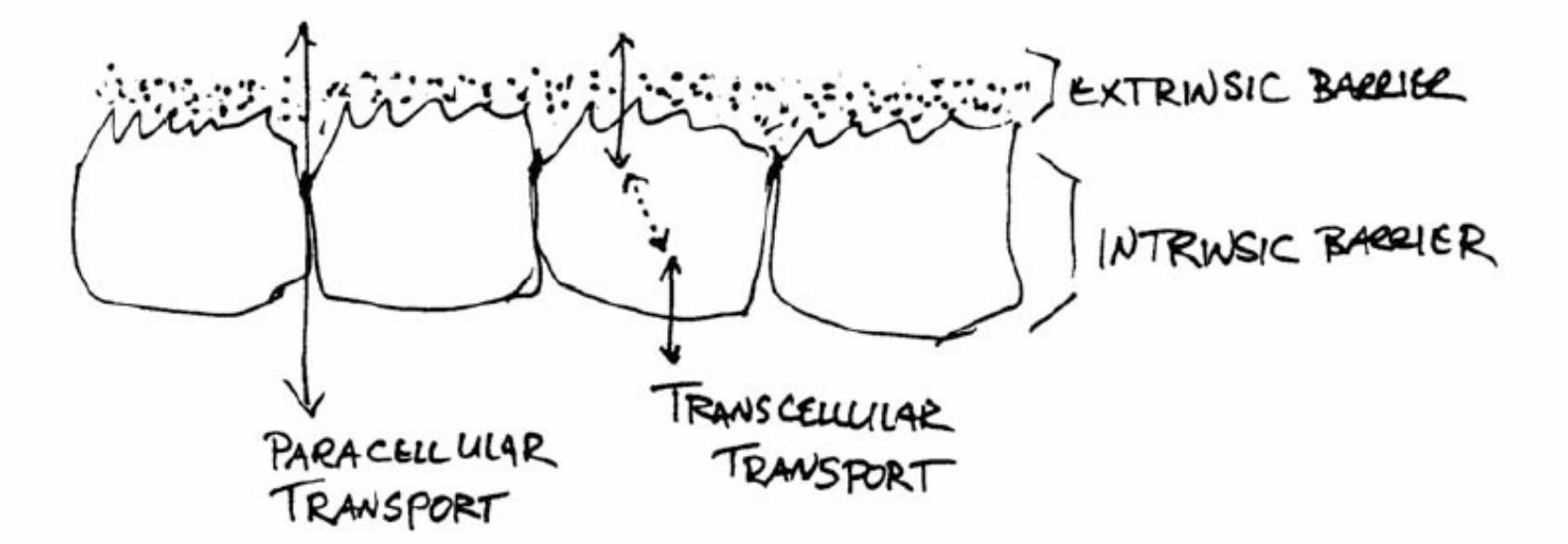


Structure	Increase in surface area	Surface area (square centimeters)
1. Intestine (as a smooth cylinder)	1	3,300
2. Folds of Kerckring	3	10,000
3. Villi	30	100,000
4. Microvilli	600	2,000,000 (over 400 square yards)



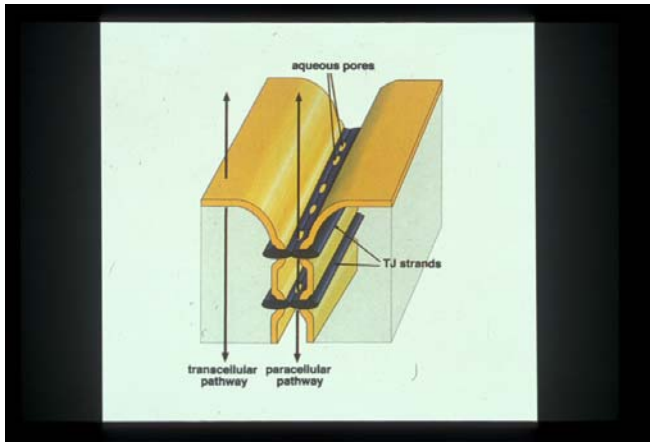


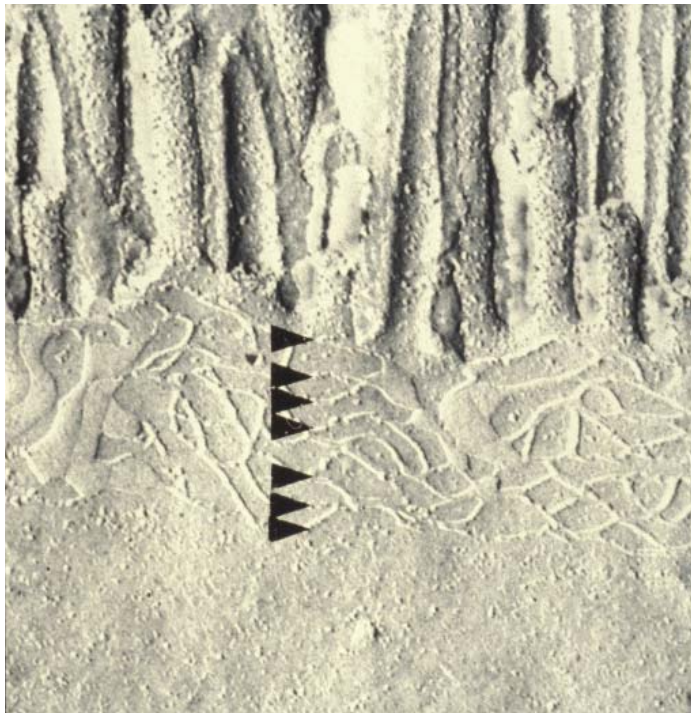
Transepithelial Transport



TJ Proteins etc.

Transepithelial Transport: paracellular





2) Physiology of the tight junction and transport across the paracellular pathway:

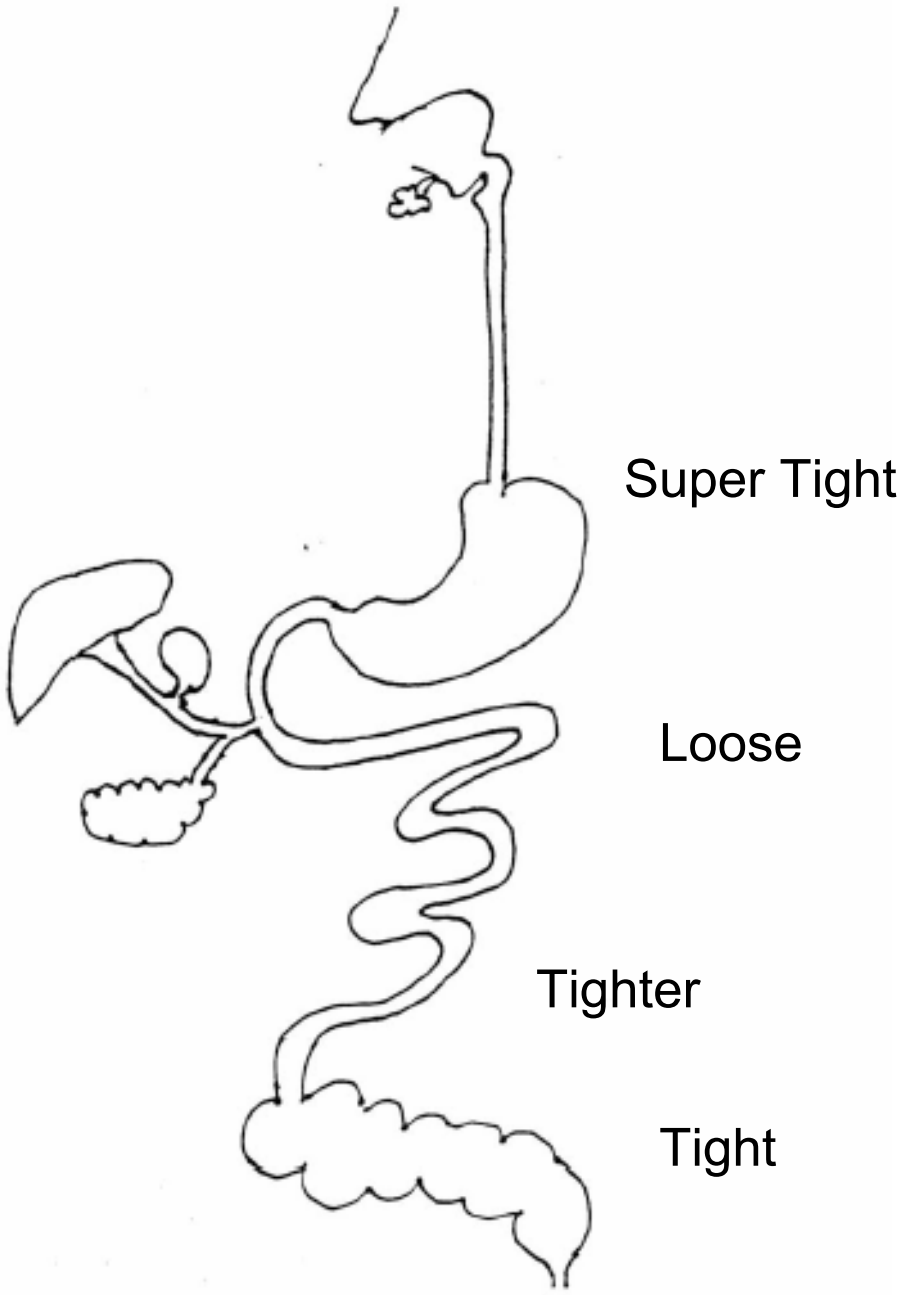
a) the tight junction separates the apical from the basolateral membrane domains of the intestinal epithelial cell, and thus contributes fundamentally in the biogenesis and maintenance of cell polarity that is essential for vectorial transport.

b) the tight junction is cation selective (important for intestinal secretion, see below) PK^+:PNa^+:PCl^- = 1.14:1.00:0.55

c) tight junctions are more restrictive (i.e. less permeant) as one proceeds distally: in the small intestine 80-90% of passive ion permeation is paracellular. In the colon 50-60% is paracellular due to greater paracellular restriction. (Effective radii for solutes crossing tight junctions in jejunum, ileum and colon - 7.5-8, 3- 3.5, and 2-2.5 □, respectively)

d) permeability through tight junctions can be regulated (see below).

e) Tight junctions interface with the cytoskeleton, probably via tight junction specific proteins (ZO-1, cingulin), and the cytoskeleton likely mediates tight junction function.


Super Tight
Loose
Tighter
Tight

- 1) Protein Losing Enteropathy: Virtually any insult <u>if severe enough</u> can manifest in protein losing enteropathy

  - a) Exaggeration of the normal secretion of serum proteins, particularly albumin, into the intestinal lumen. Intraluminal digestion of serum proteins is followed by absorption of amino acids and subsequent resynthesis of serum proteins. When loss into gut is sufficiently great, synthesis fails to maintain serum protein levels. The result is a contracted body protein pool that is turning over rapidly.

  - b) Laboratory studies show:
    - i) Hypoproteinemia, particularly hypoalbuminemia, without proteinuria
    - ii) □1-antitrypsin in stool
    - iii) In severe cases, lymphopenia and impaired immune responses

  - c) Protein losing enteropathy may be observed in a wide variety of diffuse gastrointestinal disorders but is particularly seen in intestinal lymphangiectasia, hypertrophic gastritis (Menetrier's syndrome), severe right-sided heart failure, non-topical sprue, Whipple's disease.

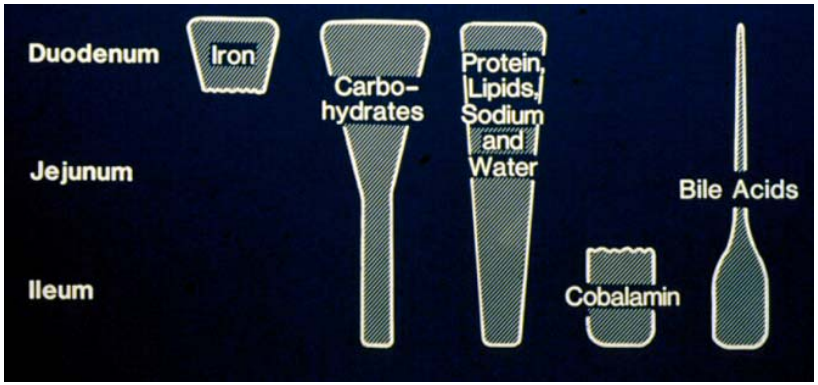
  - 2). Clostridium difficile toxin; ZOT toxin; V. cholerae HA protease, enterohemmorhagic E. coli

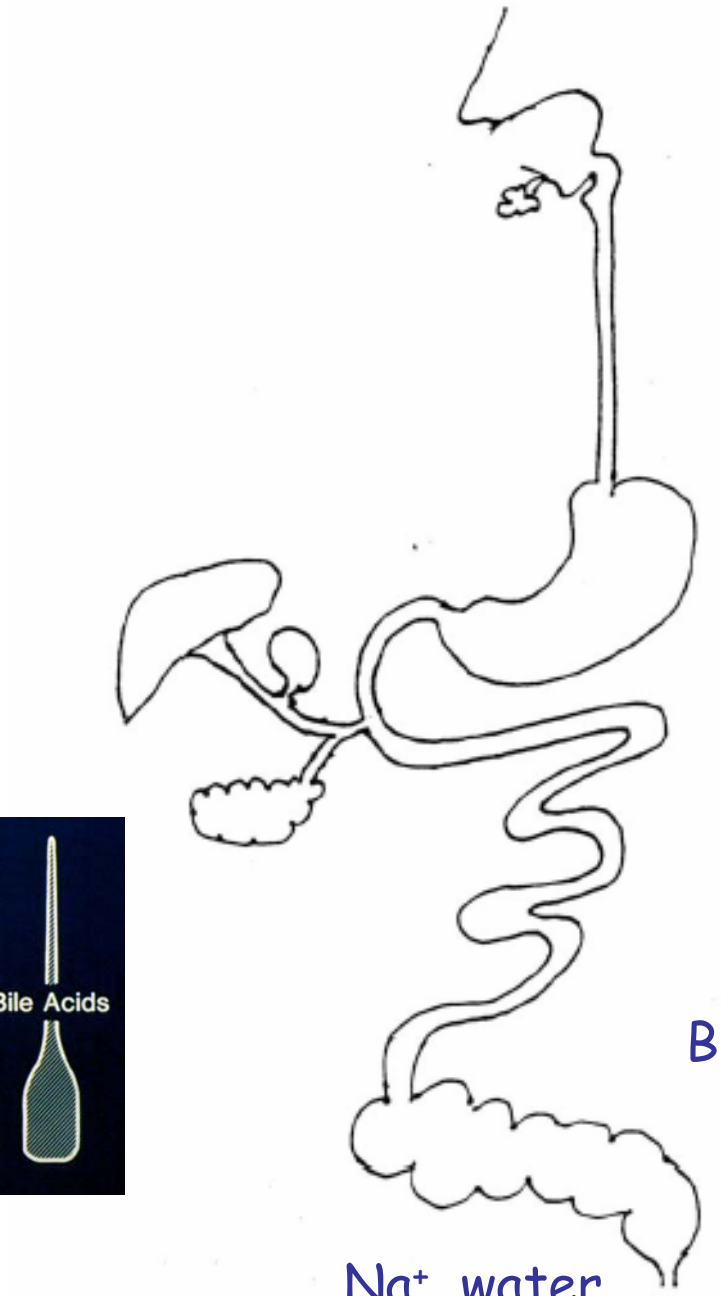
  - 3) ulcer, inflammation

	Input	Output (stool)
Protein:	~200 gm Diet ~100 gm Epithelial Sloughing ~50 gm Secretions: salivary, pancreatic, biliary ~50 gm	~1-2 gm
Fat:	~170 gm Diet ~100 gm Epithelial Sloughing ~20 gm Biliary Lipid ~50 gm	~2-6 gm
Water:	~10 L Diet ~2 L GI tract secretions ~8 L	~0.05 L
Ions (Na^+, K^+, Cl^-, Ca^{+2}, Fe^{+2}):	~0.2 M Diet: ~0.2M Secretions ~2.4 M	~0.015 M
Weight:	~22 Kg	~0.2 Kg

General Features

Proximal/Distal differentiation



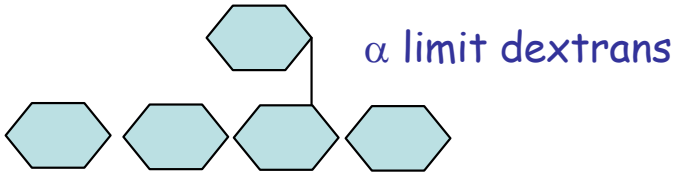


Fe^{2+}, bulk of nutrient solutes trace elements

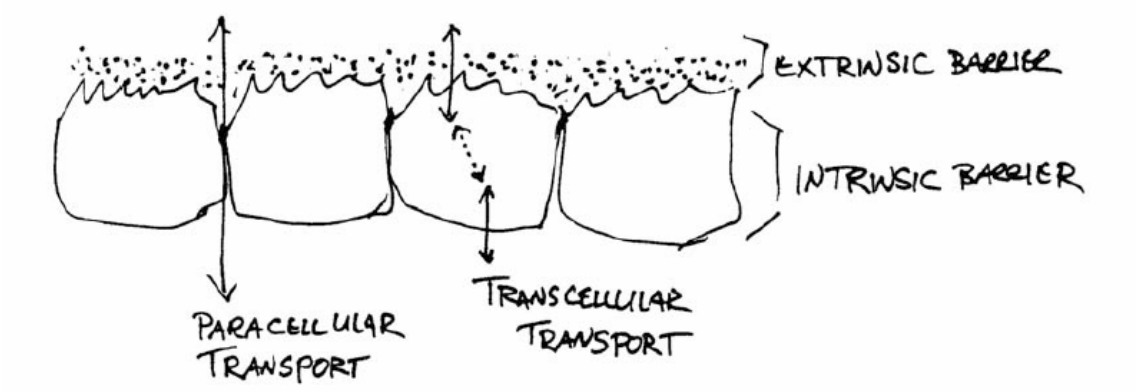
B_{12}, Bile acids, Na^+

Na^+, water

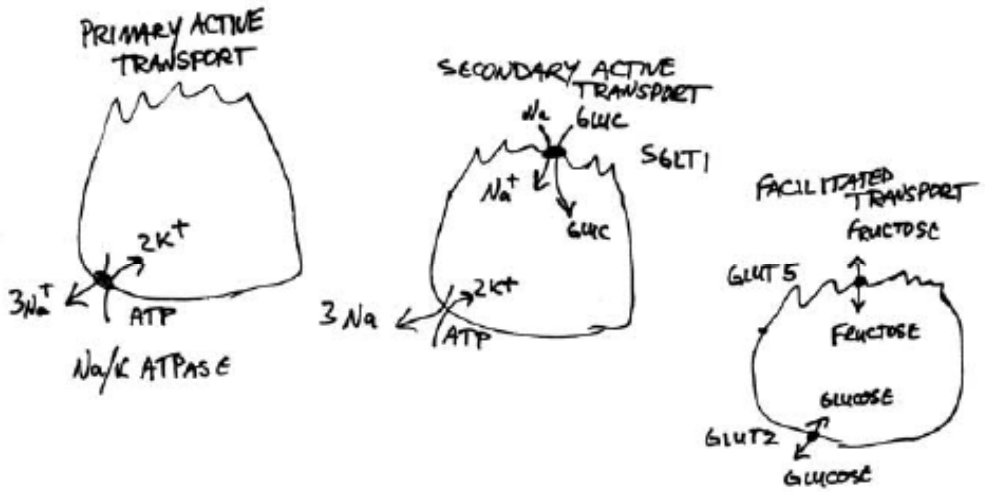
Terminal Digestion



Transepithelial Transport: Driving force, Pathway?

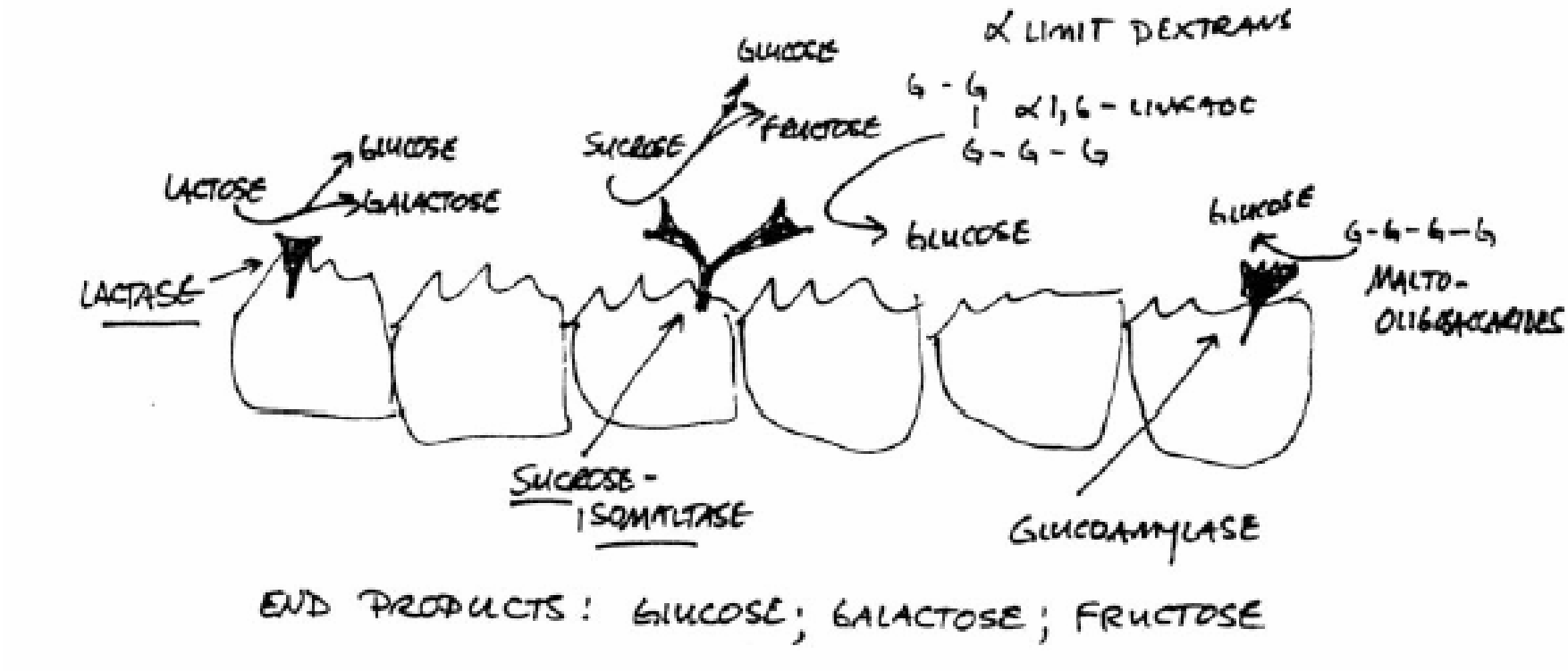


Primary active, secondary active, and facilitated transport



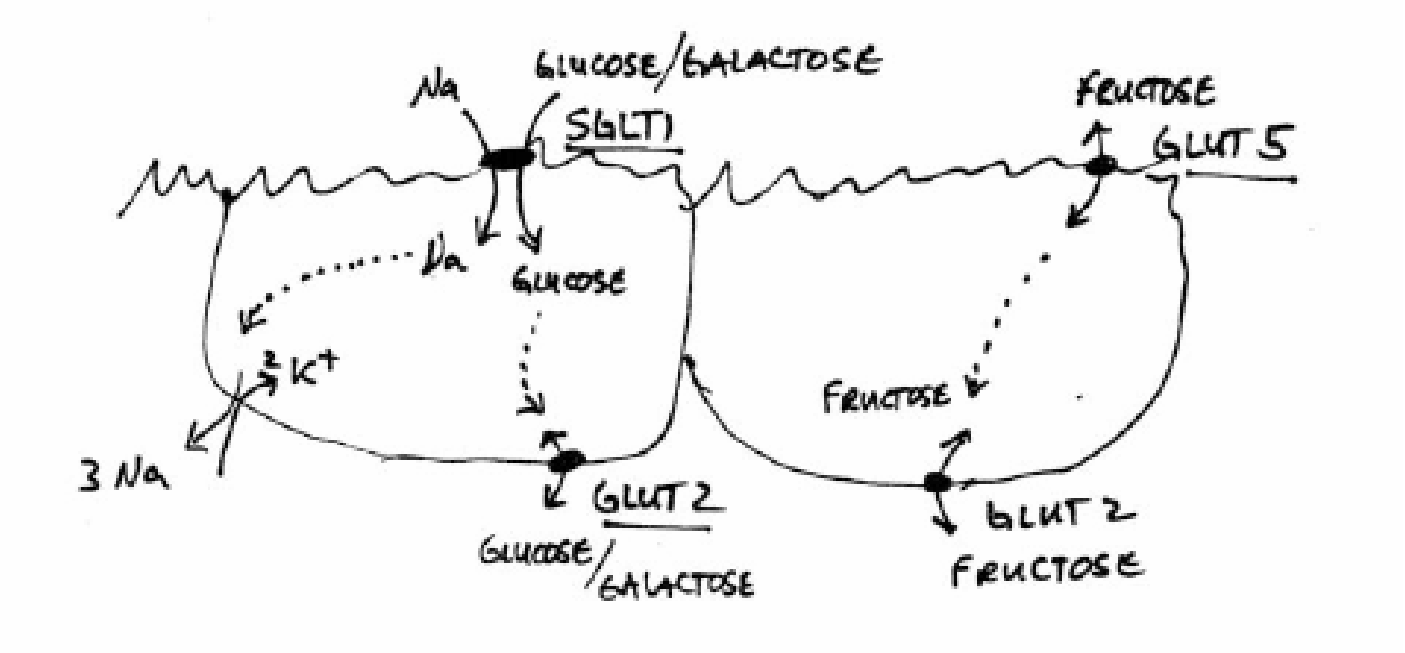
Carbohydrates

Terminal Digestion

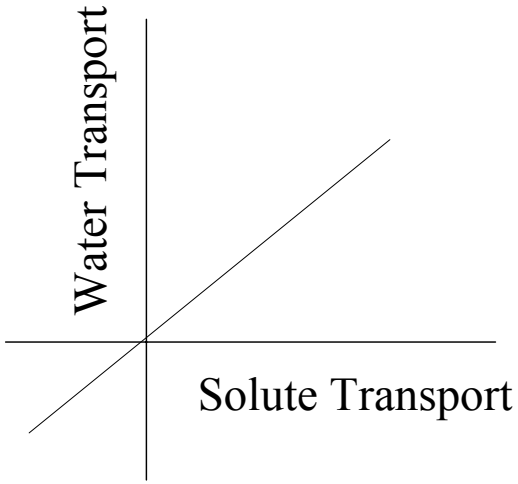


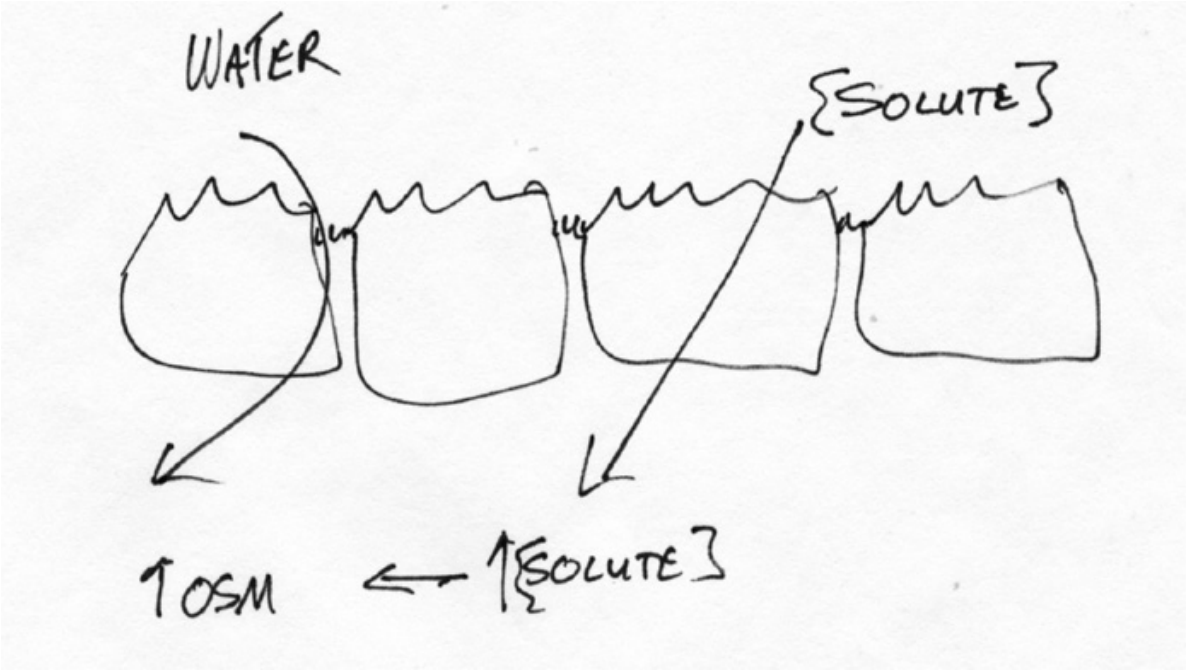
Carbohydrates

Sugar Transport/Absorption

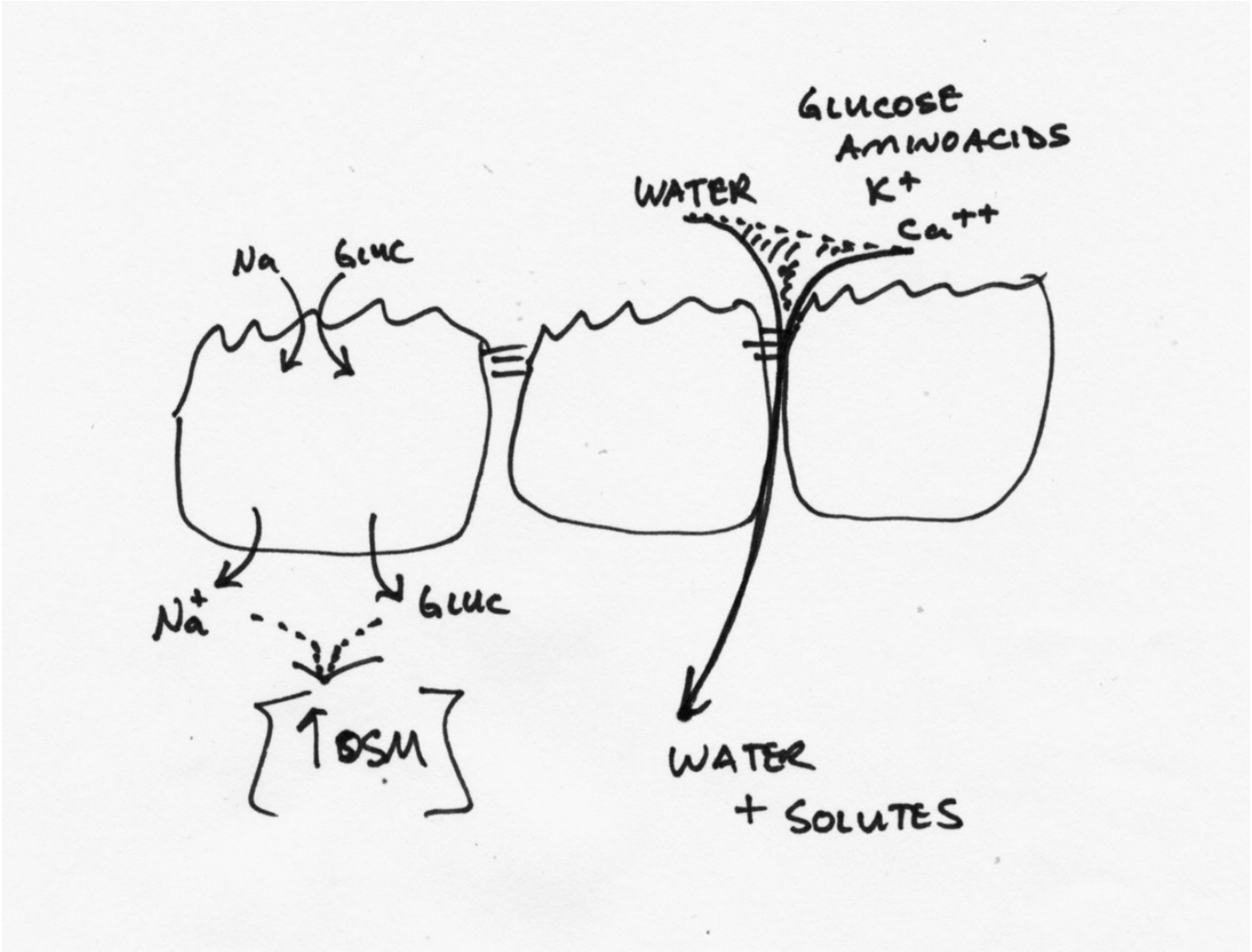


Water Transport: solvent transport by osmotic driving force





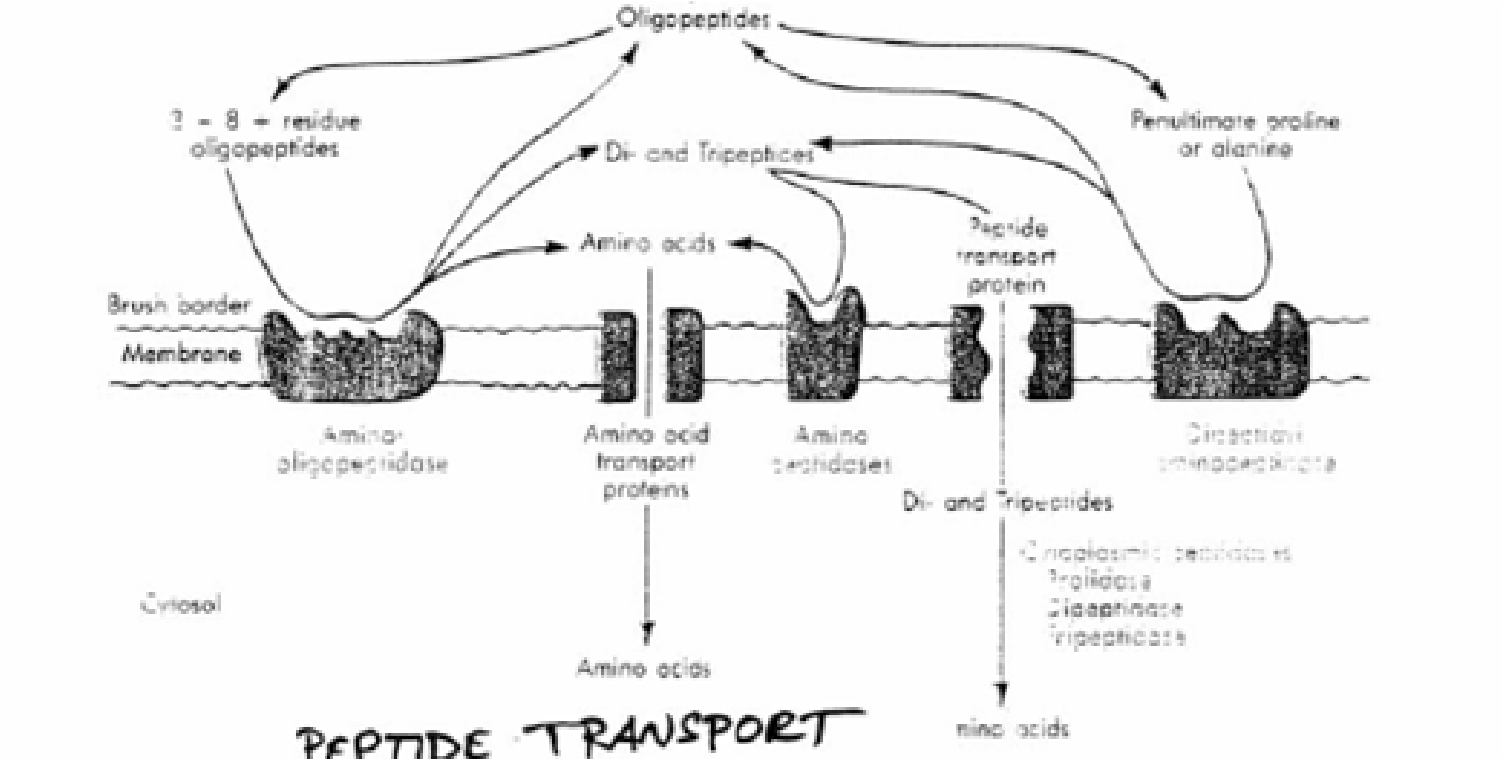
Solvent Drag: solute transport convection



Proteins

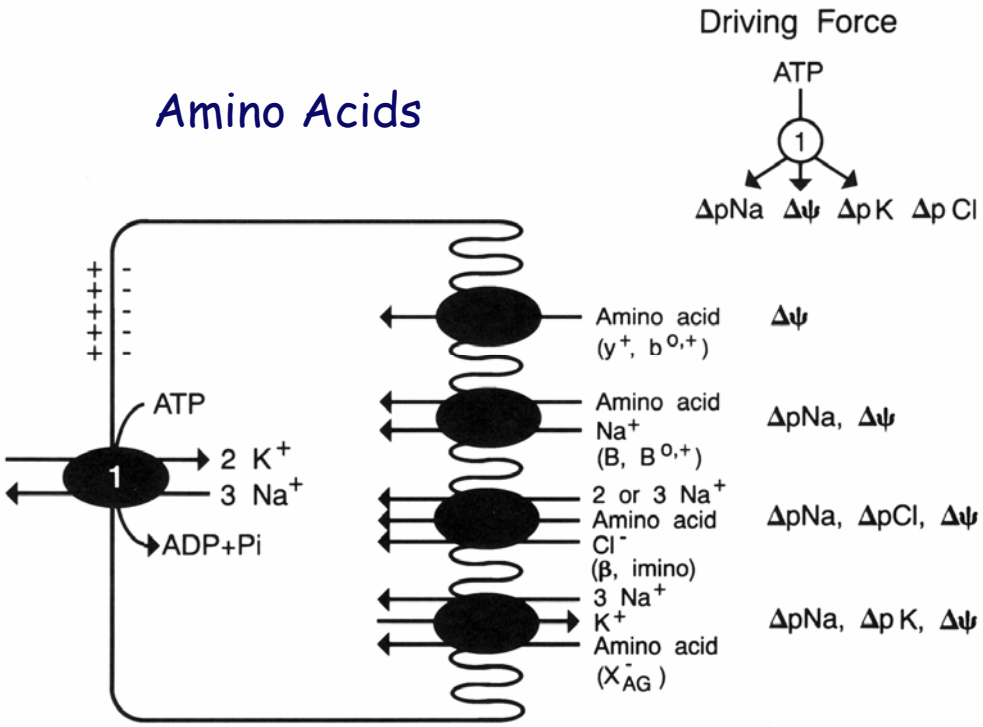
Terminal Digestion

leu-phe-tyr-ala-ser-gly-asp-lys-ser-gly-

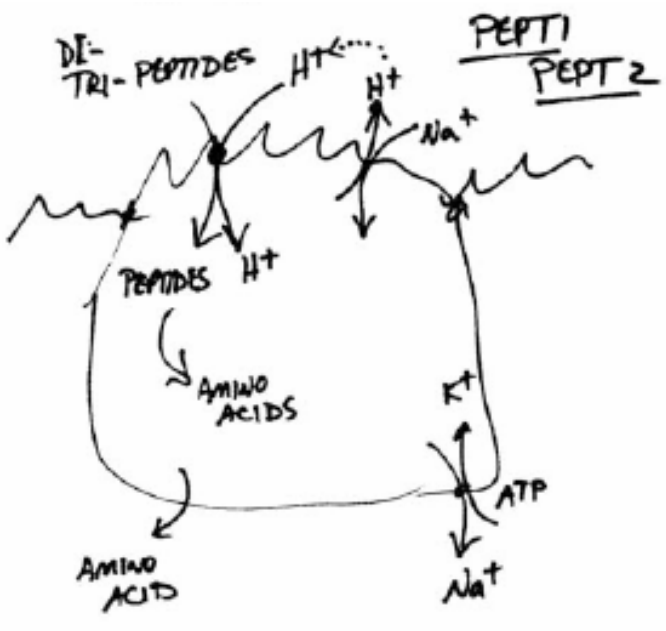


Proteins:
Amino Acid and Peptide Transport/Absorption

Amino Acids



Peptides



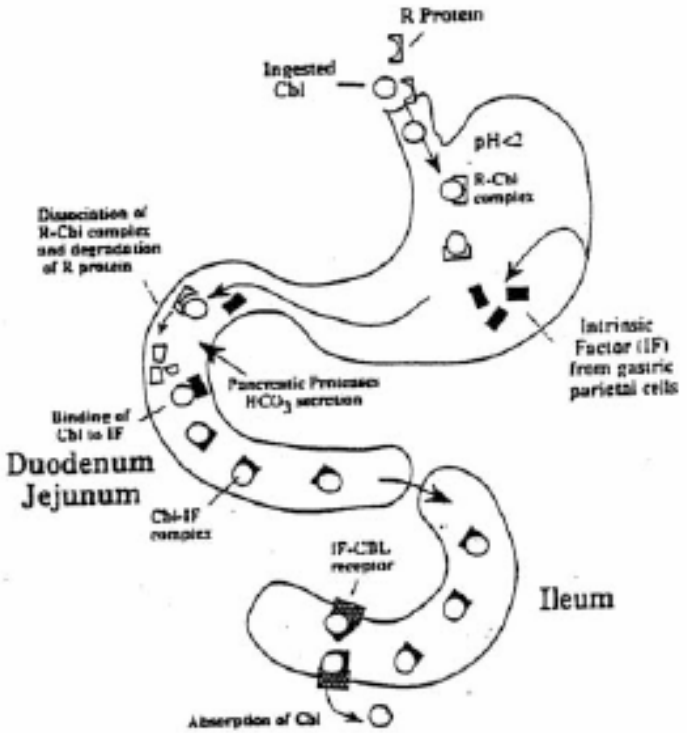
Clinical correlates related to carbohydrate absorption

1) Sucrase isomaltase defficiency
2) Lactace defficiency - primary or secondary
3) *Glucose-galactose malabsorption:* Very rare congenital defect in monosaccharide transport.
4) Oral rehydration salts

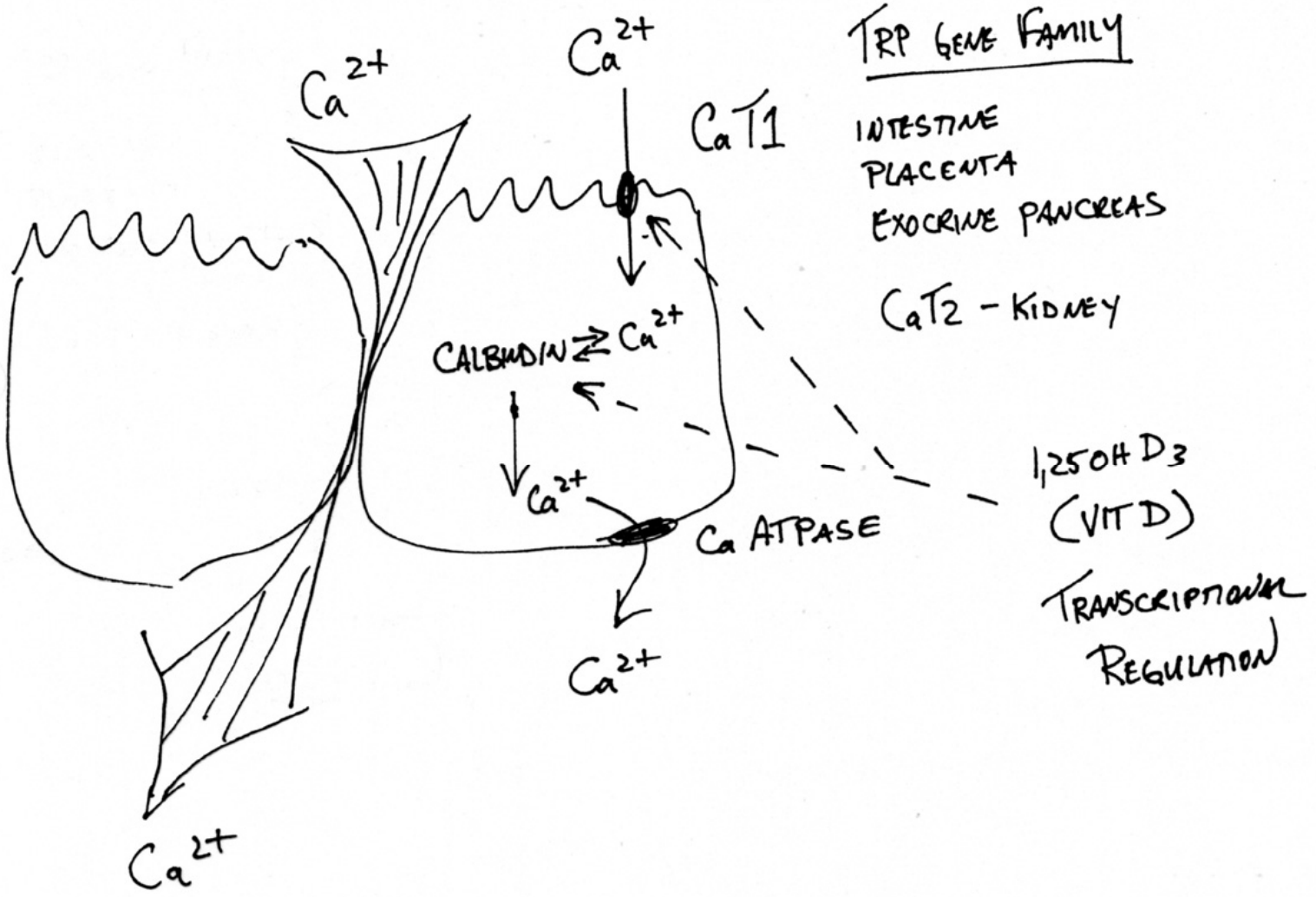
Clinical correlates related to amino acid absorption

1) Hartnup disease - defective renal tubular and intestinal resorption of tryptophan and other neutral amino acids
2) Cystinuria - defective intestinal transport for basic amino acids

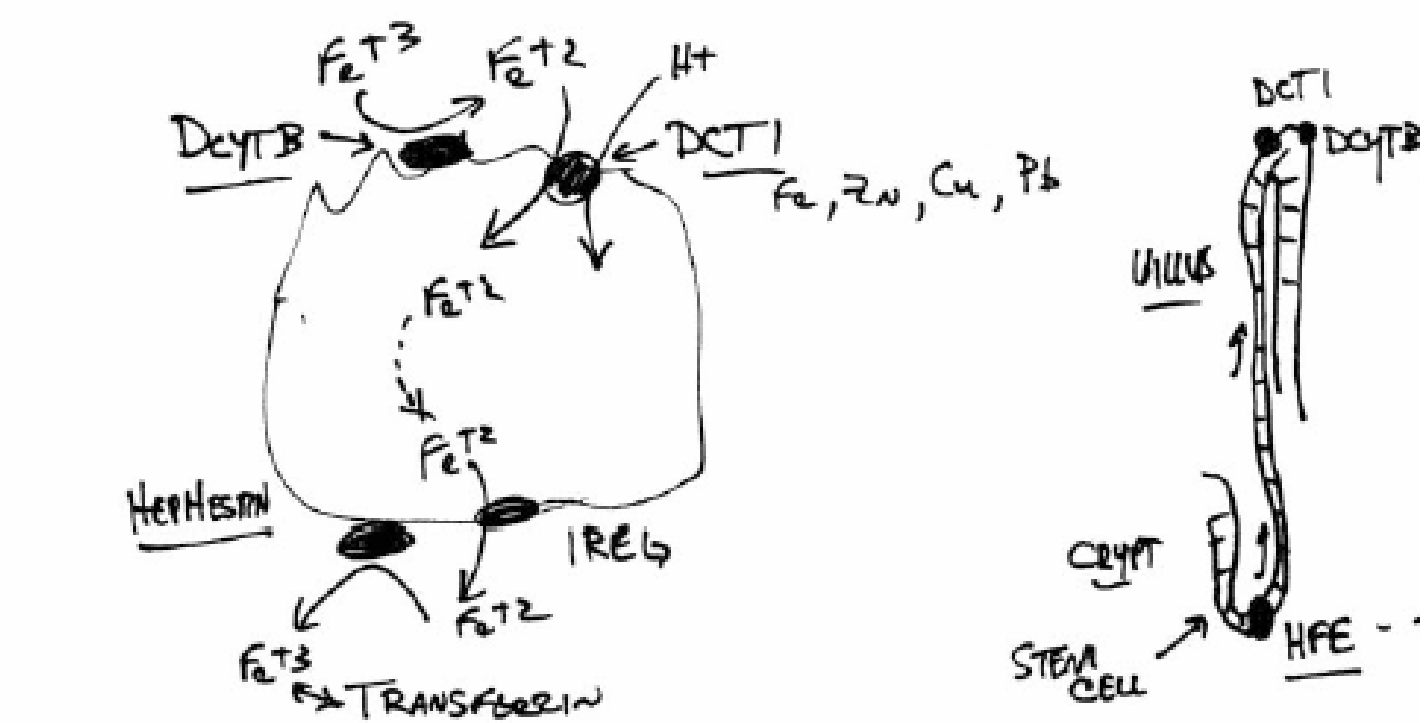
Vitamin B12: Absorption by endocytosis



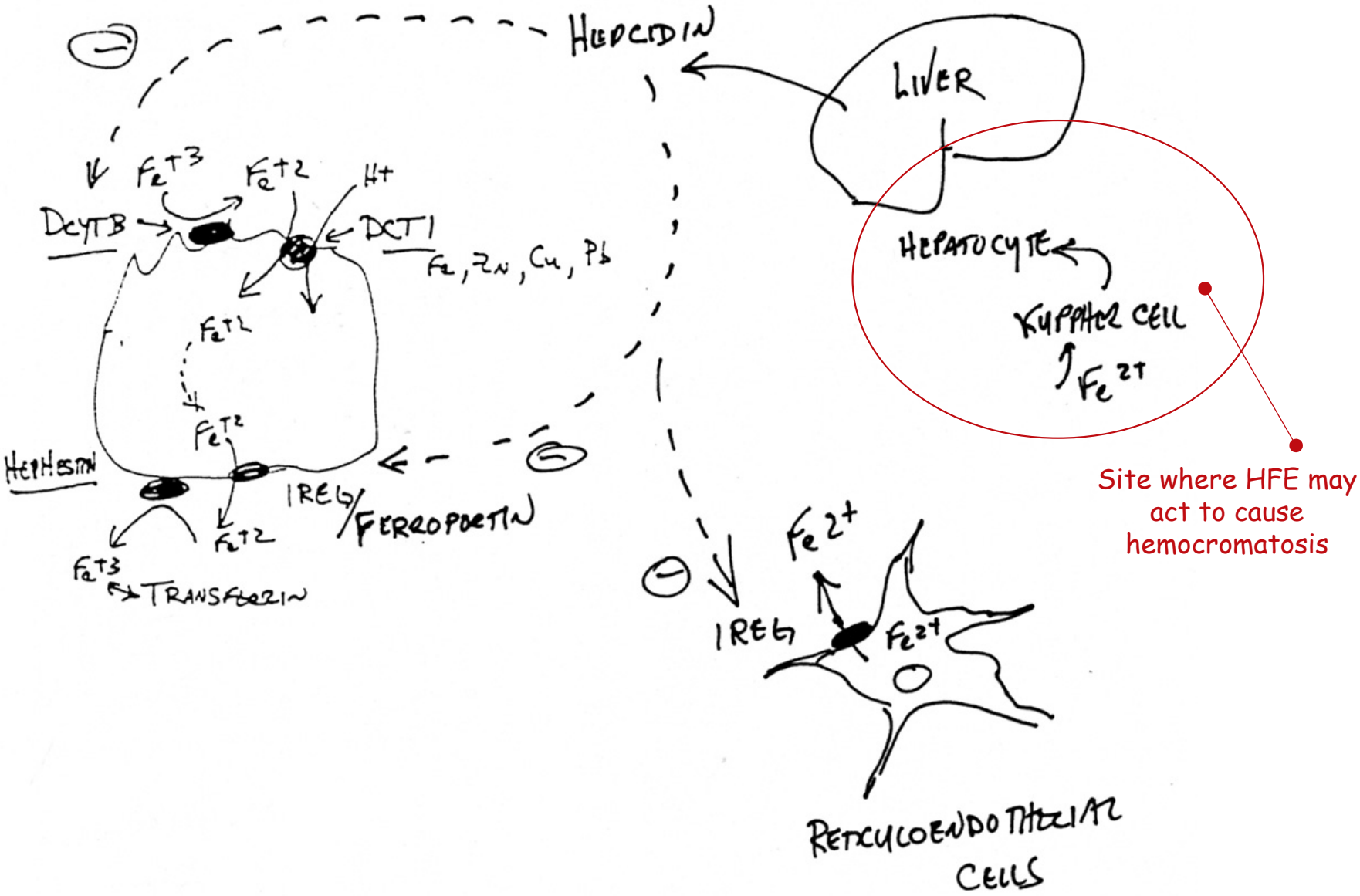
Calcium

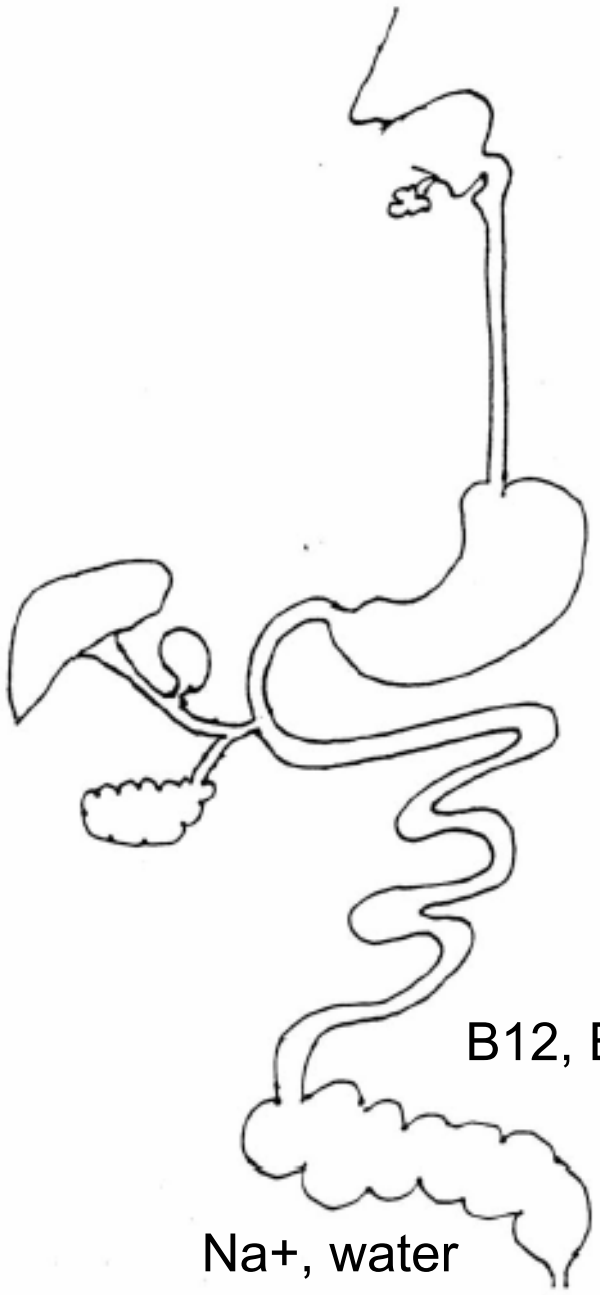

Ca2+
Ca2+
CaT1
TRP GENE FAMILY
INTESTINE
PLACENTA
EXOCRINE PANCREAS
CaT2 - KIDNEY
CALBINDIN ⇄ Ca2+
Ca2+
1,25OH D3
(VIT D)
Ca ATPASE
TRANSCRIPTIONAL
REGULATION
Ca2+
Ca2+

Iron: body stores regulated at level of intestinal absorption



Iron: Regulation of serum Fe and Fe absorption





Fe2+, bulk of nutrient solutes trace elements

B12, Bile acids, Na+

Na+, water

Surgery

Infections - rotavirus, giarrdia

IBD

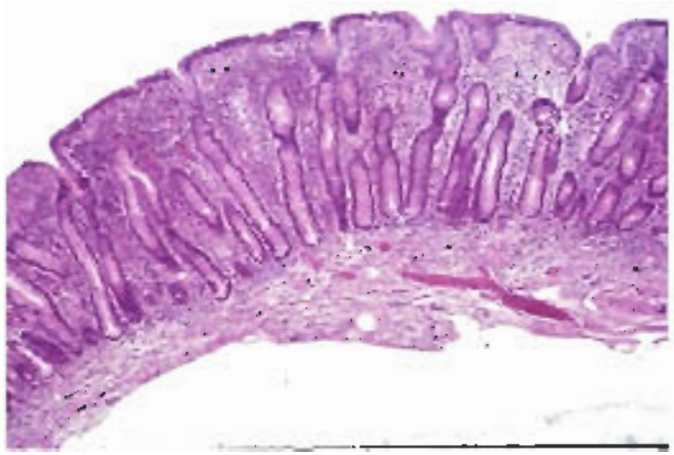
Motility

Blockage/cancer/adhesions

Allergic enteropathy

Bacterial overgrowth

Celiac disease



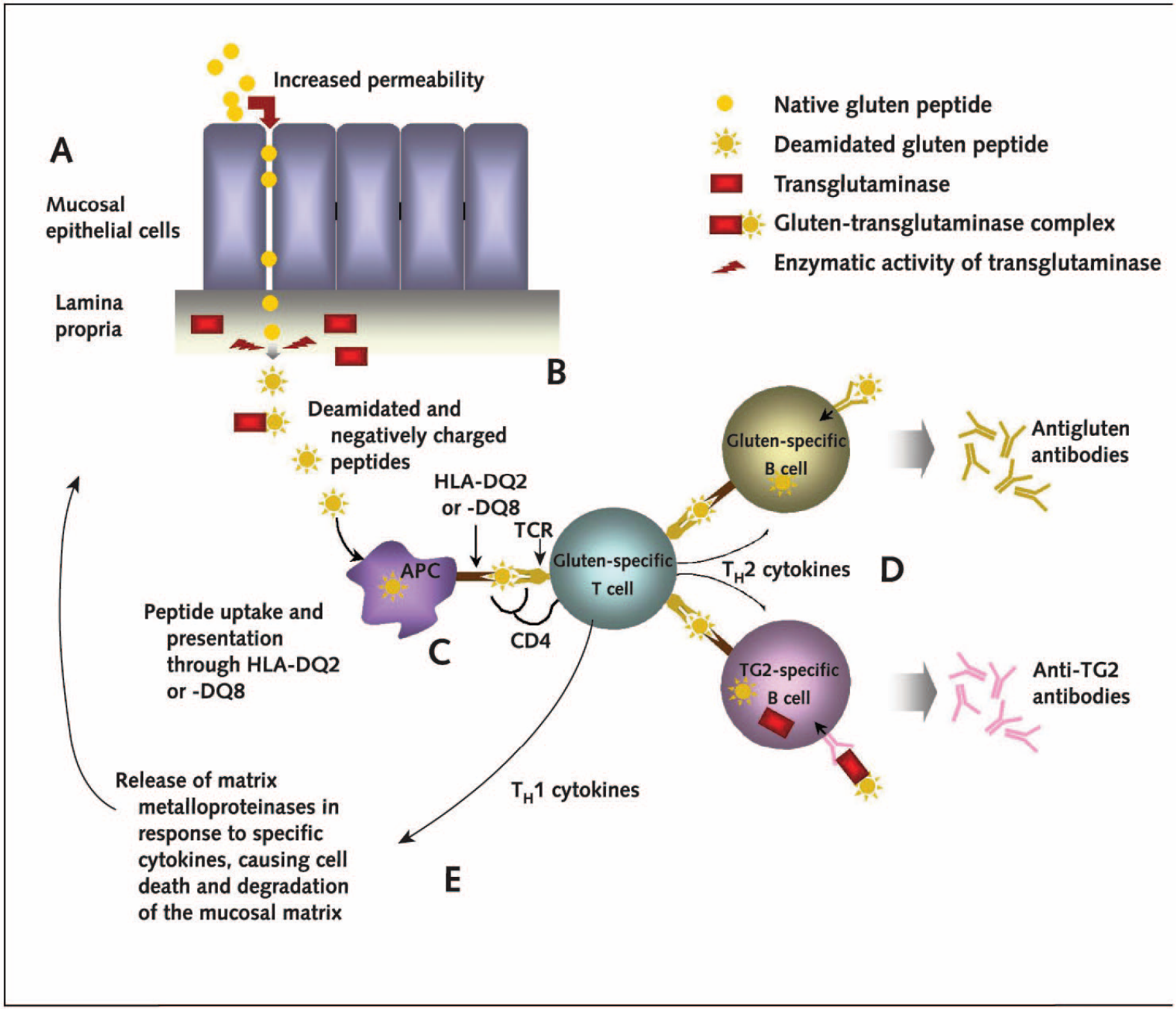
Celiac Disease

“ Immune mediated enteropathy caused by permanent sensitivity to gluten in genetically susceptible individuals”

(NASPGHAN Clinical Practice Guidelines)

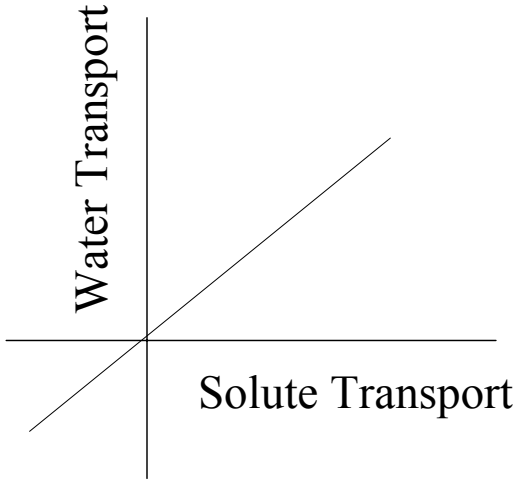
Gliadin Triggers Celiac Disease

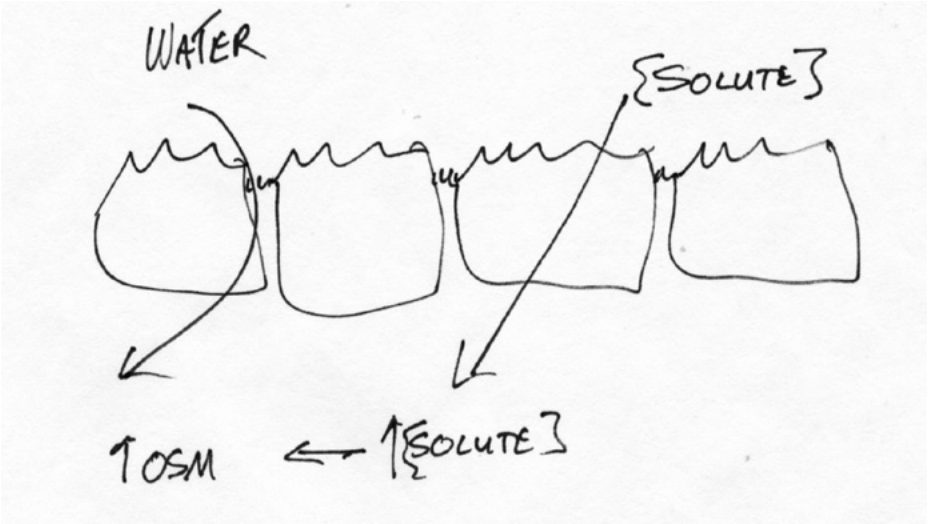
- Rich in proline & glutamine amino acids
- Resistant to digestion
- Interacts with the mucosal epithelial cell barrier (at the apical and basal layers) and is a substrate of tissue transglutaminase

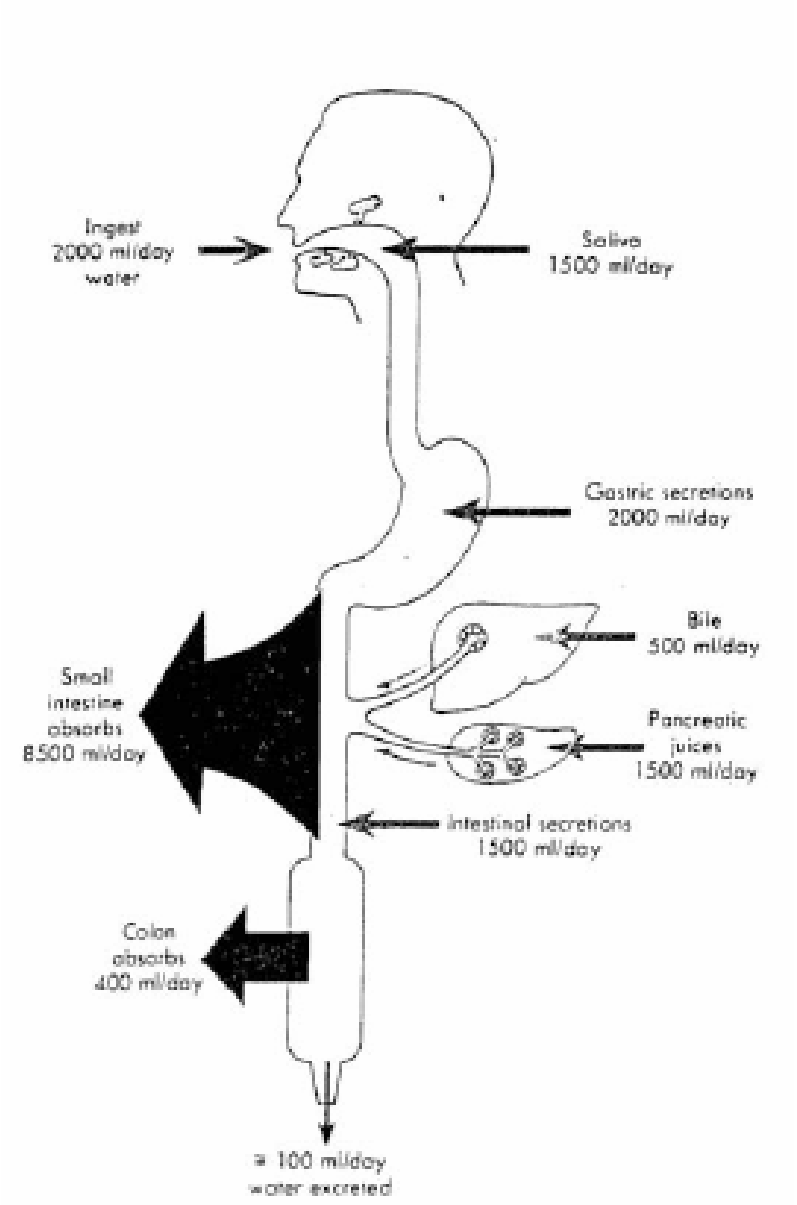


Narrative Review: Celiac Disease: Understanding a Complex Autoimmune Disorder Armin Alaedini, PhD, and Peter H.R. Green, MD, Ann Intern Med. 2005;142:289-298.

Intestinal Secretion and Water Metabolism



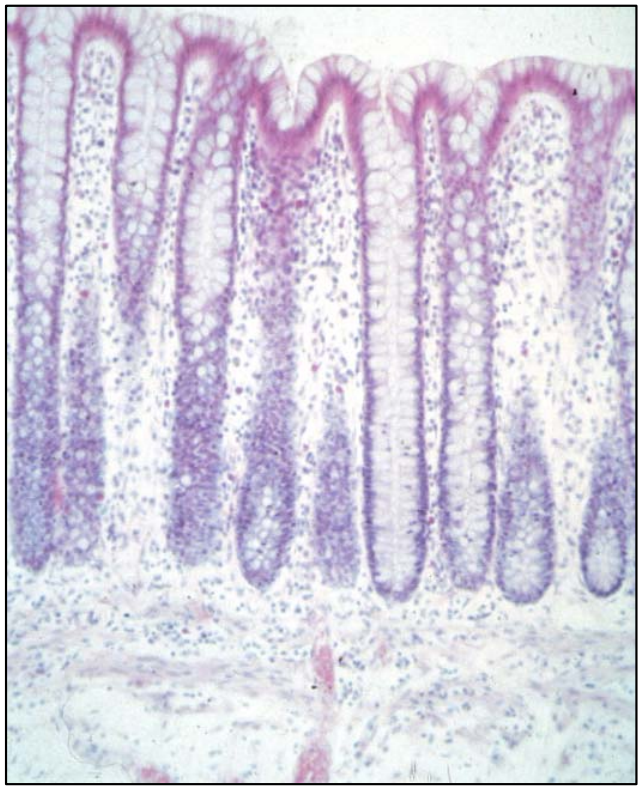




Colon

salt and water transport

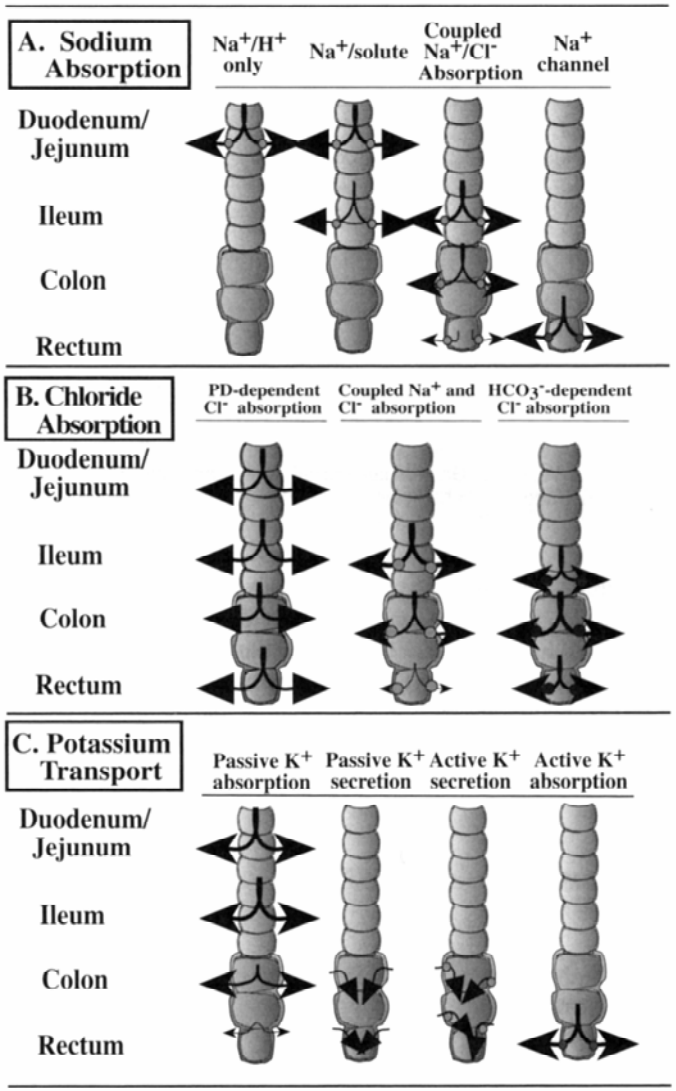
Storage

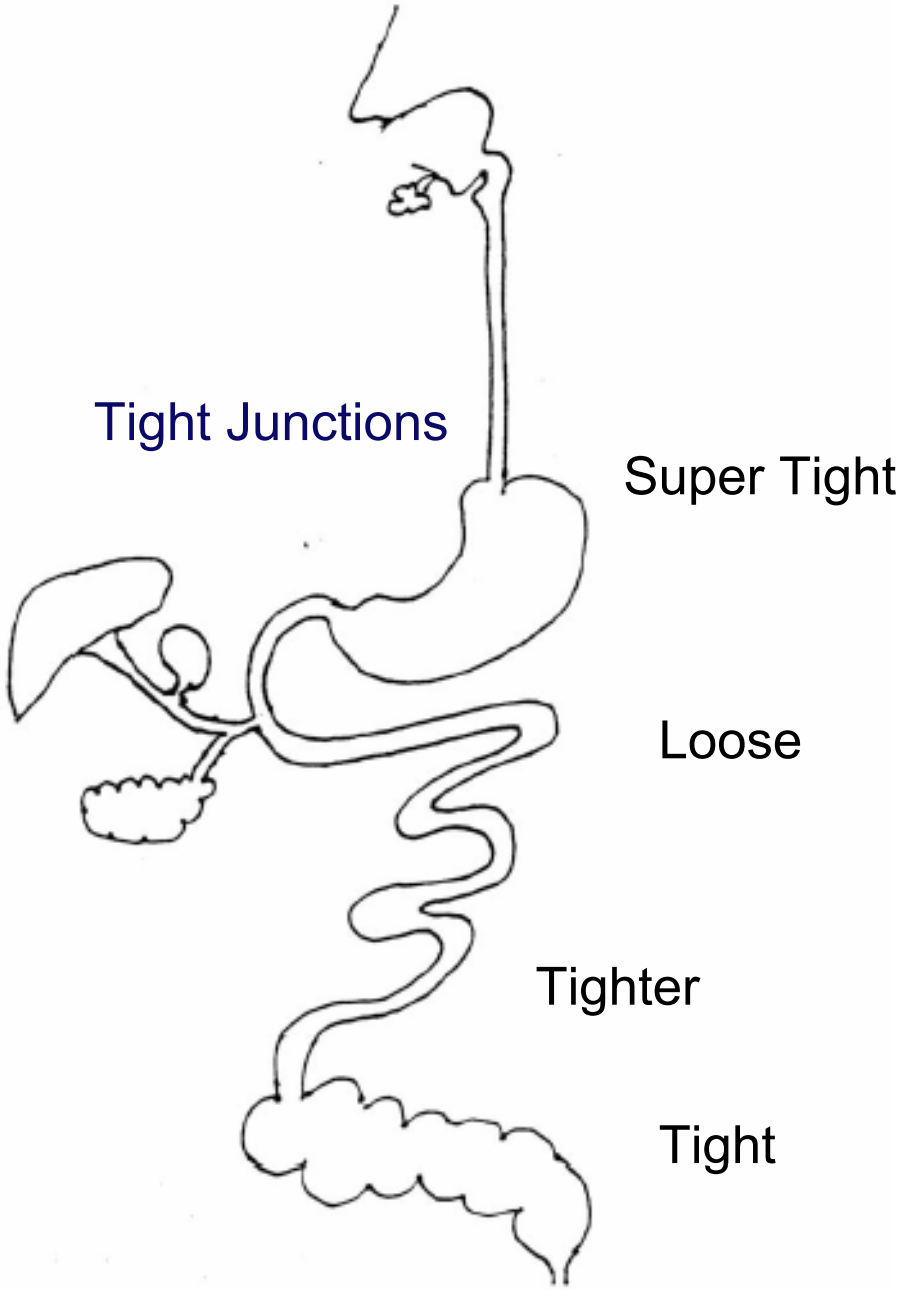


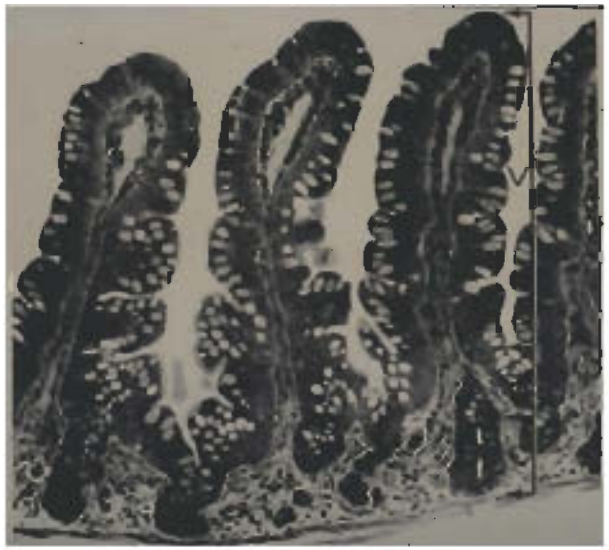
h) Regional differences of intestinal Na^+ transport in man:

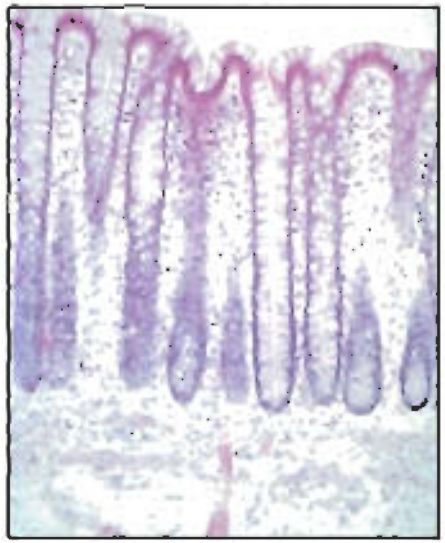
	Jejunum	Ileum	Colon
Colon			
Active transport	+	+	Yes
Solvent drag (major importance)	+	+	No
Glucose increases Na^+ absorption	+	+	No
Na^+ xchanged for H^+	+	+	???
Minimal Na^+ concentration developed (mEq/L)	130	75	25
Aldosterone increases Na^+ absorption	no	no	Yes

Na+ and Water Transport

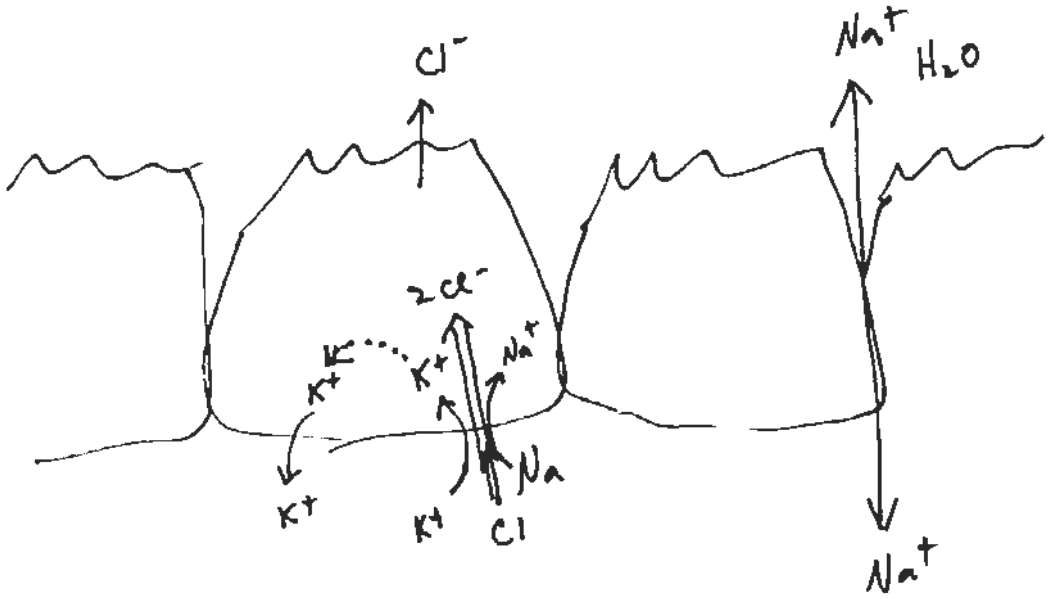




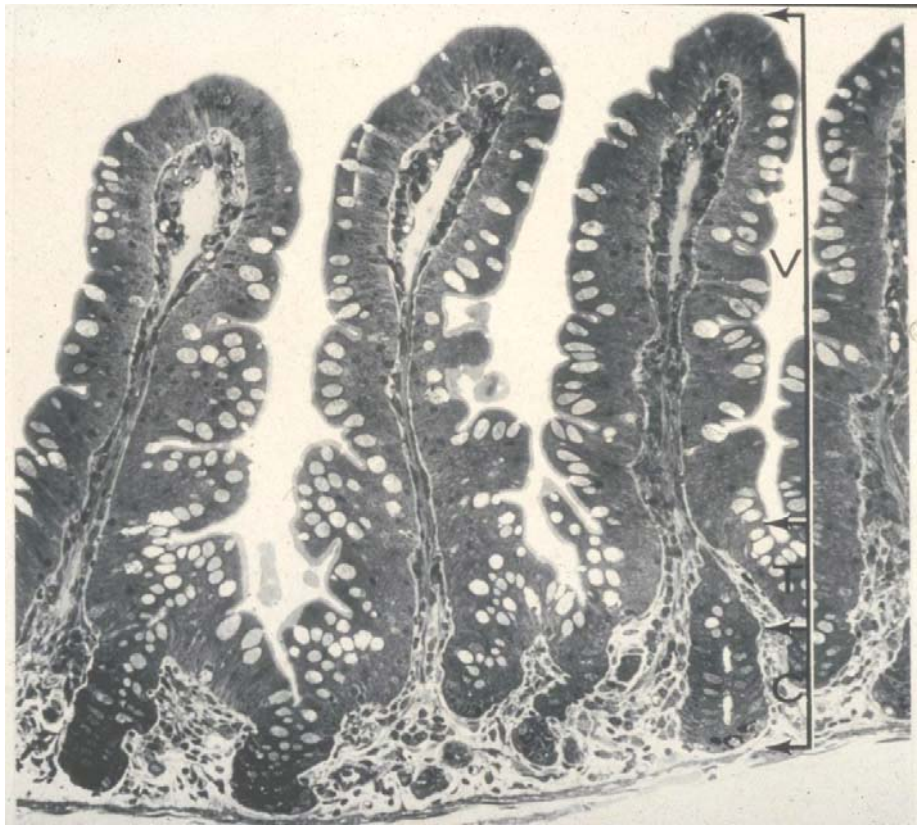


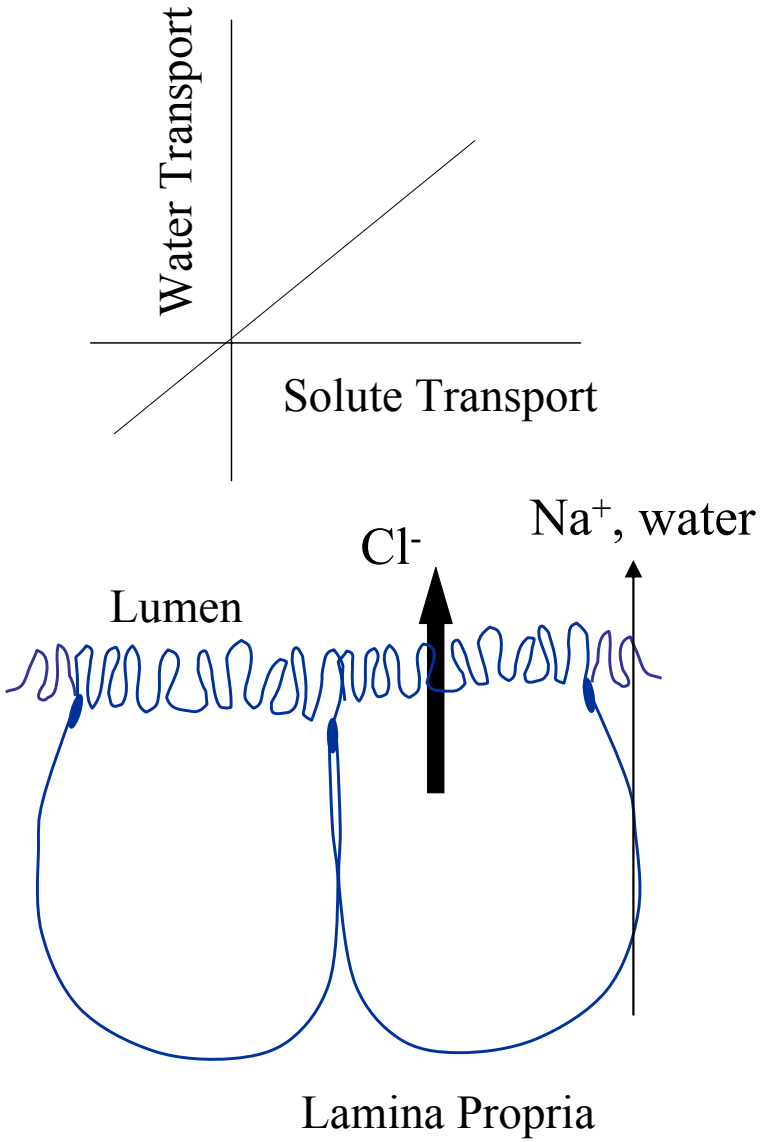


Mechanisms of Salt and Water Secretion

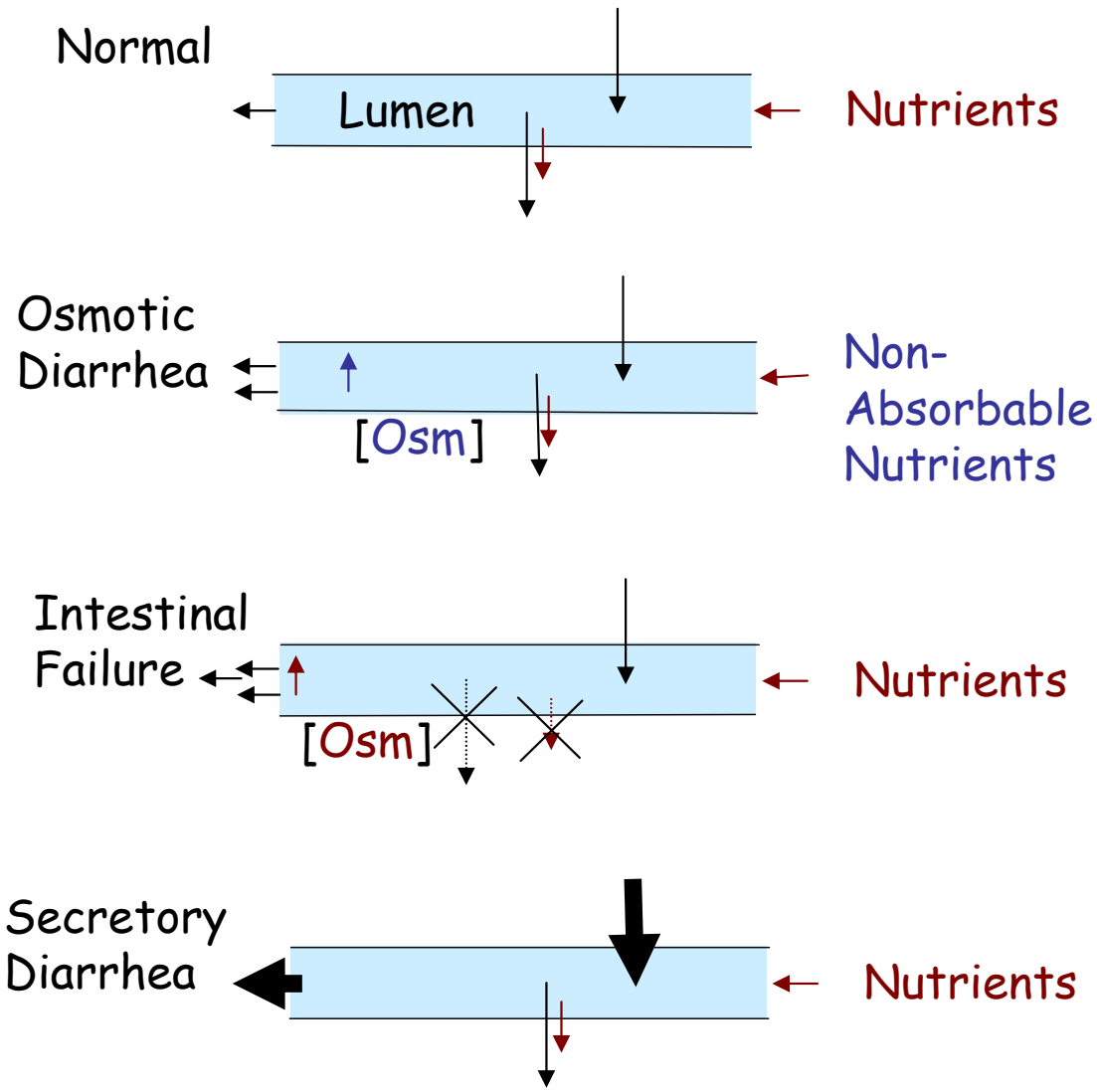


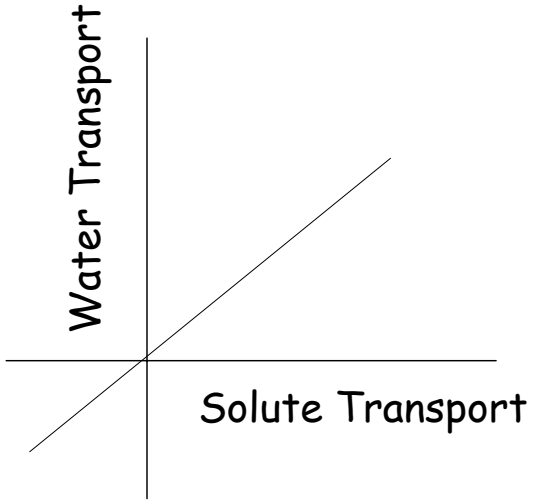
Mechanism of Salt and Water Secretion from the Intestine





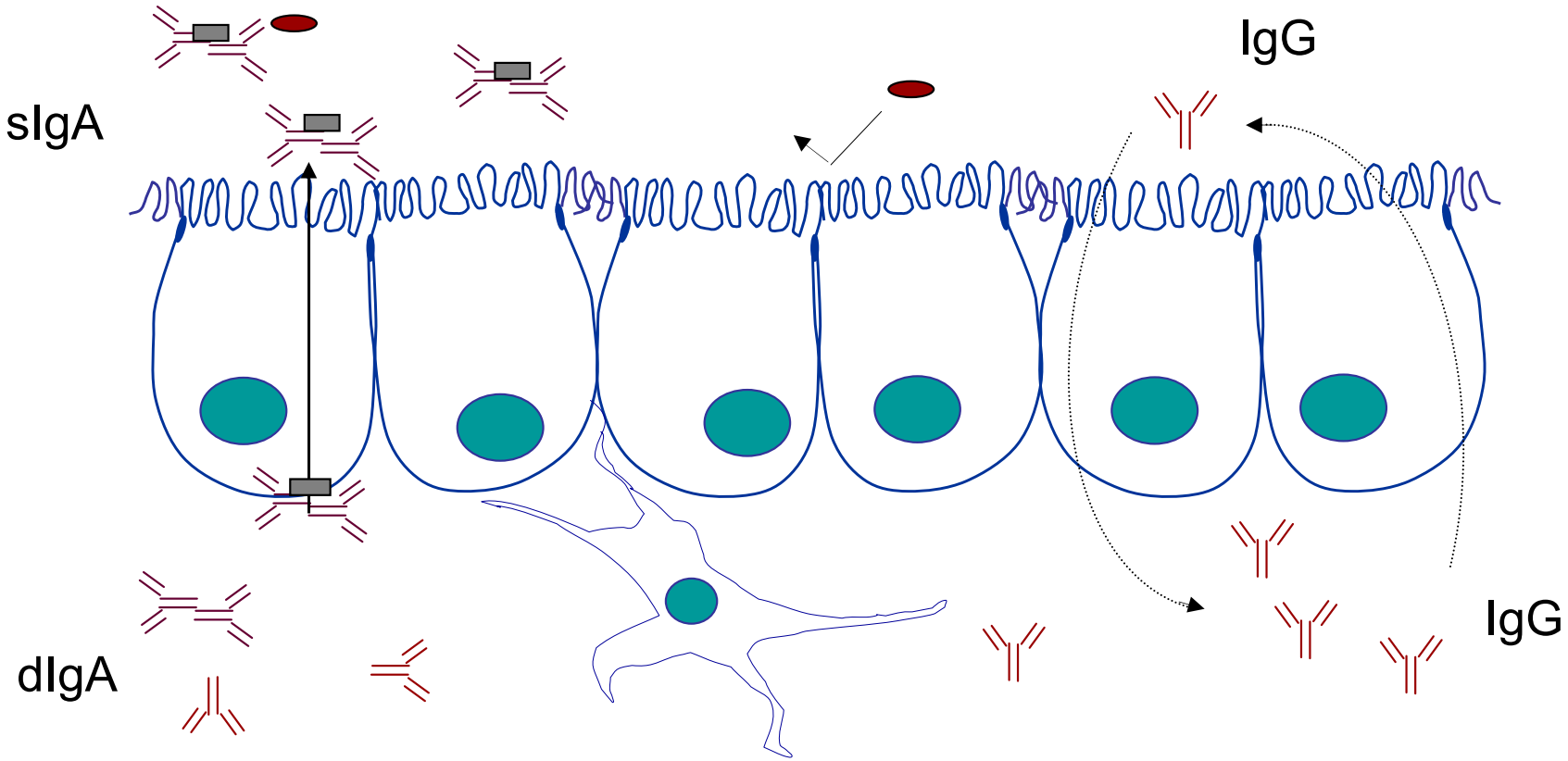
Pathophysiology of Diarrhea



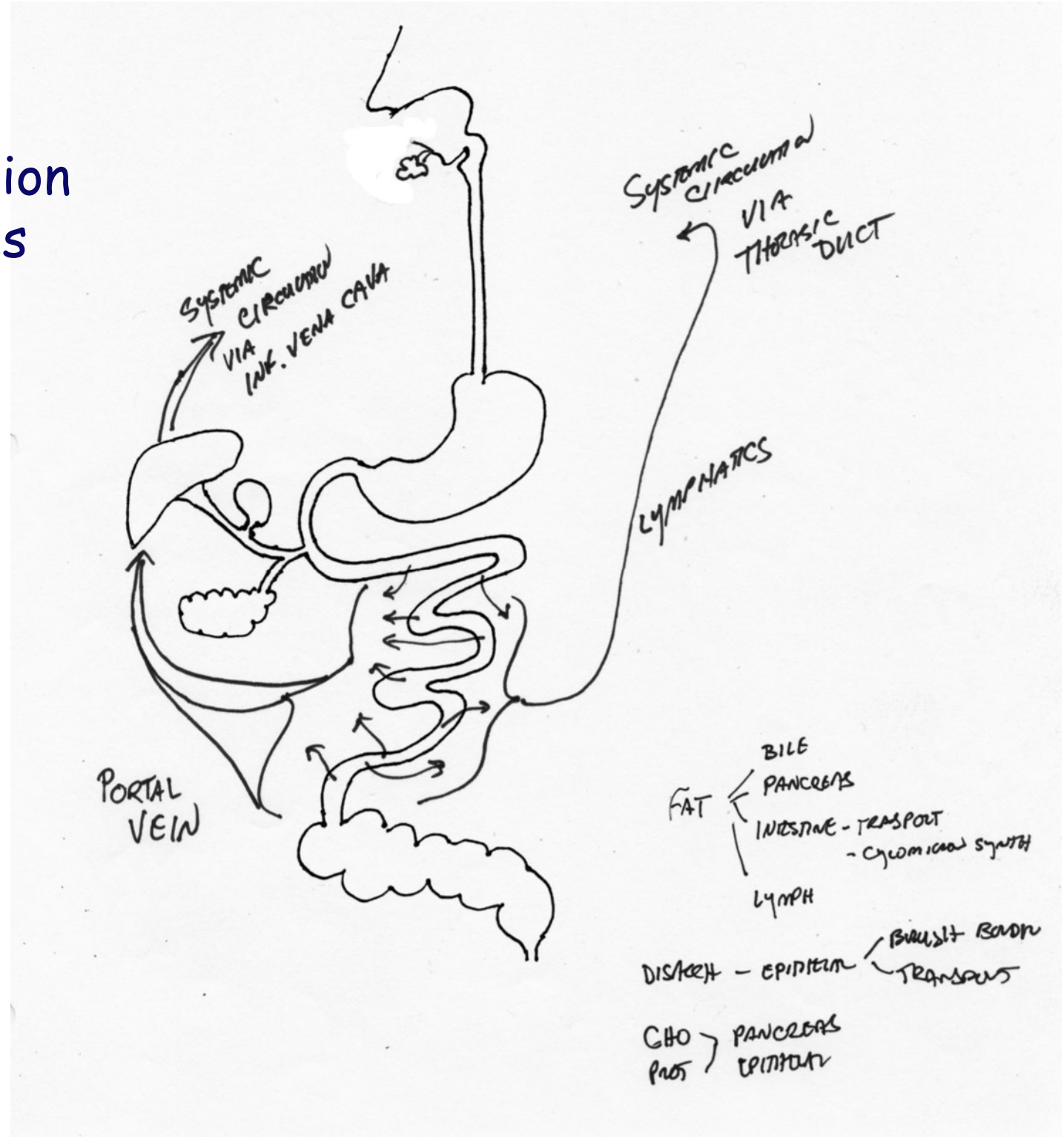


IgA Transport

IgG Transport



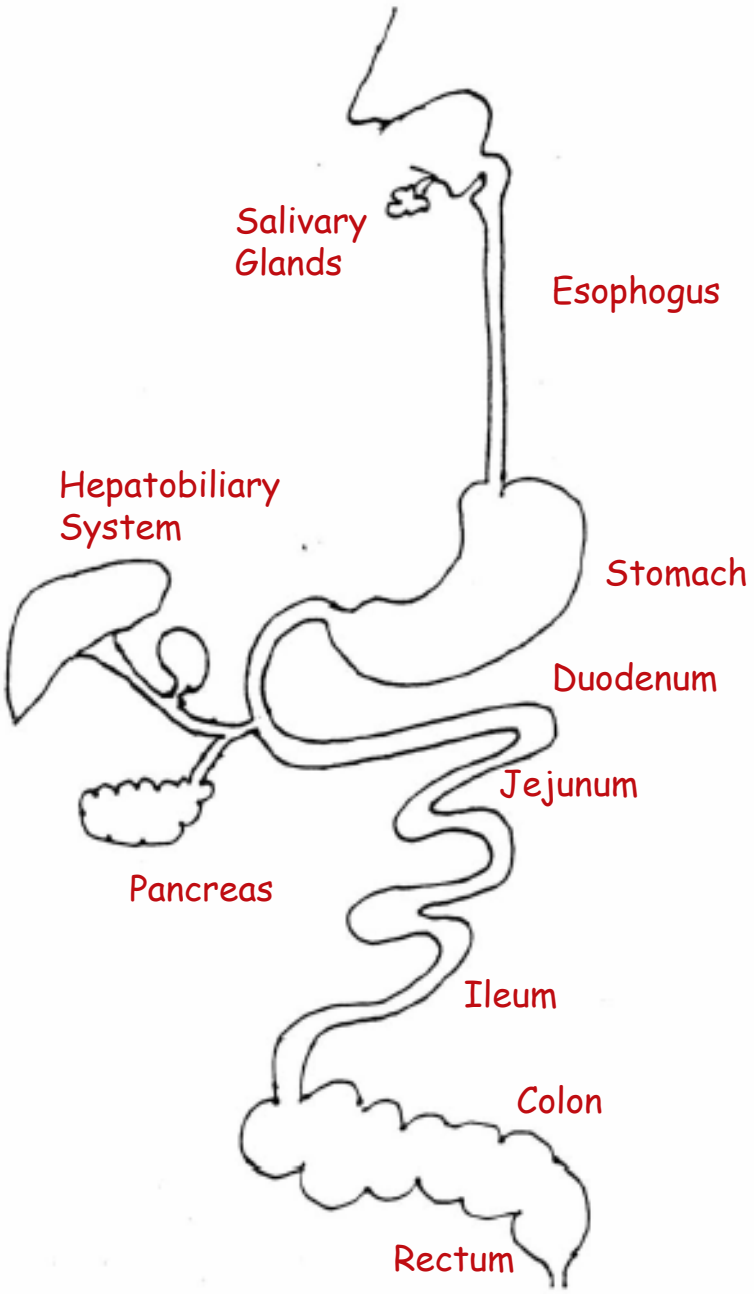
Portal circulation and Lymphatics



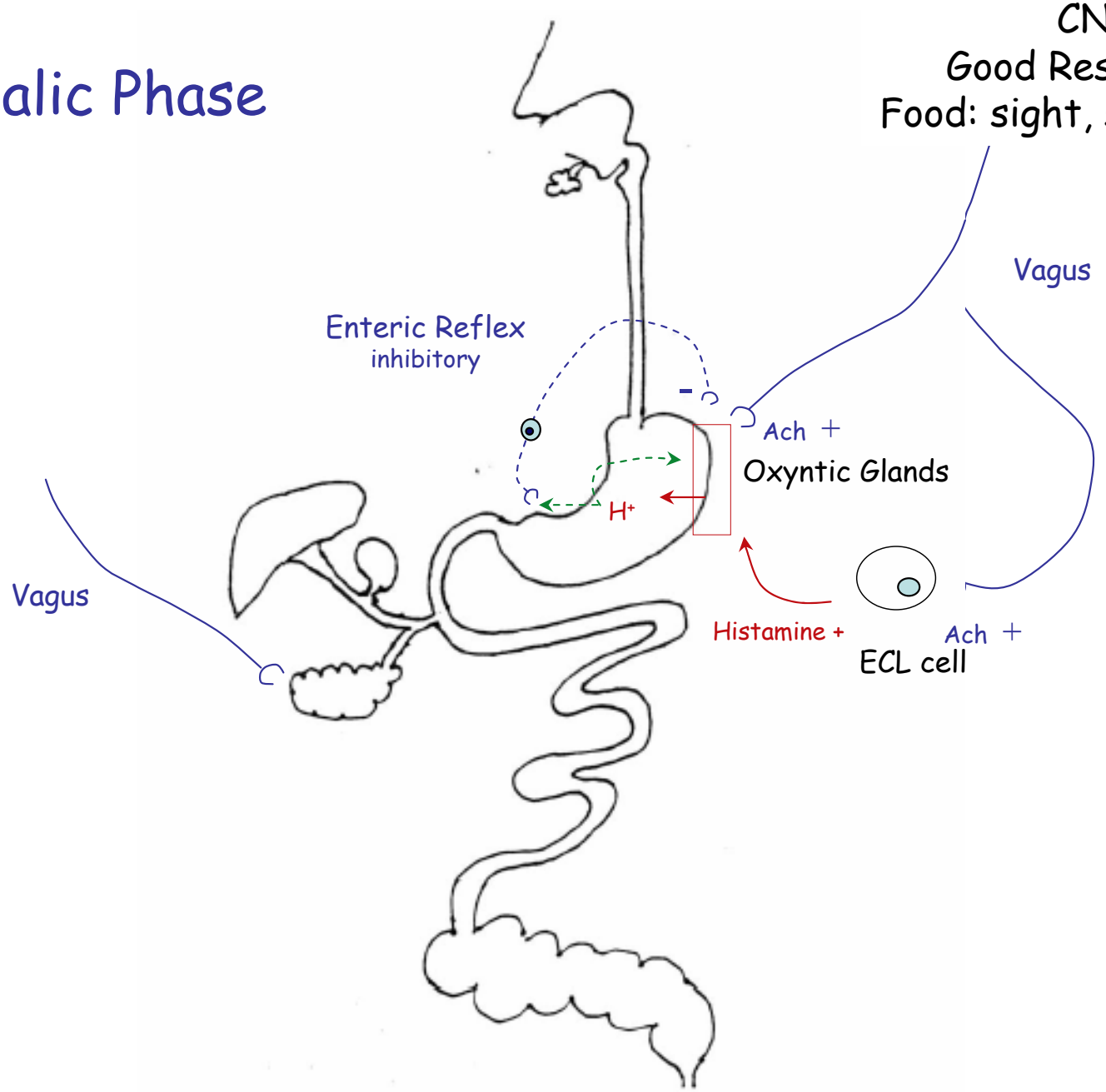
Integrated GI Physiolo

Regulation by:

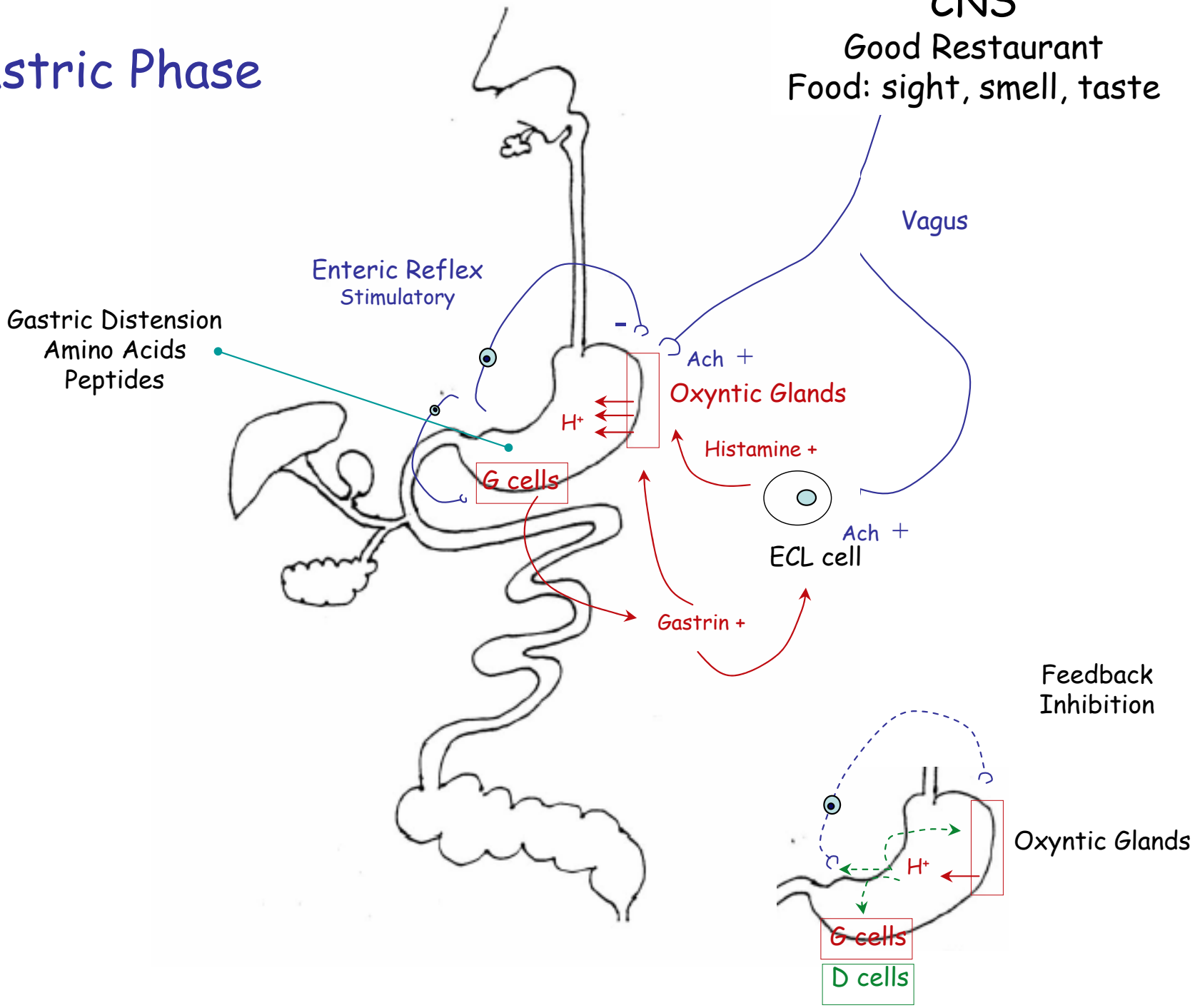
- Endocrine
- Paracrine
- Autocrine
- Neural transmission
  - CNS
  - Enteric



Cephalic Phase

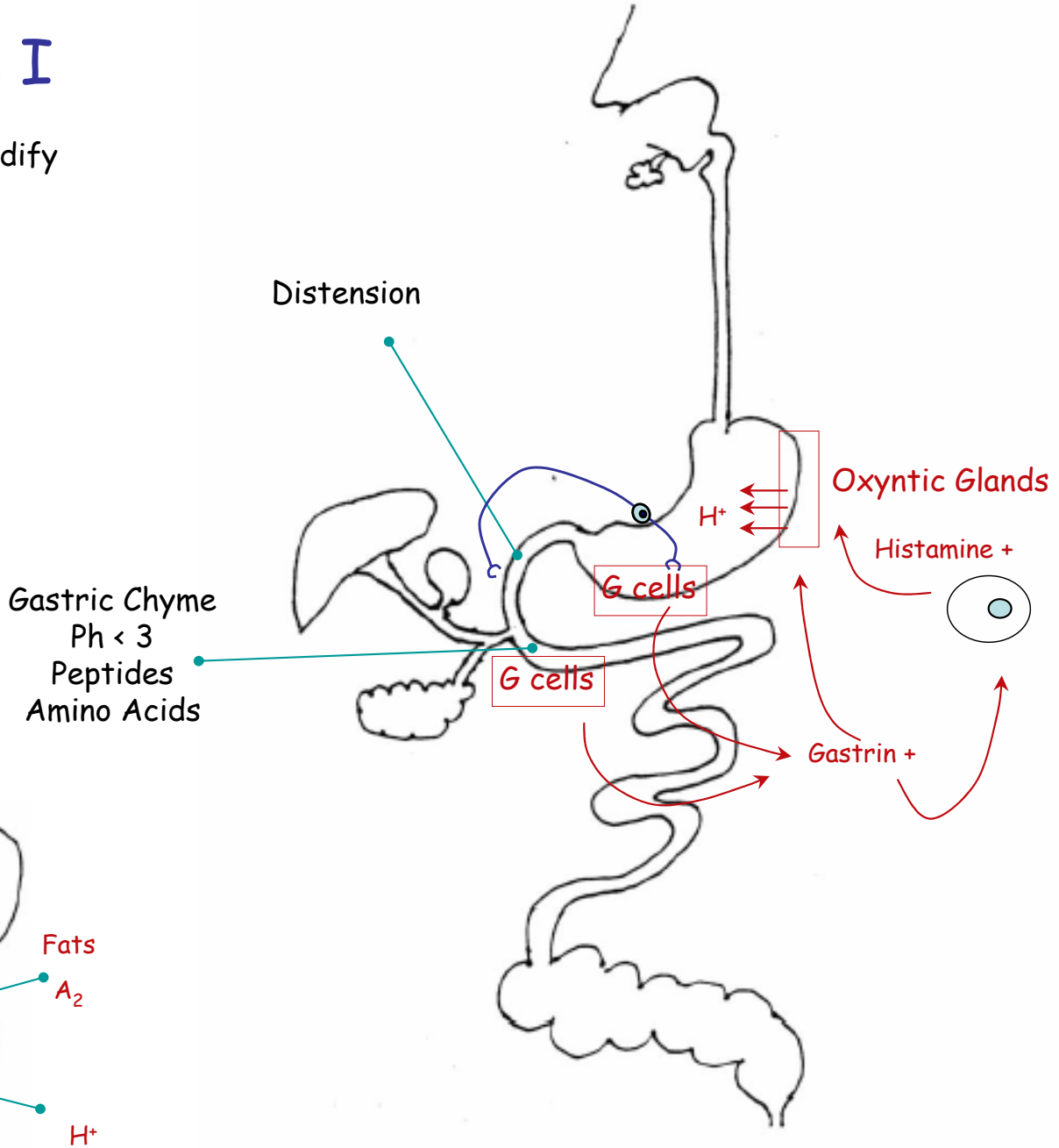


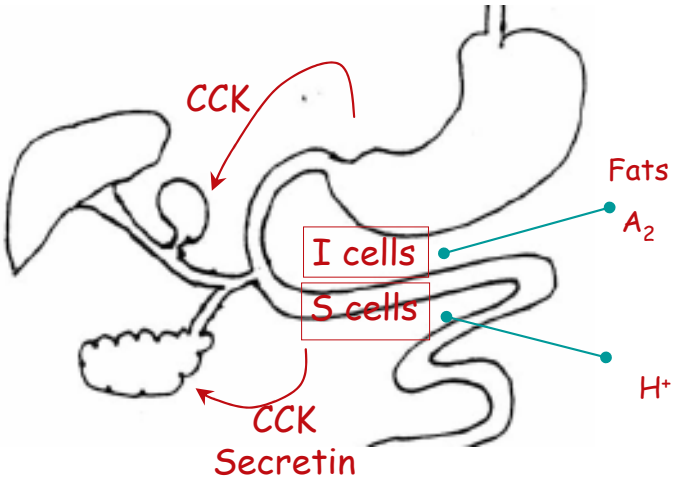
Gastric Phase



Intestinal Phase I

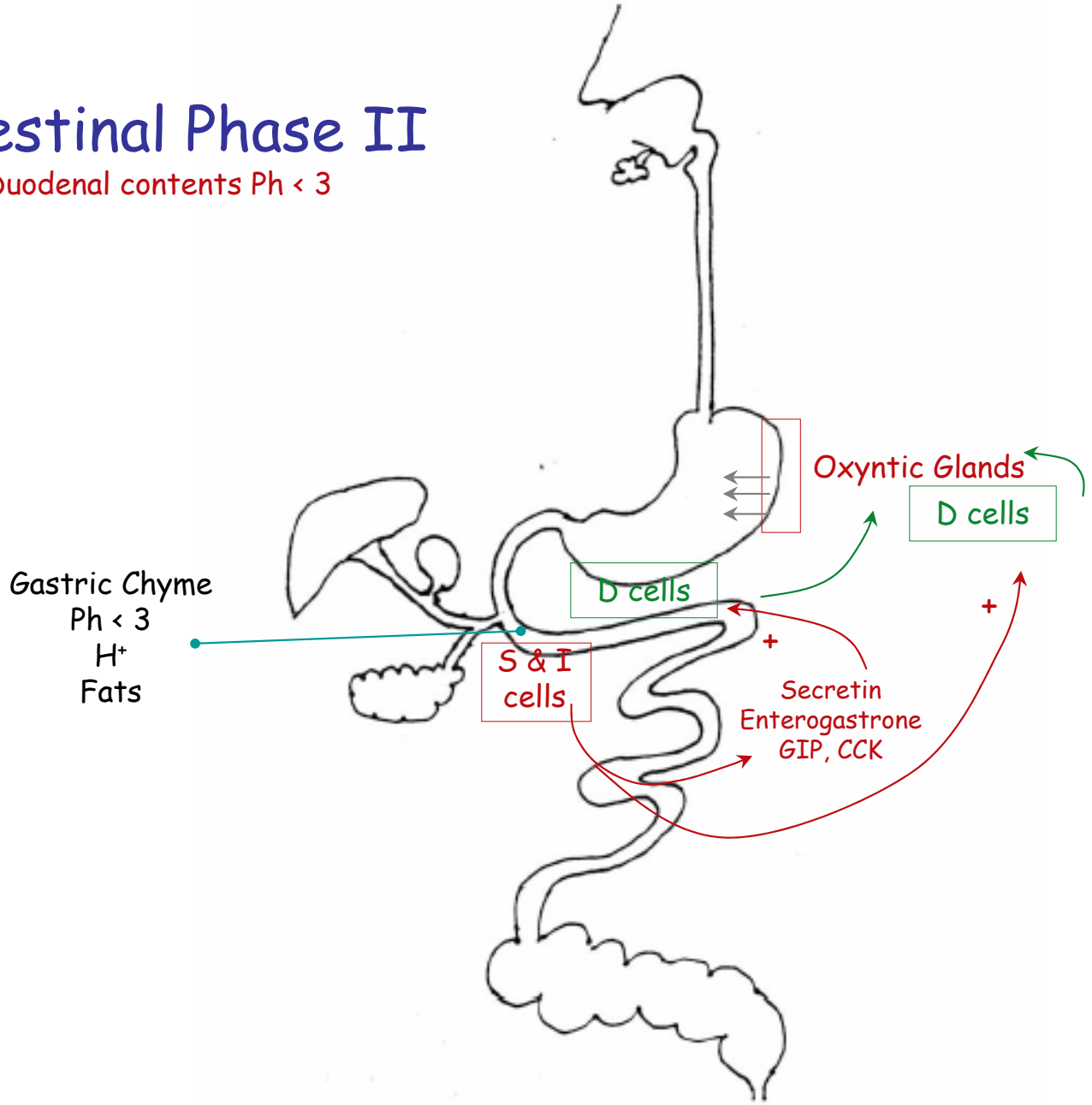
Duodenal contents Ph > 3
(it takes time for stomach to acidify contents after a meal)





Intestinal Phase II

Duodenal contents Ph < 3



Integrated GI Physiolo

Regulation by:

- Endocrine
- Paracrine
- Autocrine
- Neural transmission
  - CNS
  - Enteric