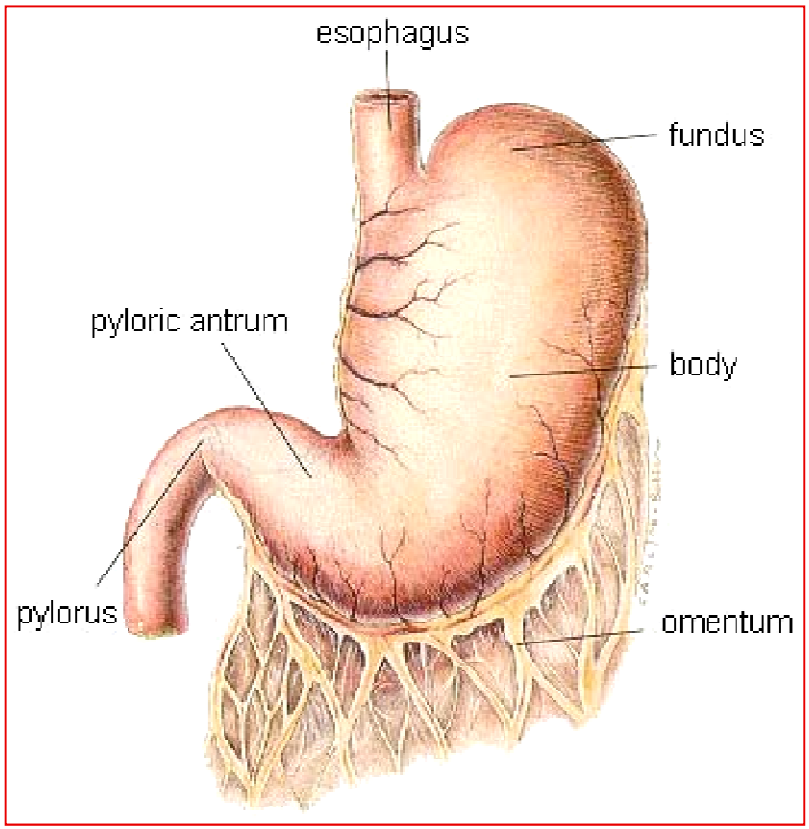
Anatomia, Istologia e Fisiologia dell’Apparato Digerente

STOMACH

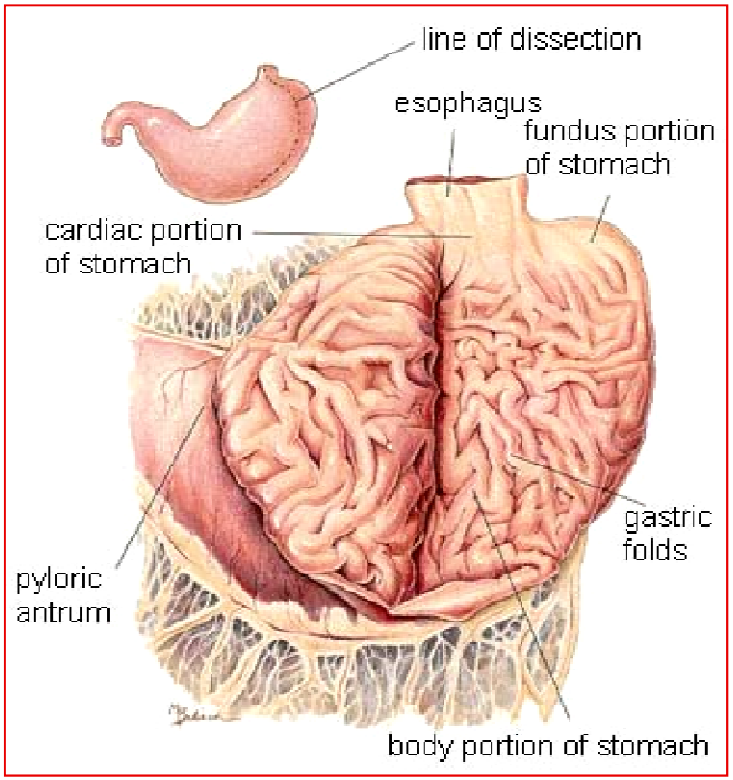
Disorders of the stomach are a frequent cause of clinical disease, with inflammatory and neoplastic lesions being particularly common. In the United States, diseases related to gastric acid account for nearly one third of all health care spending on GI disease. In addition, despite a decreasing incidence in certain locales such as the United States, gastric cancer remains a leading cause of death worldwide.

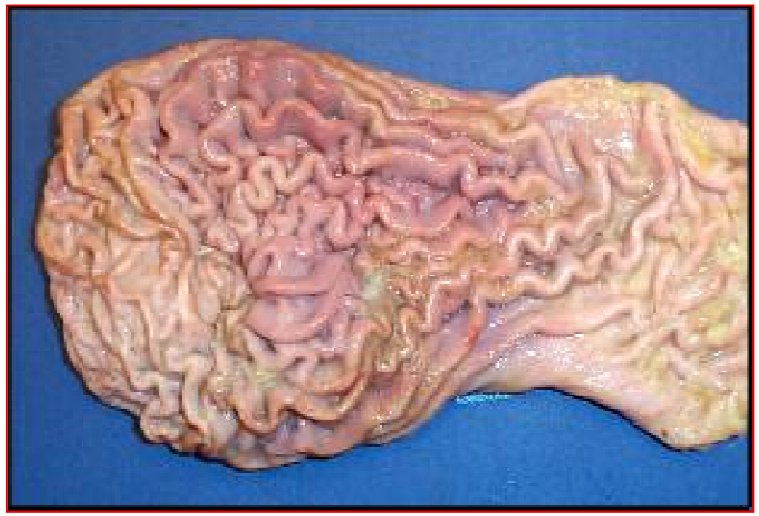
The stomach is divided into four major anatomic regions: the cardia, fundus, body, and antrum. The cardia and antrum are lined mainly by mucin-secreting foveolar cells that form small glands. The antral glands are similar but also contain endocrine cells, such as G cells, that release gastrin to stimulate luminal acid secretion by parietal cells within the gastric fundus and body. The well-developed glands of the body and fundus also contain chief cells that produce and secrete digestive enzymes such as pepsin.

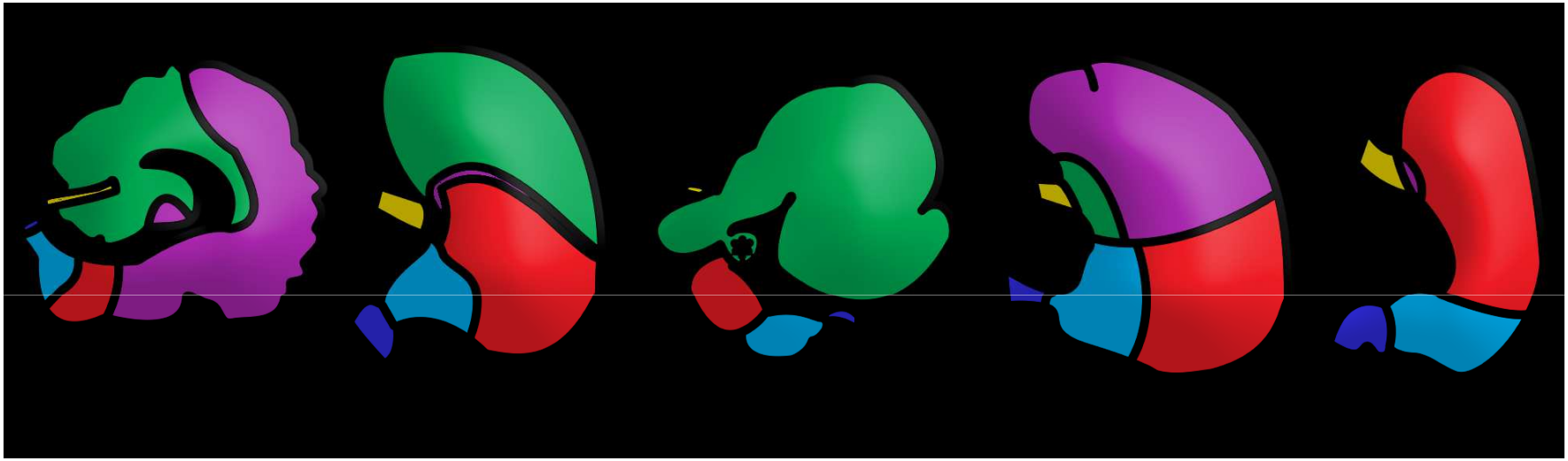
stomaco monogastrici



Washington State University

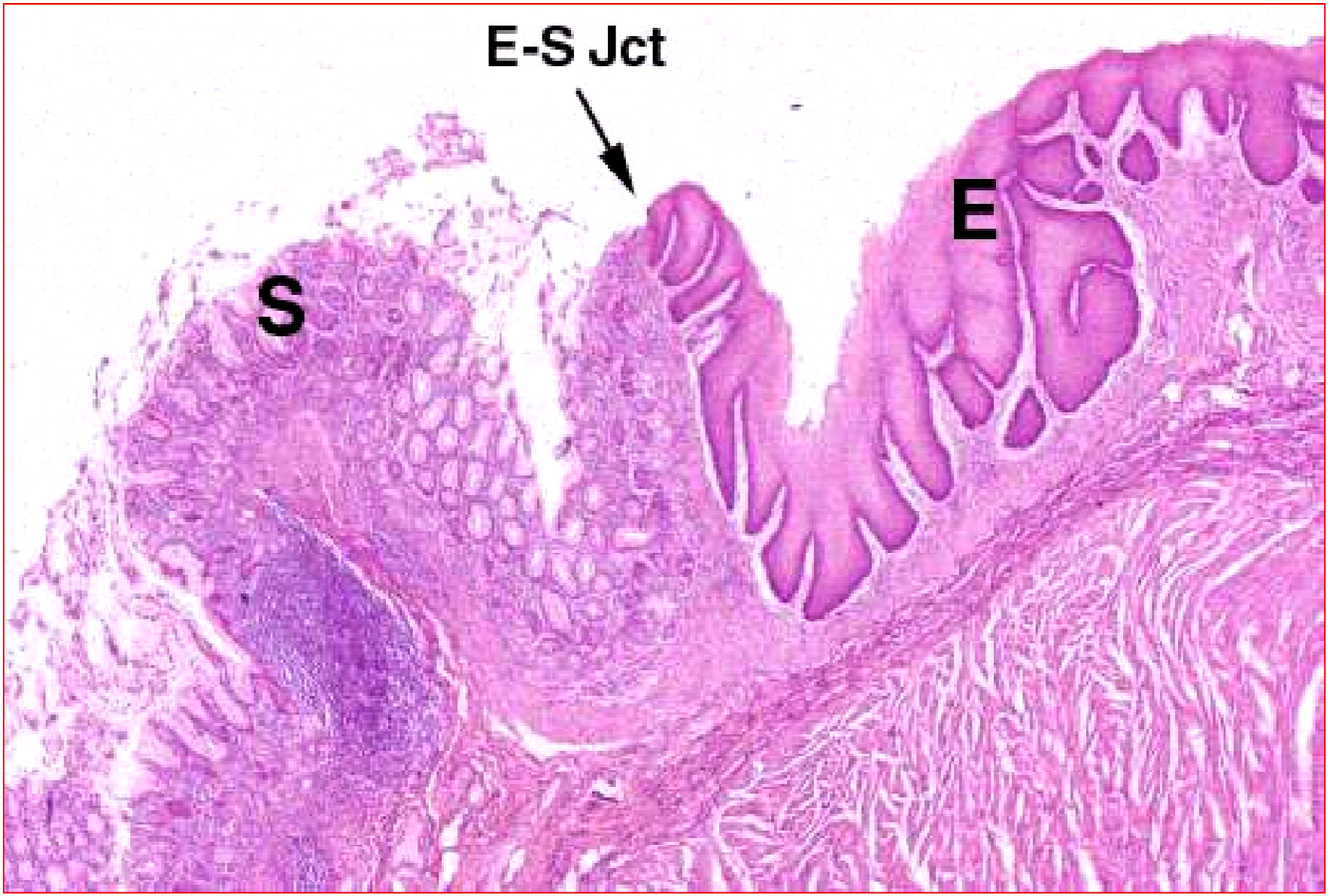


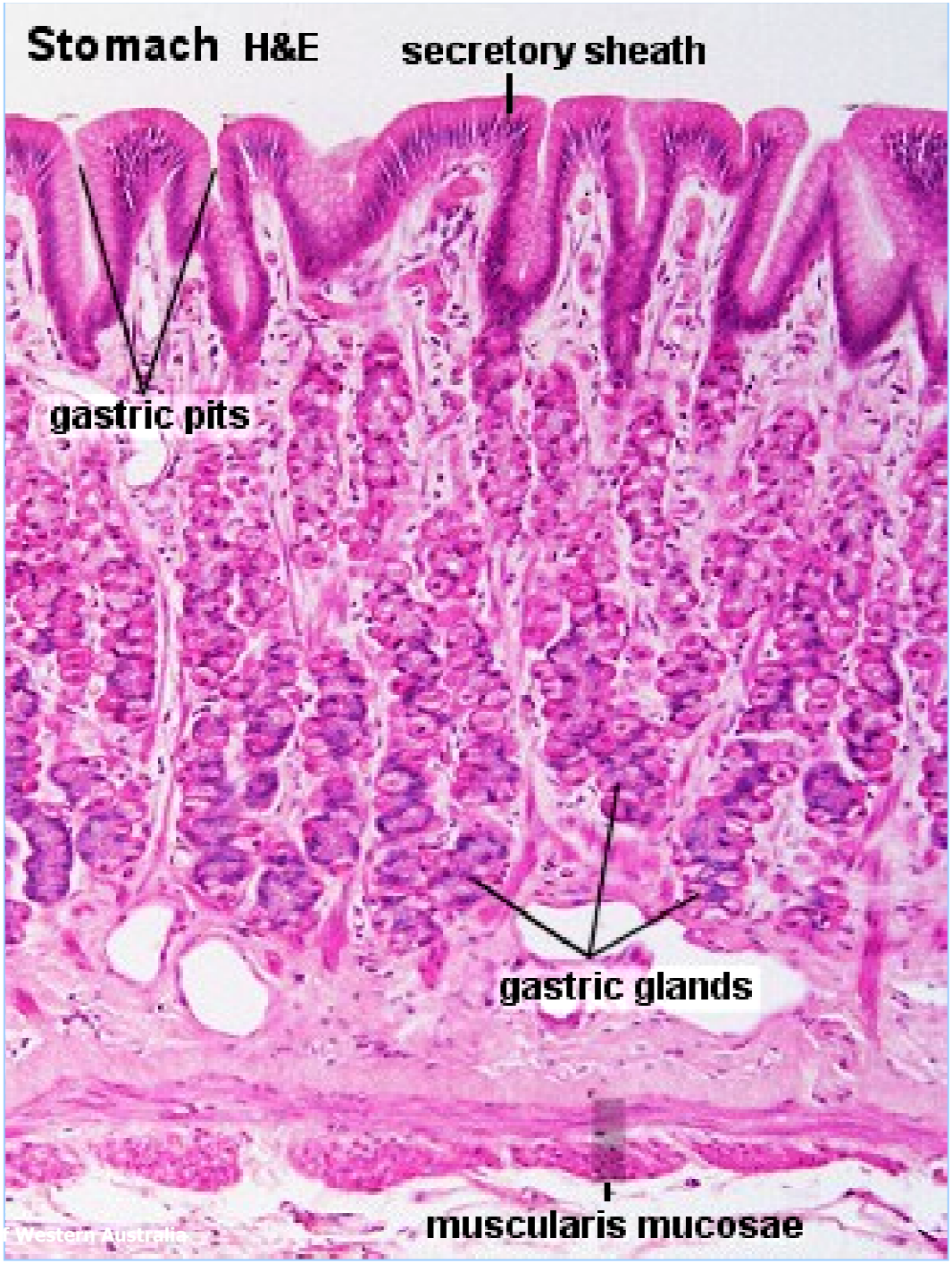


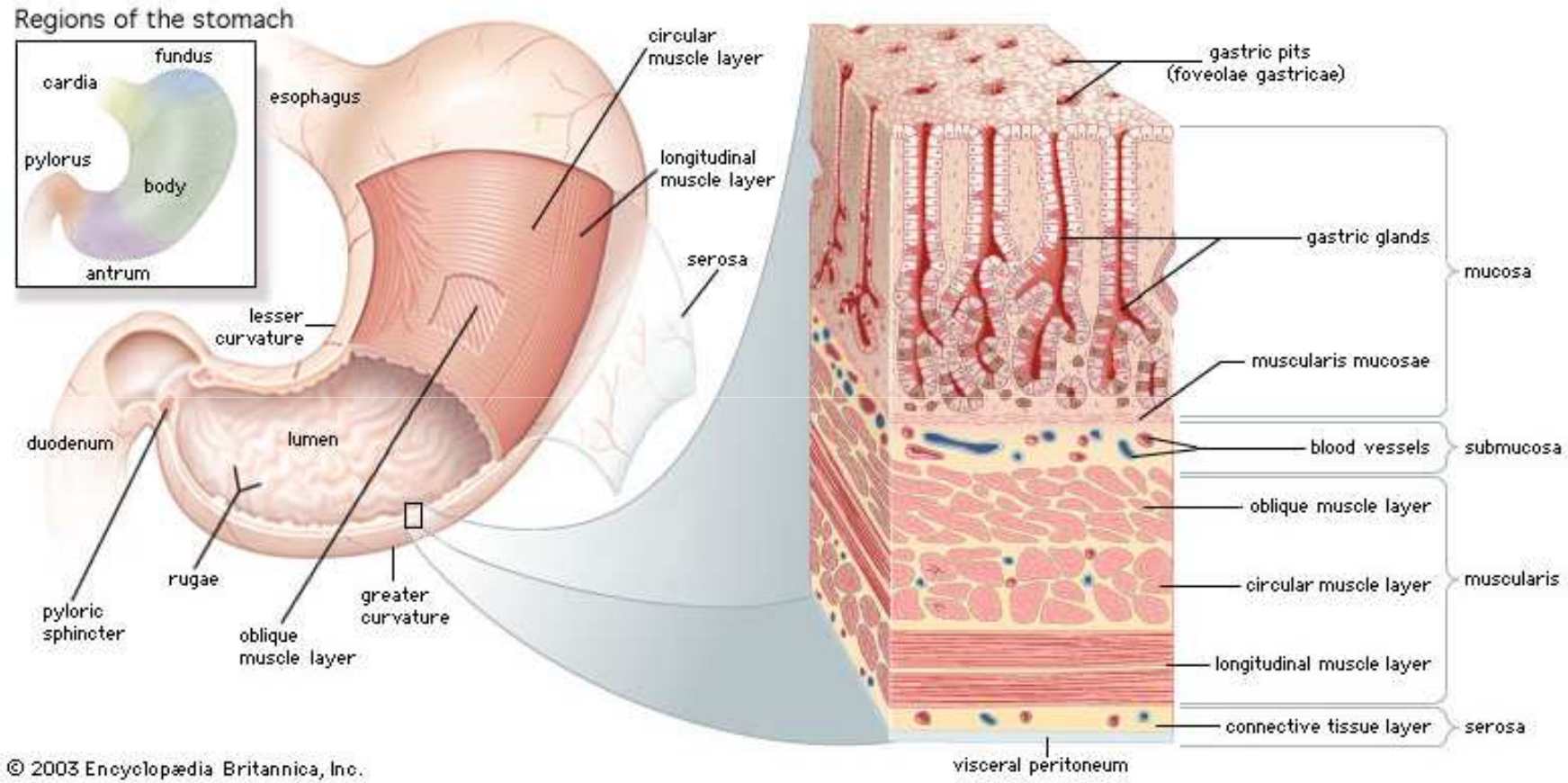


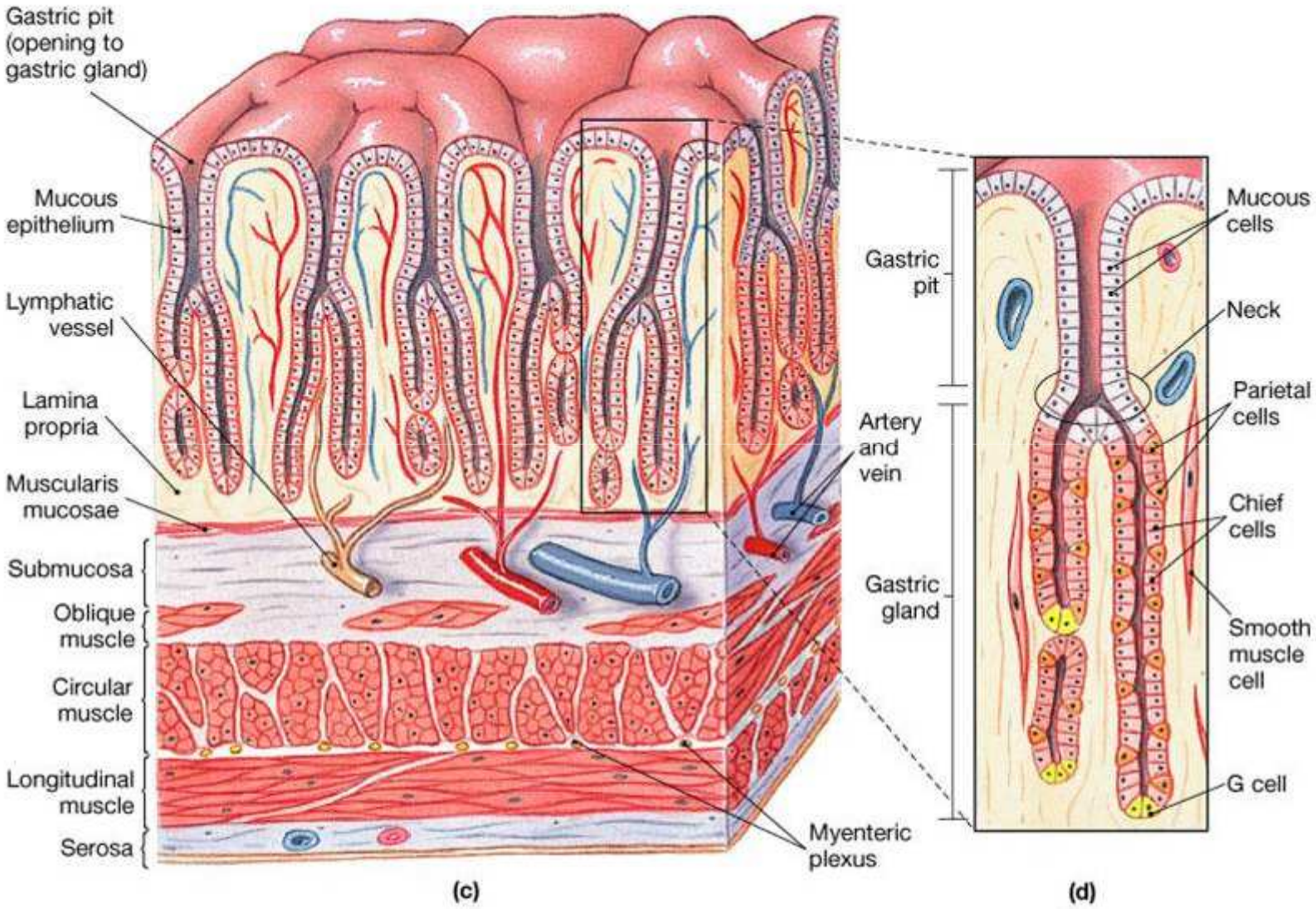
canguro topo ruminante maiale uomo

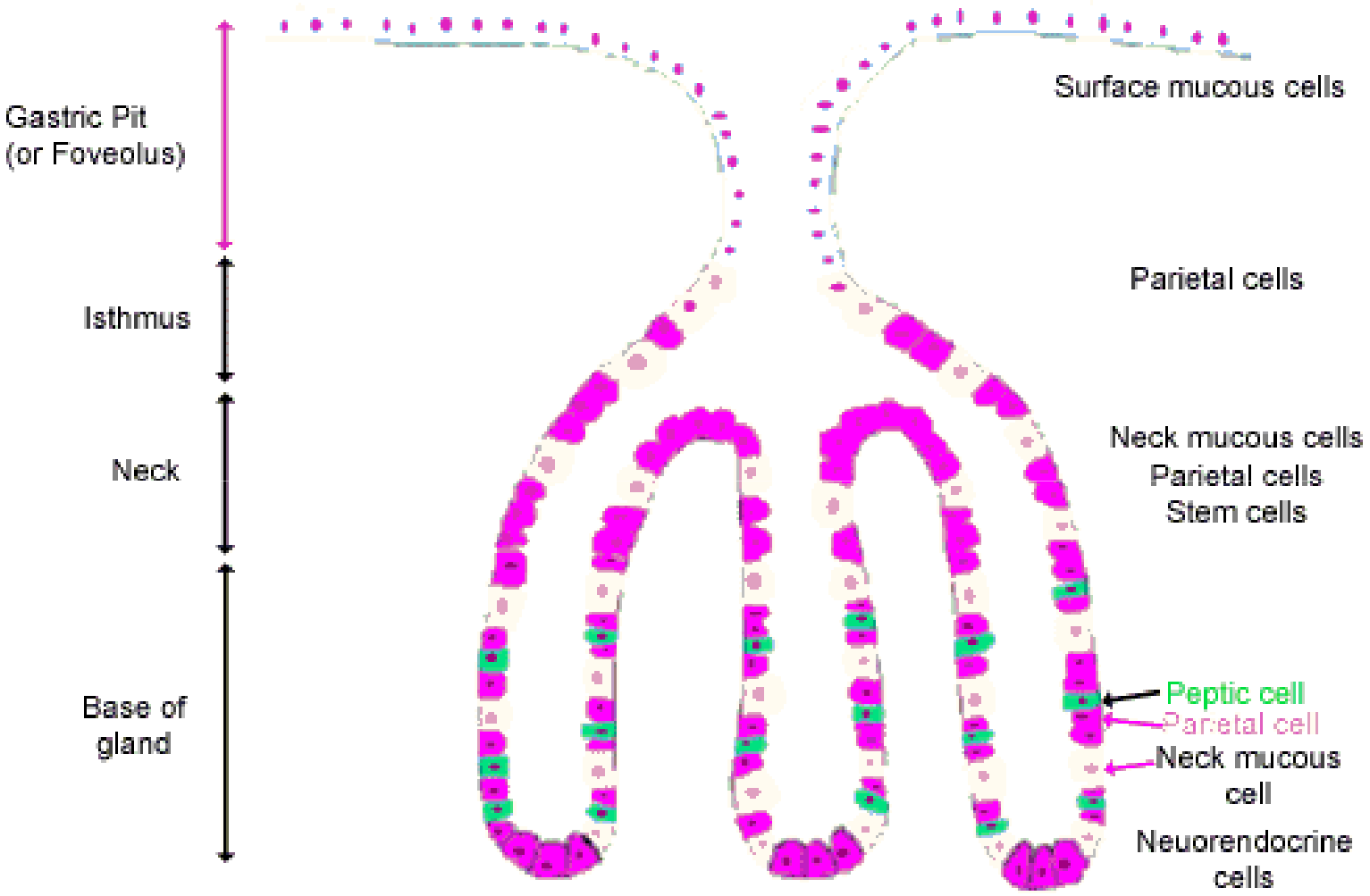
Giunzione esofago-stomaco




Stomach H&E
secretory sheath
gastric pits
gastric glands
muscularis mucosae
Western Australia




Gastric pit (opening to gastric gland)
Mucous epithelium
Lymphatic vessel
Lamina propria
Muscularis mucosae
Submucosa
Oblique muscle
Circular muscle
Longitudinal muscle
Serosa
Myenteric plexus
(c)
Gastric pit
Artery and vein
Gastric gland
Mucous cells
Neck
Parietal cells
Chief cells
Smooth muscle cell
G cell
(d)


Gastric Pit
(or Foveolus)
Isthmus
Neck
Base of
gland
Surface mucous cells
Parietal cells
Neck mucous cells
Parietal cells
Stem cells
Peptic cell
Parietal cell
Neck mucous
cell
Neuorendocrine
cells

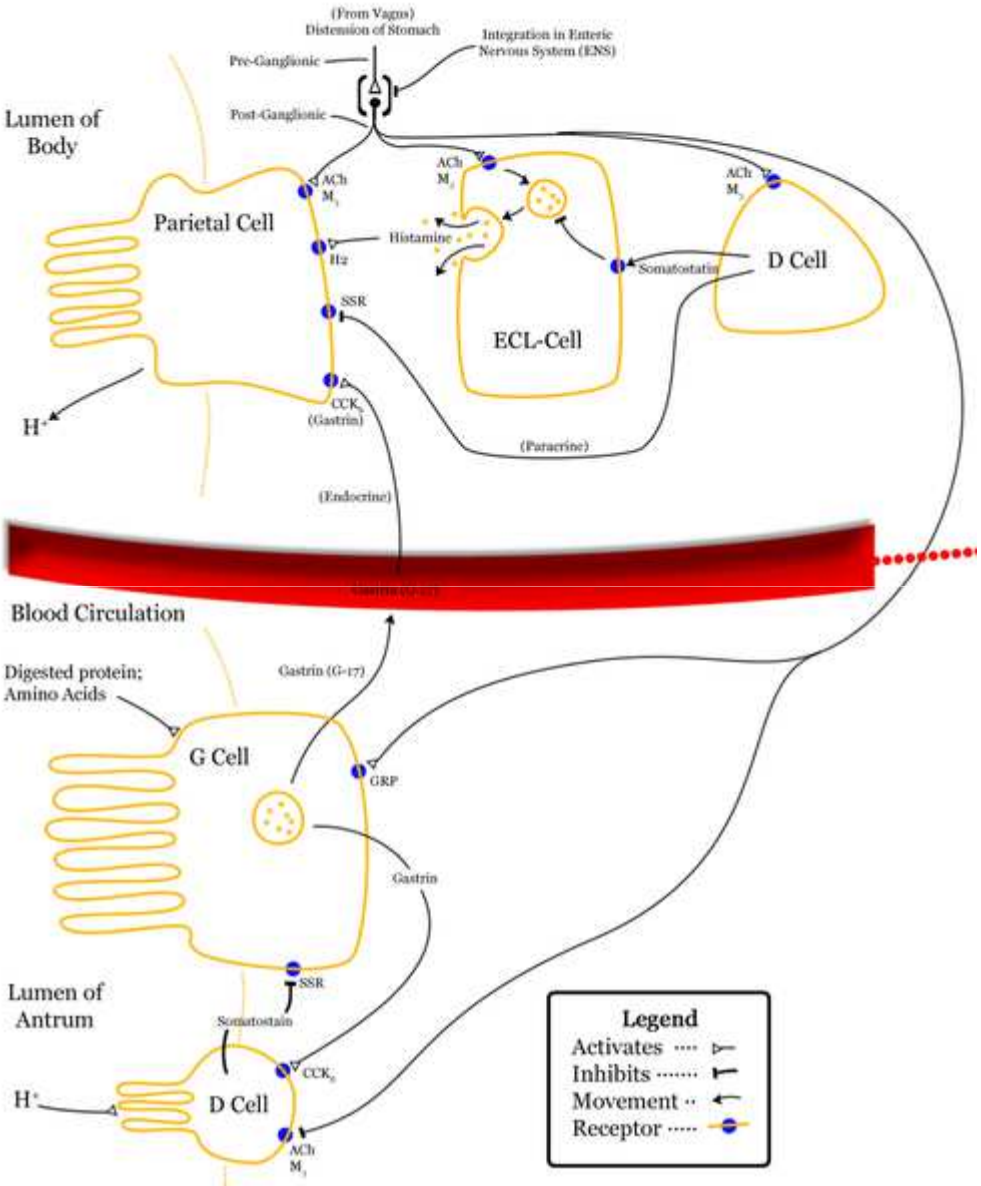
Le **cellule mucose**, possiedono una forma cilindrica, e un orletto a spazzola egualmente sviluppato. Contengono vescicole di mucina e di proteoglicani acidi Queste cellule vengono completamente sostituite ogni 3 giorni a causa dell'ambiente fortemente acido dello stomaco.

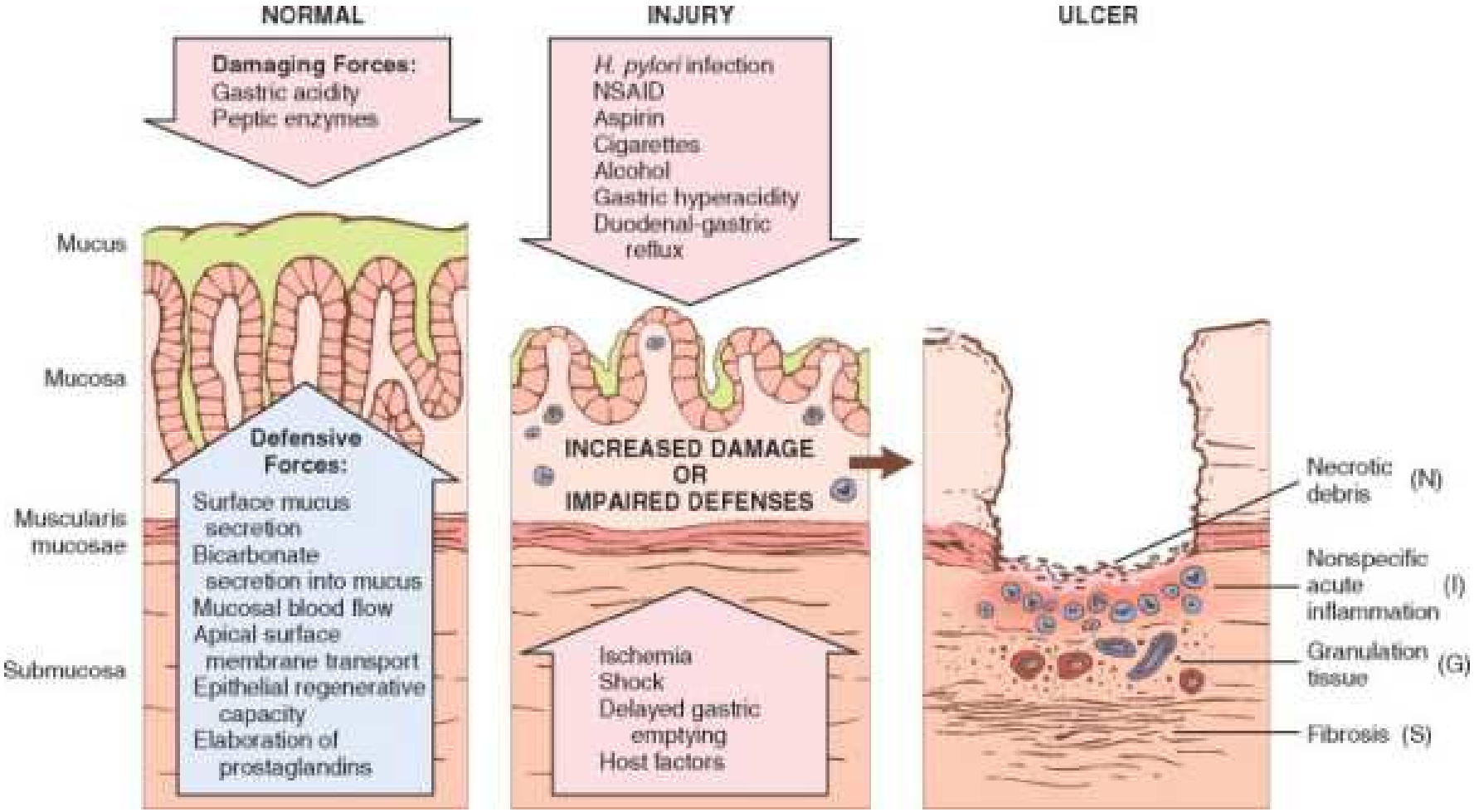
Le **cellule parietali** (ossintiche) sono disperse principalmente nel corpo della ghiandola gastrica, la cui superficie apicale si invagina in numerosi canalicoli tappezzati da microvilli che contengono sulla membrana plasmatica pompe protoniche (H+)e del potassio (K+). Questi microvilli sembrano formarsi e scindersi in continuazione in base all'attività secretoria della cellula. I canalicoli sono collegati ad un sistema tubulo-vescicolare che pervade il citoplasma della cellula. Il flusso di protoni e di ioni cloro uscente dalle cellule parietali determina la loro funzione principale, cioè la secrezione di acido cloridrico, che concorre a mantenere il pH gastrico attorno a valori compresi tra 1 e 3. Oltre a secernere acido cloridrico, producono il fattore intrinseco, una proteina essenziale per la cobalamina (vitamina B12).

Le **cellule principali** (zimogeniche) si trovano nella base e nel corpo delle ghiandole gastriche. Sono cellule di forma prismatica o cuboidale, con un orletto a spazzola meno sviluppato rispetto alle cellule mucose ed un citoplasma fortemente basofilo per l'abbondanza di ribosomi ed RNA. I granuli di zimogeno, contengono gli enzimi digestivi pepsinogeno e lipasi.

Le **cellule neuroendocrine** sono diffuse nella zona basale e nel corpo delle ghiandole gastriche, in ogni zona dello stomaco, cardias e piloro compresi. Hanno forma molto variabile, talvolta vagamente piramidale, possiedono nuclei di forma irregolare, anche se spesso tondeggianti. Nel citoplasma sono presenti mitocondri, un apparato di Golgi molto sviluppato, diverse cisterne di reticolo endoplasmatico rugoso. Piccole vescicole secretorie (0,3 µm di diametro) dal contenuto fortemente elettrondenso si concentrano in una zona vicina al nucleo. In base al contenuto vescicolare le cellule neuroendocrine dello stomaco si distinguono in cellule G (gastrina), cellule D (somatostatina), cellule ECG (istamina). Secernono inoltre fattori che controllano la motilità del viscere e la secrezione ghiandolare.

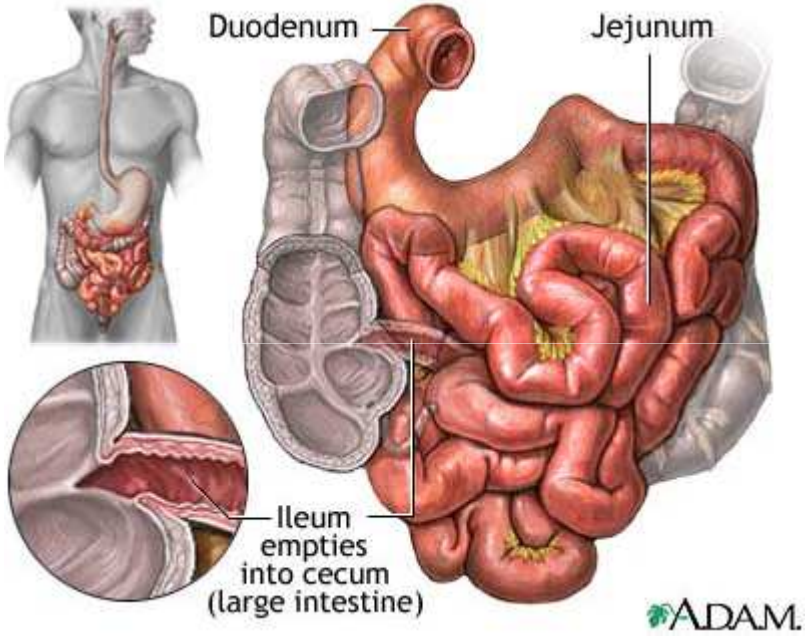
Le **cellule staminali** sono cellule indifferenziate, spesso si riscontrano in fase mitotica a livello dell'istmo e soprattutto del corpo delle ghiandole gastriche. Hanno forma cilindrica con un orletto a spazzola poco sviluppato. La loro posizione centrale nelle ghiandole gastriche permette loro di differenziarsi e migrare o verso l'istmo oppure verso la base della ghiandola, differenziandosi nelle diverse possibili cellule in base agli stimoli ricevuti dall'ambiente e dalle interazioni con le cellule vicine.

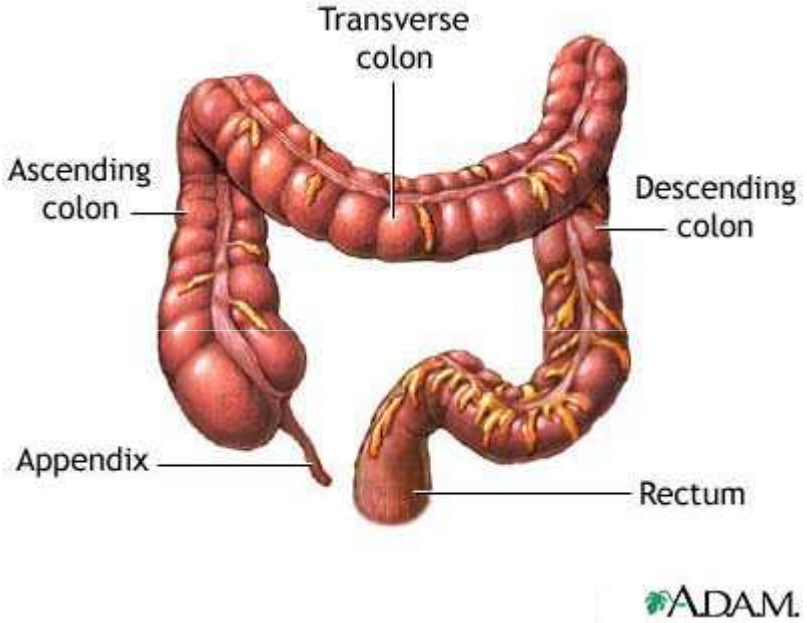

(From Vagus)
Distension of Stomach
Integration in Enteric Nervous System (ENS)
Pre-Ganglionic
Post-Ganglionic
Lumen of Body
Parietal Cell
ACh M1
Histamine
H2
SSR
CCK2 (Gastrin)
H+
ECL-Cell
ACh M3
ACh M2
Somatostatin
D Cell
(Paracrine)
(Endocrine)
Blood Circulation
Digested protein; Amino Acids
G Cell
Gastrin (G-17)
GRP
Gastrin
SSR
Somatostain
Lumen of Antrum
H+
D Cell
CCK2
ACh M3
Legend
Activates
Inhibits
Movement
Receptor


NORMAL
INJURY
ULCER
Damaging Forces:
Gastric acidity
Peptic enzymes
H. pylori infection
NSAID
Aspirin
Cigarettes
Alcohol
Gastric hyperacidity
Duodenal-gastric reflux
Mucus
Mucosa
Muscularis mucosae
Submucosa
Defensive Forces:
Surface mucus secretion
Bicarbonate secretion into mucus
Mucosal blood flow
Apical surface membrane transport
Epithelial regenerative capacity
Elaboration of prostaglandins
INCREASED DAMAGE OR IMPAIRED DEFENSES
Ischemia
Shock
Delayed gastric emptying
Host factors
Necrotic debris (N)
Nonspecific acute inflammation (I)
Granulation tissue (G)
Fibrosis (S)

SMALL INTESTINE AND COLON

The small intestine and colon account for the majority of GI tract length and are the sites of a broad array of diseases. Some of these relate to nutrient and water transport. Perturbation of these processes can cause malabsorption and diarrhea. The intestines are also the principal site where the immune system interfaces with a diverse array of antigens present in food and gut microbes. Indeed, intestinal bacteria outnumber eukaryotic cells in our bodies by tenfold. Thus, it is not surprising that the small intestine and colon are frequently involved by infectious and inflammatory processes. Finally, the colon is the most common site of GI neoplasia in Western populations.

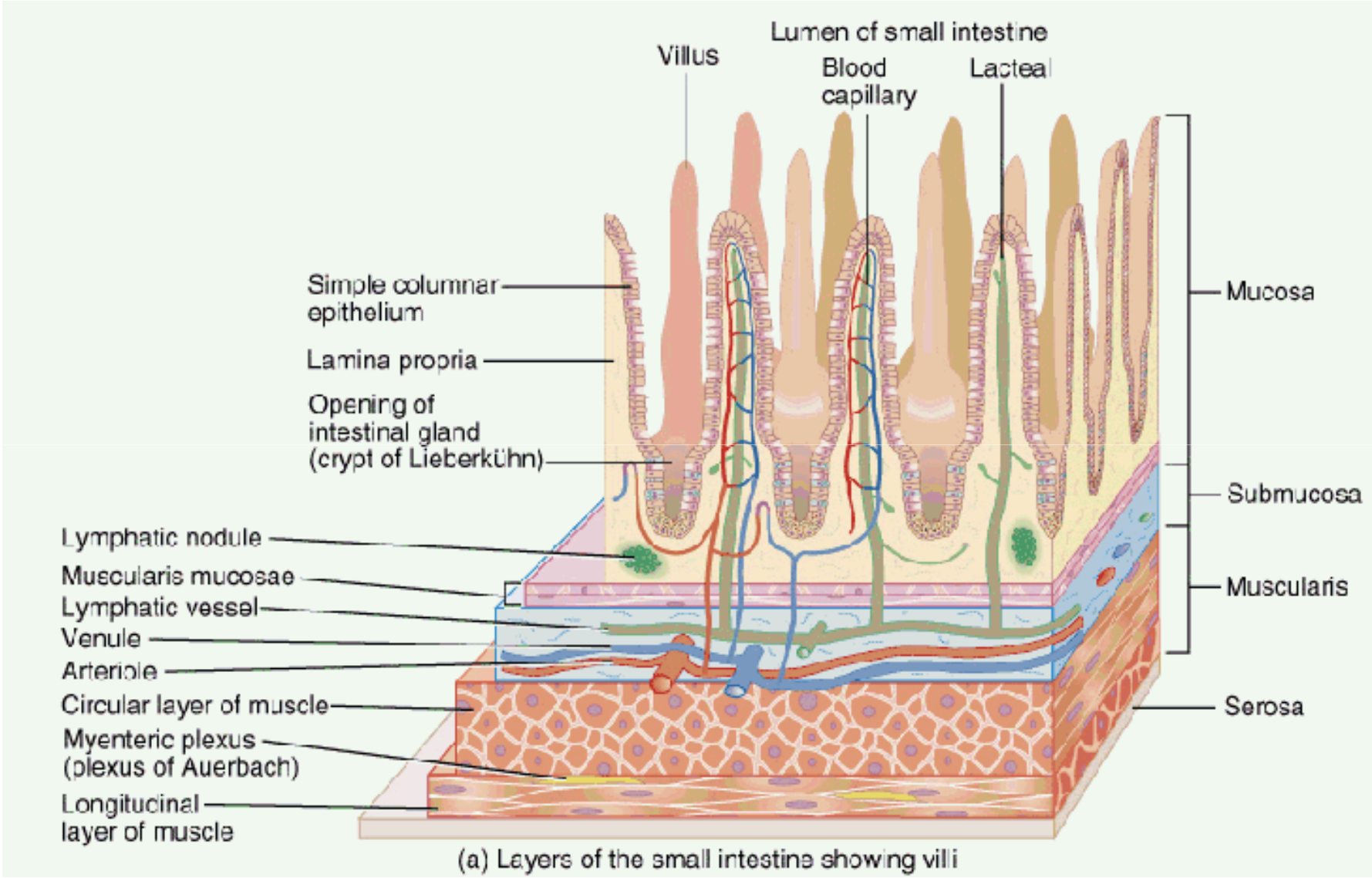

Duodenum
Jejunum
Ileum
empties
into cecum
(large intestine)
A.D.A.M.


Transverse
colon
Ascending
colon
Descending
colon
Appendix
Rectum
A.D.A.M.

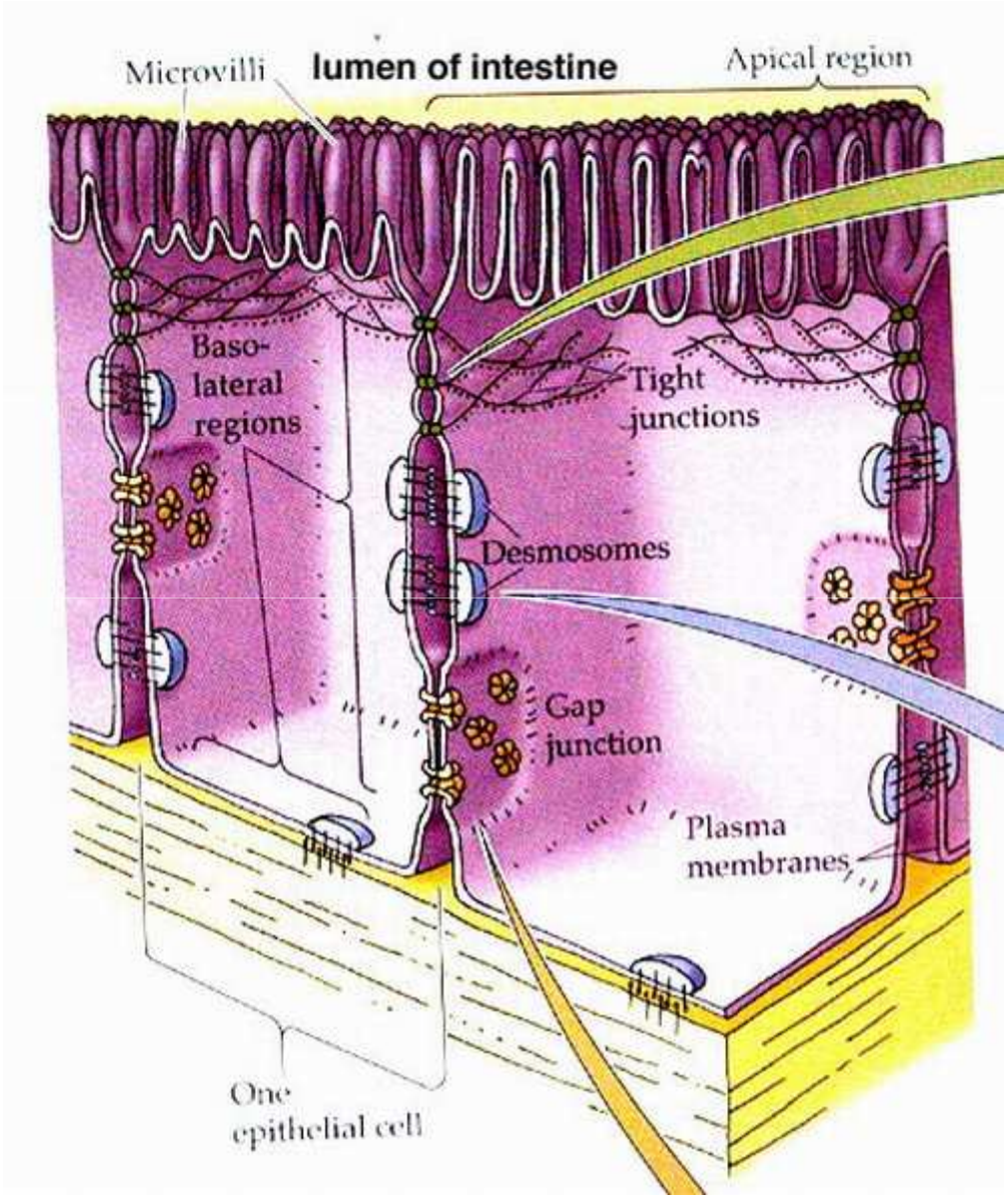
cellule epiteliali
1) Enterociti
2) Cellule delle cripte
3) Cellule caliciformi
4) Cellule di Paneth
5) Cellule enteroendocrine
6) Cellule M

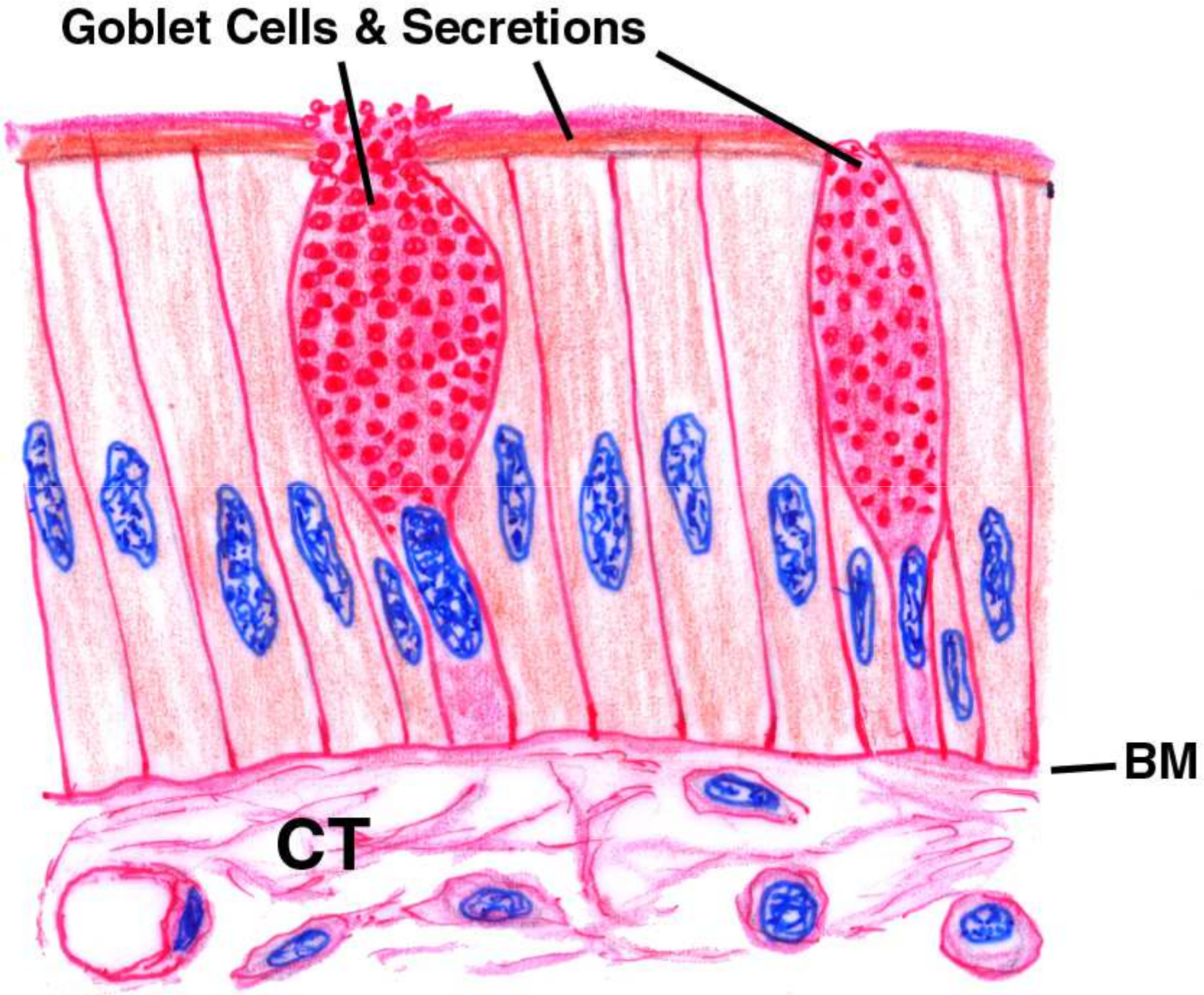
Cellule epiteliali

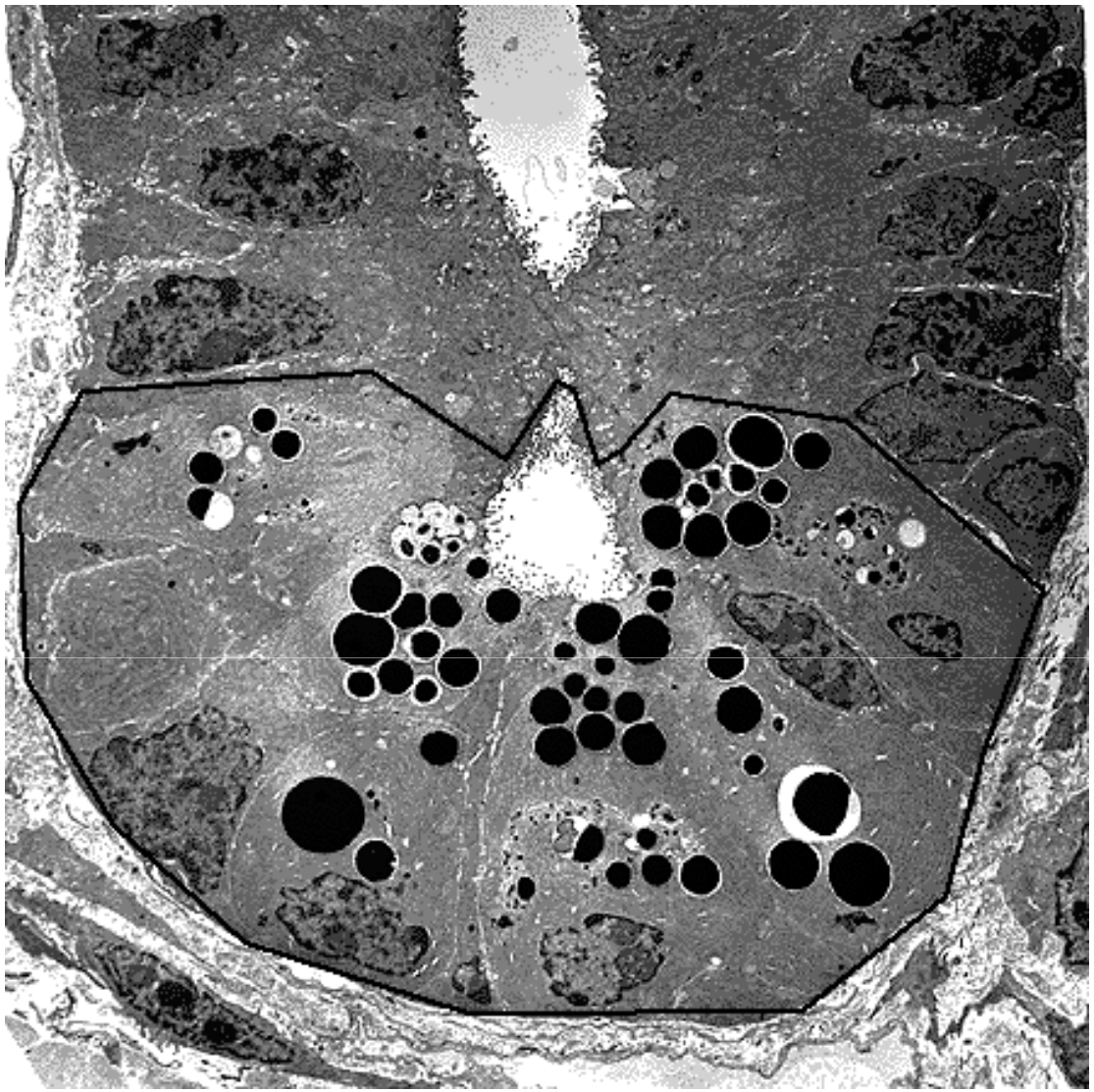
1) Enterociti: epitelio cilindrico con microvilli, contengono un glicocalice di superficie con enzimi digestivi. Molti nutrienti sono assorbiti dagli spazi intercellulari laterali tra le cellule. Non proliferano ma determinano un feed-back sulla mitosi delle cellule delle cripte;
2) Cellule delle cripte: cuboidali con pochi microvilli, scarsa capacità digestiva. Sono le cellule progenitrici che rimpiazzano tutte le altre cellule epiteliali.
3) Cellule caliciformi: si trovano nei villi e nelle cripte, secernono muco. Sono più numerose nel colon;
4) Cellule di Paneth: primati, cavalli e roditori. Producono sostanze battericide che proteggono le cripte dalle infezioni e sono fagocitanti; Ileo
5) Cellule enteroendocrine : cellule argentaffini, si trovano nelle cripte e producono serotonina, catecolamine, enteroglucagone;
6) Cellule M: ricoprono il GALT e trasportano gli antigeni dal comparto luminale al GALT.



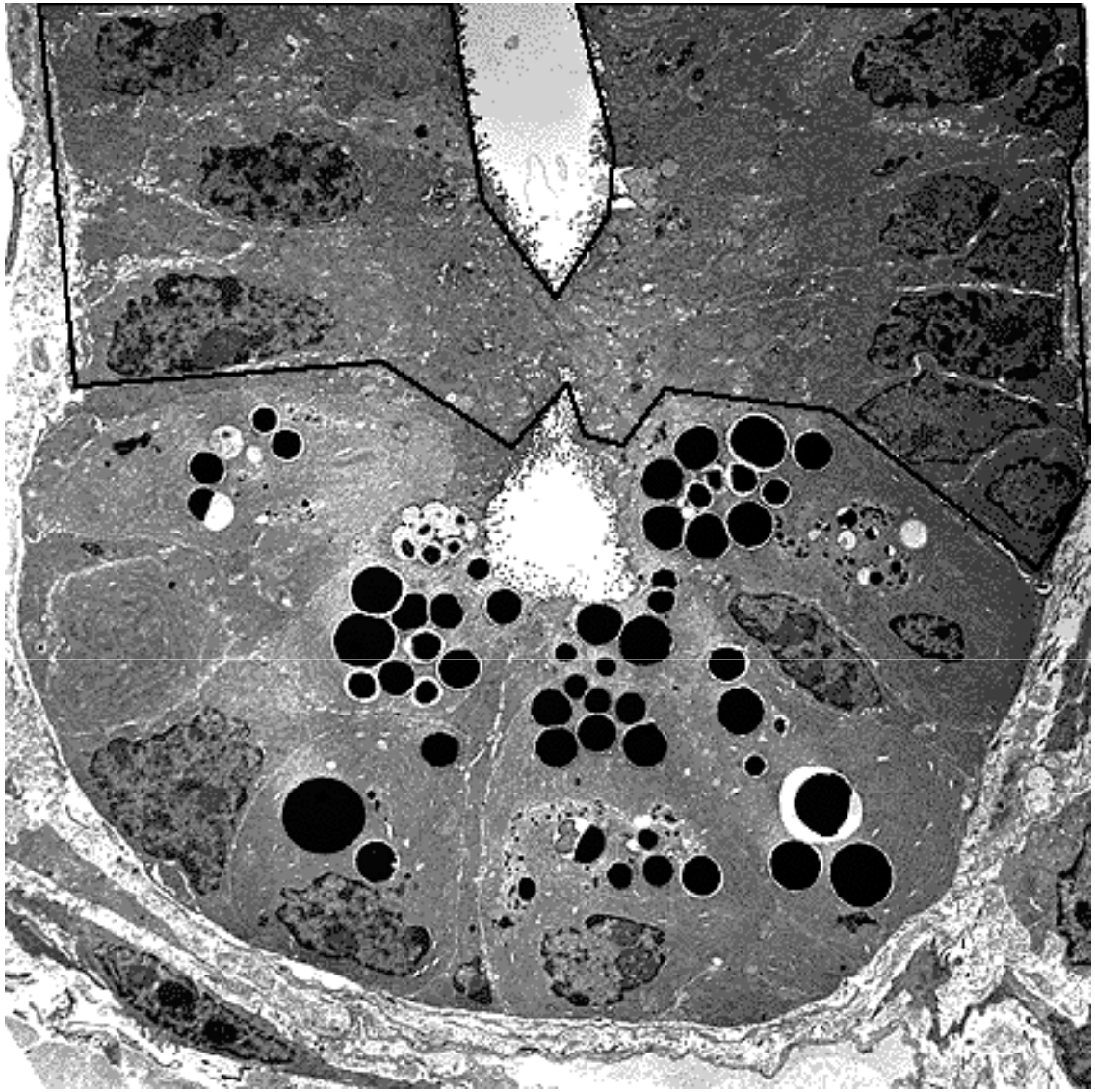
(a) Layers of the small intestine showing villi


Microvilli
lumen of intestine
Apical region
Baso-
lateral
regions
Tight
junctions
Desmosomes
Gap
junction
Plasma
membranes
One
epithelial cell

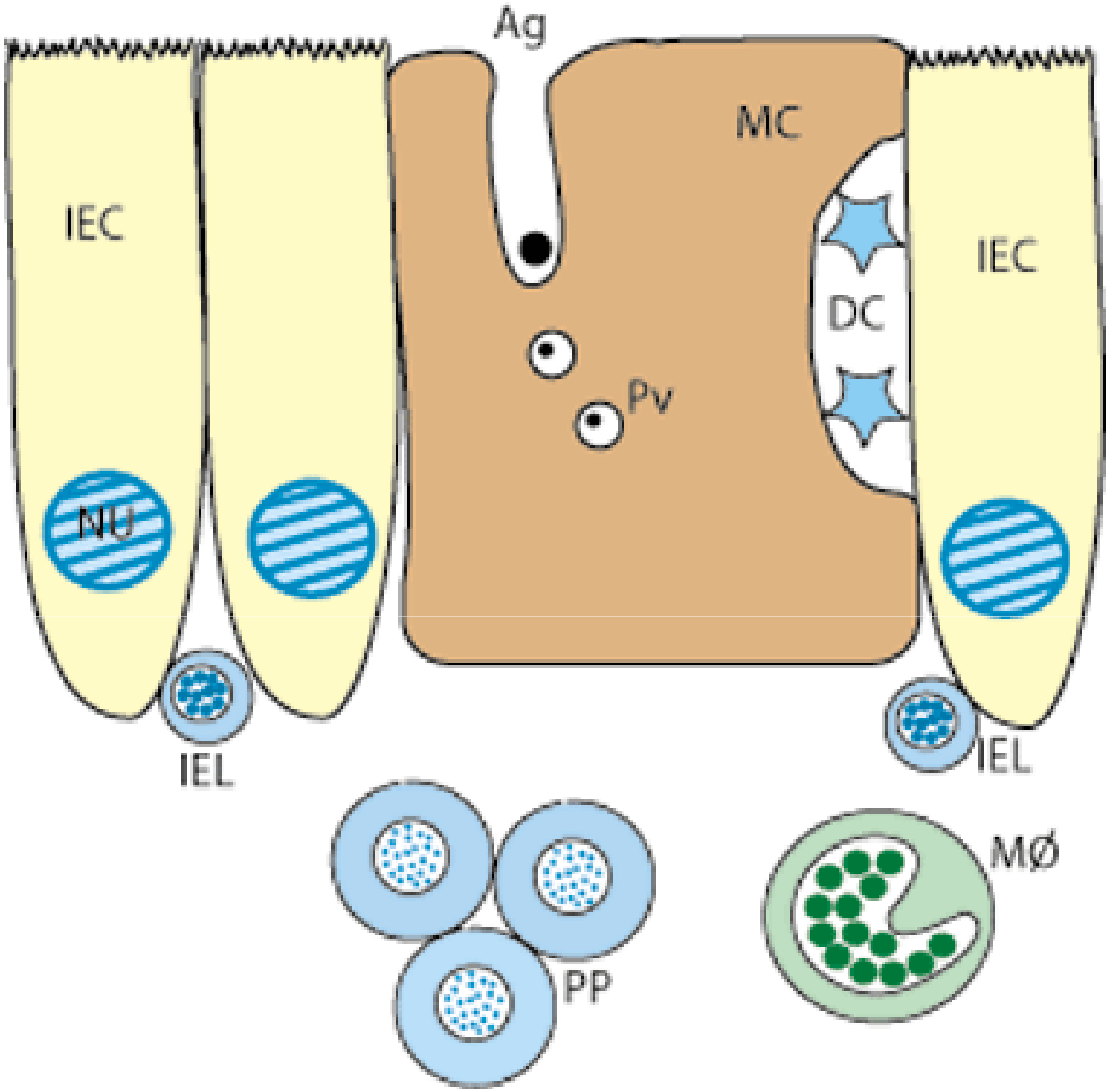

Goblet Cells & Secretions
BM
CT

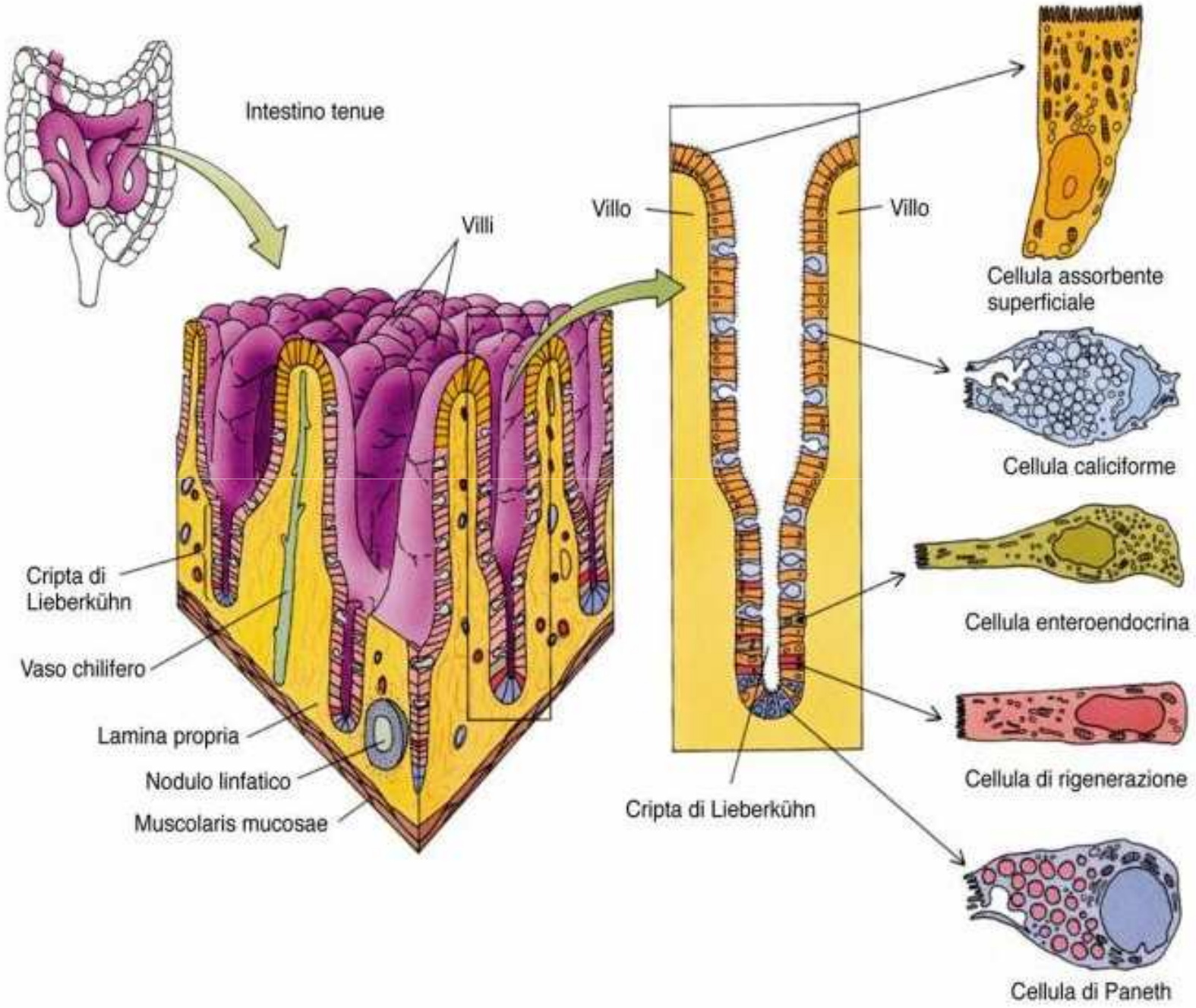


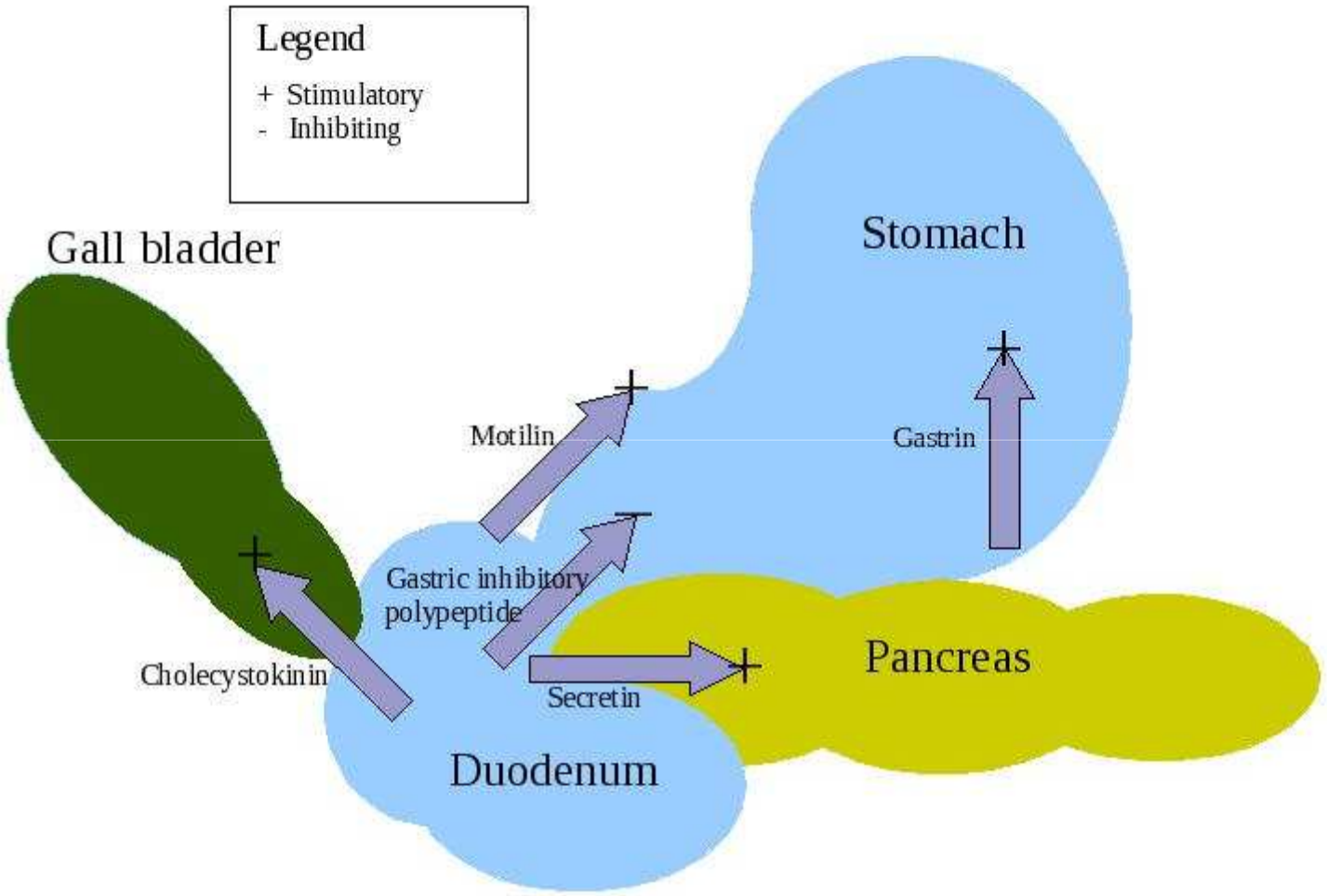
Differentiated crypt Paneth cell secretes digestive enzymes (phospholipases, peptidases), mucins and anti-microbial factors such as lysozyme, the defensin-related cryptdins and IgA taken up from lamina propria plasma cells



The **epithelial crypt stem cells** give rise to all epithelial cell lineages.

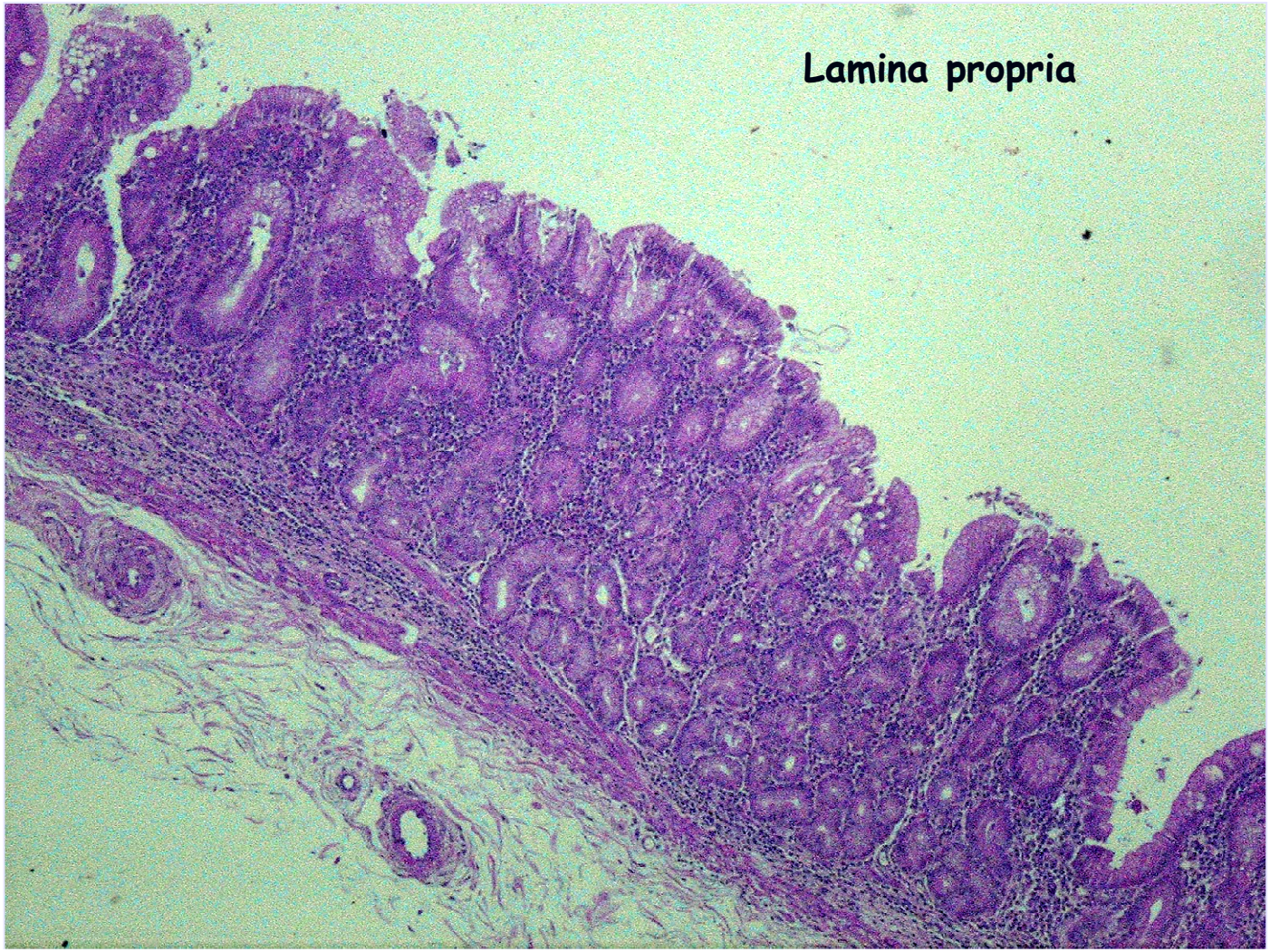

Ag
MC
IEC
IEC
DC
Pv
NU
IEL
IEL
PP
MØ


Intestino tenue
Villi
Cripta di Lieberkühn
Vaso chilifero
Lamina propria
Nodulo linfatico
Muscolaris mucosae
Villo
Villo
Cripta di Lieberkühn
Cellula assorbente superficiale
Cellula caliciforme
Cellula enteroendocrina
Cellula di rigenerazione
Cellula di Paneth

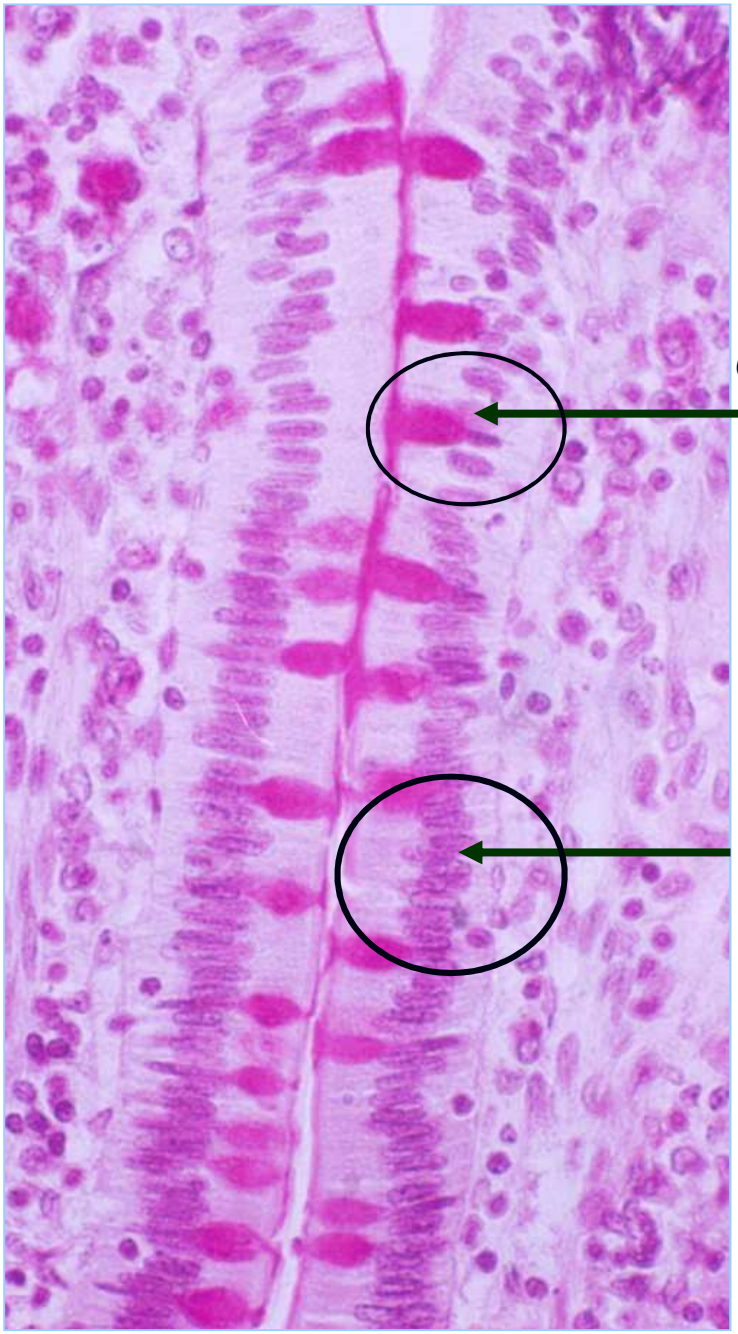

Legend
+ Stimulatory
- Inhibiting
Gall bladder
Stomach
Motilin
Gastrin
Gastric inhibitory
polypeptide
Cholecystokinin
Secretin
Pancreas
Duodenum

cellule mesenchimali
1) Miofibroblasti
2) Linfociti T
3) Granulociti neutrofili
4) Granulociti eosinofili
5) LGL (NK cells)

La lamina propria, composta da elementi mesenchimali, supporta l'epitelio della mucosa. E' composta da tessuto fibroso lasso ed è attraversata da vasi sanguigni. Nella lamina propria sono presenti miofibroblasti, cellule infiammatorie e immunoattive.



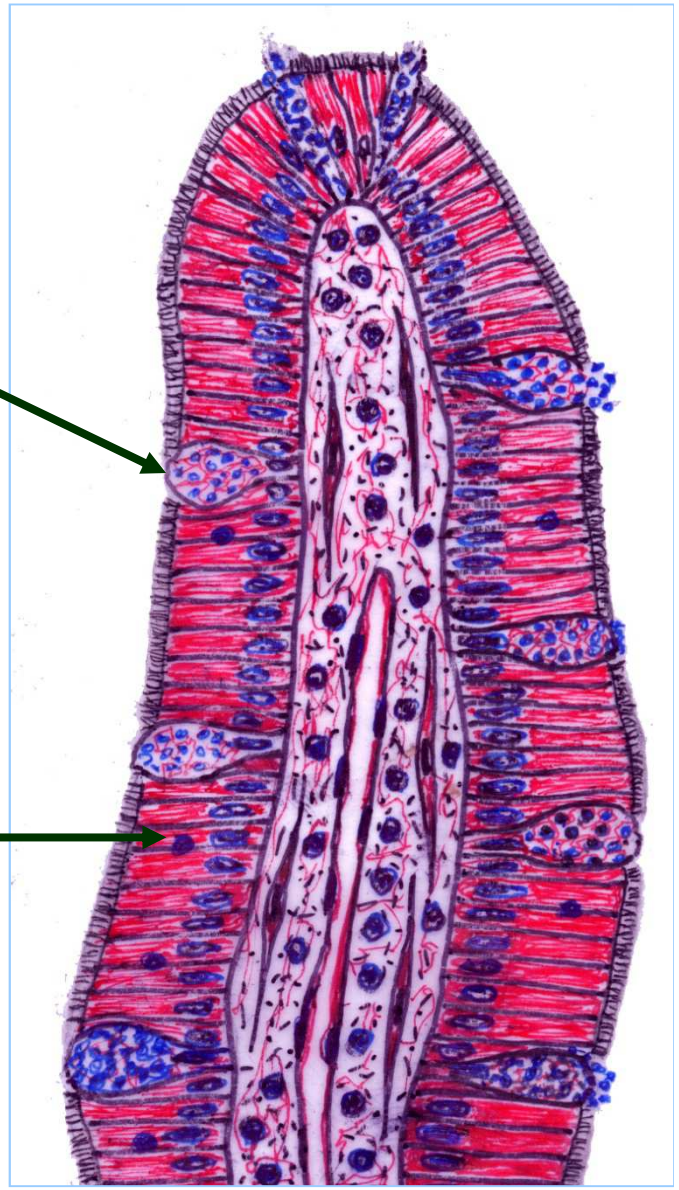
PAS-stain

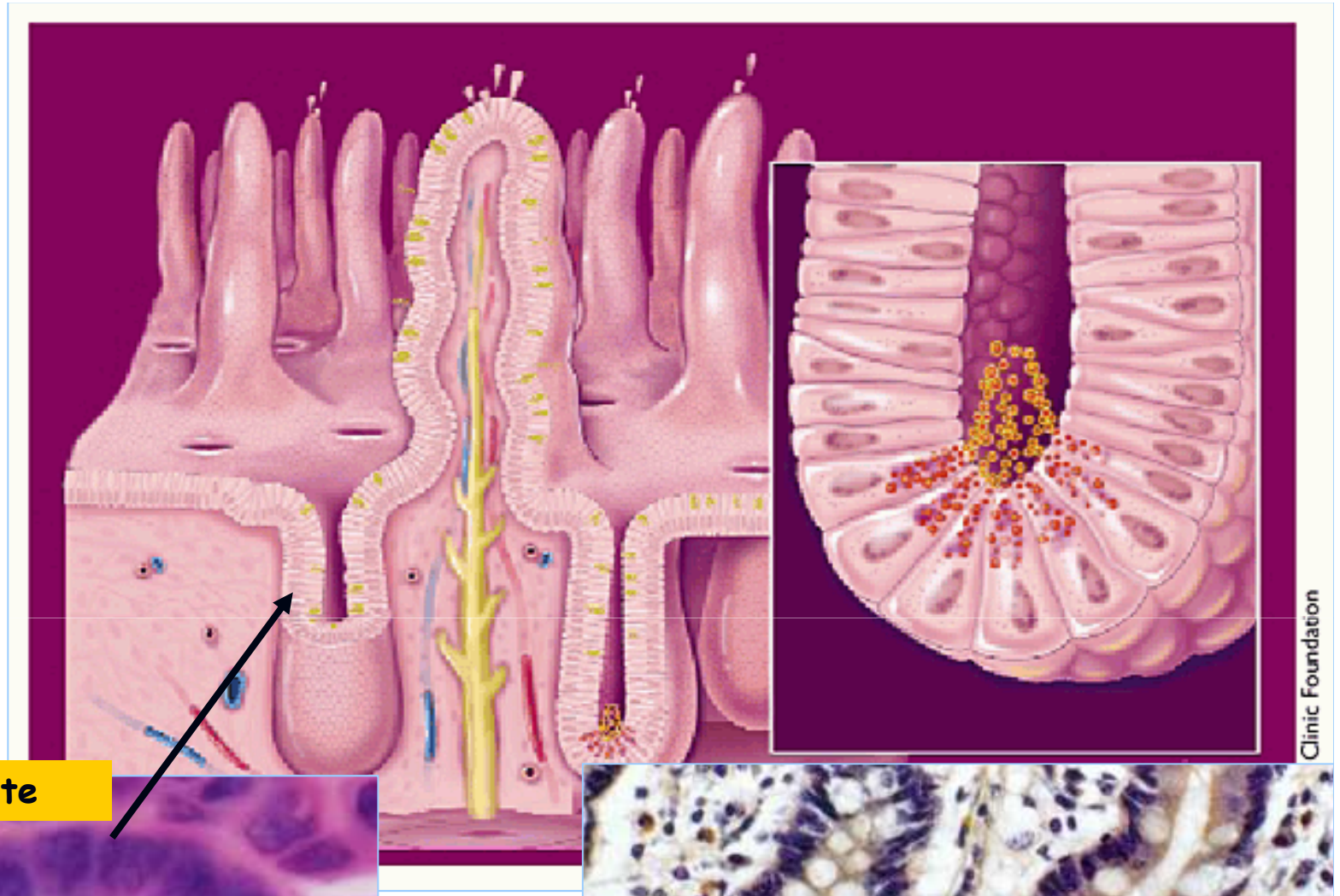


Villo

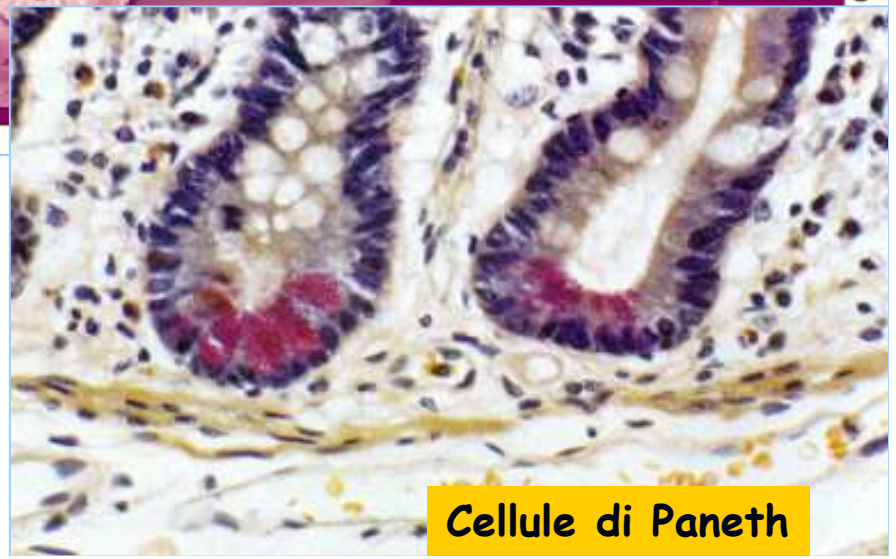
Cellule caliciformi

Enterociti

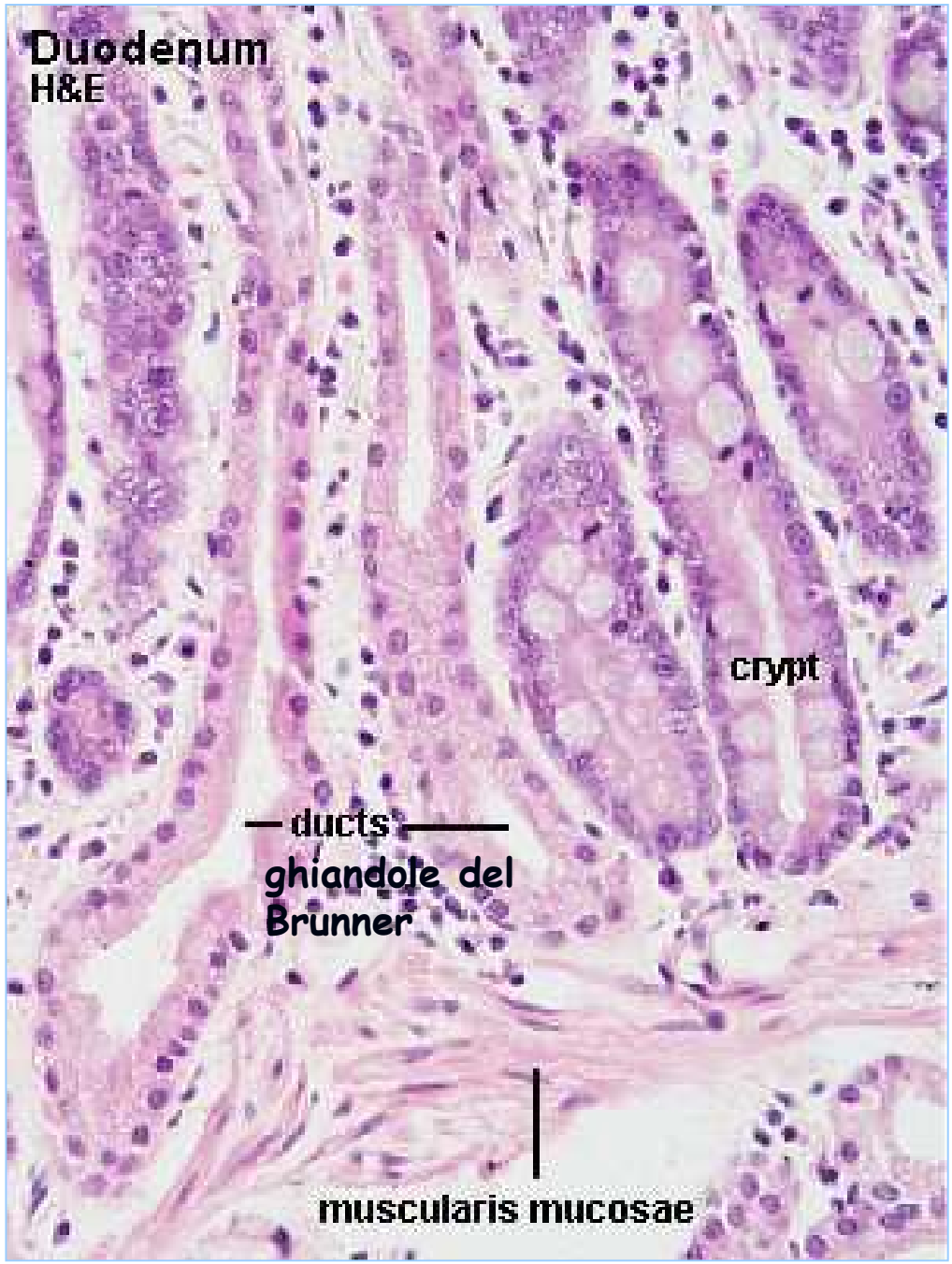


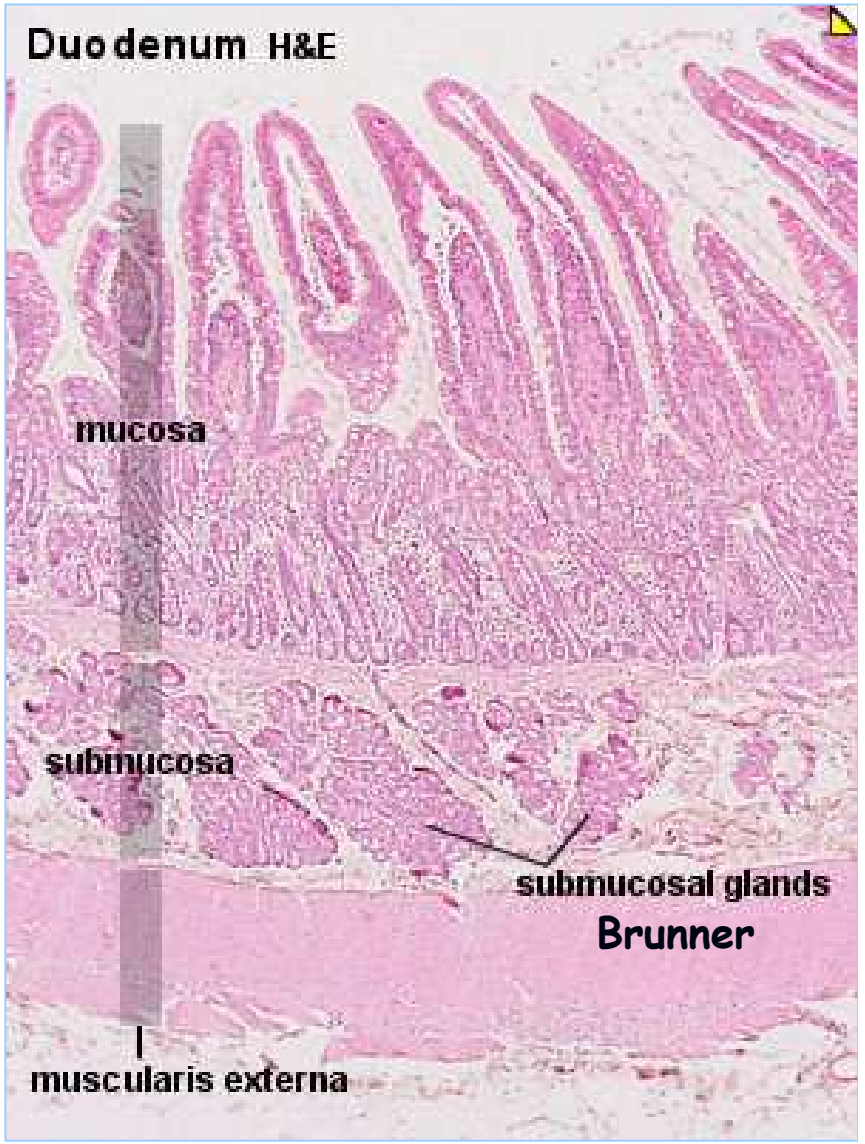


Cellule delle cripte

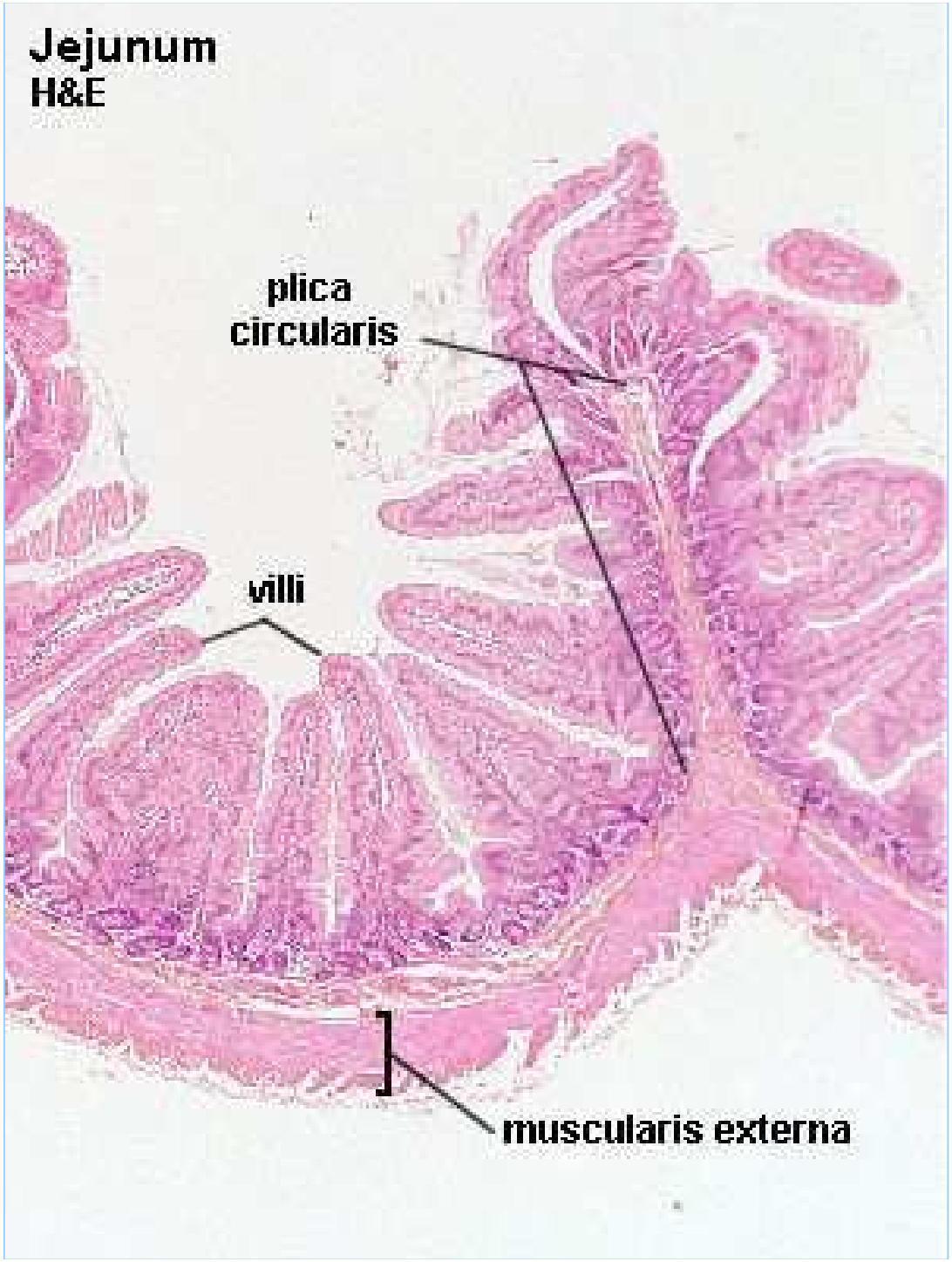


Cellule di Paneth

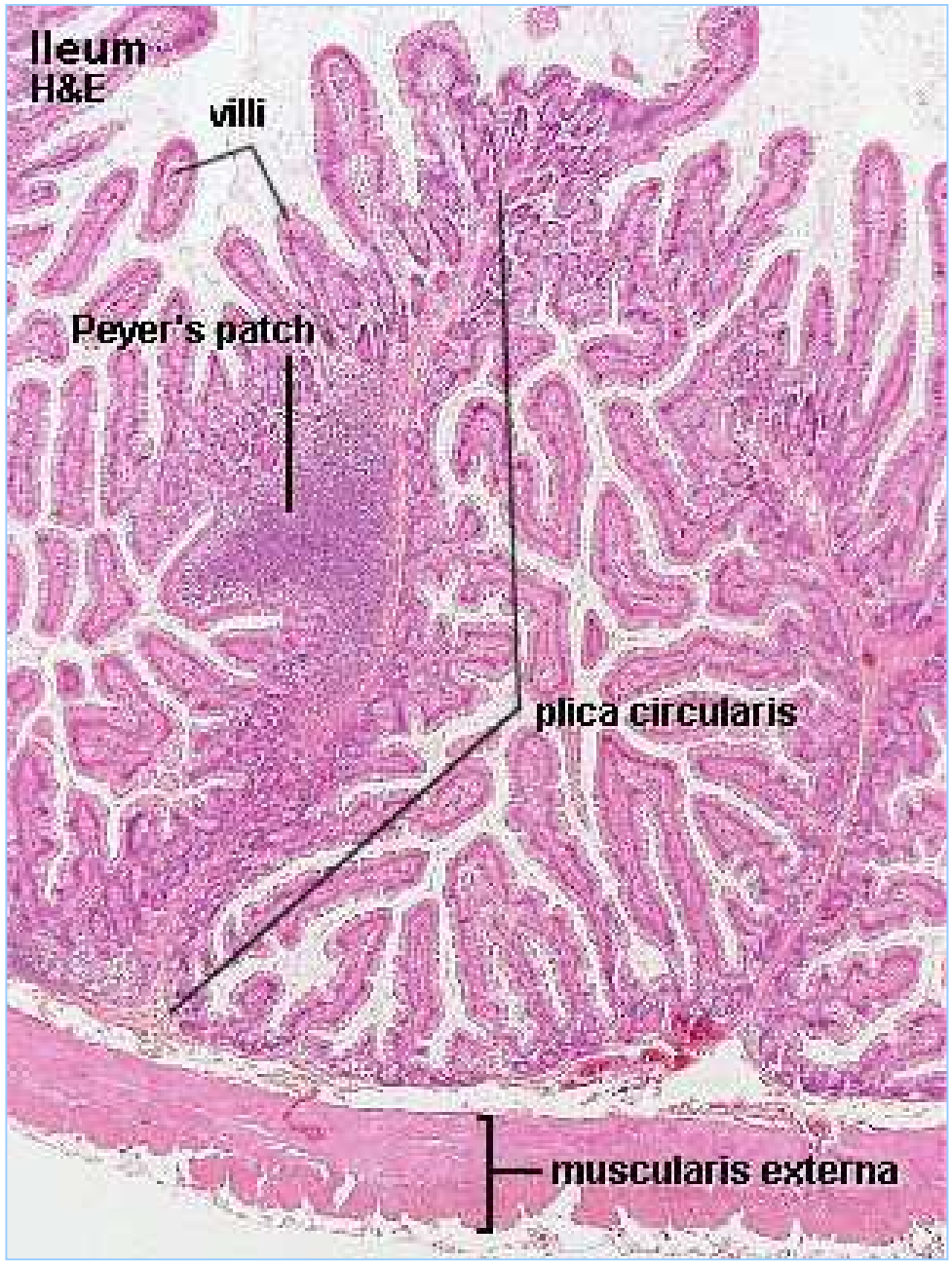


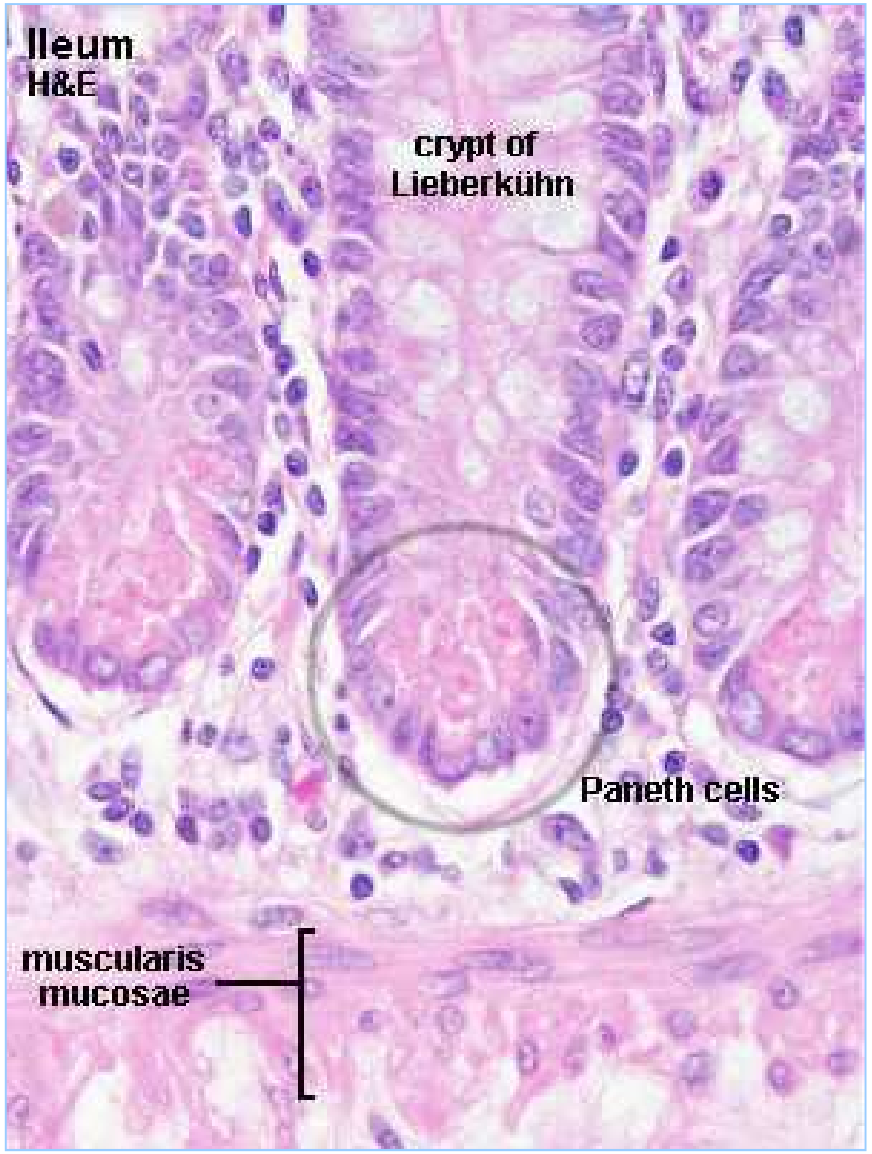


Intestino tenue: duodeno

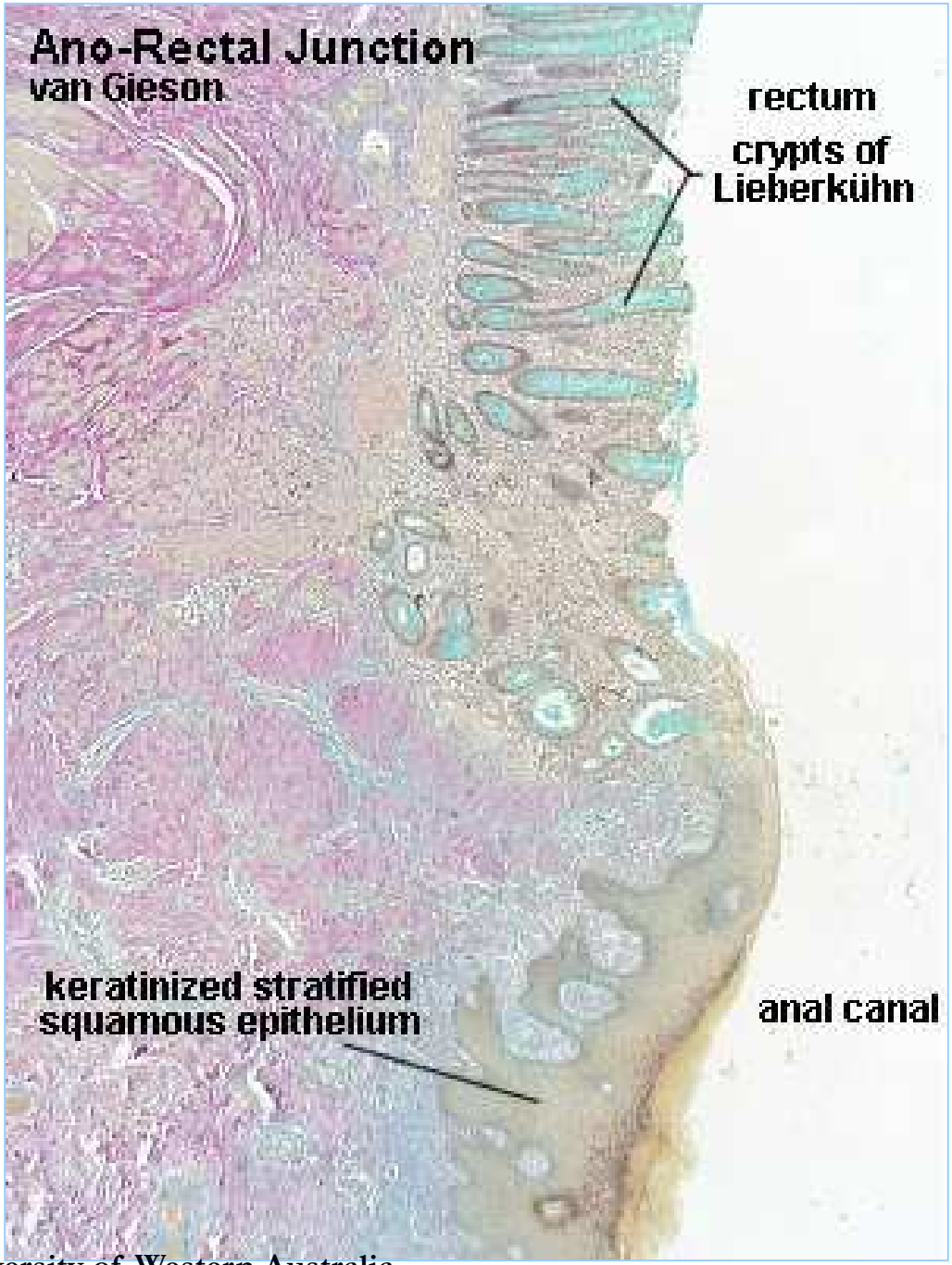


Intestino tenue: digiuno





Intestino tenue: ileo



Intestino crasso: retto

Meccanismi di difesa dell’apparato digerente

- pH acido (stomaco) o basico (intestino, cavo orale)
- Presenza di enzimi proteolitici (e.g. pepsina, tripsina)
- Secrezione di muco
- Ricambio cellulare (minore opportunità per la permanenza di patogeni intracellulari)
- Tight-junctions e orientamento delle cellule epiteliali (limiti permeabilità dell’epitelio)
- Flora batterica commensale (produzioni di sostanze inibitrici di altri batteri e.g. batteriocine, competizione per risorse/siti di adesione)
- Secrezione di sostanze antimicrobiche
- Immunità mucosale (GALT, secrezione di IgA)
- Peristalsi
- Sali biliari

Microflora intestinale
- scarsa nello stomaco e nel primo tratto dell'intestino;
- nella parte terminale dell'intestino tenue è costituita soprattutto da *E. coli*;
- nel cieco e colon ci sono coliformi, lattobacilli e anaerobi stretti (*Bacteroides*, *Fusobacterium, Clostridium, Eubacterium, Bifidobacterium*).
- se perturbata tende a ritornare alla situazione iniziale;
- resistente alle nuove specie batteriche, soprattutto patogene (anaerobi: produzione di acido acetico e butirrico che distruggono le enterobacteriaceae).

IgA: bloccano l'adesione di virus e batteri alla superficie delle cellule intestinali, neutralizzano le tossine intraluminali, limitano l'assorbimento di antigeni che derivano dal cibo e dalle fermentazioni batteriche

• >400 species of commensal bacteria

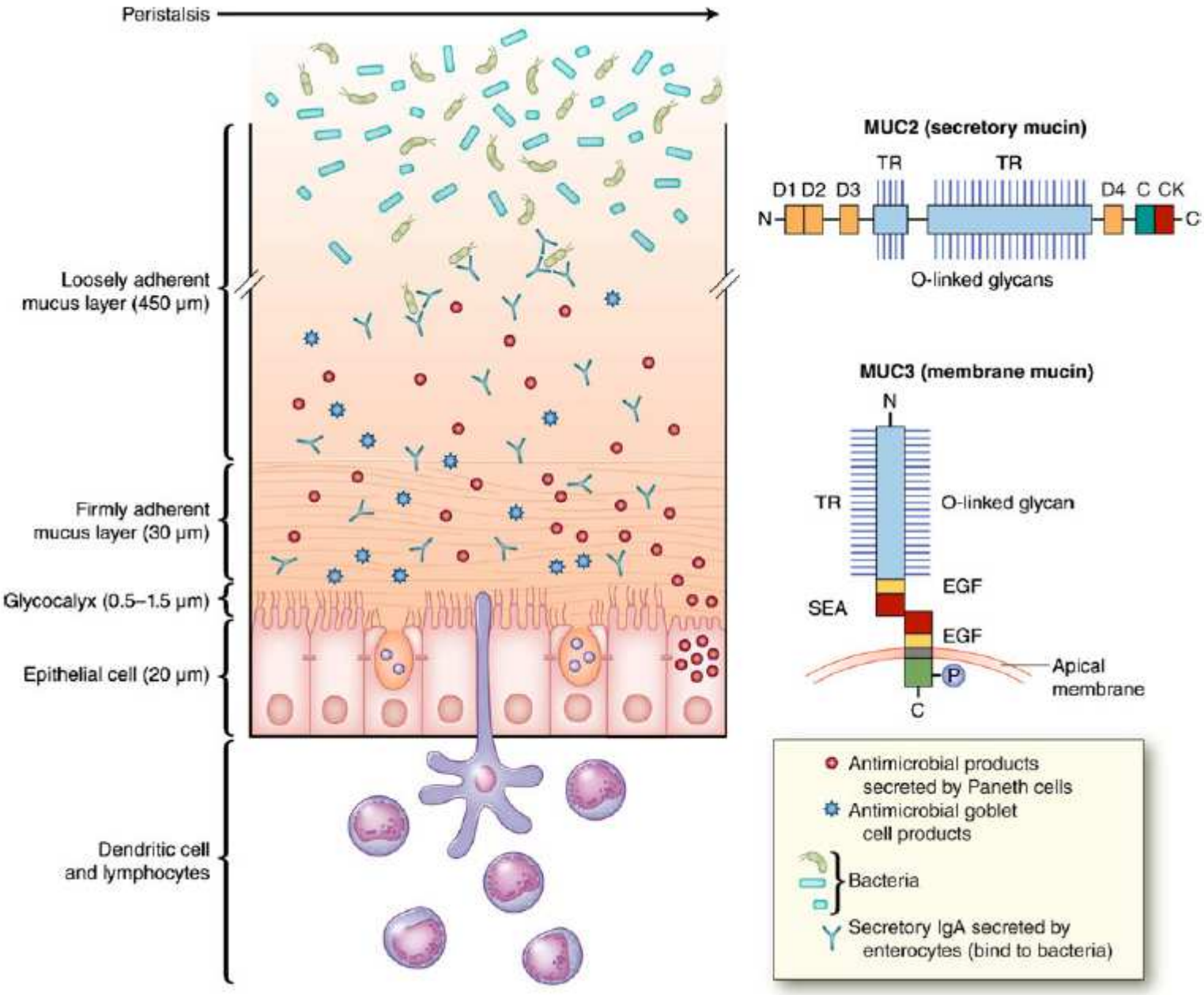
•Provide enzymatic breakdown of food

•Competes with pathogenic bacteria for space and nutrients

•Produce bacteriocins

•Prevents colonization of the gut

•Antibiotics disrupt homeostasis


Peristalsis
Loosely adherent mucus layer (450 μm)
Firmly adherent mucus layer (30 μm)
Glycocalyx (0.5–1.5 μm)
Epithelial cell (20 μm)
Dendritic cell and lymphocytes
MUC2 (secretory mucin)
TR
TR
D1 D2 D3
D4 C CK
N
C
O-linked glycans
MUC3 (membrane mucin)
N
TR
O-linked glycan
EGF
SEA
EGF
P
Apical membrane
C
Antimicrobial products secreted by Paneth cells
Antimicrobial goblet cell products
Bacteria
Secretory IgA secreted by enterocytes (bind to bacteria)

Kim e Ho 2010

Table 2 Major goblet cell products

Study	Name	Other names	Peptide	Functions
Lievin-Le Moal and Servin [1], Hollingsworth and Swanson [3], Andrianifahanana et al. [4], Gum et al. [15]	MUC2	Goblet cell mucin Secretory mucin	Monomer (2.5 MDa) Oigomer (100 MDa)	Major component of mucus layers (protective barrier, lubrication, elimination). Binding sites and nutrient sources of microbes.
Hattrup and Gendler [21], Ho et al. [22], Luu et al. [23]	MUC1/ MUC3/ MUC17	Membrane-bound mucin	Variable sizes 200–>2000 kDa	Cell surface protective barrier, extracellular portions cleaved or shed and bioactive for epithelial restitution
Taupin and Podolsky [8], Kjellev [52]	TFF3	Intestinal trefoil factor (ITF)	Monomer (6.6 kDa) Dimer (13 kDa)	Epithelial restitution and wound healing. Facilitates cell migration. Blocks apoptosis. Increases mucus viscosity and structural integrity of mucus layers.
Artis et al. [57], Nair et al. [58], Hogan et al. [59], Herbert et al. [60]	RELMβ	Resistin-like molecule β, F1ZZ2	Monomer (12.5 kDa) Dimer (25 kDa)	Upregulates MUC2 expression/secretion. Induces goblet cell hyperplasia. Functions as Th2 cytokine-induced immune-effector molecule in resistance to intestinal nematode infection. Inhibits chemotaxis of nematode by direct binding to their chemosensory apparatus.
Johansson et al. [37], Kobayashi et al. [62]	Fcgbp	Fc-γ binding protein IgG Fc binding protein	Full-length protein (596 kDa)	Binds IgG antibodies. Stabilization and cross-linking of the MUC2 mucin networks of the inner firm mucus layer.

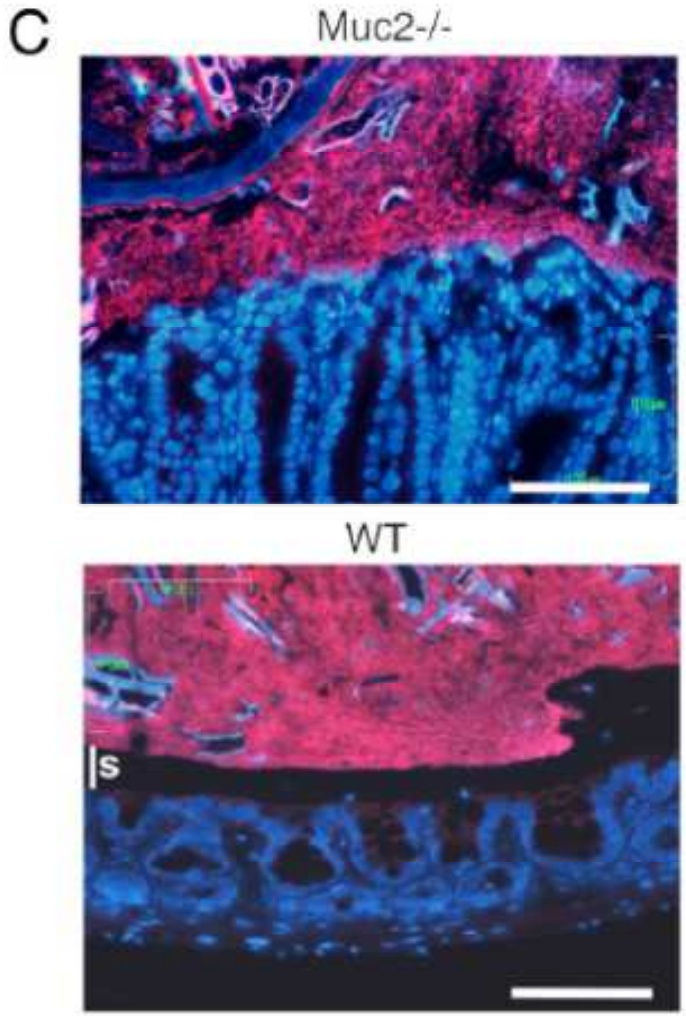
Kim e Ho 2010

The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria

Malin E. V. Johansson*, Mia Phillipson†, Joel Petersson†, Anna Velcich§, Lena Holm†, and Gunnar C. Hansson*‡

*Department of Medical Biochemistry, University of Gothenburg, 405 30 Gothenburg, Sweden; †Department of Medical Cell Biology, Uppsala University, 751 23 Uppsala, Sweden; and §Department of Oncology, Montefiore/Albert Einstein Cancer Center, Bronx, NY 10467

15064–15069 | PNAS | September 30, 2008 | vol. 105 | no. 39



GASTROENTEROLOGY 2006;131:117–129

Muc2-Deficient Mice Spontaneously Develop Colitis, Indicating That Muc2 Is Critical for Colonic Protection

MARIA VAN DER SLUIS,* BARBARA A. E. DE KONING,† ADRIANUS C. J. M. DE BRUIJN,* ANNA VELCICH,§ JULES P. P. MEIJERINK,† JOHANNES B. VAN GOUDOEVER,* HANS A. BÜLLER,‖ JAN DEKKER,¶ ISABELLE VAN SEUNINGEN,** INGRID B. RENES,* and ALEXANDRA W. C. EINERHAND‖

*Divisions of Neonatology, †Pediatric Oncology, and ‖Pediatric Gastroenterology and Nutrition, Department of Pediatrics, Erasmus MC and Sophia Children's Hospital, Rotterdam, The Netherlands; §Oncology Department, Albert Einstein Cancer Center/Montefiore Medical Center, New York, New York; ¶Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, The Netherlands; and **INSERM Unité 560, Lille, France

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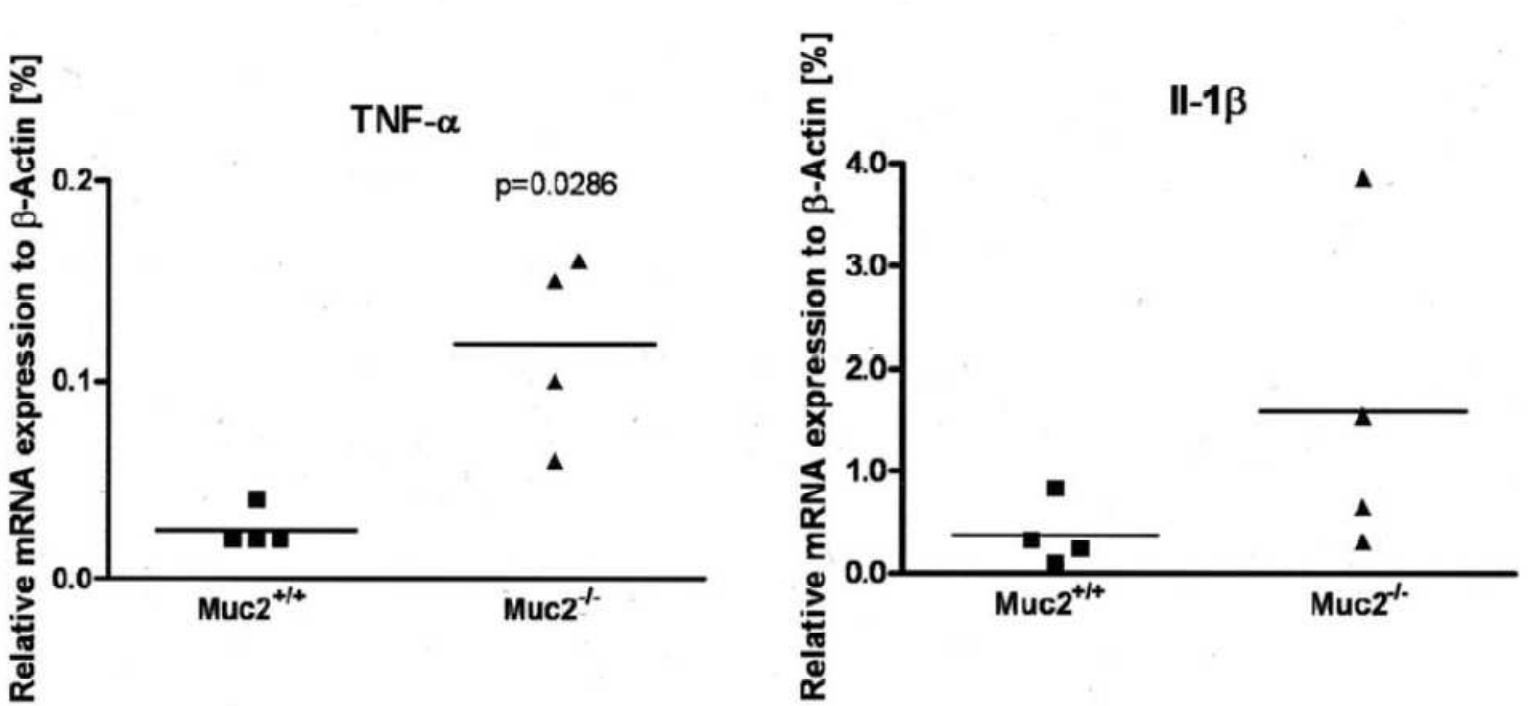
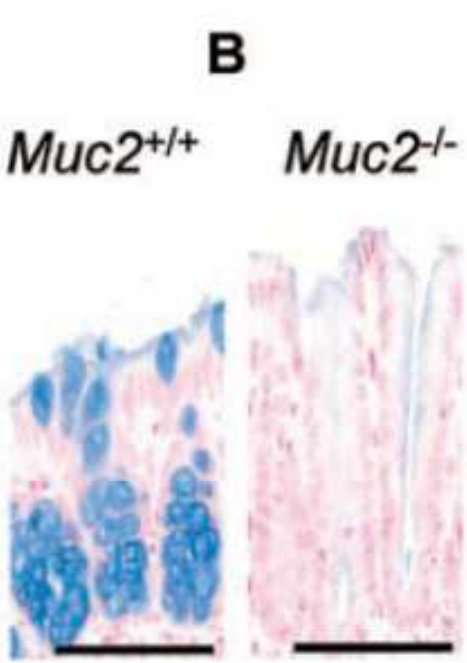
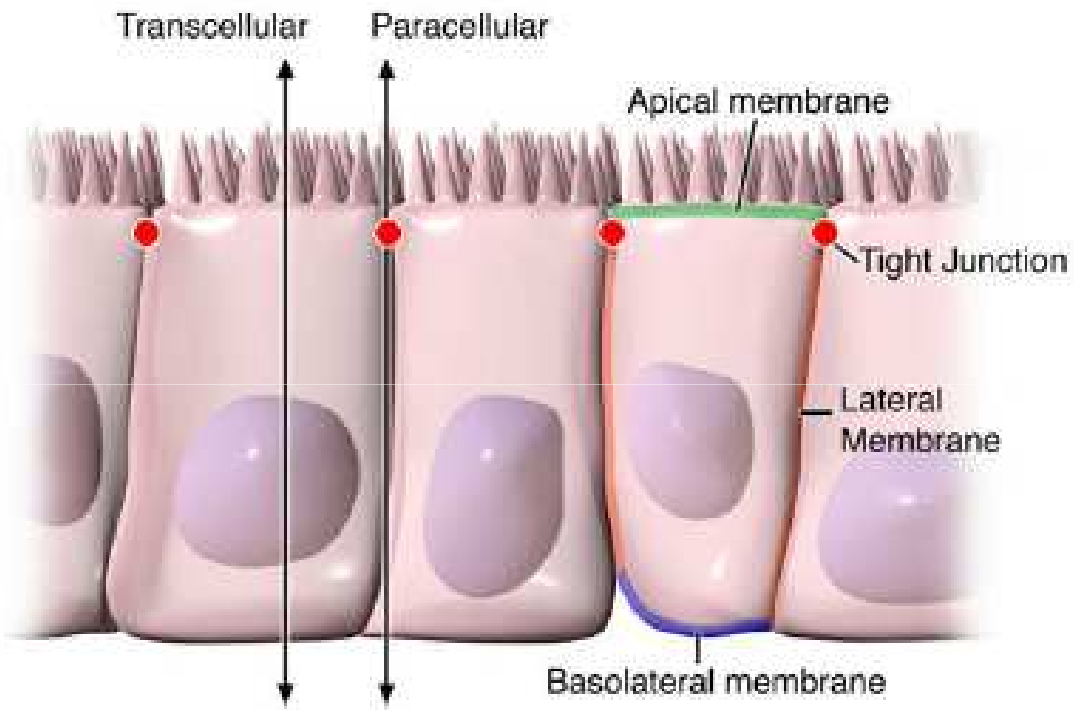




Colorectal Cancer in Mice Genetically Deficient in the Mucin Muc2

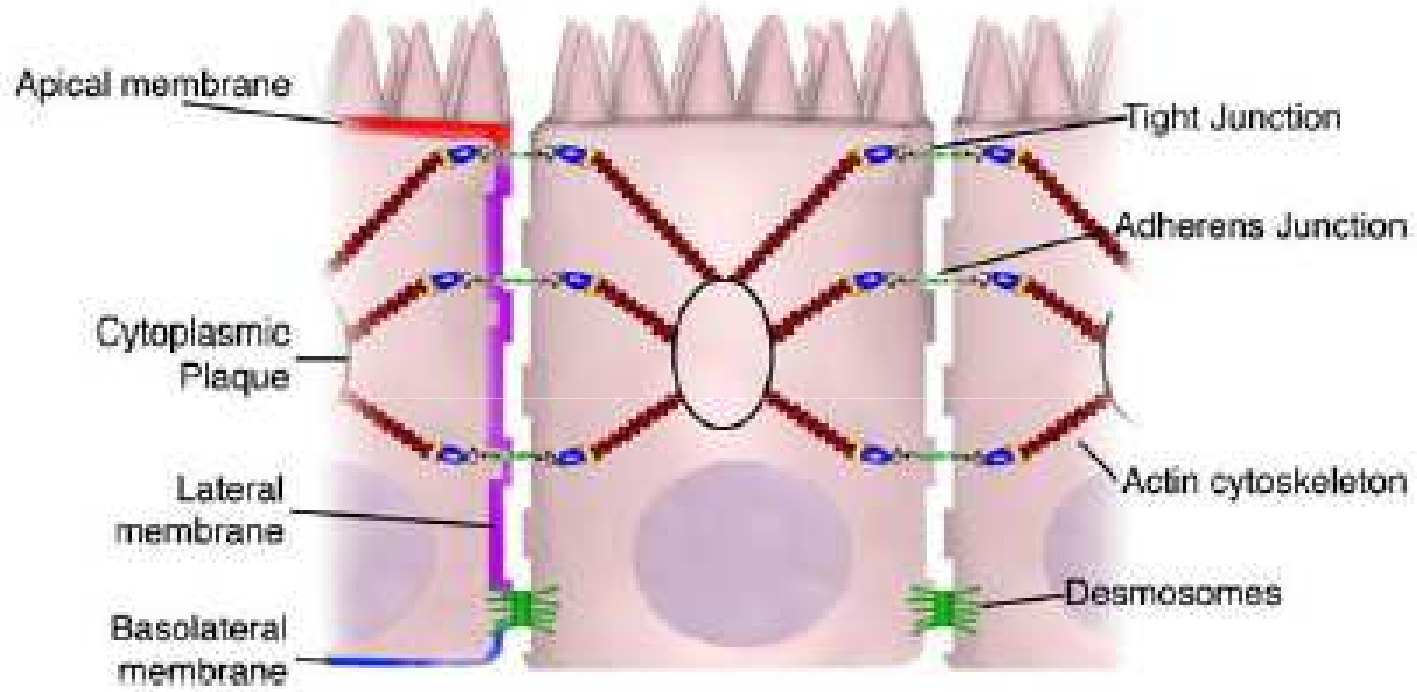
Anna Velcich,[1]* WanCai Yang,[1] Joerg Heyer,[2] Alessandra Fragale,[1] Courtney Nicholas,[1] Stephanie Viani,[1] Raju Kucherlapati,[3] Martin Lipkin,[4] Kan Yang,[4] Leonard Augenlicht[1]

The gastrointestinal tract is lined by a layer of mucus comprised of highly glycosylated proteins called mucins. To evaluate the importance of mucin in intestinal carcinogenesis, we constructed mice genetically deficient in Muc2, the most abundant secreted gastrointestinal mucin. $Muc2^{-/-}$ mice displayed aberrant intestinal crypt morphology and altered cell maturation and migration. Most notably, the mice frequently developed adenomas in the small intestine that progressed to invasive adenocarcinoma, as well as rectal tumors. Thus, Muc2 is involved in the suppression of colorectal cancer.


Transcellular
Paracellular
Apical membrane
Tight Junction
Lateral
Membrane
Basolateral membrane

Food allergy was found to be associated with increased intestinal permeability.

Disruption of the epithelial tight junctions by infection or other insults allows direct access of antigens to the dendritic cells in the lamina propria. This defect seems to be critical in the predisposition and exacerbation of various inflammatory conditions, including IBD, celiac disease, and food allergy


Apical membrane
Tight Junction
Adherens Junction
Cytoplasmic Plaque
Lateral membrane
Actin cytoskeleton
Desmosomes
Basolateral membrane

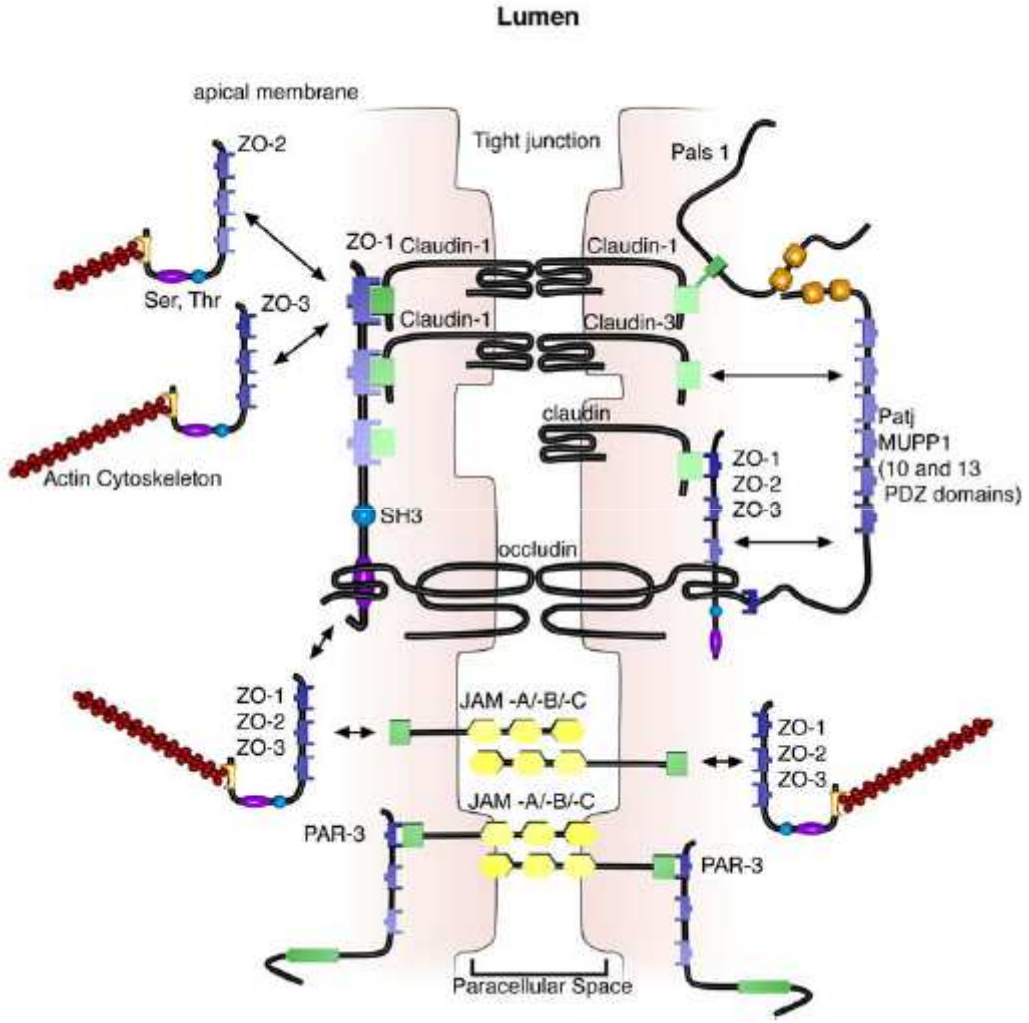
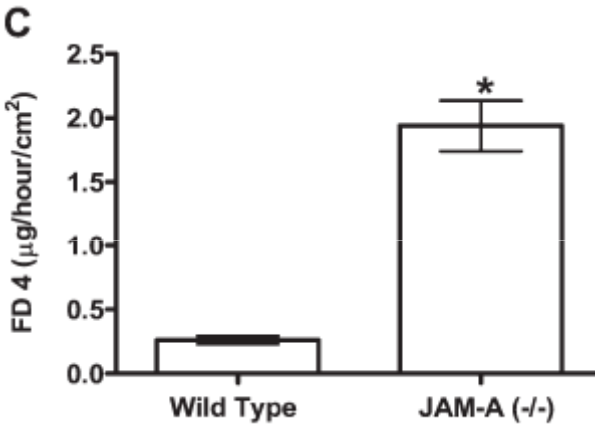

Lumen
apical membrane
Tight junction
ZO-2
Pals 1
ZO-1
Claudin-1
Claudin-1
Ser, Thr
ZO-3
Claudin-1
Claudin-3
claudin
Patj
MUPP1
(10 and 13
PDZ domains)
ZO-1
ZO-2
ZO-3
Actin Cytoskeleton
SH3
occludin
ZO-1
ZO-2
ZO-3
JAM -A/-B/-C
ZO-1
ZO-2
ZO-3
JAM -A/-B/-C
PAR-3
PAR-3
Paracellular Space

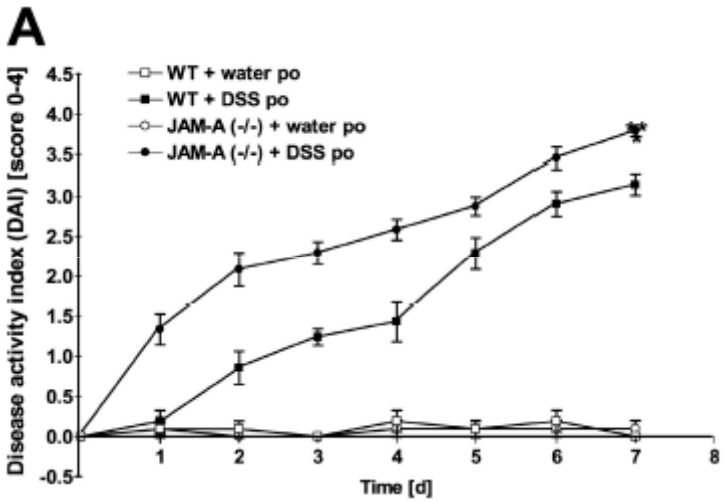
TABLE I. Transgenic or knockout mice and effects on intestinal barrier function

Protein	Transgenic or knockout	Function	Phenotype	References
Occludin	Gene deletion	TJ protein	No change in TJs or permeability	42, 43
Claudin-1	Gene deletion	TJ protein	Die within 1 d of birth	44
Claudin-6	Epidermis transgenic	TJ protein	Disrupted TJ formation and increased epithelial permeability	45
JAM-A	Gene deletion	TJ protein	Increased intestinal permeability	46
			Increased claudin-10 and claudin-15 expression	
			Increased susceptibility to DSS colitis	

JAM-A regulates permeability and inflammation in the intestine in vivo

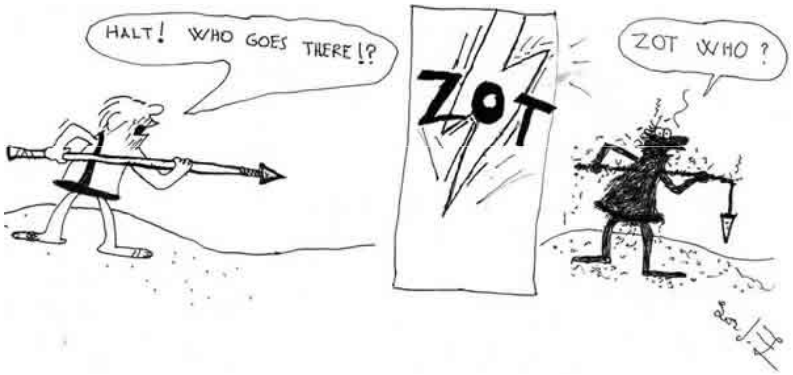
Mike G. Laukoetter,[1,3] Porfirio Nava,[1] Winston Y. Lee,[1] Eric A. Severson,[1] Christopher T. Capaldo,[1] Brian A. Babbin,[1] Ifor R. Williams,[1] Michael Koval,[2] Eric Peatman,[1] Jacquelyn A. Campbell,[4] Terence S. Dermody,[4,5] Asma Nusrat,[1] and Charles A. Parkos[1]





Vibrio cholerae
cytotoxin hemagglutinin protease (HA/P), a zinc-binding metalloprotease that degrades TJ proteins and decreases barrier function

zonula occludens toxin (Zot), an enterotoxin that reversibly increases intestinal epithelial permeability, disrupts the actin cytoskeleton, and induces
fragmentation of ZO-1 and occludin. Zot binds to the zonulin receptor on the apical side of intestinal epithelial cells and activates phospholipase C, leading to PKCa-dependent polymerization of the actin cytoskeleton. Actin polymerization is thought to promote cytoskeletal reorganization and the destabilization of TJ complexes



Enteropathogenic *Escherichia coli* (EPEC)
uses a syringe-like type III secretion system to trigger TJ disruption and alterations in intestinal epithelial ion secretion

Clostridium perfringens
CPE binds to the extracellular loop of claudin-3 and 4 on the cell surface of enterocytes, forming small protein complexes in the plasma membrane. These complexes promote oligomerization and the formation of larger plasma membrane complexes, which have been associated with increased plasma membrane permeability

Alcuni ceppi enterotossici di *E. coli* che colpiscono vitelli, suinetti, agnelli provocano una "diarrea secretoria", *Cl. perfringens* produce una citotossina non specifica che causa necrosi dell'epitelio, della lamina propria e dei vasi, determinando una enterite necrotico-emorragica.

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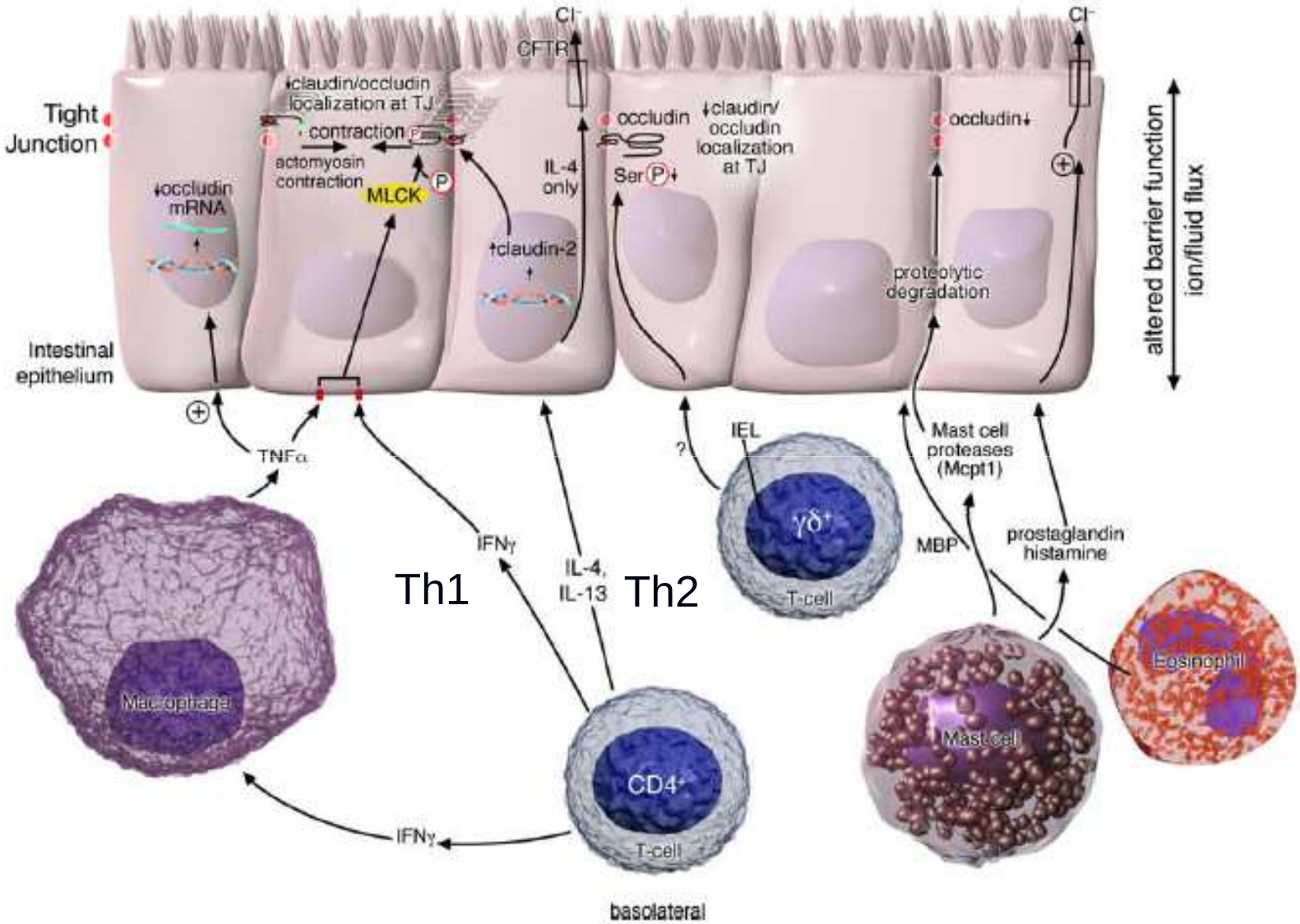
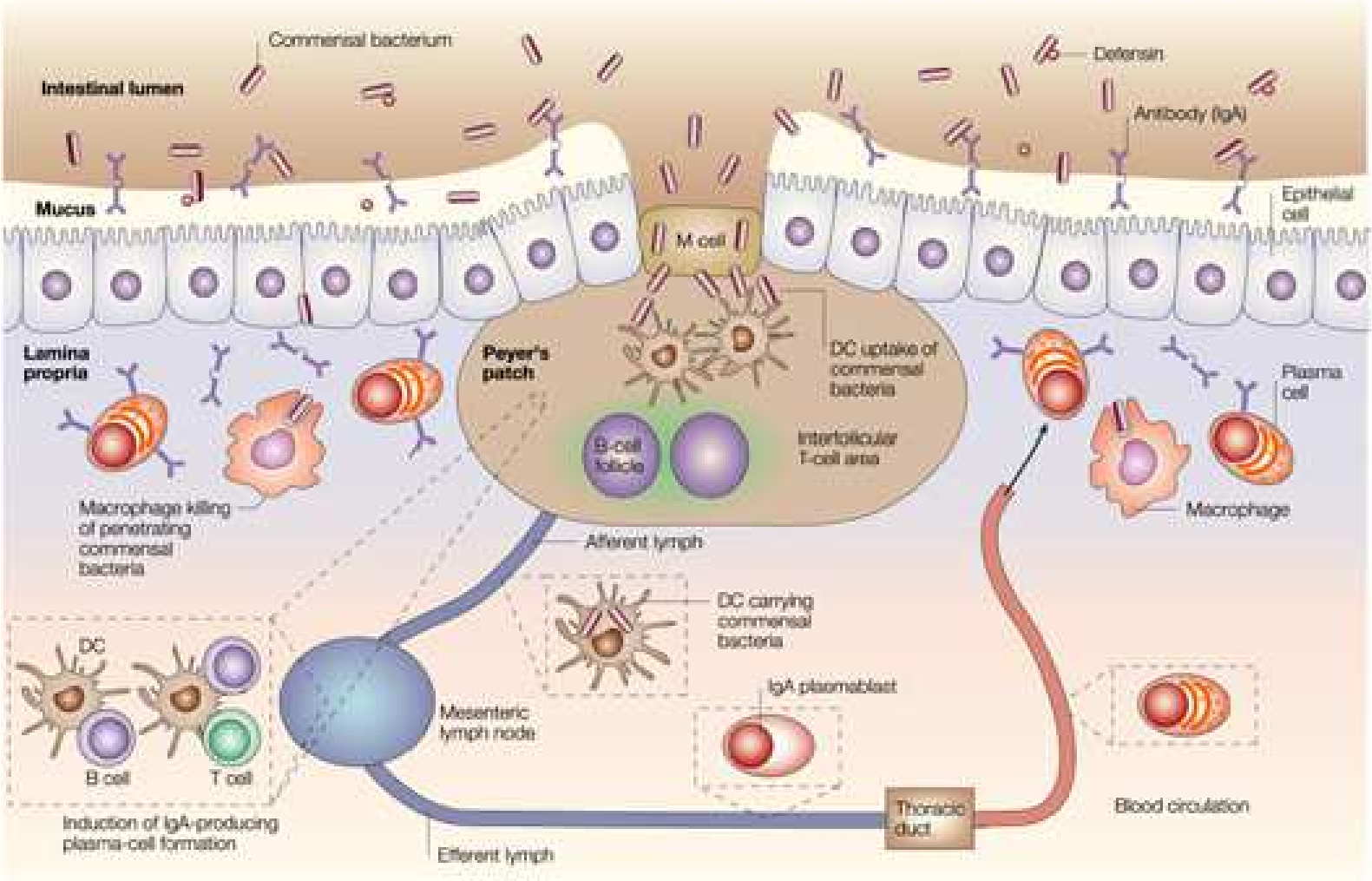
Chronic alcohol consumption has been shown to be associated with increased intestinal, inhibition of vitamin and nutrient transport, and a reduction in sodium and water absorption

Experimental analyses suggest involvement of the byproduct of ethanol metabolism, acetaldehyde, and nitric oxide (NO) in alcohol-mediated barrier dysfunction.

Nonsteroidal anti-inflammatory drug (NSAID) use is associated with a high incidence of gastrointestinal side effects, and there is substantial evidence indicating that chronic use can alter intestinal barrier function and cause significant gastrointestinal damage, including ulcers, perforation, hemorrhage, and an exacerbation of IBD.


Tight Junction
Intestinal epithelium
↓occludin mRNA
↓claudin/occludin localization at TJ
contraction
actomyosin contraction
MLCK
P
Cl⁻
CFTR
IL-4 only
↑claudin-2
occludin
Ser P ↓
↓claudin/ occludin localization at TJ
occludin↓
proteolytic degradation
altered barrier function
ion/fluid flux
TNFα
IFNγ
IL-4, IL-13
Th1
Th2
?
IEL
γδ⁺
T-cell
Mast cell proteases (Mcpt1)
MBP
prostaglandin histamine
Macrophage
CD4⁺
T-cell
Mast cell
Eosinophil
IFNγ
basolateral



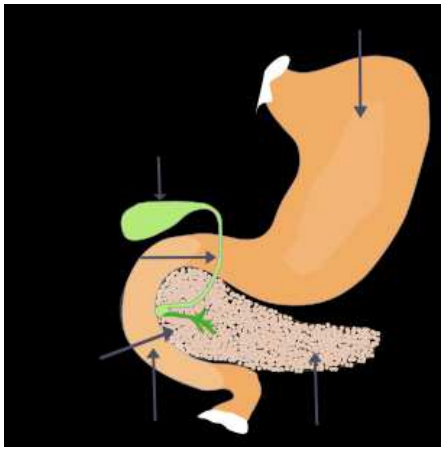
Nature Reviews | Immunology

Exocrine pancreas

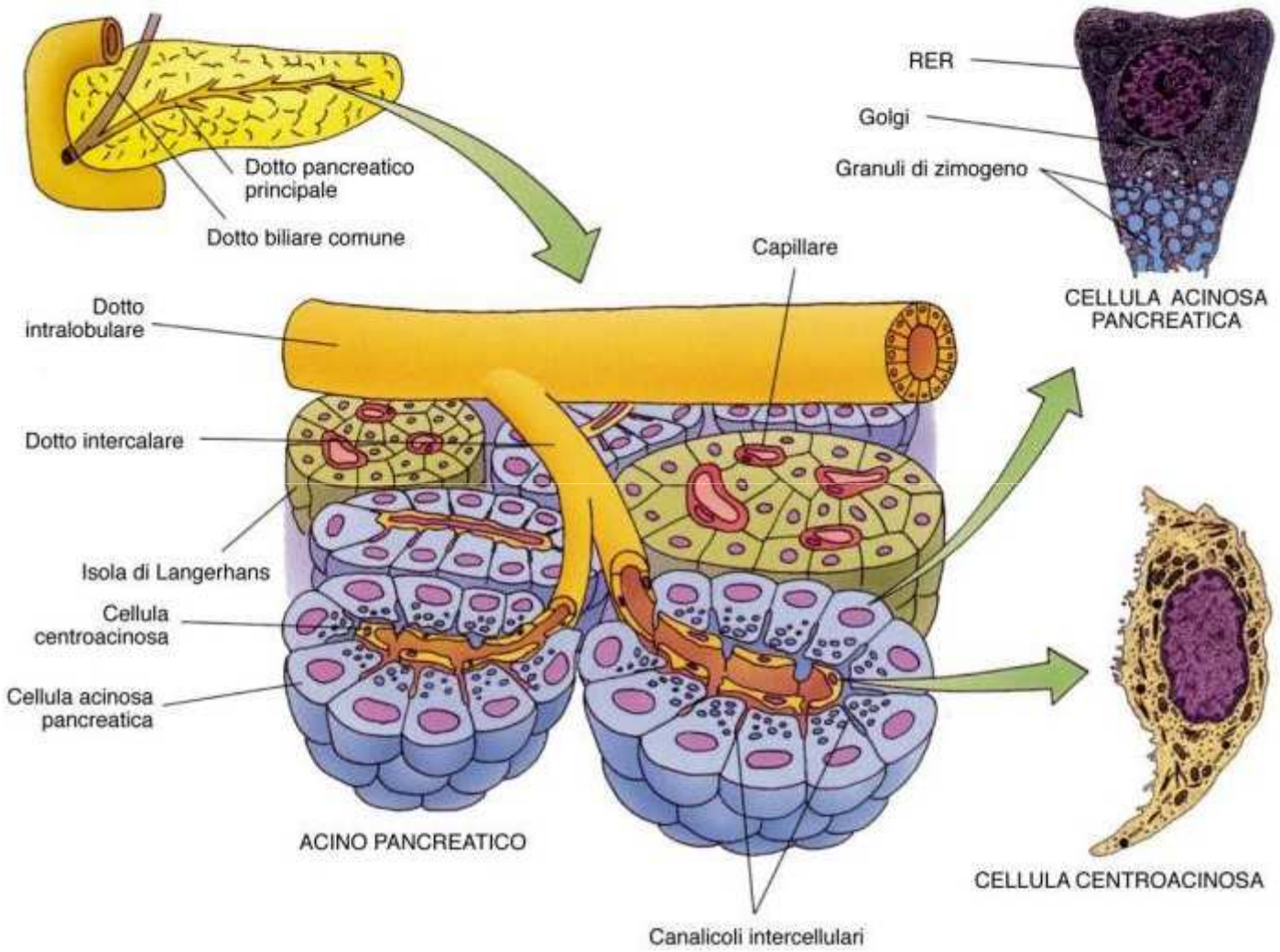
The exocrine pancreas is composed of acinar cells, which produce the enzymes needed for digestion, and a series of ductules and ducts that convey secretions to the duodenum.[1] Acinar cells are pyramidally shaped epithelial cells that are radially oriented around a central lumen (Fig. 19-2). Acinar cells contain membrane-bound zymogen granules rich in digestive enzymes.

The pancreas secretes its exocrine products as enzymatically inert proenzymes. They include trypsinogen, chymotrypsinogen, procarboxypeptidase, proelastase, kallikreinogen, and prophospholipase A and B.[1] Self-digestion of pancreatic tissue is prevented by several mechanisms:

- The majority of the enzymes are synthesized as inactive proenzymes (with the exception of amylase and lipase).
- The enzymes are sequestered in membrane-bound zymogen granules in the acinar cells.
- Activation of proenzymes requires conversion of inactive trypsinogen to active trypsin by duodenal enteropeptidase (enterokinase). Trypsin cleaves proenzymes to yield products such as chymotrypsin, elastases, and phospholipases.
- Trypsin inhibitors including serine protease inhibitor Kazal type l (SPINK1, also known as pancreatic secretory trypsin inhibitor, PSTI) are present within acinar and ductal secretions.
- Acinar cells are remarkably resistant to the action of trypsin, chymotrypsin, and phospholipase A2.



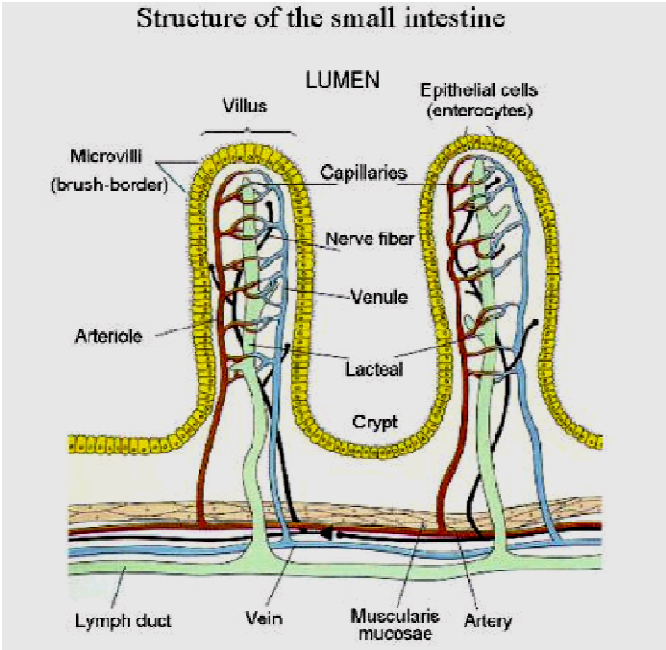
Robbins and Cotran "Pathologic Basis of Disease" 8° Edition


Dotto pancreatico principale
Dotto biliare comune
RER
Golgi
Granuli di zimogeno
CELLULA ACINOSA PANCREATICA
Capillare
Dotto intralobulare
Dotto intercalare
Isola di Langerhans
Cellula centroacinosa
Cellula acinosa pancreatica
ACINO PANCREATICO
CELLULA CENTROACINOSA
Canalicoli intercellulari

Fisiopatologia delle malattie enteriche

Malassorbimento

La digestione e l'assorbimento di nutrienti prevedono:
-<u>fase luminale</u> mediata dalle secrezioni biliari e pancreatiche (la principale causa di malassorbimento è l'insufficienza pancreatica; atrofia dei villi, deficienza di maltasi e lattasi negli enterociti)
- <u>fase epiteliale</u> mediata dai sistemi enzimatici sulla superficie e nel citoplasma degli enterociti;
- <u>fase finale</u> è data dal passaggio dei nutrienti dall'enterocita all'interstizio e da qui al sangue e alla linfa.



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Malabsorption results from disturbance in at least one of the four phases of nutrient absorption:

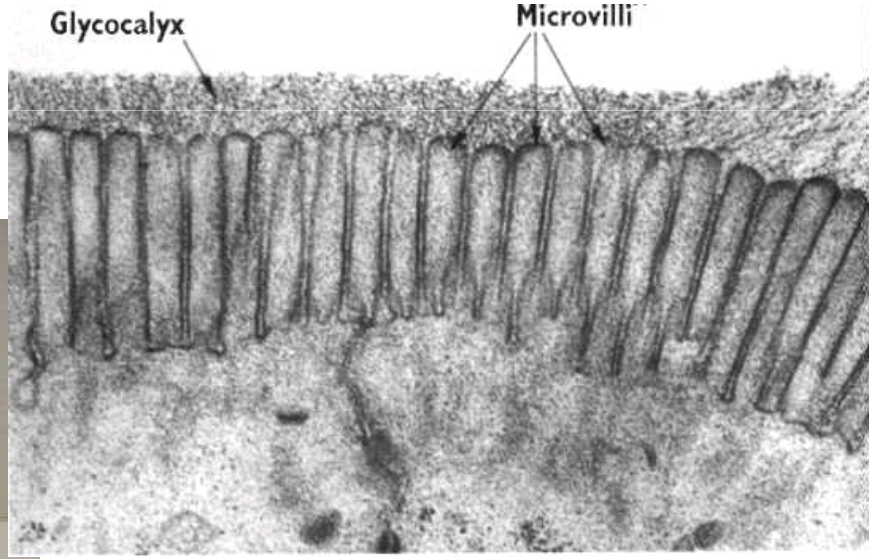
(1) intraluminal digestion, in which proteins, carbohydrates, and fats are broken down into forms suitable for absorption;

(2) terminal digestion, which involves the hydrolysis of carbohydrates and peptides by disaccharidases and peptidases, respectively, in the brush border of the small intestinal mucosa;

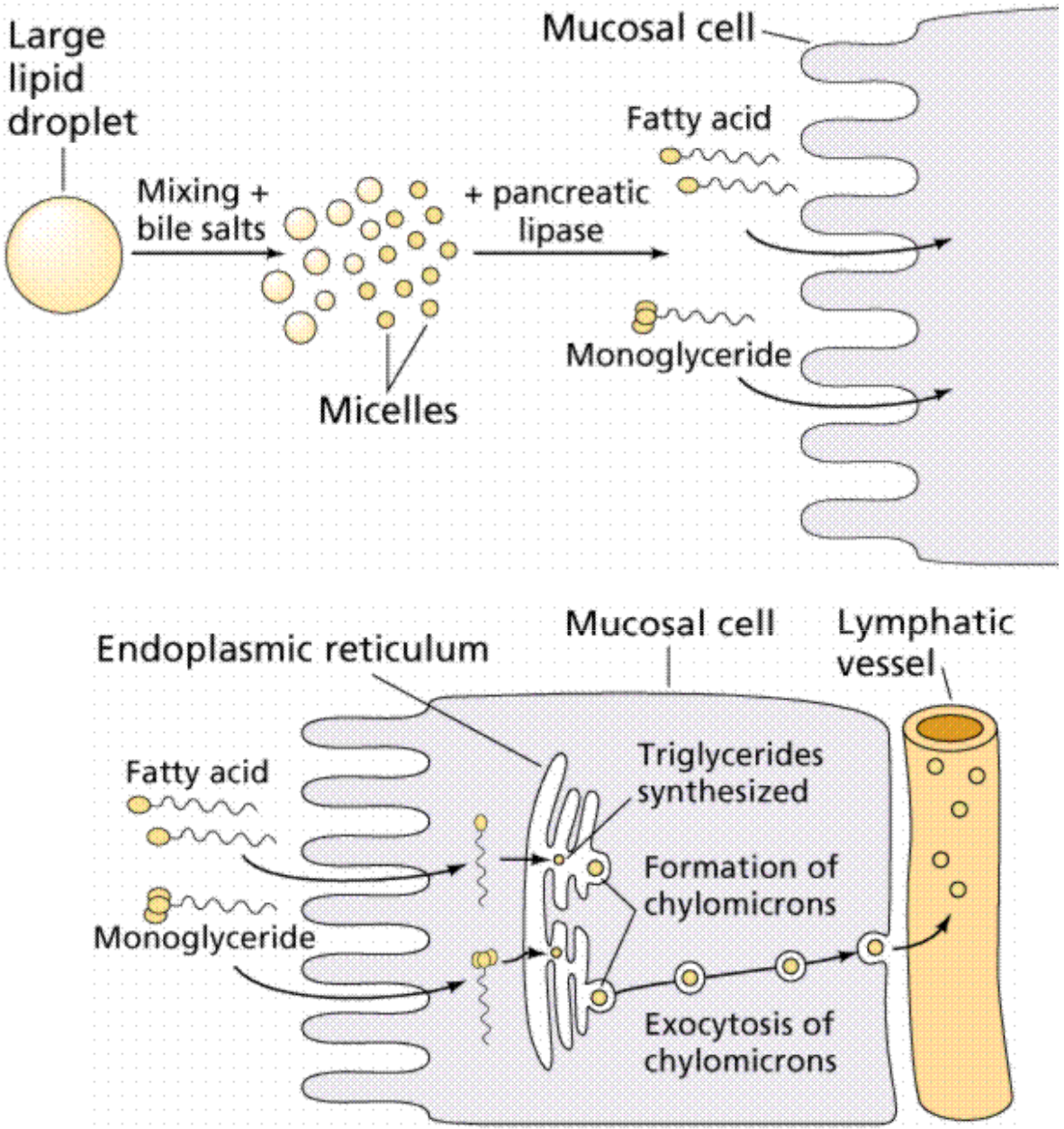
(3) transepithelial transport, in which nutrients, fluid, and electrolytes are transported across and processed within the small intestinal epithelium;

(4) lymphatic transport of absorbed lipids.

i microvilli sono responsabili dell'immensa superficie di assorbimento e il glicocalice contiene gli enzimi deputati alla digestione e all'assorbimento dei nutrienti. Un danno a queste strutture determina malfunzionamento e diarrea. Es.: individui intolleranti al lattosio, mancano della *lattasi* presente nel glicocalice, quindi il lattosio rimane nel lume, viene fermentato dai batteri del colon con conseguente drenaggio osmotico e diarrea. Istologicamente l'intestino è normale

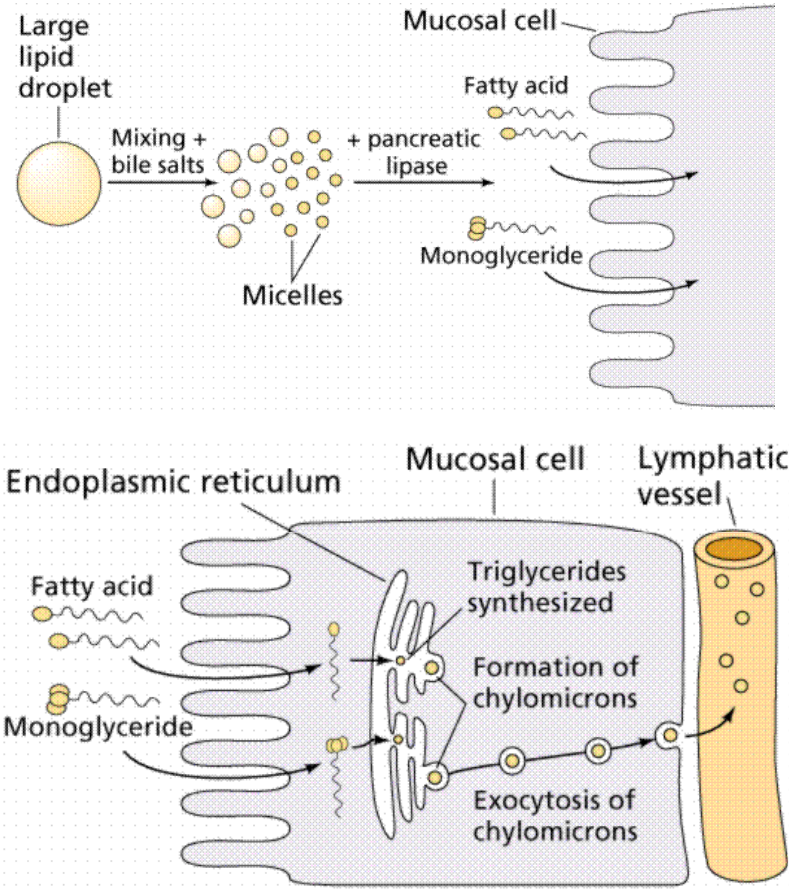


http://cellbio.utmb.edu/

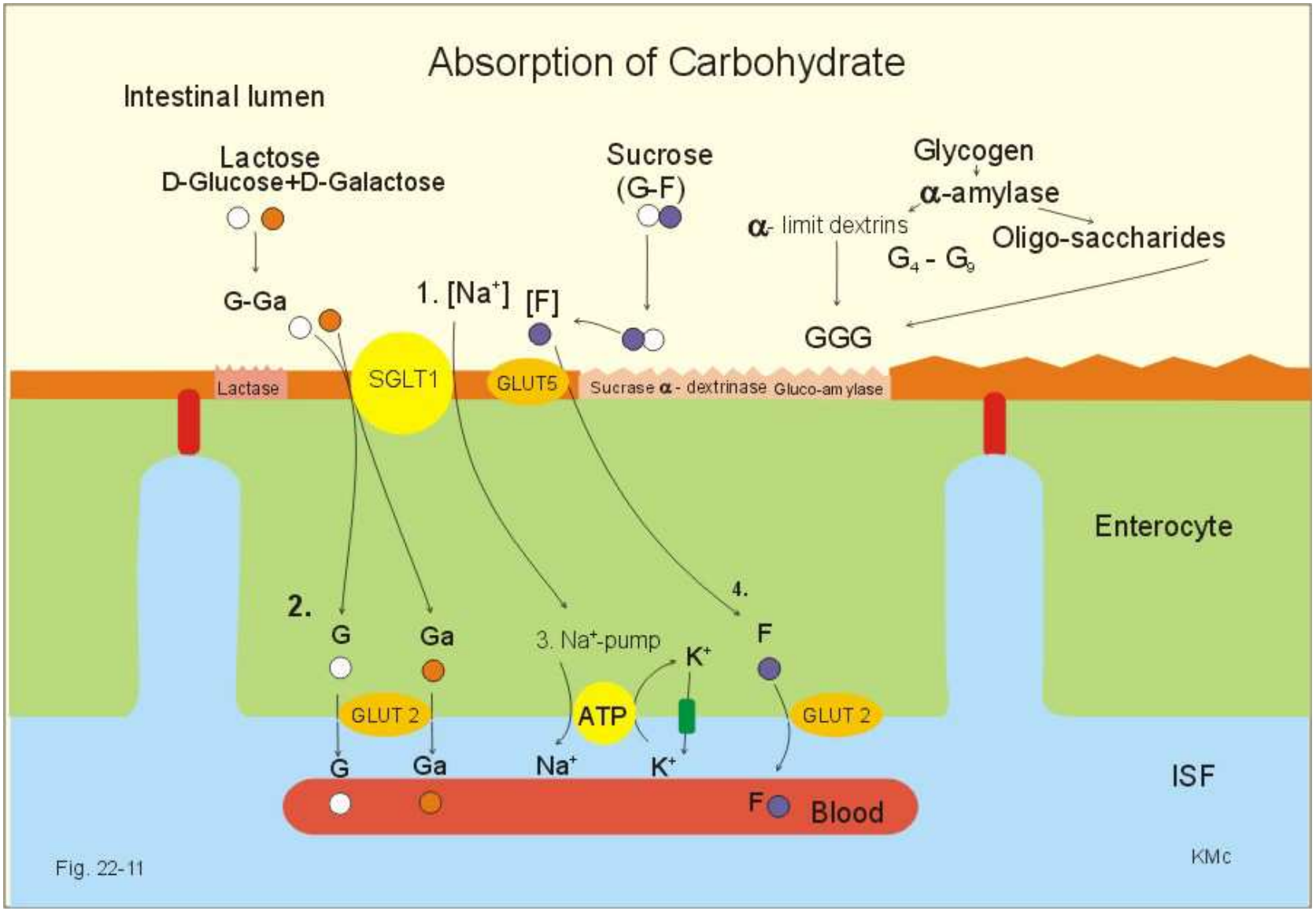

Large lipid droplet
Mixing + bile salts
Micelles
+ pancreatic lipase
Mucosal cell
Fatty acid
Monoglyceride
Endoplasmic reticulum
Mucosal cell
Lymphatic vessel
Fatty acid
Monoglyceride
Triglycerides synthesized
Formation of chylomicrons
Exocytosis of chylomicrons

A) Malassorbimento dei lipidi

1) Diminuita secrezione di lipasi:
-per atrofia o fibrosi pancreatica
-per atrofia intestinale e quindi insufficiente secrezione di enzimi che agiscono sul pancreas (colecistochinina)
2) Deficienza di sali biliari:
-colestasi intraepatica od ostruzione biliare
-riduzione dell'assorbimento di costituenti per atrofia ileale (gli acidi grassi non vengono incorporati nelle micelle ed emulsionati)
3) Atrofia intestinale:
-diminuzione dell'area disponibile per l'assorbimento
-gli enterociti scarsamente differenziati non sono in grado di riesterificare gli acidi grassi a catena lunga in trigliceridi e di produrre chilomicroni da esportare
-linfangiectasia, enterite granulomatosa, linfosarcoma provocano ostruzione
del drenaggio linfatico e quindi ostacolano il flusso di chilomicroni nel sangue.



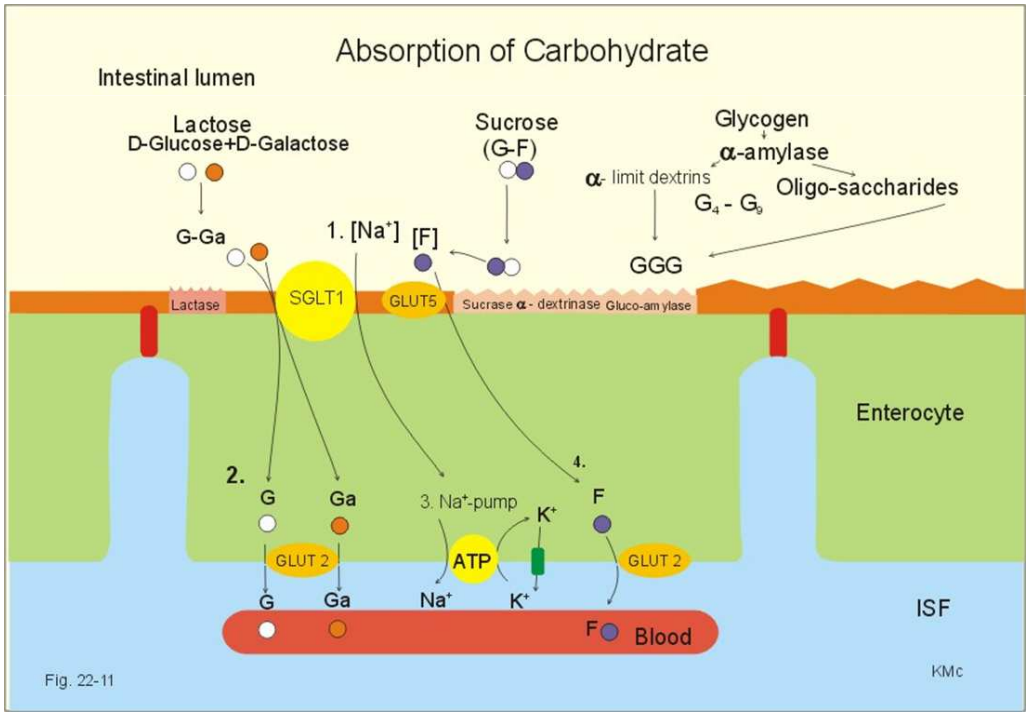
=> Steatorrea (eccesso di lipidi nelle feci)

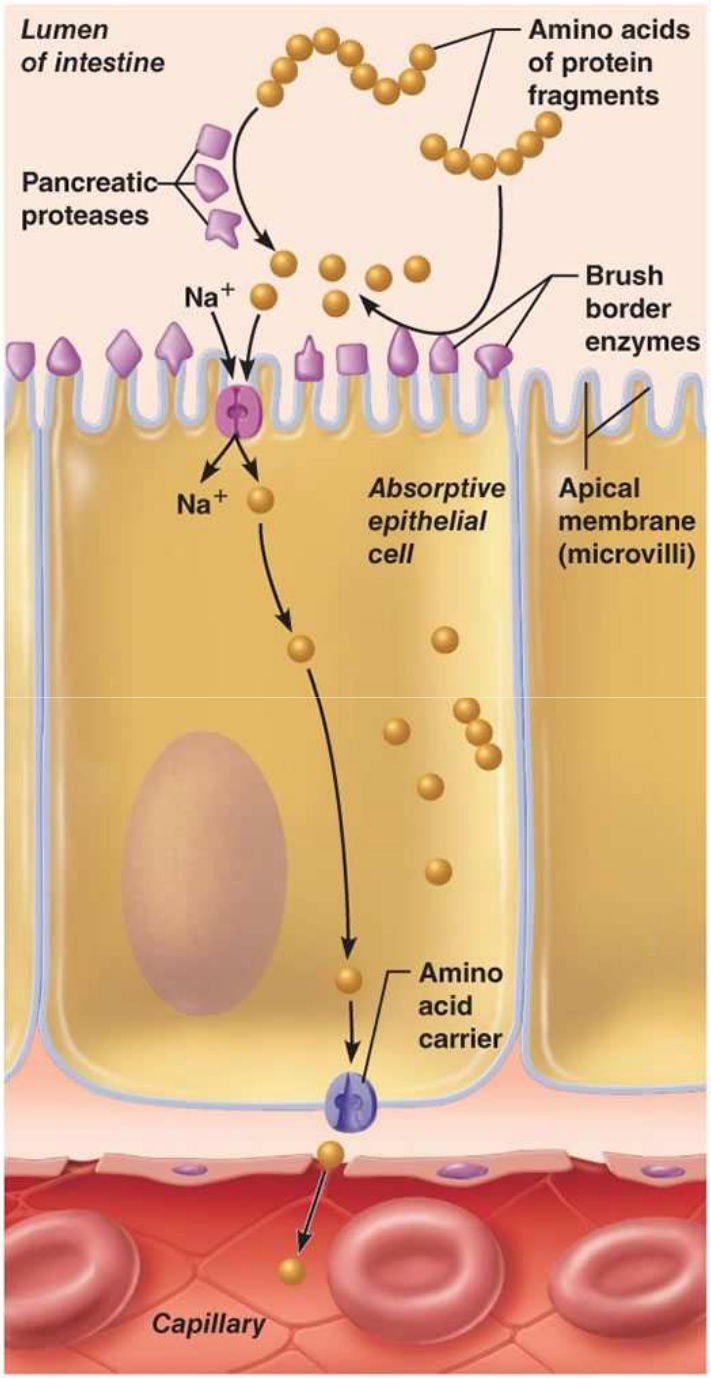

Absorption of Carbohydrate
Intestinal lumen
Lactose
D-Glucose+D-Galactose
Sucrose
(G-F)
Glycogen
α-amylase
α- limit dextrins
Oligo-saccharides
G4 - G9
G-Ga
1. [Na+]
[F]
GGG
Lactase
SGLT1
GLUT5
Sucrase α- dextrinase Gluco-amylase
Enterocyte
2.
G
Ga
3. Na+-pump
K+
4.
F
GLUT 2
ATP
GLUT 2
G
Ga
Na+
K+
F
Blood
ISF
Fig. 22-11
KMc

B) Malassorbimento dei carboidrati

Diminuita secrezione di amilasi
-per grave perdita di pancreas esocrino (vitelli e ruminanti a fine carriera)
-per atrofia intestinale (dovuta a rota e coronavirus nei cuccioli neonati)

Gli zuccheri non assorbiti vengono fermentati dalla flora intestinale, inoltre l'effetto osmotico determina accumulo di fluidi nell'intestino tenue.





① Proteins and protein fragments are digested to amino acids by pancreatic proteases (trypsin, chymotrypsin, and carboxy- peptidase), and by brush border enzymes (carboxypeptidase, aminopeptidase, and dipeptidase) of mucosal cells.

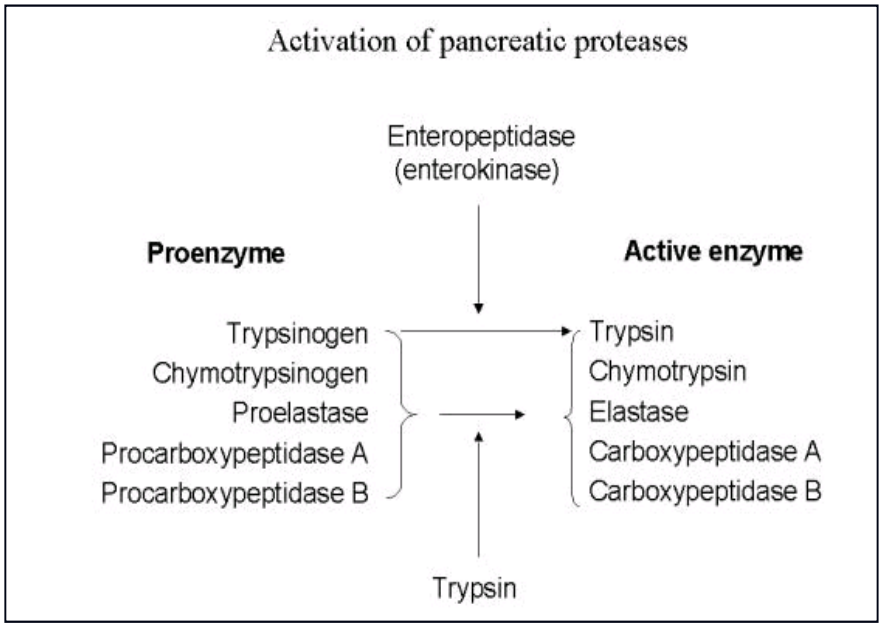
② The amino acids are then absorbed by active transport into the absorptive cells, and move to their opposite side.

③ The amino acids leave the villus epithelial cell by facilitated diffusion and enter the capillary via intercellular clefts.

C) Malassorbimento delle proteine

Diminuita secrezione di proteasi
-per diminuzione del 10% dell'attività pancreatica
-atrofia intestinale (in particolare del duodeno =>diminuzione della produzione di enterochinasi, necessario per convertire il tripsinogeno in tripsina)

Importante differenziare il malassorbimento proteico dalle enteropatie proteino-disperdenti



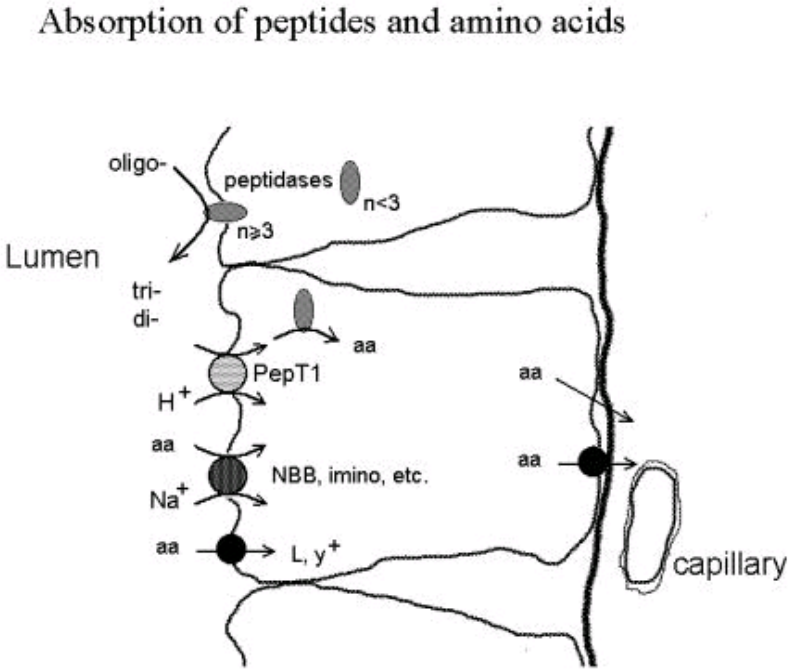


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Table 350-1. Genetic Disorders Of Membrane Transport

Class of Substance and Disorder	Individual Substrates	Tissues Manifesting Transport Defect	Proposed Molecular Basis of Defect	Major Clinical Manifestations	Mode of Inheritance
AMINO ACIDS					
Classic cystinuria	Cystine, lysine, arginine, ornithine	Proximal renal tubule, jejunal mucosa	Mutation of shared dibasic-cystine transport protein	Cystine nephrolithiasis	Autosomal recessive
Dibasicaminoaciduria	Lysine, arginine, ornithine	Proximal renal tubule, jejunal mucosa	Mutation of dibasic transport protein	Type I: Benign Type II: Protein intolerance, hyperammonemia, retardation	Autosomal recessive
Hypercystinuria	Cystine	Proximal renal tubule	Mutation of cystine transport protein	Some risk of cystine nephrolithiasis	Autosomal recessive
Lysinuria	Lysine	Proximal renal tubule, jejunal mucosa	Mutation of lysine transport protein	Seizures, physical and mental retardation	Possible autosomal recessive
Hartnup disease	Neutral amino acids	Proximal renal tubule, jejunal mucosa	Mutation of shared neutral amino acid transport protein	Constant neutral aminoaciduria, intermittent symptoms of pellagra	Autosomal recessive
Tryptophan malabsorption	Tryptophan	Jejunal mucosa	Mutation of tryptophan transport protein	Indoluria, ?hypercalcemia, ?nephrocalcinosis	Probable autosomal recessive
Methionine malabsorption	Methionine	Jejunal mucosa	Mutation of methionine transport protein	a-Hydroxybutyricaciduria, white hair, mental retardation, convulsions, hyperpneic attacks, edema	Probable autosomal recessive
Histidinuria	Histidine	Proximal renal tubule, jejunal mucosa	Mutation of histidine transport protein	Mental retardation	Autosomal recessive
Iminoglycinuria	Glycine, proline, hydroxyproline	Proximal renal tubule, jejunal mucosa	Mutation of shared glycine-imino acid transport protein	None	Autosomal recessive
Dicarboxylicaminoaciduria	Glutamic acid, aspartic acid	Proximal renal tubule, jejunal mucosa	Mutation of shared dicarboxylic amino acid transport protein	None	Probable autosomal recessive
Cystinosis	Cystine	Lysosomal membranes	Mutation of cystine transport protein	Renal failure, hypothyroidism, blindness	Autosomal recessive
HEXOSES					
Renal glycosuria	D-Glucose	Proximal renal tubule	Mutation of D-glucose transport protein	Glycosuria with normal blood glucose	Autosomal recessive
Glucose-galactose malabsorption	D-Glucose D-Galactose	Jejunal mucosa, proximal renal tubule	Mutation of shared Na^+-dependent glucose-galactose transport protein	Watery diarrhea on feeding glucose, lactose, sucrose, or galactose	Autosomal recessive
LIPIDS					
Familial hypercholesterolemia	Cholesterol	Fibroblasts, lymphoid lines, leukocytes	Mutation of membrane LDL-cholesterol receptor protein	Hypercholesterolemia, tendon xanthomas, arcus corneae, coronary artery atherosclerosis	Autosomal dominant

Diarrea

Che cos'è? Eccesso di H_2O nelle feci

Conseguenze:

La perdita di soluti e di H_2O può portare a gravi perdite di elettroliti, squilibri acido-base, disidratazione …

Grandi volumi di fluidi entrano nell'intestino tenue dal cibo, saliva, dalle secrezioni gastriche, pancreatiche, biliari ed enteriche e dagli scambi osmotici con il circolo. La maggior parte dei fluidi viene assorbita dagli enterociti del piccolo intestino, (quindi anche una piccola perturbazione di questi scambi determina effetti significativi sul movimento dei fluidi). Il colon, oltre alla funzione fermentativa, assorbe le ultime frazioni di H_2O dalla massa fecale, minimizzando le perdite. La capacità assorbente del colon è limitata per cui se la quantità di fluidi che entra è ingente si determina diarrea (*diarrea del piccolo intestino*). La *diarrea del grosso intestino* è dovuta all'incapacità del colon di non assorbire anche normali volumi di fluidi.

Diarrhea is defined as an increase in stool mass, frequency, or fluidity, typically greater than 200 g per day. In severe cases stool volume can exceed 14 L per day and, without fluid resuscitation, result in death. Painful, bloody, small-volume diarrhea is known as dysentery. Diarrhea can be classified according to four major categories:

- Secretory diarrhea is characterized by isotonic stool and persists during fasting.
- Osmotic diarrhea, such as that which occurs with lactase deficiency, is due to the excessive osmotic forces exerted by unabsorbed luminal solutes. The diarrhea fluid is over 50 mOsm more concentrated than plasma and abates with fasting.
- Malabsorptive diarrhea follows generalized failures of nutrient absorption and is associated with steatorrhea and is relieved by fasting.
- Exudative diarrhea is due to inflammatory disease and characterized by purulent, bloody stools that continue during fasting.

Diarrea del piccolo intestino

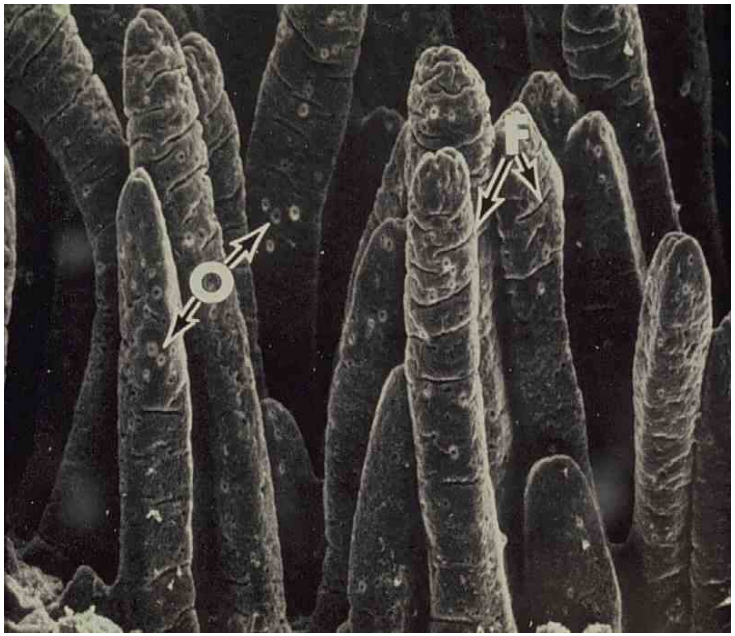
1)Diarrea secretoria: avviene quando la secrezione di fluidi eccede l'assorbimento. Per effetto delle tossine batteriche di *Vibrio cholerae*, *E. coli*, alcuni ceppi di *Salmonella*, *Yersinia enterocolitica*, *Shigella*, *Campylobacter jejuni*. Le tossine interrompono il cotrasporto di NaCl sul versante luminale degli enterociti e stimolano la secrezione di NaCl (e quindi di H_2O) dalle cripte => quindi i fluidi non vengono assorbiti e oltretutto vengono secreti nel lume. Oltre a tossine batteriche è dovuta a prostaglandine, istamina, citochine (IBD)

2) Diarrea da malassorbimento: l'atrofia dei villi e quindi degli enterociti determina scarso riassorbimento di H_2O e quindi ritenzione di fluidi e soluti nel lume

3) Diarrea da disturbi di circolo e essudativa
(ipertensione portale, insufficienza cardiaca congestizia) e ipoalbuminemia determinano un aumento della pressione idrostatica dei capillari intestinali e diminuzione di quella oncotica con conseguente fuoriuscita di liquidi dagli spazi intercellulari tra enterociti.
Anche la trasudazione e l'effusione (linfangiectasia, infiammazione) determinano perdita di liquidi nel lume.
Grave necrosi dell'epitelio e danno vascolare causano malassorbimento ed effusione di fluidi e sangue evidenti come fibrina ed emorragie nel lume
(enterotossine di *Clostridium difficile*)

Malattie infettive/parassitarie che hanno come target l'epitelio intestinale

Enterociti:
-Rotavirus, Coronavirus enterici (gastroenterite trasmissibile del suino);
-Brachyspira hyodysenteriae (dissenteria suina);
-Coccidi, Criptosporidi;
Questi patogeni causano distruzione e perdita degli enterociti con atrofia dei villi, maldigestione, malassorbimento. Inoltre le ingesta non vengono assorbite e si hanno degradazioni e fermentazioni anomale da parte della microflora con conseguente aumento dell'osmolarità del contenuto intestinale e quindi aumento di liquidi nell'intestino. Dal momento che i patogeni con tropismo per gli enterociti non attaccano le cripte, il danno non è irreversibile.



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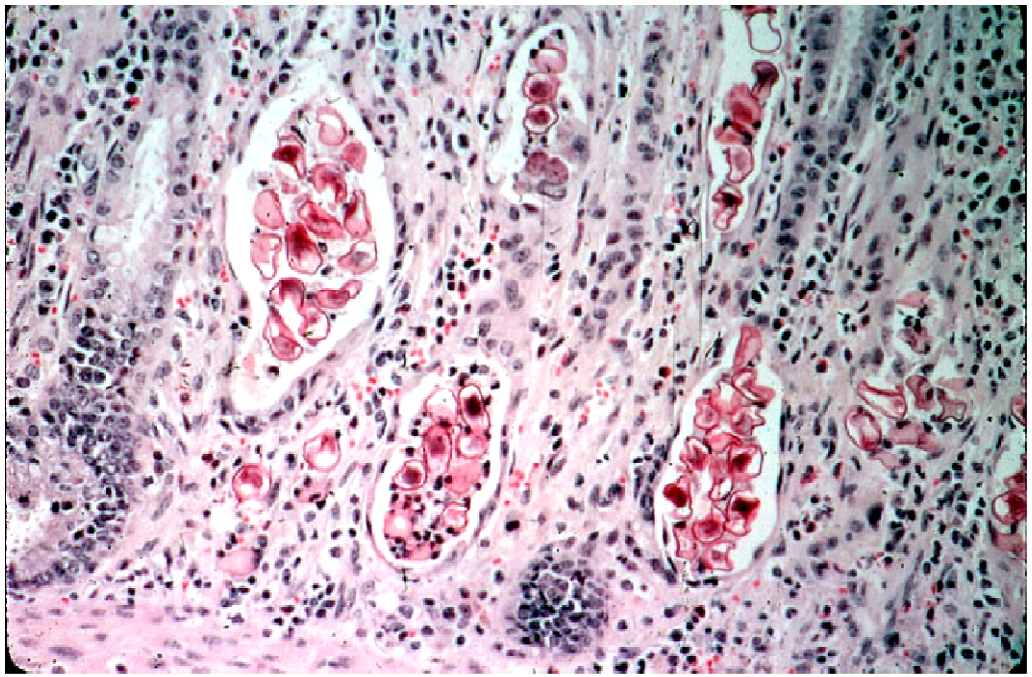
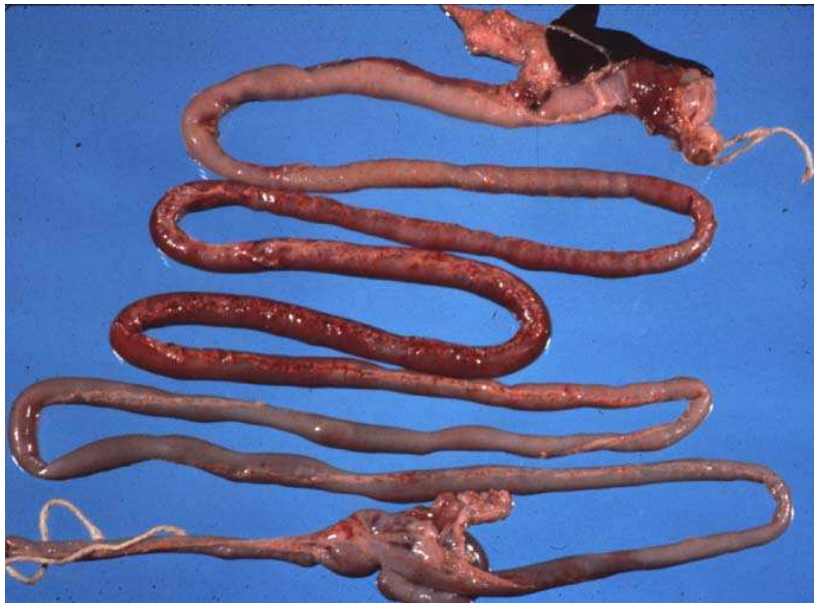


Cripte:
-(agenti radiomimetici come) Parvovirus nei carnivori, virus della BVD; Peste bovina e alcune micotossine.
La perdita delle cellule indifferenziate della cripte determina la perdita della capacità rigenerativa dell'epitelio. I villi rimangono circondati dal vecchio epitelio per cui dal momento dell'infezione a quello dei sintomi può passare del tempo.



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