Motility of the gastrointestinal tract

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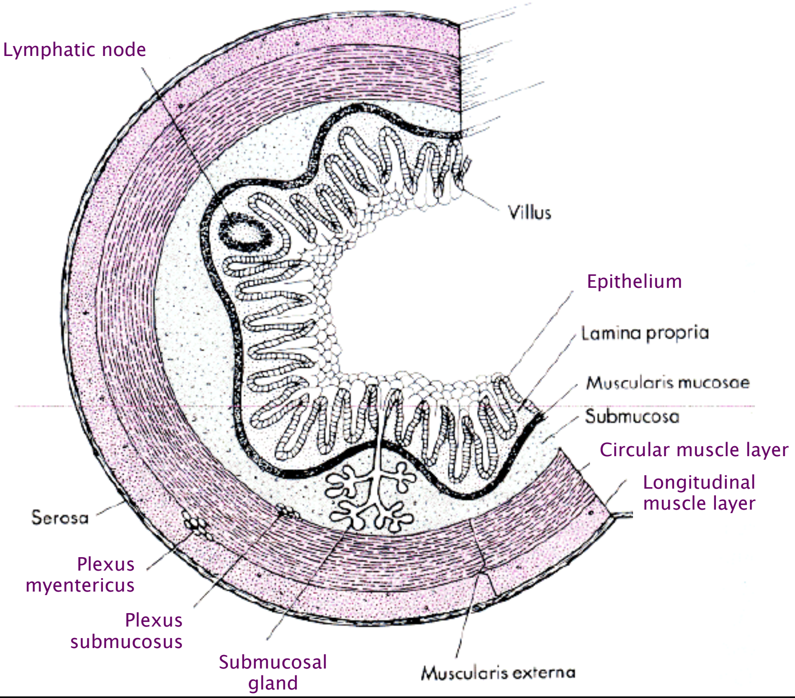

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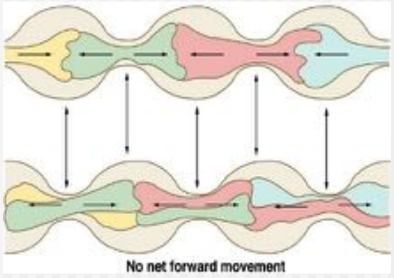
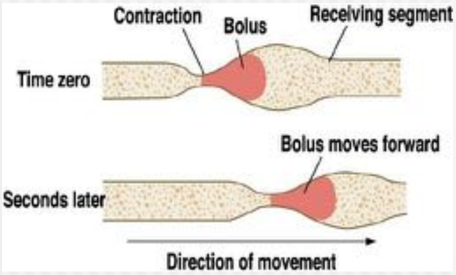
Types of movement



1. Mixing

2. Peristalsis



3. Reservoir

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Regulation of motility

- Nerves
  - **<u>Enteric nervous system (ENS)</u>**
  - 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
- Histamin, 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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ENTERIC NERVOUS SYSTEM

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

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Enteric nervous system (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, and 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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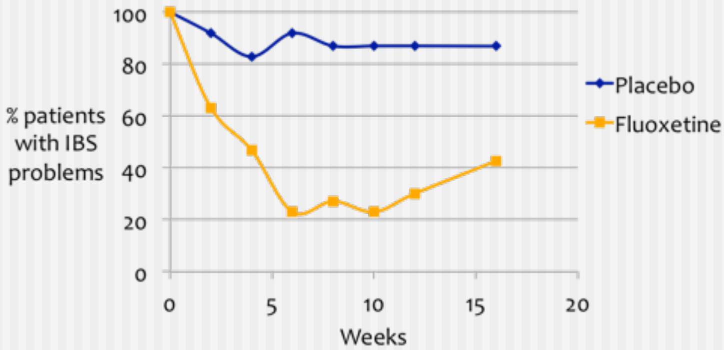
Antidepressant fluoxetine (Prozac)

Selective serotonin reuptake inhibitor (SSRI)



VAHEDI et al: The effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: a double-blind randomized-controlled study. *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 antidepressively, support learning (c.f. mood when hungry vs. after a good meal)

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Local reflexes of ENS

- sensoric neuron in ENS
  - mechano-
  - chemo-
  - thermo-
  - noci-
- interneuron(s) in ENS
- efferent neuron in ENS

e.g. peristaltic reflex

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Vegetative innervation

- Mainly co-ordination of remote parts
  - e.g. gastrocolic reflex:
    stomach filling $\rightarrow \uparrow$ 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 fibres
- Do not innervate directly the intestinal smooth muscle, but the ENS neurons
- Mostly stimulates motility & secretion

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Vegetative innervation: Sympathicus

- Postganglionic adrenergic fibers from prevertebral & paravertebral ganglia
- Do not innervate intestinal smooth muscle, rather
  - ENS neurons, they mediate the influence on muscles
  - vascular smooth muscle (vasoconstriction)
  - glandulae
- Usually blunts motility;
  increases the tone of some sphincters

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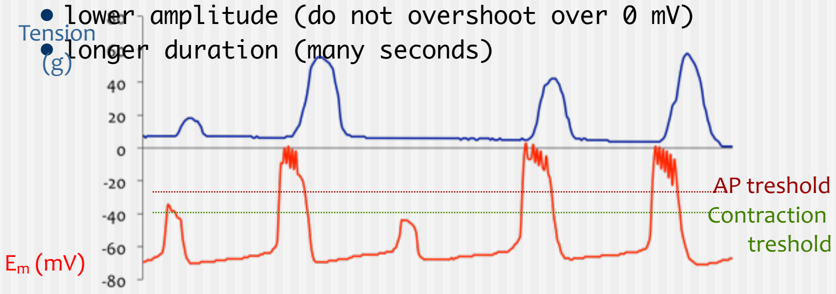
Slow E_m waves in SMC (basal electric rhytm, BER)

- ~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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BER is generated by interstitial cells (of Cajal)

- Properties of both smooth muscle and fibroblasts
- Between the 2 layers of musculature
- Gap junctions with muscles of both layers and other cells of Cajal - spreading of depolarization
- Tight synapses with neurons (mediate ENS influence on muscles)
- Separated activity of different GIT parts: discontinuity of the interstitial cells

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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)
- In humans nutrition not endangered even with substantial reduction of chewing area
- Can generate enormous force (50-80 kg [!] on molars)

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Swallowing: structure of the reflex

- 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
- <u>primary peristaltic wave</u> 3-4 cm/s (6-8 s)

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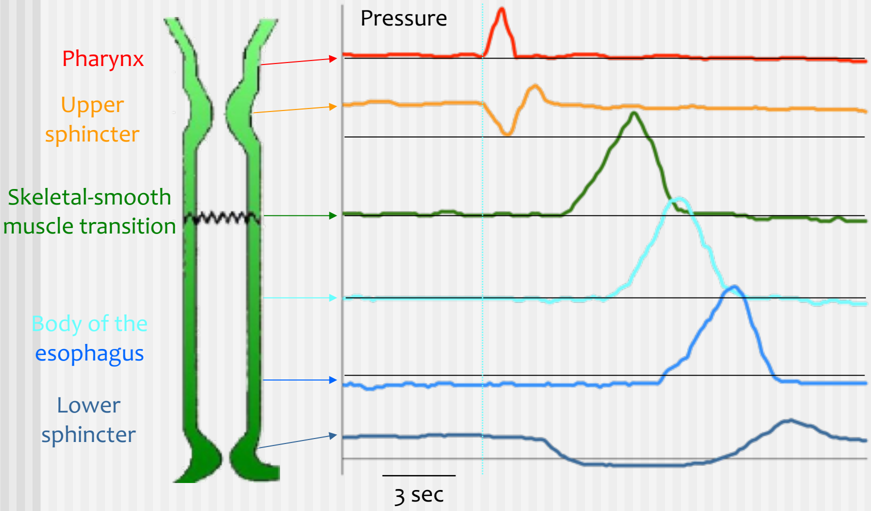
Swallowing: esophageal phase



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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 nervess → 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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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 - functions

- Reservoir
- Grinding
- Mixing with stomach secretion
- **Continuous filling of the gut plnění**

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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
  - <u>receptive relaxation</u>
    (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 and mixing with digestive fluids

- Antrum peristalsis
  - starts near central body (cluster of interstitial cells)
  - stronger & faster towards antrum
- <u>Retropulsis</u>
  - strong contractions of antrum against the direction of peristaltic wave
  - presses chymus back to stomach through narrow hole created by the peristaltic wave

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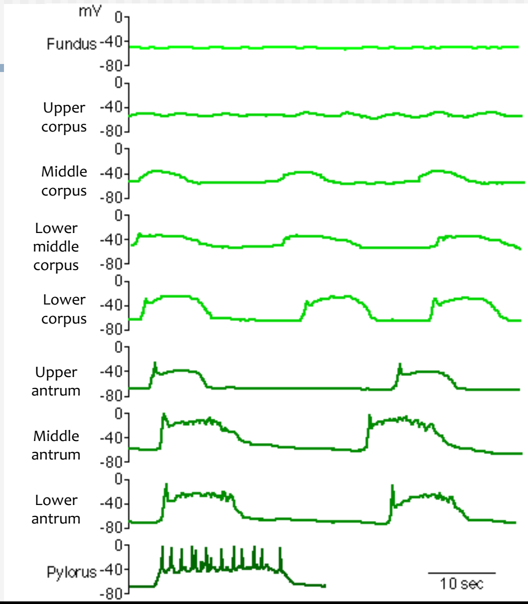
Electrical activity of the stomach

- 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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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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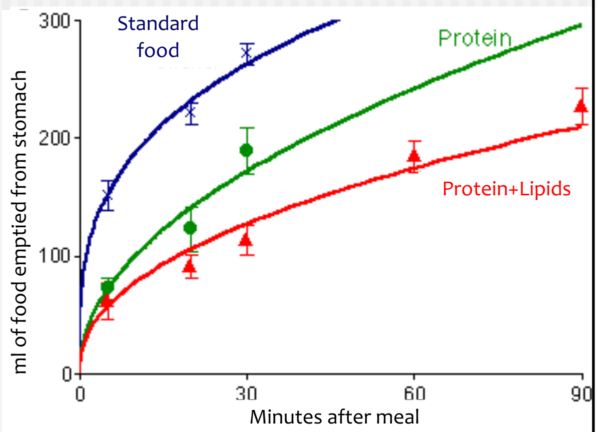
Stomach emptying depends on food composition

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

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



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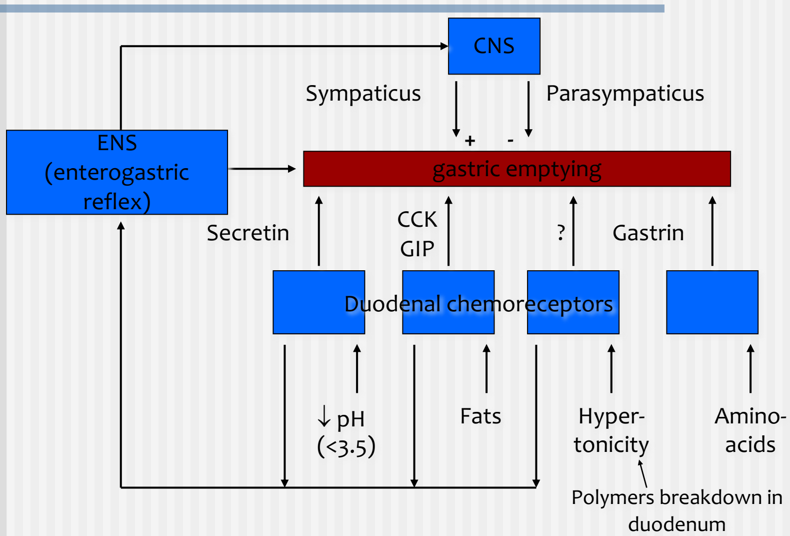
Regulation of stomach emptying



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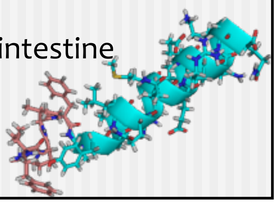
Migrating myoelectric complex (MMC)

- 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, inhibition of breathing)

- Protective reflex against toxicity x longer vomiting can cause metabolic alkalosis & dehydration

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Small intestine

- Duodenum first 5% of length, jejunum next 40, ileum the rest

- Most of digestion in duodenum & jejunum, ileum not necessary

- Peristalsis simultaneously only in short segments (~10 cm) (except MMC)

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Small intestine : segmentation

- Alternating localized contractions of circular muscles
- Mix chyme with intestinal fluid, contact with intestinal wall
- Frequency determined by BER (~11-13/min duodenum, 8-9 end of ileum)
- BER run along the whole length, AP only locally - in these places segmentation contractions
- BER independent of innervation, contractility ↑ by parasympathicus, ↓ by sympathicus (through ENS)

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Intestinal reflexes

- Local (e.g. peristaltic reflex)
  - ENS only
- Mediated by both ENS & external innervation:
  - Intestinointestinal reflex - excessive distension of one part of the gut relaxes the rest
  - Gastroileal reflex - ↑ stomach activity → ↑ chymus movement through ileocecal sphincter
  - Ileogastric reflex - ↓ stomach motility elicited by distension of ileum

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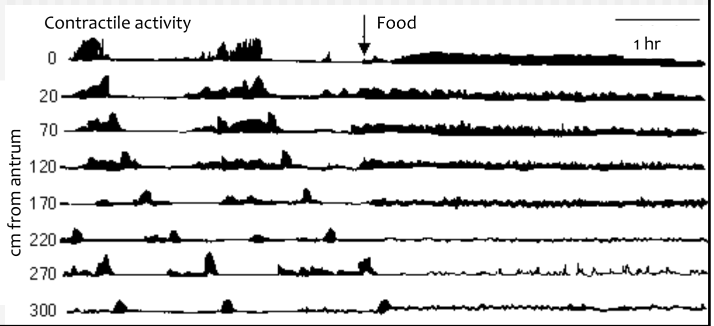
MMC in hunger

- Similar as in stomach; gradually from there → end of small intestine
- Segmentations cease
- Peristaltic waves include ~70 cm of gut
- Every 70-90 min, the whole smaller intestine traversed by a series of MMP in 1-2 hr

"Sweeps" non-digested remnants & prevents bacteria migration from colon



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Weak MMC

- bacteria remain in small intestine → they grow (plenty of food)
- they release H_2 (no other source in humans)
  - only when they can use non-digested sugars (normally not present in colon)
  - elevated H_2:
    - either undigested sugar in colon (e.g. lactose intolerance, accelerated passage)
    - or bacteria go upstream to ileum
  - some H_2 gets in blood, from there to breath, can be measured

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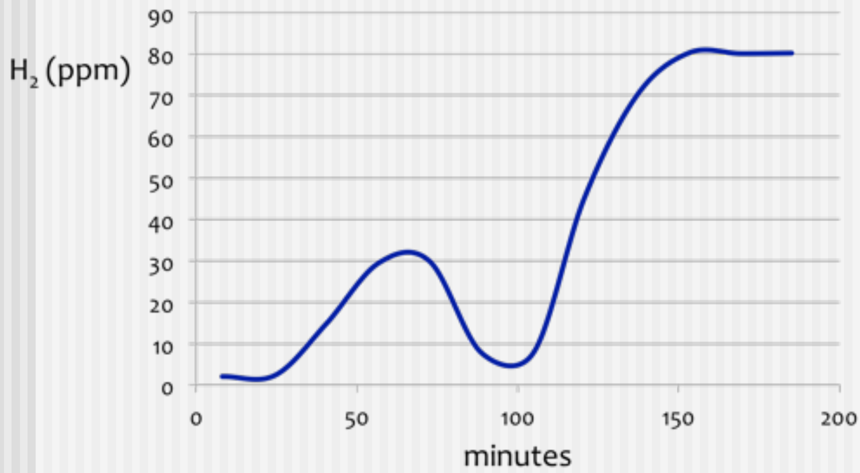
Breath H_2 test



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Contractions of muscularis mucosae

- Alter the shape of ridges & folds of mucosa, contract the villi (”milking" of the products of digestion to lymphatic passages), ”waving" of the villi
- Improve contact of chyme with mucosa, mixing
- Support lymph flow

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Emptying of ileum

- Ileocecal sphincter (valve) normally closed (e.g. because of bacteria)
- Opened by distension of end of ileum (local reflex)
- Closed by distension of proximal colon (local reflex)

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Large intestine

- Main functions:
  - water absorption (400-1000 ml/day) & ions
    (~20 l /d of water has been invested into digestion)
  - storage of food remnants that are not needed
    - typically 15-30 hr
    - up to 30% can stay in colon ~1 week)
- Therefore mainly mixing, only ~5% peristalsis
- Mixing more difficult because of increasing density
- Haustrations, swing movements, mass movement

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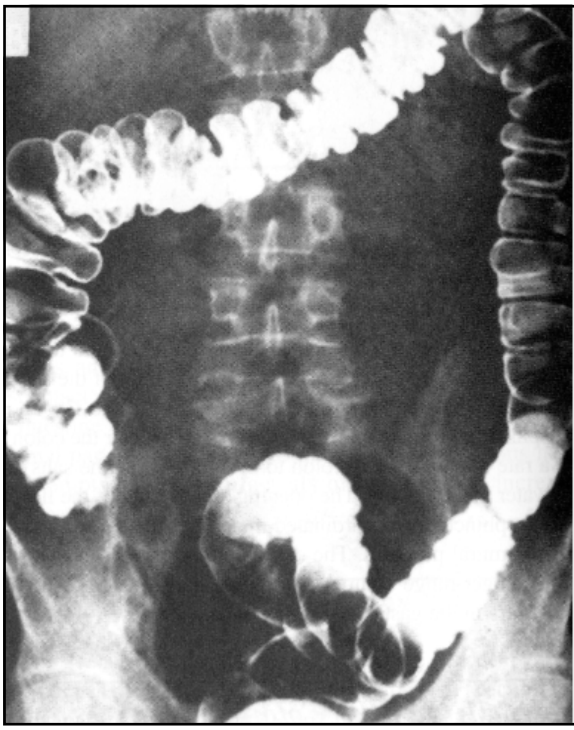

Haustrations

- Similar to segmentation, but more marked & in anatomicaly pre-defined locations of circular muscle layer
  - Governed by BER from interstitial cells (~6/min)
- Usually no AP
  - Stronger contractions (e.g. ACh) by prolonging BER

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Swing movements of large intestine

- Longitudinal muscles, mixing
- Controlled by myenteric potential oscillations (lower amplitude, higher frequency than slow waves)
- Have APs on their top, APs elicit contractions
- Contractions are stronger when APs more frequent (e.g. ACh)

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Colon motility

- Mass movement: 1-3x/day (usually after meal) wave of strong contraction moves content to larger distances (most of colon length, colon remains contracted for a while
- Overall movement is slow (max 5-10 cm/hr)
- Controlled by ENS, sympathicus blunts movements, parasympathicus stimulates haustrations of proximal parts & expulsive movements of distal parts

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Reflexes of large intestine

- Colono-colic - distension of one part relaxes the rest (partly sympathicus)
- Gastro-colic - filling of stomach increases frequency of mass movements (sympathicus, parasympathicus, CCK, gastrin)
- Similarly duodeno-colic

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Opioids

- endogenous opioids (met-enkephalin, leu-enkephalin, β-endorphin, dynorphin) & their receptors richly expressed in GI tract (ENS) → possible physiol. function, but uncertain
- morphine mostly in colon:
  - stronger contractions, but↓ forward movement → ↑ H_2O reabsorbtion
  - mainly local (μ receptors)
  - partly also central (μ a κ effect)
- also↓ gastric emptying

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How to handle opioid inhibition of motility?

- Selective inhibition of peripheral μ-receptors (analgesia is mediated by central receptors)
- Classic: naloxone – inhibits periph. & central
- Recent: methylnaltrexone, alvimopan – mainly periph. action, restore motility without reducing analgesia

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Rectum & anal channel

- Rectum usually (almost) empty (retrograde contractions return content to sigmoideum, until there is too much of it)
- Just before defecation mass movement in sigmoideum fills rectum → ↑ pressure → reflex relaxation of inner sphincter (smooth muscle) & contraction of outer sph. (skeletal muscle controlled intentionally via pudendal nerves)
- Stretch receptors in rectal wall can adapt - urge to defecate can temporarily subside id suppressed

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Defecation

- Reflex controlled from sacral spinal cord, modulated from higher levels (conscience, will)
- Efferent branch - ACh parasympathetic fibres in pelvic nerves
- Highly propulsive contraction of descending colon & sigmoideum
- Relaxation of both sphincters (outer voluntary)
- Inspiration pushes the diaphragm downwards
- Contraction of expiratory muscles with full lungs & contraction of abdominal muscles increase abdominal pressure (up to 200 mmHg)

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