Features of the GIS

- The physiological site of energy intake (~ 30 kcal/bwkg/day) vs. „parenteral” nutrition
  Basic functions: 1. motility (striated and smooth muscles): mechanical breakdown, storage, mixing, propulsion, excretion
  2. secretion 7-8 L/day! (mucosal glands, salivary glands, liver, pancreas)
  3. digestion (enzymatic hydrolysis)
  4. absorption 8-9 L/day! (macronutrients, vitamins, minerals, water)
- Maintenance of the gut flora: cca. 500 species of bacteria, 30-40 common
- High importance immune organ GALT: gut-associated lymphoid tissue, 70-80% of the immune cell are found here: immune response and tolerance
- Special forms of control: neural: CNS (somatic motor and autonomic) and the enteral nervous system (ENS), humoral control: paracrine mediators and special endocrine system (gastrointestinal hormones)
The key site of nutrient and fluid absorption is the small intestine.

Classic textbook data are now "debated" perhaps overestimating the surface quantitatively.

According to:

Intro: According to textbooks, the human gut mucosa measures 260-300 m², that is, in the order of a tennis court.

Conclusion: The total area of the human adult gut mucosa is not in the order of tennis lawn, rather is that of half a badminton court.

So the total surface area is perhaps around 32 m², from which 30 is the small intestine, and 2 the colon contribution.
Fluid secretion and absorption are restricted to different compartments, secretion in the Lieberkühn-crypts absorption in the villi

Epithelial renewal rate is high, the mature enterocyte „lives“ only ~1-2 days before shedding off.

Villus
- Enterocyte (digestion and absorption)
- Goblet cell (protective mucus)

Crypts:
- Mitotic stem cells
- Secretory glandular cells
- Paneth-cells (protective immune functions)
The microvilli provide not only large surface, but also special microenvironment: the last steps of digestion are performed by the enzymes secreted into the unstirred water layer created by the glycocalyx thus enabling fast absorption.

Epithelial transport: paracellular permeability is reduced from proximal to distal

<table>
<thead>
<tr>
<th></th>
<th>Jejunum</th>
<th>Ileum</th>
<th>Kolon</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJ pórusok átmérője</td>
<td>0,75 - 0,8 nm</td>
<td>0,3 - 0,35 nm</td>
<td>0,2 - 0,25 nm</td>
</tr>
<tr>
<td>permeability, resistance potential</td>
<td>high, small</td>
<td>medium, 0 - 3 mV</td>
<td>small, 1 - 6 mV</td>
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(renal analogy)
Overview of GIS function and control

Control:

Chewing: CNS somatomotor
Saliva secretion: CNS parasympathetic and sympathetic
Swallowing: CNS somatomotor and parasympathetic

Prox. stomach storage: CNS parasympathetic
Dist. Stomach peristalsis: ENS + hormonal
Stomach secretion: ENS + hormonal

Small intestine motility and secretions: ENS+ hormonal
Bile secretion: mainly hormonal
Pancreatic juice secretion: mainly hormonal

Colon motility: CNS
Distal colon and rectum: ENS, CNS parasympathetic and somatic motor (outer anal sphincter)

ENS: enteral nervous system
These functions operate also in the absence of CNS innervation, BUT the parasympathetic/sympathetic nerves can/will modulate them.

Oral cavity and pharynx:
Chewing, swallowing
Mucin, amylase and lipase
Drugs, glucose

Esophagus:
Swallowing

Stomach:
Storage (proximal), grinding-propulsion (distal)
Gastric juice: hydrochloric acid, pepsin, intrinsic factor, protective mucus
Drugs, alcohol

Small intestine:
Mixing, peristalsis
Intestinal juice, pancreatic juice, bile: bicarbonate, digestion of all macronutrients,
Absorption of all nutrients (B12 and bile acids ONLY in ileum)

Colon and rectum:
Storage, mixing, propulsion, defecation
Protective mucus
Electrolytes and water, drugs (rectum)
The enteral nervous system (ENS)

• NOT simply an efferent system, but a complex integrative nervous system capable to function in the absence of CNS connections (4-600 MILLION neuron!)
• Virtually all so-far (and yet to be) studied signaling molecule may be found in the ENS either as a transmitter or as a modulator.
• Major ENS neuron types: 1. intrinsic sensory neurons sensitive to mechanical and/or chemical stimuli from the mucosa, also stretch-sensitive receptors in the muscle layers 2. interneurons (excitatory or inhibitory), 3. excitatory or inhibitory effector neurons controlling the smooth muscle and glands. Complicated reflex pathways!
Example: mucosal stimulation causes serotonin release from a mucosal chromaffin cell. Serotonin will activate an ENS sensory neuron that uses CGRP as a transmitter. In the oral direction a cholinergic interneuron will be activated that will activate an excitatory effecter neuron using Substance P as transmitter (TK-tachykinin) causing smooth muscle contraction. In the caudal direction, an inhibitory interneuron using somatostatin is going to be excited that will inhibit another inhibitory interneuron using endogenous opiates as transmitters (Enk-enkephalin). The disinhibition will activate finally a VIP-ergic inhibitory effector neuron: the result will be smooth muscle dilation. (for physicians: the cause of constipation in patients with morphine abuse is also shown)

Medical Physiology: The significance of INHIBITORY smooth muscle innervation by the ENS: local absence of ENS in the colon causes Hirschsprung-disease (megacolon congenitum): constriction at the aganglionic site, proximally overdilated colon

Incidence: 1/5000
CNS modulation of ENS function (gut-brain-gut axis)

The GIS is innervated by primary sensor neurons of the somatic sensory system as well. Thus, the CNS receives sensory information about GIS events. Through autonomic innervation, the CNS will modulate GIS functions.

- The parasympathetic nerves innervate the GIS with PREganglionic fibers, some ENS neurons may be regarded as parasympathetic ganglion cells.
- The sympathetic nerves innervate the GIS with POSTganglionic fibers.
- Therefore, the parasympathetic effects can take place ONLY through the ENS, while sympathetic effect will take place MAINLY through the ENS (some direct effect).
The enteral neurons stem from the parasympathetic (mainly vagal) portions of the neural crest, the sacral origin neuronal population is important in the hindgut. In humans 4-600 MILLION neuron, similar to that of spinal cord! („visceral brain” aka „brain in the gut”) FG-MG-HG foregut-midgut-hindgut.

+ Adrenergic neurons of the sympathetic nerves can exert direct constrictor effects on vascular smooth muscle and sphincters ($\alpha_2$ receptor)
Gastrointestinal reflexes

1. Local reflex: all involved neurons are part of the ENS, the reflex is integrated within the gut wall (e.g. gut peristalsis)

2. Short reflex: the afferent is a primary sensory neuron originating from the GIS, the reflex is integrated however OUTSIDE the CNS, in the autonomic sympathetic ganglion, the efferent is a sympathetic postganglionic neurons. These reflexes are inhibitory (e.g. painful stretch inhibits gut motility)

3. Long reflexes: The reflex is integrated in the CNS through the brainstem or the spinal cord. Can be excitatory or inhibitory. Special subtype is the „vagovagal reflex“, where both the afferents and the (parasympathetic) efferents are found in the vagal nerve.

William Maddock Bayliss 1860-1924
Ernest Henry Starling 1866-1927

They have discovered the first hormone: secretin (1902). They even invented the name „hormone“. They also made significant observations to GIS function (law of the gut)
The enteroendocrine system

- The enteroendocrine cells producing peptide signalling molecules are found singly in the mucosal epithelium.
- Secretion is controlled by luminal chemical signals, ENS neurons, other enteroendocrine cells, even immune cells.
- The released molecules can control in a paracrine/endocrine manner directly GIS smooth muscle and glands, but may have also indirect effects through effects on ENS neurons or other enteroendocrine cells. GIS hormones can affect also the CNS (e.g. food intake), and can modulate insulin secretion in the pancreas (incretin effects).

Example: control of L-cell secretion of GLP-1 (glucagon-like peptide) 1. luminal chemical stimuli (glucose and fatty acids), 2. ENS effects, 3. paracrine stimulation from another enteroendocrine K-cell via GIP

The sensation of nutrients is mediated through the same receptor pathways as in the sensation of taste. Hormone secretion requires intracellular Ca²⁺ signal triggering exocytosis of storage vesicles.
Hormone families are based on amino acid sequence homology, the two most important: gastrins (gastrin, CCK) and secretins (secretin, GIP, GLP-1, VIP). Similar to the hormones their metabotropic receptors are also related, accordingly the use the same second messenger pathways: CCK and gastrin receptors use Gq/IP3/DAG, secretin family receptors the Gi/cAMP pathway.

Overview of the function of the most important GI hormones

- **Gastrin**: matching gastric motility and gastric juice secretion to the volume and composition of gastric contents
- **Cholecystokinin CCK**: matching gastric emptying, bile release and pancreatic juice enzyme secretion to the quantity and quality of small intestine nutrient (mainly fat and protein) contents
- **Secretin**: matching gastric emptying, duodenal, bileduct and pancreatic HCO$_3^-$ secretion to the pH of small intestine content (neutralization of gastric acid)
- **GIP (gastric inhibitory peptide aka glucose-dependent insulinotropic peptide)** and GLP-1: matching gastric emptying and insulin secretion to the carbohydrate contents in the small intestine
- **Motilin**: coordination of the cleansing movements of the empty stomach/small intestines in the interdigestive phase (MMC)
- **Ghrelin**: matching food intake to the fullness of the GIS and to the daily rhythm.
The parenteral administered glucose triggers bigger fluctuations in blood glucose level!!

**Special functional features of the gastrointestinal smooth muscle**
A  MACROSCOPIC VIEW OF THE WALL OF THE DUODENUM

Boron, Boulpaep, Medical Physiology, Elsevier Saunders, 2012

Sphincters in the GIS

Upper esophageal sphincter, UES
Pharynx-esophagus
Striated muscle! Its tone is maintained by neurogenic somatomotor tone!

Lower esophageal sphincter, LES
Esophagus-stomach
Pylorus-sphincter
Stomach-duodenum
Oddi-sphincter
Papilla duodeni major
d. choledochus / d. pancreaticus - small intestine
Bauhin-valve (ileocecal valve)
Small intestine-colon
Internal anal sphincter
External anal sphincter Striated muscle!
The GIS smooth muscle: single-unit smooth muscle in three layers

- T. muscularis mucosae: movement of mucosal folds and villi, local ENS control.
- T. muscularis longitudinal muscle: fewer gap junctions, mainly excitatory (cholinergic) innervation
- T. muscularis circular muscle: rhythmic variably moving contractile rings. Myogenic tone, both excitatory and inhibitory ENS innervation, also hormonal control.
- The circular muscle forms sphincters at selected points.
- The basis of rhythmic activity from the stomach to the sigmoid colon is a special electric feature called slow waves that create a basal electric rhythm (BER).
- The BERs are produced by anatomically nondescript pacemaker areas with various cycle periods: stomach: 15-20 s, small intestine 5-8 s, colon > minutes?

How is the BER created?

The slow membrane potential oscillations in the pacemaker cells are elicited by the cyclic opening-closing of K⁺ channels. If the depolarization waves reach the threshold of voltage-gated Ca²⁺ channels, then action potentials are triggered. The slow wave is propagated through the gap junction of the functional syncitium in the smooth muscle layer.
Where is the BER created? In the interstitial cells of Cajal (ICC) of the pacemaker areas.

Interstitial cells of Cajal mediate enteric neurotransmission

- Interstitial cell (ICC-I/M)
- Varicosity
- Enteric neuron
- Electrical coupling between ICC and smooth muscle cell

Experimental finding: next slide

A. lassú hullámok sejtkultúrában
B. Sanders et al. NIPS, Dec. 2000
C. lassú hullámok a jejunumban

- 20 μm

mV
- 44
- 44

mV
- 44
The significance of BER in the control of GI smooth muscle

- The BER is always present, BUT alone it cannot cause action potential (AP) and muscle contraction
- Depolarising effects (transmitters, hormones), the membrane potential first reach the threshold at the peaks of the slow waves, eliciting AP and contraction
- The contractions will be "automatically" rhythmic and travelling.

- The degree of depolarisation will control AP (spike) frequency.
- As Ca^{++} enters during the APs, the amplitude of the contraction will be changed by the length of the AP train (see next slide)

The significance of BER in the control of GI smooth muscle

- Only APs elicit contractions
- The frequency of contractions depend on the slow waves
- The force of contractions depend on the number of spikes
GIS MOTILITY TYPES

- All parts
- Peristaltic movements
- Small intestine and colon
- Segmentation
- Small intestine and colon
- Pendulum movements
- Sphincters
- Tonic contractions

Segmentation

Segmental contractions are responsible for mixing

There is no net forward movement
The law of the gut (BAYLISS-STARLING)

Stimulation in the GI tract elicits gut movements

1. Contraction on the oral side of the stimulation, and

2. ...relaxation on the caudal (aboral) side, and

3. ...the contractile ring preceded by dilatation moves in aboral direction.
MIGRATING MYOELECTRIC COMPLEX (MMC)

- Periodic electrical and motor (peristaltic) activity in the EMPTY stomach-small intestine tract (interdigestive phase or starvation)
- 6-10 min active periods followed by app. 1.5 hour long pause
- The activity originates in the stomach and propagated to the end of the ileum!
- Function: transport of undigestible remnants larger than 2 mm into the colon
- Control: motilin
Medical Physiology: inhibition of GI motility – paralytic ileus

• Obstructive ileus, inflammation, surgical trauma can all stimulate GI nociceptors.
• Activation of nociceptors can trigger short (sympathethi reflexes) but also stress hormone (CRH) responses that inhibit motility leading to gut paralysis. ENS responses and drug side effects also play a role.
• As a result, the unabsorbed fluid can cause hypovolemic shock, the overdilated gut’s blood flow can be dangerously reduced to the degree of necrosis.
• Lack of sounds over the abdomen is an alarming sign of ileus „the silence of a crypt”

Exners’s phenomenon

Needle thrown into the wall causes stimulation.
Peristalsis
Peristalsis turns the needle.
Peristalsis pulls out needle.
The splanchnic circulation

Functions of splanchnic circulation

- Supplying metabolic demands of the organs
- Supplying blood flow for the secretion of digestive juices, and also for the absorption
- A postprandial (active) hyperemia ~50% increase
- Splanchnic veins contain significant blood “store” that plays a role in systemic circulatory regulation
Blood flow in the splanchnic circulatory bed, portal circulation!

Liver
Stomach and spleen
Pancreas
Small intestine
Colon

A vérbe felszívódó tápanyagok és hormonok legnagyobb koncentrációban a májra hatnak!

Liver microcirculation

© Fleshandbones.com Davies et al: Human Physiology
Liver microcirculation

Arterial and portal blood is mixed in the sinusoids, there is no barrier between the plasma and the liver interstitium (Disse spaces. Proteins move freely, lymph production is large! Under pathological conditions fluid can move through the liver capsule into the abdominal cavity: Ascites

Control of splanchnic blood flow

- The role of sympathetic vasomotor tone is systemic circulatory control: during exercise and stress, the splanchnic flow participates in the redistribution of flow, and blood is mobilized from the splanchnic veins
- Activation of parasympathetic and ENS secretomotor effectors: vasodilation in the activated glands, basal blood flow can increase 7-8 fold, main transmitters are NO, VIP and ACh (salivary glands – only parasympathetic)
- Metabolic autoregulation, especially after a meal during digestion, (escape from sympathetic control) Conflict: exercise after a large meal...