# Digestive system

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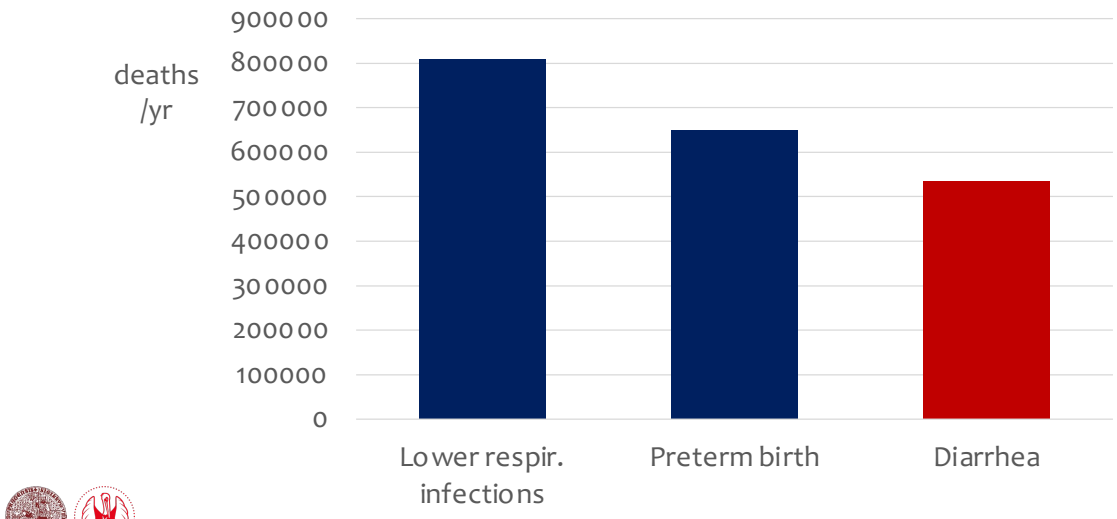
## Causes of death: children ≤5 yr

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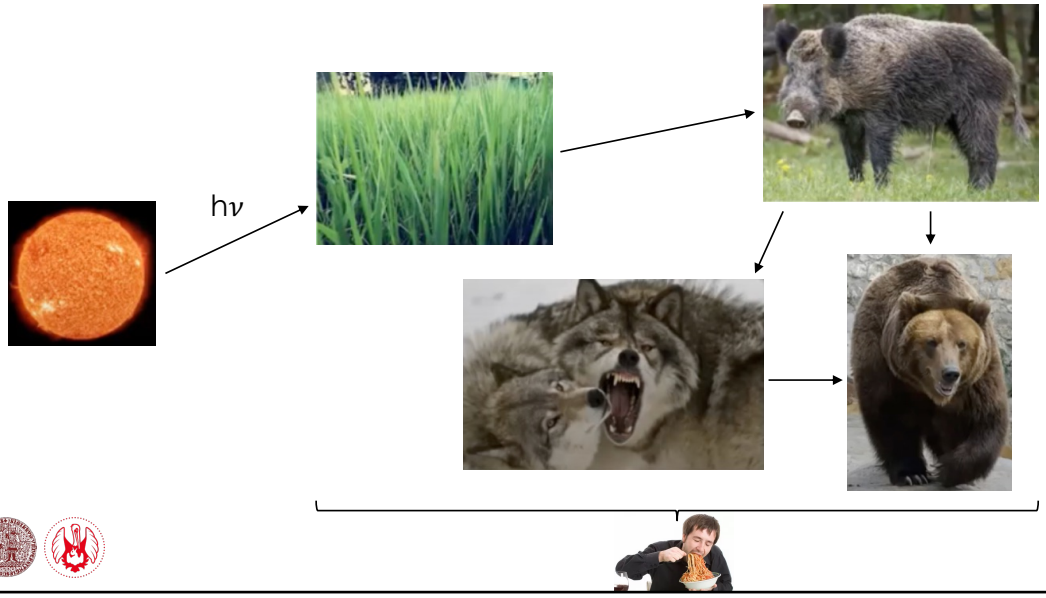
# All life depends on external energy

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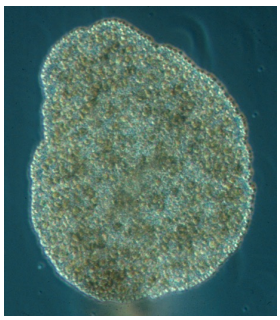
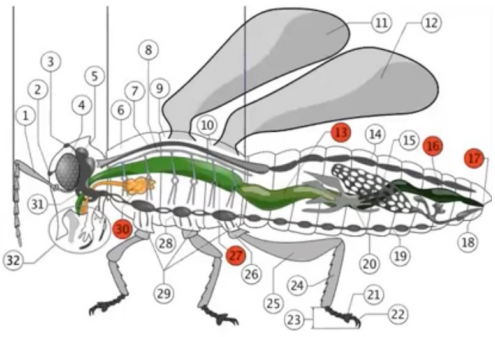
# Evolution



*Placozoa*

x



epithelial cells lining an inner lumen

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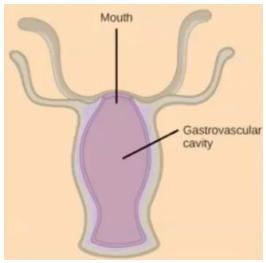
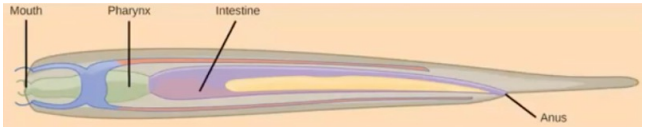
## Evolution




- gastrovascular cavity
  (e.g. coral, jelly fish, sea anemones)

- alimentary canal
  (evolutionary ancient)

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## Evolution

- phagocytosis + <u>intracellular digestion</u>:
  most common

- <u>extracellular digestion</u> + absorption of smaller molecules:
  only vertebrates & most insects

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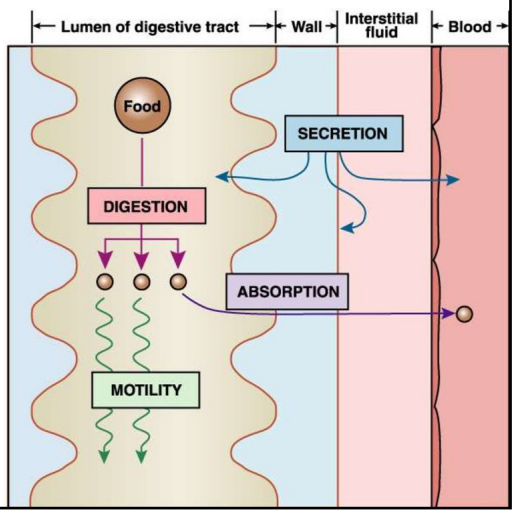
# Components of food intake

- movement
  (mouth → anus)
- within that, 2 processes:
  - secretion
    (→ *extracellular digestion*)
  - absorption
    (→ *intracellular digestion*)

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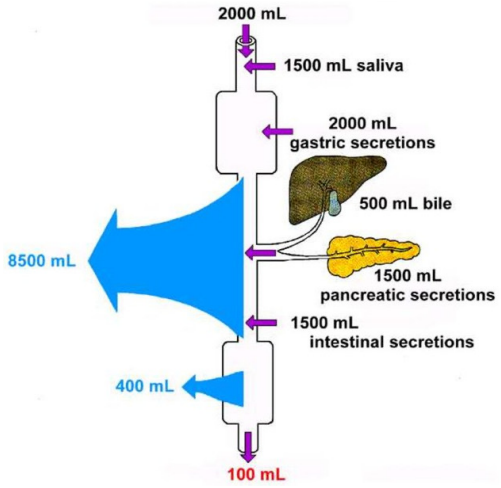
# Secretion




- $H_2O$ (enzymes work in solution)
- ions (movement of $H_2O$, sometimes also of nutrients)
- proteins
  (enzymes, mucin)
- signaling molecules

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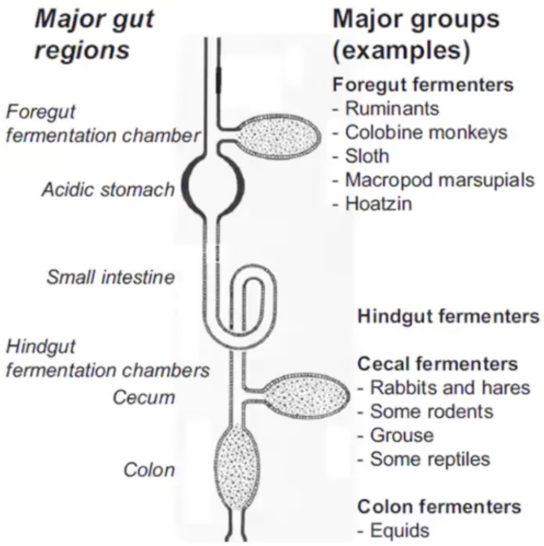
# Help from microorganisms

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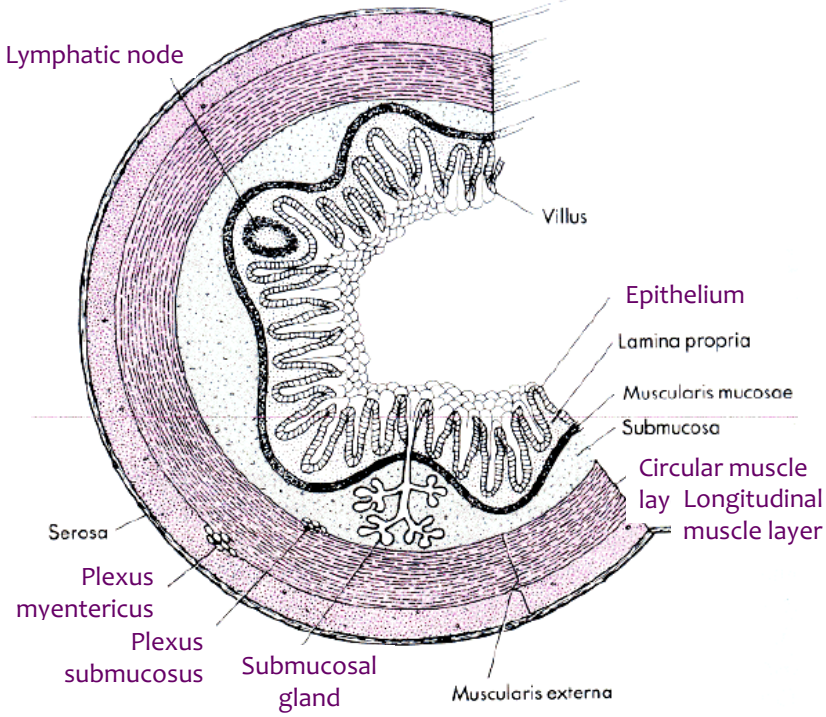


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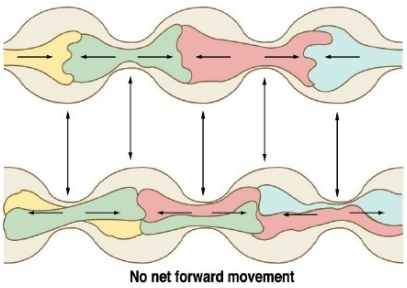
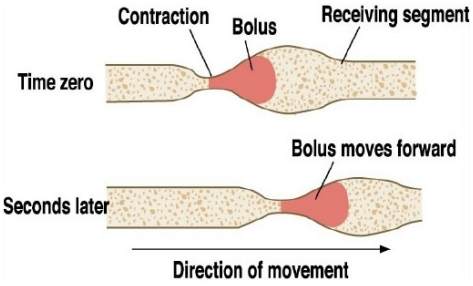
# Types of GIT movements




1. Mixing

2. Peristalsis




3. Reservoir

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# Regulation of motility

- nerves
  - **enteric nervous system (ENS)**
  - parasympaticus, sympaticus
  - partly also somatic motoneurons
- hormones
  - made in GIT
    - gastrin, secretin, cholecystokinin, motilin,...
  - partly also other
    - e.g. glucocorticoids & catecholamines in stress

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## Regulation of motility

- mediators of the GI immune system
  - has at least as many cells as the immune system of the rest of the body
- mast cells
- histamine, PGs, LTs, cytokines,...

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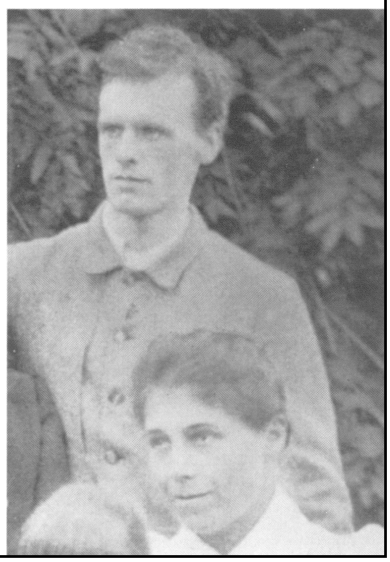
## ENTERIC NERVOUS SYSTEM

- Anatomy 19. century ~ relay ganglia
- Bayliss, Starling 1899:
  peristaltic reflex,
  persists after denervation
  other organs are stopped by denervation
- Today:
  - ENS: autonomous, complex system
  - "neurogastroenterology"



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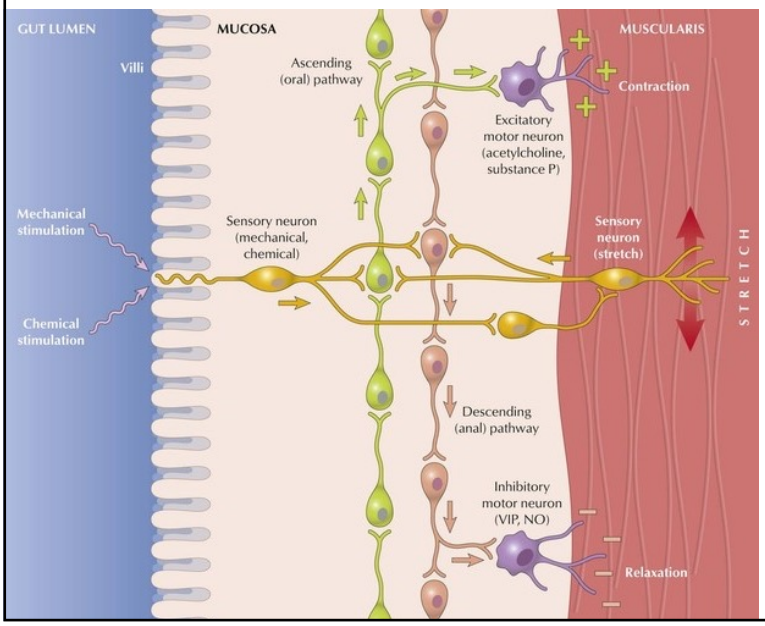
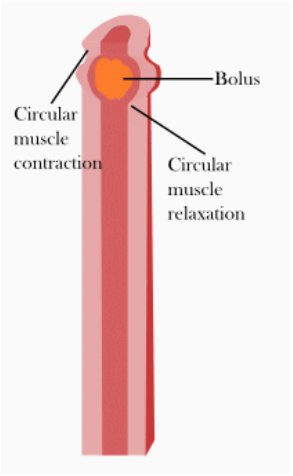
# Peristaltic reflex

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# Enteric nervous system (ENS)

- Governs many GIT functions without external inervation (modulation only)
  - motility
  - secretion
  - collaboration with immune system on defense
  - growth regulation

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## ENS

- ~$10^8$ neurons
  - ☞ $^1/_{1000}$ brain
  - ☞ > spinal cord
- no distinct neuromuscular junctions (nerve endings freely distributed among SMC)
- innervates also vessels (mainly vasodilation) & surrounding organs (bladder, pancreas)
- perhaps phylogenetically older than CNS (food needed before locomotion)

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## ENS & CNS: similarities

- Glial instead of Schwann cells (similar to astrocytes in CNS)
- All neurotransmitters so far known in CNS:
  - excitatory motoneurons: mainly ACh (muscarinic receptors on SMC)
  - inhibitory motoneurons: VIP & NO
  - interneurons: mainly ACh (nicotinic receptors on target neurons) & GABA
  - serotonin (5-HT; 95 % of all)

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# ENS & CNS: similarities

Similar sensitivity to toxins, drugs, diseases

- Antidepressants: ↓ 5-HT re-uptake in brain & ENS - nausea, diarrhea,
  then constipation (desensitization)
  - can be used to "calm down" GIT
    (ENS more sensitive than CNS)
- Lewy's bodies (Parkinson's disease), amyloid plaques & neurofibrilar clusters (Alzheimer's disease) also in the gut (diagnosis by rectal biopsy?)
- Therefore: GI & psychic problems often co-exist

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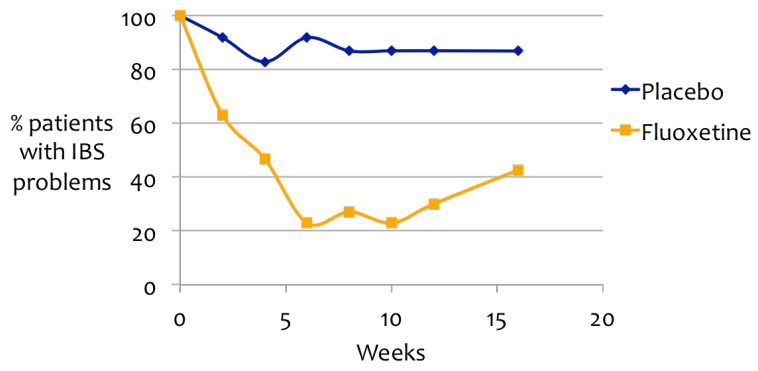
# Antidepressant fluoxetine (Prozac)

Selective serotonin reuptake inhibitor (SSRI)




VAHEDI et al: *Aliment. Pharmacol. Therap.* 2005

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## ENS & CNS: similarities

Can learn

- Hirschsprung's disease - genetically determined absence of nerves in the most distal GIT part - inability to defecate
- within 18 months after resection of the defect, the more proximal part "learns" to defecate (it couldn't do it at the beginning)

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## ENS & CNS: communication

- ~10x more AP ENS → CNS than CNS → ENS
- e.g. gastric ulcers:
  - history: psychosomatic ("soul" → GI)
  - today: vice versa - *Helicobacter pylori* is primary, psychic discomfort follows ENS irritation (GI → "soul")
- afferentation from ENS to CNS can act anti-depressively, support learning (c.f. mood when hungry vs. after a good meal)

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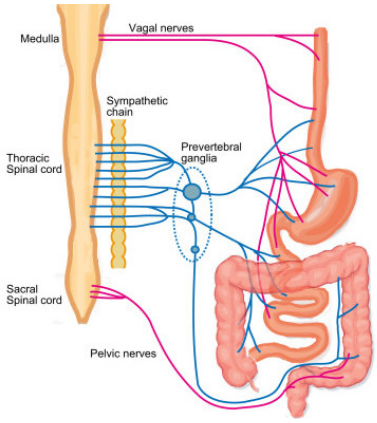
# Vegetative innervation

- mainly co-ordination of remote parts
  - e.g. gastrocolic reflex:
    stomach filling → ↑ colon activity
- parasympathicus
- sympathicus

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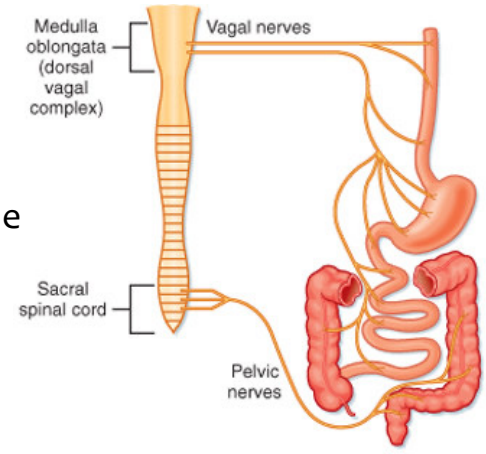
# Vegetative innervation: Parasympathicus

- down to the transverse colon: vagus branches;
  the rest: pelvic nerves
- preganglionic, mostly cholinergic fibers
- innervates ENS neurons, not the intestinal smooth muscle
- mostly ↑ motility & secretion

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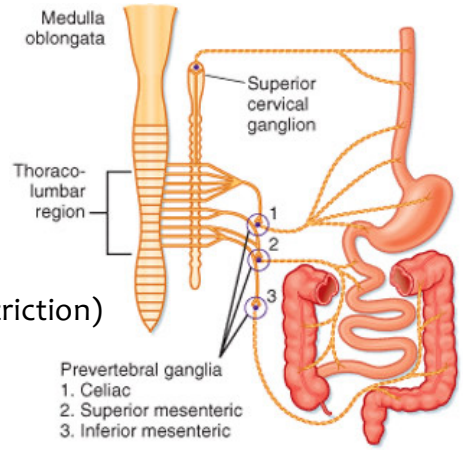
# Vegetative innervation: Sympathicus

- postganglionic adrenergic fibers from prevertebral & paravertebral ganglia
- does not innervate intestinal smooth muscle, rather
  - ENS neurons; they mediate the influence on muscles
  - glandulae
  - vascular smooth muscle (vasoconstriction)
- usually ↓ motility; ↑ tone of some sphincters

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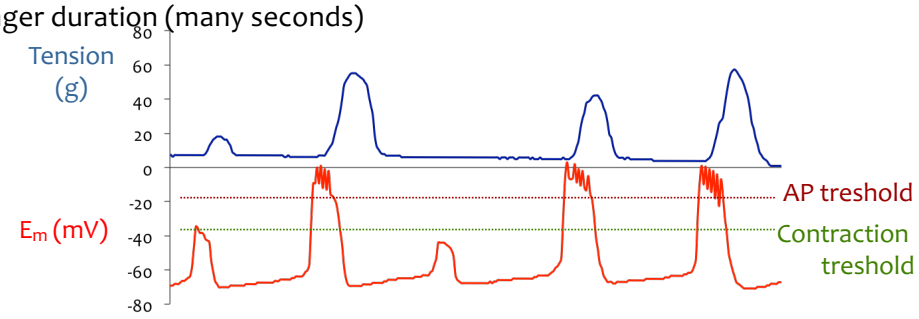
# Slow $E_m$ waves in SMC (basal electric rhytm, BER)

- ~3/min in stomach, 12/min in duodenum
- easily spreads through el. connections → GIT segments synchro
- BER differs from spontaneous activity in heart etc.:
  - lower frequency (max ~40/min, typically 3-12/min)
  - lower amplitude (do not overshoot over 0 mV)
  - longer duration (many seconds)

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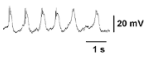


# Action potentials in GIT smooth muscle

- mainly opening of L type $Ca^{2+}$ channels, also slow $Na^{+}$ channels
- in some places this can be prevented by activation of voltage-gated $K^{+}$ channels
- quite long (10-20 ms), little or no overshoot
- time summation, tetany

most GIT smooth muscle cells have non-zero tension even at rest

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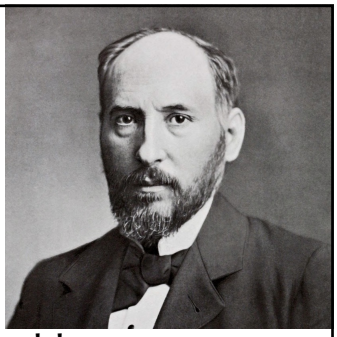
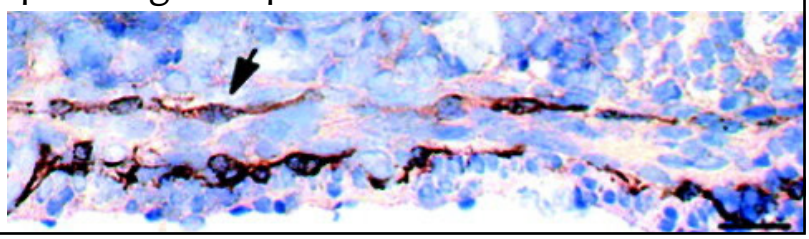
# BER is generated by interstitial cells (of Cajal)



- Between the 2 layers of musculature
- Properties of both smooth muscle and fibroblasts
- Gap junctions with muscles of both layers and other cells of Cajal - spreading of depolarization



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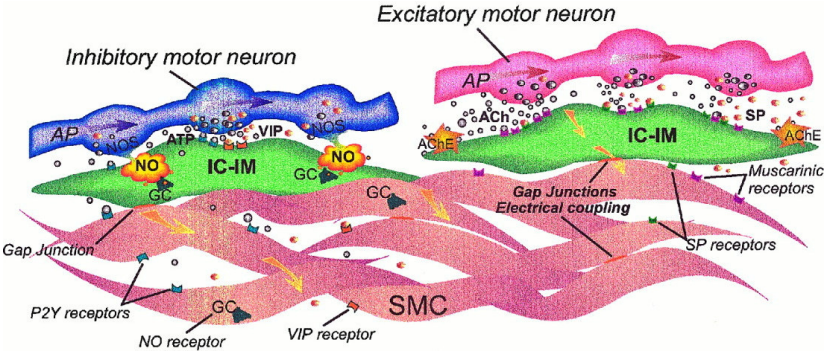
# Interstitial cells (of Cajal)

- Tight synapses with neurons (mediate ENS influence on muscles)
- Separated activity of different GIT parts: discontinuity of the interstitial cells

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# Integrated response to meal

- cephalic & oral phases
- esophageal phase
- gastric phase
- small intestinal phase
- colonic phase

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## Cephalic phase

- stimuli:
  - cognitive
    - anticipation, thinking, talking,...
  - olfactory
  - visual
  - auditory

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## Oral phase

- stimuli:
  - mechanical in mouth
  - taste

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## Cephalic & oral phase

- parasympathetic activation:
  - ↑ saliva secretion
  - ↑ gastric acid secretion
  - ↑ pancreatic enzymes secretion
  - gallbladder contraction
  - sphincter of Oddi relaxation

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## Mouth

- mastication
- saliva
  - lubrication (mucus)
  - solubilization for taste
  - amylase (starch)
  - antibacterial
- lingual lipase
- minimal absorption (alcohol, some drugs)

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# Chewing (mastication)

- Conscious & unconscious (lighter phases of sleep)
- Function:
  - small pieces (5-15 ml) from large
  - lubrication
  - amylase (starts breakdown of starch)
- Can generate enormous force (50-80 kg on molars)
- In humans nutrition not endangered even with substantial reduction of chewing area

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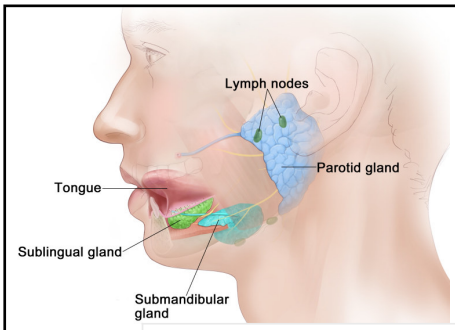


# Salivary glands

| | serous | mixed | mucous |
|---|---|---|---|
| parotid | ■ | | |
| sublingual | | | ■ |
| submandibular | | ■ | |
| small in mouth | | ■ | |

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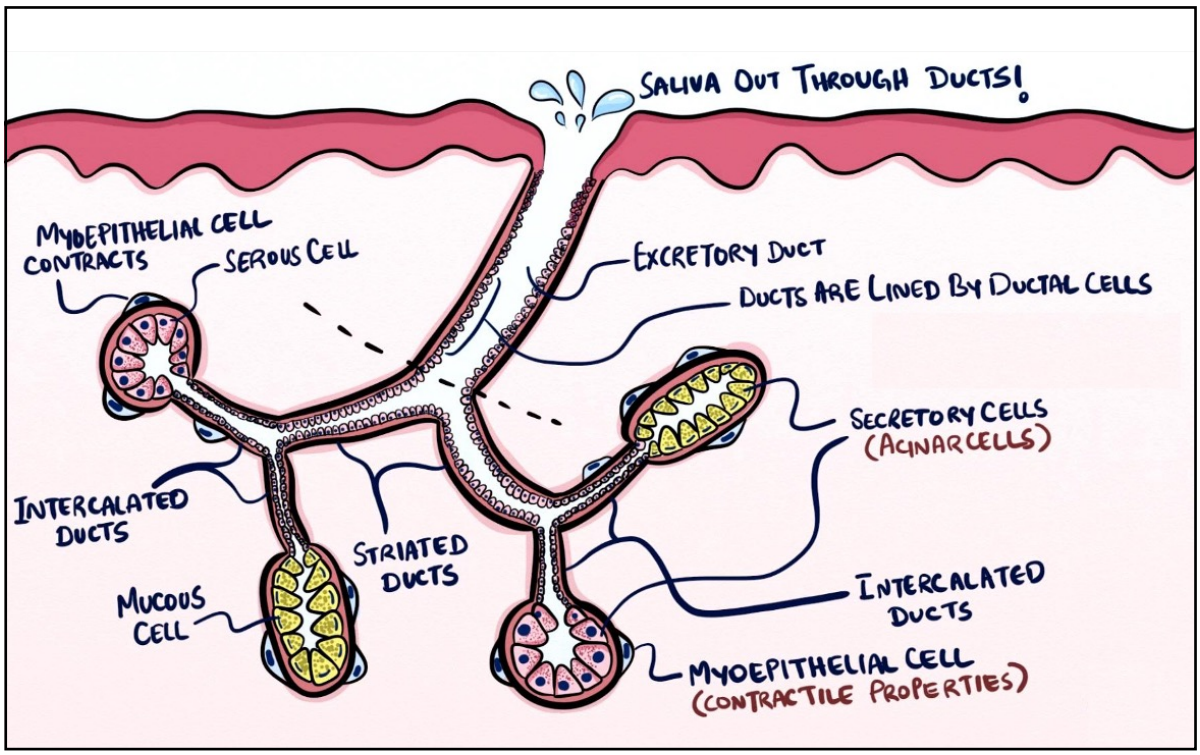


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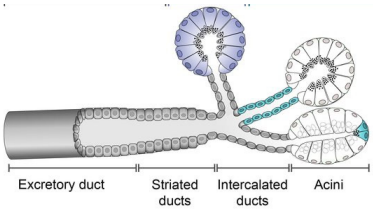
## Saliva




- large flow rate relative to size
- hypotonic, alkaline (pH≤8), high $K^+$
  - primary secretion isotonic (driven by apical $Cl^-$ channels ⟶ osmotic & el. gradient ⟶ $Na^+$ & $H_2O$ follow paracellularly)
  - duct cells reabsorb $Na^+$ & $Cl^-$ & secrete $K^+$ & $HCO_3^-$ (CFTR)
- amylase, lipase, mucin (glycoproteins), lysozyme (antibacterial)
- growth factors (GIT lining maintenance)

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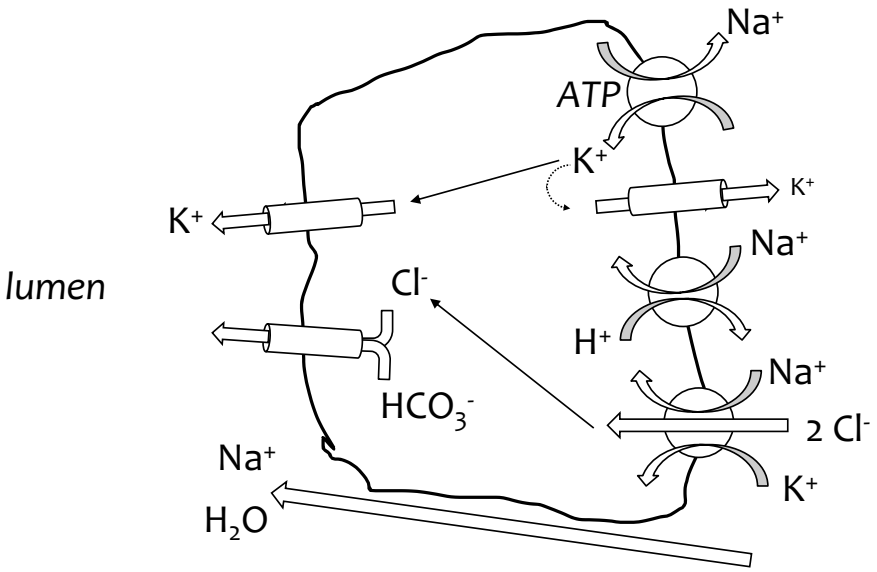
# Saliva secretion: acinar cell

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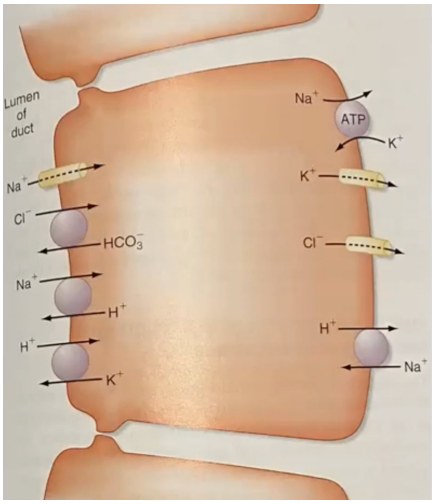
# Saliva secretion: ductal cell

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## Regulation of salivation

- parasympathicus:
  - main after a meal
  - ↑ secretion of amylase & mucin
  - ↑ transport in ducts

  → more saliva
- sympathicus
  - ↑ protein secretion

  → *sticky mouth*

*the only secretion in the GIT exclusively under nervous control*

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## Response to meal - Esophageal phase: Swallowing

- afferent branch:
  - tactile receptors mainly in entry to pharynx
- swallowing center in medulla & lower pont
  - easily impaired in CNS injury (stroke,...)
- efferent branch:
  - head nerves to pharynx and upper esophagus
  - vagus to rest of esophagus
  - to respiratory center
- but vagus X evokes alternative ways of peristalsis (ENS, myogenic mechanisms)

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## Swallowing: oral phase

- conscious
- or (more often) reflex pharynx stimulation by saliva or food (~ 1000x/day, incl. sleep)
- tongue moves food to upper pharynx by pressing against hard palate

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## Swallowing: pharyngeal phase

- <1 sec
- reflex, activation by mech. stimulation
- soft palate ↑, closes entry to nose
- vocal cords close, larynx ↑ (epiglottis closure)
- ↓ breathing
- short relaxation of upper esophageal sphincter (reflex opening after food passage)
- contraction of upper esophagus (skeletal muscle)
- peristaltic wave initiation

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# Swallowing: esophageal phase

- upper ~1/3 of esophagus = skeletal muscle (longitudinal & circular layer)
- then "gradient" skeletal → smooth
- last ~1/3 = smooth muscle
- skeletal & smooth: innervation by vagus
  - in skeletal muscle part, vagus fibres end by neuromuscular plates (myenteric plexus only sensoric function)
  - in smooth muscle part, vagus fibres end at ENS neurons
- primary peristaltic wave 3-4 cm/s (6-8 s)

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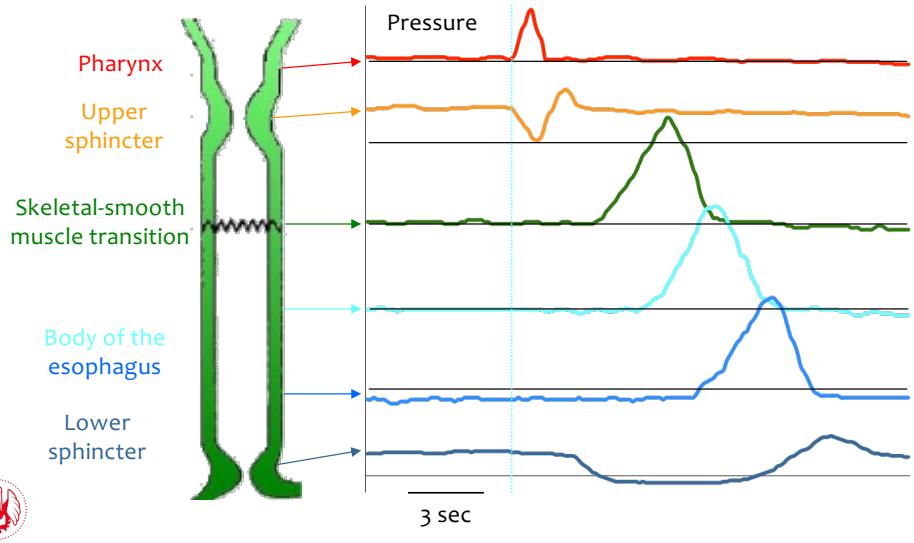
# Swallowing: esophageal phase

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## Swallowing vs. gravity

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## Secondary peristaltic wave

- if primary not successful
- not full swallowing reflex
- only esophageal afferents
- peristaltic activity restricted to esophagus
- no pharyngeal contraction, no UES relaxation
- local reflex similar to peristaltic reflex in the intestine
  - distention of esophagus → activation of local sensory nerves → contraction above the distention and relaxation below it

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## Esophageal reflux

- lower sphincter sometimes opens even without swallowing (~ physiological reflux)
- if too much → esophagitis ("burning")
- pressure in esophagus ~ thoracic < abdominal
  - used for measuring intrapleural pressure
  - promotes reflux
- esophagus crosses the diaphragm at the level of the lower sphincter → diaphragm contraction helps to close the sphincter - does not work in diaphragmatic hernia

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## Disorders of swallowing

- Dysphagia - ineffective swallowing
  - e.g. in neuromuscular diseases
- Achalasia - insufficient relaxation (mainly of the lower esophageal sphincter)

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## Response to meal: Gastric phase

- reservoir
- grinding
- mixing with stomach secretion
- **continuous filling of the gut**

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## Stomach - structure

- circular muscles thickens towards the antrum
- longitudinal essentially missing in the upper 1/3
- oblique only the lower 1/2

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# Stomach - reservoir

- mainly fundus & body
  - weak or no contractions - minimal mixing for a long time
  - thin muscular layer
- empty volume 50 ml, pressure ~ 5 mmHg
- volume can ↑ to ~ 4 l
- pressure ↑ only when volume ↑ by >1-1.5 l
  - receptive relaxation
    (vago-vagal reflex, i.e. afferentation from stretch receptors through vagus to CNS [~same area as swallowing], efferentation to SMC also through vagus)

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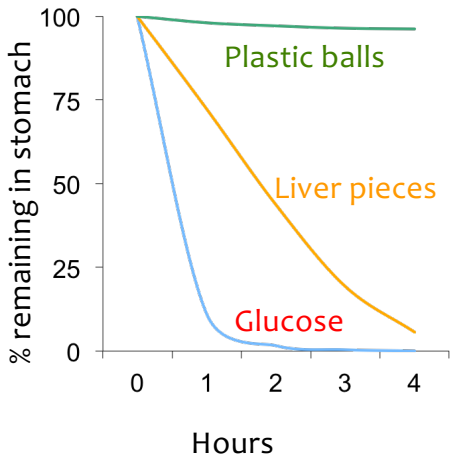
# Stomach - reservoir

- chymus settles to layers according to density, large pieces leave the last
- lipids form film on surface ⟶ digested last
- fluids ”by-pass"

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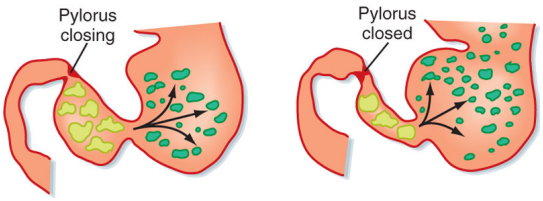
# Stomach – grinding, mixing with digestive fluids

- antrum peristalsis
  - starts near central body (cluster of interstitial cells)
  - stronger & faster towards antrum
- retropulsis
  - strong contractions of antrum against the direction of peristaltic wave
  - presses chyme back to stomach through narrow hole created by the peristaltic wave

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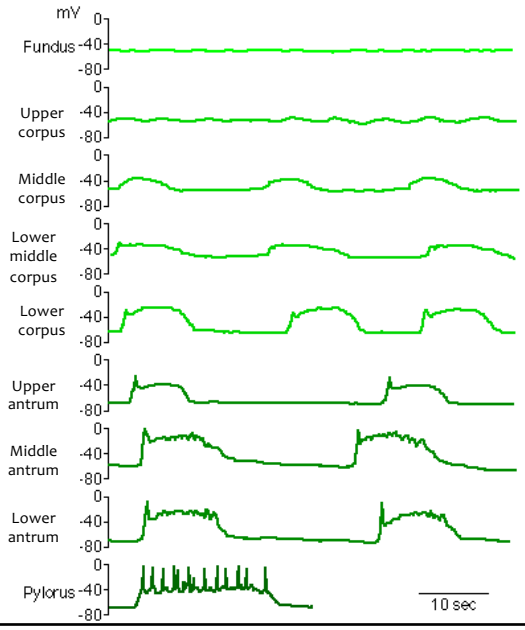
# Electrical activity of the stomach

- slow waves (BER) spread from pacemaker zone ~ middle corpus
- BER ↑ towards antrum
- only in antrum BER amplitude > threshold for AP
- shape similar to AP in heart but 10x longer

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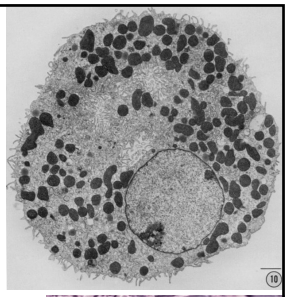
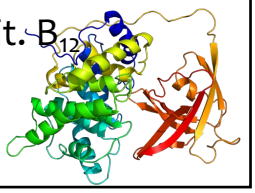
# Gastric secretion



- stomach = strange organ
  - full of strong acid (pH 5 to 1)
    - ↑↑ energy demand ($10^6$ gradient: pH ~7 vs. 1)
    - need to protect itself
  - just to activate pepsin**?** (+denaturing)
    - 20% of protein digestion, not essential
  - protection against microbes from food
    - (not all do mind)
  - intrinsic factor – glycoprotein necessary for vit. $B_{12}$ (cobalamin) absorption in ileum, needs ↓ pH



  - grinding, storage

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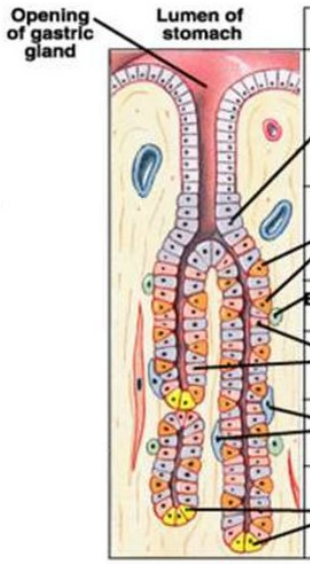
# Gastric juice




| Source | Substance Secreted | Function |
|---|---|---|
| Mucous neck cell | Mucus | Physical barrier between lumen and epithelium |
| | Bicarbonate | Buffers gastric acid to prevent damage to epithelium |
| Parietal cells | Gastric acid (HCl) | Activates pepsin; kills bacteria |
| | Intrinsic factor | Complexes with vitamin $B_{12}$ to permit absorption |
| Enterochromaffin-like cell | Histamine | Stimulates gastric acid secretion |
| Chief cells | Pepsin(ogen) | Digests proteins |
| | Gastric lipase | Digests fats |
| D cells | Somatostatin | Inhibits gastric acid secretion |
| G cells | Gastrin | Stimulates gastric acid secretion |

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## Pepsins

- activation by small N-terminal fragment cleavage
  - only at pH<5, slow at pH 3-5, very fast at pH<3
  - autoactivation
- activity also pH dependent
  - pH optimum = 1.8-3.5 (reversible inactivation at pH>3.5)
  - irreversible inactivation at pH>7.2

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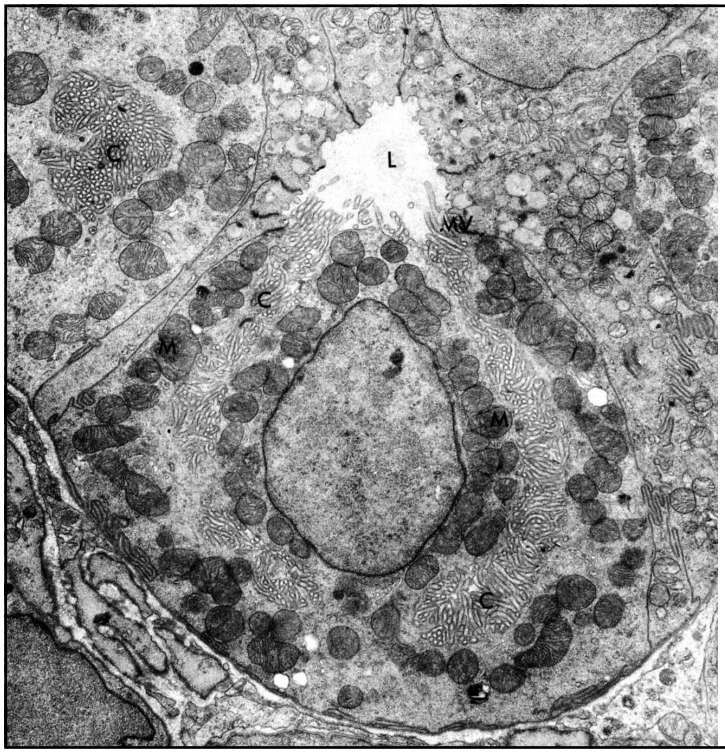


## HCl secretion: parietal cells

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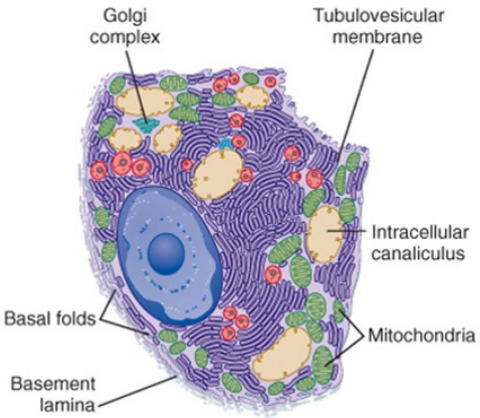
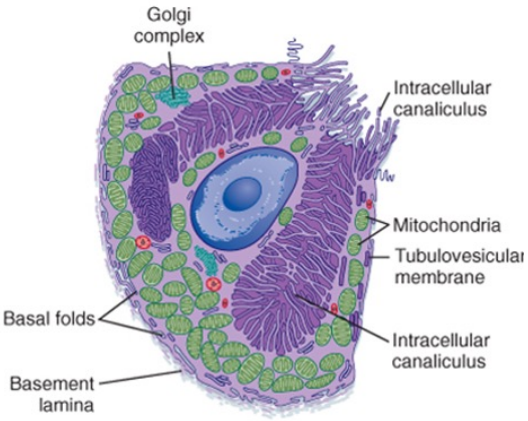
# HCl secretion: parietal cells

rest




activation

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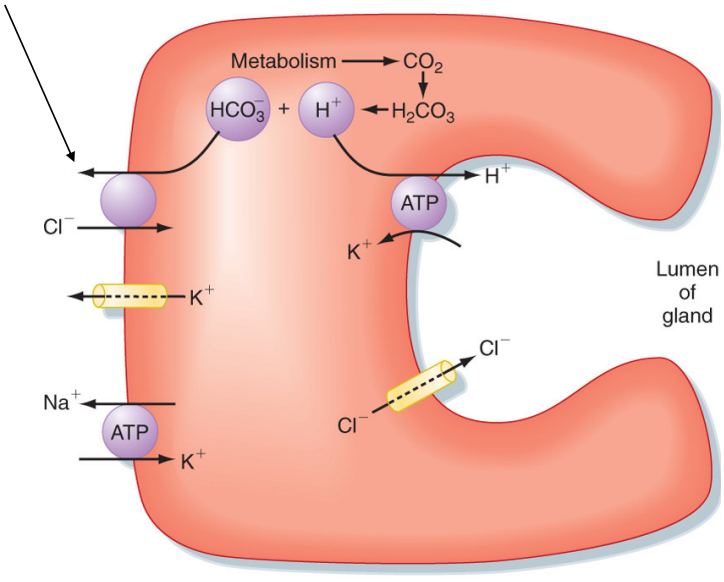
# HCl secretion

→ high $HCO_3^-$ in blood leaving stomach

- apical H/K antiporter
- basolateral Na/K pump

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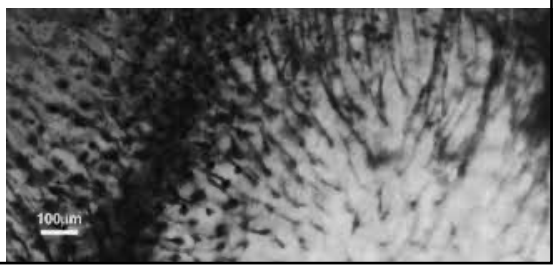
## Protection of mucosa from acid

- continuously renewed mucus layer (~0.2 mm)
  - large glycoproteins – sugars shield the proteineous part
- $HCO_3^-$ secretion underneath mucus (& into it)
- viscous fingering
- protection of glands???

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## Regulation of gastric secretion

proteins in stomach

cephalic & oral phase

distension

parasympathetic activation (via ENS)

strongest stimulus for HCl secretion,

+ pepsinogen, $HCO_3^-$, mucus

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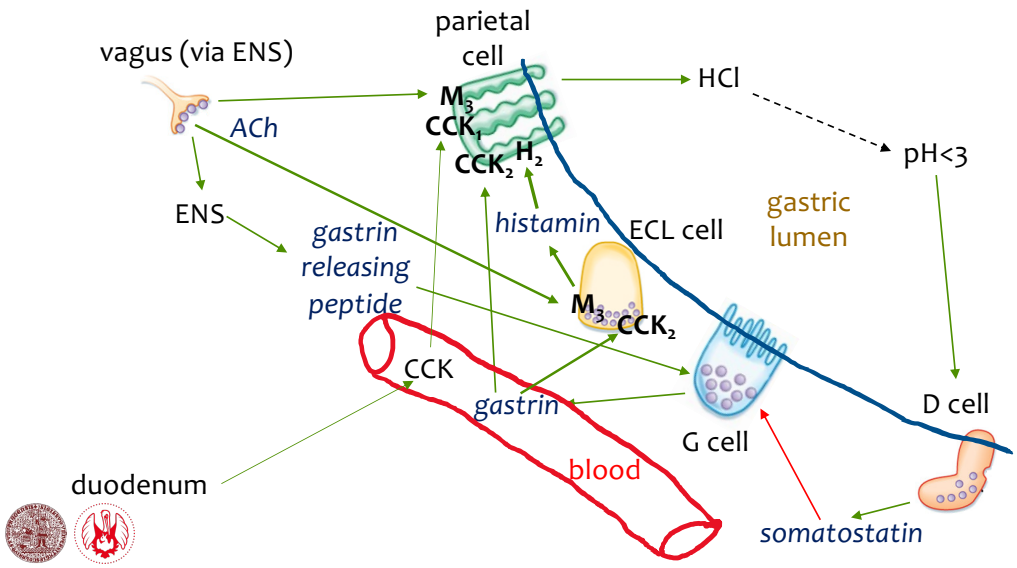
# Regulation of HCl secretion

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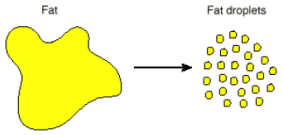
# Other digestion in stomach

- saccharides
  - remnants of amylase activity, negligible
- lipids
  - emulsification (mixing movements)
  - gastric lipase: ~10% of all lipid hydrolysis, not essential

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# Stomach - filling the gut

- continuous processing by duodenum (despite irregular pattern of food intake)
- prevents injury to duodenum by acid
- strong contractions of antrum (strong muscles, middle oblique layer) against almost closed pylorus (prevents regurgitation - bile could damage stomach wall)
- stomach empties in ~ 3 hours

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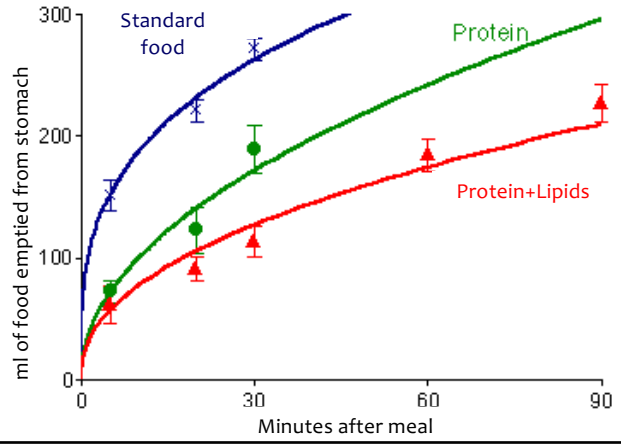
# Stomach emptying depends on food composition

Intestine digests different nutritients at varying rates.
This "dictates" the rate at which it is filled

That 's why fats help prevent drunkenness: fat stays longer in the stomach, keeps alcohol there, alcohol resorption from stomach is slower than from gut

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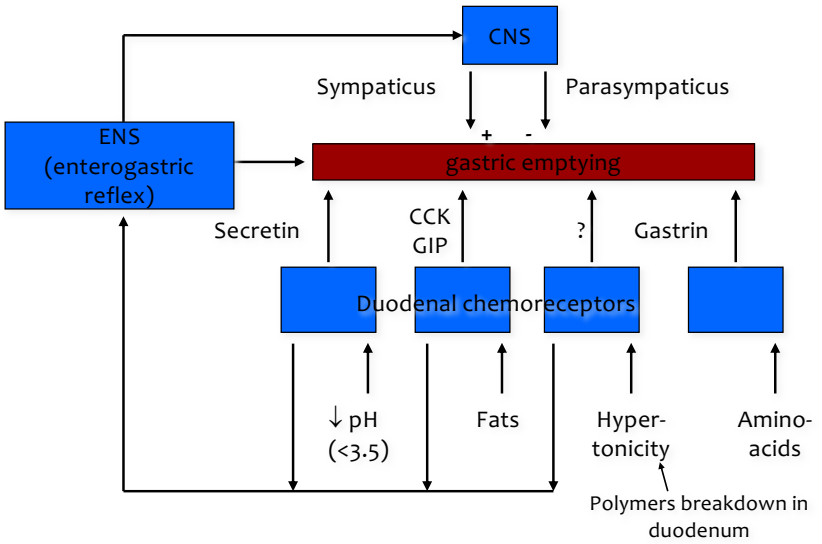
# Regulation of stomach emptying

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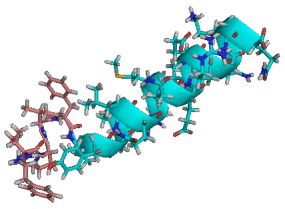
# Migrating myoelectric complex (MMC)

- empty stomach rests ~75-90 min, then 5-10 min intense contractions of antrum with relaxed pylorus
- removes non-digested remnants (even large pieces)
- stimulated by motilin
  - polypetide (22 AA) hormone from small intestine
  - produced in hunger, perhaps stimulated by high pH in duodenum?



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## Vomiting (emesis)

- usually preceded with nausea, sometimes anorexia, autonomic reactions (salivation, sweating, cold skin,...)
- vomiting center in medulla (next to cardiovascular & respiratory centers)
- mechanical stimuli (distension), injury, pain
- stomach/duodenum, larynx entry, inner ear
- emetics (chemoreceptors in stomach/duodenum or bottom of 4th chamber)

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## Vomiting

- reverse peristalsis
  from the middle of small intestine to larynx
- forced inspiration against closed glottis -
  ↓ intrathoracic pressure, ↑ abdominal (diaphragm)
- strong contraction of abdominal muscles & diaphragm
- relaxation, then closure of pylorus, relaxation of LES and finally UES (glottis closure, ↓ breathing)
- protective reflex against toxicity x longer vomiting can cause metabolic alkalosis & dehydration

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