GASTROINTESTINAL MOTILITY PHYSIOLOGY

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CASE STUDY 1

- **14 year old female**
- **With no significant past medical history**
- **Presents with persistent vomiting and 20 lbs weight loss x 3 months**
- **Initially emesis was intermittent, occurred before bedtime or soon there after, 2-3 hrs after a meal**
- **Now occurring immediately or up to 30 minutes after a meal**
- **Emesis consists of undigested food and is nonbloody and nonbilious**
- **Associated with heartburn and chest discomfort**

CASE STUDY 1

- **Initial screening blood work was unremarkable**
- **A trial of acid blockade was started with improvement in heartburn only**
- **Antiemetic therapy with ondansetron showed no improvement**
- **Upper endoscopy on acid blockade was normal**

CASE STUDY 1

Differential for functional/motility disorders:

- **Esophageal disorders:**
  - Achalasia
  - Gastroesophageal Reflux
  - Other esophageal dysmotility disorders

- **Gastric disorders:**
  - Gastroparesis
  - Rumination syndrome
  - Gastric outlet obstruction : pyloric stricture, pyloric stenosis

- **Small bowel:**
  - Small bowel Neuropathy or Myopathy

CASE STUDY 2

- **12 year old male**
- **Presents with a history of chronic constipation**
- **Mother does not remember when he first passed meconium but does report frequent use of glycerin suppositories in infancy**
- **Toilet training attempted at 3 years of age; Witholding behavior (potty dance; hiding behind the furniture)**
- **Fecal incontinence began around 4-5 years of age**
- **Currently no stooling in the toilet**
- **Fecal incontinence several times a day with no sensation**

CASE STUDY 2

Differential for functional/motility disorders:

- Functional Constipation
- Hirschsprung's Disease
- Irritable Bowel Syndrome
- Internal Sphincter Damage or Weakness
- Nerve Damage (e.g.: Meningomyelocele repair)
- Pelvic Floor Dyssynergia

SECTION I

OBJECTIVES

Understand the components of Gastrointestinal Motility

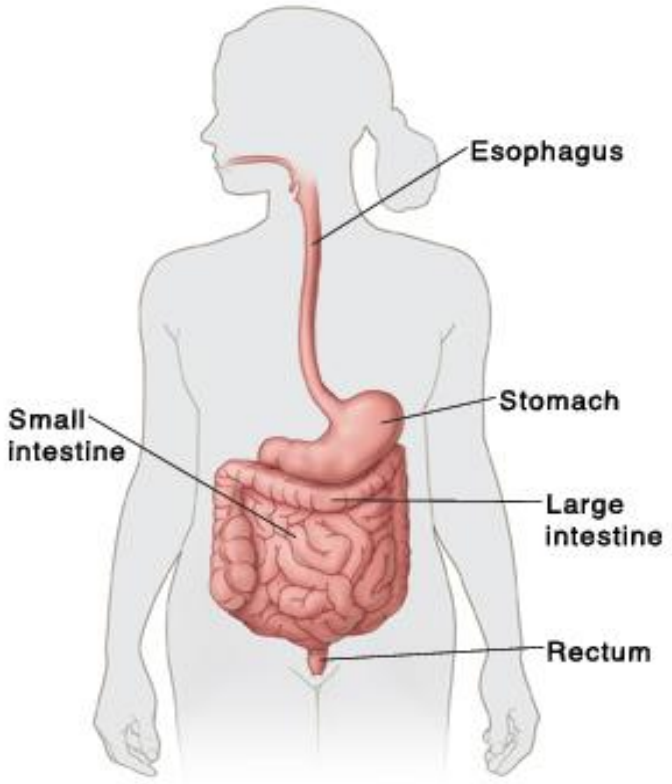
Esophageal

Gastric

Small Intestinal

Colonic

Anorectal



WHAT IS GASTROINTESTINAL MOTILITY ?

- **Gastrointestinal (GI) motility is defined as the coordinated contractions and relaxations of the muscles of the GI tract necessary to move contents from the mouth to the anus**

- **Peristalsis is the result of a series of local reflexes**

- **Contraction of intestinal muscle above an intraluminal stimulus associated with simultaneous relaxation of muscle below the stimulus**

STARLING'S LAW OF THE INTESTINE

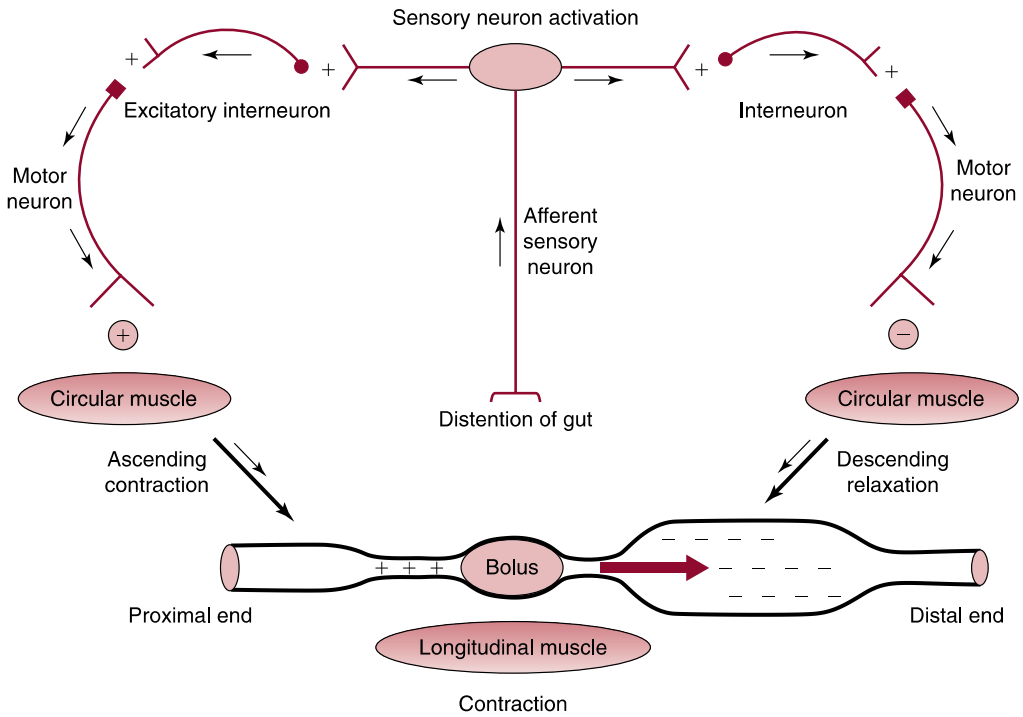
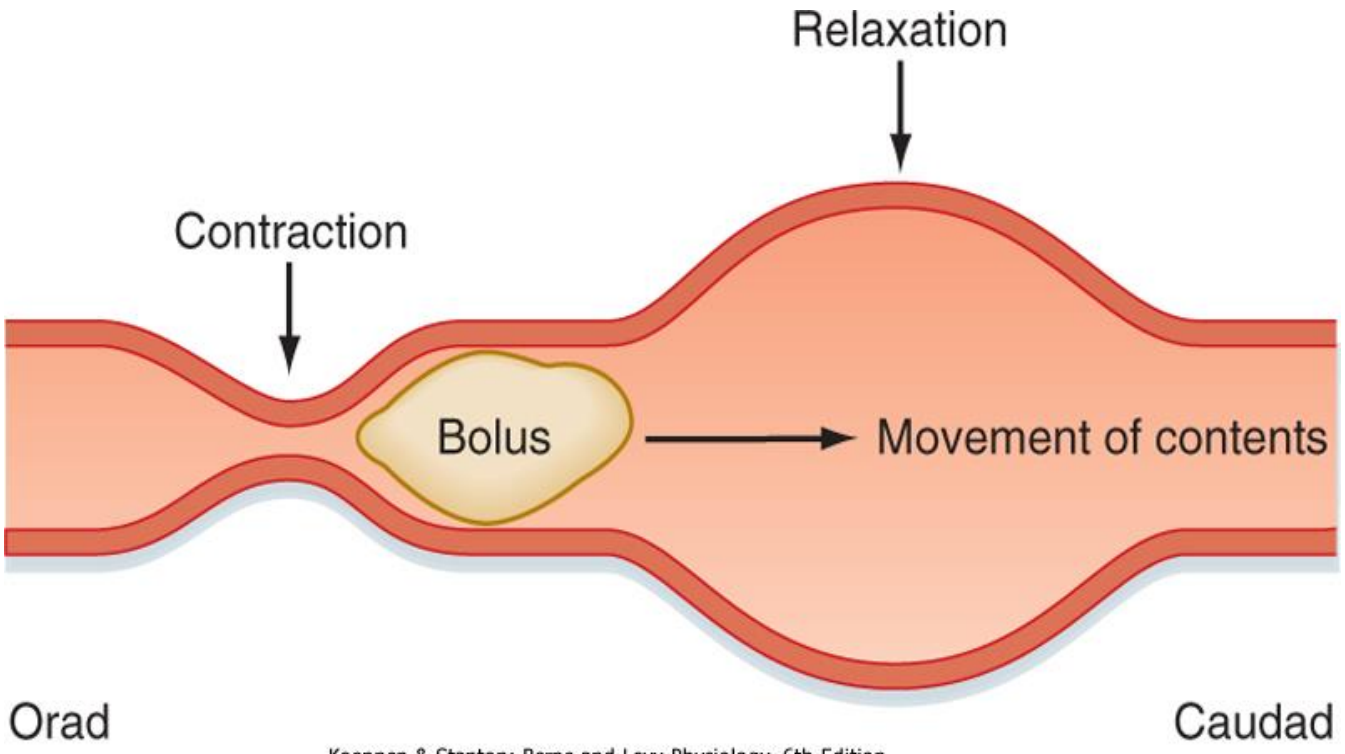
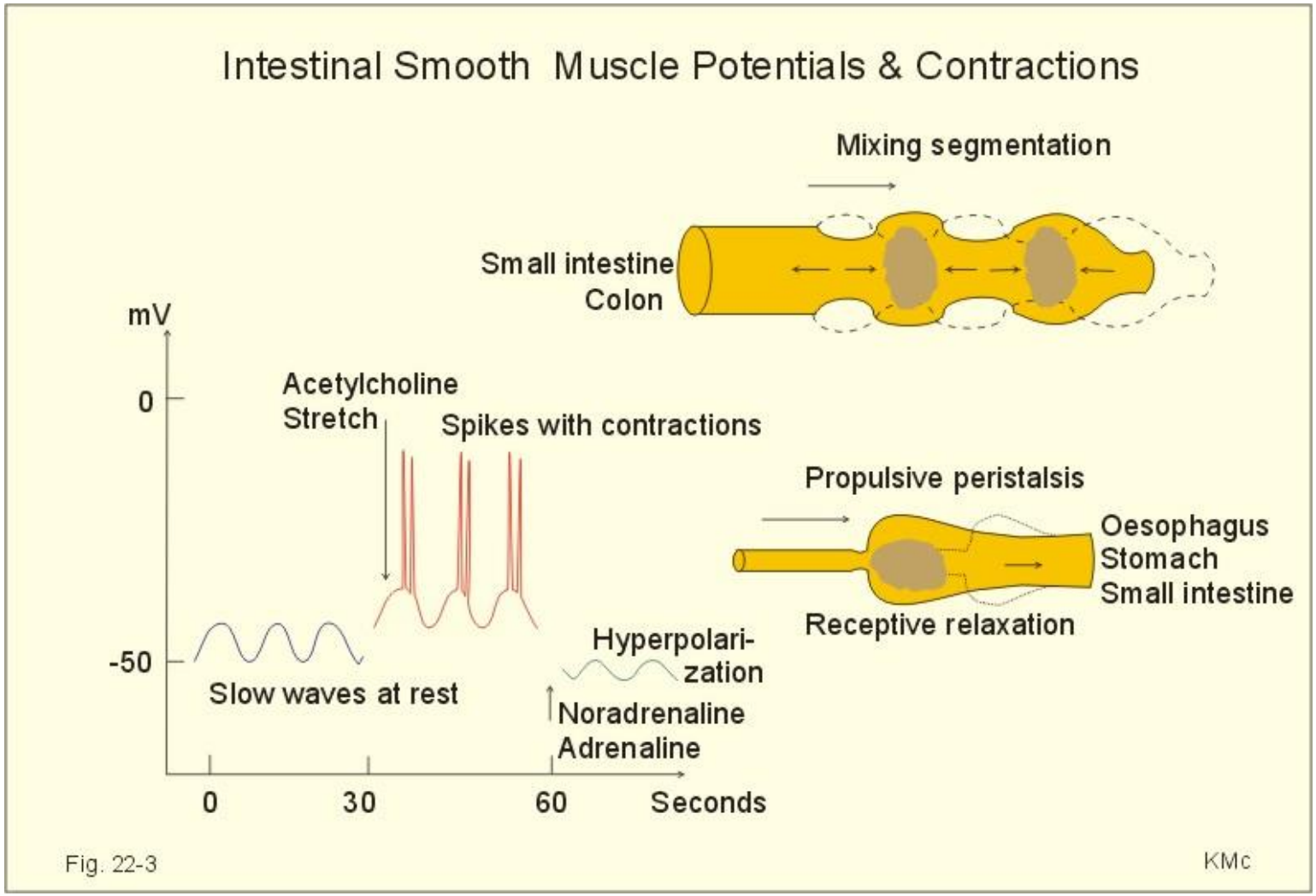


Image from: Biology of Gastrointestinal tract textbook. Chapter 1 Gastrointestinal Hormones and Neurotransmitters Rodger A. Liddle

MECHANISMS OF PERISTALSIS

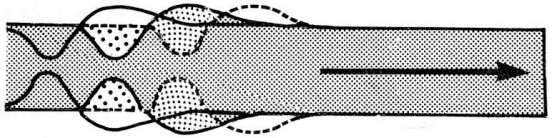
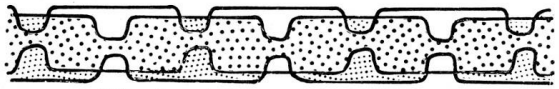
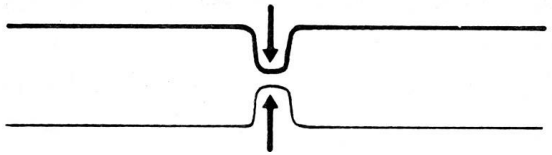


PATTERNS OF MOTILITY

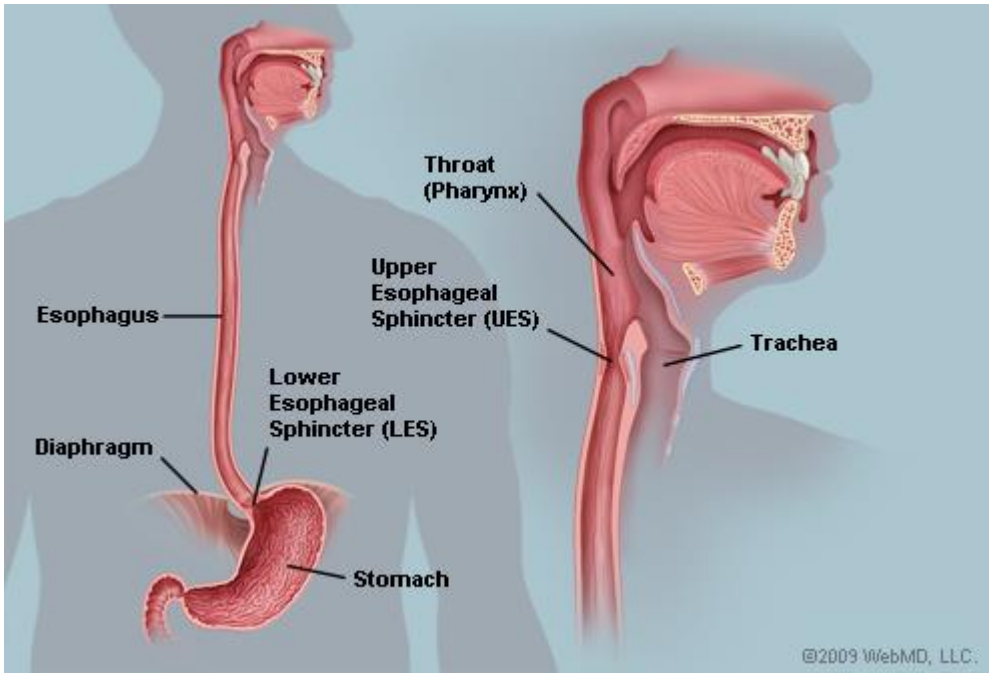


Images from http://http://www.zuniv.net/physiology/book/images/22-3.jpg

PATTERNS OF MOTILITY

Motility pattern	Site	Function
 Peristalsis	Esophagus Stomach Small intestine	Propulsive causes transport non-propulsive causes mixing
 Rhythmic segmentation	Small and large intestines	Mixing
 Tonic contraction	Gastrointes-tinal sphincters	Blocking passage Separation

ESOPHAGEAL MOTILITY



Esophageal peristalsis results from sequential contraction of circular muscle, which serves to push the ingested food bolus toward the stomach

Image from: http://www.webmd.com/digestive-disorders/picture-of-the-esophagus

ESOPHAGEAL MOTILITY

Upper Esophageal Sphincter (UES)

- **Briefly opens during swallowing and initiates primary peristalsis**

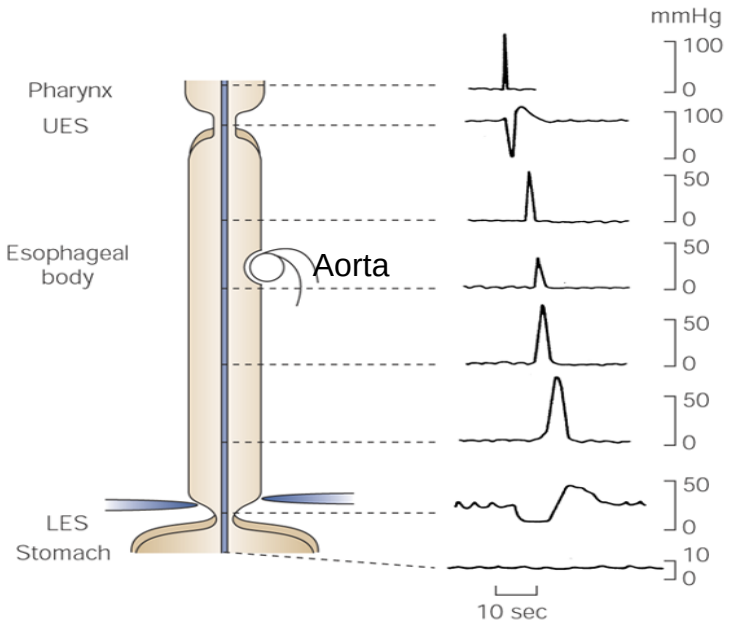
Esophageal Body (Hollow Tube)

- **Primary Peristalsis : Swallow induced peristalsis, primary function is to keep the esophagus empty**
- **Secondary Peristalsis : is induced by esophageal distention and not by swallow. It is important for clearance of retained material and refluxate from the stomach**
- **Tertiary Peristalsis : Non-propulsive, irregular contractions, at times synchronous, exact physiological function unknown**

Lower Esophageal Sphincter (LES)

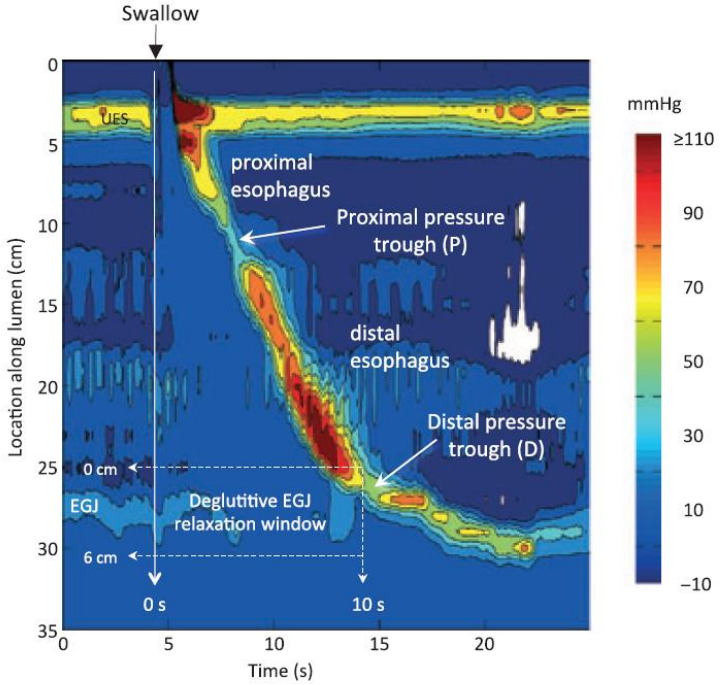
- **2 to 4 cm in length, tonically contracted 15- 40mm Hg**
- **Relaxes 1-2 seconds after swallow, remains open for 6-8 seconds**

Primary Esophageal Peristalsis



Conventional manometry tracing

Image from GI Motility online (May 2006) |



High resolution manometry topography

Image from Neurogastroenterol Motil. 2012 Mar 24; Suppl 1:57-65.

ESOPHAGEAL PRESSURE TOPOGRAPHY SCORING OF INDIVIDUAL SWALLOWS

Integrity of contraction	
Intact contraction	20 mmHg isobaric contour without large or small break
Weak contraction	a) Large break in the 20 mmHg isobaric contour (>5 cm in length) b) Small break in the 20 mmHg isobaric contour (2–5 cm in length)
Failed peristalsis	Minimal (<3 cm) integrity of the 20 mmHg isobaric contour distal to the proximal pressure trough (P)
Contraction pattern (for intact or weak peristalsis with small breaks)	
Premature contraction	DL < 4.5 s
Hypercontractile	DCI > 8000 mmHg-s-cm
Rapid contraction	CFV > 9 cm s^{-1}
Normal contraction	Not achieving any of the above diagnostic criteria
Intrabolus pressure pattern (30 mmHg isobaric contour)	
Panesophageal pressurization	Uniform pressurization extending from the UES to the EGJ
Compartmentalized esophageal pressurization	Pressurization extending from the contractile front to a sphincter
EGJ Pressurization	Pressurization restricted to zone between the LES and CD in conjunction with hiatus hernia
Normal pressurization	No bolus pressurization >30 mmHg

Chicago classification criteria of **esophageal motility** disorders defined in high resolution **esophageal** pressure topography.
Bredenoord AJ, Smout AJ; International High Resolution Manometry Working Group. Neurogastroenterol Motil. 2012 Mar;24 Suppl 1:57-65.

ACHALASIA SUBTYPES

- Type I - achalasia with minimum esophageal pressurization
- Type II - achalasia with esophageal compression or pan-esophageal pressurization
- Type III - achalasia with distal esophageal body spasm.

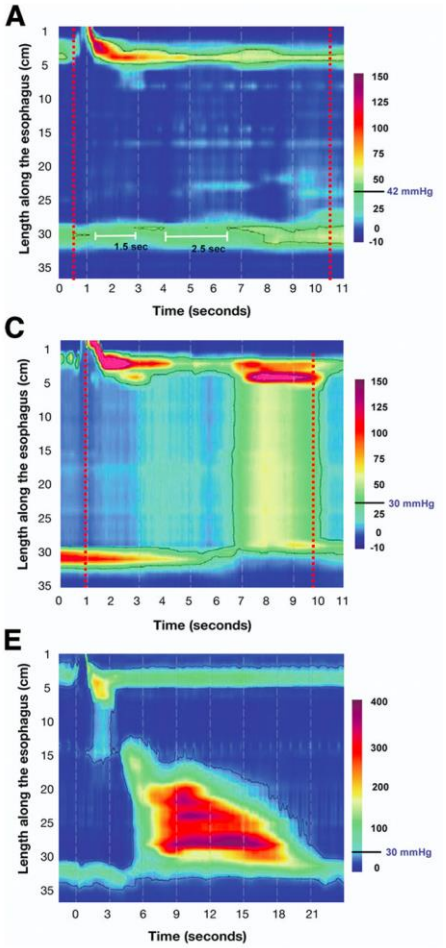


Image from : Gastroenterology. 2008 Nov;135(5):1526-33.

Motility Patterns in other Esophageal Smooth Muscle Disorders

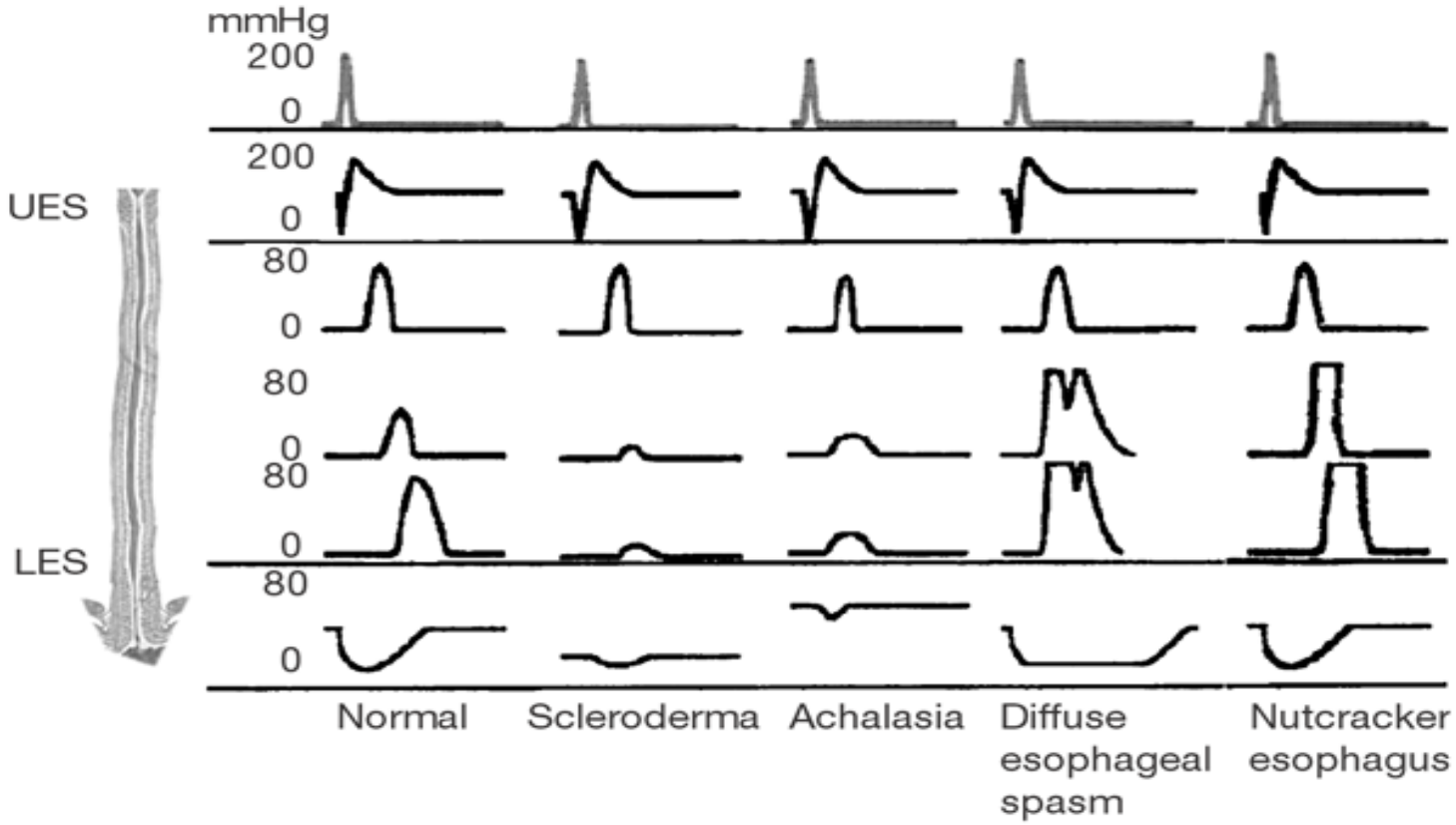
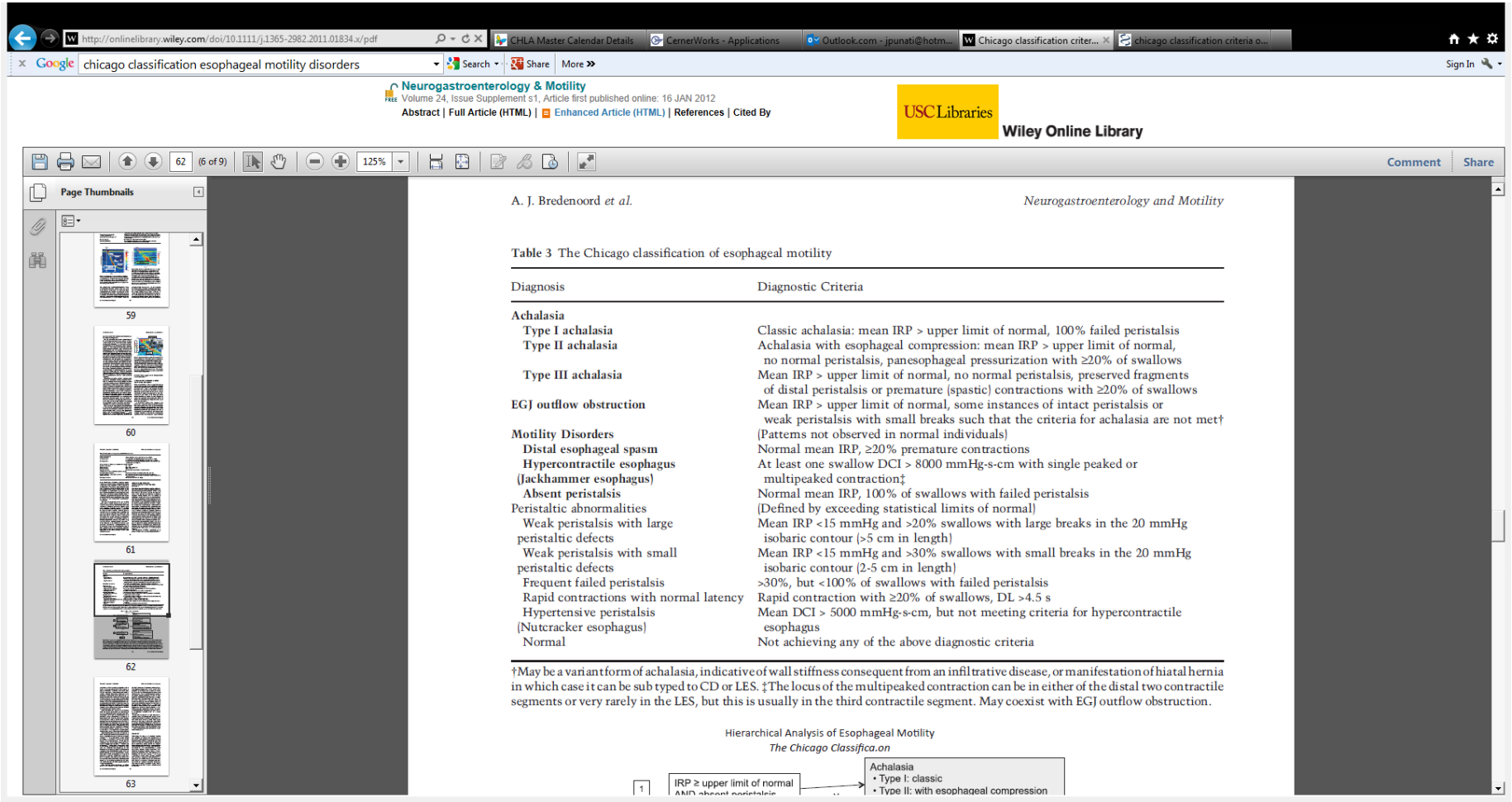


Image from Dr Shaker - GI Motility online (May 2006)

CHICAGO CLASSIFICATION OF ESOPHAGEAL MOTILITY DISORDERS



Neurogastroenterology & Motility
Volume 24, Issue Supplement s1, Article first published online: 16 JAN 2012
Abstract | Full Article (HTML) | Enhanced Article (HTML) | References | Cited By

Table 3 The Chicago classification of esophageal motility

Diagnosis	Diagnostic Criteria
Achalasia	
Type I achalasia	Classic achalasia: mean IRP > upper limit of normal, 100% failed peristalsis
Type II achalasia	Achalasia with esophageal compression: mean IRP > upper limit of normal, no normal peristalsis, panesophageal pressurization with ≥20% of swallows
Type III achalasia	Mean IRP > upper limit of normal, no normal peristalsis, preserved fragments of distal peristalsis or premature (spastic) contractions with ≥20% of swallows
EGJ outflow obstruction	Mean IRP > upper limit of normal, some instances of intact peristalsis or weak peristalsis with small breaks such that the criteria for achalasia are not met†
Motility Disorders	(Patterns not observed in normal individuals)
Distal esophageal spasm	Normal mean IRP, ≥20% premature contractions
Hypercontractile esophagus (Jackhammer esophagus)	At least one swallow DCI > 8000 mmHg-s-cm with single peaked or multipeaked contraction‡
Absent peristalsis	Normal mean IRP, 100% of swallows with failed peristalsis
Peristaltic abnormalities	(Defined by exceeding statistical limits of normal)
Weak peristalsis with large peristaltic defects	Mean IRP <15 mmHg and >20% swallows with large breaks in the 20 mmHg isobaric contour (>5 cm in length)
Weak peristalsis with small peristaltic defects	Mean IRP <15 mmHg and >30% swallows with small breaks in the 20 mmHg isobaric contour (2-5 cm in length)
Frequent failed peristalsis	>30%, but <100% of swallows with failed peristalsis
Rapid contractions with normal latency	Rapid contraction with ≥20% of swallows, DL >4.5 s
Hypertensive peristalsis (Nutcracker esophagus)	Mean DCI > 5000 mmHg-s-cm, but not meeting criteria for hypercontractile esophagus
Normal	Not achieving any of the above diagnostic criteria

†May be a variant form of achalasia, indicative of wall stiffness consequent from an infiltrative disease, or manifestation of hiatal hernia in which case it can be sub typed to CD or LES. ‡The locus of the multipeaked contraction can be in either of the distal two contractile segments or very rarely in the LES, but this is usually in the third contractile segment. May coexist with EGJ outflow obstruction.

Hierarchical Analysis of Esophageal Motility
The Chicago Classifica.on

Image from: Gastroenterology. 2008 Nov;135(5):1526-33.

INTERSTITIAL CELLS OF CAJAL

Interstitial cells of Cajal (ICC) are the pacemaker cells in the gut

Generate and propagate slow waves in gastrointestinal muscles

The frequency of slow waves determines the frequency of contractions of the stomach, intestine and colon

Slow waves also determine the direction and velocity of propagation of peristaltic activity, in concert with the enteric nervous system

GASTRIC MOTILITY

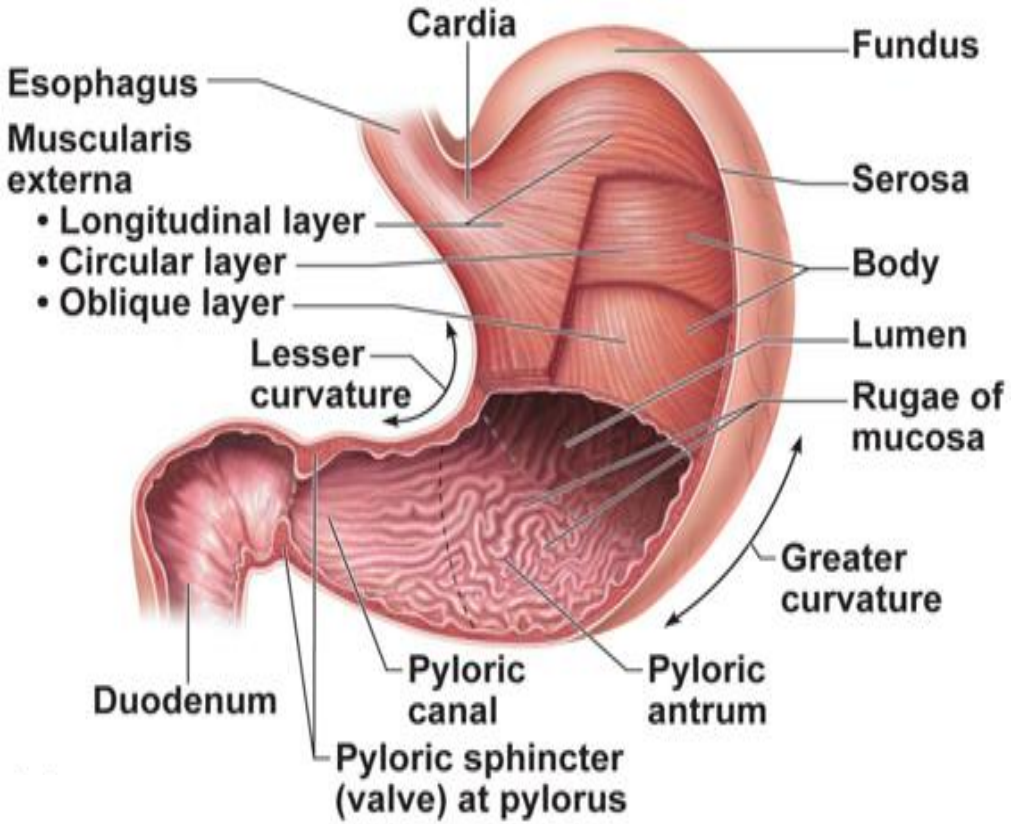
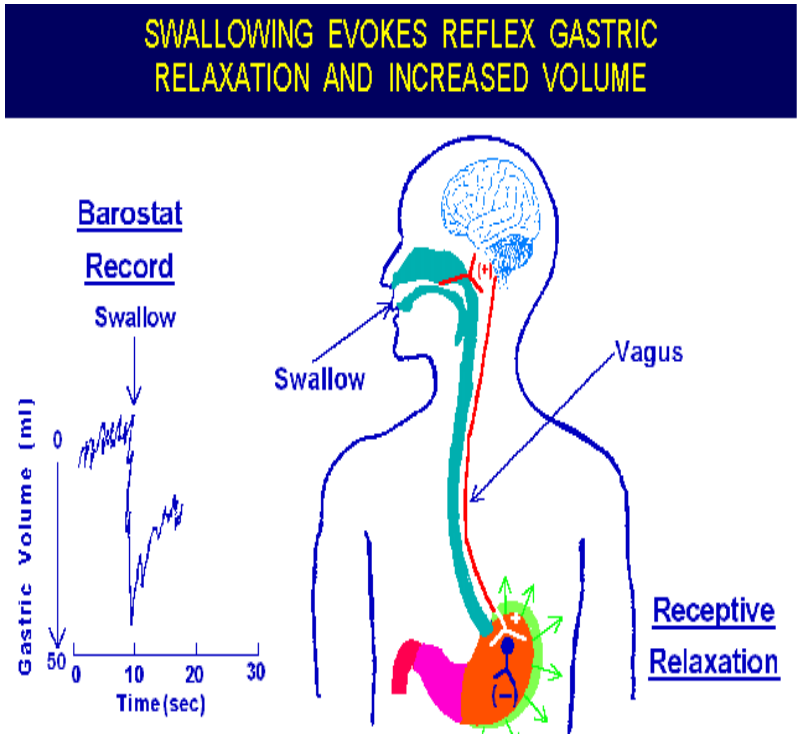
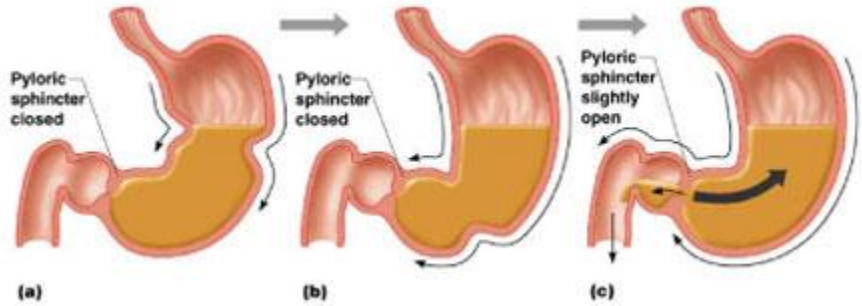


Image from J Thompson, PhD

GASTRIC MOTILITY





SMALL INTESTINAL MOTILITY

- Slow waves initiated by Interstitial Cells of Cajal
- Always present, but requires spike potentials to initiate contractions
- Frequency is 3/min stomach, 12/min duodenum, 7/min ileum, 9/min cecum, and 16/min sigmoid colon
- Whether spike potentials and, hence, contractions occur depends on neural, hormonal and local influences

INTESTINAL REFLEXES

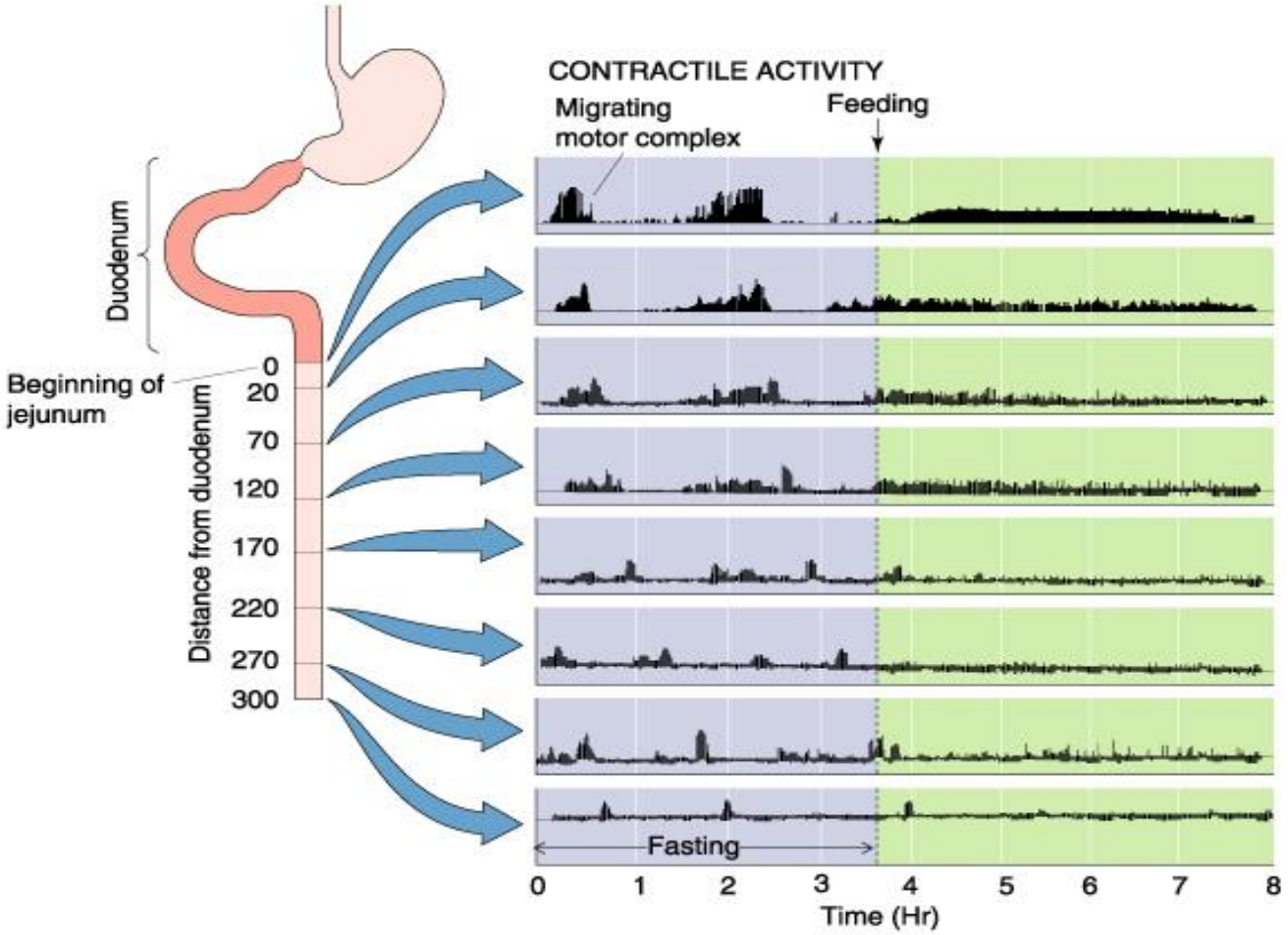
- **Peristaltic reflex or "law of the intestines", i.e., upstream contraction and downstream receptive relaxation when a bolus distends the intestine**

- **Intestinointestinal reflex is an inhibition of contractile activity when the intestine is severely distended**

- **Gastroileal reflex is a relaxation of the ileocecal sphincter after a meal that moves chyme into the colon. This reflex is mediated by vagus nerve and gastrin**

- **Gastrocolic reflex is stimulation of high or low amplitude colonic contractility with gastric distention or nutritive stimulus**

MIGRATING MOTOR COMPLEXES

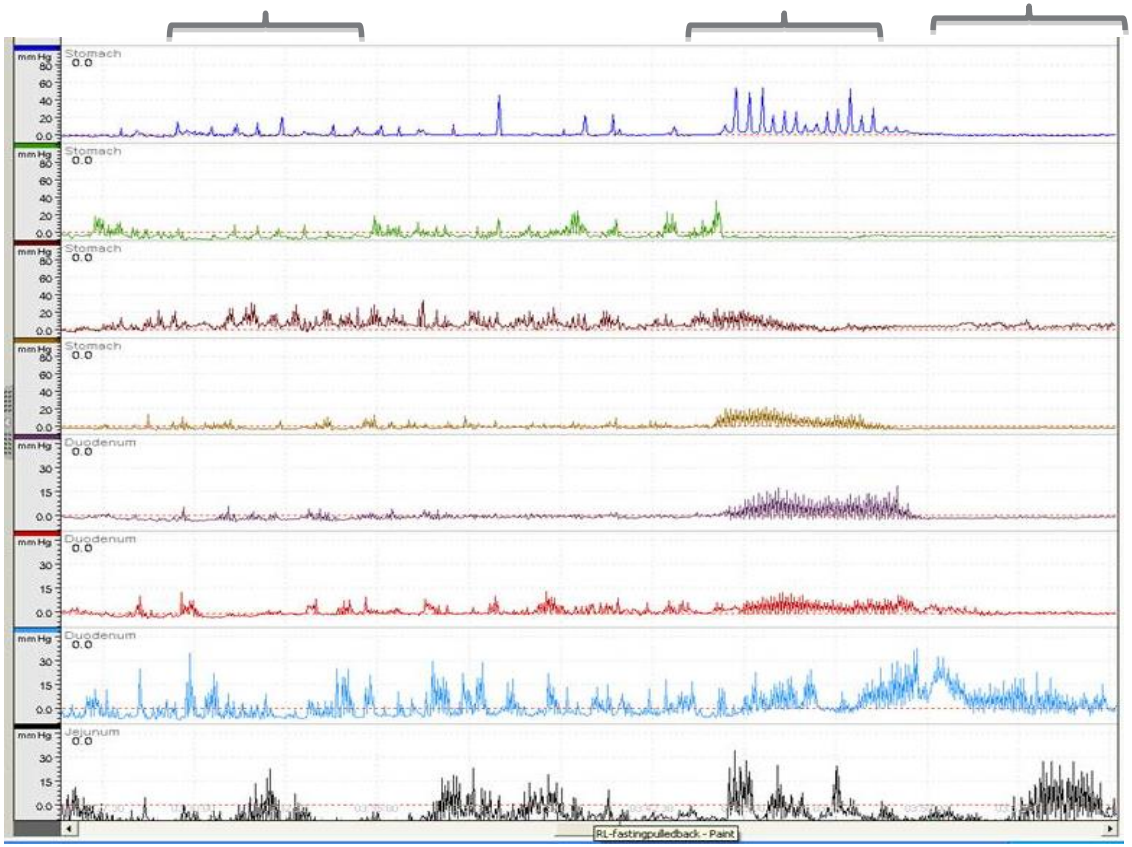


MIGRATING MOTOR COMPLEX (MMC)

Phase II-Mixing

Phase III – Propulsive

Phase I – Quiet



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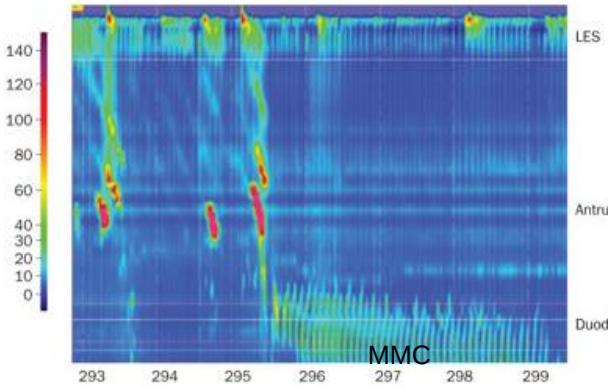
High resolution topography of MMC



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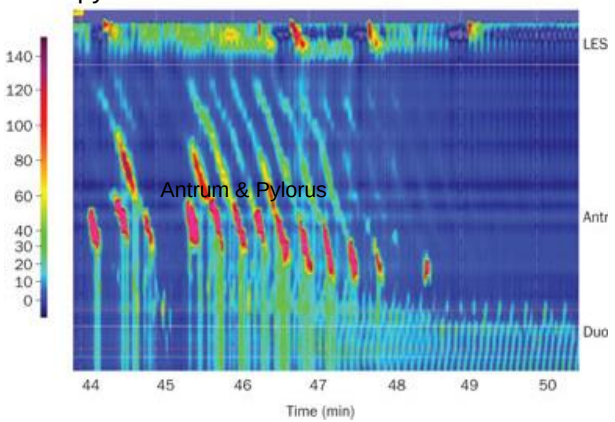
High resolution topography of antrum pyloric contractions



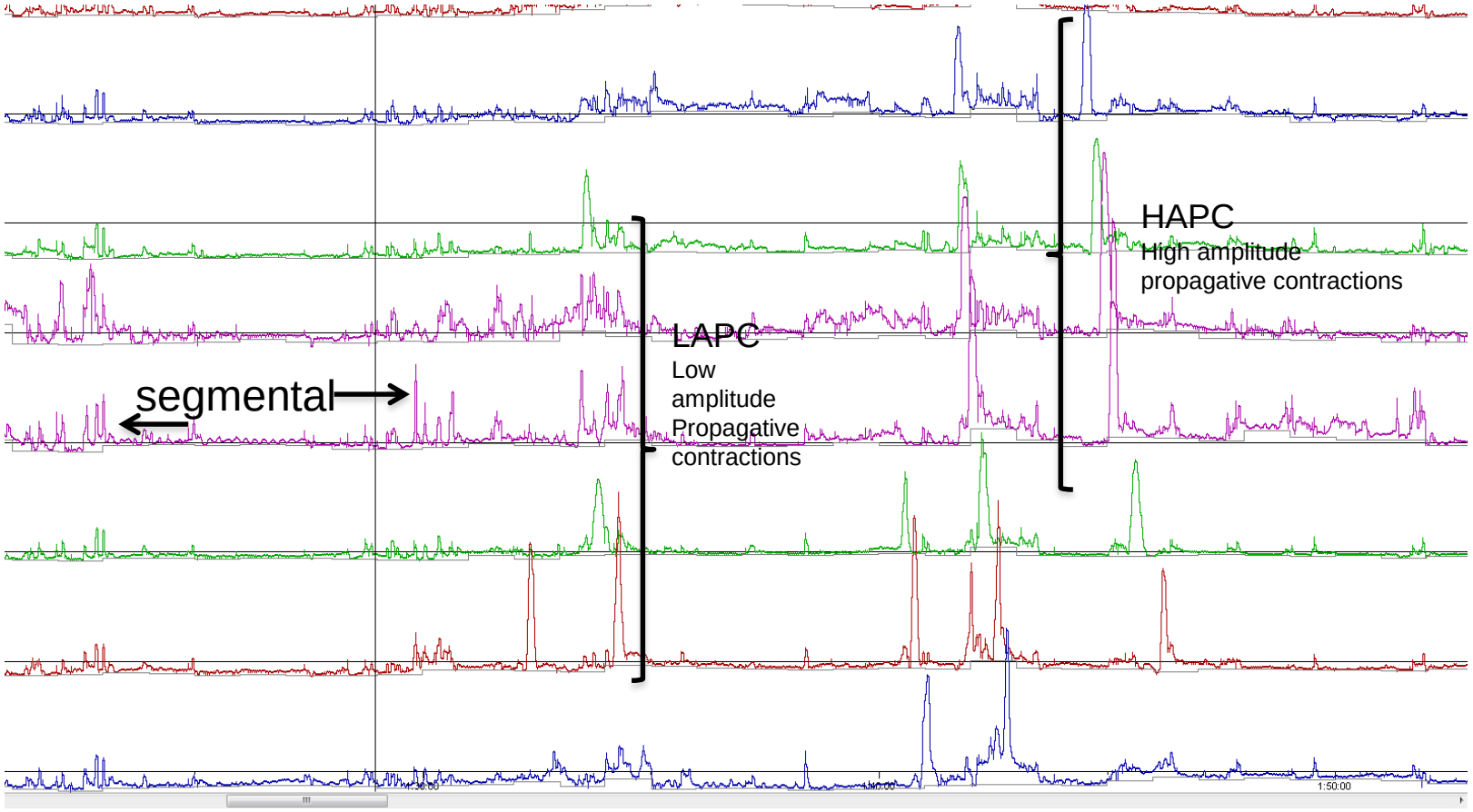
Patient images from Jaya Punati, MD - CHLA

HUMAN COLONIC CONTRACTILE PATTERNS

- **Segmental Activity**
  - Single Contractions
  - Groups (Bursts) of Contractions
    - Rhythmic
    - Arrhythmic

- **Propagated Activity**
  - Low Amplitude Propagated Contractions
  - High Amplitude Propagated Contractions

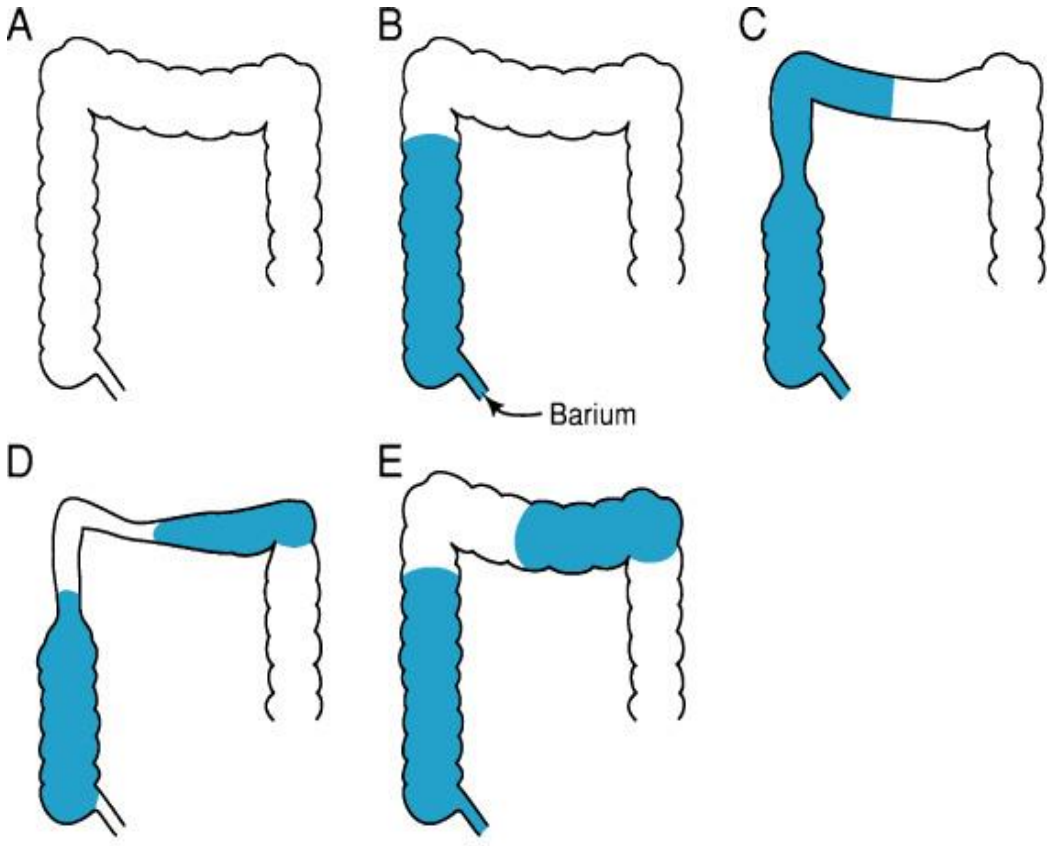
COLONIC PROPULSIVE ACTIVITY



Patient images from Jaya Punati, MD - CHLA

HIGH AMPLITUDE PROPAGATIVE CONTRACTIONS

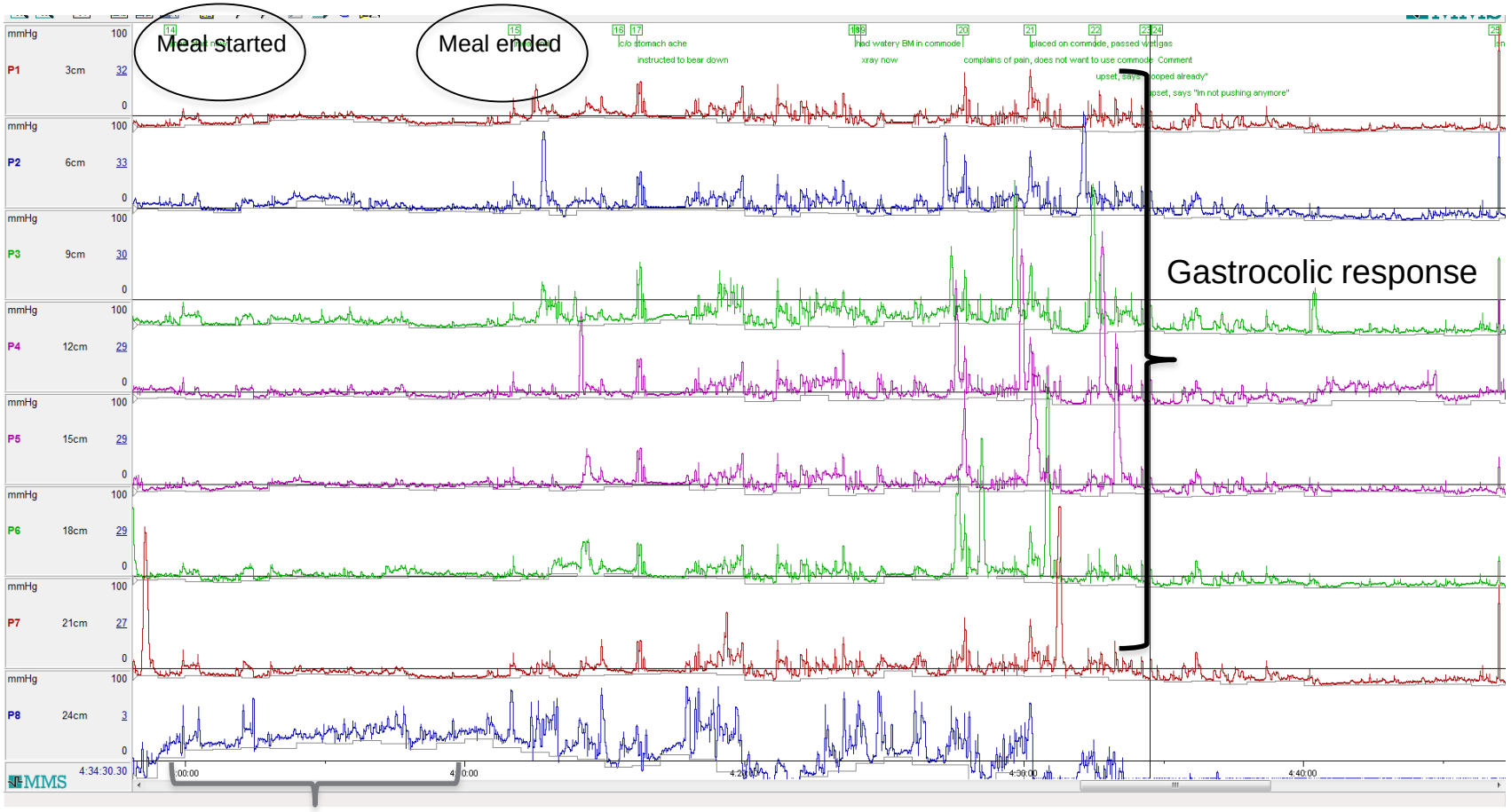
Mass movements and haustral changes associated with colonic contractions as noted by barium enema.



CONTROL OF PROXIMAL DESCENDING AND SIGMOID COLON

- Distension of the ileum causes the ileocecal sphincter to relax (ileocecal reflex)
- Distension of the colon causes the ileocecal sphincter to contract
- 1 to 3 times per day a peristaltic mass movement propels material through the colon
- Gastroileal and gastrocolic reflexes with relaxation of ileocecal valve produces a mass movement in the proximal colon shortly after a meal due to the action of gastrin and extrinsic autonomic nerves

GASTROCOLIC REFLEX



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ANORECTAL MOTILITY - DEFECATION

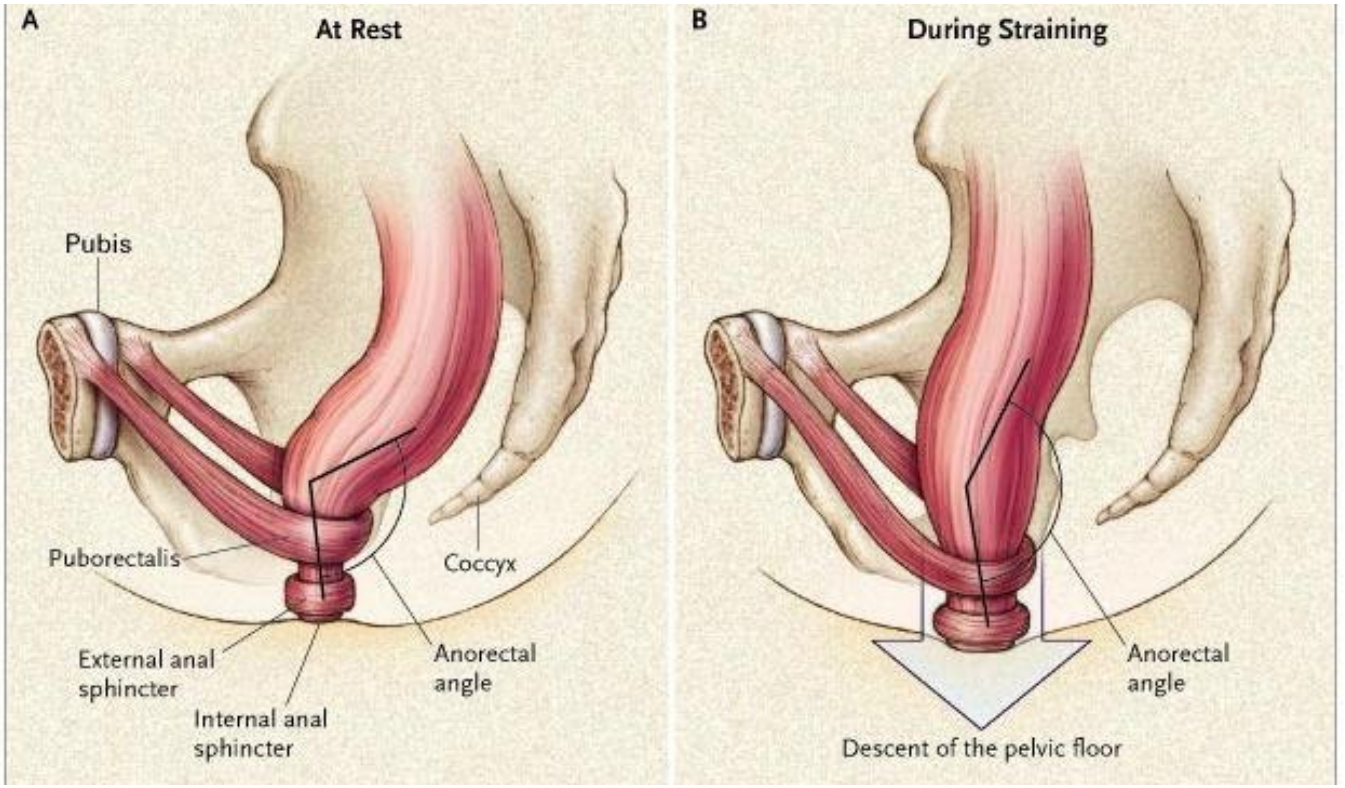
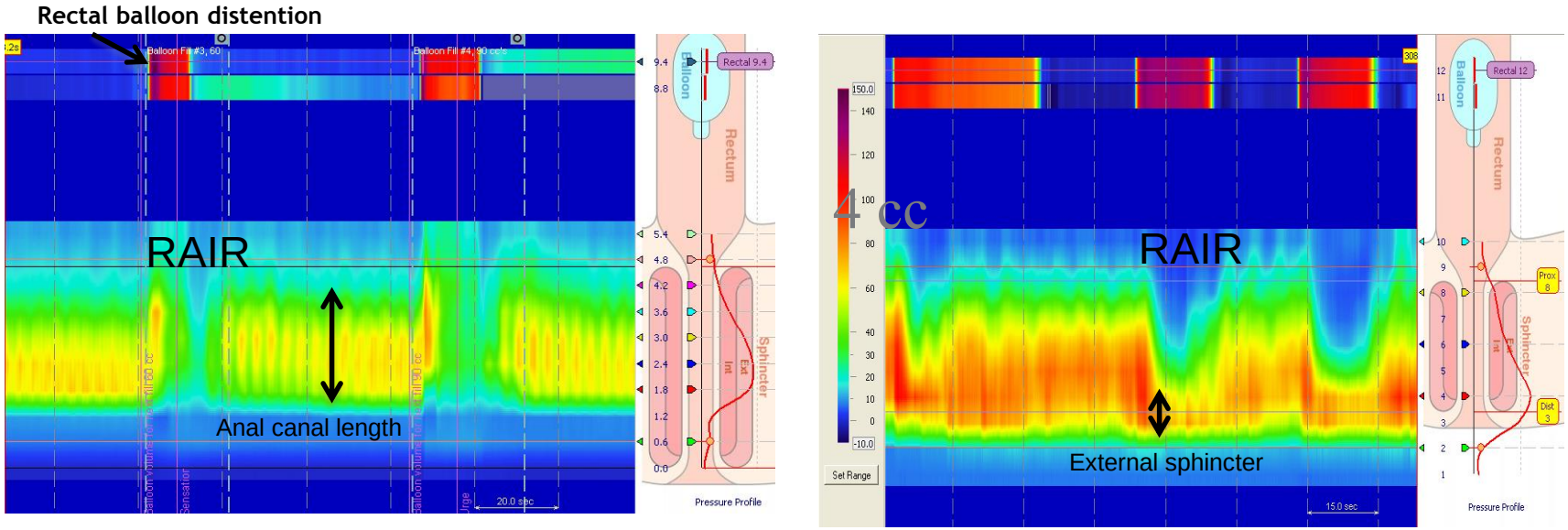


Image from http://msk-anatomy.com/

RECTOANAL INHIBITORY REFLEX - RAIR



High Resolution topography

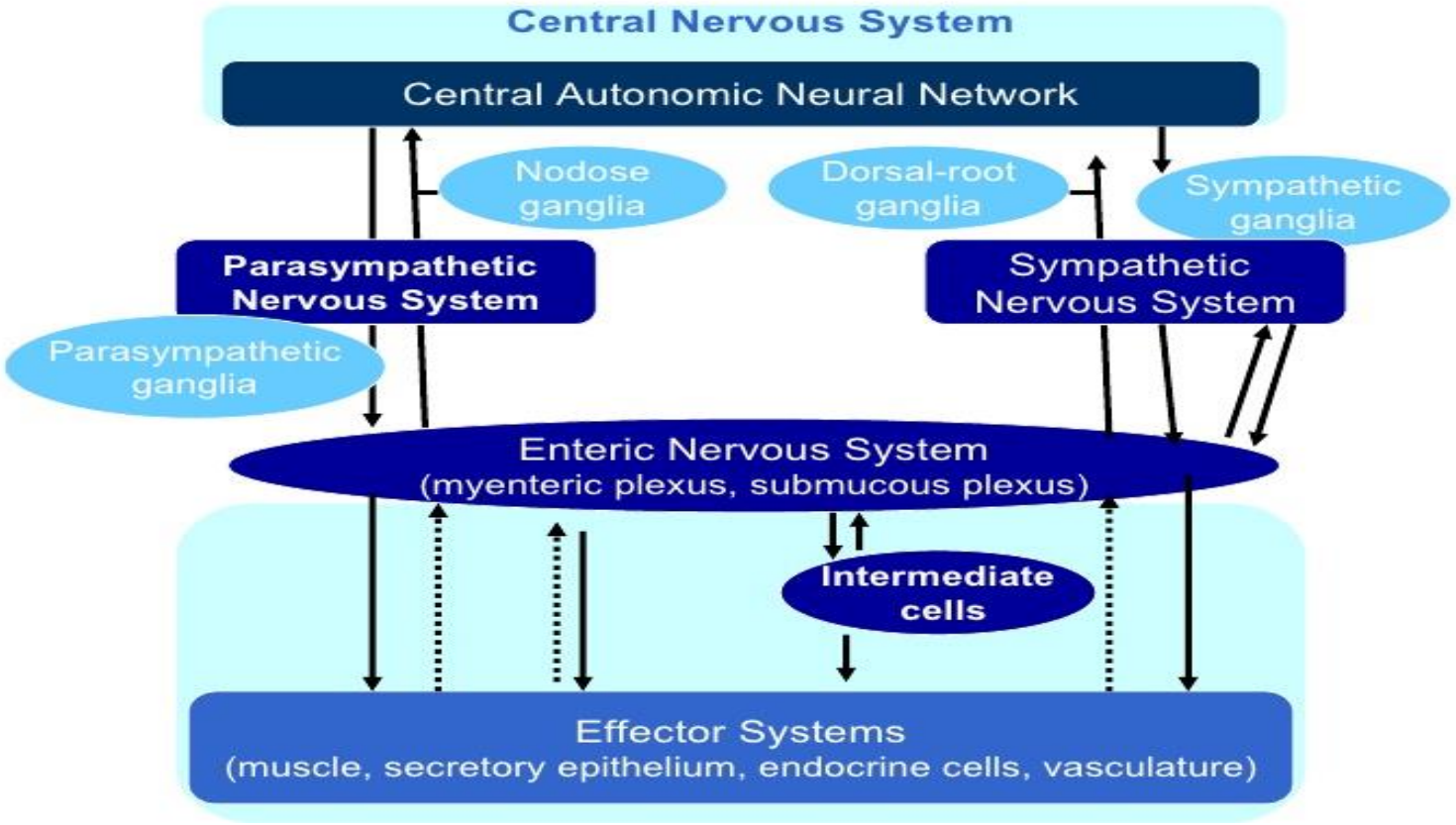
Modified from source: Sierra scientific

SECTION II

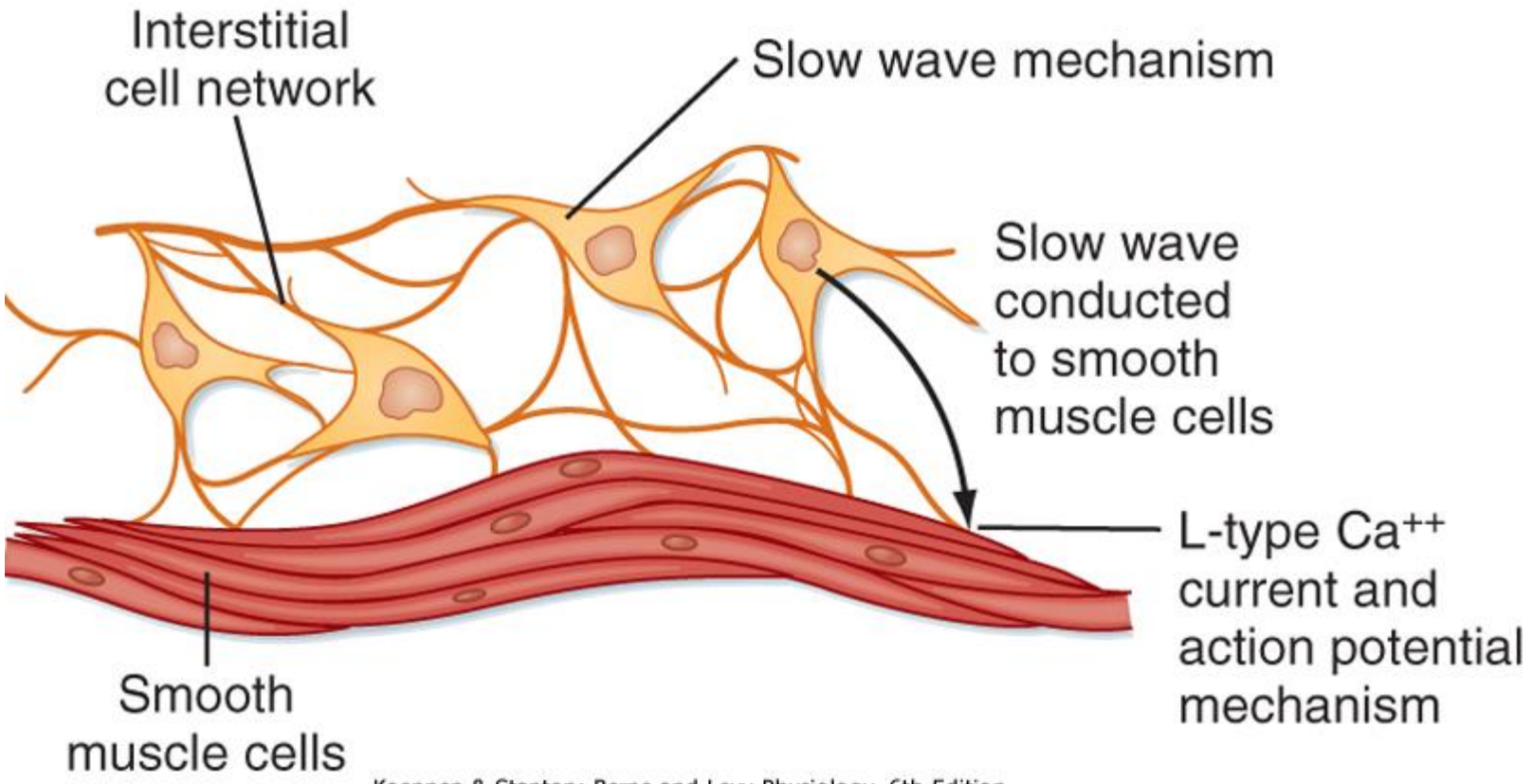
OBJECTIVE

Understand the Neuronal and Hormonal Peptides that modulate Gastrointestinal Motility

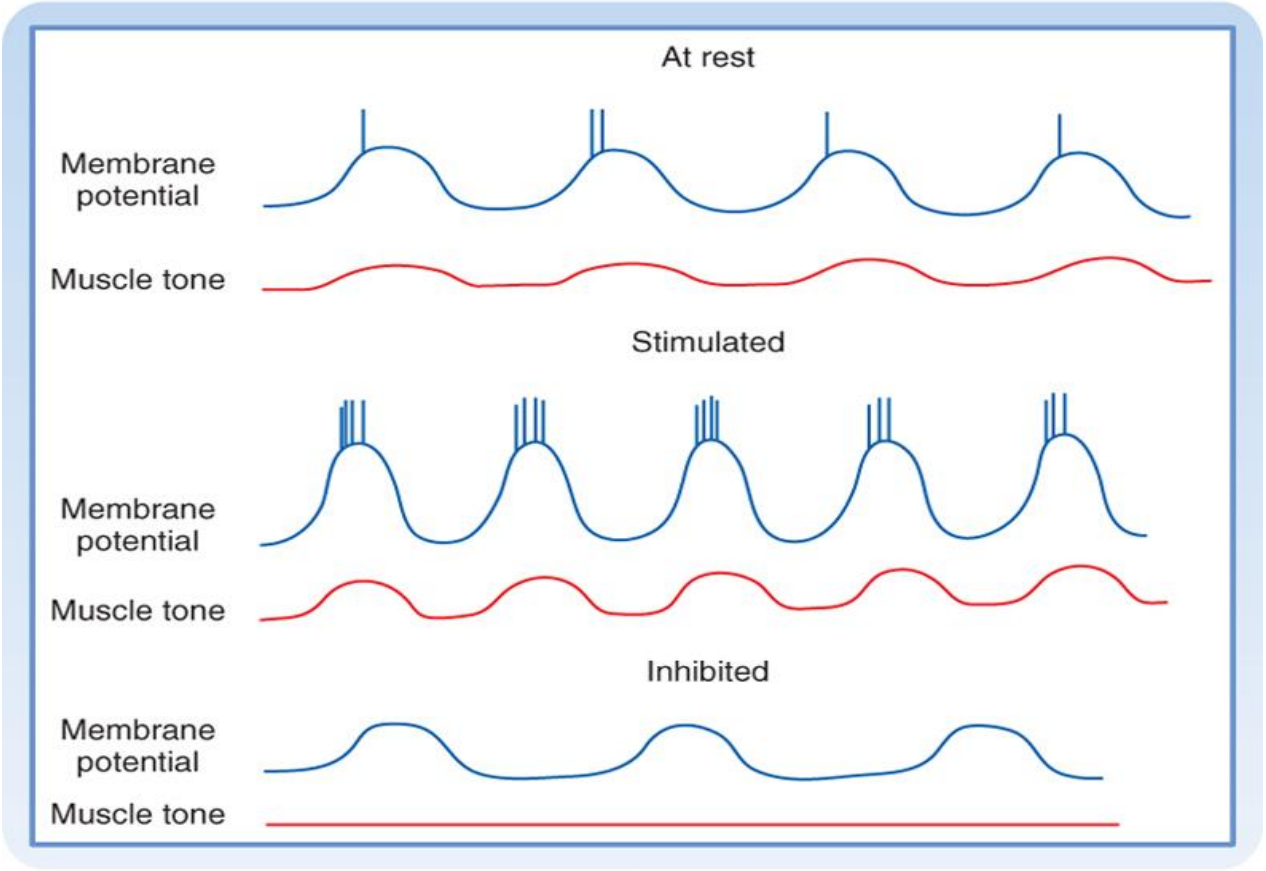
Regulation of GI Motility



INTERSTITIAL CELLS OF CAJAL (ICC) - PACEMAKERS



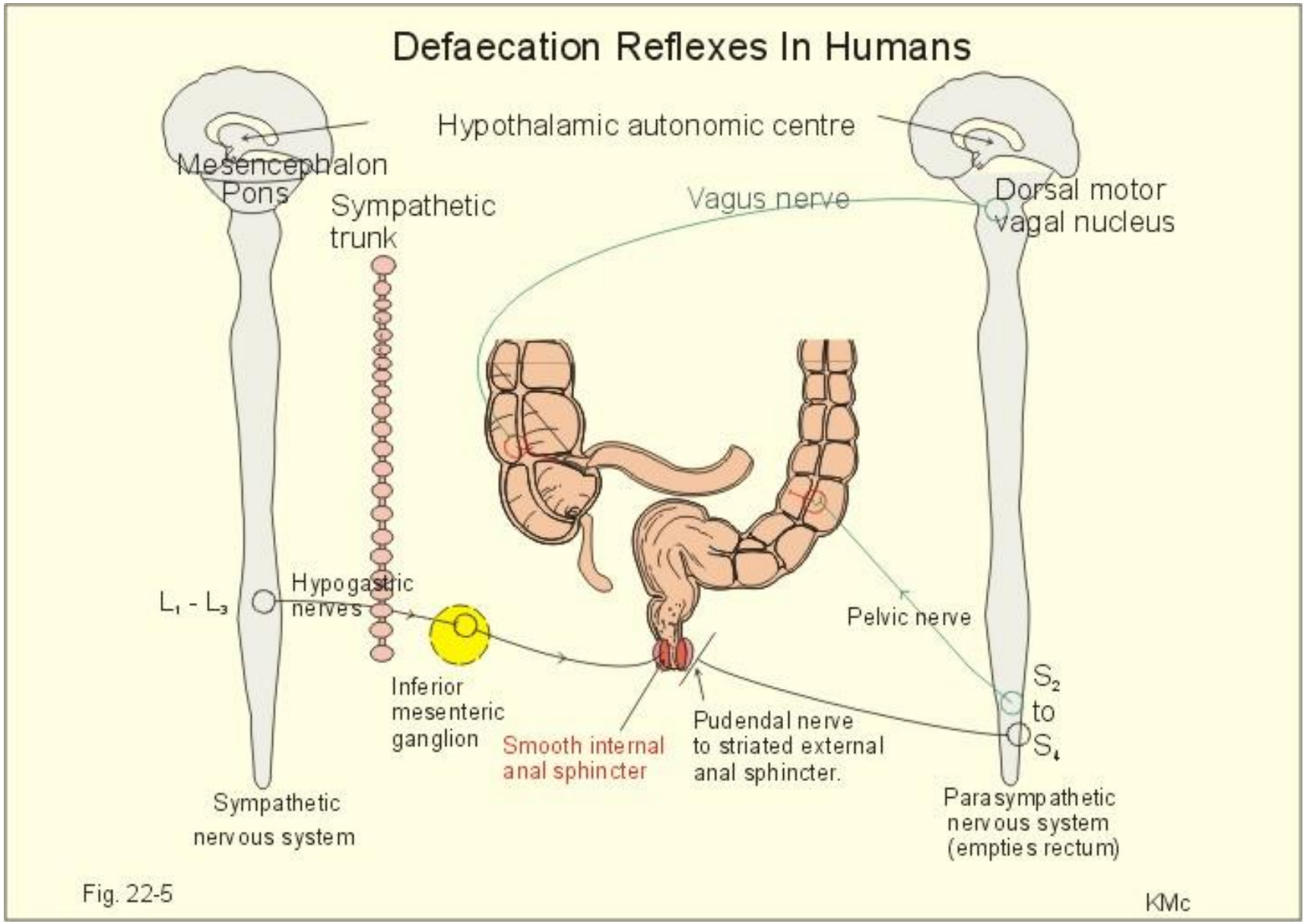
EXCITATION CONTRACTION COUPLING STIMULATING PERISTALSIS



NEURAL CONTROL OF GASTRODUODENAL MOTILITY

Phase	Stimulus	Mechanism	Effect on Motility
Gastric	Increase Gastric motility and emptying	Long neural reflexes (gastroileal reflex) Gastrin	Increased activity in the ileum Increased segmenting movements in ileum; relaxes ileocecal sphincter
Intestinal	Distention of the small intestine Reduced intestinal volume: fasting	Long and short neural reflexes Long and short neural reflexes; initiated by increased blood levels of motilin	Increased strength of segmentation Initiates MMC (peristalsis); repeats until next meals

NEURAL CONTROL OF DEFECATION



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HORMONAL REGULATION OF GUT MOTILITY

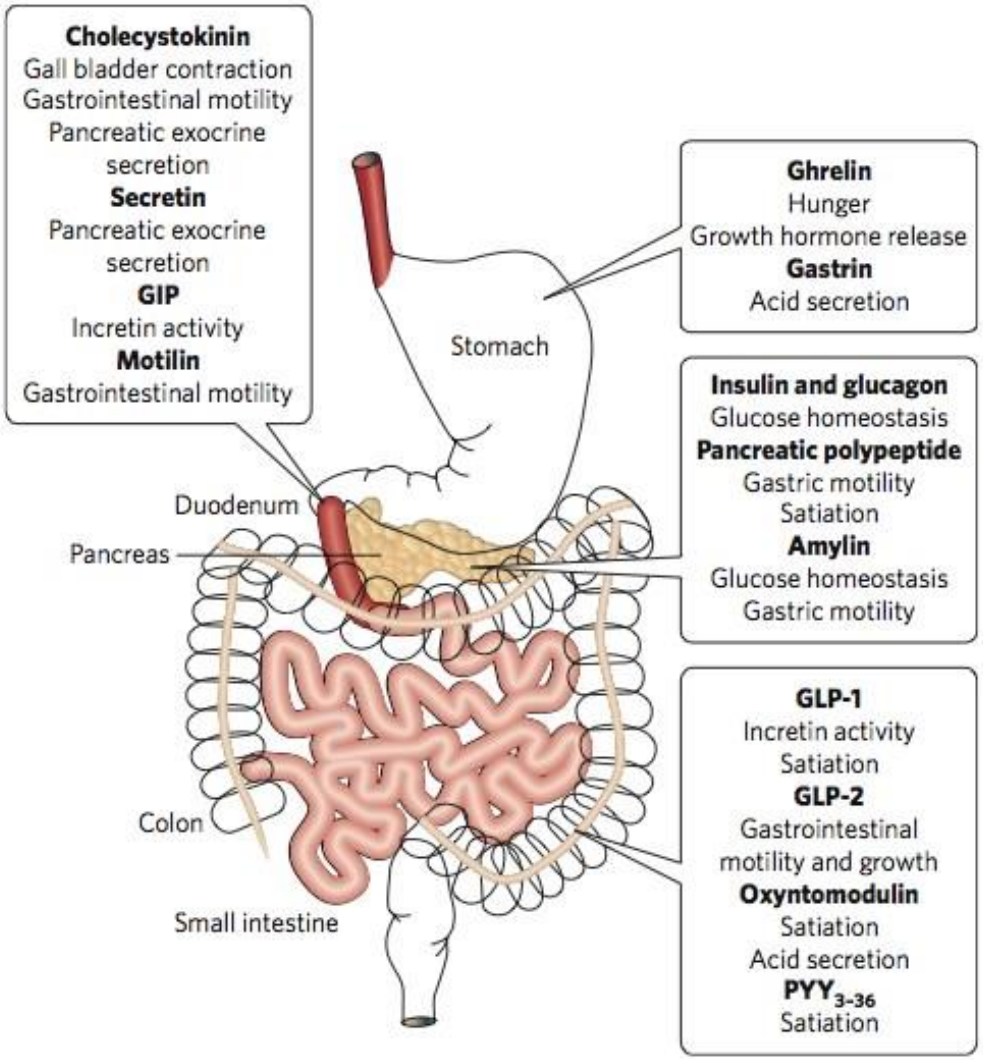


Image from: Gut hormones and the regulation of energy homeostasis; Kevin G. Murphy and Stephen R. Bloom; Nature 444, 854-859(14 December 2006)

HORMONAL REGULATION OF GUT MOTILITY

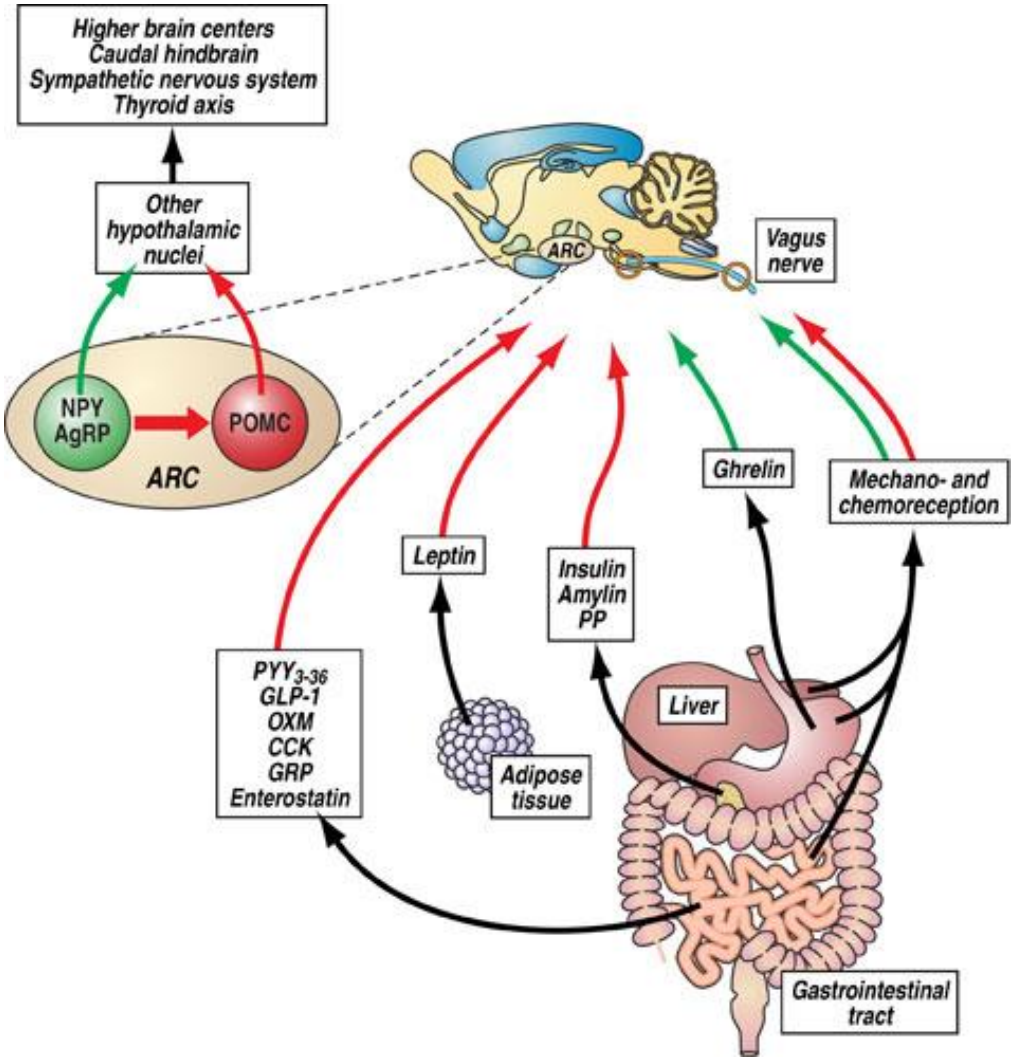


Image from: Biology of Gastrointestinal tract textbook. Chapter 1 Gastrointestinal Hormones and Neurotransmitters Rodger A. Liddle

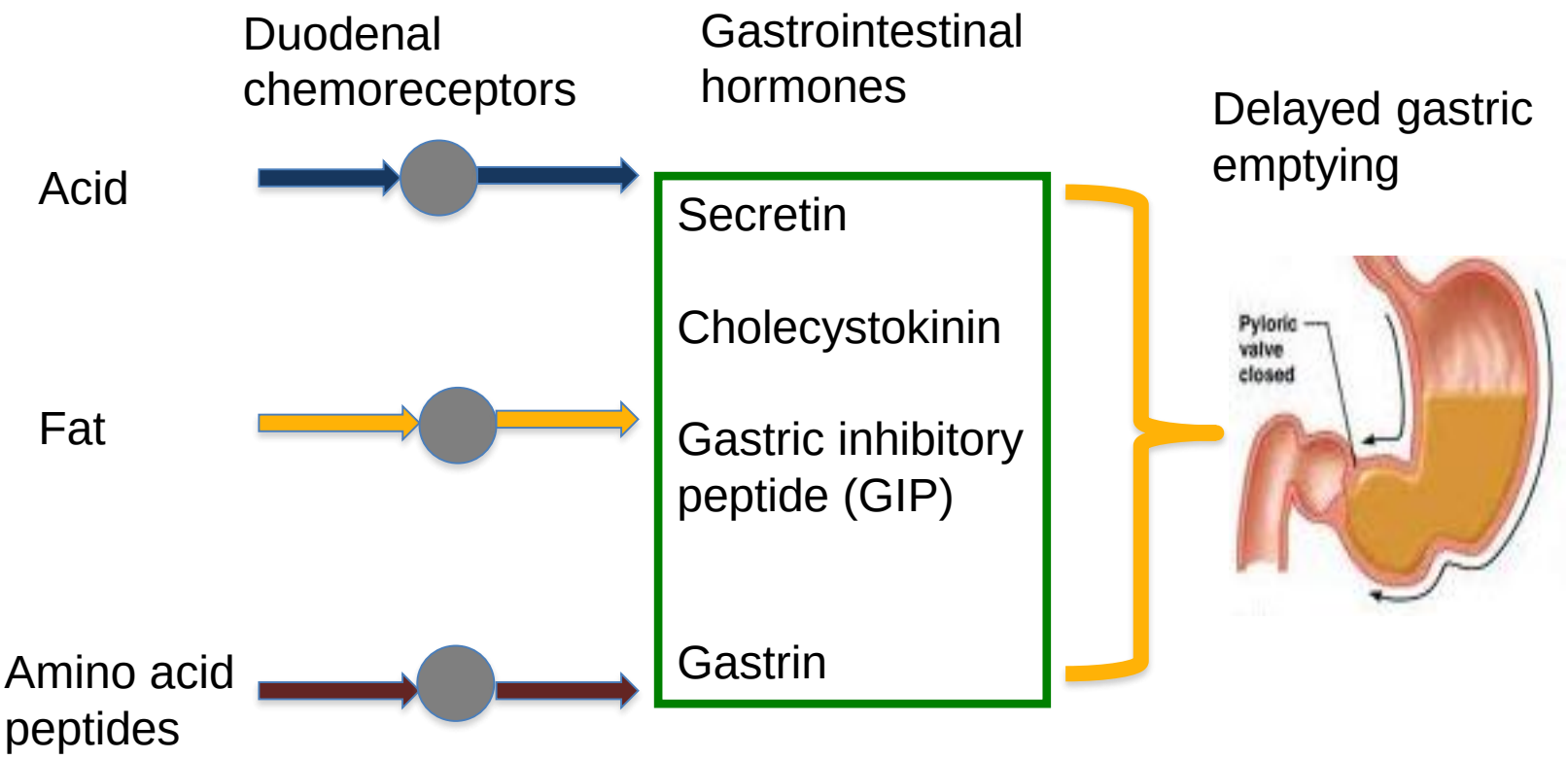
HORMONAL REGULATION OF GUT MOTILITY

Hormone	Site of Production	Stimulus For Production	Target Organ	Activity
Cholecystokinin (CCK)	Duodenal mucosa	Fatty Chyme	Stomach Liver/pancreas Pancreas Gallbladder Hepatopancreatic sphincter	Inhibits stomach's secretory activity Potentiates secretin's actions Increase pancreatic secretion Stimulate contraction and expulsion of bile Relaxes sphincter allowing secretions into duodenum
Gastric inhibitory peptide (GIP)	Duodenal mucosa	Fatty Chyme	Stomach Pancreas (beta cells)	Inhibits HCl production Stimulates insulin release
Gastrin	Stomach mucosa – G cells	Partially digested food; acetylcholine released from nerve cells	Stomach (parietal cells) Small intestine Ileocecal valve Large intestine	Increases HCl secretion Stimulates gastric emptying Stimulates small intestine contractions Relaxes ileocecal valve Stimulates movement
Histamine	Stomach mucosa	Food in stomach	Stomach	Activates parietal cells to release HCl
Intestinal gastrin	Duodenal mucosa	Acidic and partially digested food in duodenum	Stomach	Stimulates gastric glands and motility

HORMONAL REGULATION OF GUT MOTILITY

Hormone	Site of Production	Stimulus For Production	Target Organ	Activity
Motilin	Duodenal mucosa	Fasting; periodic release by neural stimuli (1.5-2 hrs)	Proximal duodenum	Stimulates MMC
Secretin	Duodenal mucosa	Acidic chyme	Stomach Pancreas Liver	Inhibits gastric gland secretion Inhibits gastric motility during gastric secretion Increases pancreatic juice secretion: potentiates CCK Increases bile output
Serotonin	Stomach mucosa	Food in stomach	Stomach	Causes contraction of the stomach
Somatostatin	Stomach mucosa and duodenal mucosa	Food in stomach; sympathetic nerve stimulation	Stomach Pancreas Small intestine Gallbladder and liver	Inhibits gastric secretion Inhibits secretion Inhibits GI blood flow and intestinal absorption Inhibits contraction and bile release
Vasoactive intestinal peptide (VIP)	Enteric neurons	Partially digested food	Small intestine Pancreas Stomach	Stimulates buffer secretion Dilates intestinal vasculature Relaxes intestinal smooth muscle Increases secretion Inhibits acid secretion

FACTORS AFFECTING GASTRIC EMPTYING



REGULATION OF GI MOTILITY

EXCITATORY

Ach

Adenosine

Bombesin

CCK

GRP

Histamine

Motilin

- Neurokinin A
- Opioids
- PGE2
- Serotonin
- SP
- TRH

INHIBITORY

- CGRP
- GABA
- Galanin
- Glucagon
- NPY
- Neurotensin
- NO

PACAP

PHI

PYY

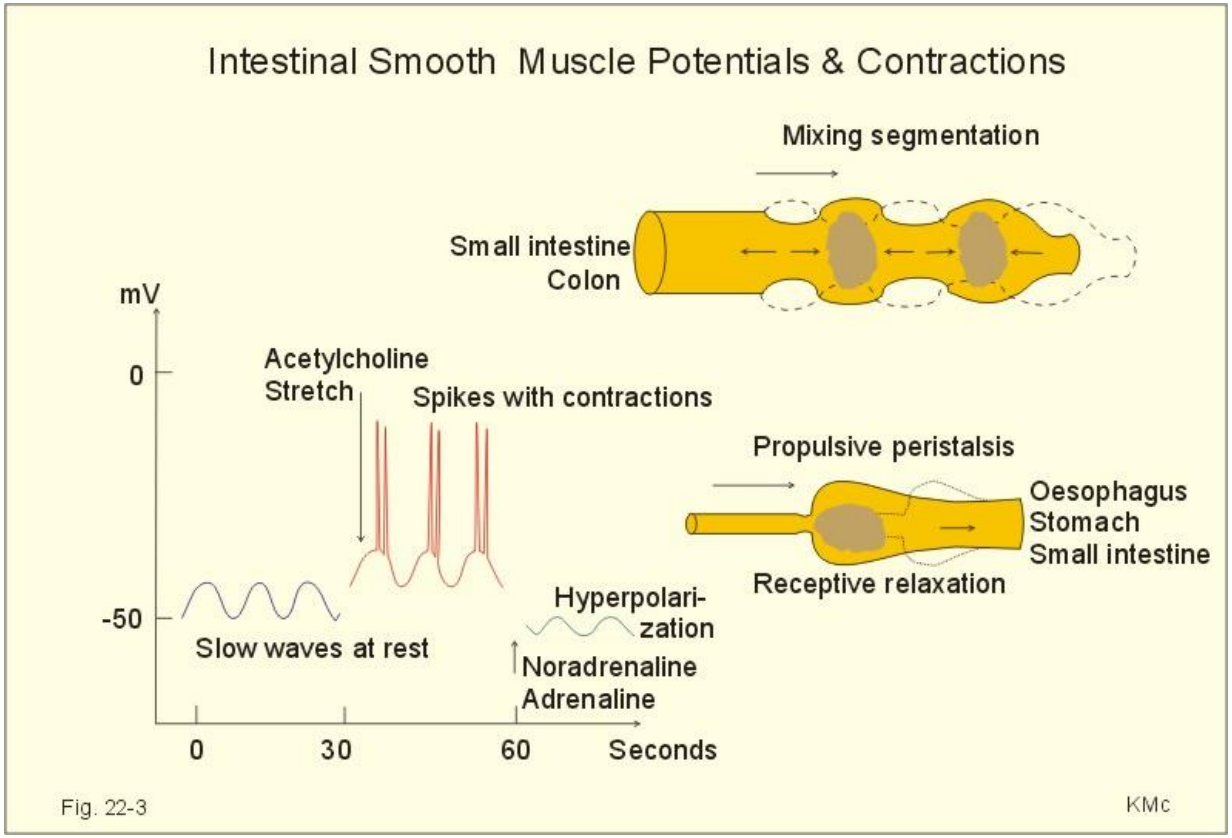
Serotonin

Secretin

Somatostatin

VIP

Regulation of GI Motility



http://www.zuniv.net/physiology/book/chapter22.html

SECTION III

OBJECTIVE

Understand the Ontogeny of Gastrointestinal Motility

EMBRYOLOGIC ASPECTS OF MOTILITY DEVELOPMENT

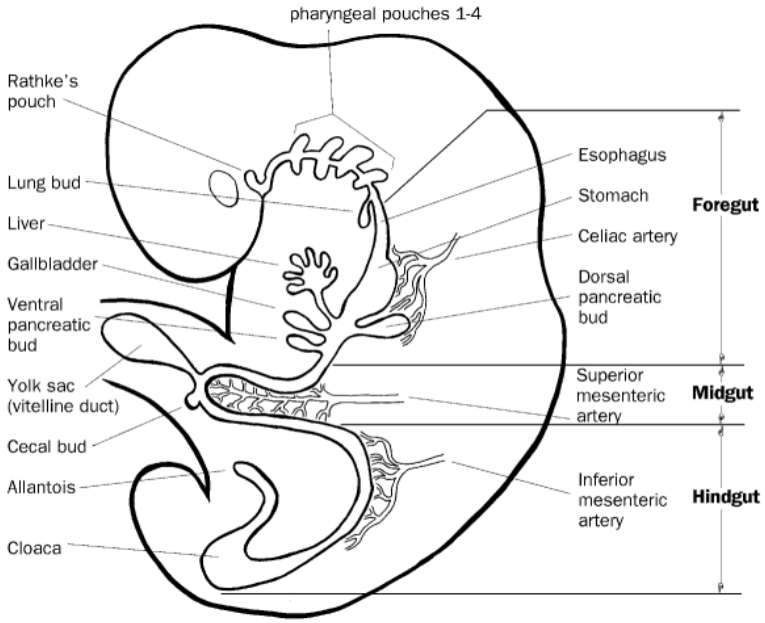


Image from http://www.med.umich.edu/

MATURATION OF MOTOR FUNCTIONS

The average resting UES pressure (mean ± SD) in preterm neonates at 33 weeks postmenstrual age (PMA) is 17 ± 7 mm Hg

In full-term neonates, it is 26 ± 14 mm Hg and in adults, it is 53 ± 23 mm Hg

With growth and maturation, the muscle mass, tone and activity of the UES improve

Similarly, changes in LES length and tone have been observed with growth

MATURATION OF MOTOR FUNCTIONS

- The specific characteristics of UES and primary esophageal peristalsis exist by 33 weeks PMA

- **At 36 weeks PMA, completely propagated secondary peristalsis, greater with liquids than with air, is developed**

- **Although fetal peristalsis is recognized and the muscles and neural structures are present by 32 weeks gestation, local neural transmission and integration of peristalsis mature throughout fetal life and *continue to develop during the first postnatal year***

Maturation of motor functions

- **The gastric compliance is low in the first hours of life and is normal by 3 days (Zangen T et al, 2001)**
- **Gastric emptying is not altered by feeding temperature or non-nutritive sucking**
- **Calorically denser formula and infant massage (vagal mediation) hastens gastric emptying.**
- **Bolus feedings delay gastric emptying due to rapid distention**

MATURATION OF MOTOR FUNCTIONS

- **The absence of the MMC in the very preterm infant <32 weeks gestation**
  - appears to result from immaturity of motor patterns,
  - absence of the motilin receptor, and
  - absence of fluctuating levels of motilin

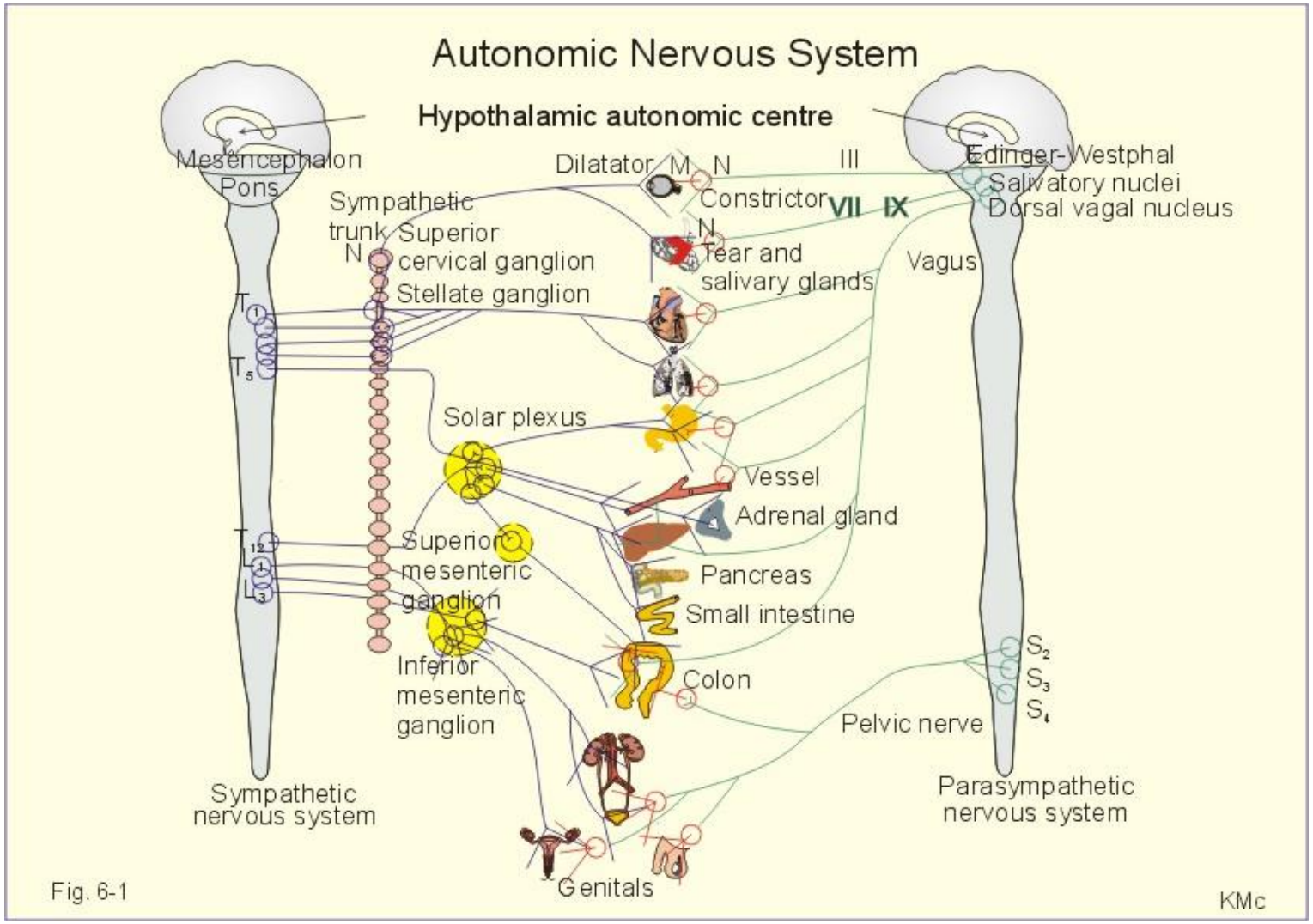
- **There is a lack of data on colonic motility in preterm human infants**

SECTION IV

OBJECTIVE

Understand the Nonpeptide Neurotransmitters that control Gastrointestinal Motility

AUTONOMIC NERVOUS SYSTEM REGULATION OF MOTILITY



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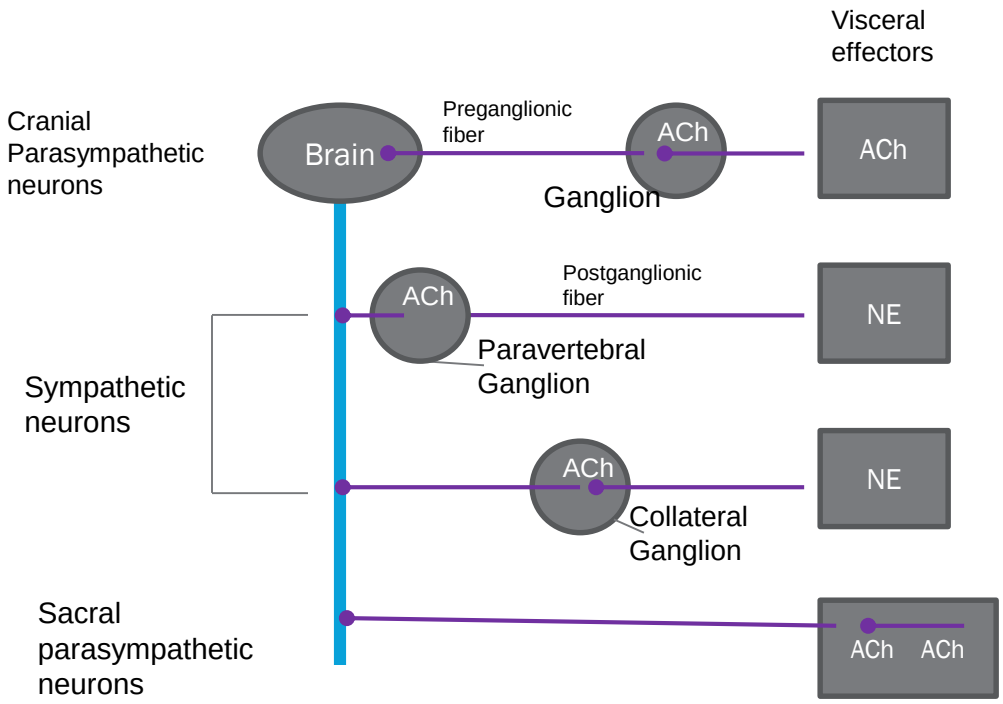
ACETYLCHOLINE AND NOREPINEPHRINE



ACh = acetylcholine (cholinergic)
NE = norepinephrine (adrenergic)

DOPAMINE

Dopamine is the predominant catecholamine neurotransmitter

Dopamine is synthesized from Tyrosine by tyrosine hydroxylase

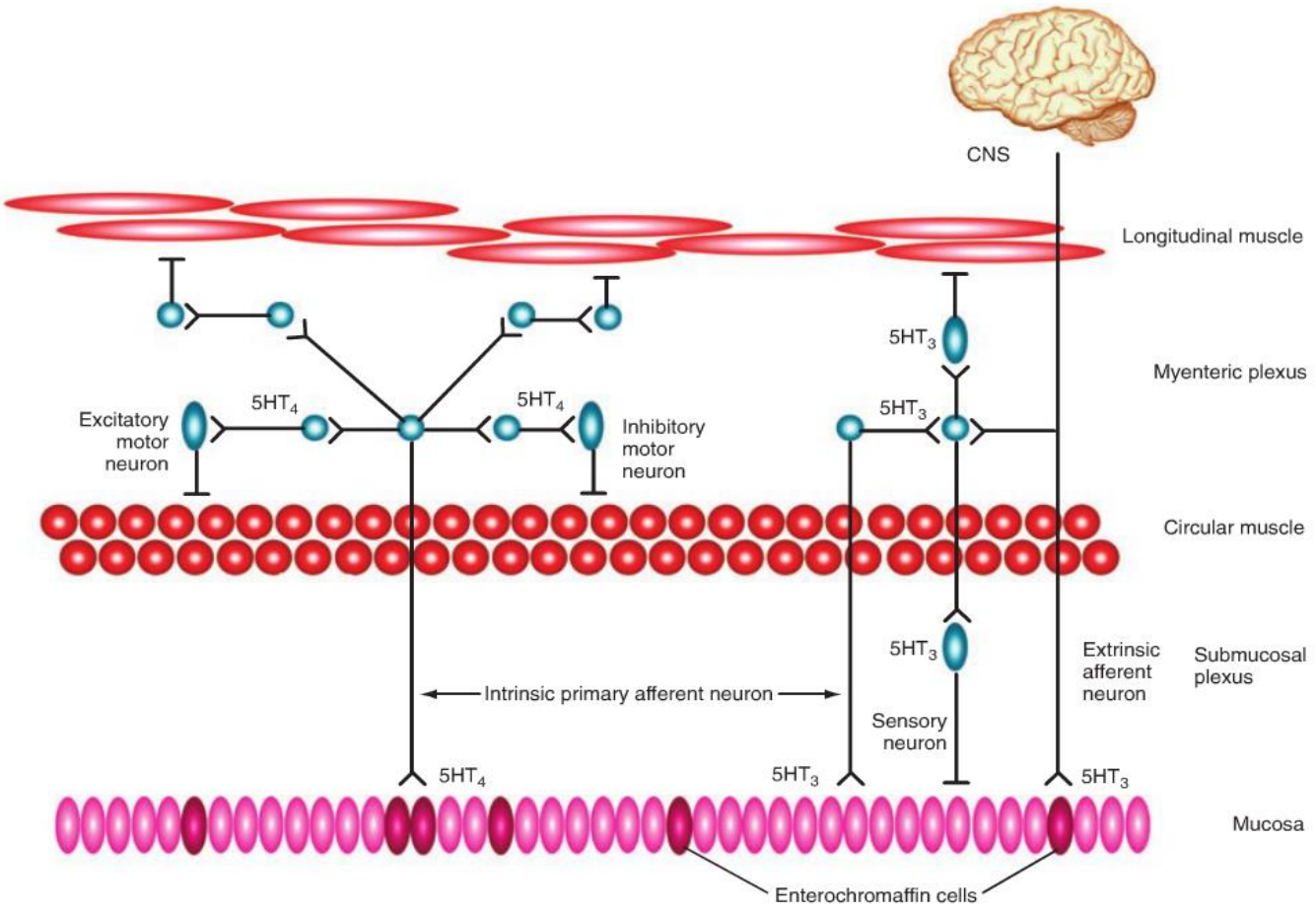
Dopamine actions:

- Central: regulates food intake and vomiting reflex,
- Peripherally: controls hormone secretion, vascular tone, and gastrointestinal motility

Dopamine acts via two distinct receptor subtypes: types 1 and 2

- The presynaptic Dopamine receptors have an excitatory response, occurring at a low agonist concentration
- The postsynaptic receptors mediate inhibitory effects

SEROTONIN



(Modified from Talley NJ: Serotoninergic neuroenteric modulators. Lancet 358:2061, 2001).

EFFECT OF 5HT RECEPTORS ON GI MOTILITY

Receptor / gut segment	Lower esophageal sphincter	Stomach	Small intestine	Large intestine	Rectum
1	-	–	-	–	–
2	?	-	-	-	-
3	-	-	-	-	?
4	-	-	-	– -	–
7	?	?	-	–	–

– *- inhibition of motility or tone,* - *- stimulation of motility or tone,* ? *- unknown effect.*

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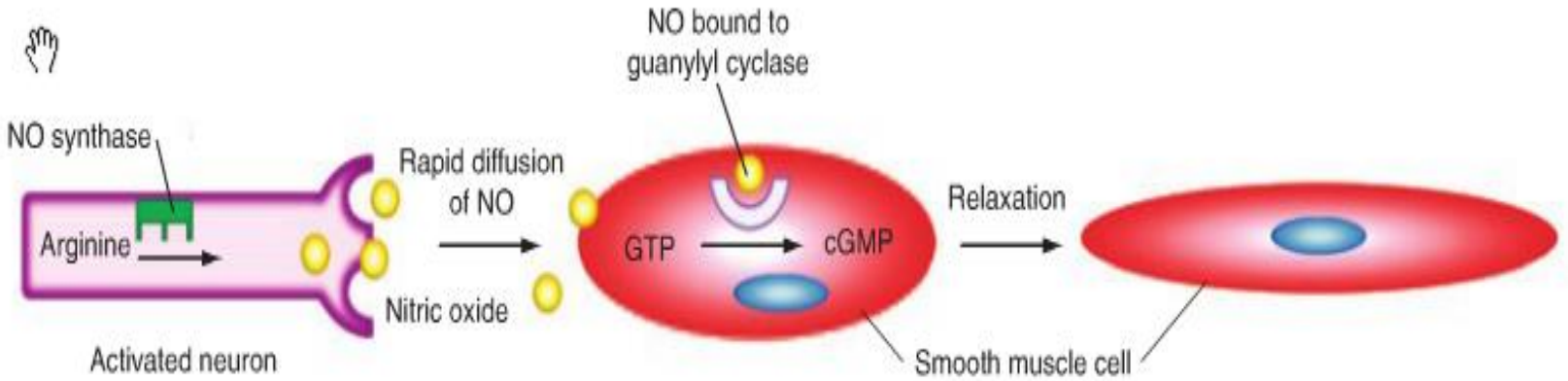
NITRIC OXIDE



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NITRIC OXIDE

Impaired NO synthesis of the myenteric plexus seems to be an important contributing factor to the pathogenesis of

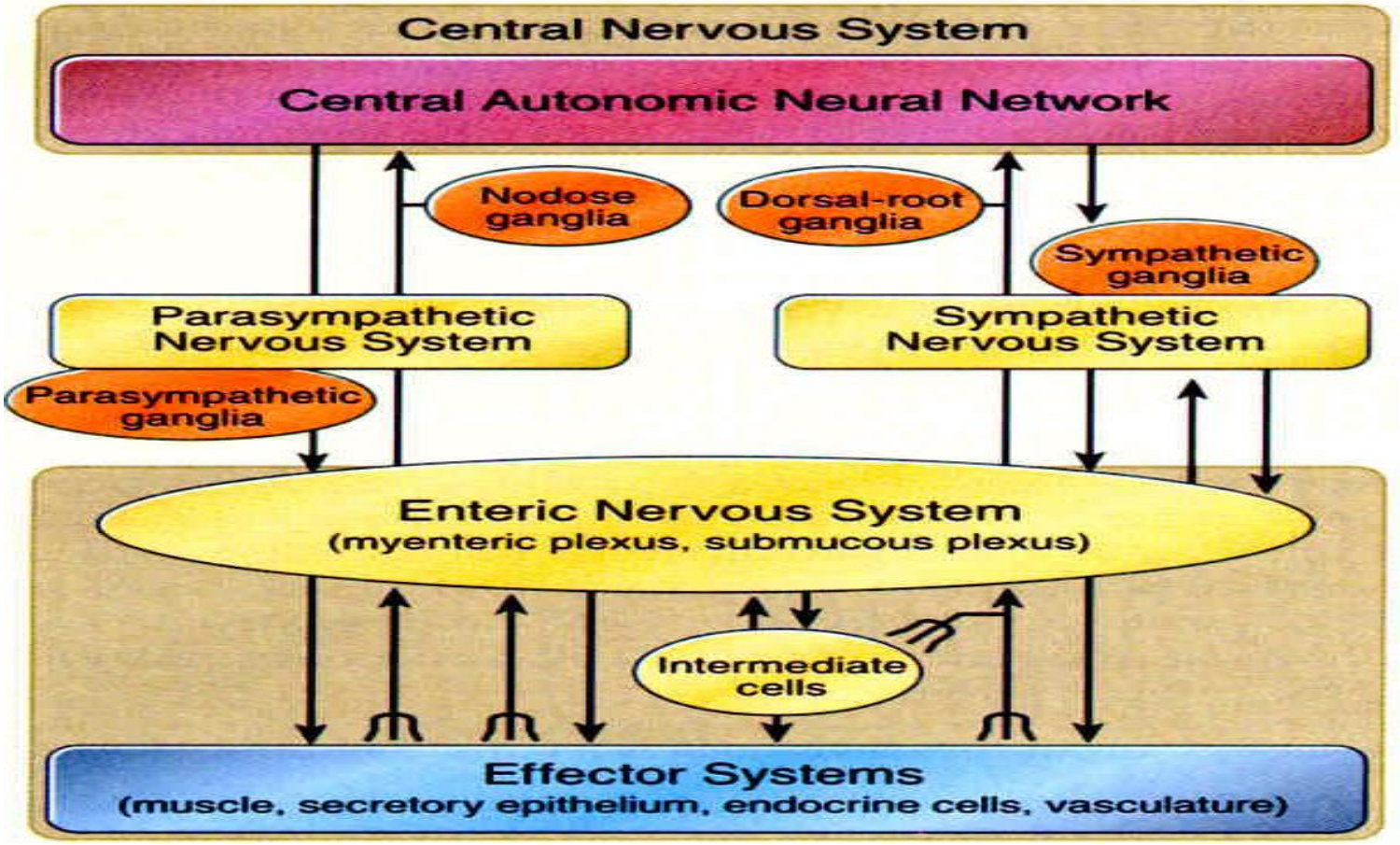
- **Achalasia**
- **Diabetic gastroparesis**
- **Infantile hypertrophic pyloric stenosis**
- **Hirschsprung's disease**
- **Chagas' disease**

SECTION V

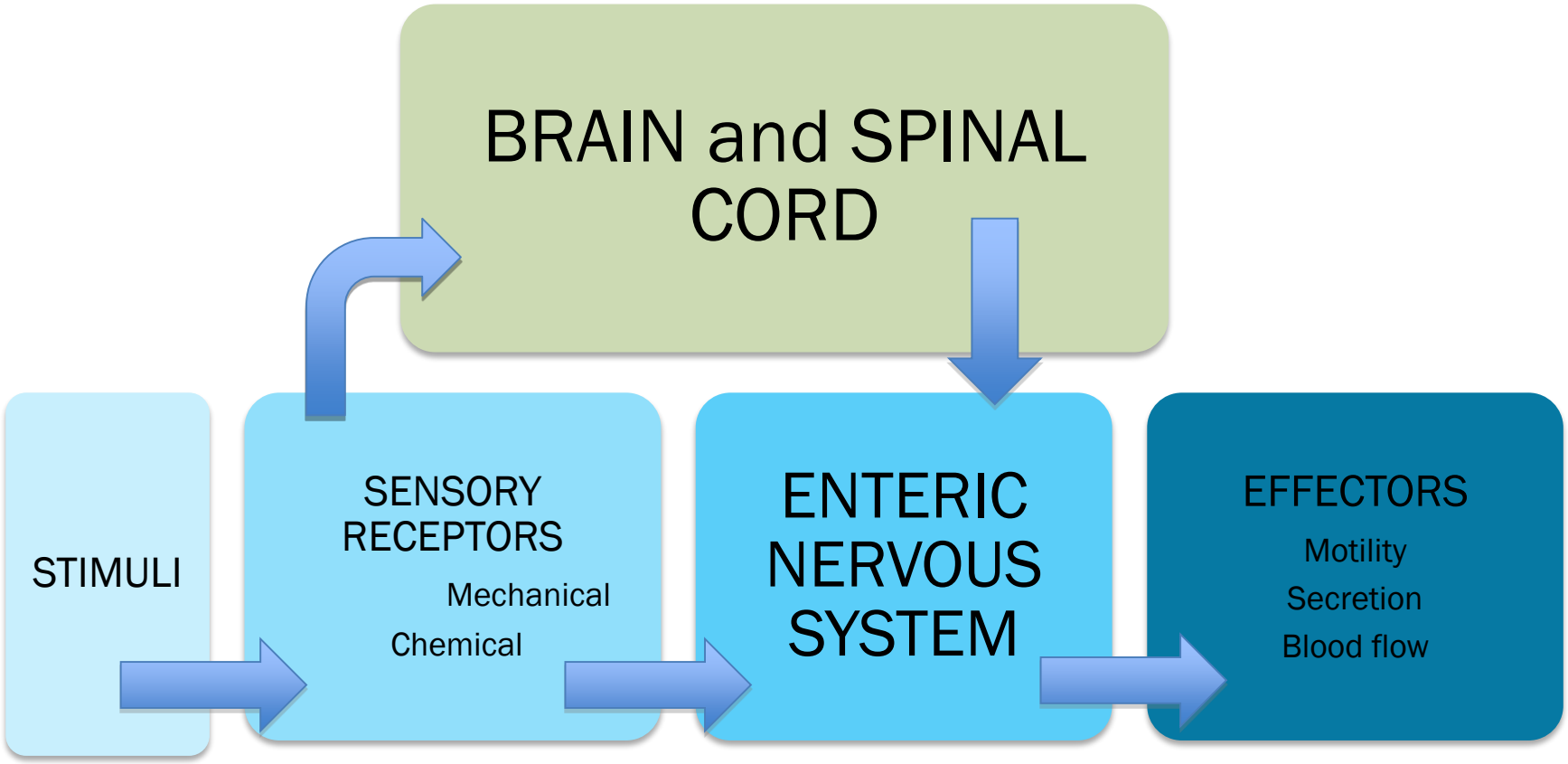
OBJECTIVE

Understand the Role of Extrinsic Nervous System and the Enteric Nervous System in modulating Gastrointestinal Motility

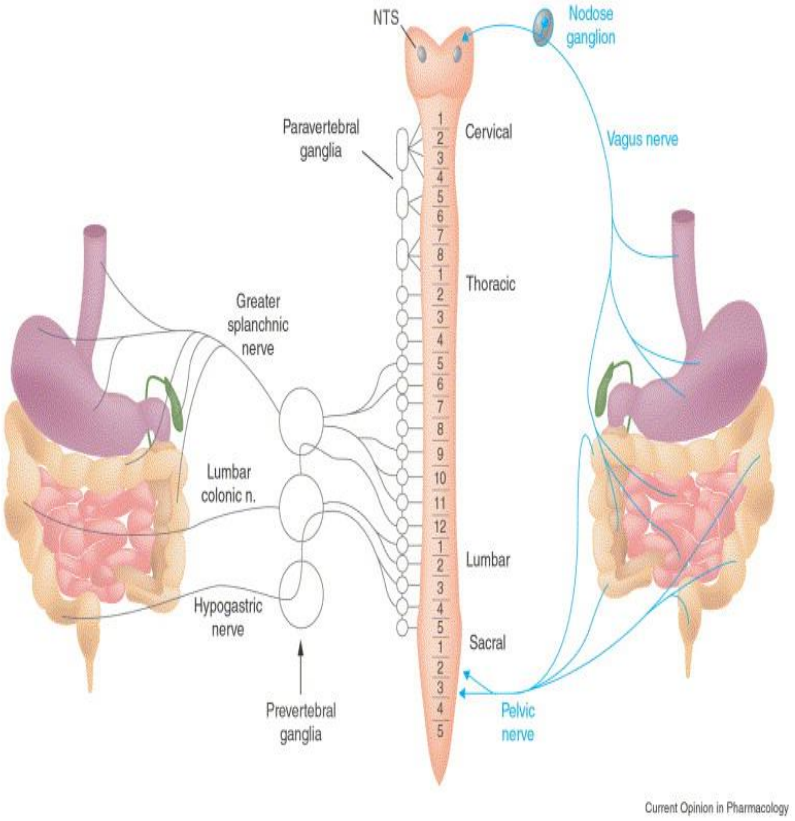
ENTERIC NERVOUS SYSTEM

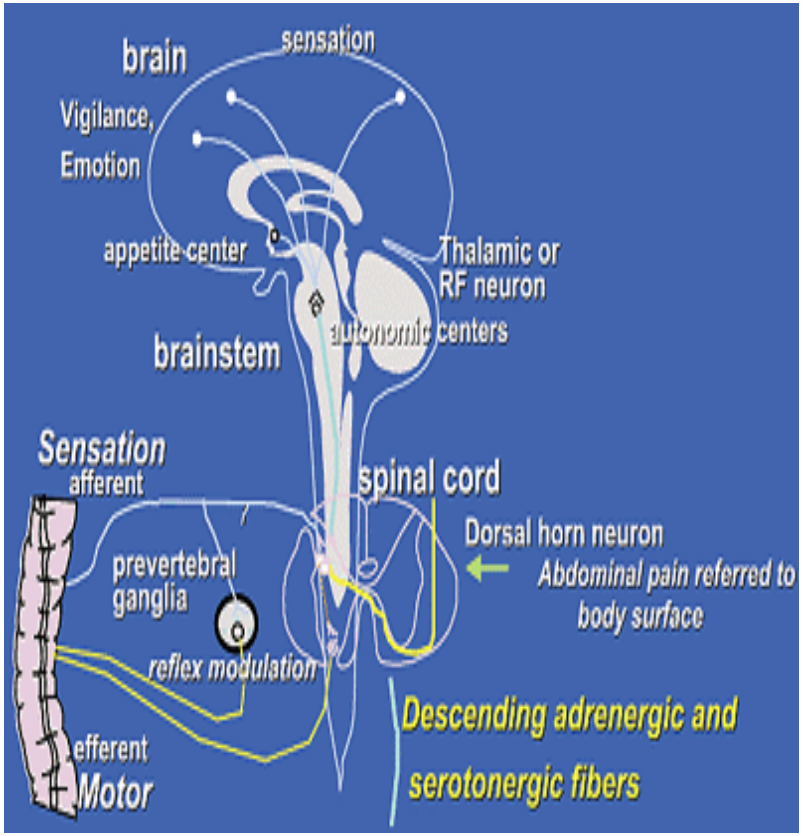


BRAIN GUT AXIS

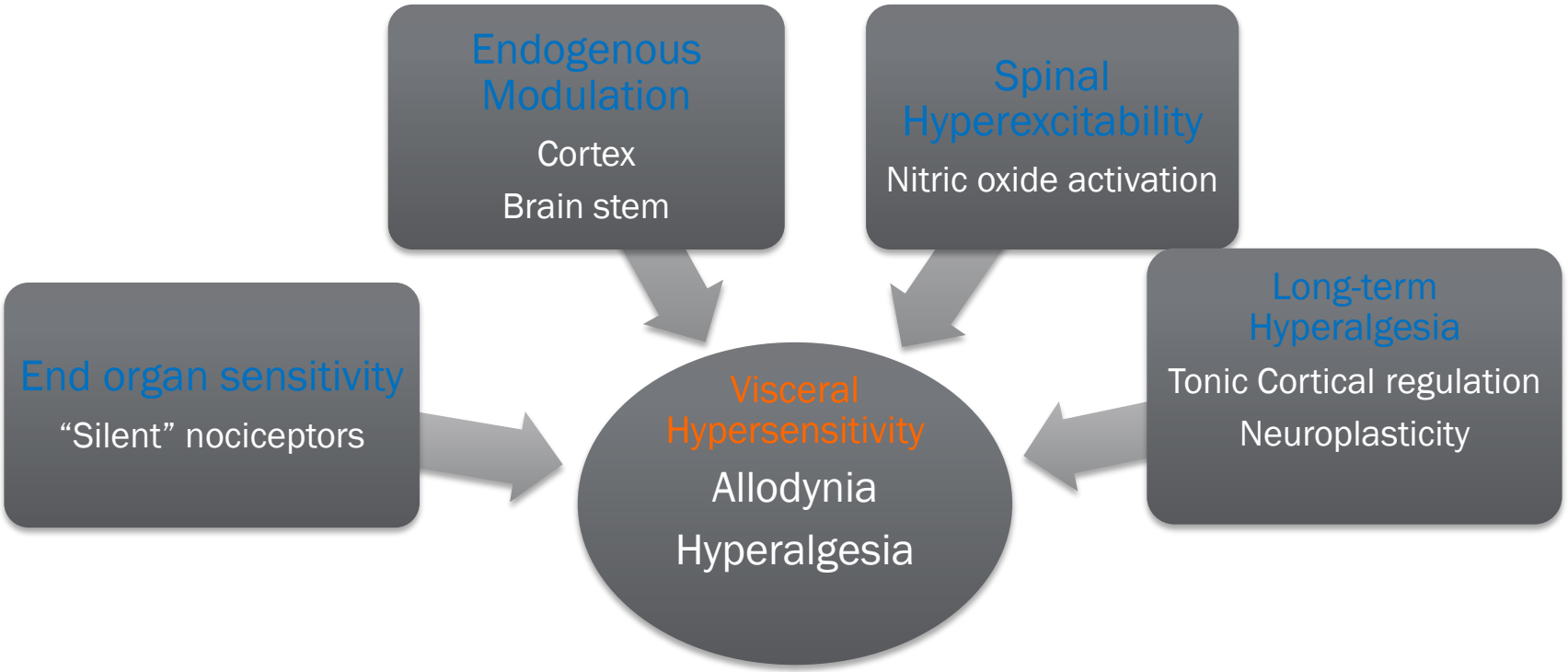


SENSORY INNERVATION AND VISCERAL PAIN

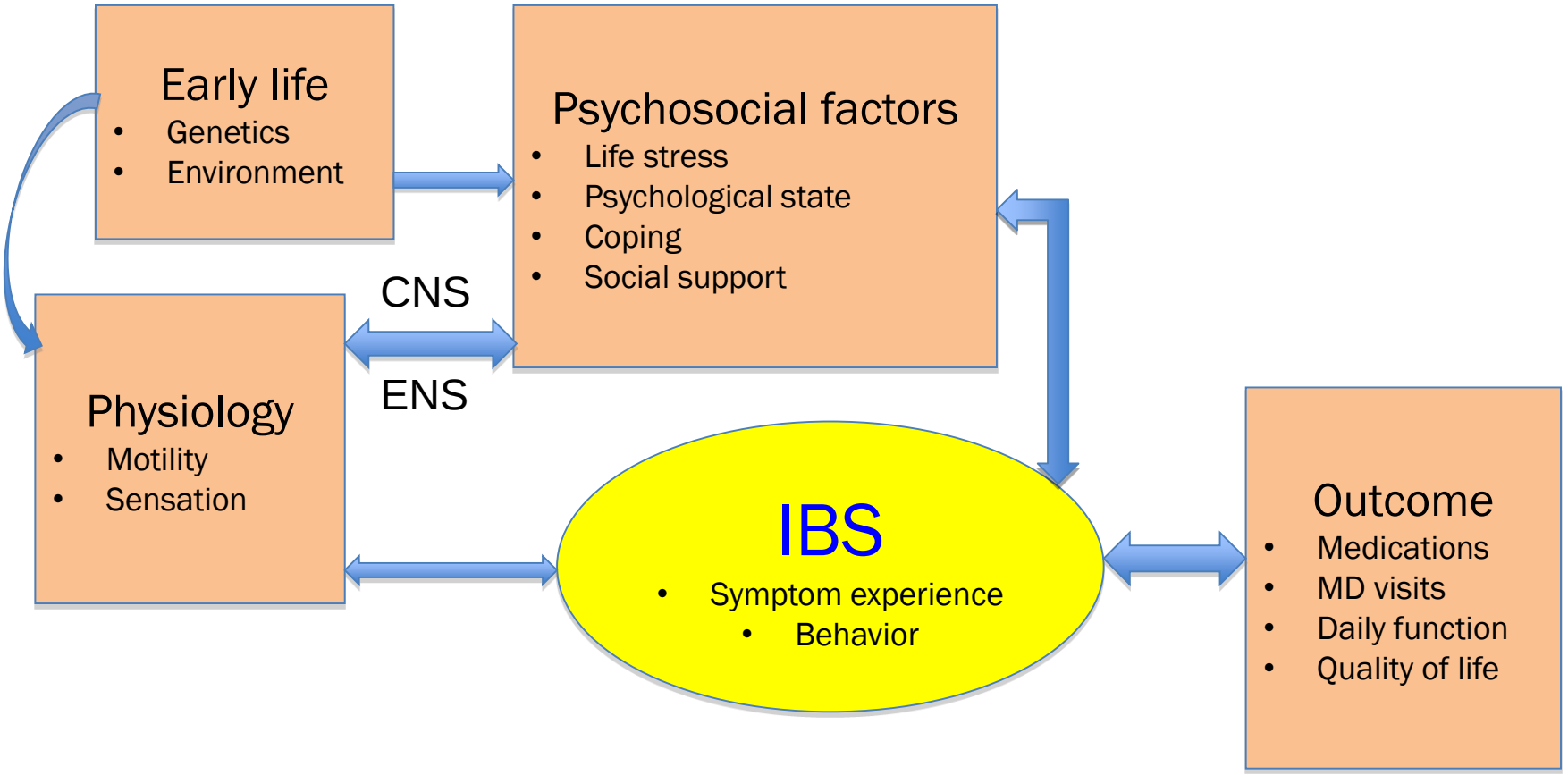




VISCERAL HYPERALGESIA



BIOPSYCHOSOCIAL MODEL OF DISEASE IN IBS



BRAIN/GUT INTERACTION IN POST-INFECTIOUS IBS

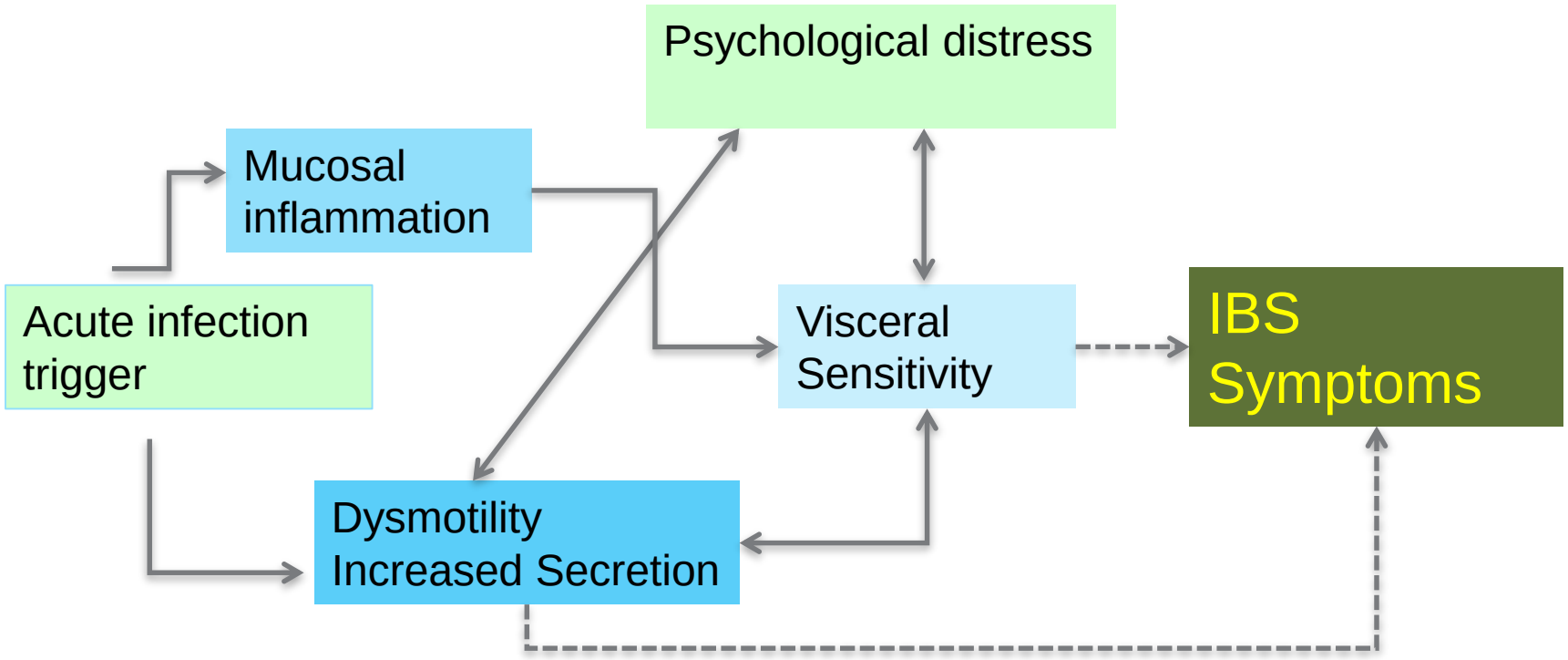


Image from: Drossman, Gut 1999; 44: 306 Gwee et al. Gut 1999: 44: 400

SUMMARY

Gastrointestinal smooth muscle cells contract as a unit because of anatomic and electrical coupling

Smooth muscles contractions may last for a few seconds *(phasic)*, or minutes to hours *(tonic)*

Material moves through the gastrointestinal (Gl) tract from regions of higher to lower intraluminal pressure

Interstitial cells of Cajal are the pacemaker cells of the gut leading to regularly occurring depolarizations (3-5/ min) called *slow waves*

SUMMARY

Primary peristaltic contractions **are initiated in the esophagus by swallowing and are responsible for moving most material through the esophagus;** ***secondary peristaltic contractions*** **initiated by distension and local reflexes remove any "leftover" material**

The principal motility function of the orad (proximal) stomach is ***receptive relaxation*****, the caudal (distal) stomach is mixing, trituration and emptying**

Small intestinal motility is characterized by brief, irregular contractions interrupted during fasting approximately every 60-90 min by a wave of intense contractions, migrating motor complexes, (MMCs) that sweeps the entire length of the small intestine.

SUMMARY

- **The *ileocecal sphincter* relaxes when the ileum is distended and contracts when the colon distends, thus allowing material to enter the colon and preventing reflux**

- **The principal movements of the *proximal colon* are weak peristaltic contractions that permit storage of contents and absorption of most remaining water**

- **Two or three times a day, a peristaltic mass movements, *High Amplitude propagating contractions*, propel a significant amount of material into the distal colon or rectum. Distension of the rectum triggers the rectosphincteric reflex**

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