ANATOMY, PHYSIOLOGY & PATHOLOGY NOTES OF THE

GASTROINTESTINAL SYSTEM

SECOND EDITION

PRE-SUMMARIZED
READY-TO-STUDY
HIGH-YIELD NOTES

FOR THE TIME-POOR
MEDICAL, PRE-MED,
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Table Of Contents:

What's included: Ready-to-study anatomy, physiology and pathology notes of the gastrointestinal system presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your iPad or tablet PC.

File List:

- Meckel's Diverticulum
- Miscellaneous GI Tumours
- Oesophageal Varices
- Oesophagitis
- Pancreatic Cancer
- Pancreatitis
- Parasitic Gut Infections
- Pilonidal Sinus
- Polyps & Colon Cancer
- Pseudomembranous Colitis
- Radiation Enteritis
- Rectal Bleeding DDX
- Secondary Liver Diseases
- The Acute Abdomen - Surgical Approach
- TORONTO - Gastroenterology
- TORONTO - General Surgery

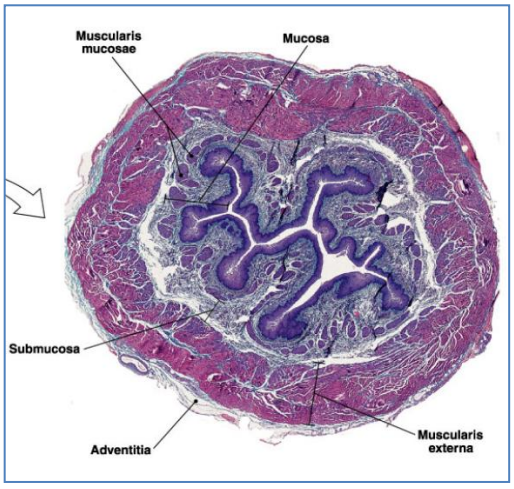
BASIC A&P
GASTROINTESTINAL SYSTEM

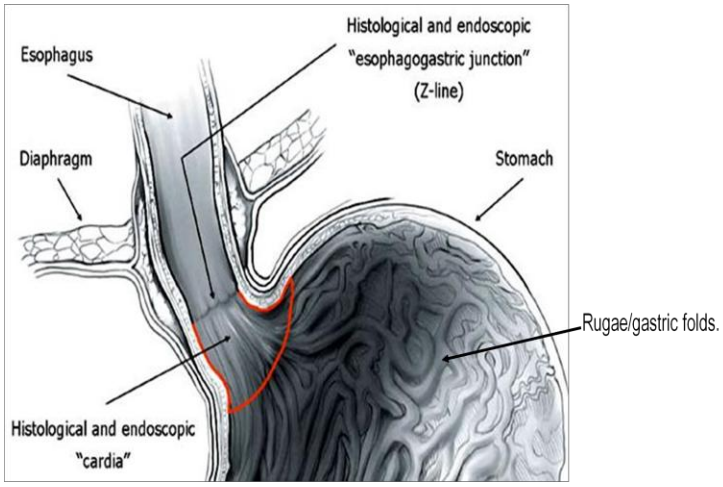
Functions:

- Ingestion (via mouth)
- Mechanical breakdown
- Propulsion – swallowing
    - Initiated voluntarily
    - Continued via peristalsis
        - Contractile waves of smooth muscle
- Chemical Digestion
    - Molecular breakdown
    - Via enzymes + acids
- Secretion (mucus/bile/alkaline)
- Absorption
    - Passage of nutrients from GI into blood/lymph
- Excretion/Defecation
    - Elimination of indigestible substances

Oesophagus:

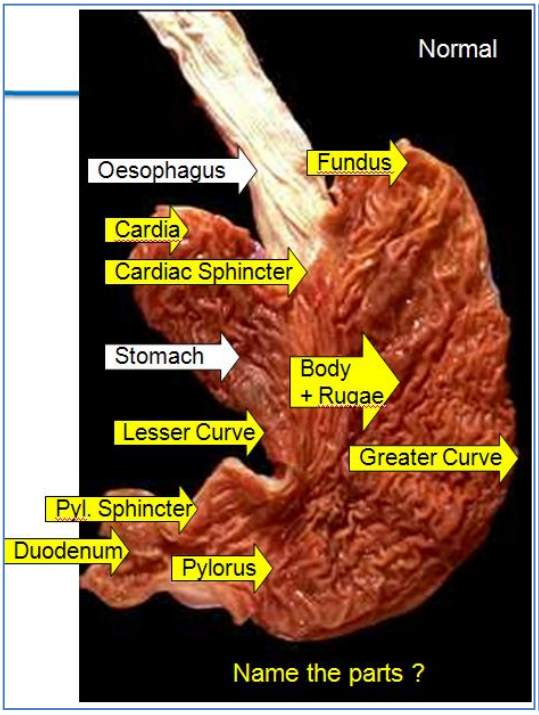
- **Macro Anatomy:**
    - Approx 25cm long
    - Pierces the diaphragm at the **oesophageal hiatus** to enter abdomen
    - **Sphincter: 'Gastro-oesophageal' / 'Cardiac'** (Malfunction → GORD)
- **Histology:**
    - **Oesophagus:** Stratified Squamous
    - **Oesophago-Gastric Junction (Z-Line):** Transition to Cuboidal Gastric Epithelium
    - Upper 1/3 = striated muscle
    - Lower 2/3 = smooth muscle

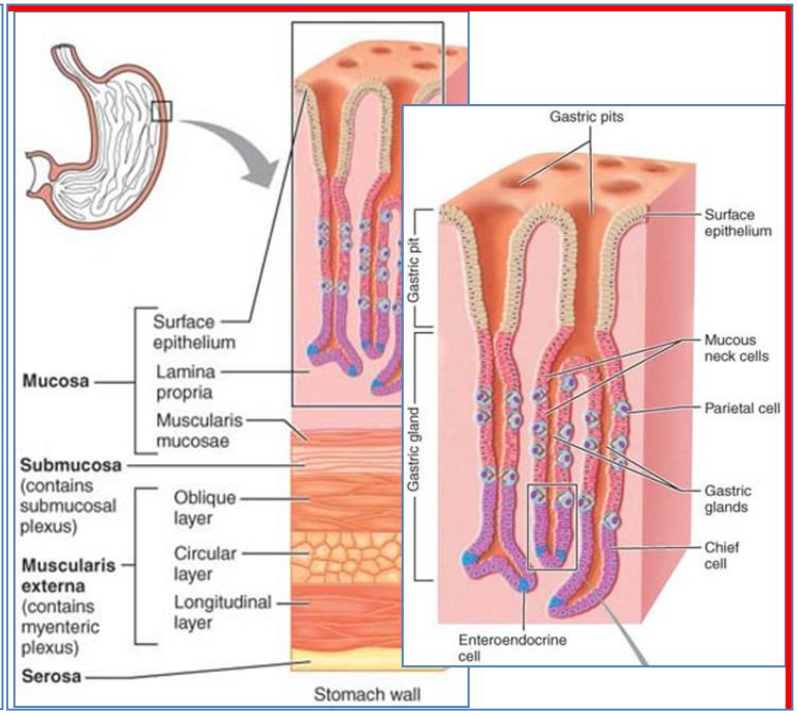




Stomach:

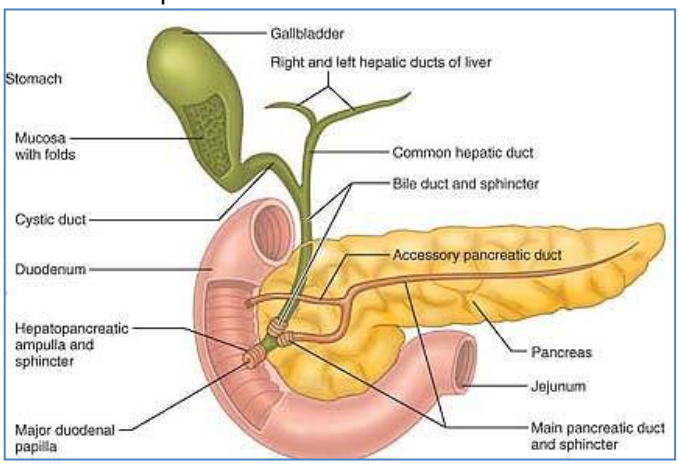
- **Macro Anatomy:**
    - See Picture
- **Histology:**
    - Gastric Pits
    - Simple Cuboidal (Protected by Mucus & Alkaline Secretion) + Goblets
    - + Parietal Cells → Secrete Acid + Intrinsic Factor (for B12 Absorption)
    - + Chief Cells → Secrete Pepsinogen (Precursor to Pepsin → Digests Collagen)
    - + Endocrine Cells (G-Cells → Stimulate Parietal Cells; D-Cells → Inhibit G-Cells)

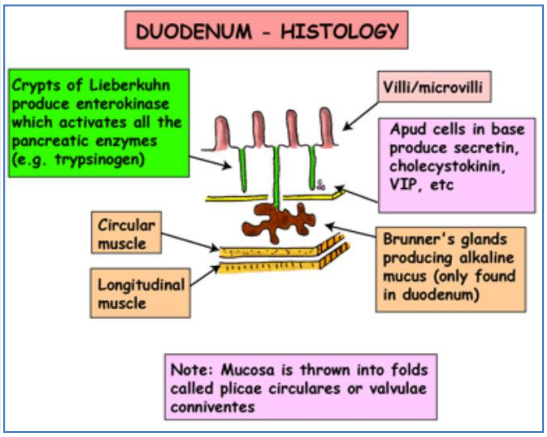




Duodenum:

- **Macro Anatomy:**
  - C-Shaped part of SI from Stomach → Jejunum
  - "Hepatopancreatic Sphinct./Sphinct.of Oddi/Duodenal Ampulla/Ampulla of Vater"
- **Histology:**
  - Microvilli & Crypts of Lieberkuhn
  - Simple Cuboidal + Goblet Cells + "Brunner's Glands" → Secrete ↑↑Alkaline Mucus



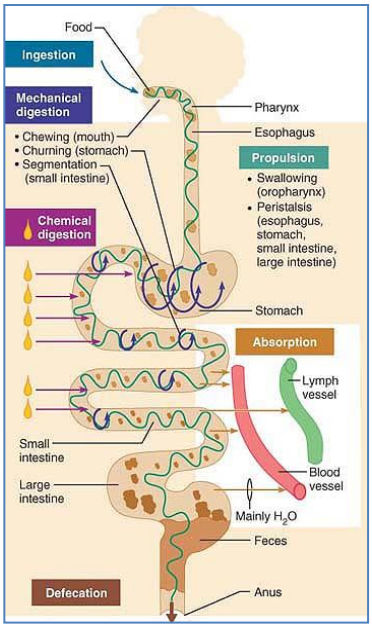


- **Physiology**
  - **Motility:**
    - **Peristalsis –** Oesophagus (5-10sec), Stomach (1-3hrs).
      - Combination of Segmentation & Pendular Contraction.
      - **Segmentation**
        - Contractions of circular muscle
      - **Pendular**
        - Contractions of longitudinal muscles
        - Shortens & lengthens tube.
    - **Migrating Motor Complex –** Small Intestines (7-9hrs)
    - **Mass Movement –** Large Intestines (25-30hrs)
    - **Defecation Reflex –** Rectum & Anus (After 40hrs)

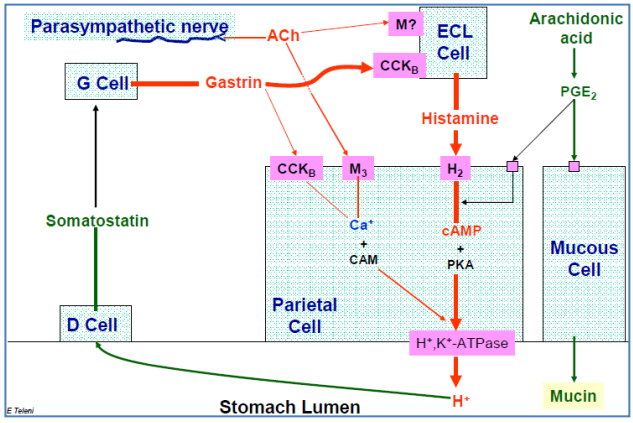
  - **Digestion Phases & Enzymes:**
    - **Mechanical Digestion:**

- Chewing
- Stomach

- **Chemical Digestion:**
  - Saliva – Salivary Amylase (Simple Carb Digestion)
  - Stomach – Acid + Pepsin (Protein Digestion)
  - Liver – Bile (Fat Emulsification)
  - Pancreatic Amylase – (Carb Digestion)
  - Pancreatic Lipase – (Fat Digestion)
  - Pancreatic Proteases – (Protein Digestion)
  - Pancreatic Nucleases – (DNA/RNA Digestion)
- **Intestinal Absorption:**
  - Fluid + Nutrients → Blood Vessels
  - Fluid + Fats → Lymph Vessels

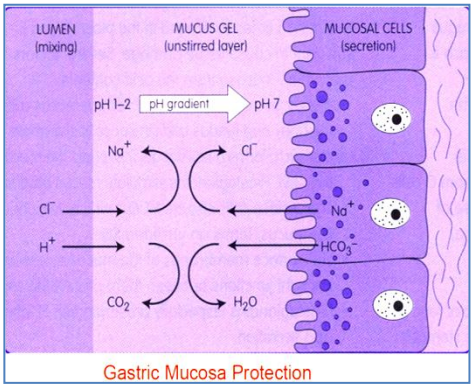


- **<u>Hormonal Control of</u>**
  - **<u>Gastric Acid Secretion:</u>**
    - **Cephalic Phase**
      - Gastric Secretion *Before* a Meal – Stimulated by taste/smell/thought:
        - G-Cells → **Gastrin** Secretion →
          - ↑Parietal-Cell HCl Secretion
          - ↑Cheif-Cell Pepsin Secretion
    - **Gastric Phase**
      - Food has entered & distended the stomach.
        - Distension of Stomach → Further **Gastrin** Secretion
        - Low Acidity Stimulates G-Cells → **Gastrin**
    - **Intestinal Phase**
      - Acidic Chyme enters Duodenum → Release of **3 local Hormones**:
        - **Secretin** → Stimulates Pancreas → Bicarbonate Secretion
        - **Cholecystokinin** → Stimulates Gallbladder → Bile Secretion
        - **Vasoactive Intestinal Peptide (VIP)** → ↓Gastric Acid Production



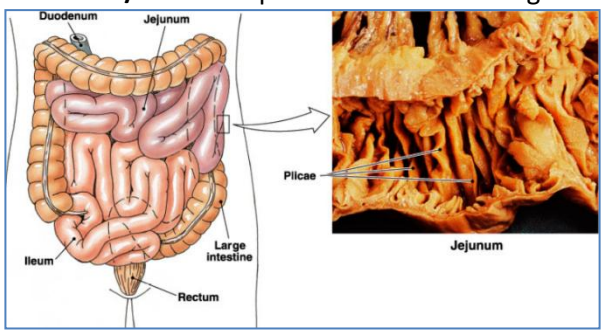
- **<u>Gastric Emptying:</u>**
  - Regulated by the Duodenum
  - Fatty Foods/Alcohol/Caffeine/Smoking → Delayed Gastric Emptying

- **<u>Maintaining Luminal Homeostasis & Integrity</u>**
  - **'Attackers':**
    - **Acid:** Parietal Cells → HCl + Intrinsic Factor
    - **Pepsinogen:** Chief Cells → Pepsinogen → Pepsin
  - **'Defenders':**
    - **Mucous:** Goblet Cells → Mucin → mucous →Barrier from Acid + Lubrication.
    - **Tight Junctions:** Prevents Leakage of Mucous/Acid & Infection.
    - **High Cell Turnover:** Stem-Cell Regeneration in Gastric Pits
    - **Alkaline Fluid:** Brunner's Glands in Duodenum → Secrete Alkaline Fluid
    - **Bile:** Hepatocytes → Bile Salts (Emulsifiers) + Alkaline
    - **Pancreatic Bicarb:** Exocrine Pancreatic Cells → Bicarb Secretion → Neutralises

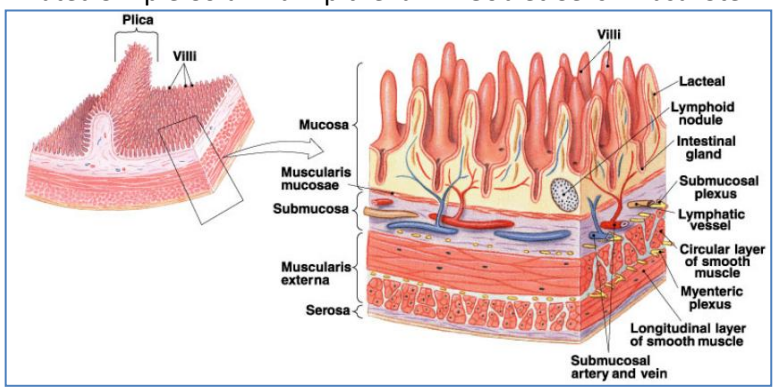


Anatomy:

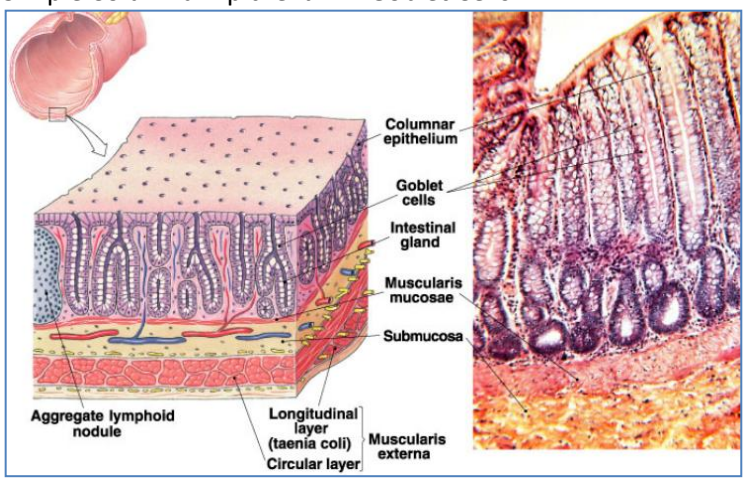
- **Small Intestine:**
  - **Macro:**
    - **Duodenum** – C-shaped
    - **Jejunum** – High surface area (plicae, villi & microvilli) – **Nutrient** Absorption.
    - **Ileum** – Lower surface area (fewer plicae, villi & microvilli) – **Fluid** Absorption
    - **Ileo-cecal Junction/Valve:** empties into Cecum of large intestine.



  - **Micro:**
    - Viliated Simple Columnar Epithelium + Goblet Cells + Basal Stem Cells



- **Large Intestine:**
  - **Macro:**
    - **Ileocecal valve → Cecum + Appendix**
    - **Ascending Colon** → Right Colic Flexure
    - **Transverse Colon** →Left Colic Flexure
    - **Descending Colon**
    - **Sigmoid Colon**
    - **Rectum** → Anal Canal
    - **NB: Teniae Coli** – 3 ribbons of smooth muscle along the colon's entire length
    - **NB: Haustra** – Sections slows down the movement of wastes
  - **Micro:**
    - Simple Columnar Epithelium + Goblet Cells
    -



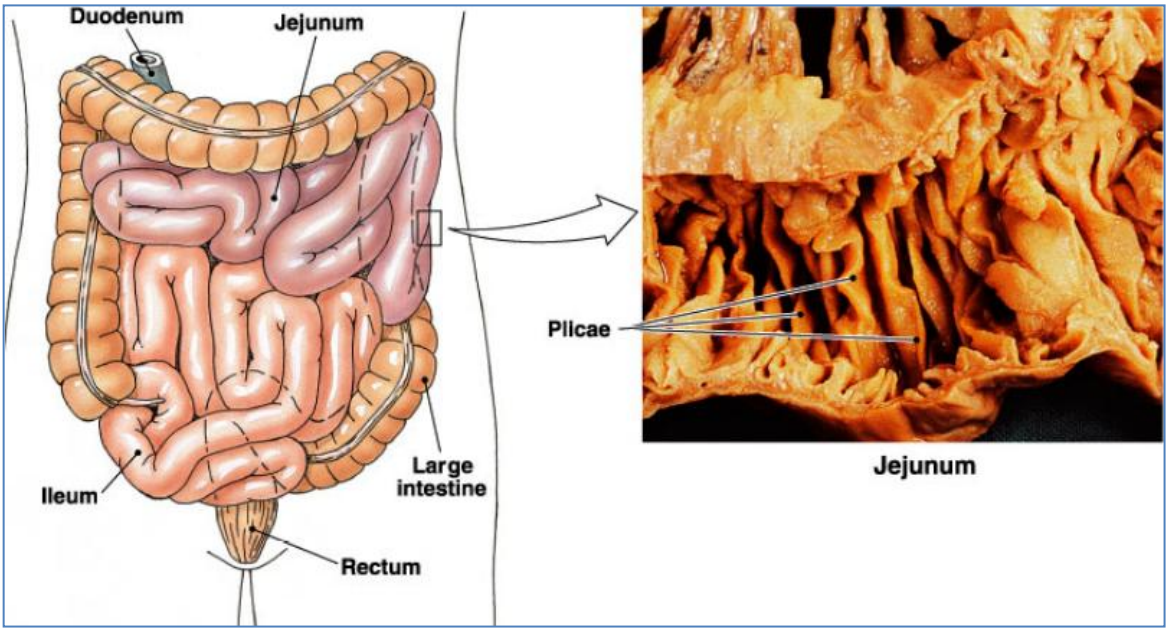
Physiology:

- **Motility:**

- **Small Intestine:**
  - **Peristalsis: "*Migrating Motor Complex*"**
  - Initiated by pacemaker cells in smooth muscle layer
    - 12-14 contractions / minute
    - →Initiates peristalsis in duodenum → lasts for about 50-70cm then dies out.
    - Successive waves are initiated further along small intestines (Hence 'migrating').
    - Takes approx 2 hrs for waves to reach Ileocecal valve.
    - Process then repeats itself → sweeps food remnants, bacteria, etc.
- **Large Intestine:**
  - **Peristalsis: "*Mass Movements*"**
  - Inactive most of the time
  - When presented with food→colon becomes motile
  - Long, slow-moving, but powerful contractile waves.
  - Move over large areas of colon
  - 3x Daily
  - Force contents towards rectum
- **Rectum:**
  - ***Defecation Reflex***
  - Rectum wall stretches → initiates <u>defecation reflex:</u>
  - Force on anal canal signals brain – 'the urge'
  - Sigmoid-Colon & Rectum contracts + Internal Anal Sphincter relaxes

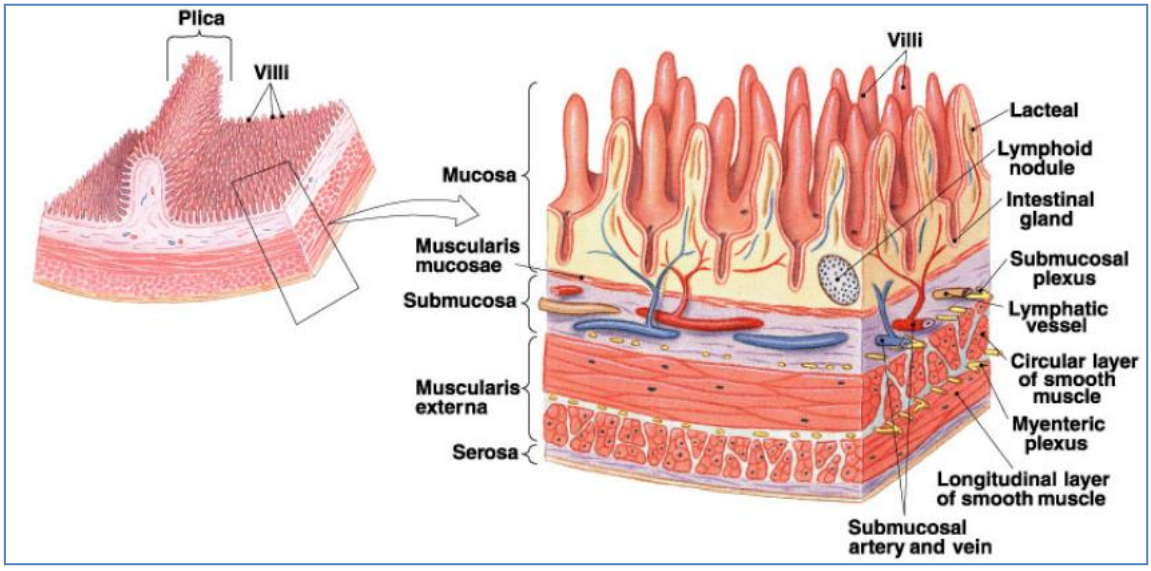
- **<u>Secretions:</u>**
  - **Mouth – 1500mLs:**
    - Saliva
  - **Stomach – 2500mLs:**
    - Acid + Pepsin Solution
    - Mucous
  - **Liver – 500mLs:**
    - Bile (Bicarbonate + Bile Salts + Cholesterol)
  - **Pancreas – 1500mLs:**
    - Bicarbonate – Neutralises Acidity
    - Amylase, Lipase, Proteases, Nucleases
  - **Intestines – 1000mLs:**
    - Intestinal Juice – Slightly Alkaline
    - **Duodenum (Brunner's Glands):**
      - Bicarbonate – Neutralises Acidity
      - Mucous
  - **Colon - Negligible:**
    - Mucous
  - ***NB: Plus 2000mLs Drinking Water, Total = 9000mLs***
- **<u>Absorption:</u>**
  - **Intestines – 7000mLs**
    - NB: VitB12 & Bile Salts – Absorbed by specific transporters in Terminal Ileum
      - (:. Malabsorption of these can occur in Ileal Resection)
  - **Colon – 1500mLs**
  - ***NB: 500mLs Faeces @ 80% water.***
- **<u>Defences:</u>**
  - **Physical –** Mucous, Mucosal Shedding, Constant Movement of Contents
  - **Chemical –** Lysozyme, Defensins, Mucosal IgA, B-Cells, T-Cells, Commensal Bacteria

Anatomy of Small Intestine:



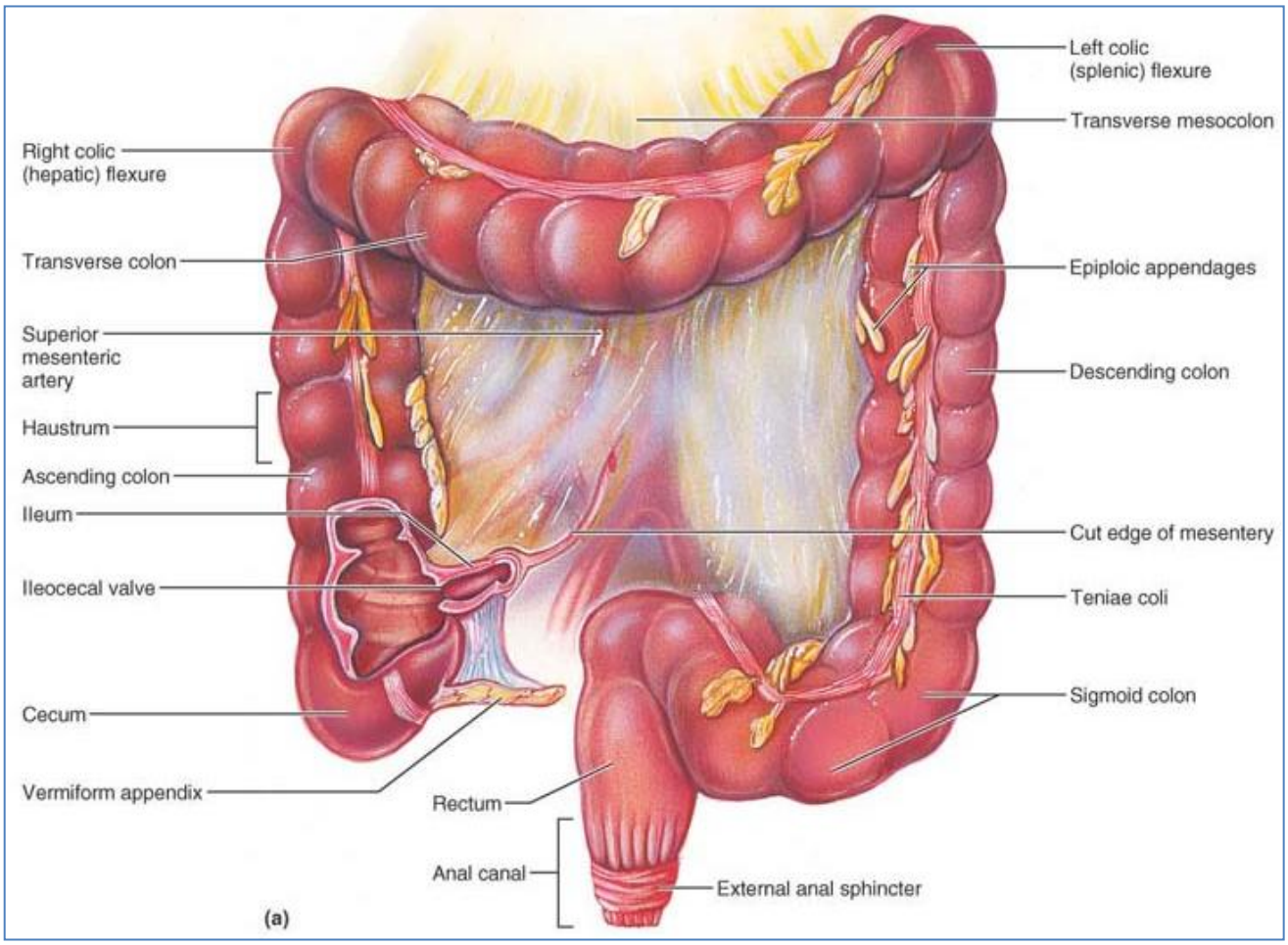
1. **Duodenum** – C-shaped
2. **Jejunum** – High surface area – Maximum **nutrient** absorption (many plicae, villi & microvilli)
3. **Ileum** – Lower surface area – Absorption of **fluids** (fewer plicae, villi & microvilli)
4. **Ileo-cecal Junction/Valve:** empties into Cecum of large intestine.

Intestinal Wall



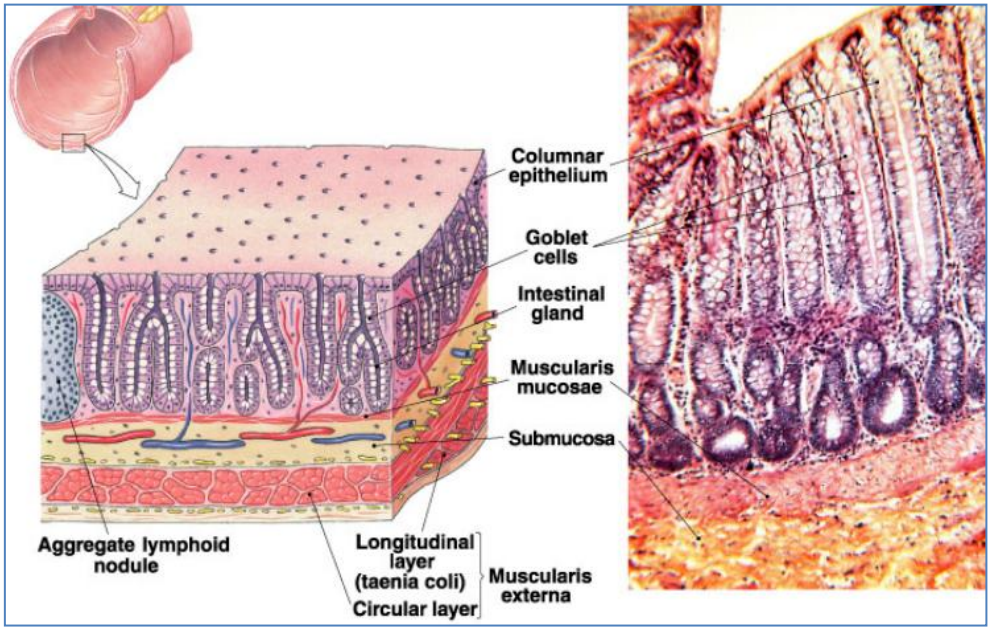
Anatomy of Large Intestine:

- Absorbs H_2O from indigestible food
- Temporarily stores waste
- Eliminates semisolid faeces



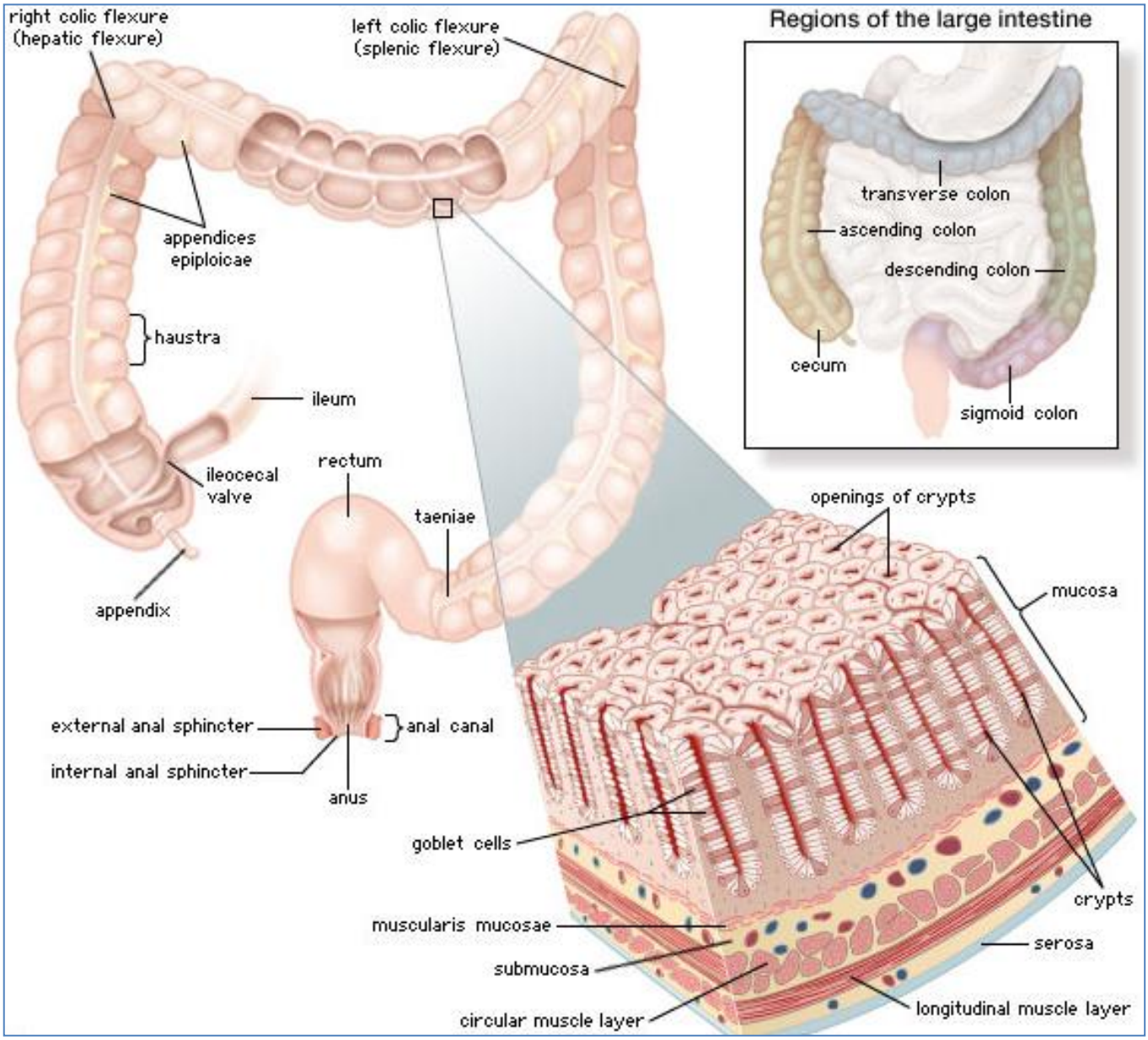
Important Structures

- Ileocecal valve
- Cecum
- Appendix
- Ascending Colon
- Right Colic Flexure
- Transverse Colon
- Transverse Mesocolon
- Left Colic Flexure
- Descending Colon
- Sigmoid Colon
- Rectum
- Anal Canal



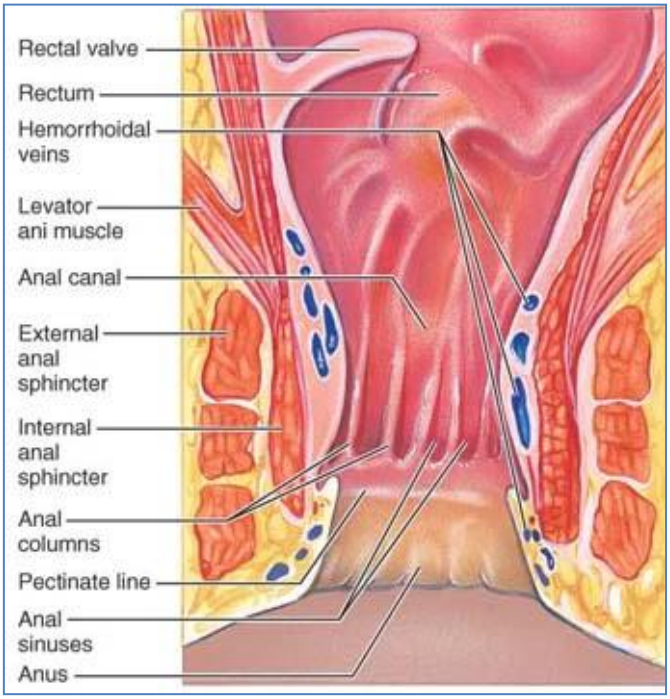
- **Unique Structures**
  - **Teniae Coli** – 3 ribbons of smooth muscle along the colon's entire length
    - Causes the large-intestine wall to form segments (**Haustra**)
  - **Haustra** – slows down the movement of wastes.
    - Aid in packing and compacting
  - **Epiploic Appendages** – fatty pouches of visceral peritoneum (purpose unknown)

Histology of Large Intestine & Rectum:



Anatomy of Rectum & Anus:

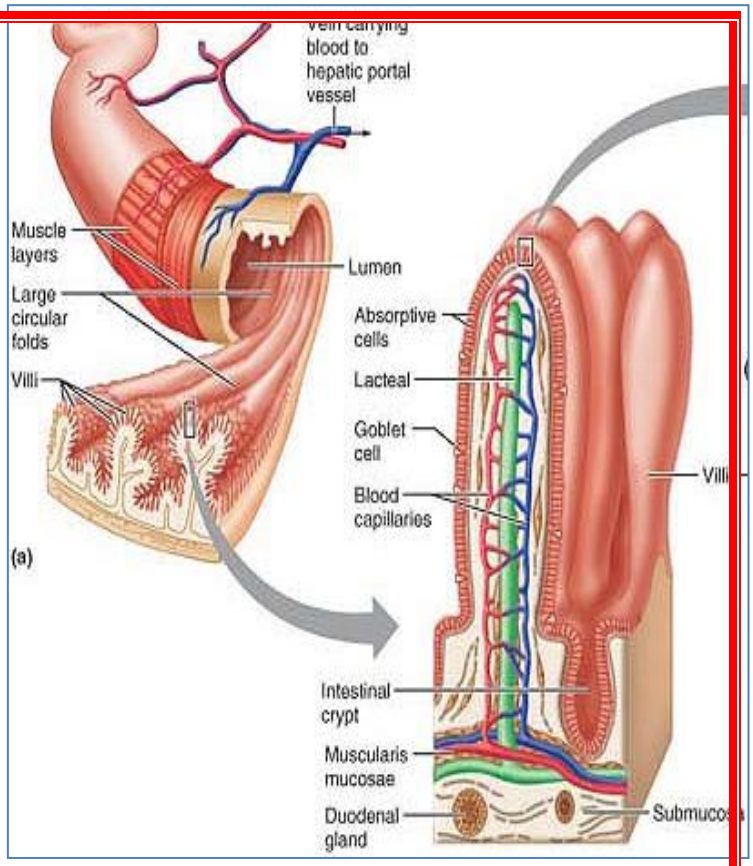
- **Important Structures:**
  - Levator Ani Muscle
  - Anal Canal
  - External anal Sphincter - voluntary
  - Internal anal Sphincter – involuntary
  - Anus

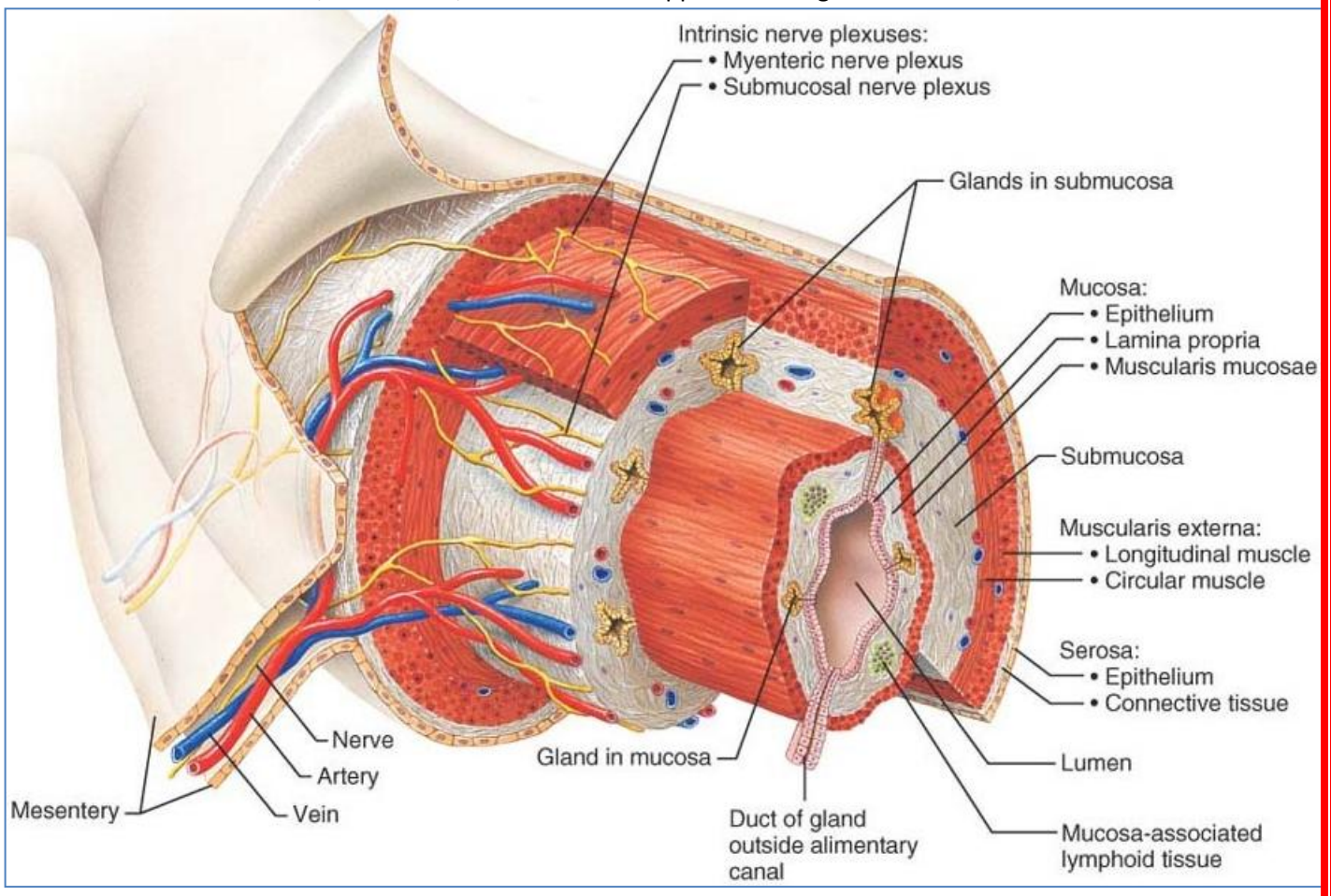

Rectal valve
Rectum
Hemorrhoidal veins
Levator ani muscle
Anal canal
External anal sphincter
Internal anal sphincter
Anal columns
Pectinate line
Anal sinuses
Anus

MICROSCOPIC ANATOMY

4 Layers of GIT Lining (Histology & Function):

1. **Mucosa**
   - Folds (plicae)
   - Epithelium (simple columnar + goblet)
   - Lamina Propria (loose areola tissue)
   - Muscularis mucosae (smooth muscle)
   - ➢ Secretion of mucin, digestive enzymes & hormones
   - ➢ Absorption of nutrients & fluids.
   - ➢ Protection from:
     - Acid
     - Bacteria
     - Mechanical stresses
2. **Submucosa**
   - Dense conn. Tissue
   - Nerves
   - Blood vessels
   - Glands
   - ➢ Vasculates & innervates GI tract wall
3. **Muscularus**
   - Circular smooth muscle
   - Longitudinal smooth muscle
   - ➢ Responsible for peristalsis
   - ➢ Forms sphincters (valves) – control passage of food
4. **Serosa/Peritoneum**
   - Areolar Connective Tissue
   - Mesothelium (single layered squamous epithelium)
   - (Dual layered peritoneum = mesentery)
   - ➢ Lubrication, vasculation, innervations & support of GI organs.





System: Gastrointestinal

Overview:

- **The Alimentary Canal (9m approx)**
  - **Mouth**
  - **Pharynx**
  - **Oesophagus**
    - 25 cm long
    - Stratified Squamous
    - Upper 1/3 = striated muscle
    - Lower 2/3 = smooth muscle
  - **Stomach**
  - **Small intestine**
    - Duodenum
    - Jejunum
    - Ileum
  - **Large intestine**
    - Vermiform appendix
    - Cecum
    - Ascending Colon
    - Transverse Colon
    - Descending Colon
    - Sigmoid Colon
    - Rectum
  - **Anus**
- **Accessory Digestive Organs**
  - **Teeth**
  - **Tongue**
  - **Salivary Glands**
    - Parotid
    - Sublingual
    - Submandibular
  - **Glandular Organs**
    - Liver
    - Pancreas
  - **Gallbladder**

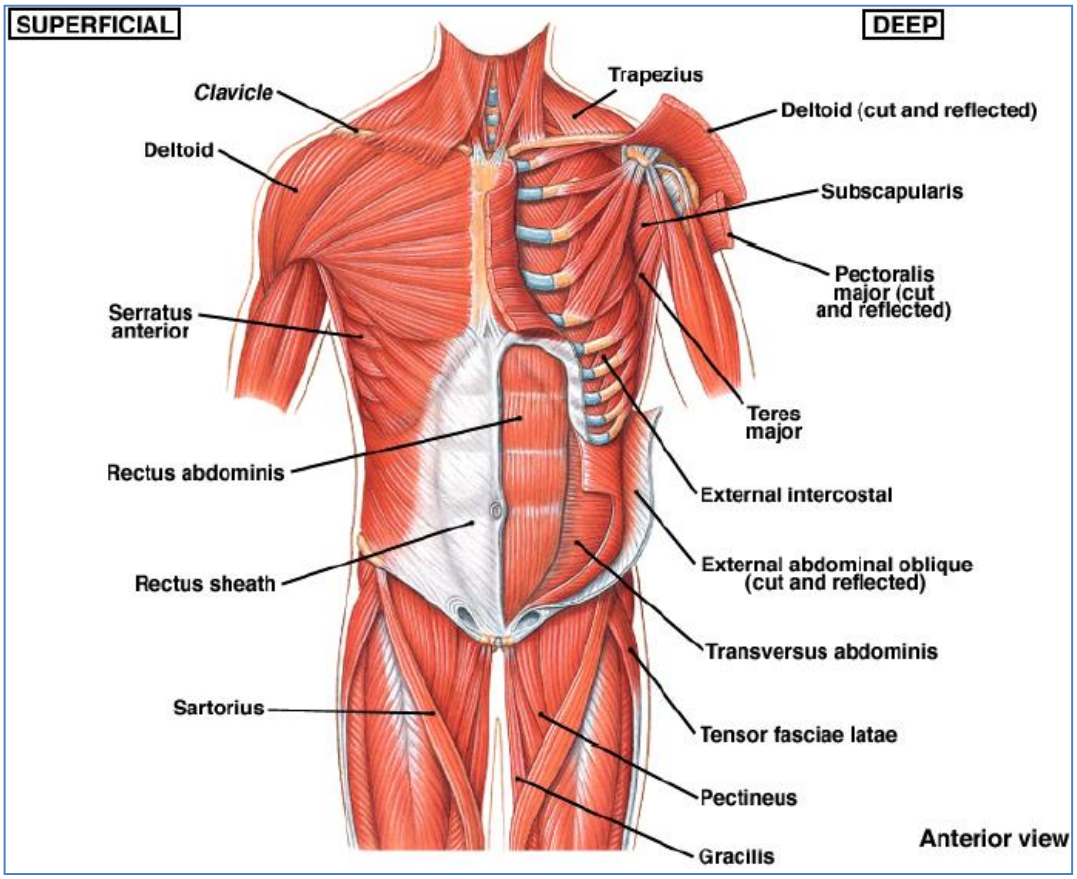
Abdominal Cavity:

- **Boundaries:**
  - Diaphragm of lungs (**thoracic diaphragm**)
  - Broad Ligament of Pelvis
- **Layers of Abdominal Wall**
  - **Skin**
  - **Superficial Fascia**
    - Fatter Layer
    - Membranous Layer
  - **3 Muscle Layers – Separated by Deep Fascia**
    - Deep Fascia
    - External Oblique Muscle
    - Deep Fascia
    - Internal Oblique Muscle
    - Deep Fascia
    - Transverse Abdominal Muscle
    - Trasversalis Fascia
  - **Parietal Peritoneum**

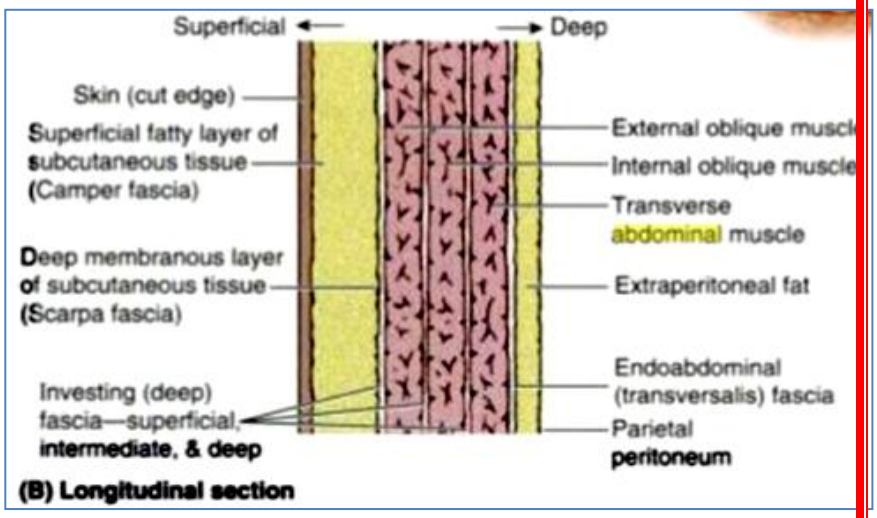
SURFACE ANATOMY:

Abdominal Cavity:

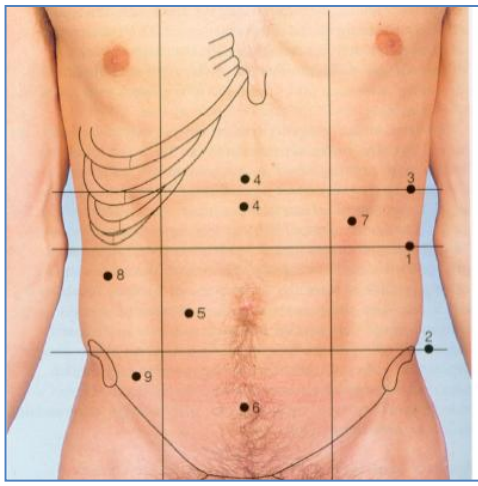
- **Boundaries:**
  - Diaphragm of lungs (**thoracic diaphragm**)
  - Broad Ligament of Pelvis
- **Muscles**



- **Layers of Abdominal Wall**
  - **Skin**
  - **Superficial Fascia**
    - Fatter Layer
    - Membranous Layer
  - **3 Muscle Layers – Separated by Deep Fascia**
    - Deep Fascia
    - External Oblique Muscle
    - Deep Fascia
    - Internal Oblique Muscle
    - Deep Fascia
    - Transverse Abdominal Muscle
    - Trasversalis Fascia
  - **Parietal Peritoneum**

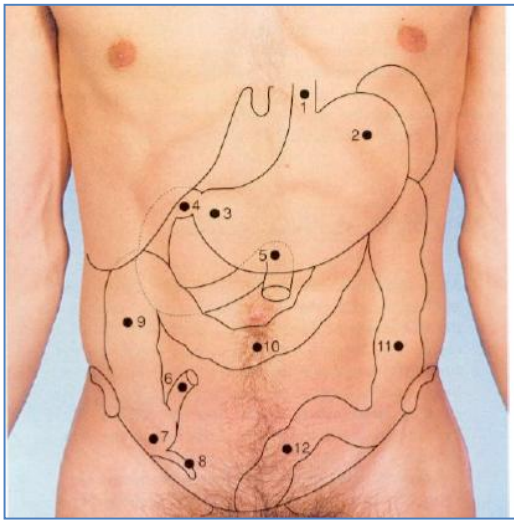


- **Regions:**



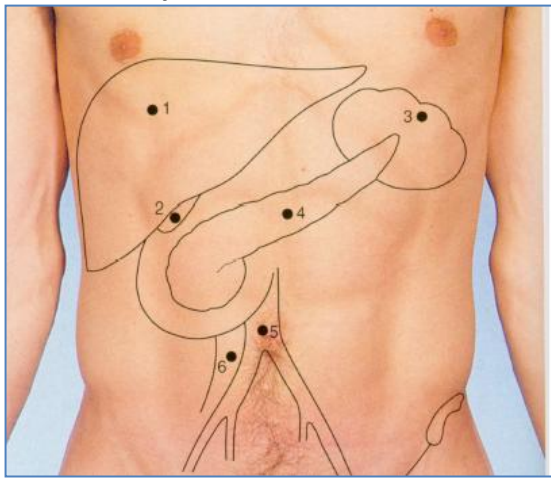
1. Subcostal plane
2. Transtubercular plane
3. Transpyloric plane
4. Epigastrium
5. Umbilical
6. Suprapubic
7. Hypochondrium
8. Lumbar
9. Iliac

- **Placement of Abdominal Organs**



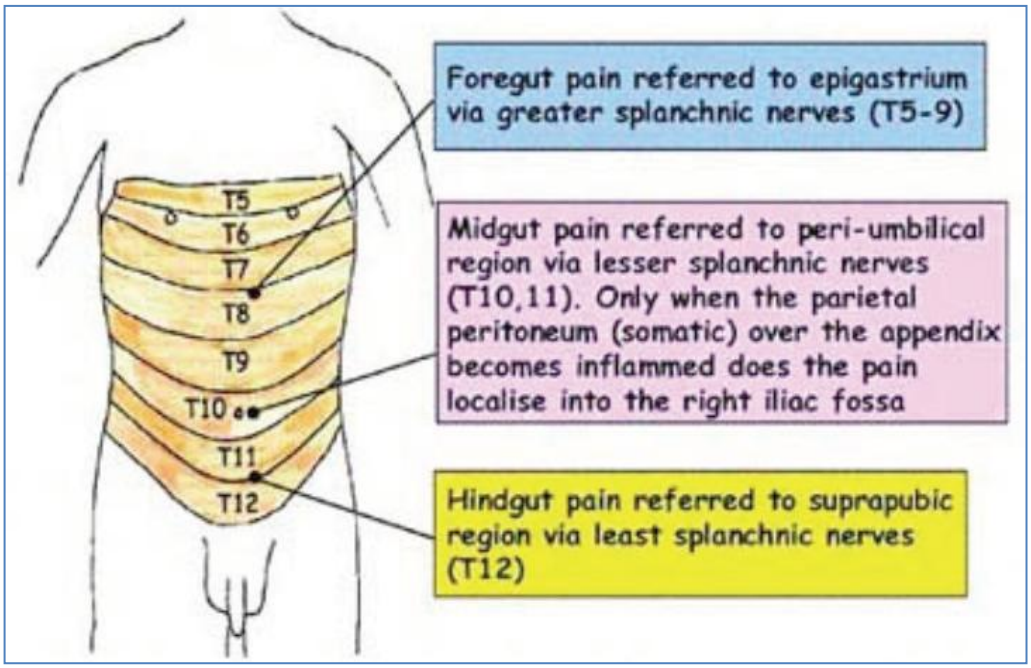
1. Esophagus
2. Stomach
3. Pyloric antrum
4. Duodenum
5. Duodenojejunal flexure
6. Terminal ileum
7. Caecum
8. Appendix
9. Ascending colon
10. Transverse colon
11. Descending colon
12. Sigmoid colon

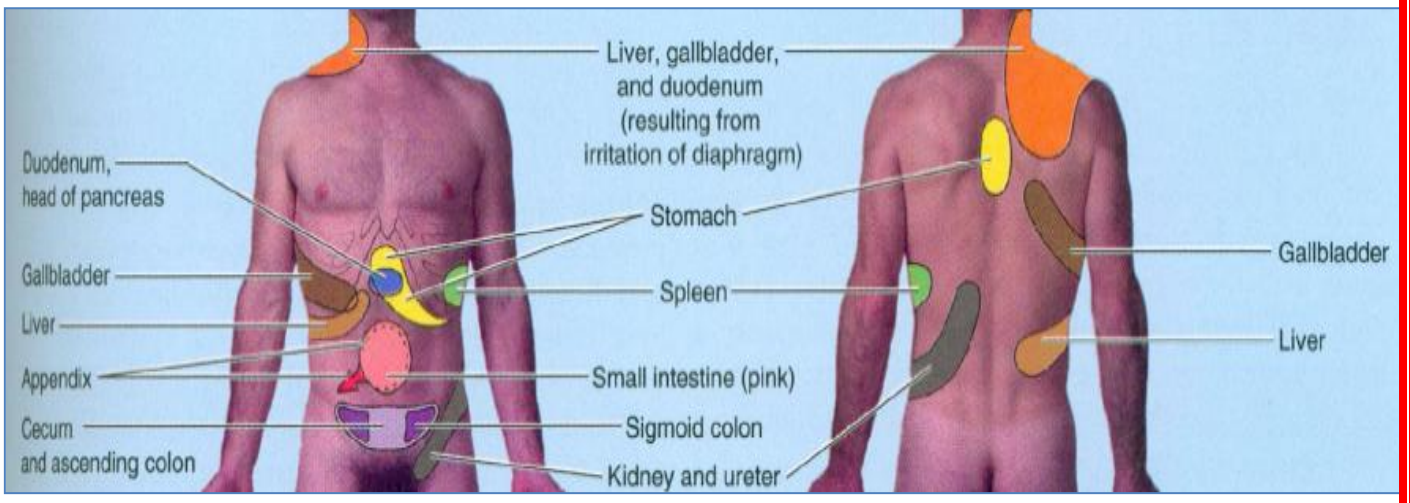
- **Placement of Accessory Structures**



1. Liver
2. Gall Bladder
3. Spleen
4. Pancreas

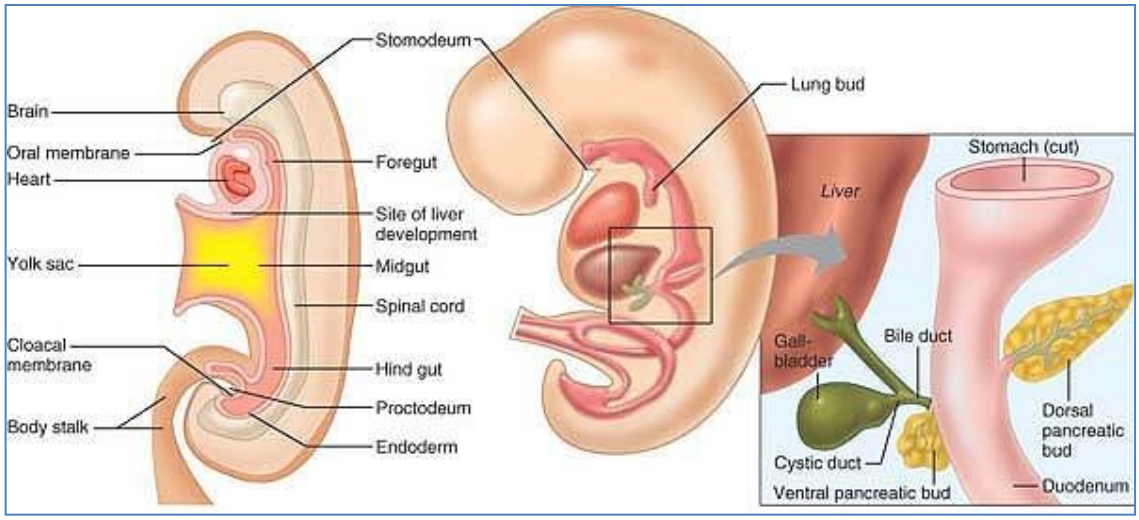
- **Referred Pain:**
  - Pain felt at a site away from the location of affected organ
  - Due to lack of dedicated sensory pathways from internal organs.
  - Pain is relayed to areas of skin and muscle instead.
  - Known as “viscera-somatic convergence.”



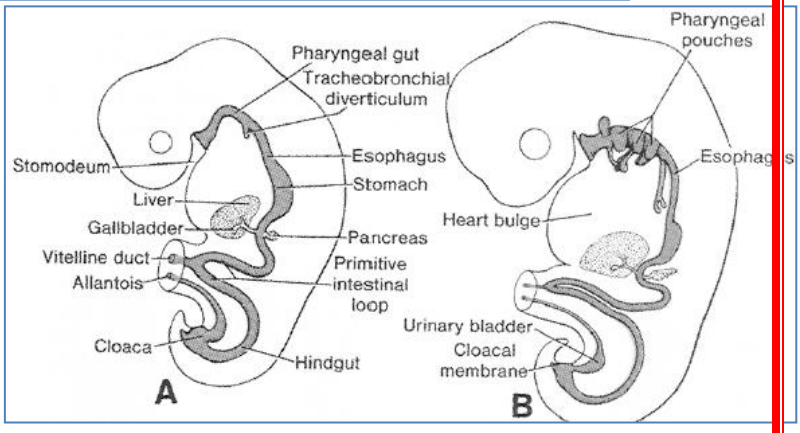


Embryonic Development of GIT:

- **Week 3:**
  - **3 Primary Germ Layers:**
    - Ectoderm
    - Mesoderm
    - Endoderm
- **Week 3 – 4:**
  - **GIT develops from the Endoderm & Mesoderm:**
    - **Endoderm:**
      - The epithelial lining of the primitive gut (alimentary tube)
    - **Mesoderm:**
      - The rest of the wall:
        - Submucosa
        - Muscularis Externa
- **Week 4 – 8:**
  - **Openings of GIT:**
    - **Mouth:**
      - The end of the **foregut merges with** the **ectoderm** on the head of the embryo at the **"stomodeum".**
      - Forms the **oral membrane** – later breaks to form the mouth opening.
    - **Anus:**
      - The end of the **hindgut merges with** the **ectoderm** on the tail of the embryo at the "**proctodeum".** (procto = anus)
      - Forms the **cloacal membrane** – later breaks through to form the anus.
  - **Budding of Glandular Organs:**
    - **Salivary Glands** - foregut
    - **Liver** - midgut
    - **Pancreas** – midgut
    - ➢ Glands retain their connections, which later become ducts to GIT.
  - **Stomach Appears**
    - Different rates of growth causes rotation & greater/lesser curvatures



  - **Respiratory Diverticulum**
  - **Dorsal Tube→Oesophagus**
    - Rapidly lengthens with descent of heart & lungs

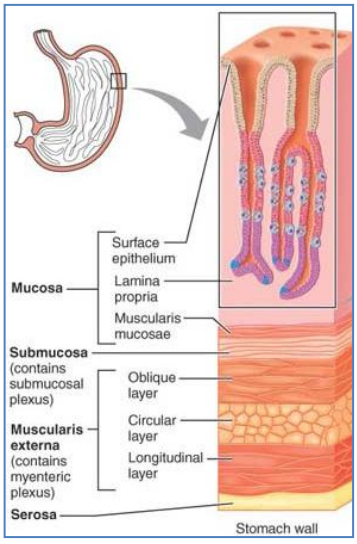


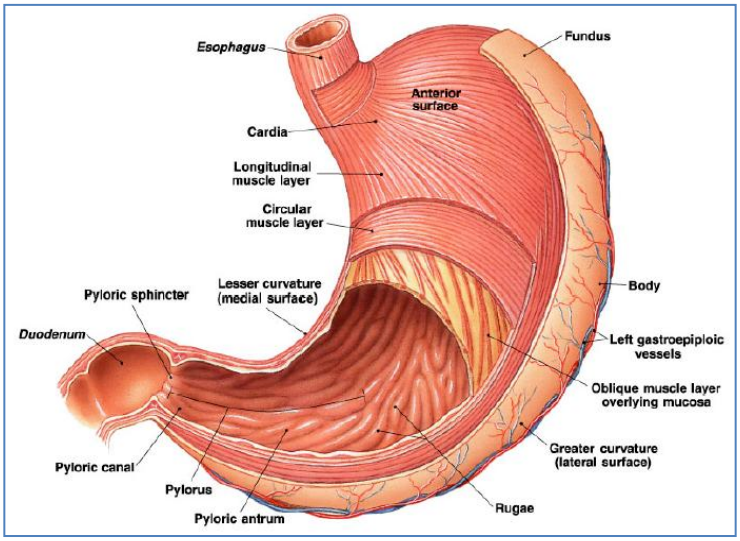
Anatomy of the Oesophagus:

- **Important Structures**
  - Approx 25cm long
  - Pierces the diaphragm at the **oesophageal hiatus** to enter abdomen
  - Joins the stomach at the **cardiac orifice**
  - **Sphincter: 'Gastro-oesophageal' / 'Cardiac'**
    - Malfunction of this sphincter → heartburn
- **Histology:**
  - **Mucosa:**
    - Epithelium
      - Upper 1/3 = stratified squamous
      - Lower 2/3 = simple columnar

Anatomy of Stomach:

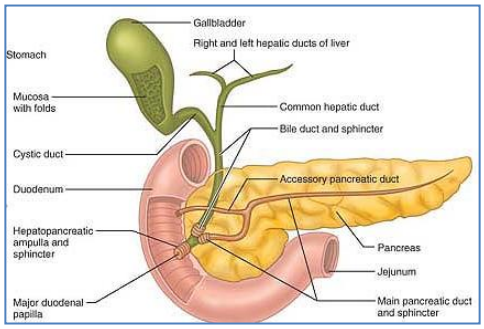
- **Histology:**
  - Gastric Pits
    - Surface Epithelium
  - Gastric Glands
    - Mucous Neck Cells
    - Parietal Cells – HCl producers.
    - Chief Cells – Pepsinogen producers (protein digesting enzyme – when mixed with acid)





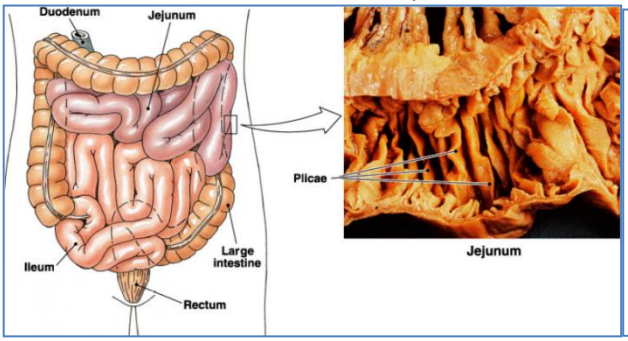
Anatomy of Duodenum:

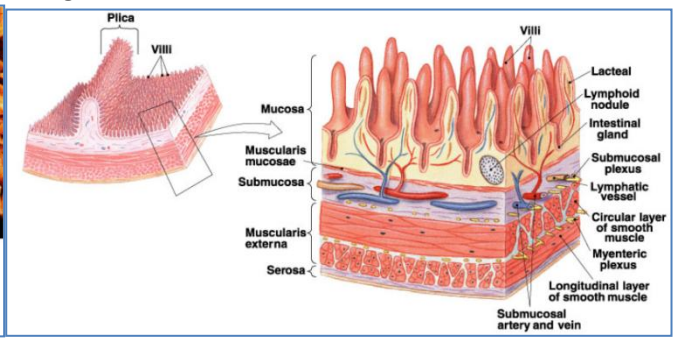
- **Important Structures:**
  - Gallbladder
    - Cystic Duct
  - Hepatic ducts of liver
    - Common Hepatic Duct
  - Bile Duct
  - Pancreas
  - Pancreatic Duct
  - Major Duodenal Papilla
  - Jejunum



Anatomy of Small Intestine:

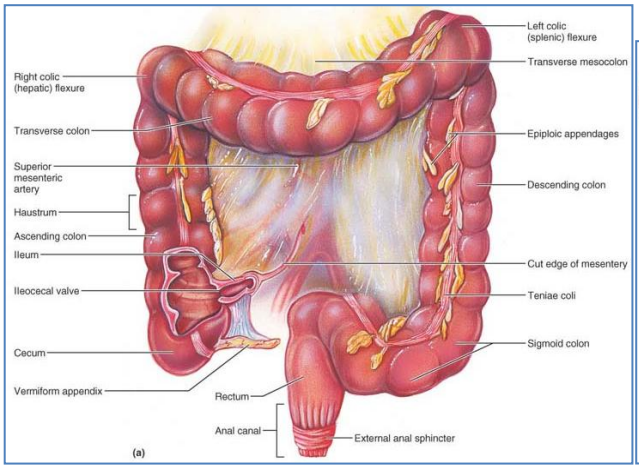
1. **Duodenum** – C-shaped
2. **Jejunum** – High surface area – Maximum **nutrient** absorption (many plicae, villi & microvilli)
3. **Ileum** – Lower surface area – Absorption of **fluids** (fewer plicae, villi & microvilli)
4. **Ileo-cecal Junction/Valve:** empties into Cecum of large intestine.

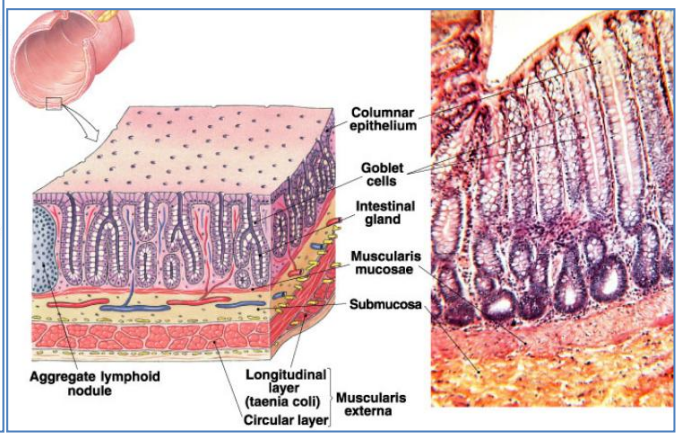




Anatomy of Large Intestine:

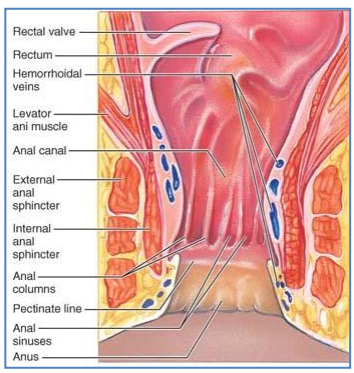
- Absorbs H_2O from indigestible food
- Temporarily stores waste
- Eliminates semisolid faeces
- **Unique Structures**
  - **Teniae Coli** – 3 ribbons of smooth muscle along the colon's entire length
    - Causes the large-intestine wall to form segments (**Haustra**)
  - **Haustra** – slows down the movement of wastes.
    - Aid in packing and compacting
  - **Epiploic Appendages** – fatty pouches of visceral peritoneum (purpose unknown)





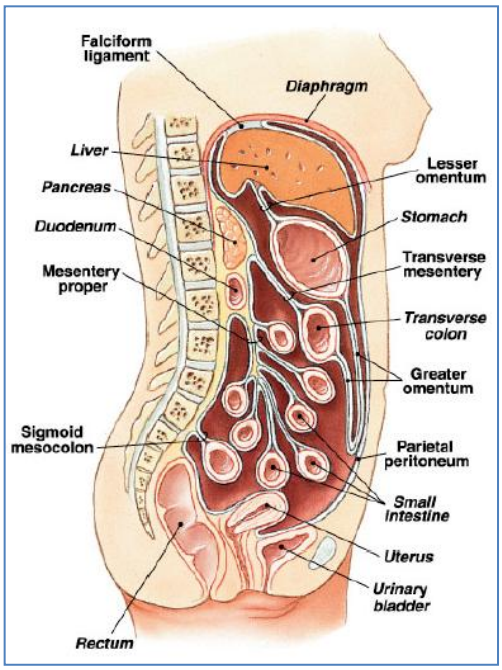
Anatomy of Rectum & Anus:

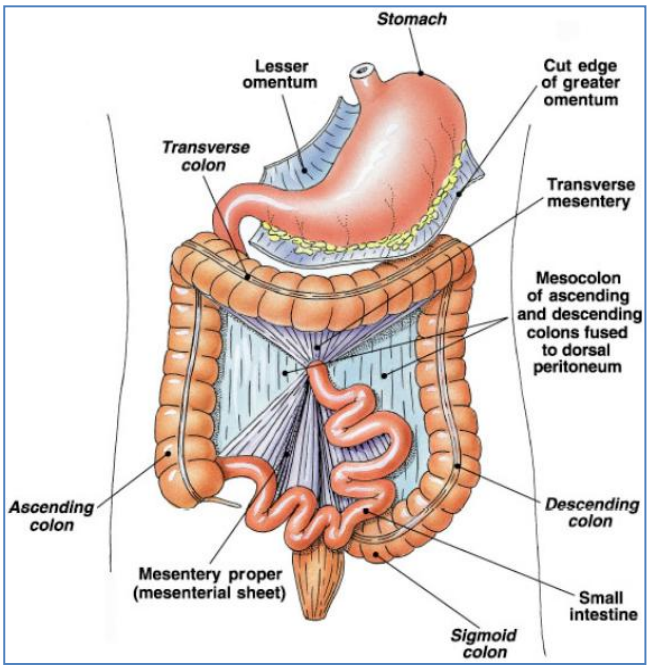
- **Important Structures:**
  - Levator Ani Muscle
  - Anal Canal
  - External anal Sphincter - voluntary
  - Internal anal Sphincter – involuntary
  - Anus



The Peritoneum:

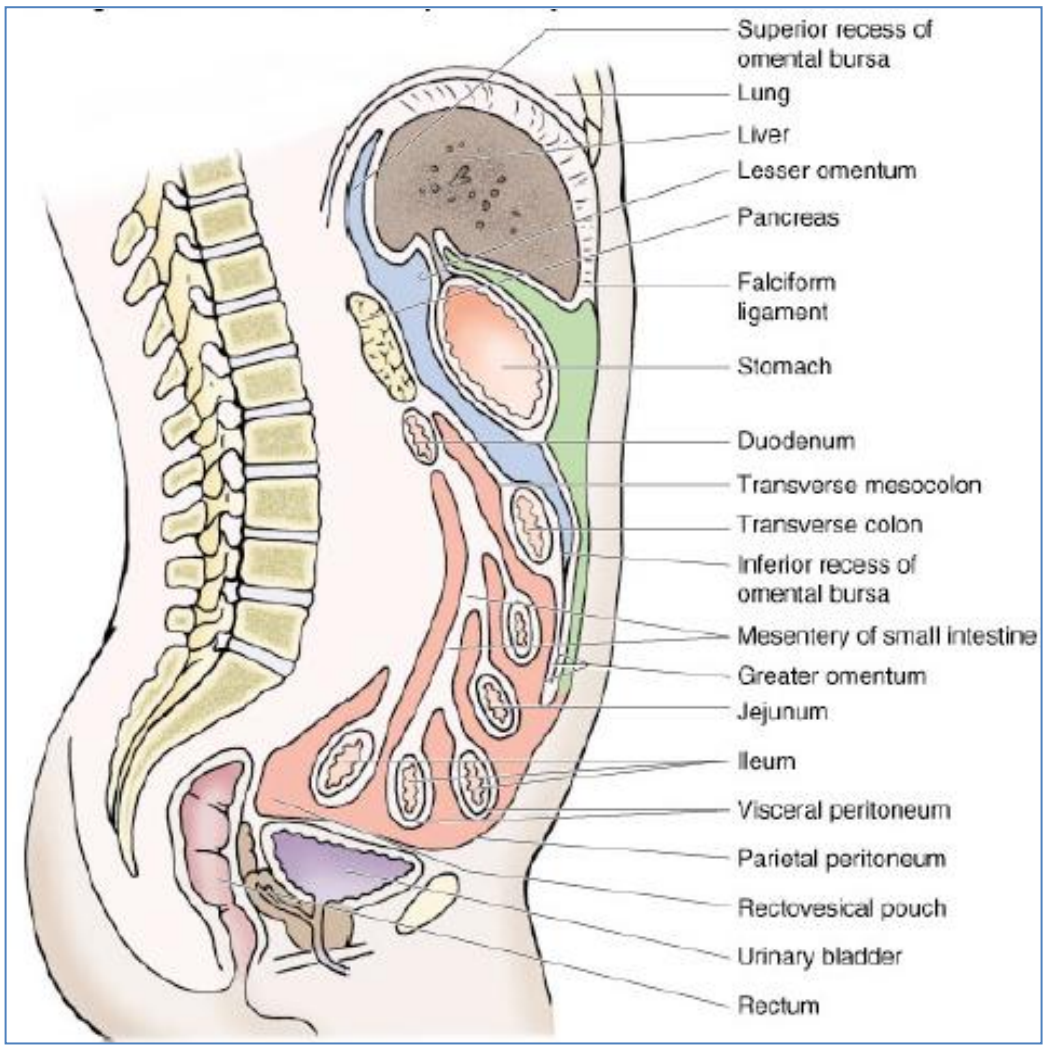
- The slippery **serous membrane** of the abdomio-pelvic cavity:
  - **Visceral Peritoneum**
    - Covers external surfaces of most digestive organs
  - **Parietal Peritoneum**
    - Lines the body cavity wall
- **Mesenteries:**
  - Sheets of double-layered peritoneum
  - Connects digestive organs to the body wall
  - Contains blood vessels, nerves & lymphatics
  - **Lesser Omentum**
    - Lesser Curvature of Stomach
  - **Greater Omentum**
    - Greater Curvature of Stomach
  - **Transverse Mesentery**
    - Transverse Colon
  - **Mesocolon**
    - Ascending Colon
    - Descending Colon
  - **Mesentery Proper**
    - Jejunum
    - Ileum
- **Intra Vs. Retro – Peritoneal Organs:**
  - **Intra:** Inside the peritoneal cavity & suspended by mesentery.
    - Stomach
    - Gallbladder
    - Jejunum
    - Ileum
    - Cecum
    - Transverse Colon
    - Sigmoid Colon
  - **Retro:** Posterior to (outside) the peritoneal cavity adhered to the dorsal abdominal wall.
    - Parts of duodenum
    - Most of pancreas
    - Ascending & Descending Colon
    - Rectum





Greater & Lesser Sacs

- **Greater Sac**
  - **Supracolic Compartment**
  - **Infracolic Compartment**
- **Lesser Sac**
  - **Omental Bursa**



- **Intra Vs. Retro – Peritoneal Organs:**
  - **Intra:** Inside the peritoneal cavity & suspended by mesentery.
    - Stomach
    - Gallbladder
    - Jejunum
    - Ileum
    - Cecum
    - Transverse Colon
    - Sigmoid Colon
  - **Retro:** Posterior to (outside) the peritoneal cavity adhered to the dorsal abdominal wall.
    - Parts of duodenum
    - Most of pancreas
    - Ascending & Descending Colon
    - Rectum

ABDOMINAL INFRASTRUCTURE

The 3 Gut Segments:

- Each give rise to specific gut structures during foetal development.
- Structures derived from the gut proper develop as swellings/dilations of the primitive gut.
- Gut-related structures develop as outpouchings of the primitive gut.

1. **Foregut:**
   - **Arterial Supply:** Celiac Trunk.

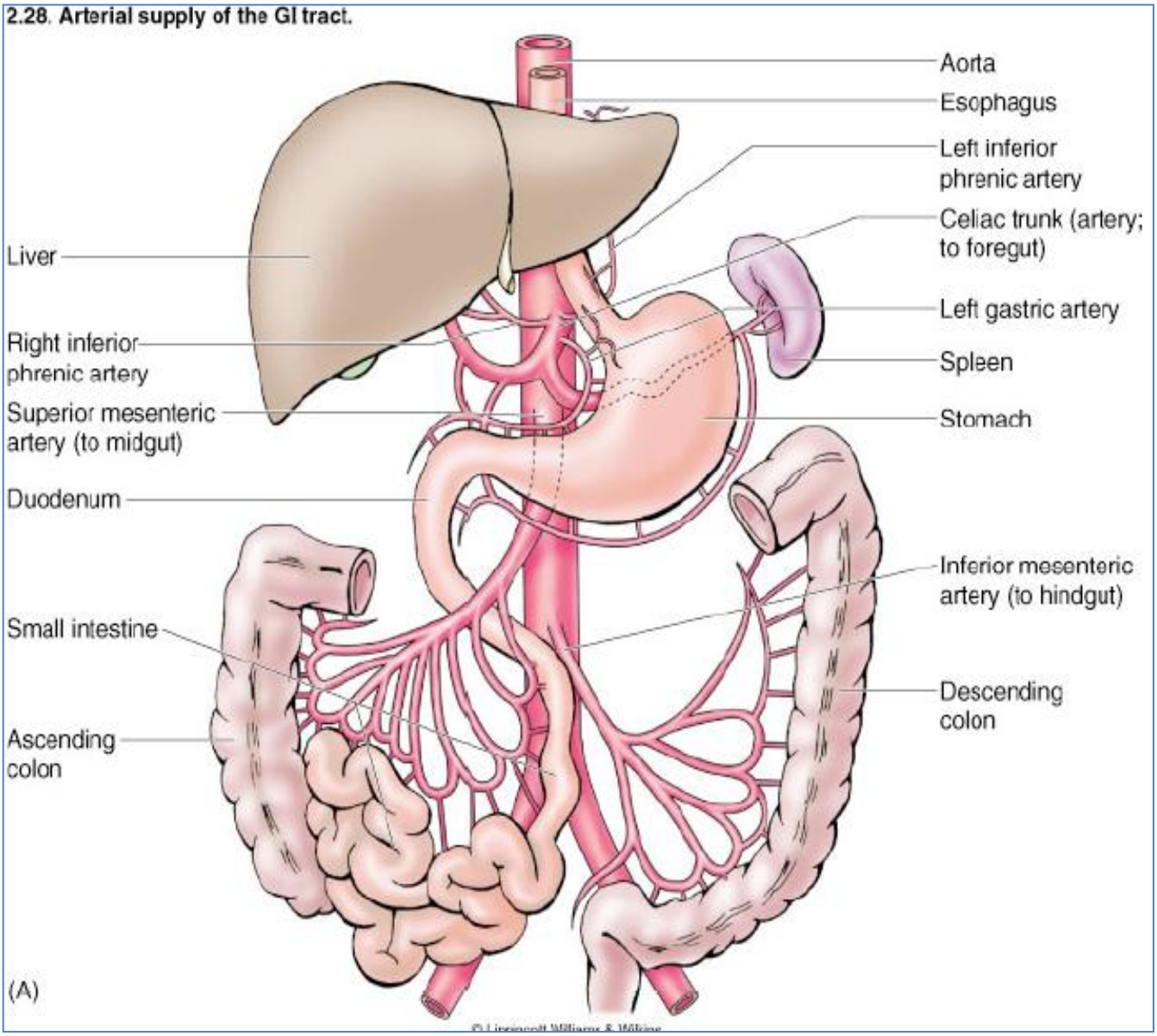
   - Pharynx
   - Oesophagus
   - Stomach
   - Upper Duodenum
   - Respiratory tract (incl. Lungs)
   - Liver
   - Gallbladder
   - Spleen
   - ½ of Pancreas
2. **Midgut:**
   - **Arterial Supply:** Superior Mesenteric Artery

   - ½ of Pancreas
   - Lower duodenum
   - Jejunum
   - Ileum
   - Cecum
   - Appenix
   - Ascending colon
   - 1st 2/3 of transverse colon
3. **Hindgut:**
   - **Arterial Supply:** Inferior Mesenteric Artery

   - Last 1/3 of transverse colon
   - Descending colon
   - Sigmoid colon
   - Rectum
   - Upper anal canal

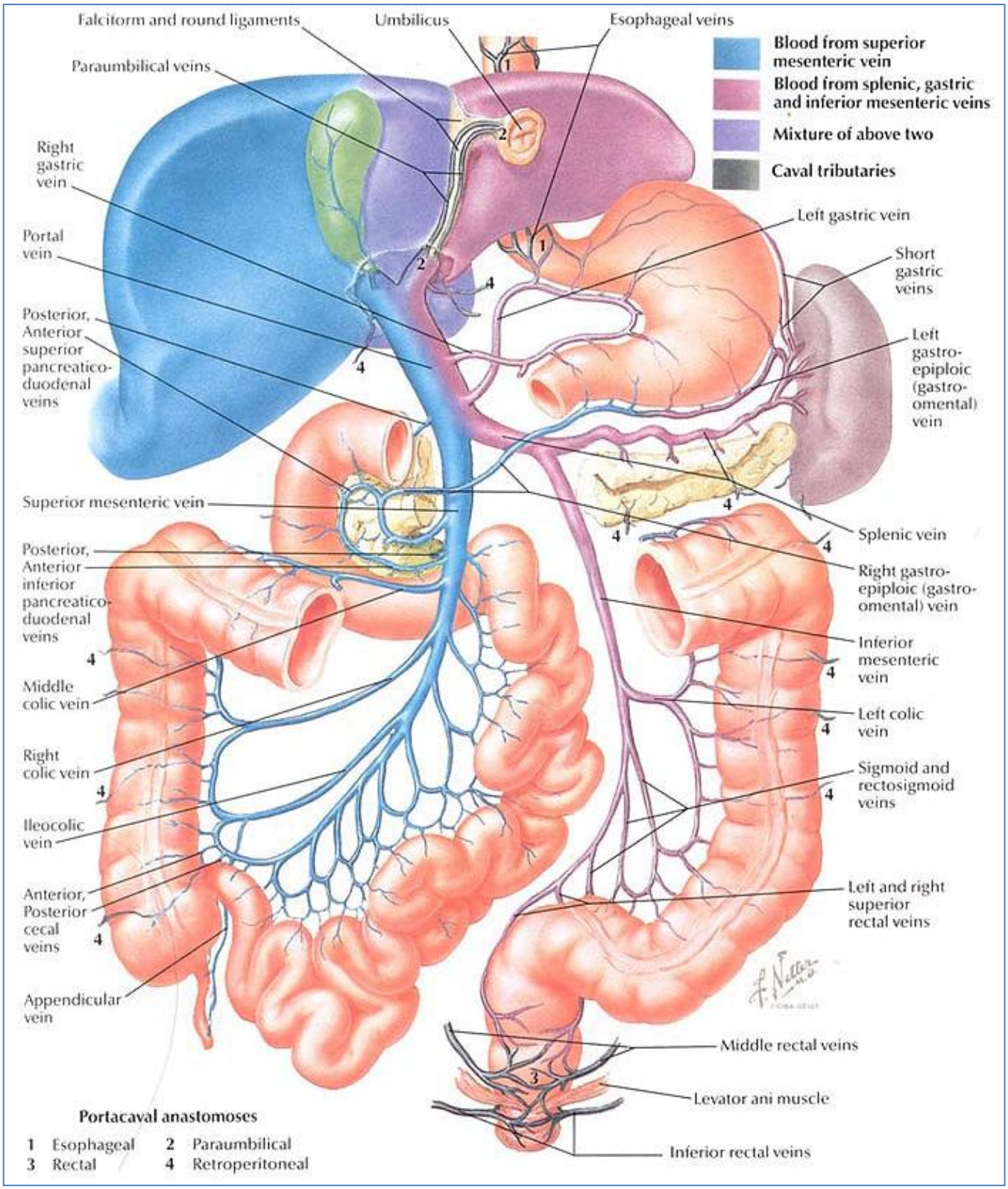
Arterial Supply of GIT:

- **Foregut:**
  - **Celiac Trunk**
- **Midgut:**
  - **Superior Mesenteric**
- **Hindgut:**
  - **Inferior Mesenteric**

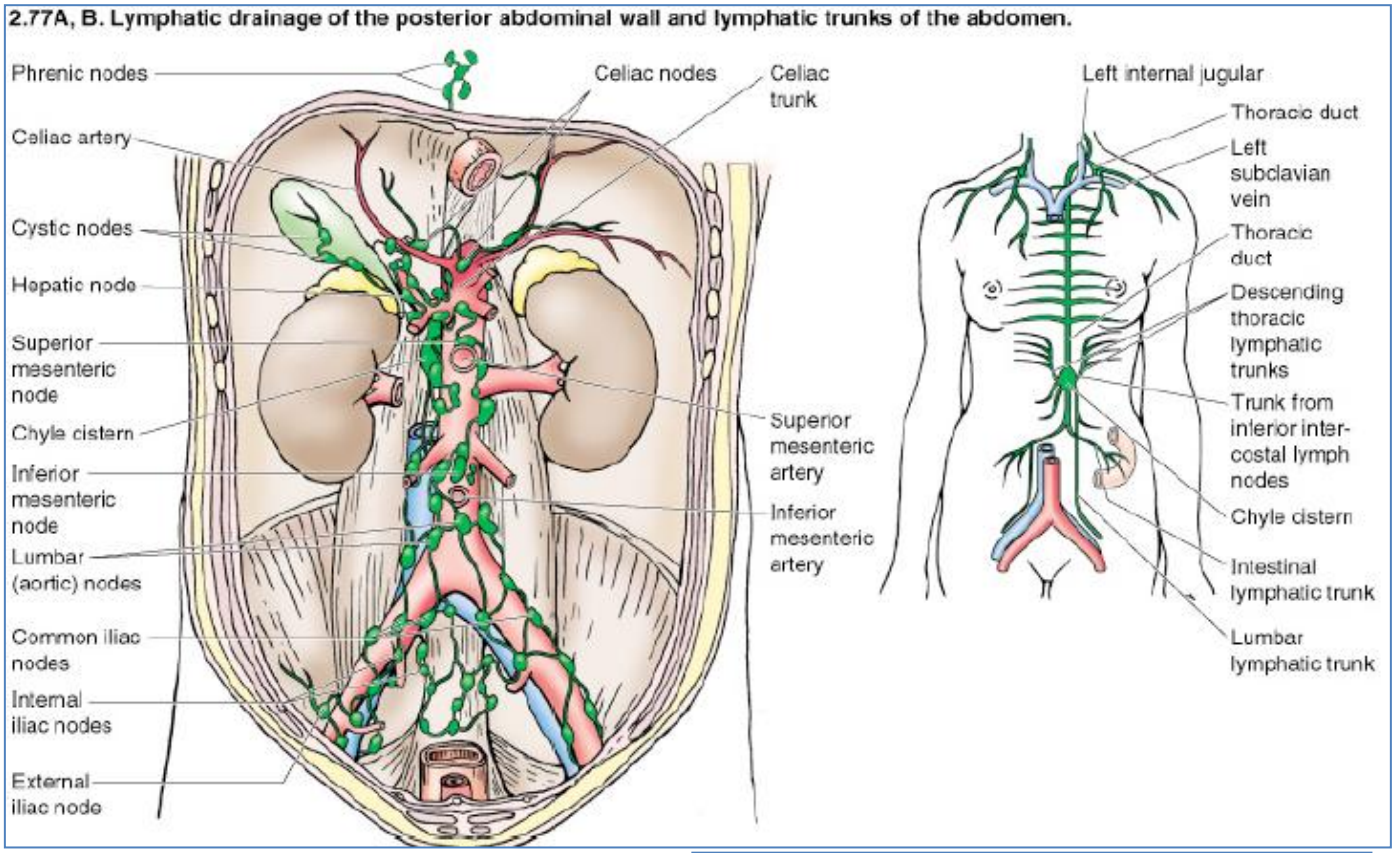


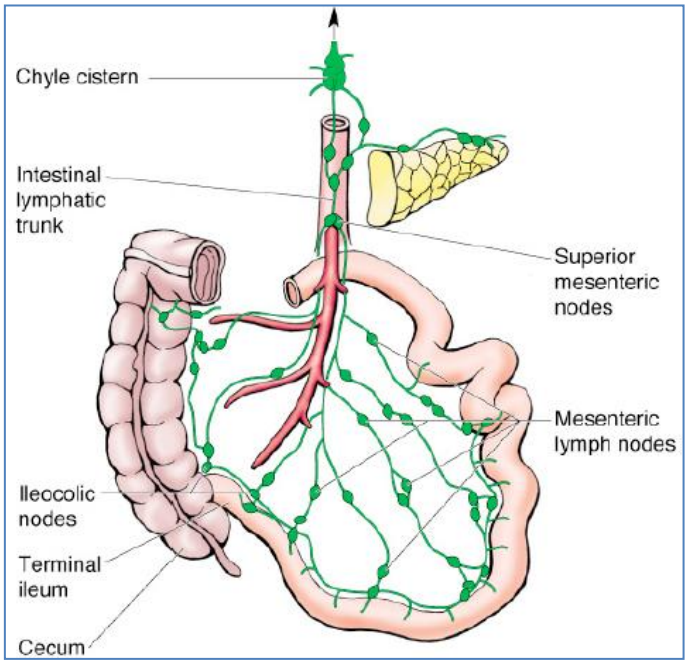
Venous Drainage of GIT

- **Foregut:**
  1. **Portal Vein → Liver**
  2. **Left Gastric → Portal**
  3. **Right Gastric → Portal**
  4. **Splenic Vein →Portal**
- **Midgut:**
  - **Superior Mesenteric → Portal**
- **Hindgut:**
  - **Inferior Mesenteric → Splenic → Portal**

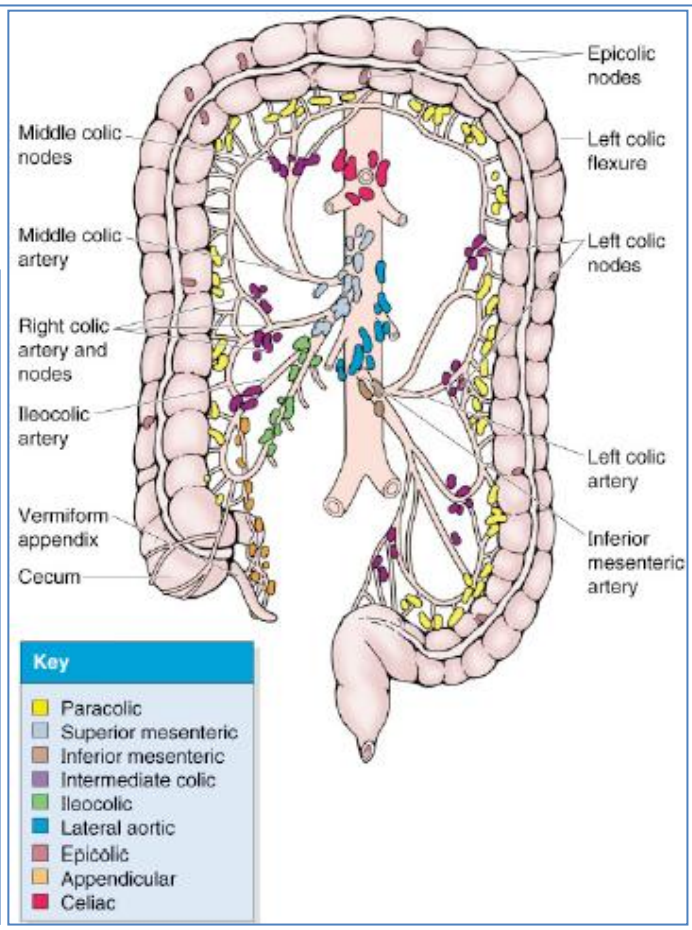


Lymphatic Drainage of the GIT:





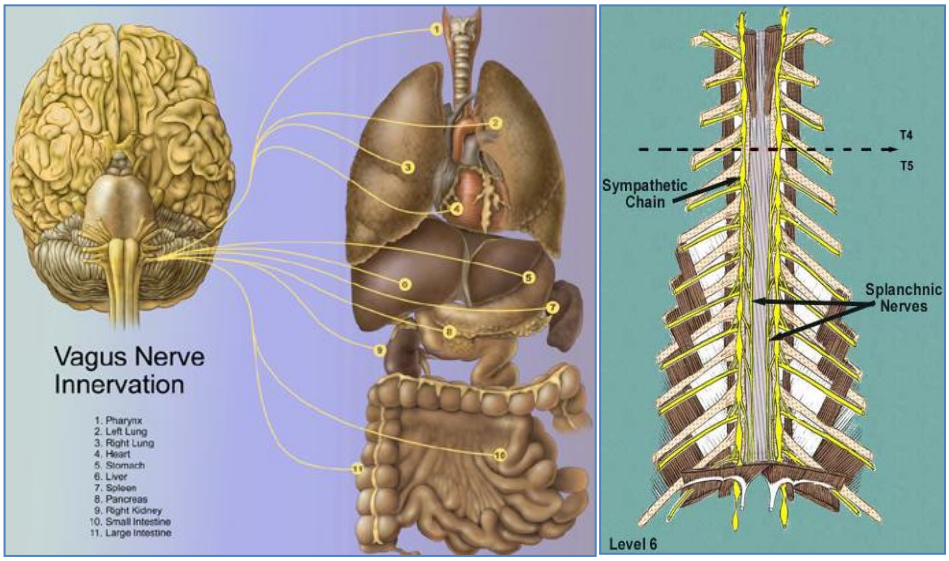
Mesentric Lymph Nodes



Lymph Nodes of Large Intestine

Innervation of GIT:

- **Extrinsic Innervation:**
  - From **Sympathetic Splanchnic nerves**
  - From **Parasympathetic Vagus (CNS)**



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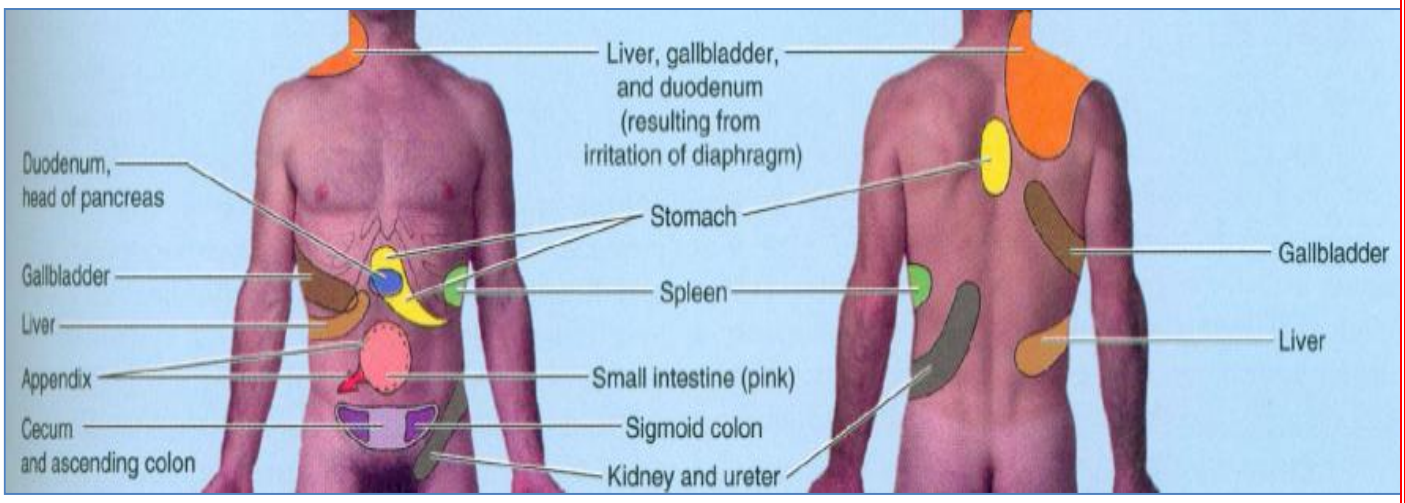


GI Motility & Function

Motility

- Keeps things moving
- Food-matter must stay in specific places long enough → optimal digestion & absorption:
  - Oesophagus: 5-10s
  - Stomach: 1-3hrs
  - Small Intestine: 7-9hrs
  - Large Intestine: 25-30hrs **Total:** approx. 40hrs

Categories of Motility:

- **Accommodation**
  - Stretching – stomach
  - Smooth muscle relaxes
- **Tonic Contraction**
  - Continual partial contraction of GI Tract
- **Peristalsis**
  - Combination of Segmentation & Pendular Contraction.
  - **Segmentation**
    - Contractions of circular muscle
  - **Pendular**
    - Contractions of longitudinal muscles
- **Migrating Motor Complex –** Small Intestines
- **Mass Movement –** Large Intestines
- **Defecation Reflex –** Rectum & Anus

Motility Mechanisms In Specific Places:

- **Stomach**
  - **Peristalsis**
  - 3 waves per minute
  - Waves move down body
  - Very intense waves at pylorus – mashes food into chyme (homogenous solution)
  - Usually each wave spits 3ml of chyme into duodenum
- **Small Intestine**
  - **Segmentation** is the most common motion.
  - 12-14 contractions / minute
  - **Peristalsis: *Migrating Motor Complex***
    - Successive waves are initiated further along small intestines.
    - Hence the 'migrating' motor complex.
    - Takes approx 2 hrs for waves to reach ileocecal valve.
    - Process then repeats itself → sweeps food remnants, bacteria, etc.
- **Large Intestine**
  - Inactive most of the time
  - Contractions are sluggish & short-lived
  - ***Mass Movements***
  - Long, slow-moving, but powerful contractile waves.
- **Rectum**
  - Faeces are forced into rectum by Mass Movements.
  - Rectum wall stretches → initiates defecation reflex:
  - ***Defecation Reflex***
  - Sigmoid-Colon & Rectum contracts + Internal Anal Sphincter relaxes

Neural & Hormonal Regulation of:

- **Stomach Secretion:**
  - **Cephalic Phase**
    - (Where gastric secretion is stimulated before food enters stomach)
    - The taste/smell/thought of food sends nervous impulses to medulla oblongata (in brainstem)
    - Medulla→Vagus Nerves →Parasympathetic Neurons→stimulates HCl & Pepsin secretion in upper & middle stomach.
      - Also stimulates Gastrin secretion in lower part of stomach
      - Gastrin→bloodstream→further stimulates HCl & Pepsin secretion
  - **Gastric Phase**
    - Food has entered & distended the stomach.
    - **Stimulated by:**
      - **Distension of Stomach:**
        - Continued secretion of HCl & Pepsin & Gastrin
      - **Gastrin (hormone):**
        - Produced by **G-Cells** in stomach
        - Main function: stimulate **parietal cells** → spew out **HCl**
      - **Low Acidity:**
        - Stimulates gastrin acid production.
  - **Intestinal Phase**
    - Acidic chyme enters duodenum
    - Initially this stimulates **intestinal gastrin** secretion → encourages gastric gland secretion.
    - Shortly after, gastric secretion is inhibited via the **enterogastric reflex:**
      - **Inhibits parasympathetic** stimulation from medulla.
      - **Activates sympathetic** fibres → tightens pyloric sphincter + decreases gastric secretion.
      - Causes the release of **3 local hormones** into blood →inhibits gastric secretion:
        - **Secretin**
        - **Cholecystokinin**
        - **Vasoactive Intestinal Peptide (VIP)**

- **Gastric Emptying:**
  - **Normal:**
    - Depends on contents of duodenum rather than contents of stomach.
    1. Acidic chyme enters duodenum
    2. Chemical & stretch receptors in duodenum wall → causes enterogastric reflexes.
    3. Reflexes inhibit acid & pepsin secretion
    4. Also prevents further duodenal filling by reducing force of pyloric contractions
  - **Vomiting Reflex:**
    - Caused by either:
      - Extreme stretching of stomach
      - Irritants (Bacterial toxins/Alcohol/Spicy foods/Drugs/etc)
    - Bloodborne molecules or sensory impulses → **emetic centre** of medulla.

Secretory Structures:

- **Salivary Glands:**
  - **Parotid**
    - Enzyme: Alpha-Amylase (breaks down amylose – straight chain starch)
    - Anti-Microbial Agents
  - **Submandibular**
    - Mucous
    - Enzyme: Alpha-Amylase
  - **Sublingual**
    - Mucous
- **Stomach:**
  - **Mucosa:**
    - Composed entirely of **Goblet Cells**
    - Secretes viscous **mucous**
    - Secretes **HCO_3^-** → neutralises H^+ ions in mucus gel (unstirred layer)
  - **Gastric Pits:**
    - **Parietal Cells**
      - Secrete **HCl** &
    - **Chief Cells**
      - Produce **pepsinogen** (inactive form of pepsin – a protease)
      - Pepsinogen + HCl → **Pepsin**
    - **Enteroendocrine Cells**
      - Release chemical messengers into interstitium.
      - Eg. **Histamine, Seratonin, Gastrin**
- **Duodenum – Brunner's Glands:**
  - Compound tubular glands
  - Secrete **alkaline fluid** & mucus
  - Helps neutralise acidic chyme from stomach.
- **Liver**
  - Produces bile for absorption of fats.
  - **Bile**
    - Bile salts, phospholipids & emulsifiers
- **Pancreas (Exocrine)** – secretes:
  - **Bicarb** – neutralises acidity
  - **Pancreatic Amylase** – hydrolyses starch → maltose + glucose
  - **Pancreatic Lipase** – hydrolyses fats → fatty acids + monoglycerides
  - **Proteases** – proteolytic enzymes
  - **Nucleases** – hydrolyses nucleic acids (DNA & RNA) → nucleotides.
- **Intestine & Colon – Crypts of Lieberkuhn (intestinal crypts)**
  - **Epithelial Cells**
    - Secrete intestinal juice: slightly alkaline mucous.
  - **Goblet Cells**
    - mucous

Secretions	
Saliva	1500 mL
Gastric juice	2500 mL
Bile	500 mL
Pancreatic juice	1500 mL
Small intestinal	1000 mL
Drinking water:	2000 mL
Total into GI lumen	9000 mL
Absorption	
Jejunum	3000-5000 mL
Ileum	2000-4000 mL
Colon	1000-2000 mL
(Colonic capacity	~ 3000 mL)
Excretion	< 200 g faeces (65 – 85% water)

Carbohydrate Digestion:

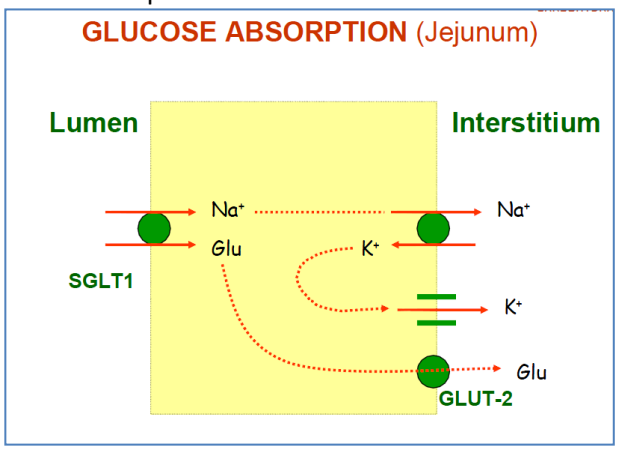
- **Mouth:**
  - Salivary α-Amylase:
    - Breaks down starch polysaccharides→smaller chunks of a few units
- **Small Intestine Lumen:**
  - Pancreatic α-Amylase:
    - Continues breakdown of starch→even smaller chunks
- **Small Intestine Brush Border:**
  - Brush-Border Enzymes:
    - Membrane-bound
    - Act on Oligosaccharides & Disaccharides → Monosaccharides
      - Sucrase: Sucrose→ Glucose + Fructose
      - Lactase: Lactose→ Glucose + Galactose
      - Maltase: Maltose→ Glucose + Glucose
      - Isomaltase: Maltriose→Glucose + Galactose
- **Large Intestine:**
  - Non-Starch-Polysaccharides & Resistant Starches escape enzymatic breakdown until now.
  - Microbial Enzymes:
    - Break down NSPs & RSs → short chain fatty acids. (SCFAs) + CO_2/H_2/Methane (Flatus)
    - **SCFAs:** Acetate/Propionate/Butyrate
      - **SCFAs** are absorbed into blood

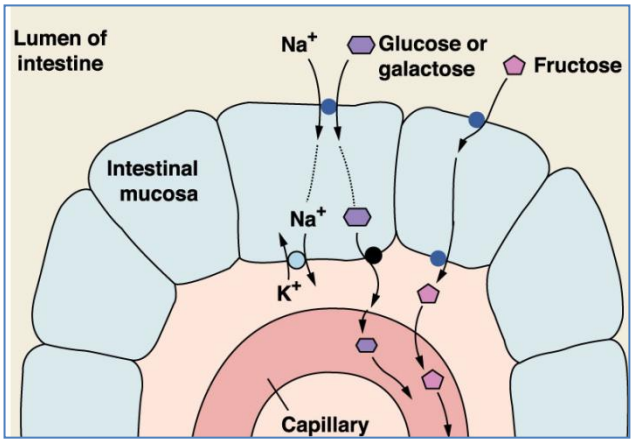
	Lumen	Epithelium	Portal Vein (blood)
Small Intestine	Monosaccharides ----------→	----------→	---→Monosaccharides
	Disaccharides ----------→	-----→ Brush ----------→ Border	---→Monosaccharides
	Starch → Pancreatic Amylase --→	-----→ Enzymes ----------→	---→Glucose
Large Intestine	Resistant Starch & Non-Starch-Polysaccharides -----→ (dietary fibre)	----------→	----→ Acetate Proprionate
	Fermentation of RS & NSP -------→	-----→ n-Butyrate	

Carbohydrate Absorption:

- **Mouth**
  - None
- **Stomach**
  - None
- **Small Intestine**

  Via Secondary Active Transport:
  - Apical **GLUT 1:** Glucose & Galactose **GLUT 2:** Basal
  - Apical **GLUT 5:** Fructose **GLUT 2:** Basal





- **Large Intestine:**
  - **Diffusion:** Short Chain Fatty Acids

Protein Digestion:

- **Stomach:**
  - **Chief cells –** secrete **pepsinogen**
  - **Parietal Cells –** secrete **HCl**
  - **Pepsinogen + HCl → Pepsin** (protease) [more specifically – an endopeptidase]
  - **Pepsin:** breaks peptide bonds in the middle of proteins → smaller polypeptides
- **Small Intestine:**
  Proteases break large polypeptides → smaller polypeptides → single amino acids.
  - **Pancreatic Proteases:**
    - Trypsinogen → **Trypsin** (Zymogen [trypsinogen] is activated by brush border enzymes)
    - Chymotrypsinogen → **Chymotrypsin** (activated by Trypsin)
    - Procarboxypeptidase → **Carboxypeptidase** (activated by Trypsin)
  - **Brush-Border Proteases:**
    - **Aminopeptidase:** - cleaves 1 amino acid at a time
    - **Dipeptidase:** **-** cleaves 1 amino acid at a time

Protein Absorption:

- Single Amino Acids + some Di/Tri-Peptides
- Absorbed mainly **in Small Intestine:**
  - **By Enterocytes** (absorptive cells of SI)
  - Via **cotransport** with **Na^+ ions**.
  - **Intracellular Peptidases** continue breakdown of Di/Tri-Peptides
  - **Basolateral transporters** – A.As & Peptides →Enter capillary blood in villi.

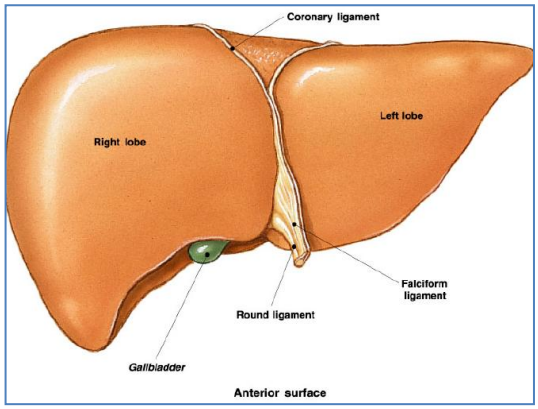
Digestion/Absorption of LIPIDS:

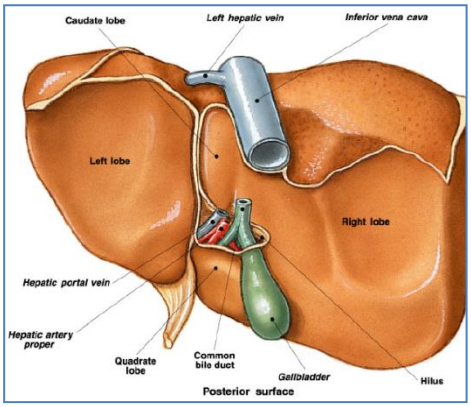
- **Emulsification:**
  - Pre-treated with Bile-Salts
  - **Bile Salts**: Amphiphilic molecules – polar & non polar ends
    - Emulsify Large Lipid Droplets → tiny tiny droplets → High Surface Area
    - High S.A. = more access to lipases
- **Digestion: Lipases**
  - **Gastric Lipase:** Stomach – Secreted by Chief Cells
  - **Pancreatic Lipase:** Pancreas – Secreted in Active Form
  - Mostly yields **1 MonoAcylGlyceride + 2 Free Fatty Acids**
  - Rarely yields **1 Glycerol + 3 Free Fatty Acids**
- **Absorption: Micelles**
  - **Monoglycerides + Fatty Acids:**
    - Retain association with **Bile Acids** → **Aggregate** to form **Micelles**.
    - **Micelles**: aggregates of mixed lipids & bile acids suspended within chyme.
    - Micelles in contact with brush-border-membrane of Enterocytes release **FAs & Monoglycerides** →$diffuse_{simple}$ into **Enterocyte**.
    - **FAs & Monoglycerides → Endoplasmic Reticulum** → used to synthesise **Triglycerides**
    - Triglycerides → **Golgi Apparatus** → Packaged with **Cholesterol+Lipoproteins** → **Cholymicrons** (The lowest-density Lipoprotein)
    - **Cholymicrons** in **Vesicles** → transported to **Basolateral Membrane** → **Exocytosed** into Interstitium.
    - Interstitial cholymicrons → **Lacteal** (Lymphatic Vessel in Villus) → Lymphatic System → **Blood**
  - **Cholesterol:**
    - **Absorbed** in Small Intestine via **specific transporter** → enterocyte.
    - Cholesterol is **incorporated into cholymicrons** → → → shuttled into blood by process above.

Hepatobiliary

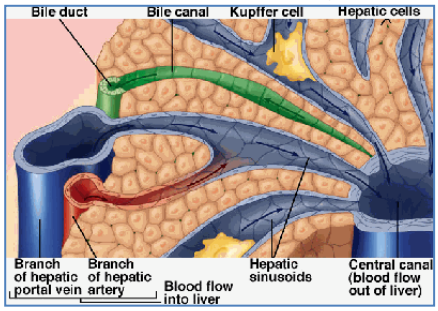
Liver Structure:

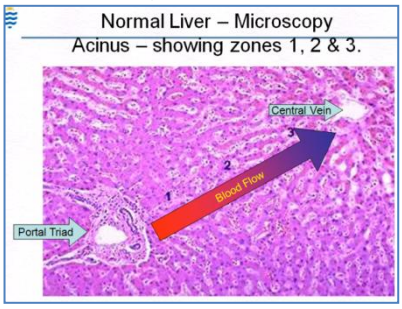
- **General Structure:**
  - Large Gland– 1.5kg
  - Wedge-shaped.
  - 2 Surfaces - Diaphragmatic & Visceral
  - 4 Lobes – Right, Left, Quadrate, Caudate (tail).
  - Dual Blood Supply:
    - Hepatic Artery 25%
    - Portal Vein 75%
  - All Blood *From the Liver* → Inferior Vena Cava





  - **Hepatic Blood Supply**
    - **To Liver:**
      - **Hepatic Artery** (From Celiac Trunk) – 20% - Oxygenated.
      - **Hepatic *Portal* Vein** (Drainage from GIT) – 80% - Nutriated; Deoxygenated.
    - **From Liver:**
      - **Central Veins (In each Lobule) → Hepatic Vein** → IVC
  - **Microscopic Structure – Liver Lobules:**
    - **Portal Triad:**
      - Bile Duct
      - Branch of Portal Vein
      - Branch of Hepatic Artery
    - **Zones:**
      - 1 – Peripheral (Closest to Portal Triad)
      - 2 – Middle
      - 3 – Centrilobular (Closes to Central Vein)





- **Biliary Tree:**
  - **Structures Within the Liver:**
    - Hepatocytes secrete bile into **Bile Canaliculi** → Drain into Larger **Bile Ducts**
    - Many Bile Ducts converge → eventually →**Common Bile Duct**.
  - **Structures Exiting The Liver:**
    - **R & L Hepatic ducts** of liver → **Common Hepatic Duct**
      - → **Cystic Duct** → Gallbladder
      - → **Common Bile Duct**
    - Pancreas → **Pancreatic Duct**
    - **Common Bile Duct + Pancreatic Duct** → **Hepatopancreatic Ampulla**.

Bile Composition:

- H_2O
- Electrolytes
- Bile Salts -Digestion & Absorption of Lipids
- Phospholipids -Digestion & Absorption of Lipids
- Cholesterol
- Bilirubin

Functions of Bile:

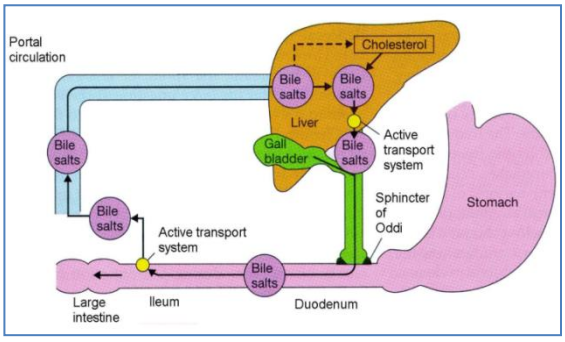
- Critical for Digestion/Absorption of FATS in Small Intestine
- Provides a medium for disposal of some bodily wastes:
    - Wastes secreted into bile
        - Eg. Endogenous:
            - Calcium
            - Cholesterol (Soluble in bile salts)
            - Steroid Hormones
            - Bilirubin
        - Eg. Exogenous:
            - Antibiotics
            - Metabolites of Drugs
    - Eliminated in Faeces....OR
    - Reabsorbed by Small Intestine→blood→kidneys→Urine.

Bile Release:

- Acidic, fatty chyme enters duodenum-
    - Stimulates Secretion of:
        - Secretin:
            - Stimulates bicarbonate ion secretion (pancreas)
            - Stimulates bile secretion (liver)
        - CCK (cholycystokinin):
            - Increases pancreatic enzyme secretion
            - Stimulates gallbladder contraction
            - Relaxes the hepatopancreatic sphincter (Sphincter of Oddi)
        - Vasoactive Intestinal Peptide:
            - Relaxes smooth muscle of stomach – slows gastric emptying
- Bile is released into duodenum via hepatopancreatic sphincter (Sphincter of Oddi)

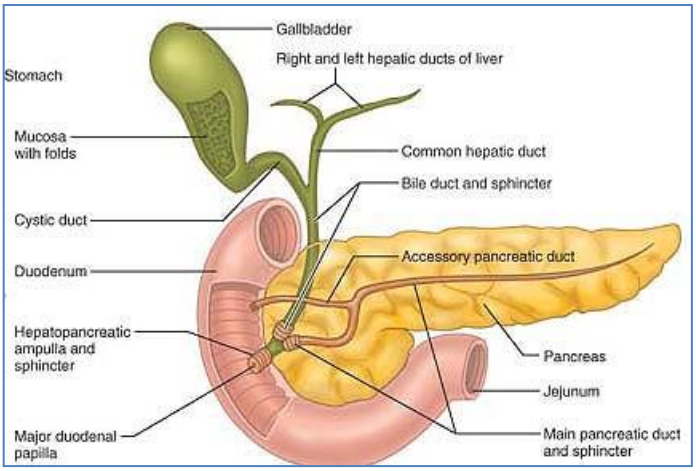
EnteroHepatic Circulation ("Intestine→Liver"):

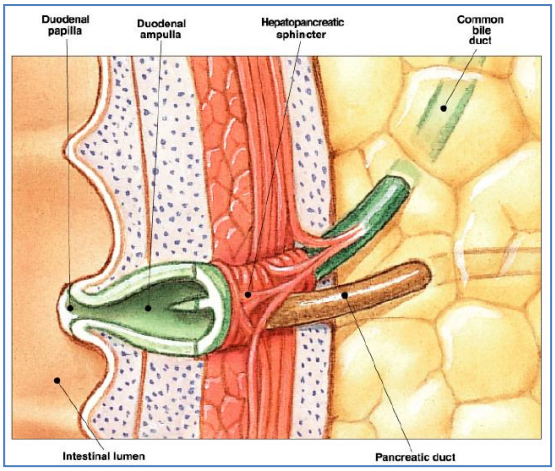
- Ie. Recycling of Bile Salts
- 90% of bile salts are reabsorbed (in ileum) into blood.
- Ileum venous blood→Portal Vein→Liver:
    - Hepatocytes extract bile salts from blood
    - Bile salts are re-secreted into canaliculi.
- Each bile salt molecule is reused approx: 18-20 times.
    - Ie. On average, bile salts are turned over every 18-20 meals.



Gallbladder:

- **Function:** Storage & Concentration of Bile
  - Greenish-yellow fluid
  - Alkaline – neutralises stomach acid in duodenum
  - Composed of cholesterol, bile salts (emulsifiers) & metabolic wastes of liver (Incl. Bilirubin).
- **Regulation:** Hormone = CCK Cholecystokinin: ("move the bile-sac")
  - Secreted by duodenum → Contracts Gall Bladder & Relaxes Hepatopancreatic Sphincter
    - →Causes release of Bile & digestive enzymes





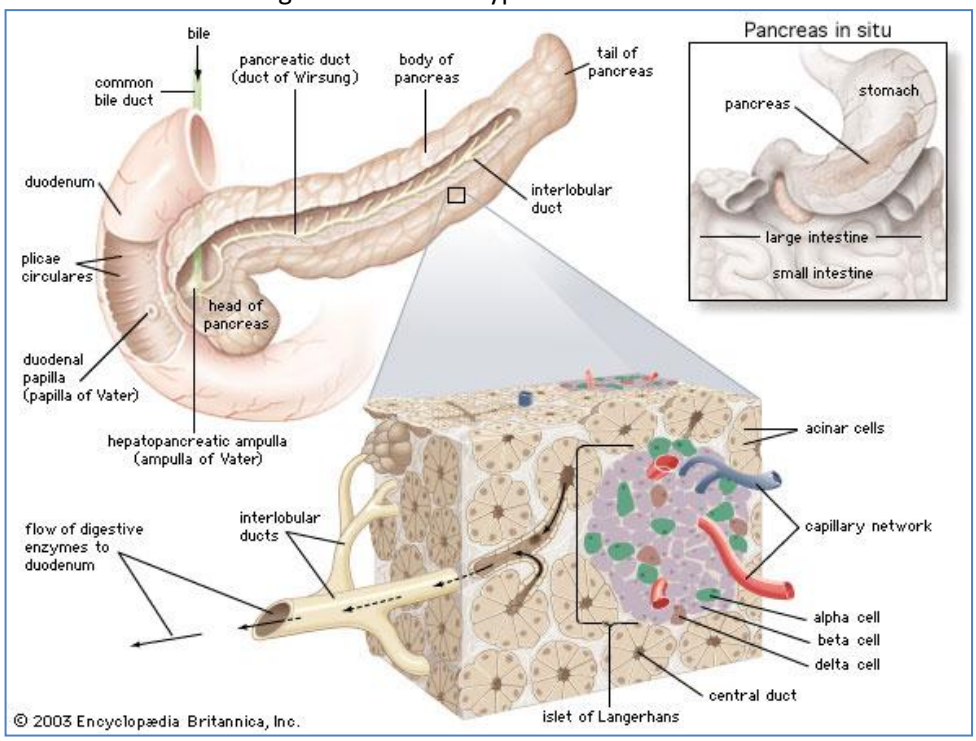
Physiology:

- **Normal Bilirubin Metabolism:**
  - **Where Bilirubin Comes From:**
    - Metabolism of Protoporphyrin, a Breakdown product of Heme in Haemoglobin in RBCs.
  - **Spleen's Role:**
    - Primary organ of RBC sequestration & breakdown.
  - **Process of Haemoglobin Breakdown & Bilirubin Formation:**
    - Haemoglobin → Heme & Globin.
    - Heme → Iron & Protoporphyrin
    - Protoporphyrin → Biliverdin (Green) → Unconjugated Bilirubin (Yellow)
  - **Bilirubin Metabolism:**
    - 1. Unconjugated Bilirubin in Spleen is NOT Water-Soluble
      - :. Transported to Liver via Albumin → Uptake into Hepatocytes.
    - 2. Hepatocytes Conjugate Bilirubin with Sugar Residues → Water Soluble
    - 3. Conjugated Bilirubin is Excreted with Bile into Gut.
      - Most is Excreted as Stercobilin in Faeces.
      - Some is Reabsorbed but Excreted as Con-Bilirubin and Urobilinogen in Urine.
  - **Jaundice:**
    - Jaundice occurs when a fault in the above sequence → ↑↑Bilirubin in the Blood

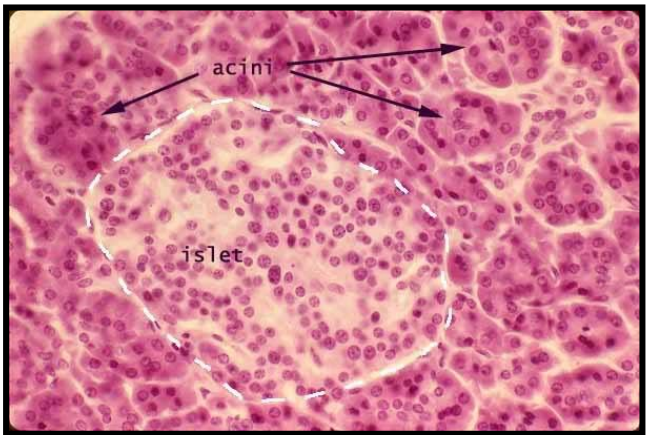
- **Other Liver Functions:**
  - **Bile Synthesis**
  - **Protein Metabolism** (Synthesis, Storage & Degradation[transamination])
  - **Carbohydrate Metabolism** (Synthesis, Storage & Metabolism).
  - **Lipid Metabolism & Transport** (VLDL Synthesis, HDL Synthesis
  - **Vitamin A production & storage**
  - **Makes Heparin** – blood thinner (anti-clotting agent)
  - **Drug Detoxification/Activation**
  - **Immunological Function** (Kupffer Cells – Macrophages attached to endothelium)

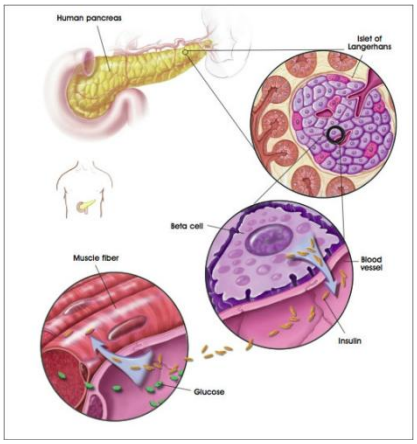
Pancreas:

- **Anatomy**
  - Elongated, Horizontal, Retroperitoneal
  - Head –Cupped by the Duodenum
  - Tail – abuts the spleen
  - Exocrine – Acinar Epithelial Cells + Duct Network
  - Endocrine – Islets of Langerhans + 4 Cell Types



- **Pancreas Physiology**
  - **85% Exocrine (Acini):**
    - **Pancreatic Juice:** 1. Membrane-Bound Vesicles of ***Zymogens*** in Epithelial Cells → 2. Active Secretion into Pancreatic Ducts → 3. Drains from the **Main Pancreatic Duct** → Duodenum:
      - Amylase (Digests Carbohydrates)
      - Lipase (Digests Fats)
      - Chymotrypsin (Digests Protein)
      - Aminopeptidase (Digests Protein)
      - Elastase (Digests Protein – Esp. Elastin)
      - Nuclease (Digests Nucleic Acids)
      - Bicarbonate (Helps neutralise acid)
  - **15% Endocrine (Islets):**
    - **Hormones – By 4 Different Cells in the Islets of Langerhans:**
      - β-Cells → Insulin (↓BSL)
      - α-Cells → Glucagon (↑BSL)
      - δ-Cells →
      - PP-Cells→



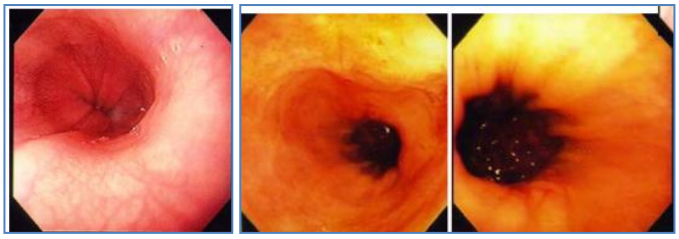


COMMON DISORDERS OF THE GASTROINTESTINAL TRACT:

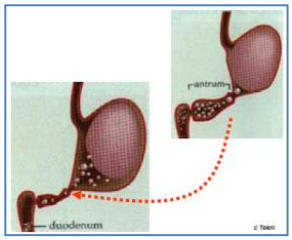
Disorders of the Upper GI Tract:

- *** GORD (Gastro-oesophageal Reflux Disease)**
  - **Definition:**
    - **=** "Reflux of highly acidic gastric juices into oesophagus, leading to ↓Oesophageal Integrity"

  - **Factors normally preventing GORD:**
    - **Lower Oesophageal Sphincter Tone (Pic: Left = Good; Right = Bad)
      - NB: This is decreased in smoking.



    - *Gravity
    - Crura (The ring of muscle around the lower-oesophageal sphincter – supportive role to LOS)
    - The slight '*kink*' where the oesophagus joins to the stomach.
    - Plasticity of Stomach → keeps Gastric Pressure Low.
    - Contraction/Relaxation Synchronisation (of Sphincter Muscles & Peristalsis)
      - Sphincter tone must be High at times of High Gastric Pressure.
      - However, The sphincter must also open to allow entry of food into stomach.

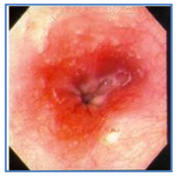


    - Gastric emptying → Keeps Gastric Pressure low.

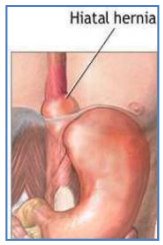
  - **Symptoms:**
    - **Common:**
      - Heartburn
      - Regurgitation
      - Belching
      - Epigastric Pain
      - Chest Pain
      - Dyphagia
      - Acid Brash (Regurge of Acid or Bile)
    - **Less Common:**
      - Odynophagia (Pain on swallowing)
      - Globus (Sensation of a 'ball' in the throat)
      - Nausea

  - **Diagnosis:**
    - Usually based on symptoms
    - Tests include:
      - pH-Monitoring
      - Barium Series
      - Upper Endoscopy.

- **Clinical Manifestations:**
  - Reflux Oesophagitis

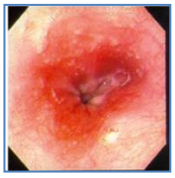


  - Chest Pain (sometimes mistaken for heart attack)
  - Hiatus Hernia – herniation of stomach through diaphragm.



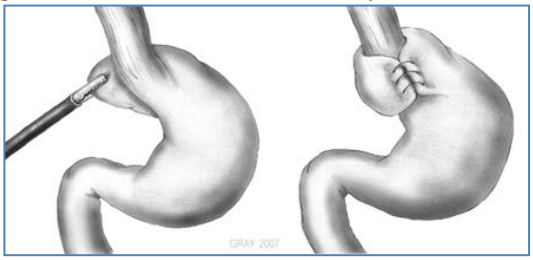
  - Haematemesis (vomiting blood)
  - Iron deficiency
  - Coughing (if aspiration of acid into airway)

- **Potential Outcomes:**
  - Oesophagitis (Inflammation of Oesophagus)

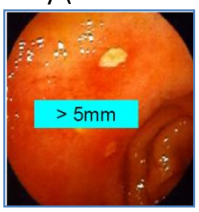


  - Oesophageal Ulcers
  - Stricture (From fibrous/scar tissue build-up → Ineffective Peristalsis)
  - Columnar Metaplasia (Change from Squamous Epithelium to Columnar Epithelium)
    - (Aka. **Barrett's Oesophagus**)
    - **NB:** Columnar Metaplasia of the Oesophagus (Barrett's) can develop into Oesophageal Adenocarcinoma (Cancer).
  - Oesophageal Cancer – Adenocarcinoma (Due to DNA damage from acid & free radicals)

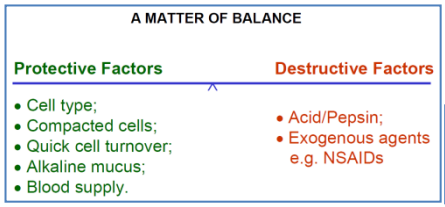
- **Phase I Treatment – Lifestyle Modification:**
  - Elevate bed-head
  - Avoid lying down for 3hrs after meals
  - Decrease fat intake (to → Increase Gastric Emptying)
  - Quit Smoking
  - Weight Loss (to → ↓Intra-abdominal Pressure)
  - Avoid Certain Foods (Caffeine/Chocolate/Spicy food/Alcohol/Citrus Fruits)
- **Phase II Treatment – Pharmacological (As Needed):**
  - **Antacids -** (1st line in GORD).
  - **Alginates -** (Often Combined with Antacids)
  - **NB:** Antacids can affect the Pharmacokinetics of other Oral Drugs due to pH Change.
- **Phase III Treatment – Pharmacological (Scheduled):**
  - **H_2 Histamine Receptor Antagonists -** (↓Histamine-Mediated Acid Secretion)
  - **Proton-Pump Inhibitor**
- **Phase IV Treatment – Maintenance Therapy:**
  - *Lowest Effective Dose* of **H_2 Antagonist or PPI.**
- **Stage V Treatment – Surgery:**
  - Nissen or Toupet Fundoplication – (Upper portion of stomach is wrapped around lower end of oesophagus → creates a 'new' valve to prevent reflux)



- **Peptic Ulcer Disease:**
  - **Where does it Occur?**
    - Duodenum
    - Stomach
    - Oesophagus (a result of GORD)
    - Margins of Gastrojejunostomy (Ie. Sometimes a side effect of surgery)



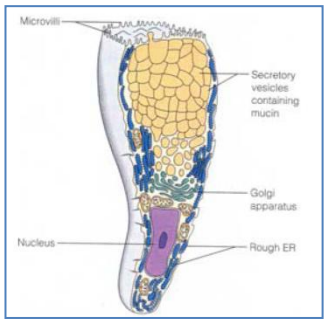
  - **Aetiology:**
    - **Matter of imbalance of protective & Destructive factors:**
      - Ie. Breakdown of protective mucosal barrier
      - Or. Excessive Chronic Exposure to Acid/Pepsin

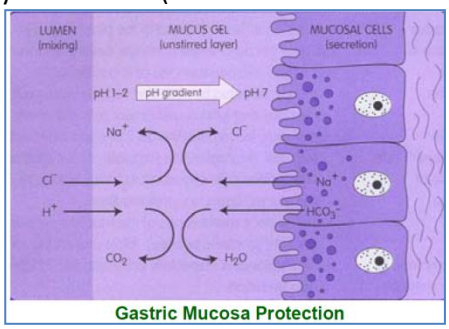


Proposed Mechanisms for Development of PUD

1. Breakdown of protective mucosal barrier;
2. Excessive chronic exposure to acid/pepsin.

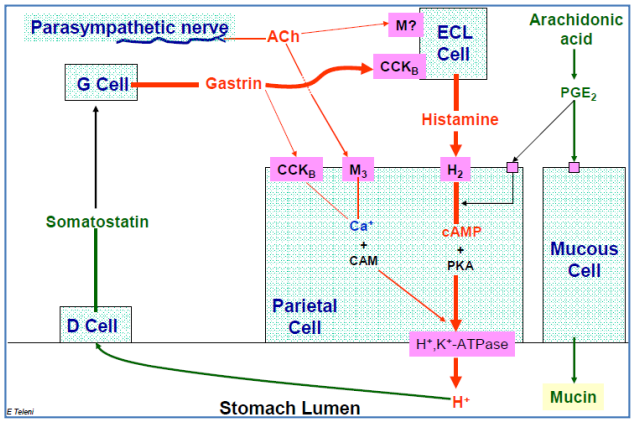
    - **Protective Factors:**
      - *Thick Alkaline Mucus Lining & Epithelial Barrier:
        - From Goblet Cells:
          - Mucin Synthesis is stimulated by Prostaglandin
          - Mucin protein synthesized in Endoplasmic Reticulum
          - Mucin is added to water → mucus
        - Unstirred Layer of mucus (closest to stomach lining) is neutral.



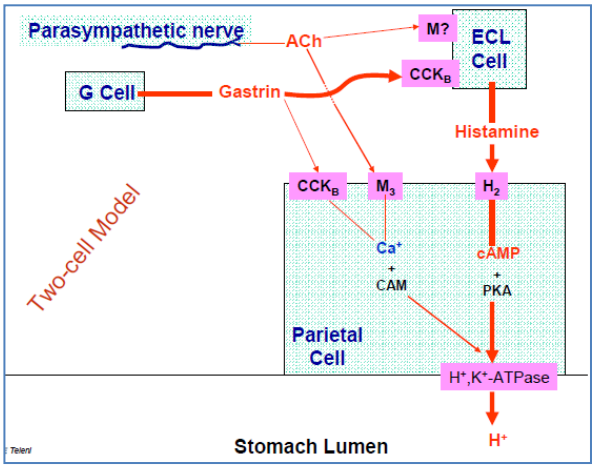


Gastric Mucosa Protection

      - *Prostaglandin:
        - → Stimulates ***Mucin*** Synthesis by Goblet Cells
        - → Inhibit *Histamine-Mediated* Acid Secretion by Parietal Cells.
      - *D-Cells
        - Detect H^+ in the stomach lumen → Secrete Somatostatin
        - Somatostatin = Negative Feedback to the G-Cell → Inhibits Gastrin Secretion



- **Destructive Factors:**
  - ***Acid:**
    - Two Cell Model: Stimulated by Gastrin → ECL Cell → Parietal Cells via Histamine → Stimulates Hydrogen (Proton) Pump from Parietal Cells.



  - ***Pepsin:**
    - Digestive Proteolytic Enzyme Secreted by Chief Cells.
  - ***NSAIDs – (Non Steroidal Anti-Inflammatory Drugs) – (Eg. Aspirin/Ibuprofen):**
    - 15-20% of NSAID users develop gastric ulcer.
    - **Why??**
      - NSAIDs Inhibit Cyclo-oxygenase (→↓Prostaglandin) → - ↓Prostaglandin-Mediated Mucin-Secretion from Goblet Cells; AND - ↓Inhibition of Parietal Cell Acid Secretion.
  - ****Helicobacter Pylori:**
    - Can burrow under the mucus layer (where the ph is neutral) → Survives
    - Also has an enzyme (urease?) which can neutralise the acid.
    - Love Columnar Cells

  - **Stress (Zollinger-Ellison Syndrome):**
    - = A Rare condition characterised by Treatment-Resistant Peptic Ulcers Resulting From 'Gastrinomas' (Acid-Secreting tumour) in the Pancreas/Duodenum → Peptic Ulcers in Duodenum.

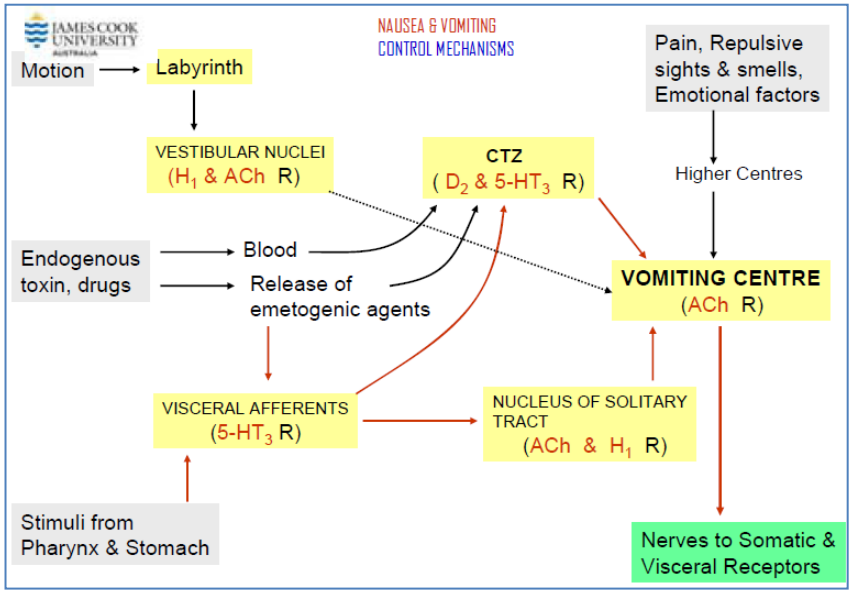
- **Pathogenesis – Helicobacter Pylori:**
  - **Gastric Ulcer:**
    - HP → Gastritis → Damage to Epithelial Layer → Exposure to Acid → Gastric Ulcer → ↓Antral D-Cells (&Somatostatin) → Decreased Inhibition of G-Cells → ↑ Gastrin → ↑Histamine-Mediated Acid Secretion by Parietal Cells→ Potentiates Gastric Ulcer.
  - **Duodenal Ulcer:**
    - GORD → ↑Exposure to Acid → Gastric Metaplasia → Colonised by HP → Duodenitis → Duodenal Ulcer.

- **(Therapeutic Management of H.Pylori-*Positive* Peptic Ulcers:)**
  - **Proton Pump Inhibitors** – (To reduce destructive acid)
  - **Antibiotics** – (To kill the H.Pylori)
  - **A Mucosal-Protective Drug: *Bismuth-Containing* Preparation ("Bismuth Chelate")**
    - – (Toxic effects on H.Pylori, Inhibits Adherence to Mucosa, & Inhibits Bacterial Proteolytic Enzymes)
    - Also has Mucosal Cytoprotective Properties (See below)

- **Nausea & Vomiting:**
  - **Control Mechanisms:**
    - **3 Phases:**
      - **1.** Afferent Signals to Emetic Centre (From Noxious Stimuli)
      - **2.** CNS send out efferent emetic signals
      - **3.** Coordinated Respiratory & Abdominal muscle Contraction; & GI Smooth Muscle Relaxation → Vomiting.
  - **NB The Vomiting Centres monitor Blood & Other Emetic Stimuli:**
    - **Stimulated by:**
      - CTZ → Endogenous Toxins in blood
      - GI Tract (Ie. From Pharynx [gag reflex]/Stomach [if too full]) - (Via Vagus)
      - Labyrinth (Inner Ear) → Motion Sickness (Nausea)
      - Cortex & other Higher Centres (Ie. Senses/Emotions).
  - **Central Vomiting Centres – In the Medulla Oblongata:**
    - **Chemoreceptor Trigger Zone (CTZ):**
      - Sensory Stimuli
      - Blood-Brain Barrier is Semi-Permeable.
      - Senses Chemicals & other stimuli in blood (Toxins/Drugs/Uraemia/Infections/etc)
      - Relays Emetic Signals to the VC.
    - **Vomiting Centre (VC):**
      - The Integrative centre for *Incoming Emetic Signals*.
      - Coordinates *Efferent* Emetic signals → Respiratory/Abdominal Muscle Contraction AND GI-Smooth Muscle Reverse Peristalsis → Vomiting.
  - **Agonists & Receptors:**

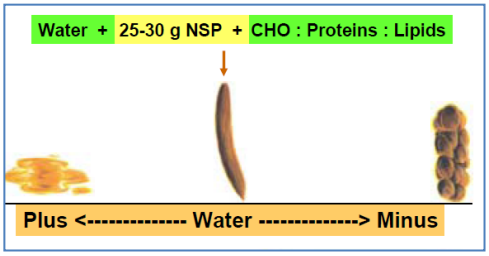
Agonists	Receptors
Histamine	H_1
Acetylcholine	M
Dopamine	D_2
5-hydroxytryptamine (serotonin)	5-HT_3
Enkephalin	Opioid

  - **Diagram:**
    - Pain;Repulsive stimuli → Higher Centres → Vomiting Centre → Nerves to Somatic & Visceral Receptors.
    - Motion (determined by inner ear vs. Eye) → Directly stimulates vomiting centre
    - Endogenouus Toxins/Drugs → Absorbed into blood → Crosses BBB → CTZ → Stimulates Vomiting Centre.
    - Visceral Afferents (eg. Toxins/Stimuli from stretch of stomach/Pharynx) → Stimulates vomiting centre.

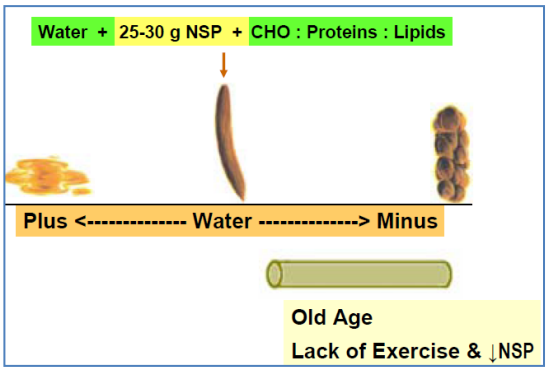


Disorders of the Lower GI Tract:

- **Diarrhoea:**
  - **Types:**
    - Acute (a few days)
    - Chronic (4 wks+)
    - Episodic
  - **Causes of Acute Diarrhoea:**
    - Food Poisoning
    - Gastroenteritis
    - Various Tropical Diseases (Eg. Cholera/Typhoid)
    - Anxiety or Emotional Stress
    - Excess Alcohol
    - Medications (Eg. Antibiotics/Antacids/Antihypertensives/Antiarthritics)
    - Various Pathogens (Eg. Viruses/Bacteria - E.Coli, Cholerae, Salmonella/Parasites – Giardia)
  - **Causes of Chronic Diarrhoea:**
    - Coeliac (Gluten Intolerance) & Lactose Intolerance
    - Chronic Constipation (→ *Overflow* Diarrhoea – Typically in Elderly)
    - Hormone Disorders (Eg. Diabetes)
    - Cancer (Eg. Bowel Cancer)
    - Inflammatory Bowel Diseases (Eg. Crohn's Disease/Ulcerative Colitis)
    - Irritable Bowel Syndrome
  - **Potential Risks With Diarrhoea:**
    - *DEHYDRATION
    - Electrolyte Disturbances
    - Infections
  - **Aetiology & Pathogenesis – 4 Major Mechanisms:**
    - **Osmotic Diarrhoea:**
      - Disaccharidase Deficiency
      - Lactulose
      - Antacids
      - Primary Bile Acid Malabsorption
    - **Secretory Diarrhoea:**
      - Infectious:
        - Viral damage to mucosal epithelium
      - Enterotoxin Mediated:
        - Eg. Cholera
      - Neoplastic:
        - TUmor elaboration of peptides, Serotonin, Prosatglandins.
    - **Exudative Diarrhoea (NB:Mech is actually osmotic)**
      - Active inflammation → Mucus Blood & protein → ↑Osmotic Load
      - Infectious → Same diff.
    - **Diarrhoea related to Motility Disturbances:**
      - Fluid in colon
      - Fluid vs Colon absorptive capacity
      - See lecture

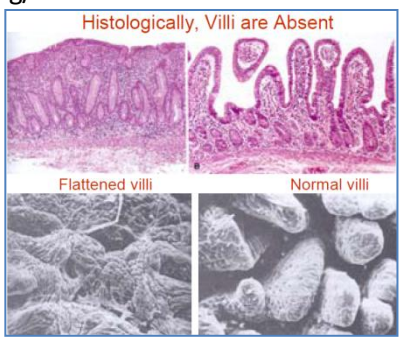


- **Constipation:**
  - **Common Causes:**
    - Chonic Laxative Abuse →Lazy Bowel Syndrome→ Constipation
    - Drug related (Eg. Opioids)
    - Pathological conditions (physical obstruction/diverticulitis/neurological)
  - **See lecture for the rest!!!**



Malabsorptive Disorders:

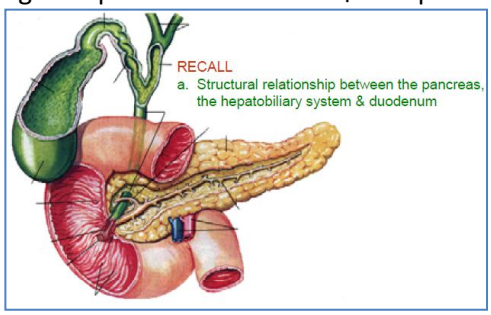
- **4 Main Causes:**
  - **1. Impaired Intraluminal Digestion:**
    - Eg. Pancreatitis, Cystic Fibrosis, etc.
  - **2. Impaired Mucosal Cell Function:**
    - Eg. Bacterial Infection, Disaccharidase Deficiency, Lactase Deficiency, Brush Boarder Damage.
  - **3. Reduced Functional Surface Area in Small Intestine:**
    - Eg. Coeliac Disease:
      - Abnormal Sensitivity to Cereal Gluten
      - Leads to an Immune-Mediated destruction of Mucosa.
    - Eg. Crohn's Disease:
      - Cause Unknown.
      - = Regional Inflammation of the Ilium.
      - → Formation of Fibrous Tissue, Reduction in Absorptive Area, Narrowing/Obstruction.



  - **4. "Latrogenic" – ("brought about by doctors, but not implying liability"):**
    - Eg. Surgical Resection of Stomach or Small Intestine.
    - Eg. Loss of Motility Patterns/Absorptive Area
    - → Dumping Syndrome (Loss of Gastric Emptying)
    - → Short Bowel Syndrome (Severe Diarrhoea & Malabsorption)

Disorders of Accessory Digestive Organs:

- **Pancreatitis:**
  - **Differentiating between Acute or Chronic:** (NB: Acute can be life-threatening)
    - **Acute:**
      - **An Inflammatory Disorder → Oedema, Haemorrhage, & possibly Necrosis.**
      - Vacuoles of Fat + Calcium (aka. "Soaps")
      - **Symptoms:**
        - Upper Abdo Pain & Vomiting
        - Elevated Serum Amylase
    - **Chronic:**
      - **Progressive Destruction of the Pancreas → Marked Decline in Pancreatic Function:**
        - **↓Exocrine Functions:** ↓Pancreatic Enzymes → Nutritional Malabsorption.
        - **↓Endocrine Functions:** ↓Insulin & Glucagon → Diabetes Mellitis.
      - **3 Subtypes:**
        - **Chronic Calcifying Pancreatitis –** Calcium plug blocks pancreatic ducts.
        - **Chronic Obstructive Pancreatitis –** Stenosis of pancreatic Sphincter.
        - **Cystic Fibrosis-Related Chronic Pancreatitis –** Destruction of Acinar Cells.
  - **Common Causes:**
    - **- Alcohol Abuse:**
      - Alcohol is directly toxic to Acinar cells (The *Exocrine* cells which secrete digestive enzymes).
      - Sphincter of Oddi Dysfunction (Hepatopancreatic Sphincter)
      - Increases Ductal Permeability → Digestive enzymes permeate through the walls of the pancreatic ducts into the pancreas & surrounding Tissue → Inflammation → Pancreatitis.
    - - **Biliary Tract Disorder:**
      - Blockage of Sphincter of Oddi → ↑Intrapancreatic Ductal Pressure



    - - **Primary Acinar Cell Injury:**
      - Eg. Viruses, Drugs, Trauma.
    - - **Inappropriately Activated Pancreatic Enzymes → *Auto-Digestion*:**
      - Mechanism of Inappropriate Activation is Unclear
      - Hypothesis = Auto-Trypsinogen Activation → Trypsin:
        - Trypsin → Activates Pro-Enzymes → Active Enzymes → Auto-Digestion.
        - (Thus Trypsin-Activation Peptide (TAP) is a marker)
  - **A 2-Stage Disease:**
    - **Stage 1 –** Systemic Inflammatory Response Syndrome:
      - Cytokines & Vasoactive Mediators Released.
      - Failure to resolve Spontaneously (or with intervention)
    - **Stage 2 –** Complications Develop:
      - **- In & around Pancreas** – Cysts/Stones/Stenosis/Pancreatic Cancer.
      - **- Elsewhere in the abdomen** – Portal Hypertension
  - **Pathogenesis:**
    - **Microvascular Leakage** → Oedema
    - **Lipolytic Enzymes** → Fat Necrosis
    - **Acute Inflammatory Reaction**
    - **Proteolytic Enzymes** → Destruction of Pancreatic Tissue
    - **Destruction of Blood Vessels** → Haemorrhage.

- **Diagnosis:**
  - **Main:** Elevated ***Serum Amylase*** (Enzyme released into blood during inflammatory process)
  - **Others:**
    - Trypsin Activation Peptide (TAP)
    - Lipase
    - Aminotransferase
    - Alkaline Phosphatase (suggests Biliary disease)
- **Treatment:**
  - **Acute Pancreatitis:**
    - Analgesia (Pethidine is best → Causes less Pancreatic Sphincter Spasms)
    - Replace Plasma Volume
    - Nutritional Support (Parenteral Nutrition – Via Naso-Jejunal Tube)
    - Antibiotic Prophylaxis
    - New Therapies – Inhibitors of Digestive Enzymes.
  - **Chronic Pancreatitis:**
    - Analgesia (Since Chronic Pancreatitis is an Inflammatory Process, NSAIDs are useful)
      - However, consider risk of gastric ulcers with NSAID use.
    - Manage Coincidental Bile-Duct Disease if Present
    - Low Fat Diet.
    - Treat Malabsorption by *Replacing* Digestive Enzymes (eg. Common in CF Patients)
    - Manage Diabetes with Exogenous Insulin.

GI Tract Secretions

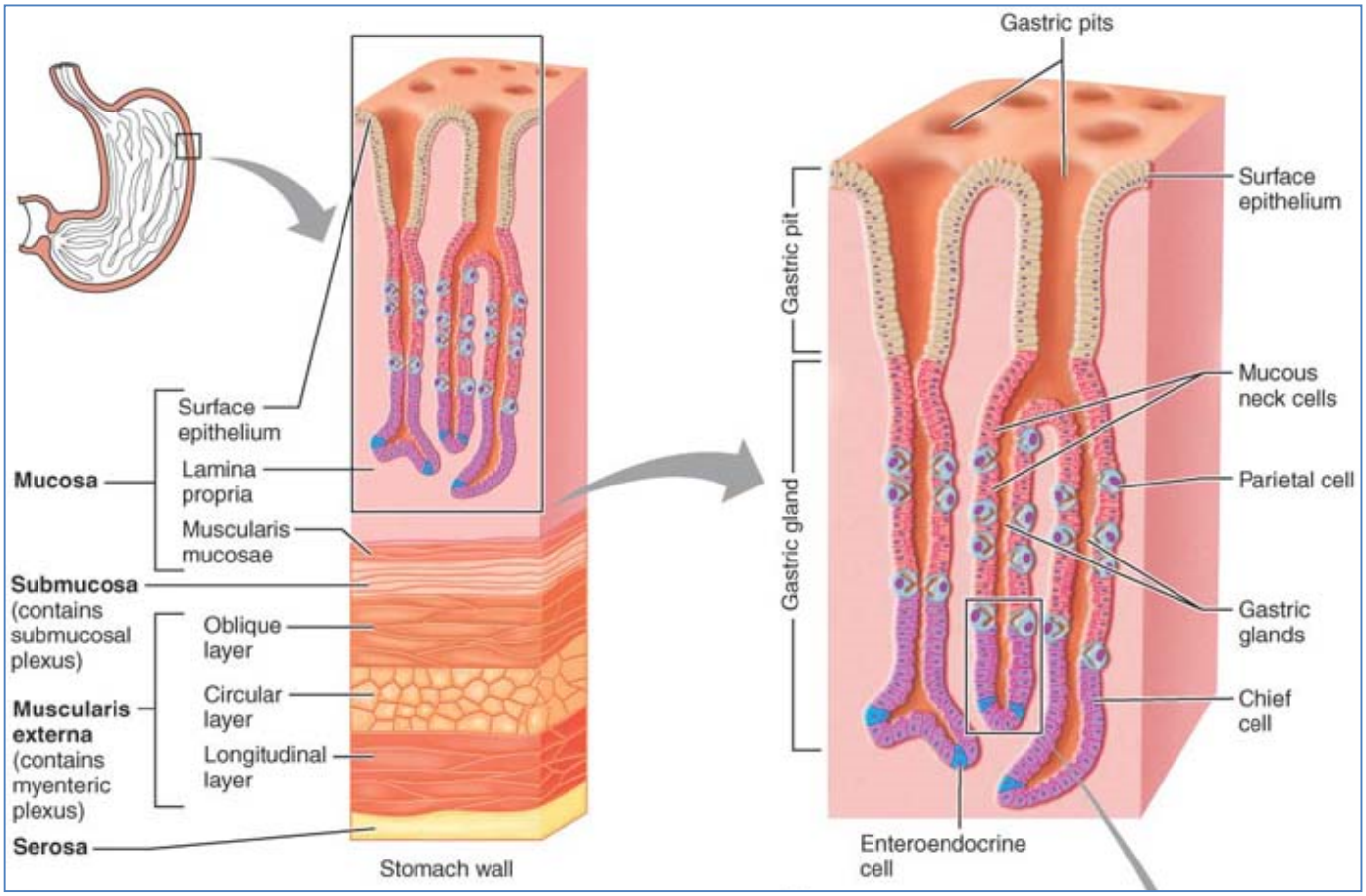
Functions of Secretions

- **Proteins**
  - Digestion: Enzymes
  - Protection/Lubrication: Mucin
  - Antimicrobial: Immunoblobulins in saliva
  - Hormonal: Peptide hormones
- **Ions**
  - Acid/Base balance: Maintain pH
  - Maintains Osmolality: Maintains concentration of dissolved ions in lumen (300mOsmols ☺)
  - Electrochemical Gradient: Facilitates ion transfers into & out of the cell
- **Water**
  - Acts as solvent
  - Transport medium
  - Needed for chemical reactions
  - Maintains Osmolality
  - Needed for consistency: For – ingestion/digestion/ & excretion.

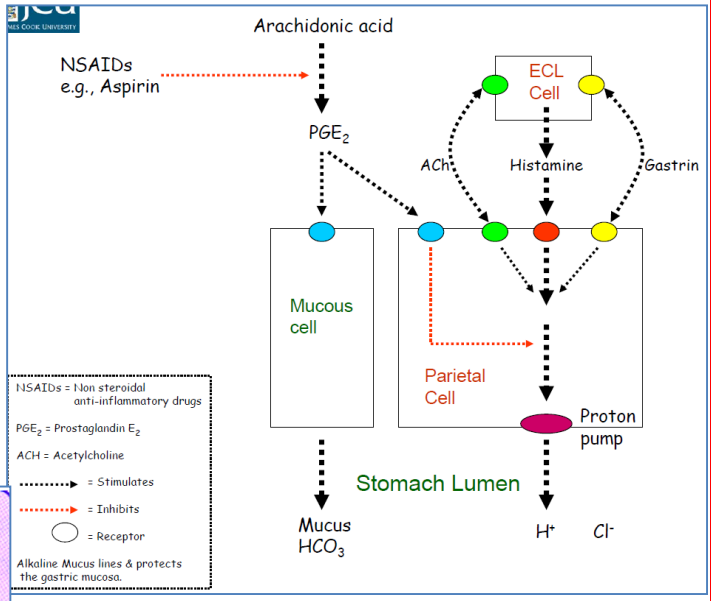
Secretory Structures:

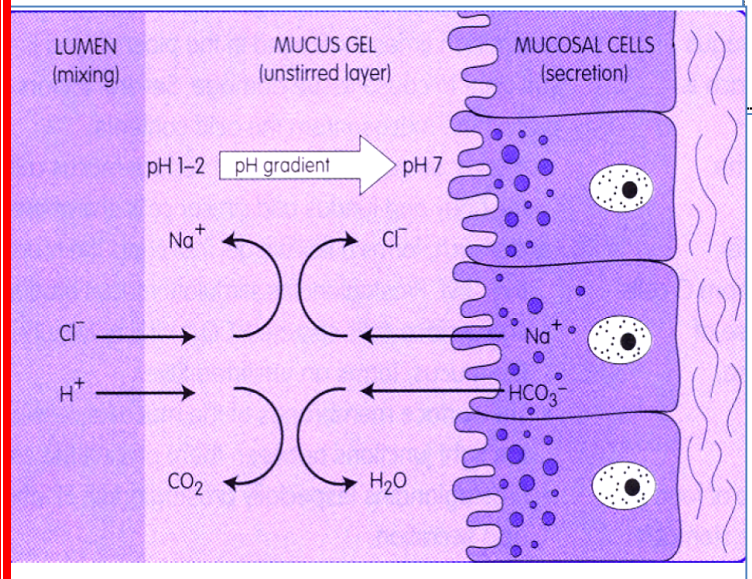
- **Salivary Glands:**
  - **Parotid**
    - Enzyme: Alpha-Amylase (breaks down amylose – straight chain starch)
    - Proline-rich proteins
    - Anti-Microbial Agents
  - **Submandibular**
    - Mucous
    - Enzyme: Alpha-Amylase
  - **Sublingual**
    - Mucous

- **Stomach:**
  - **Mucosa:**
    - Composed entirely of **Goblet Cells**
    - Secretes viscous **mucous**
    - Secretes **HCO_3^-** → neutralises H^+ ions in mucus gel (unstirred layer)
  - **Gastric Pits:**
    - Produce gastric juice.
      - **Mucous Neck Cells**
        - 'Neck' regions of the glands
        - Produce a thin ***acidic*** **mucous**
      - **Parietal Cells**
        - Middle regions of glands scattered amongst chief cells
        - Secrete **HCl** &
        - **Intrinsic Factor** – binds ingested vitamin B_{12} – allows it to be absorbed.
      - **Chief Cells**
        - Basal regions of glands
        - Produce **pepsinogen** (inactive form of pepsin – a protease)
        - Pepsinogen + HCl → **Pepsin**
      - **Enteroendocrine Cells**
        - Release chemical messengers into interstitium.
        - Eg. **Histamine, Seratonin, Gastrin**



- **Mucosal Protection Barrier:**
  - Alkaline Mucous
  - Cell Arrangement – tight junctions, epithelia, etc
  - Cell Turnover – every 5-7 days
  - Prostaglandin (PGE_2) secretion:
    - Increases goblet cell secretion – Mucus + HCO_3
    - Decreases acid secretion from parietal cell
    - Increases blood-flow to cells





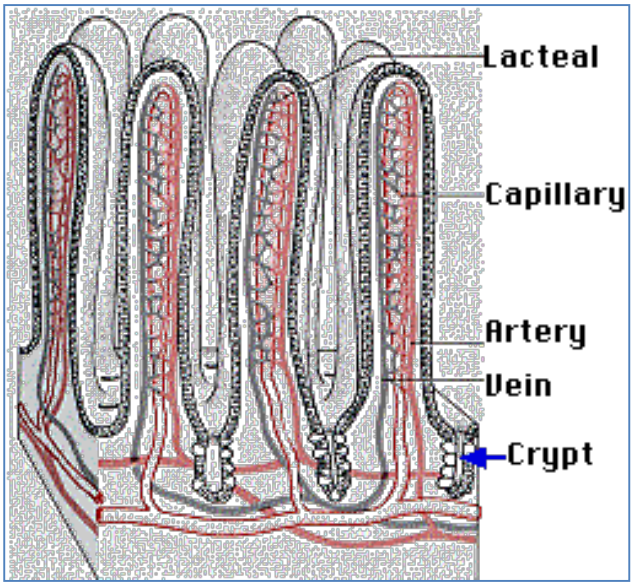
Gastric Mucosa Protection

- **Duodenum – Brunner's Glands:**
  - Compound tubular glands
  - In the area of the duodenum above the hepatopancreatic sphincter.
  - Secrete **alkaline fluid** & mucus
  - Helps neutralise acidic chyme from stomach.

- **Liver**
  - Produces bile for absorption of fats.
  - **Bile**
    - Bile salts, phospholipids & emulsifiers
  - **Gallbladder**

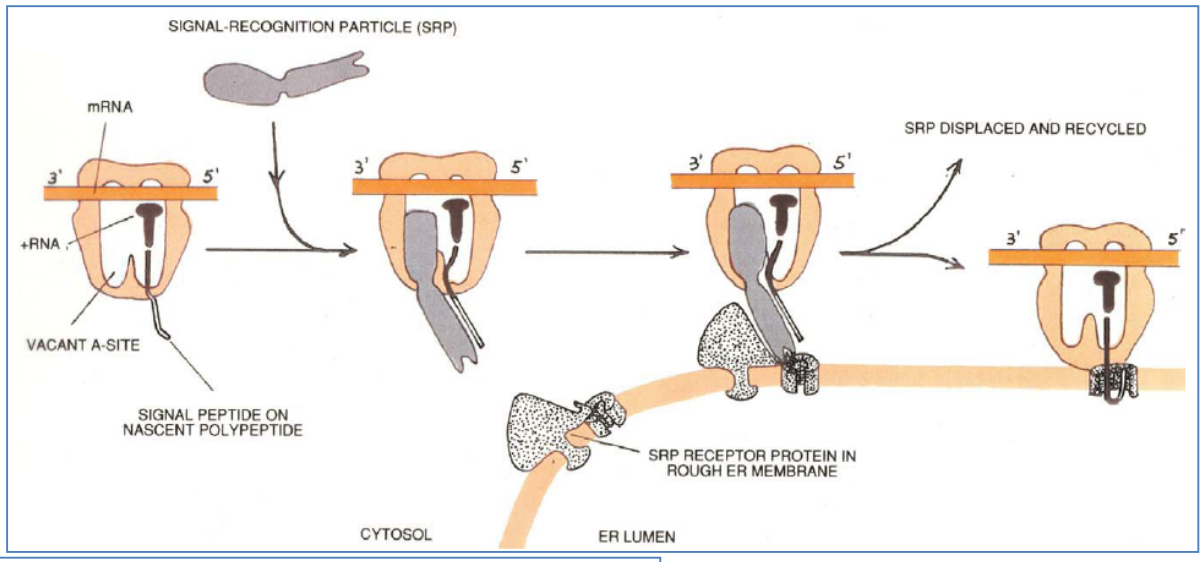
- **Pancreas (Exocrine) –** secretes:
  - **Bicarb** – neutralises acidity
  - **Pancreatic Amylase** – hydrolyses starch →maltose + glucose
  - **Pancreatic Lipase** – hydrolyses fats →fatty acids + monoglycerides
  - **Proteases** – proteolytic enzymes
  - **Nucleases** – hydrolyses nucleic acids (DNA & RNA) → nucleotides.

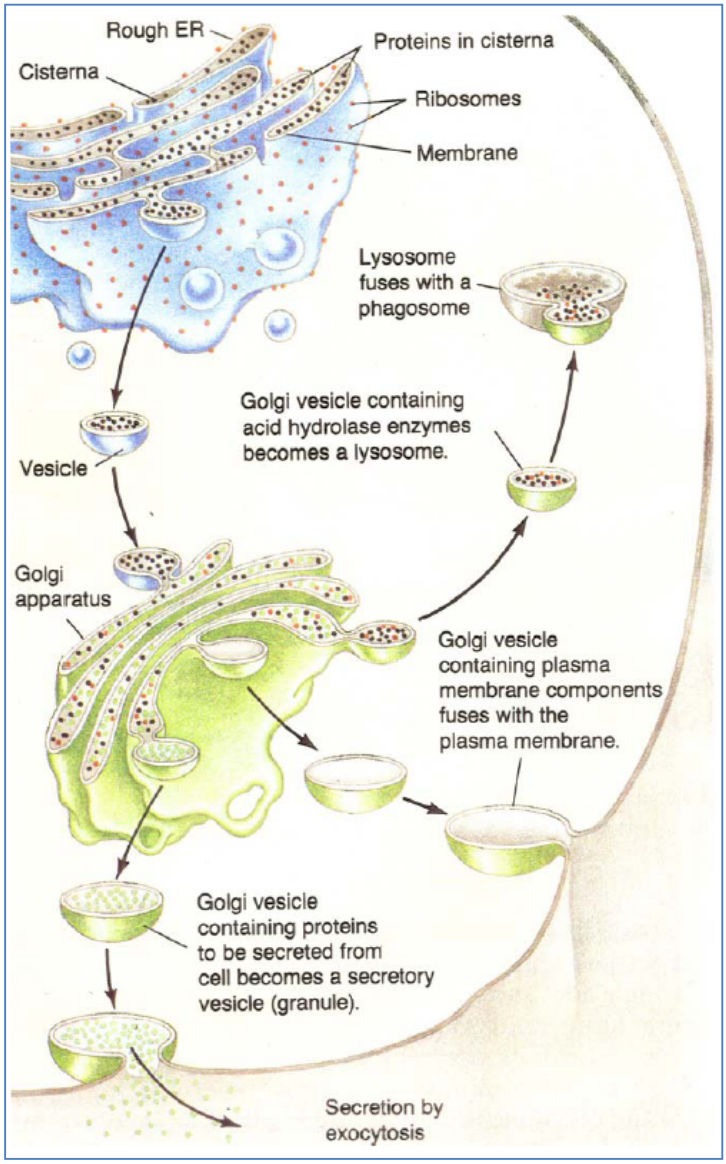
- **Intestine & Colon – Crypts of Lieberkuhn (intestinal crypts)**
  - **Paneth Cells**
    - Secrete defensins (antimicrobial agents) & lysozyme (an antibacterial enzyme)
    - Aid in intestinal immune defence
  - **Stem Cells**
    - At the bases of the crypts
    - Divide rapidly → replace the various cells of the intestinal wall.
    - Migrate up the villi and are sloughed off every few days.
  - **Epithelial Cells**
    - Secrete intestinal juice: slightly alkaline mucous.
  - **Goblet Cells**
    - mucous

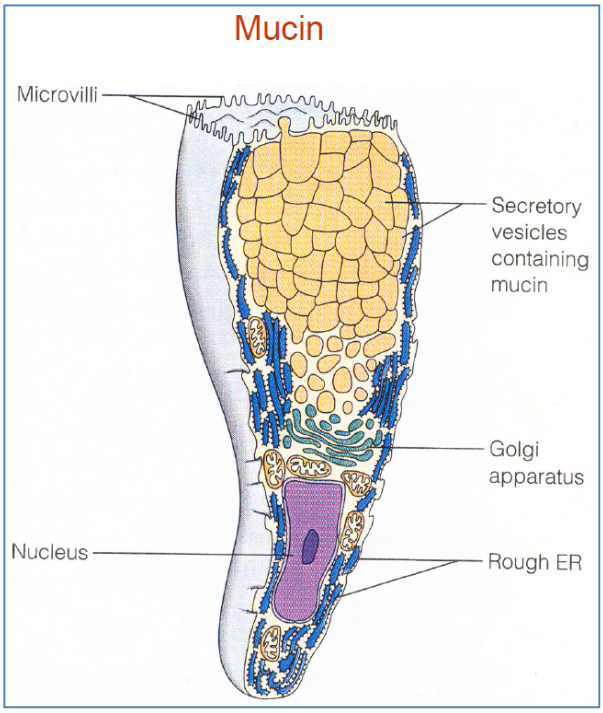


Mechanisms of Secretions

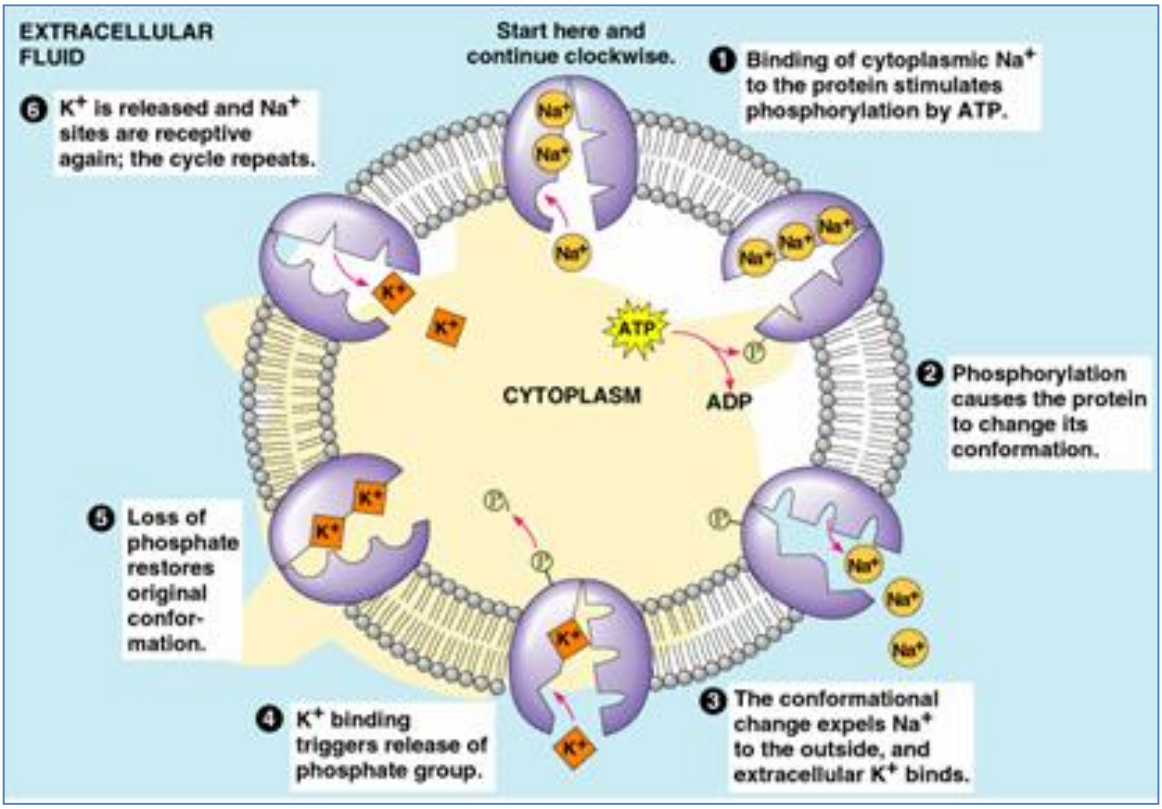
- **Exportable Protein Secretion**
  - Ribosome transcribes mRNA →protein
  - Ribosome attaches to receptor on Rough ER via **Signal-Recognition Particle**
  - →delivers protein into Rough ER.
  - Vesicles of protein bud off from Rough ER →sent to Golgi
  - Golgi modifies protein → sends vesicles to apical region of cell
  - Proteins Exocytosed OR Fused with membrane
  - Eg. Goblet Cell – Mucin



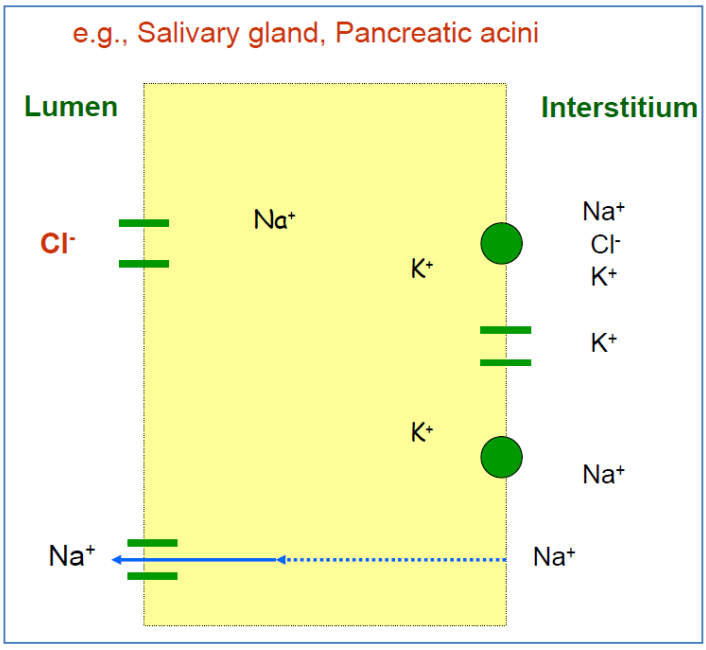




- **Ion & Water Secretion**
  - All ion transfers in & out of cells are either:
    - Active transport,
    - Down a concentration gradient, or
    - Down an electrical gradient
  - **<u>Ion Transfer often causes Water Transfer</u>**
  - **Na/K ATPase**
    - Uses ATP to set up concentration & electrical gradients.
    - Couples to secondary transporters to transport other substances.

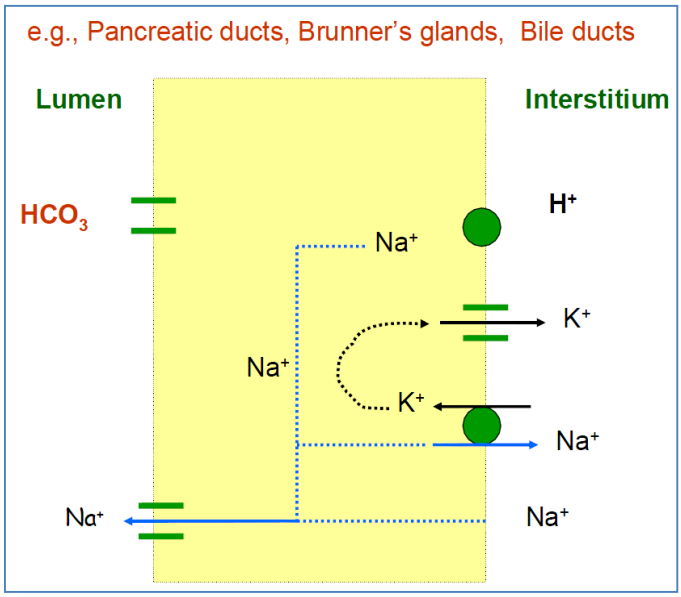


- **Fluid Secretion of Salivary Glands & Pancreatic Acini**
  - **Aim:** to move water into the lumen.
  - **Why:** because saliva & pancreatic juice have a high H_2O content – needed as a medium for solutes (enzymes, ions, bicarb, antibodies, etc)
  1. **Na/Cl/K-Cotransporter** imports **Cl** into cell via the Na conc. Gradient set up by Na/K-ATPase.
  2. Secretion of **Cl^-** into lumen (and Na^+ to balance electrical charge)
  3. Luminal ion conc. Increases → drags **H_2O into lumen** via **osmosis**.
  4. **Ions** are actively **reabsorbed** as the solution travels down the duct – but **not H_2O**



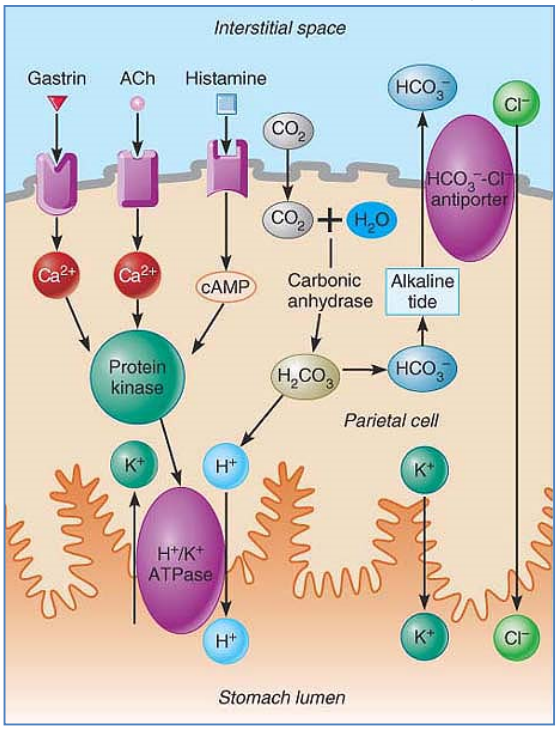
NB: Na/Cl/K-Cotransporter + Na/K-ATPase + Luminal Ion Channels

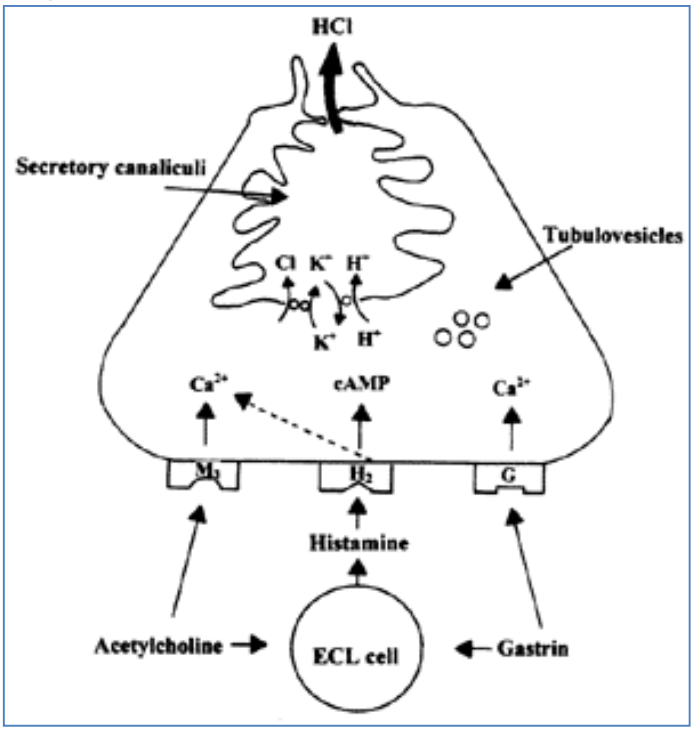
- **HCO_3 Secretion of Pancreatic Ducts, Brunner's Glands, Bile Ducts:**
  - **Aim:** to secrete **HCO_3**
  - **Why:** for **Acid Neutralising Properties** of **Pancreatic Juice, Duodenal Mucosa** & **Bile.**
  1. **CO_2** from blood diffuses into cell.
  2. **H_2O** in cell reacts with **CO_2** in the presence of **Carbonic-Anhydrase → H_2CO_3**
  3. **H_2CO_3 dissociates** in solution into **H^+** & **HCO_3^-**
  4. **H^+** is actively removed via **Na/H-Antiporter** via Na conc. grad. set up by Na/K-ATPase.
  5. **HCO_3^-** conc. builds up in cell → **diffuses out** through ion channel **into lumen**.
  6. **Na** also diffuses out to balance electrical charge.



NB: Na/H-Antiporter + Carbonic-Anhydrase + Na/K-ATPase + Ion Channels

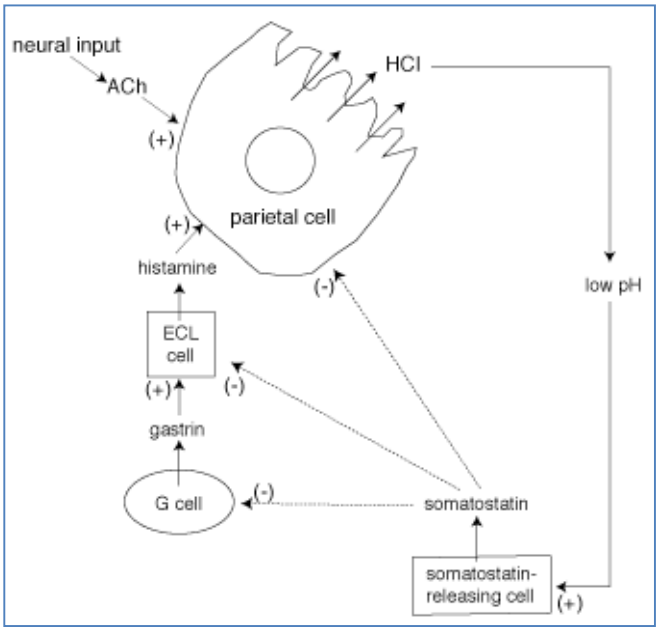
- **H^+ Secretion of Parietal Cells in Stomach:**
  - **Mechanism**
    - Stimulated by 3 Chemicals: ***Acetylcholine, Gastrin & Histamine***.
    - **ACh & Gastrin** both increase intracellular **Ca^+** concentrations → needed for **ProteinKinase** Activity.
    - **Histamine → cAMP → Protein Kinase** → activates **H/K-ATPase**.
    - **H/K-ATPase** → pumps **H^+** ions into lumen.
    - **H^+** ions supplied by **Carbonic Anhydrase** – combines **$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H + HCO_3$**
    - Remaining **HCO_3^-** ions leave cell via **HCO_3/Cl-Antiporter**
    - **HCO_3/Cl-Antiporter** bring in **Cl^-**

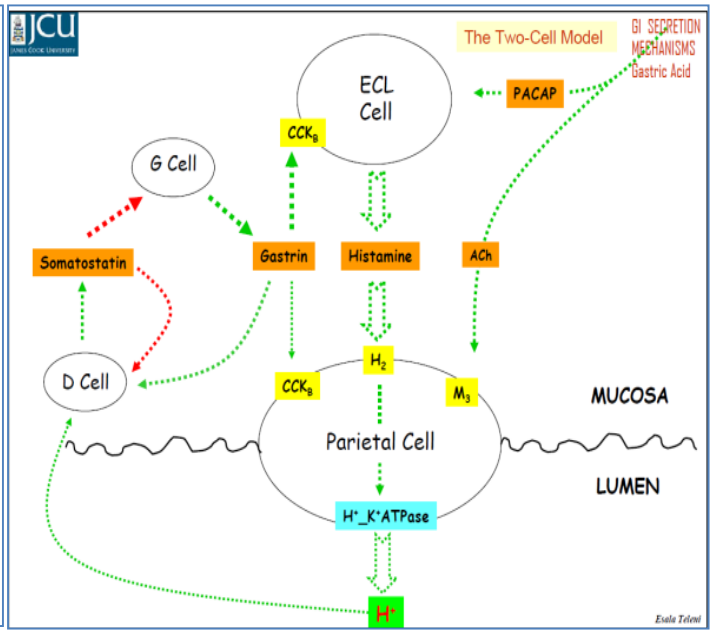


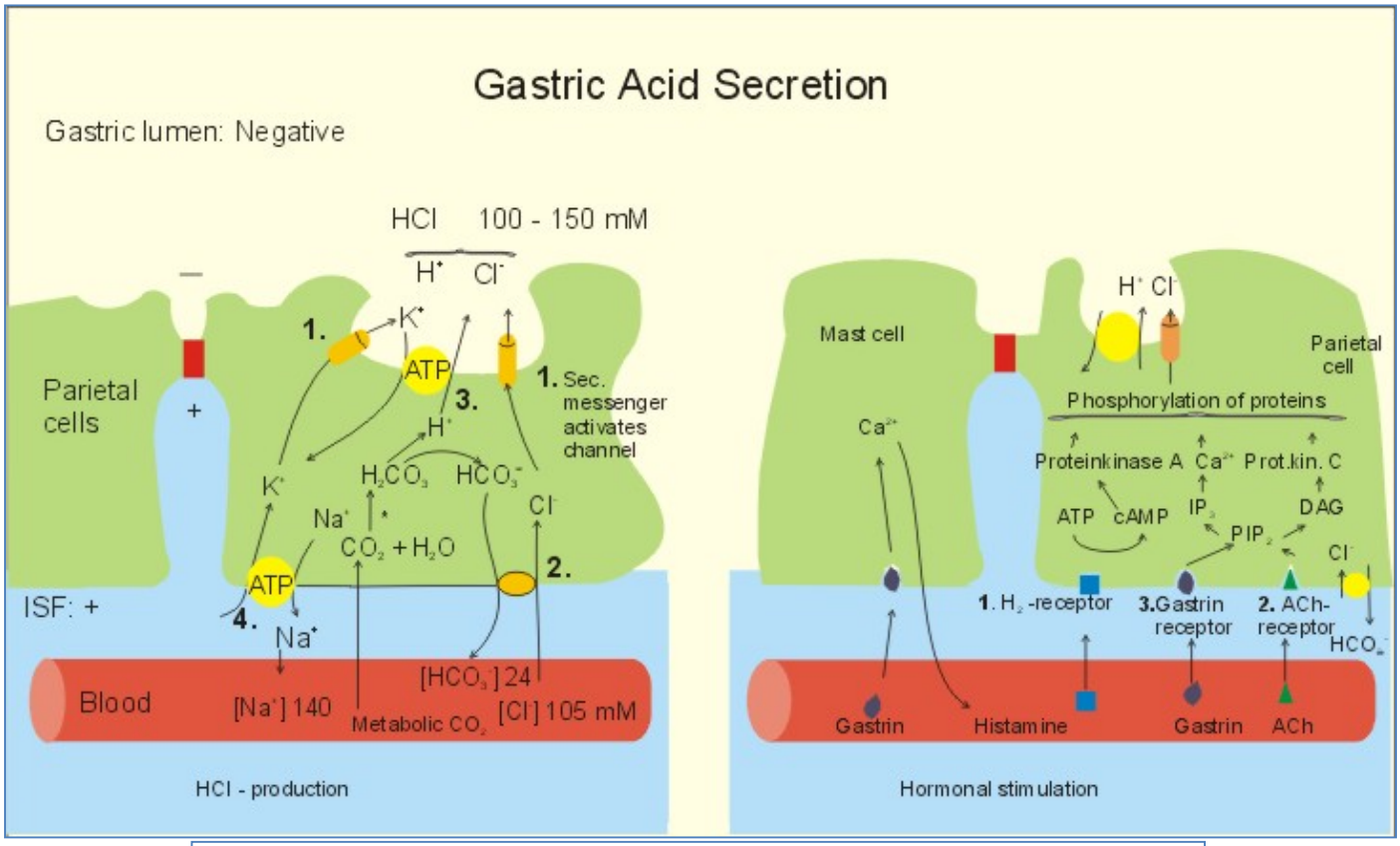


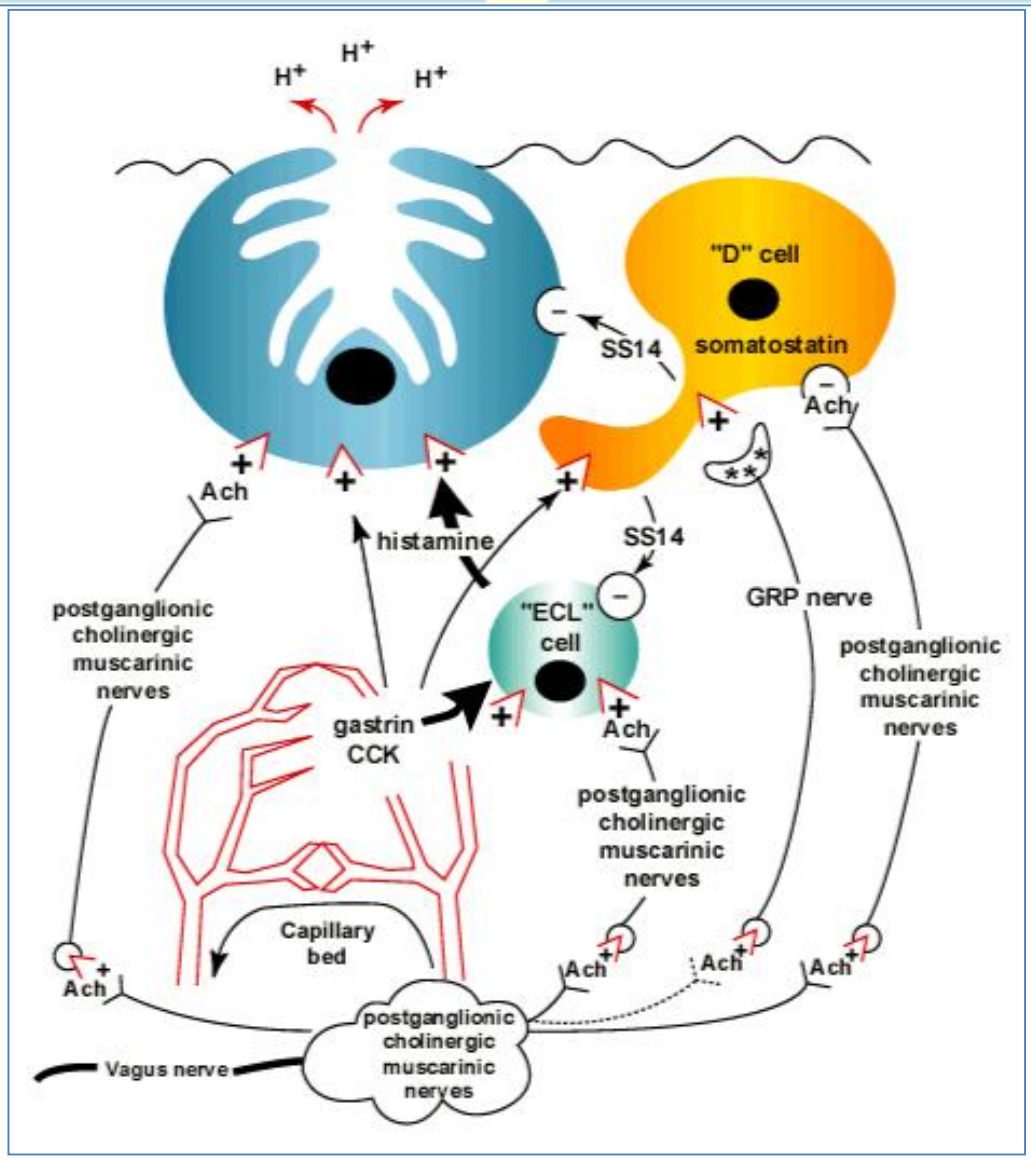
  - **Regulation**
    - **Stimulants: Acetylcholine, Histamine & Gastrin.**

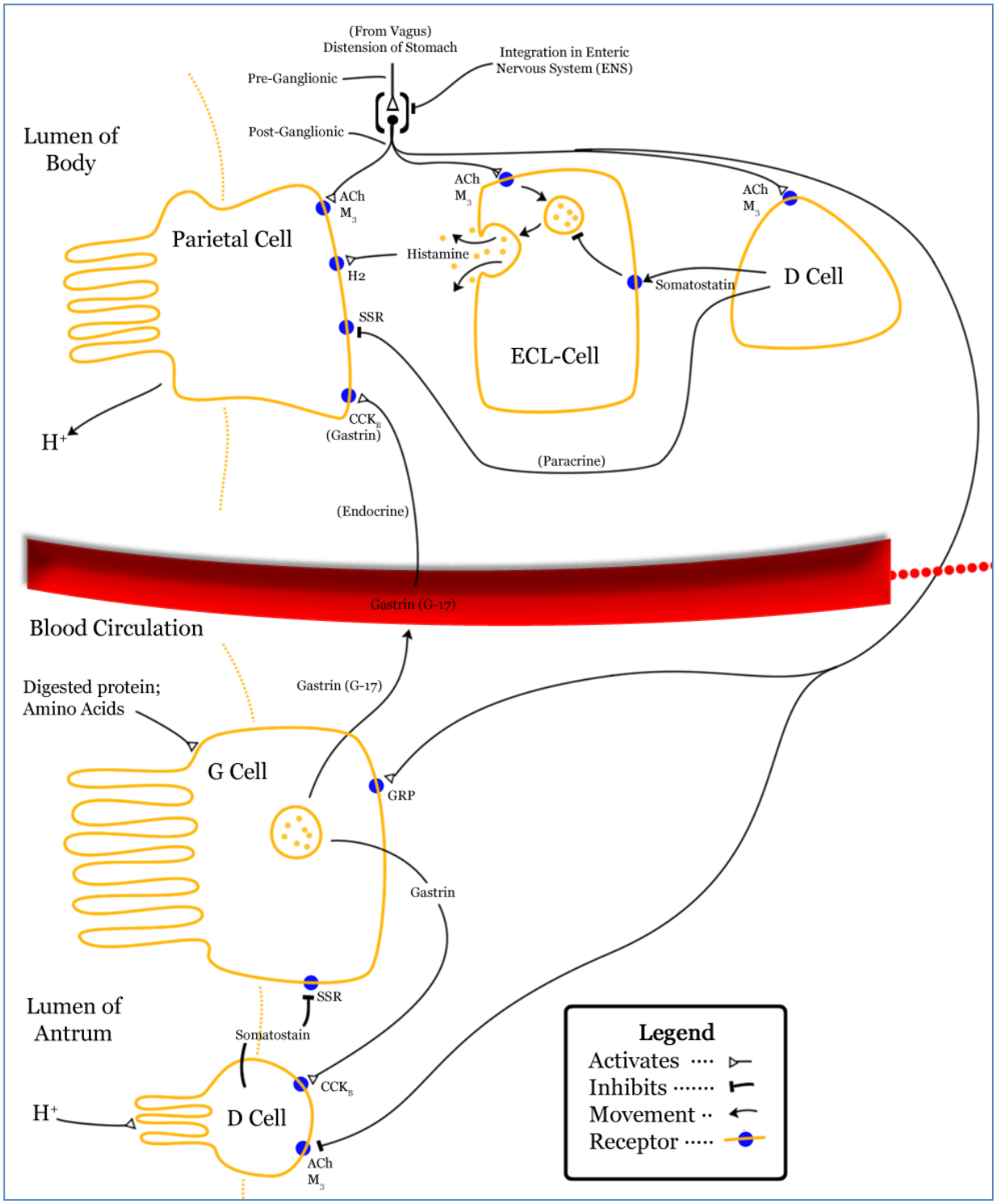
- **Acetylcholine = neurotransmitter** released by **enteric neurons**.
- **Histamine** = a **paracrine** released by **ECL** (**enterochromaffin-like**) **cells**.
- **Gastrin** = a **hormone** released by **G cells**, endocrine cells in the gastric epithelium.
    - **Inhibitor: Somatostatin**
- **Somatostatin** = **paracrine/hormone** also secreted by endocrine **D cells** of the gastric epithelium.





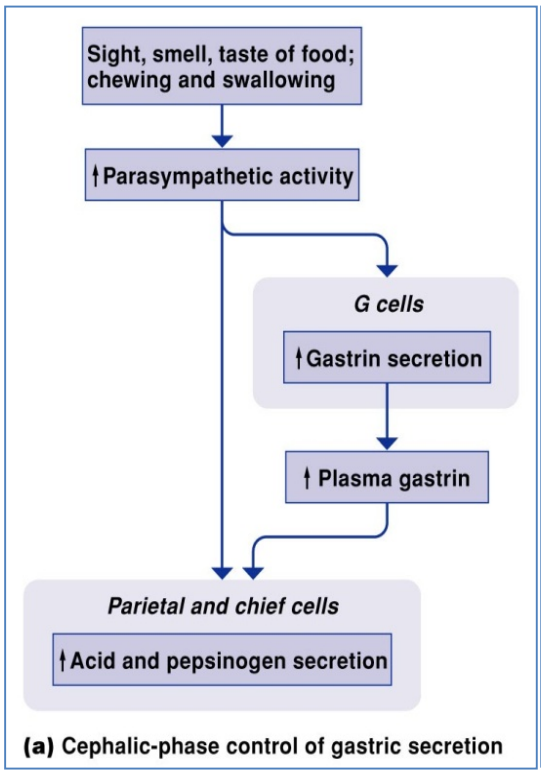




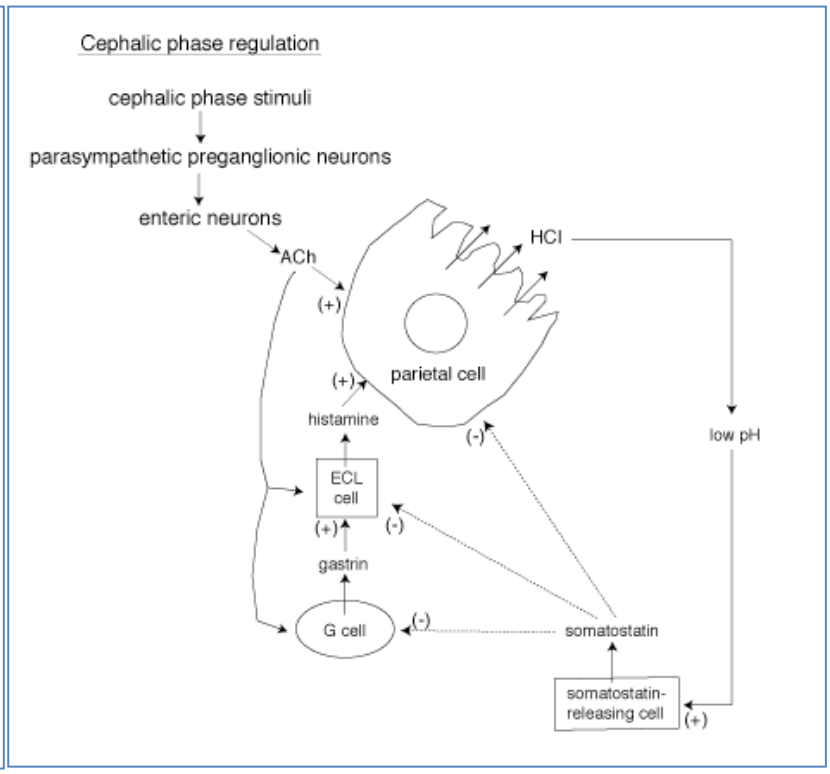


- **Effects of Exogenous Agents:**
  - **Omeprazole:**
    - Proton-Pump Inhibitor
    - Inhibits the *source* of H^+ → most efficient & effective.
  - **Ranitidine:**
    - Histamine H_2-receptor antagonist
    - No cAMP → stomach acid production slows
  - **Caffeine:**
    - Blocks the phosphodiesterase
  - **Pentagastrin:**
    - Synthetic gastrin-like hormone.
    - Increases gastric secretion.

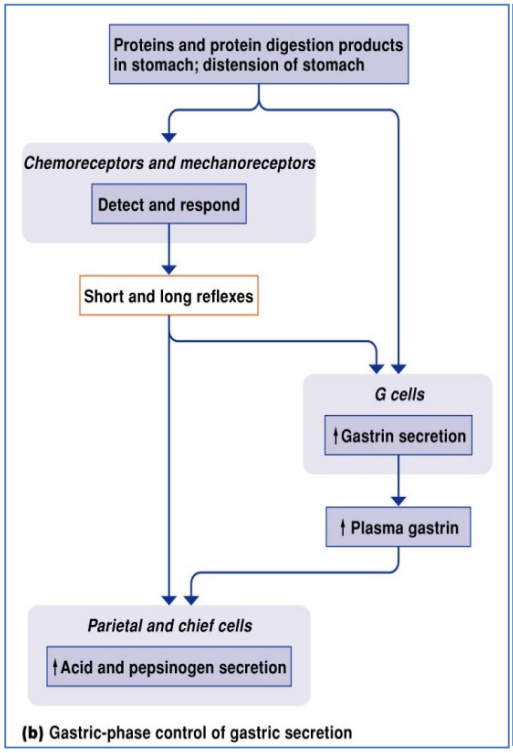
- **Regulation of Stomach Secretion Ctd.– 3 Phases:**
  - **Cephalic Phase**
    - (Where gastric secretion is stimulated before food enters stomach)
    - The taste/smell/thought of food sends nervous impulses to medulla oblongata (in brainstem)
    - Medulla→Vagus Nerves →Parasympathetic Neurons→stimulates HCl & Pepsin secretion in upper & middle stomach.
      - Also stimulates Gastrin secretion in lower part of stomach
      - Gastrin→bloodstream→further stimulates HCl & Pepsin secretion

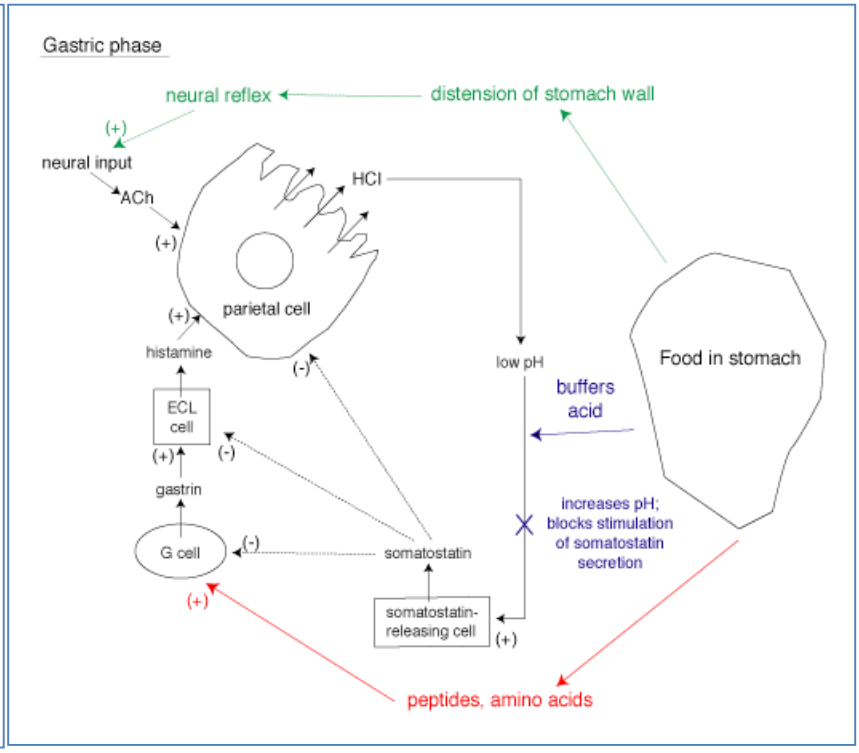


(a) Cephalic-phase control of gastric secretion

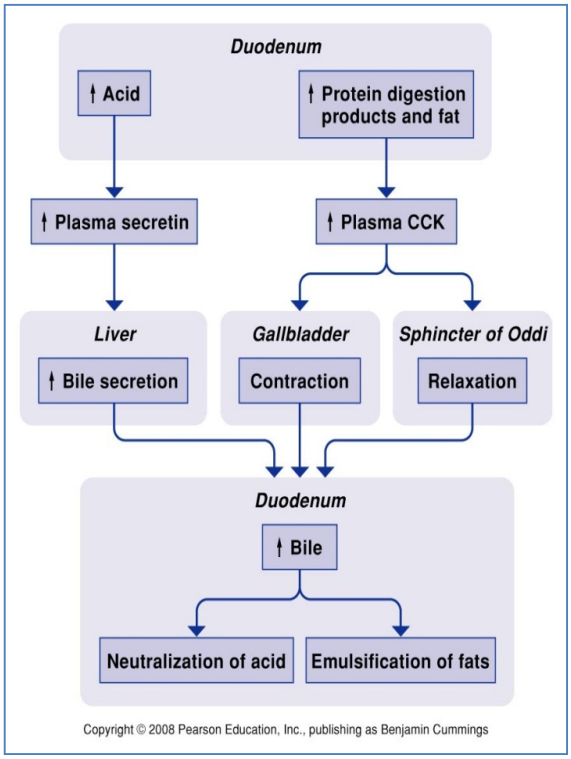


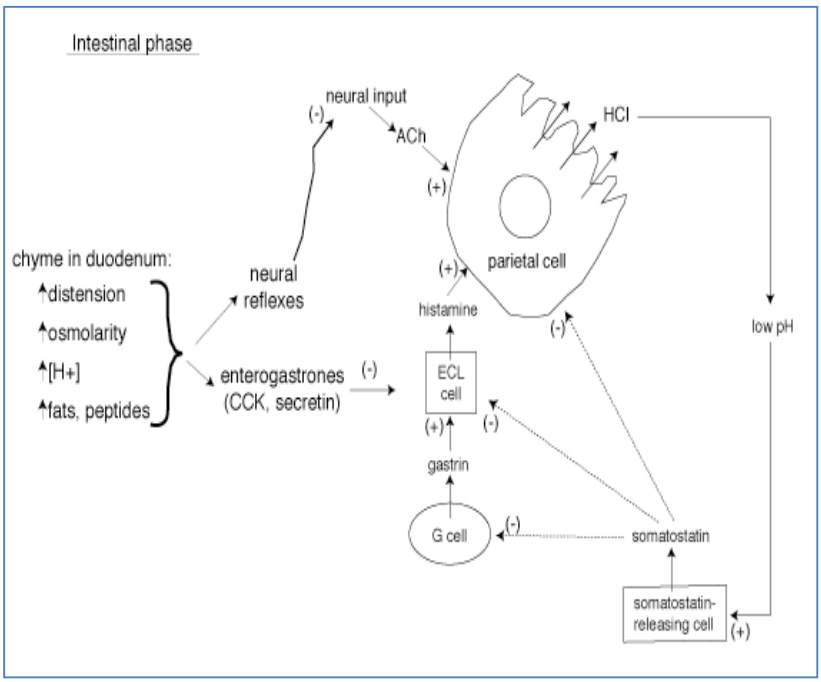
- **Gastric Phase**
  - Food has entered & distended the stomach.
  - Takes approx 3-4hrs
  - **Stimulated by:**
    - **Distension of Stomach:**
      - Stretch receptors
      - Distention provides positive feedback to the parasympathetic reflex above (via the medulla oblongata)
      - Continued secretion of HCl & Pepsin & Gastrin
    - **Gastrin (hormone):**
      - Produced by **G-Cells** in stomach
      - Triggered by parasympathetic nerves + partially digested proteins + rising pH
      - High acidity (pH<2)→ ˉve feedback
      - Main function: stimulate **parietal cells** → spew out **HCl**
    - **Low Acidity:**
      - Stimulates gastrin acid production.
      - HCl secretion stimulated by a combination of:
        - **AcetylCholine** – from parasympathetic nerve fibres
        - **Gastrin** - G-cells
        - **Histamine** – ECL Cells in response to gastrin





- **Intestinal Phase**
  - Acidic chyme enters duodenum
  - Initially this stimulates **intestinal gastrin** secretion → encourages gastric gland secretion.
  - Shortly after, gastric secretion is inhibited via the **enterogastric reflex:**
    - **Inhibits parasympathetic** stimulation from medulla.
    - **Activates sympathetic** fibres → tightens pyloric sphincter + decreases gastric secretion.
    - Causes the release of **3 local hormones** into blood that inhibit gastric secretion:
      - **Secretin**
        - Stimulates bicarbonate ion secretion (pancreas)
        - Stimulates bile secretion (liver)
      - **Cholecystokinin**
        - Increases pancreatic enzyme secretion
        - Stimulates gallbladder contraction
        - Relaxes the hepatopancreatic sphincter
      - **Vasoactive Intestinal Peptide (VIP)**
        - Relaxes smooth muscle
        - Stimulates secretion of H_2O & electrolytes in intestine





Water Balance in GI Tract

Secretions	
Saliva	1500 mL
Gastric juice	2500 mL
Bile	500 mL
Pancreatic juice	1500 mL
Small intestinal	1000 mL
Drinking water:	2000 mL
Total into GI lumen	9000 mL

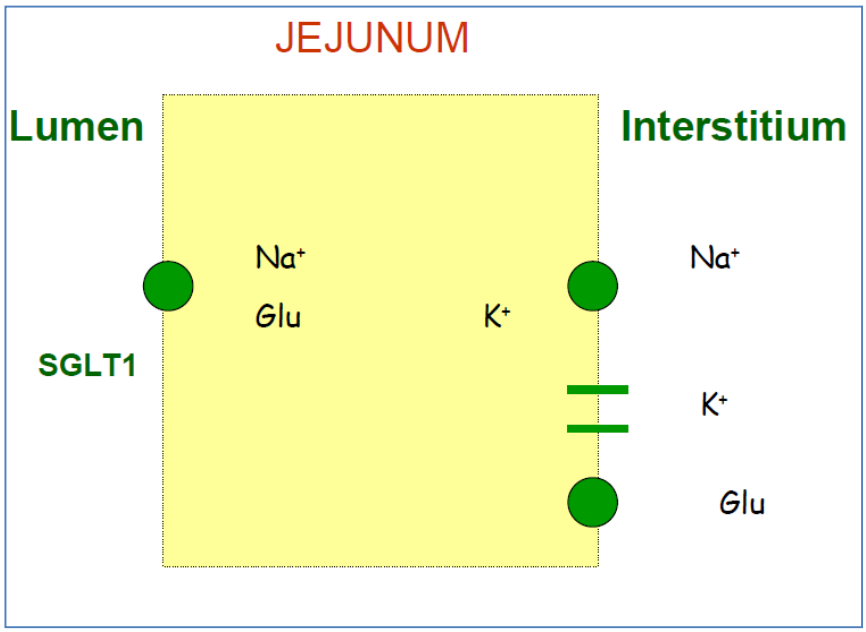
Absorption	
Jejunum	3000-5000 mL
Ileum	2000-4000 mL
Colon	1000-2000 mL
(Colonic capacity	~ 3000 mL)

Excretion	< 200 g faeces (65 – 85% water)

- Ie. Less than 170mL of H_2O is excreted from the GI per day.
- Therefore the rest of it is absorbed into the bloodstream.

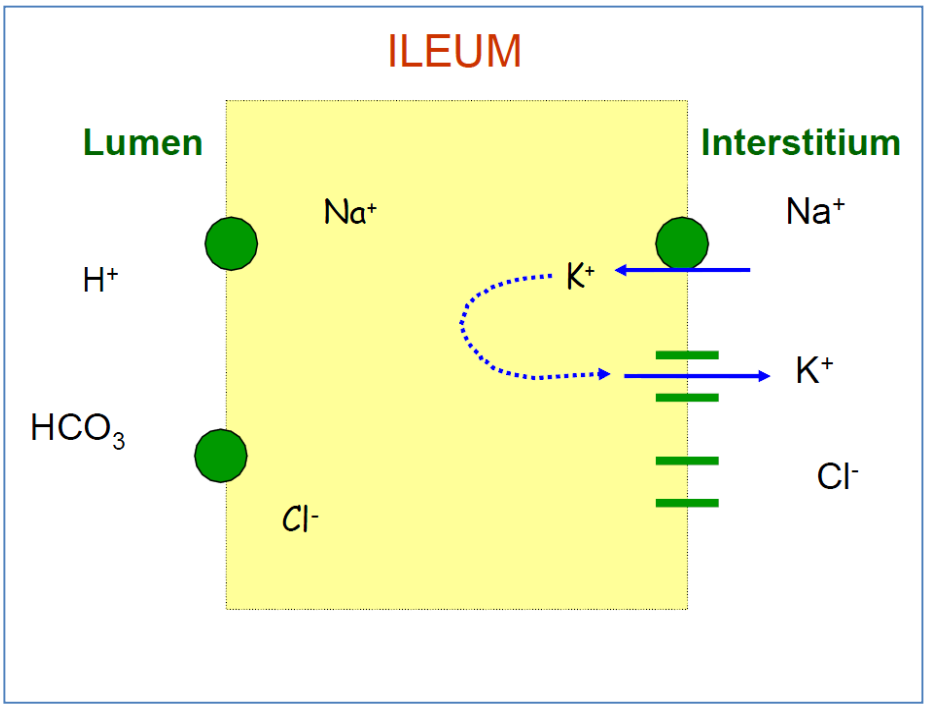
- **Water Absorption:**
  - Water flows by **osmosis**
    - **Towards** the **hypertonic** solution
    - Generally **H_2O follows Na^+ ions** (not always)
  - Facilitated by **aquaporins** – channel proteins specific to water

- **Principle Sites of H_2O Absorption:**
  - **Jejunum**
    - Na/K-ATPase sets up negative Na conc. grad. within cell.
    - Na causes SGLT1 to import Na & Glucose.
    - As Na flows in, H_2O follows.
    - Basal GLUT2 transporter: Glucose → interstitium.
    - *Clinical relevance: for treatment of severe dehydration, a solution of Na & Glucose optimises H_2O absorption.*



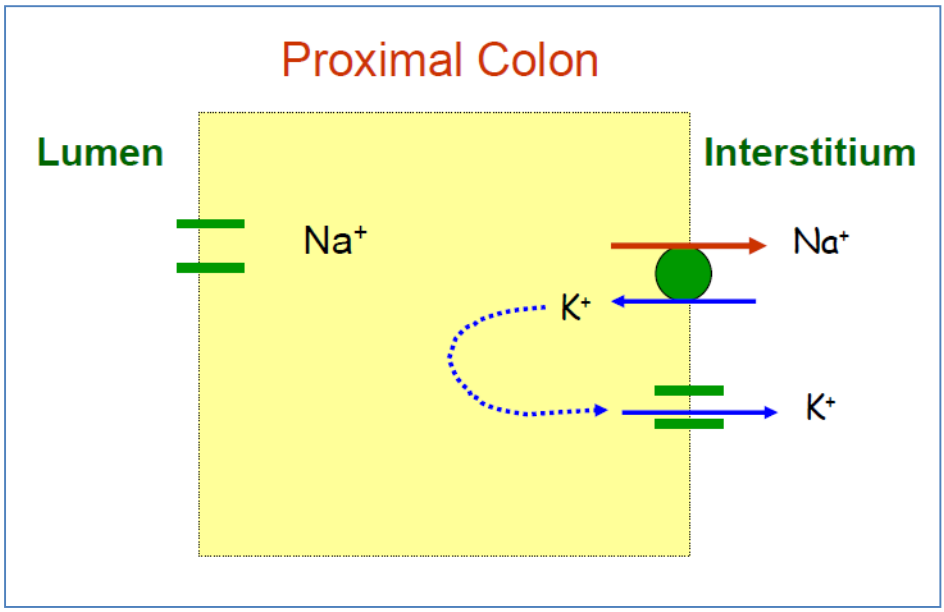
NB: Na-Dependent Glucose Transporter #1 + GLUT2 + Na/K-ATPase

- **Ileum**
  - Na/K-ATPase sets up negative Na conc. grad. within cell.
  - Draws Na through Na/H-Antiporter
  - H^+ →lumen
  - HCO_3^- → lumen to balance electrical charge
  - Cl^- →cell →interstitium to balance Na^+.



NB: Na/K-ATPase + Na/H-Antiporter + HCO_3/Cl-Antiporter + Ion Channels

- **Proximal Colon**
  - Na/K-ATPase sets up negative Na conc. grad. within cell
  - Draws Na through ion channel in apical membrane.
  - Excess K leaks back to interstitium through leakage channels.



NB: Na/K-ATPase + Na ion channel + K Leakage Channel.

GI Motility & Function

Principle Functions:

- Extract Nutrients
  - Energy
  - Carbohydrates
  - Amino acids
  - H_2O
- Excrete Waste Products
  - Indigestible Stuff
  - Metabolic wastes

***NB**: Gut Functions @ Approximately 90% Efficiency!!*

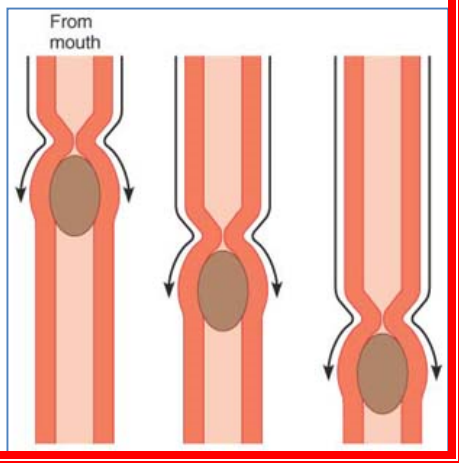
How Does it Achieve This?:

Motility

- Keeps things moving
- Food-matter must stay in specific places long enough → optimal digestion & absorption:
  - Oesophagus: 5-10s
  - Stomach: 1-3hrs
  - Small Intestine: 7-9hrs
  - Large Intestine: 25-30hrs **Total:** approx. 40hrs
- **Involves Contraction & Relaxation of Muscles**
  - **Contration:**
    - Mechanical digestion
    - Ensures contact between digest & epithelium
    - Propulsion of digest
    - Restriction of movement – Sphincters.
  - **Relaxation:**
    - Facilitates accommodation reflexes
    - Essential component of peristalsis
    - Essential component of swallowing
    - Opening of sphincters - movement

Categories of Motility:

- **Accommodation**
  - Stretching – stomach
  - Smooth muscle relaxes
- **Tonic Contraction**
  - Continual partial contraction of GI Tract
- **Peristalsis**
  - Combination of Segmentation & Pendular Contraction.
  - **Segmentation**
    - Contractions of circular muscle
    - Follows no particular pattern – happens anywhere & anytime
    - Mixes GI Contents both backwards & forwards
    - Ensures all food contacts luminal wall → absorption
  - **Pendular**
    - Contractions of longitudinal muscles
    - Shortens & lengthens tube.
    - Similar to caterpillar action
  - Similar to squeezing a tube of toothpaste.
  - Moves forward about 40cm at a time.
- **Migrating Motor Complex –** Small Intestines
- **Mass Movement –** Large Intestines
- **Defecation Reflex –** Rectum & Anus



Motility Mechanisms In Specific Places:

- **Oesophagus**
  - **Peristalsis: *Deglutition* (swallowing)**
    - **Buccal Phase**
      - Voluntary
      - Tip of tongue placed against hard palate
      - Tongue contracts →forces bolus of food into oropharynx
      - Food stimulates tactile receptors → start of Pharangeal-oesophageal phase.
    - **Pharyngeal-Oesophageal Phase**
      - Involuntary – controlled by swallowing centre in medulla of brain-stem.
      - Once receptors are activated, respiration is inhibited:
        - Tongue blocks off mouth
        - Soft palate blocks off nasopharynx
        - Larynx rises → epiglottis covers its opening
      - Upper oesophageal sphincter relaxes → then tightens
      - Peristaltic contractions move bolus down oesophagus
      - Gastro-Oesophageal sphincter relaxes → food into stomach → then tightens
- **Stomach**
  - **Peristalsis**
  - Initiated by Cajal cells (pacemaker cells in longitudinal smooth muscle of fundus)
  - Spontaneously depolarise & repolarise
  - 3 waves per minute
  - Waves move down body
  - Waves gradually increase in intensity
  - Very intense waves at pylorus – mashes food into chyme (homogenous solution)
  - Usually each wave spits 3ml of chyme into duodenum
- **Small Intestine**
  - **Segmentation** is the most common motion.
  - Initiated by pacemaker cells in longitudinal smooth muscle layer
  - 12-14 contractions / minute

  - **Peristalsis: *Migrating Motor Complex***
  - Occurs after most nutrients have been absorbed.
    - Duodenal mucosa releases the hormone ***motilin***.
    - →initiates peristalsis in duodenum → lasts for about 50-70cm then dies out.
    - Successive waves are initiated further along small intestines.
    - Hence the 'migrating' motor complex.
    - Takes approx 2 hrs for waves to reach ileocecal valve.
    - Process then repeats itself → sweeps food remnants, bacteria, etc.
- **Large Intestine**
  - Inactive most of the time
  - When presented with food→colon becomes motile
  - Contractions are sluggish & short-lived
  - ***Mass Movements***
  - Long, slow-moving, but powerful contractile waves.
  - Move over large areas of colon
  - 3x Daily
  - Force contents towards rectum
- **Rectum**
  - Faeces are forced into rectum by Mass Movements.
  - Rectum wall stretches → initiates defecation reflex:
  - ***Defecation Reflex***
  - Sigmoid-Colon & Rectum contracts + Internal Anal Sphincter relaxes
  - Force on anal canal signals brain – 'the urge'
  - If defecation is delayed voluntarily, the defecation reflex dissipates within a few seconds.
  - However with the next mass movement, the defecation reflex initiates again.

Neural & Hormonal Regulation of:

- **Stomach Secretion:**
  - **Cephalic Phase**
    - (Where gastric secretion is stimulated before food enters stomach)
    - The taste/smell/thought of food sends nervous impulses to medulla oblongata (in brainstem)
    - Medulla→Vagus Nerves →Parasympathetic Neurons→stimulates HCl & Pepsin secretion in upper & middle stomach.
      - Also stimulates Gastrin secretion in lower part of stomach
      - Gastrin→bloodstream→further stimulates HCl & Pepsin secretion
  - **Gastric Phase**
    - Food has entered & distended the stomach.
    - Takes approx 3-4hrs
    - **Stimulated by:**
      - **Distension of Stomach:**
        - Stretch receptors
        - Distention provides positive feedback to the parasympathetic reflex above (via the medulla oblongata)
        - Continued secretion of HCl & Pepsin & Gastrin
      - **Gastrin (hormone):**
        - Produced by **G-Cells** in stomach
        - Triggered by parasympathetic nerves + partially digested proteins + rising pH
        - High acidity (pH<2)→ ⁻ve feedback
        - Main function: stimulate **parietal cells** → spew out **HCl**
      - **Low Acidity:**
        - Stimulates gastrin acid production.
        - HCl secretion stimulated by a combination of:
          - AcetylCholine – from parasympathetic nerve fibres
          - Gastrin - G-cells
          - Histamine – ECL Cells in response to gastrin
  - **Intestinal Phase**
    - Acidic chyme enters duodenum
    - Initially this stimulates **intestinal gastrin** secrection → encourages gastric gland secretion.
    - Shortly after, gastric secretion is inhibited via the **enterogastric reflex:**
      - **Inhibits parasympathetic** stimulation from medulla.
      - **Activates sympathetic** fibres → tightens pyloric sphincter + decreases gastric secretion.
      - Causes the release of **3 local hormones** into blood →inhibits gastric secretion:
        - **Secretin**
        - **Cholecystokinin**
        - **Vasoactive Intestinal Peptide (VIP)**

- **Gastric Emptying:**
  - **Normal:**
    - Depends on contents of duodenum rather than contents of stomach.
    1. Acidic chyme enters duodenum
    2. Chemical & stretch receptors in duodenum wall → causes enterogastric reflexes.
    3. Reflexes inhibit acid & pepsin secretion
    4. Also prevents further duodenal filling by reducing force of pyloric contractions
  - **Vomiting Reflex:**
    - Caused by either:
      - Extreme stretching of stomach
      - Irritants (Bacterial toxins/Alcohol/Spicy foods/Drugs/etc)
    - Bloodborne molecules or sensory impulses → **emetic centre** of medulla.
    - Diaphragm contracts, cardiac sphincter relaxes & soft palate rises to block off nasal passage.

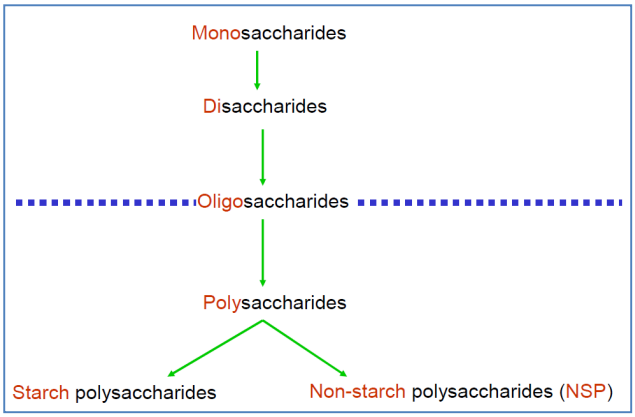
Maintaining Luminal Homeostasis & Integrity

- **Secretion**
  - **Mucous**
    - Goblet Cells
    - Mucin → mucous
    - Protects stomach lining from acid
    - Lubricates lining – less scratching + nothing gets stuck
  - **Acid**
    - Barrier to infectious microbes
    - Dissolves solids
- **pH Values:**
  - Maintained for optimal enzyme function.
  - Mouth pH: 6.4 – 7.3
  - Stomach pH: 1.5 – 4
  - Duodenum →Rectum: 7 – 8

Specialised Structures

- **Sphincters**
  - Upper Oesophageal
  - Lower Oesophageal
  - Pyloric
  - IleoCecal
  - Internal Anal
  - External Anal
- **Pacemaker Zones:**
  - Set basic electrical rhythm
  - Controls rate of peristalsis in particular areas.
    - Stomach: 3 per min
    - Duodenum: 9-12 per min
    - Large Intestines: 2 per hour
- **Temporary Storage Sites:**
  - Mouth
  - Stomach
  - Colon
  - Rectum
- **Plicae, Villi & Microvilli:**
  - Increase surface area of absorptive areas
  - More effective absorption

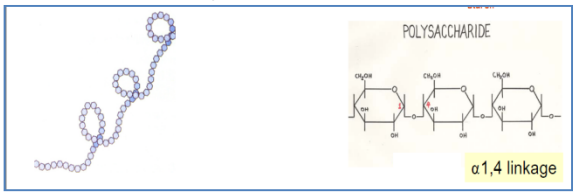
Absorption of Carbohydrates & Proteins



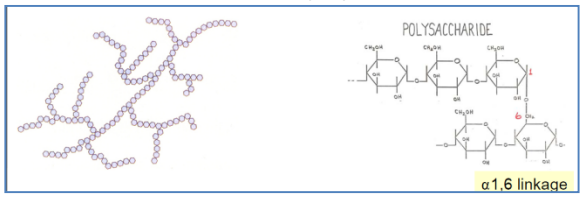
Carbohydrates:

- **Monosaccharides** – single sugars
  - Glucose
  - Galactose
  - Fructose
- **Disaccharides** – 2 sugar units
  - Lactose = Glucose + Galactose
  - Sucrose = Glucose + Fructose
  - Maltose = Glucose + Glucose
- **Oligosaccharides** – "a few sugars" (up to 10 units – incl. Disaccharides)
- **Polysaccharides:**
  - **Starch Polysaccharides (α-1,4 linkage or α-1,6 linkage)**
    - Amylose
    - Amylopectin
    - Resistant Starch (impervious to digestive enzymes of the body)
      - Ends up fermented by microflora of Large intestine.
    - Glycogen* (animal "starch")

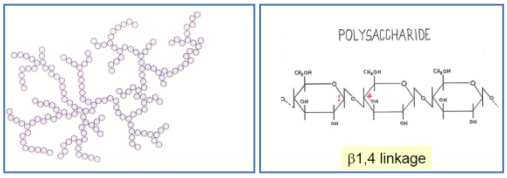
Amylose



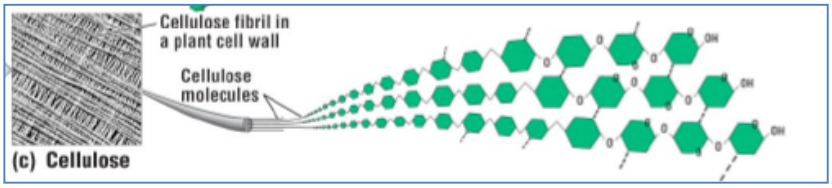
Amylopectin



Glycogen



  - **Non-Starch-Polysaccharides (NSPs - β-1,4 Linkage)**
    - Soluble Fibre (non-cellulosic)
    - Insoluble Fibre (cellulosic)
    - RDI: 30g/day

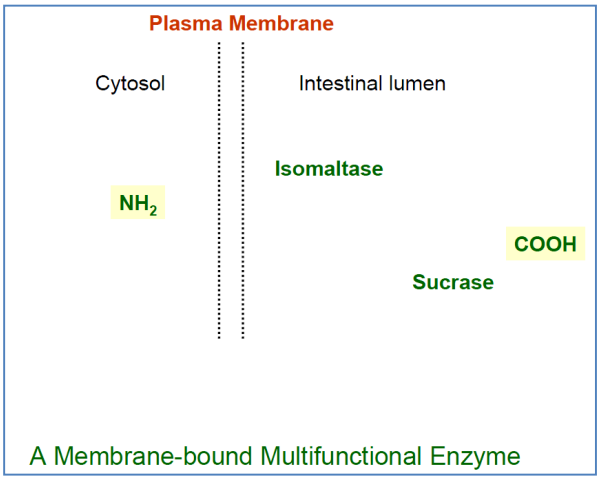


Carbohydrate Intake:

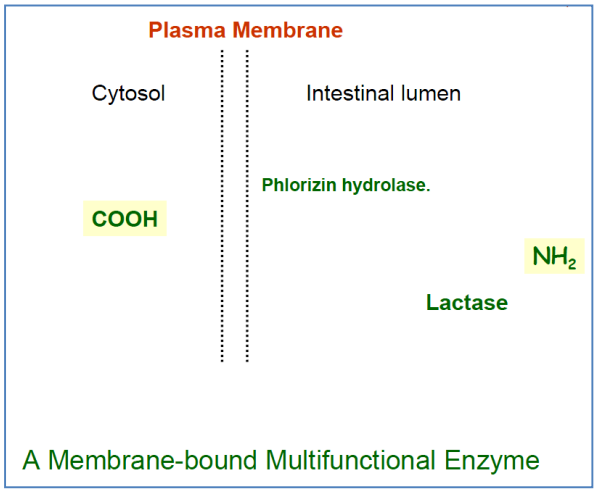
- Approx 200-600g/day
- About 50% of energy needs – met by carbs.
- Complex carbs – best for slow-release energy.
- Energy Content: 16kJ/g (measured in Joules)

Carbohydrate Digestion:

- **Mouth:**
  - Salivary α-Amylase:
    - Breaks down starch polysaccharides→smaller chunks of a few units
    - Requires correct pH – works in mouth but not stomach
    - From parotid & submandibular glands.
- **Small Intestine Lumen:**
  - Pancreatic α-Amylase:
    - Secretion stimulated by CCK
    - (+ Secretin stimulates bicarb-secretion → neutralises chyme→optimum pH)
    - Continues breakdown of starch→even smaller chunks
- **Small Intestine Brush Border:**
  - Brush-Border Enzymes:
    - Membrane-bound
    - Act on Oligosaccharides & Disaccharides → Monosaccharides
    - Enzymes are **multifunctional** – ie. **2 Enzymes in 1** (2 different active sites)
    - Eg:
      - Sucrase: Sucrose→ Glucose + Fructose
      - Lactase: Lactose→ Glucose + Galactose
      - Maltase: Maltose→ Glucose + Glucose
      - Isomaltase: Maltriose→Glucose + Galactose



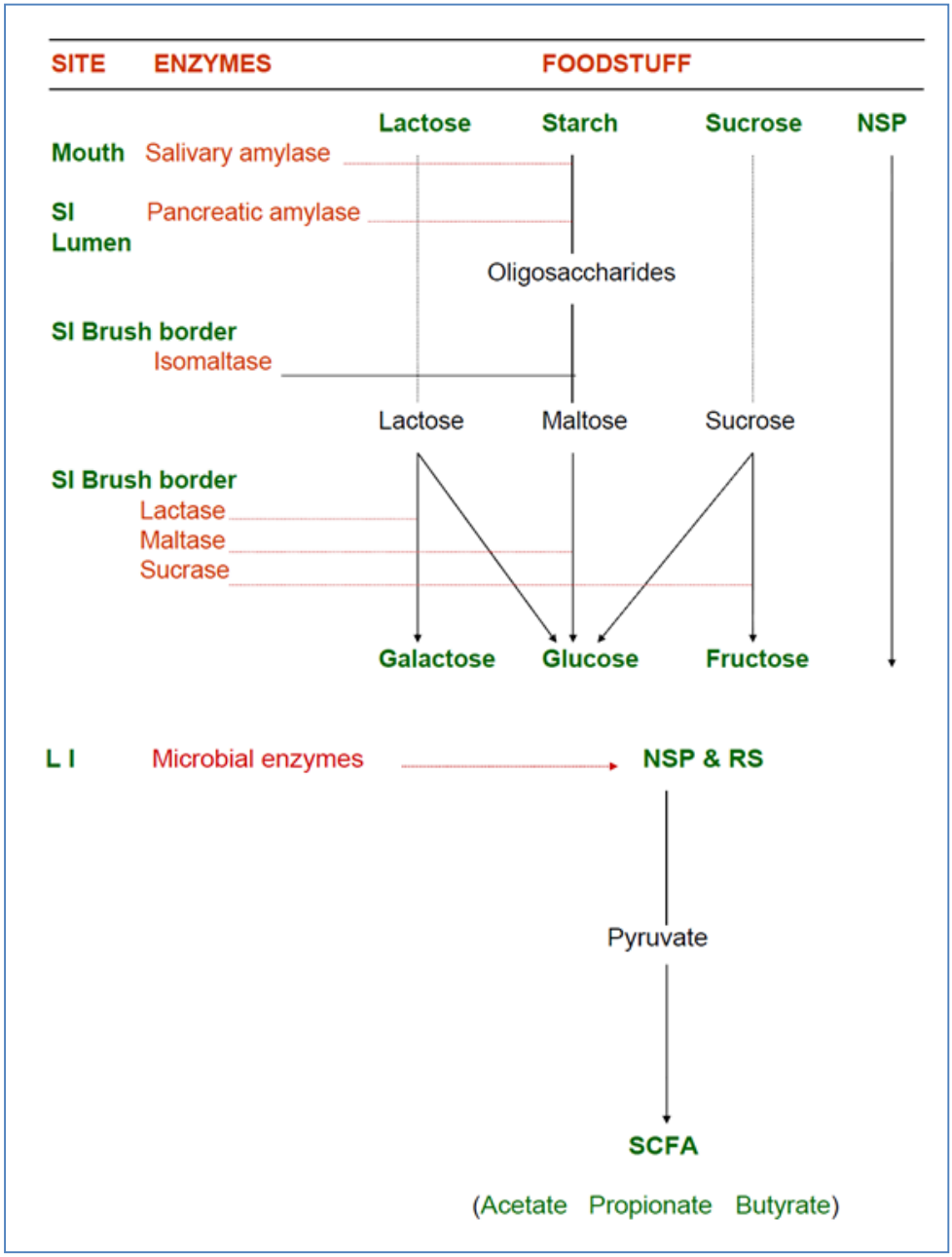
A Membrane-bound Multifunctional Enzyme



A Membrane-bound Multifunctional Enzyme

- **Large Intestine:**
  - Non-Starch-Polysaccharides & Resistant Starches escape enzymatic breakdown until now.
  - Microbial Enzymes:
    - Break down NSPs & RSs → short chain fatty acids. (SCFAs) + CO_2/H_2/Methane (Flatus)
    - **SCFAs:** Acetate/Propionate/Butyrate
      - **SCFAs** are absorbed into blood

Breakdown Locations of Carbs

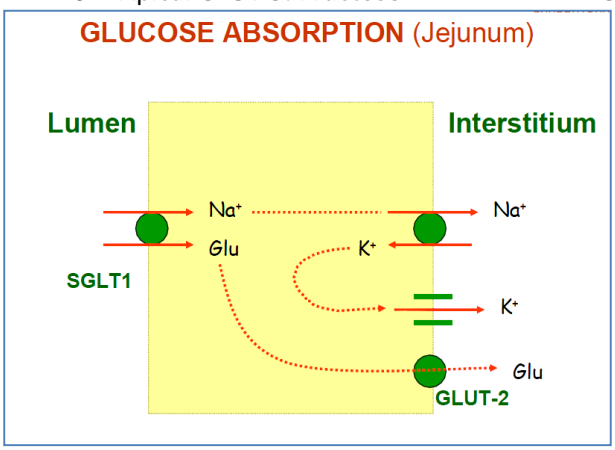


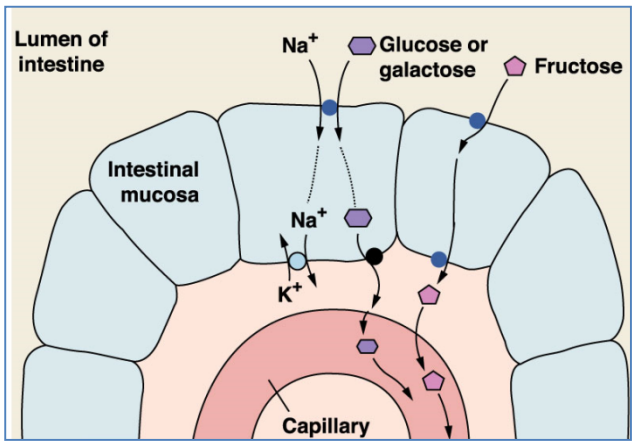
	Lumen	Epithelium	Portal Vein (blood)
Small Intestine	Monosaccharides ----------→	----------→	---→Monosaccharides
	Disaccharides ----------→	-----→ Brush Border ----------→	---→Monosaccharides
	Starch → Pancreatic Amylase --→	-----→ Enzymes ----------→	---→Glucose
Large Intestine	Resistant Starch & Non-Starch-Polysaccharides -----→ (dietary fibre)	----------→	----→ Acetate Proprionate
	Fermentation of RS & NSP -------→	-----→ n-Butyrate	

Carbohydrate Absorption:

- **Mouth**
  - None
- **Stomach**
  - None
- **Small Intestine**

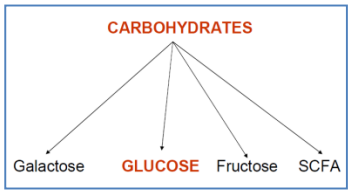
  Via Secondary Active Transport:
  - Apical **GLUT 1:** Glucose & Galactose **GLUT 2:** Basal
  - Apical **GLUT 5:** Fructose **GLUT 2:** Basal





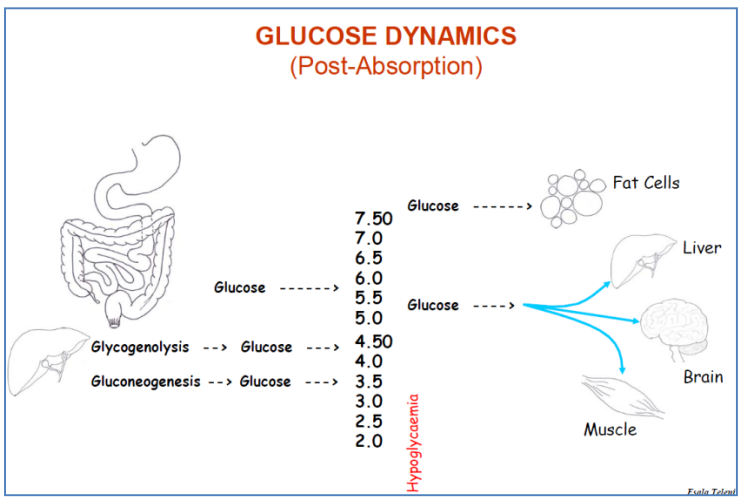
- **Large Intestine:**
  - **Diffusion:** Short Chain Fatty Acids

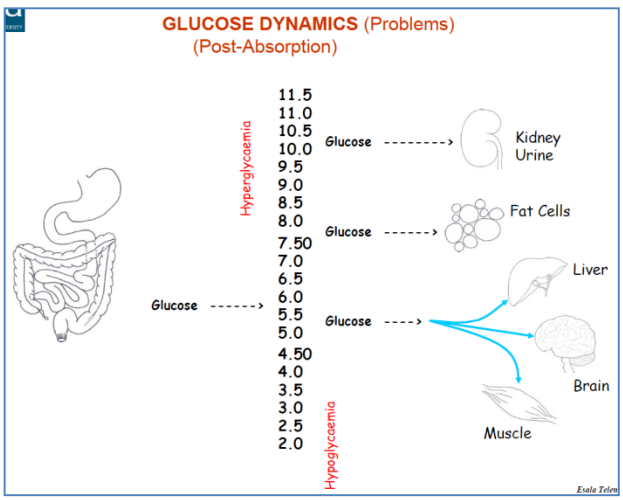
NB: approx 80% of carbs absorbed is Glucose



Glucose Dynamics: Blood-Glucose

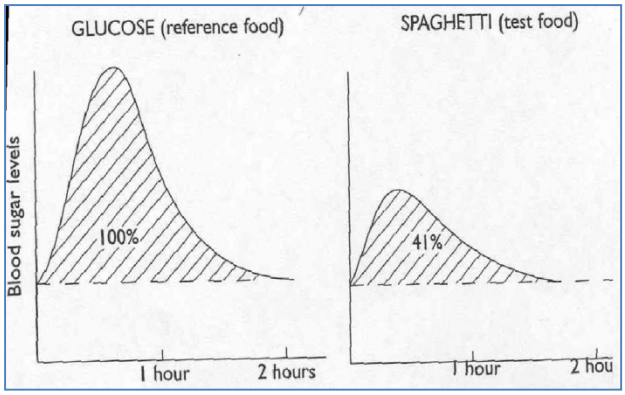
- **Insulin Dependent:**
  - Fat synthesis/deposition
  - Glucose uptake into muscles (glycogenolysis)
  - NB: if insulin dependent paths are blocked (diabetes) blood glucose increases→ glucose excreted through urine.
- **Insulin Independent:**
  - Glucose uptake into liver (glycogenolysis)
  - Glucose uptake into brain - fuel.





Glycaemic Index (GI)

- A measure of how rapidly a carbohydrate releases glucose into the blood during digestion.
- High GI – Quick glucose release
- Low GI – Slow glucose release



Dietary Fibre:

- **NSPs**
  - **Soluble Fibre**
    - Non-cellulose
    - In fresh fruit/vegetables/oats/seeds
    - Increases viscosity of intestinal contents
    - End up fermented by bacteria in colon
  - **Insoluble Fibre**
    - Cellulose (plant walls)
    - Provides bulking to colonic contents.
    - Keeps people regular
    - Most not fermented in colon
- ***Starch**
  - **Resistant Starch (RS)**
    - Escapes digestion in small intestine
    - Passes through to large intestine.
    - Has similar effects as NSPs

NB: *starch isn't strictly a 'dietary fibre', but **RS** has **similar effects** as both **soluble & insoluble fibre**.

Health Outcomes of Dietary Fibre (or lack of):

a. **Constipation:**
   i. Diet: low NSP intake
   ii. NSP promotes regular bowel motion (decrease transit time)
      - Increases bacterial biomass → increases mass of stool → defecation more regular.
   iii. Low NSP increases transit time → increased H_2O absorption → hard stool

b. **Diverticular Disease:**
   i. Outward protruding pouch on wall of bowel – particularly sigmoid colon
   ii. Due to lack of NSP (fibre) in diet
   iii. Common in high meat, low fibre diets.

c. **Short Chain Fatty Acids & Health of Colonocytes:**
   i. Product of fermentation of SCFAs → butyric acid → preferred fuel for colonocytes → keeps them healthy (generally)
   ii. NSPs also decreases transit time → less contact between colonocytes & any ingested carcinogens.

d. **Colon Cancer:**
   i. Experiments have shown that bathing colonocytes in butyric acid decreases colon cancer growth in culture.

e. **Management of Diabetes:**
   i. Viscous soluble NSPs:
   - decrease rate of gastric emptying
   - dilutes gastric contents – ie. Lower sugar conc. of chyme → slower sugar uptake to blood.

Proteins:

- **RDI:** approx 125g/day
- **Sources:** meats, eggs, dairy, seeds, nuts, legumes.....
- **Why eat proteins:**
  - Proteins consist of amino acids
  - Some **"essential" amino acids** can't be synthesised by the body →**must be ingested**
  - Other **"non-essential" amino acids** can be synthesised in the body.

Protein Digestion:

- **Stomach:**
  - **Chief cells –** secrete **pepsinogen**
  - **Parietal Cells** – secrete **HCl**
  - **Pepsinogen + HCl → Pepsin** (protease) [more specifically – an endopeptidase]
  - **Pepsin:** breaks peptide bonds in the middle of proteins → smaller polypeptides

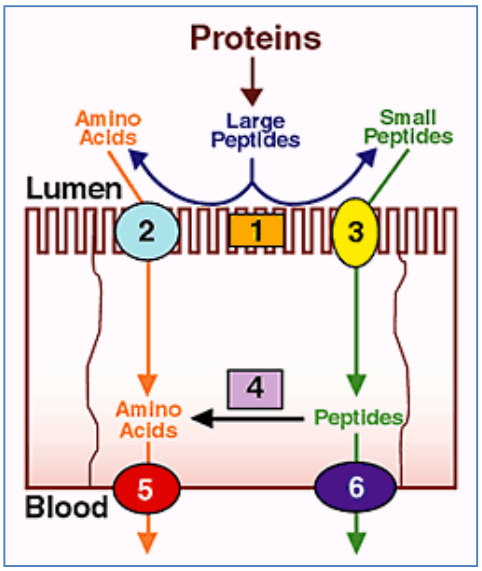
NB: pepsin is secreted as a ***ZYMOGEN***. Ie. An inactive form → doesn't activate until it reacts with HCl in the stomach lumen. That way it doesn't digest the cells that secreted it. A ZYMOGEN requires a biochemical change for it to become an active enzyme.

NB: newborns lack the ability to digest proteins – prevents breakdown of **IgA antibodies** in the **colostrum**
- Protects infant's GI tract from infection + antibodies endocytosed into bloodsteam – even broader immunity.

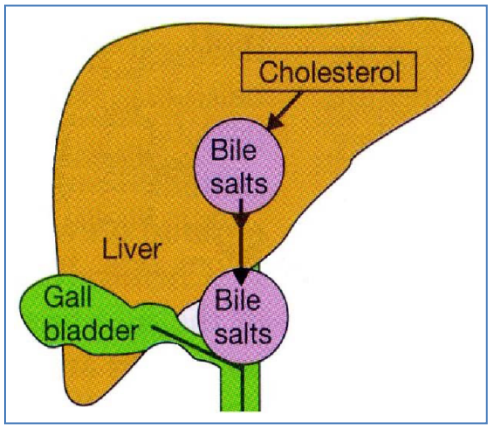
- **Small Intestine:**
  Proteases break large polypeptides → smaller polypeptides → single amino acids.
  - **Pancreatic Proteases:**
    - Trypsinogen → **Trypsin** (Zymogen [trypsinogen] is activated by brush border enzymes)
    - Chymotrypsinogen → **Chymotrypsin** (activated by Trypsin)
    - Procarboxypeptidase → **Carboxypeptidase** (activated by Trypsin)
  - **Brush-Border Proteases:**
    - **Aminopeptidase:** - cleaves 1 amino acid at a time
    - **Dipeptidase:** - cleaves 1 amino acid at a time

Protein Absorption:

- Single Amino Acids + some Di/Tri-Peptides
- Absorbed mainly **in Small Intestine:**
  - **By Enterocytes** (absorptive cells of SI)
  - Via **cotransport** with **Na^+ ions**.
  - **Intracellular Peptidases** continue breakdown of Di/Tri-Peptides
  - **Basolateral transporters** – A.As & Peptides →Enter capillary blood in villi.



Liver Function: Lipid Digestion & Absorption + Drug Metabolism

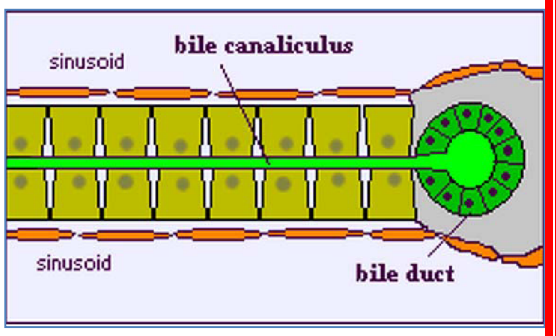


Bile Salts:

- Formed in liver
- Bile Acids/Salts are derived from cholesterol
- Cholesterol → Bile Salts:
  - Cholic Acid
  - Chenodeoxycholic Acid
- Bile Salts are Conjugated:
  - Amino acids added on
    - 75% Glycine
    - 25% Taurine (derivative of cysteine)
  - Bile Salt becomes H_2O Soluble.

Bile Composition:

- H_2O
- Electrolytes
- Bile Salts -Digestion & Absorption of Lipids
- Phospholipids -Digestion & Absorption of Lipids
- Cholesterol
- Bilirubin

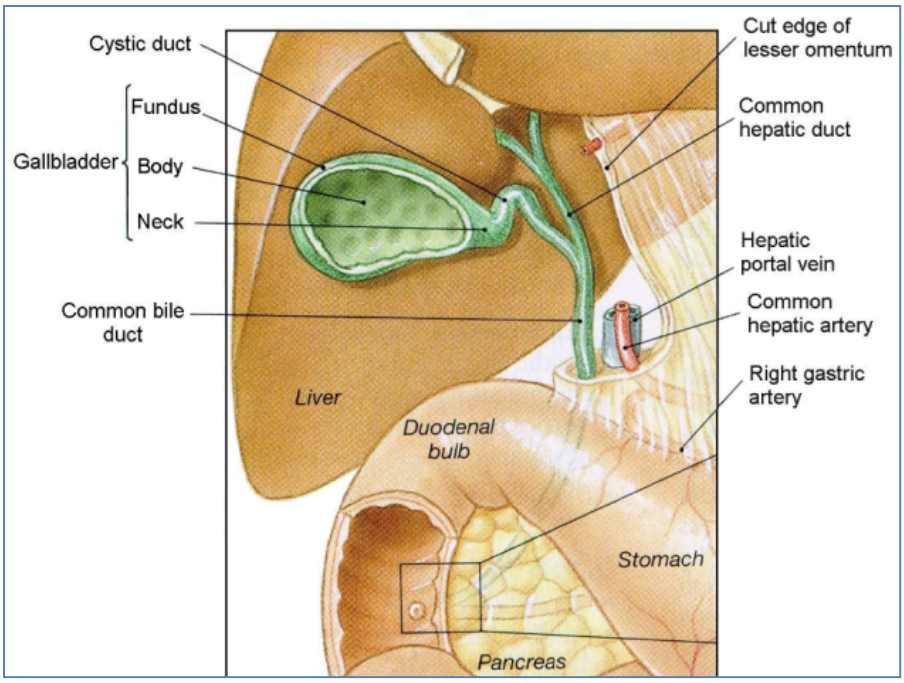


Bile Secretion & Transport:

- Hepatocytes secrete bile into Bile Canaliculus
- Bile flows into larger Bile Ducts
- Many Bile Ducts converge → eventually →Common Bile Duct.
- Epithelium of Bile Ducts secrete watery, bicarbonate rich solution.

Bile Storage:

- In Gallbladder
- When bile isn't flowing, it backs up into gallbladder
- Gallbladder dehydrates (concentrates) bile.
- Bile concentration increases by 5x

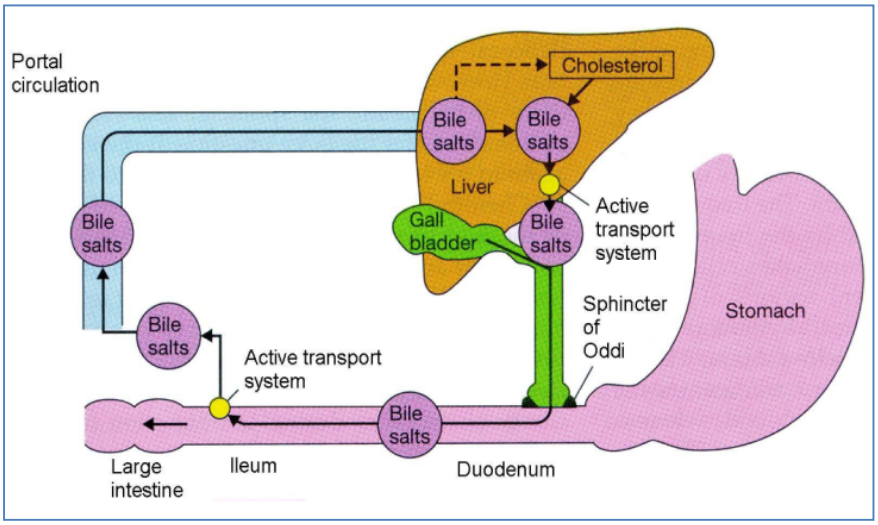


Bile Release:

- Acidic, fatty chyme enters duodenum-
  - Stimulates Secretion of:
    - Secretin:
      - Stimulates bicarbonate ion secretion (pancreas)
      - Stimulates bile secretion (liver)
    - CCK (cholycystokinin):
      - Increases pancreatic enzyme secretion
      - Stimulates gallbladder contraction
      - Relaxes the hepatopancreatic sphincter (Sphincter of Oddi)
    - Vasoactive Intestinal Peptide:
      - Relaxes smooth muscle of stomach – slows gastric emptying
- Bile is released into duodenum via hepatopancreatic sphincter (Sphincter of Oddi)

EnteroHepatic Circulation ("Intestine→Liver"):

- Ie. Recycling of Bile Salts
- 90% of bile salts are reabsorbed (in ileum) into blood.
- Ileum venous blood→Portal Vein→Liver:
  - Hepatocytes extract bile salts from blood
  - Bile salts are re-secreted into canaliculi.
- Each bile salt molecule is reused approx: 18-20 times.
  - Ie. On average, bile salts are turned over every 18-20 meals.

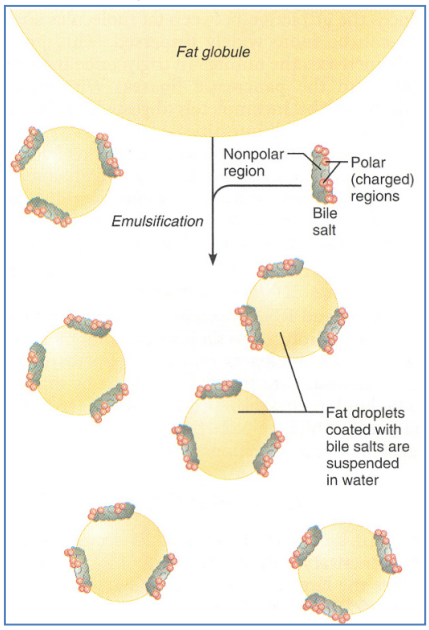


Functions of Bile:

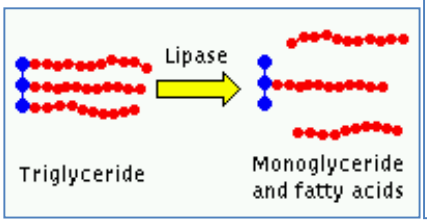
- Critical for Digestion/Absorption of FATS in Small Intestine
- Provides a medium for disposal of some bodily wastes:
  - Wastes secreted into bile
    - Eg. Endogenous:
      - Calcium
      - Cholesterol (Soluble in bile salts)
      - Steroid Hormones
      - Bilirubin
    - Eg. Exogenous:
      - Antibiotics
      - Metabolites of Drugs
  - Eliminated in Faeces....OR
  - Reabsorbed by Small Intestine→blood→kidneys→Urine.
- **NB: Gallstones** – precipitated cholesterol in Cystic Duct due to:
  - Excess cholesterol
  - Insufficient Bile Salts

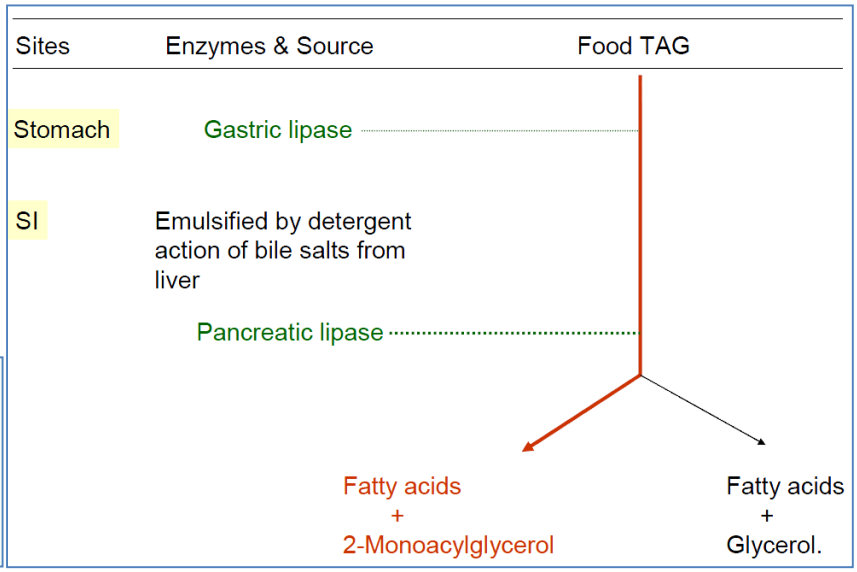
Digestion/Absorption of LIPIDS:

- **Average Intake:**
  - 60-100g/day
- **Composition:**
  - 90% Triglycerides (TAGs)
  - 10% Cholesterol/Cholesterol Esters/Phospholipids/Fat-Soluble Vitamins A,D,E,K.
- **Emulsification:**
  - Lipids insoluble in H_2O
  - Gastric contractions disperse fat 'pools' evenly amongst chyme.
  - Fatty Chyme→Duodenum
  - Pre-treated with Bile-Salts
  - **Bile Salts**: Amphiphilic molecules – polar & non polar ends
    - Emulsify Large Lipid Droplets → tiny tiny droplets → High Surface Area
    - High S.A. = more access to lipases

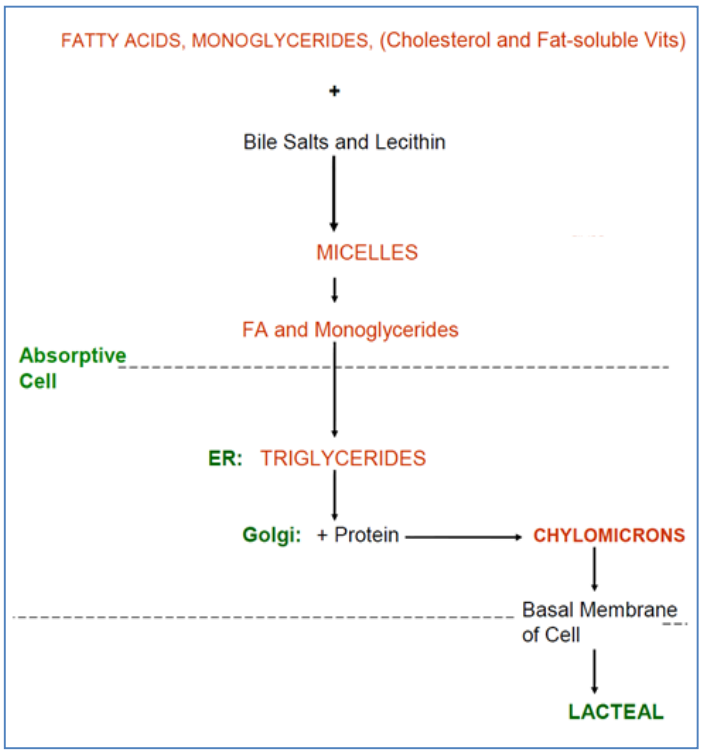


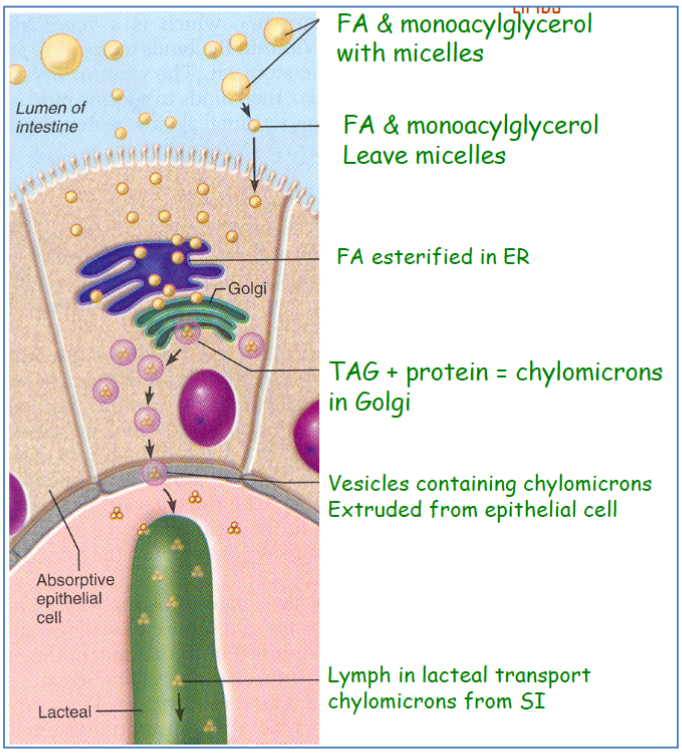
- **Digestion: Lipases**
  - **Gastric Lipase:** Stomach – Secreted by Chief Cells
  - **Pancreatic Lipase:** Pancreas – Secreted in Active Form
  - H_2O soluble enzymes
  - Catalyse Hydrolysis of Ester bonds between the Glycerol Backbone & Fatty Acids of Triglycerides.
  - Mostly yields **1 MonoAcylGlyceride + 2 Free Fatty Acids**
  - Rarely yields **1 Glycerol + 3 Free Fatty Acids**



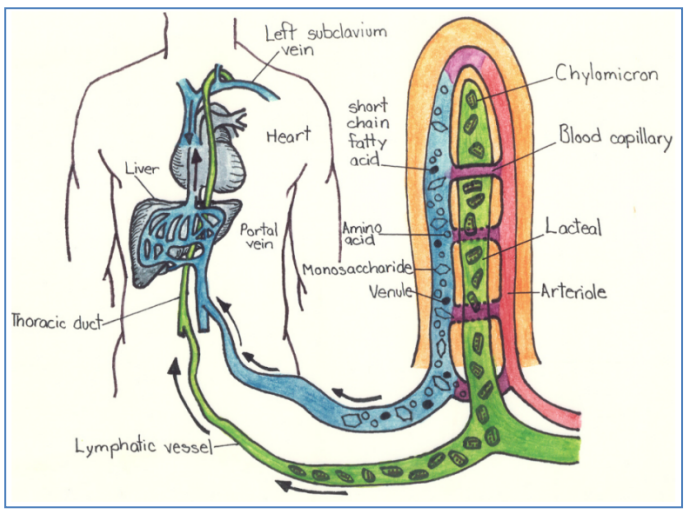


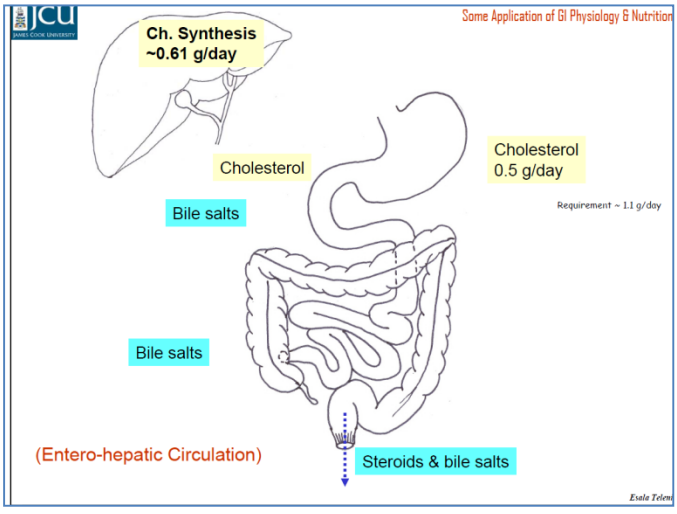
- **Absorption: Micelles**
  - **Monoglycerides + Fatty Acids:**
    - Retain association with **Bile Acids** → **Aggregate** to form **Micelles**.
    - **Micelles**: aggregates of mixed lipids & bile acids suspended within chyme.
    - Micelles in contact with brush-border-membrane of Enterocytes release **FAs & Monoglycerides** →diffuse$_{simple}$ into **Enterocyte**.
    - **FAs & Monoglycerides → Endoplasmic Reticulum** → used to synthesise **Triglycerides**
    - Triglycerides → **Golgi Apparatus** → Packaged with **Cholesterol+Lipoproteins** → **Cholymicrons** (The lowest-density Lipoprotein)
    - **Cholymicrons** in **Vesicles** → transported to **Basolateral Membrane** → **Exocytosed** into Interstitium.
    - Interstitial cholymicrons → **Lacteal** (Lymphatic Vessel in Villus) → Lymphatic System → **Blood**
    - **Blood-Borne Cholymicrons** rapidly utilized throughout the body.
  - **Cholesterol:**
    - **Absorbed** in Small Intestine via **specific transporter** → enterocyte.
    - Cholesterol is **incorporated into cholymicrons** → → → shuttled into blood by process above.
    - **Cholesterol Homeostasis:** Balance of Synthesis/Absorption/Excretion$_{(in\ bile)}$ of Cholesterol.





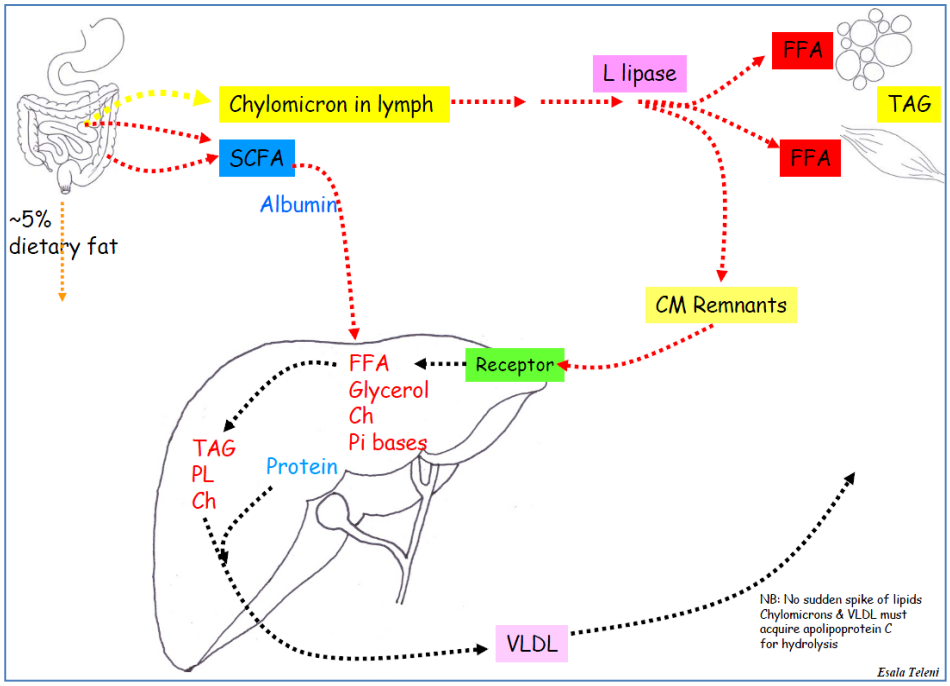
Cholesterol Recycling



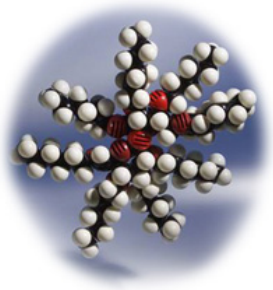


FAT ABSORPTION & THE LIVER:

- **Chylomicrons** (Fat Shuttles) **in Lymph:**
  - Travels through lymph →
  - Muscle/Adipose Tissue →
  - Lipoprotein Lipase→Liberates Free Fatty Acids→
  - Muscle/Adipose Tissue → reconverts FFA's → Triglycerides.
  - **Chylomicron Remnants** (Empty Fat Shuttles) →**Liver** → **Dismantled** → **Glycerol + FFA's + Cholesterol + P_i**
- **Short Chain Fatty Acids:**
  - **SCFA's** → absorbed into Blood in Intestines→ transported in blood by **Albumin**
  - **SCFA's add to** breakdown products of Cholymicron Remnants (**Glycerol + FFA's + Cholesterol + P_i**)
- **Construction of VLDLs:**
  - (Very Low Density Lipoproteins – High TAG percentage)
  - **Liver:** **Glycerol + FFA's + SCFA's = Triglycerides** (TAG's)
  - **Liver:** **P_i + FFA's + SCFA's = Phospholipids** (PL's)
  - **Liver:** **Cholesterol** - remains free.
  - **Liver:** **Triglycerides + Phospholipids + Cholesterol + ApoLipoproteins = VLDLS** →→ ***Circulation***
  - **VLDLs** → carry (newly synthesised) **Triglycerides** → **Adipose Tissue**



- **NB: Olestra:**
  - Fat substitute that adds no fat, calories or cholesterol to products.
  - Same taste & feel as fat
  - Instead of a Glycerol-backbone, **Olestra** has a **Sucrose-'backbone'**.
  - Sucrose-backbone holds 6-8 Fatty Acids (arranged radially)
  - Sucrose-FA bonds can't be broken by lipase → Olestra molecule stays intact→too big to be absorbed
  - **Downside:** Olestra **binds fat-soluble vitamins**→malabsorption of vitamins A,D,E & K.
    - Also results in Stomach Cramps/Fatty Stools/& Diarrhoea



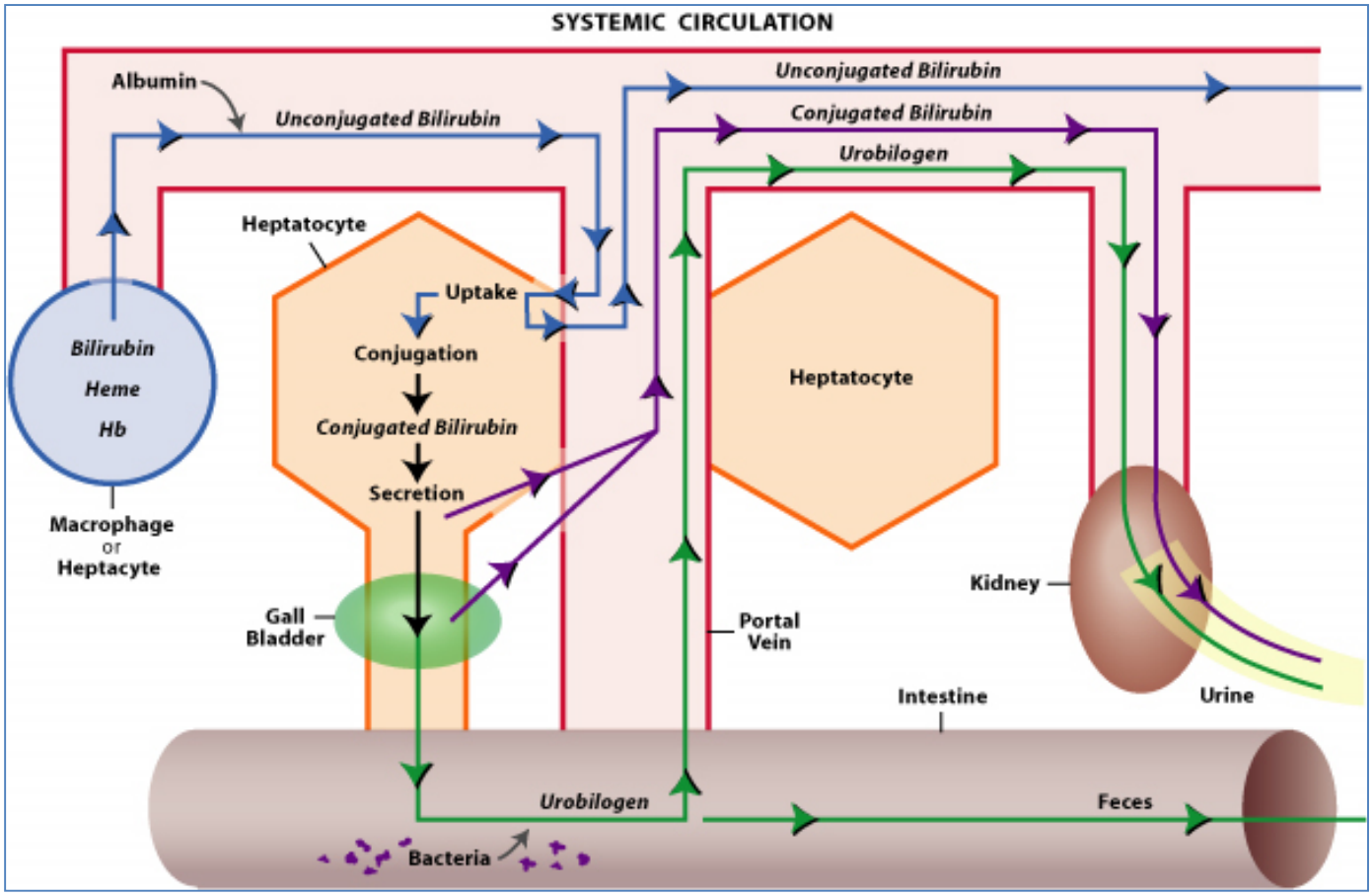
Bilirubin Metabolism:

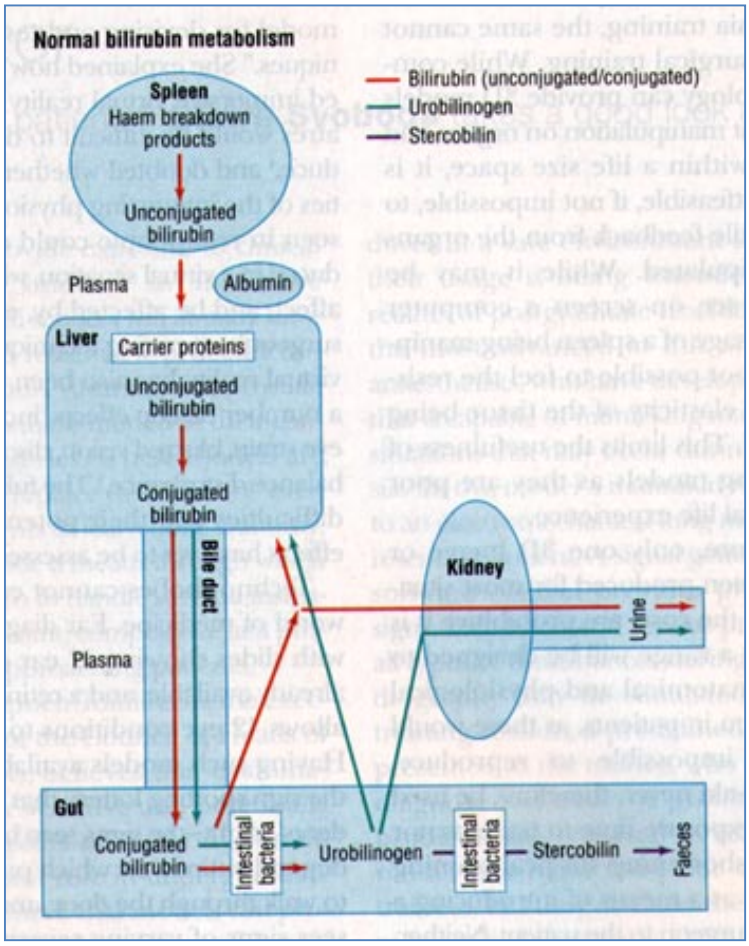
- **Bilirubin:**
  - Yellow waste-product of Heme catabolism
  - Powerful cellular antioxidant
  - Free Bilirubin = Toxic
  - Conjugated Bilirubin = H_2O Soluble & Non-Toxic.
  - 75% bilirubin in body – from haemoglobin of senescent red blood cells.
  - Secreted into Bile by Hepatocytes.

- **Bilirubin Formation - Spleen** (mainly)**:**
  - Senescent **Red Blood Cells** → **Phagocytosed** by macrophages of ***Spleen**, Bone Marrow & Liver
    - **Haemoglobin** is **released** → **broken down** into **Heme & Globin**
    - **Heme** -----Heme Oxygenase----→ **Biliverdin + Ferric-Iron (Fe^{3+})**
    - **Biliverdin** -----Biliverdin Reductase---→ **Bilirubin (unconjugated & insoluble)**
  - **Unconjugated Bilirubin** → bound to **albumin** in blood→ sent to **Liver**

- **Bilirubin Processing in Liver:**
  - Bilirubin is **Conjugated** in liver:
    - Hydrophilicity of **bilirubin** is increased by **esterification** of 1 or both **of its carboxylic acid side chains** with either **glucuronic acid**/xylose/or ribose.
    - **Conjugated bilirubin**→ Secreted into Biliary system(by hepatocytes)
      - Excess flows into blood → kidneys → urine.

- **Bilirubin Processing in Large Intestines:**
  - Bilirubin (in bile) secreted into small intestine→large intestine
  - Colonic **Bacteria** metabolise **Bilirubin** → **Urobilinogen** → Stercobilinogen →**Stercobilin** → **Faeces.**
    └→ Kidneys→**Urine**





Iron:

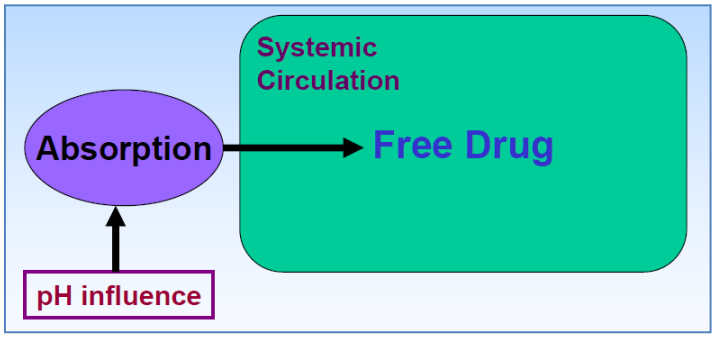
- In the 1st step where **Heme** is converted to **Biliverdin, Iron is released.**
  - **Heme -----**Heme Oxygenase----→ **Biliverdin + Ferric-Iron (Fe^{3+})**
  - **Fe^{3+}** is transported in blood via **Transferrin**
  - **Tranferrin** → Erythroblasts in **Bone Marrow** → for haemoglobin in new Red Blood Cells
    → Hepatocytes in **Liver -** storage
- **Storage: Liver:**
  - Iron is **stored**, mostly in the **liver**, as **ferritin** or **hemosiderin**.
  - **Ferritin**= protein with a capacity of about 4500 iron (III) ions per protein unit.
  - If **ferritin** iron stores are full, a complex of iron with phosphate and hydroxide forms→ **hemosiderin**

Jaundice:

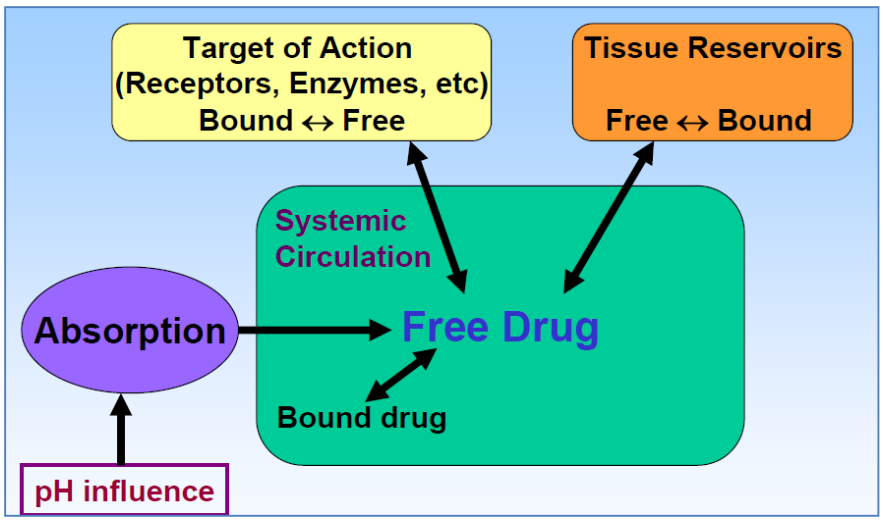
- Yellowish discolouration of skin, whites of eyes & mucous membranes.
- Caused by **Hyperbilirubinemia** (excess bilirubin in extracellular fluids)
- **Root Causes:**
  - **Pre-Hepatic:** Anything that causes hyper-hemolysis (RBC breakdown)
  - **Hepatic:** Eg. Hepatitis, Hepatoxicity, Alcoholic Liver Disease, Hepatocyte Necrosis.
  - **Post-Hepatic** (Obstructive)**:** Blockage of drainage of bile in Biliary System. (commonly gallstones)
- **Tests:**
  - **Enzymes that indicate Hepato-Cellular Injury / Inflammation:**
    - AST
    - ALT
  - **Biochemical Markers indicating pathology affecting the intra- or extra-hepatic biliary tree:**
    - Alkaline Phosphatase
    - γGT
  - **Tests that may reflect synthetic function of liver:**
    - Blood Serum albumen
    - Blood Urea
    - Clotting Factors.

Drug Metabolism & PharmacoKinetics:

- **Drug Absorption:**
  - From **Adminstration → Systemic Circulation**
  - Ease & Rate depends on **Route of Administration:**
    - Oral
    - Intravenous (IV)
    - Intramuscular (IM)
    - Rectal
    - Intrathecal (IT; into cerebrospinal fluid)
    - Subcutaneous (SC)
    - Intracerebroventricular (ICV)
    - Others.....
  - **Influences:**
    - pH: Eg. Oral route → Stomach pH → affects whether drug is in dissociated form → affects uptake.



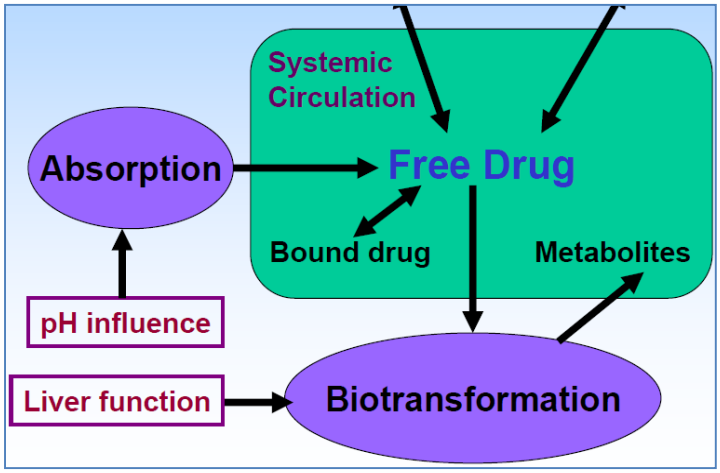
- **Drug Distribution:**
  - Systemic **Circulation → Site of Desired Action**
  - Most drugs are lipophilic → Enables diffusion through membranes → target.
  - Where does the drug go? – May be:
    - Bound to circulating proteins
    - Associate with tissue reservoirs
    - Access target tissue/organ (Receptors/Enzymes/Transporters/etc.)



- **Drug Metabolism (BioTransformation):**
  - Circulating **drug → Liver**
  - (drugs ***enzymatically*** metabolised not only the liver)
  - (one of) **Liver's role** is to remove drugs/toxins/others from blood.

  - **First-Pass Metabolism:**
    - Orally Administered drugs pass through intestines + liver ***first;*** before site of action.
    - Some drugs metabolised in liver; Some in Intestines.
    - Due to biotransformation, **Dose ≠ Amount Available to Body (Bioavailability)**
  - **Enzymes in liver metabolically alter drugs** → inactive/active/toxic/non-toxic metabolites

  - **BioActivation:**
    - Some administered drugs are 'pro'-drugs.
      - Administered in the inactive form
      - Relies on body to metabolise them into active agents.
    - Some administered drugs are active, but their metabolites are also active.
      - Eg. Codeine – good for cough relief
        - Metabolised to morphine – analgesic effects.
  - **Toxification:**
    - Metabolism creates a compound significantly more toxic than the drug.
  - **BioInactivation:**
    - Termination of drug action by creating inactive metabolites.
  - **Detoxification:**
    - Terminate toxin action through creating a less effective metabolite/s.
  - **Pre-Elimination:**
    - Most drugs are **lipophilic**
    - Therefore must be converted into hydrophilic metabolites →elimination by urine.
      - Otherwise lipophilic compounds will be reabsorbed in kidneys.



- **Biotransformation Pathways:**
  - **Phase I**
    - **Functional Group** of drug is *Exposed* or *Added to*.
      - New functional groups
      - Interchange existing functional groups
      - Expose existing functional groups
    - **Types of Phase I Reatctions:**

· **oxidation** (hydroxylation) = create new group
» RH → ROH

· **reduction** = interconvert group
» C=O → CH-OH

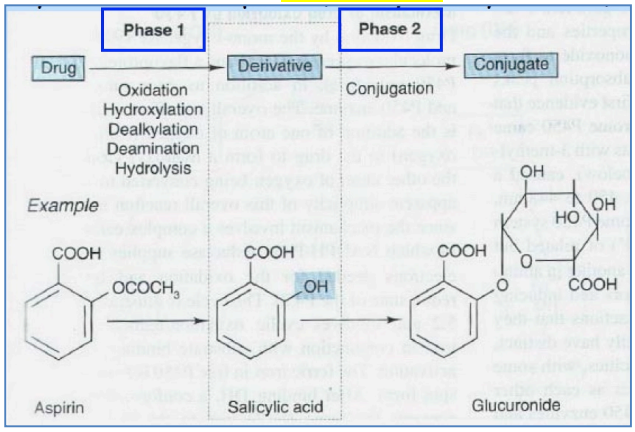
· **hydrolyses** = expose group
» R-CO_2CH_3 → RCOOH + CH_3OH

    - **NB: Oxidation Reactions** are the **most common.**
    - **NB: Oxidation Enzymes**: part of the **Cytochrome P450 Mono-Oxygenase** family:
      - Present in all tissues except skeletal muscle & erythrocytes.
      - Enzymes require $NADPH^+$ (from FA. Synthesis)
        - Are therefore sensitive to nutritional & metabolic disruption.

$$CYP(Fe^{+3}) + RH + O_2 + NADPH + H^+ \downarrow CYP(Fe^{+2}) + ROH + NADP+ + H_2O$$

      - **Other Roles of Cytochrome P450 Mono-Oxygenases:**
        - **Synthesis:**
          - Conversion of cholesterol → bile acid
          - Hydroxylation of steroids & Vit. D.
          - Conversion of Alkanes → Fatty Acids
          - Conversion of FA's → eicosanoids.
        - **Catabolism:**
          - -of Fatty Acids
          - -of Steroids
          - -of eicosanoids

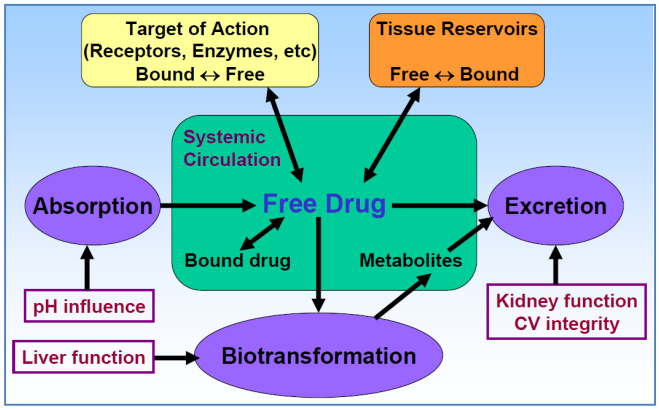
  - **Phase II** *('Conjugation')*
    - **Drug/ Drug Metabolite** is conjugated.
      - Ie. It is **merged with** an endogenous **polar compound**.
      - Aim: to ensure H_2O solubility → excretion through kidneys.



    - **Types of Phase II Reactions:**
      - Glucuronide Conjugation – Most Common
      - Glutathione Conjugation
      - Amino Acid Conjugation
      - Sulphate Formation
      - Acetylation
      - Methylation

- **Factors Influencing Biotransformation:**
  - **Interactions Between Drugs:**
    - Drug-induced alterations of liver-enzymes: (includes herbal medicines & natural remedies)
      - Ie. Changes in expression
      - Activity
      - Competition for enzymes
    - Competition for metabolic pathways
  - **Genetics:**
    - Some people vary in their expression of the Cytochrome-P450-Enzymes
    - May alter the effectiveness of a drug (may have no effect/may overdose)
      - Eg. CYP2D6 is absent in 7% of Caucasians → no response
      - CYP2D6 is hyperactive in 30% of East Africans → same dose = toxic.
  - **Disease Status:**
    - Compromised organs:
      - Liver
      - Kidney
      - Heart
      - Vasculature
    - Viral infections can alter enzyme activity
    - Bacterial infections can produce toxins → alter drug activity/metabolism.
  - **Hormone Status:**
    - Oestrogen can affect metabolic enzyme activity
  - **Age/Gender:**
    - Enzyme expression & activity changes with age.
    - Gender differences related to hormonal status.
  - **Diet:**
    - Enzyme activity is affected by some foods

- **Drug Elimination:**
  - Circulating drug/metabolites → OUT!
    - Urine
    - Sweat
    - Faeces
    - Exhalation
    - Others...
  - Time in body depends on:
    - Drug's 'half-life'
    - Solubility of Drug
    - Kidney Function
    - CardioVascular Integrity.

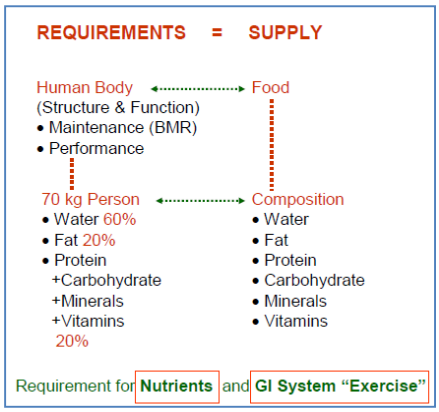


Nutrition I

Nutrition Basics:

- **Optimal Nutrition:**
  - Where the body's REQUIREMENTS = SUPPLY

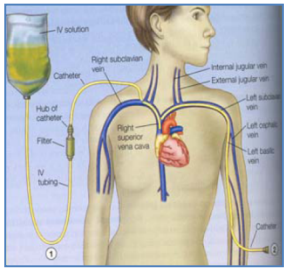
- **Food provides the requirements for:**
  - **Maintenance**
    - The basic requirements
    - Indicative of Basal Metabolic Rate (BMR)
    - The energy the body expends just to stay alive.
  - **Performance/Activity**
    - Extra energy expended in movement, cognitive & digestive function.
    - NB: Food is not only required for nutrients; but also for GI System "Exercise"



- **Administration of Nutrition:**
  - **Self:** Eating

  - **Enteral:** Via Nasogastric Tube → directly to stomach/jejunum.

  - **Parenteral:** Via a Catheter → directly into venous-system (eg. Subclavian Vein)

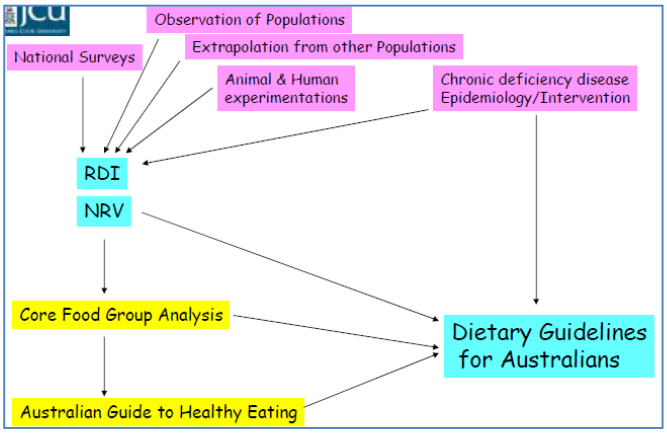


Dietary Guidelines for Australians: (NHRMC '98)

- Eat a Wide Variety of Nutritious Foods
- Eat Plenty of Breads, Cereals, Vegetables & Fruits.
- Eat a diet Low in Fat (particularly saturated fats)
- Maintain a Healthy Body Weight
- Balance Physical Activity with Food Intake
- Encourage & Support Breast-Feeding
- Moderate intake of Sugars/Sweet Foods
- Eat Low-Salt Foods
- Limit Alcohol Intake

- **Nutrient-Specific Guidelines:**
  - Eg. Eat foods containing Calcium (Especially women)
  - Eg. Eat foods containing Iron (Especially women)

- **Formation of Dietary Guidelines:**
  - Research →
  - Recommendations →
    - RDI – Recommended Dietary Intake (for specific nutrients)
    - NRV – Nutrient Reference Value (measure used by Canadians & United States)
  - Core Food Group Analysis – which foods have which nutrients & how much? →
  - Dietary Guidelines



The Healthy Food Plate

Healthy Diet Pyramid

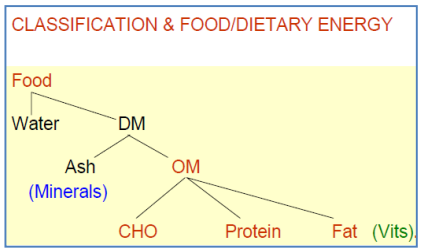
Requirements:

Energy:

- The biggest nutrient requirement of them all.
- Assumes: if energy needs are met, other nutrient needs will be met also (not always the case)
- **Basal Metabolic Rate (BMR):**
  - AKA – Resting Metabolic Rate (RMR)
  - Energy expended when:
    - Lying Down
    - Completely at rest (mentally & physically)
    - In a *Thermo-Neutral* environment.
    - In the *Post-Absorptive* state – ie. Not digesting anything (digestion uses energy)
- **Food Energy Unit:**
  - The **'Joule' (J):**
    - 'Energy used to move a 1kg object 1m by 1Newton of Force.'
    - Normally in kJ/MJ
    - Rate: **Watts (1W = 1J/sec)**
  - Old Measure: **Calorie = 4.184 J**

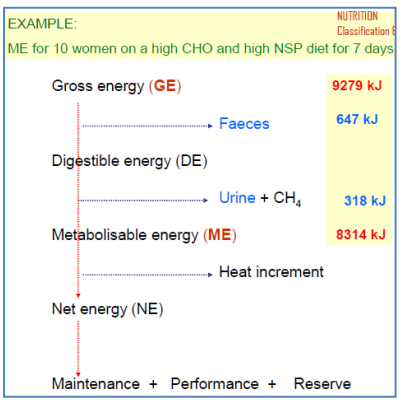
Food Analysis/Breakdown in the Lab:

- 1. Food is dehydrated → removes the H_2O component = **Dry Matter (DM)**
- 2. Food is incinerated → burns off **organic manner (OM** – containing all the energy in the food**)** → **Ash**
- **Ash = Carbon + Minerals.**



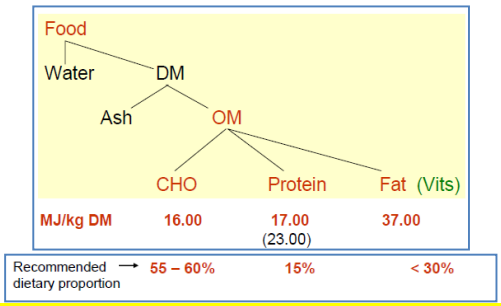
Harvesting Energy From Food: KNOW

- Energy in foods is harvested fairly efficiently by the body.
- However, there are energy losses along the way. (Faeces, Urine, Methane, Heat)
- **Gross Energy (GE):**
  - Total energy content in a certain food.
- **Digestible Energy (DE):**
  - Gross energy – Energy losses through Faeces.
- **Metabolisable Energy (ME):**
  - The energy content (in a food) available to the body after Digestion.
  - Ie. ME = Gross Energy – Faeces – Urine – CH_4
- **Net Energy (NE):**
  - NE = ME – Body Heat lost to the surrounds.
  - The energy left over for Maintenance (BMR)/Movement/Reserve (storage – fat/glycogen)



Energy Contents Of:

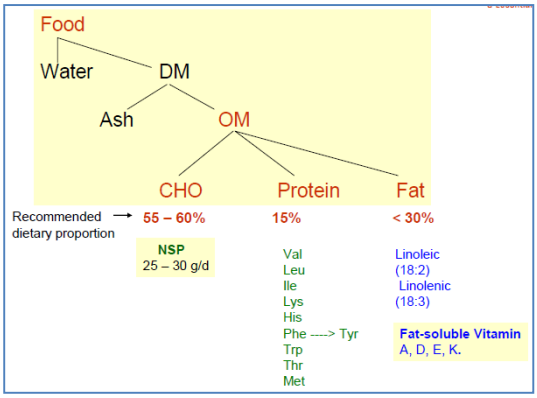
- Energy contents of foods are Expressed as Metabolisable Energy.
- It is measured in this fashion: Energy /Per/ Mass of Dry Matter (DM)
  - kJ/g of DM
  - MJ/kg of DM
- **CHO:** 16 kJ/g DM
  - Dietary Proportion: 55-60%
- **Proteins:** 17 kJ/g DM (net ≈1.5xCHO) (NB: Actual = 23 kJ/g DM - 6 kJ/g DM lost in Metabolism)
  - Dietary Proportion: 15%
- **Fats:** 37 kJ/g DM (≈2.5xCHO)
  - Dietary Proportion: 30%



NB: KNOW Energy Content & Dietary Proportions of CHO/Proteins/Fats

Importance of Consuming CHOs/Proteins/Fats:

- **CHOs:**
  - Mainly for energy.
  - Also for Dietary Fibre → Faecal Bulk/Regular bowel movements/Colonocite Health
- **Proteins:**
  - 9 of the 20 Amino Acids are Essential (must come from dietary sources – body cannot synthesise)
    - Histadine
    - Isoleucine
    - Leucine
    - Lycine
    - Methionine → Cysteine
    - Phenylalanine → Tyrosine
    - Threonine
    - Tryptophan
    - Valine
- **Fats:**
  - Fat cannot be completely eliminated from the diet.
  - Some Fatty Acids are essential:
    - Eg. Linoleic Acid$_{(Plant\ Oils)}$ (OMEGA 6) → Arachidonic Acid (precursor of Prostaglandin)
    - Eg. Linolenic Acid$_{(Plant\ Oils)}$ (OMEGA 3) →EPA & DHA
  - Essential Fat-Soluble Vitamens:
    - Vits. A, D, E & K



- **Minerals:**
  - Important Dietary Minerals:

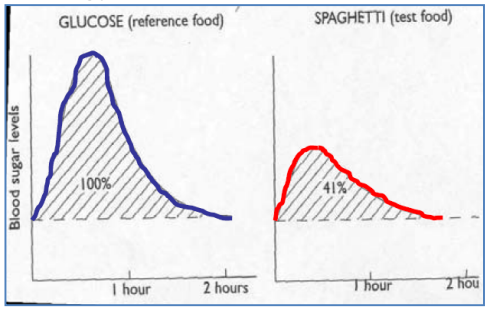
MAJOR (>5 g)	Amounts (g) in a 60 kg Human Body
Calcium	1150 g
Phosphorus	600
Potassium	210
Sulphur	150
Sodium	90
Chloride	90
Magnesium	30

TRACE (Only nine listed but more than 12)	
Iron	2.4
Zinc	2.0
Copper	0.09
Manganese	0.02
Iodine	0.02
Selenium	0.02
Molybdenum	
Fluoride	
Chromium	

- **Vitamins:**
  - Important H_2O Soluble Vitamins:
    - Vit B_{12} FA Metabolism
    - Biotin FA Metabolism
    - Vit C
  - Important Fat-Soluble Vitamins:
    - Vit A
    - Vit D
    - Vit E
    - Vit K

Glycaemic Index (GI):

- The propensity of a food to produce an increase in Blood Glucose Level over a 2hr period.
- Reference is Pure Glucose = 100% of the area under the graph
  - Foods with more complex carbohydrates will have a lower GI – take longer to digest
- High GI Foods → Quick, Short Release of Energy
- Low GI Foods → Long Sustained Energy Release



  - Have a general idea of the GI values of these general foods:

G.I. VALUES:

- Glucose = 100
- White bread = 70
- White bread with butter = 59
- Refined cane sugar = 60
- Boiled Australian Calrose white rice = 83
- Boiled Australian Doongara white rice = 50
- Porridge = 42

Nutritional Status Assessment

Malnutrition:

- Excess/Deficiency of:
  - Energy
  - Nutrients
- **Undernutrition:**Deficiency
- **Overnutrition:** Excess

Nutrition – What Can Go Wrong:

- NB: Advanced malnutrition is easy to recognize (eg. Obesity/anorexia) due to the appearance of physical complications & symptoms. It is therefore important that malnutrition is diagnosed early in order to provide nutritional support/dietary advice before the occurrence of complications.

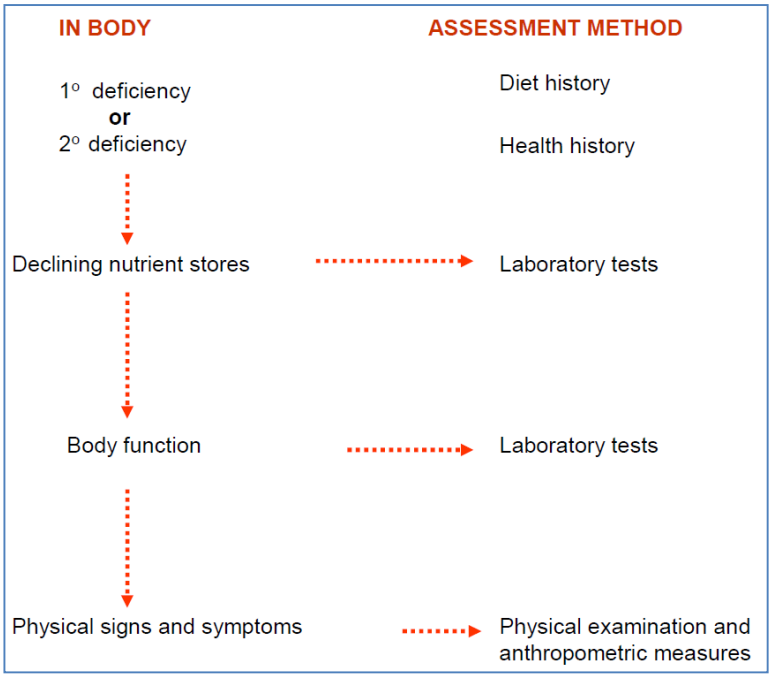
- **Stages of Malnutrition:**
  - **Deficiency:**
    - **Primary Deficiency:**
      - The patient's diet doesn't satisfy the needed nutrients or contains insufficient amounts.
    - **Secondary Deficiency:**
      - Where the patient's body has a problem with digestion/absorption/processing of nutrients in the food.
      - Ie. Diet is fine, but the body can't absorb/utilize the nutrients available.

  Leads to:
  - **Declining Nutrient Stores**

  Leads to:
  - **Change in Body Function**

  Leads to:
  - **Physical Signs/Symptoms**

What to Assess & When:



Assessing Nutritional Status:

Historical Information:

- **Assessment of Dietary History:**
  - Food Diary
  - 24hr recall
  - Diet History
  - Food Frequency Questionaire

Biochemical Tests:

- (laboratory tests)
- **Blood & Urine Tests:**
  - Most common
  - May *directly* reflect nutritional status....OR...
  - May show things that may have an impact on nutritional status in the future:
    - Ie. Electrolyte Balance,
    - Acid-base Balance (Acidosis/Alkanosis)
    - Organ Function
  - **Limitations:**
    - Results open to interpretation
    - Hydration levels can affect results.
    - Requires multiple tests over time.
    - Levels may be unrelated to nutrition.
  - **Examples:**
    - **Analysing Protein-Energy Malnutrition (PEM):**
      - **Serum Protein Levels:**
        - Examples:
          - *Albumin*
          - *Transferrin*
          - *Transthyretin* (Binds Thyroid Hormone)
          - *Retinol-Binding Protein* (Binds Vit. A)
          - *Clotting Factors*
        - May Reflect:
          - Liver Function (liver synthesizes many serum proteins)
          - Protein Intake
          - Protein Distribution [cellular vs. Blood]
          - Protein Utilisation
        - Test Sensitivity:
          - Depends on the Halflife of the protein.
          - Ie. The shorter the $t_{1/2}$ the more sensitive the test = better.

Indicator	Normal	$t_{1/2}$
Albumin (g/L)	35 - 50	~ 18 days
Transferrin (g/L)	2 - 4	~ 8 days
Transthyretin (g/L)	0.20 - 0.40	~ 2 days
Retinol-binding protein (g/L)	0.03 - 0.08	~ 12 hours
IGF-1 (μg/L)	300	~ 12-15 hours.

      - **Total Body Protein Level:**
        - Nitrogen Balance:
          - Protein intake minus nitrogen in faeces/urine
        - Urinary Creatine:
          - Conc. of creatine in urine is proportional to muscle mass
        - Urinary/Blood Urea:
          - Increase in proteolysis → increase in urea.

- **Analysing Fat Malnutrition:**
  - Amount & Distribution
    - Lipoprotein levels [ie. TAG, Phospholipids, Cholesterol]
      - Chylomicrons (from intestine)
      - VLDLs (High % TAG; Liver → Peripheries)
      - LDLs (High Cholesterol %)
      - HDLs (High Protein %)
    - Good for testing for Cardio-Vascular Disease.

- **Analysing Glucose Malnutrition: (ie. Type 2 Diabetes)**
  - **Blood Glucose Levels** (Gives a 'snapshot' for that instant → need many)
  - **Urinary Glucose Levels** (indicates elevated blood-glucose levels [10^{+}])
    - Conclusions: Normal?/Impaired?/Diabetes?
  - **Then – Glucose Tolerance Test**
  - **And/Or – Glycosylated Haemoglobin (HbA_{1c})**
    - Sustained elevated blood-glucose levels causes glucose to combine with blood proteins – ie. Haemoglobin → Glycosylated
    - High HbA_{1c} indicates elevated blood-glucose levels over the last 120 days.
      - NB: RBC only live for 120 days

GLUCOSE

- Blood glucose (instant in time)
- Urinary glucose (glycosuria)

⇩

Normal ? Impaired ? Diabetes ?

⇩

Glucose Tolerance Test

Glycosylated Haemoglobin (HbA_{1c}) [longer term (e.g., 2-3 months) picture].

EXAMPLES

HbA1c	Blood glucose
6%	120 mg/100mL (6.7 mM) --- Good
8%	180 mg/100 mL (10 mM) ---- Warning
10%	240 mg/100 mL (13 mM) ---- Bad
13%	330 mg/100 mL (18 mM) ---- **Dangerous.**

- **Analysing Mineral & Vitamin Malnutrition:**
  - **Eg. Nutritional Anaemia:** Any anaemia resulting from a dietary deficiency of materials essential to red blood cell formation:

Due to:
- Inadequate Intake 1^{o}
- Poor Absorption 2^{o}
- Abnormal Metabolism 2^{o}

OF:

    - **Iron:**
      - **Assessment:**
      - Haemoglobin Levels (amt of Hb in RBCs)
      - Haematocrit (the %age of RBC in Blood)
      - Serum Ferritin (iron store)
      - Transferrin Saturation (serum iron/tot. Iron-binding capacity)
    - **Folate:**
      - **Assessment:**
      - Serum Folate
      - Mean Corpuscular Volume (Average size of RBCs)
    - **Vit. B_{12}:**
      - **Assessment:**
      - Serum Vit. B_{12}
      - Schilling's Test – tests for malabsorption
        - Saturate a person with Vit.B_{12} injection.
        - Then give oral radioactive Vit.B_{12}
        - Then test urinary levels of the 'marked' Vit.B_{12}.
      - **NB**: malabsorption may be due to lack of intrinsic factor

- Other causes of Anaemia:
  - Massive blood loss
  - Infections
  - Hereditary (eg. Sickle-cell)
  - Chronic Liver disease

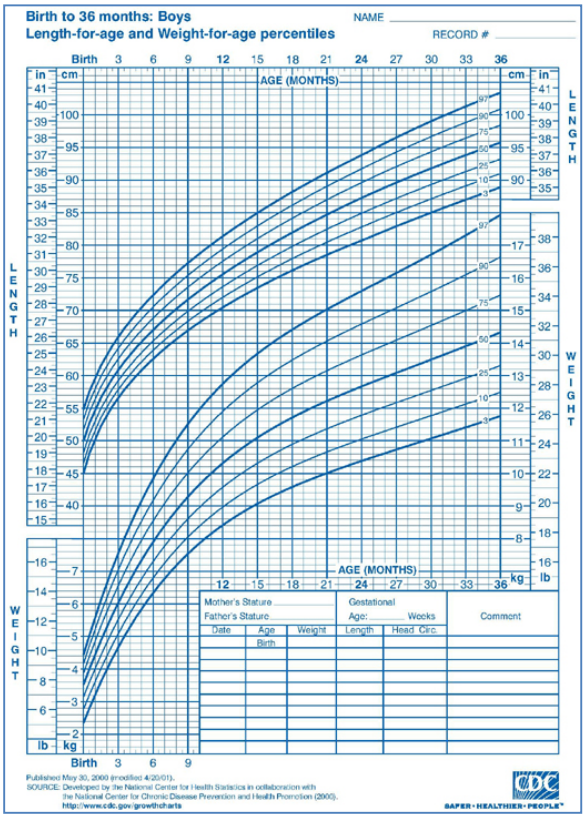
NB: Anaemia = Lower than normal RBC volume And/OR Haemoglobin levels.

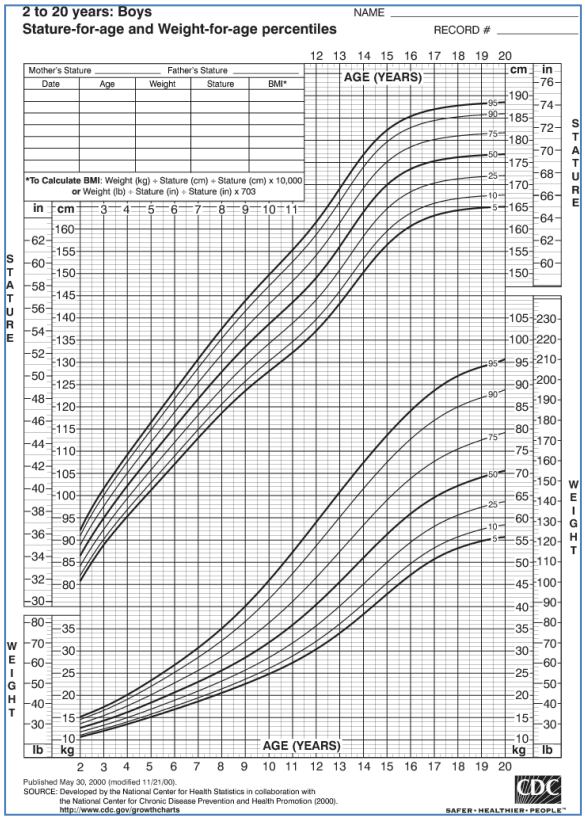
Physical Examination:

- (Clinical Assessment)

Anthropometric Tests:

- "Body measurements"
- **Growth Charts:**
  - 'Growth' shown in *percentiles* (length/weight/height/etc.)
  - It's only a problem when someone jumps between %ile → %ile
  - Ie. A boy born in the 25th %ile would be expected to stay in the same %ile throughout his development. (give/take within reason)





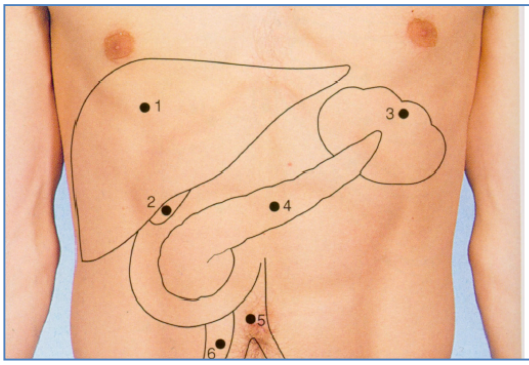
- **Skinfold (Pinch) Tests**

- **BMI – Body Mass Index**
  - Mass (kg) / height^2 (m)
    - Underweight: <18.5
    - Acceptable: 18.5-25
    - Overweight: 25-30
    - Obese: 30+

- **Waist:Hip Ratio:**
  - Recommended:
    - Men: 0.8
    - Women: 0.9

Macro-Anatomy & Functions of Accessory Structures of GIT

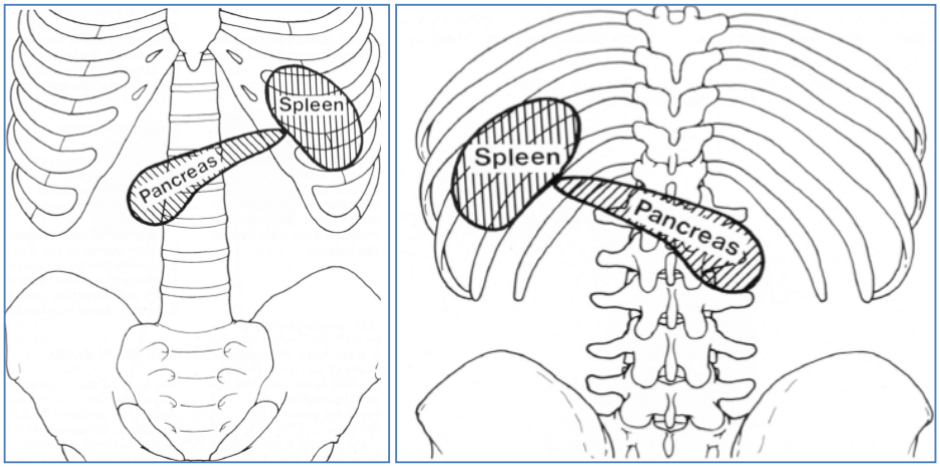
Surface Anatomy of GIT Accessory Structures:



1. Liver
2. Gall Bladder
3. Spleen
4. Pancreas

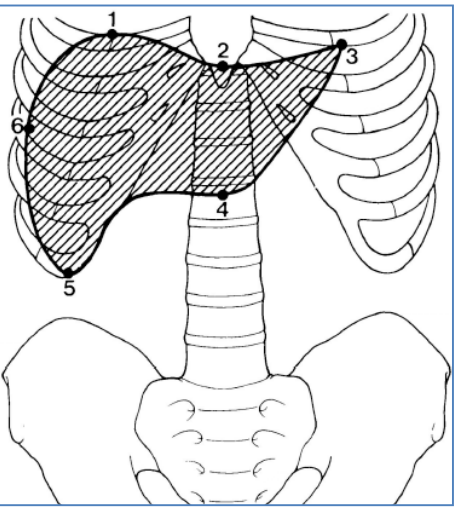
Surface Projections:

Pancreas & Spleen



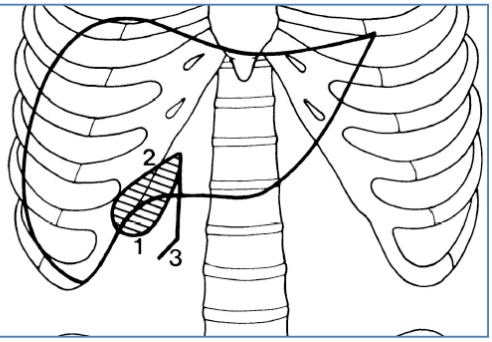
Liver

1. R upper limit
2. Upper border
3. L upper limit
4. Lower border
5. R lower limit
6. R border



Billary System

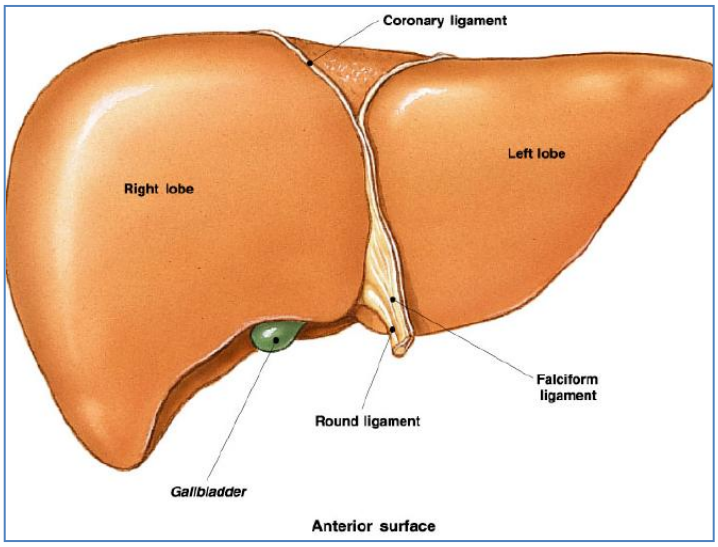
1. Fundus of gall bladder
2. Body of gall bladder
3. Bile duct

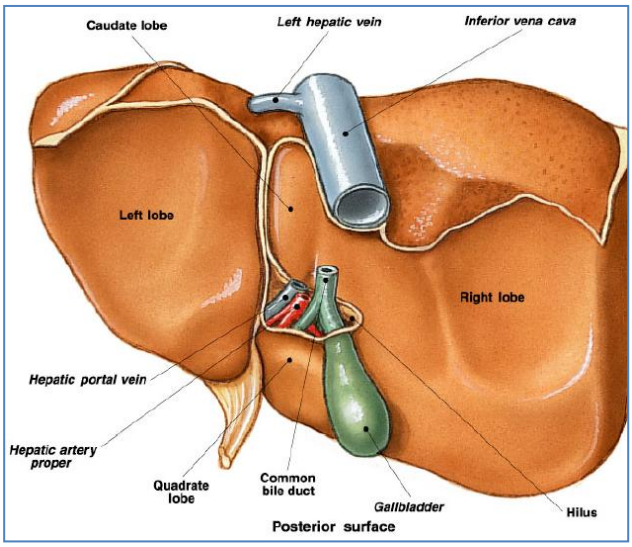


REVIEW OF HEPATOBILIARY…

Anatomy:

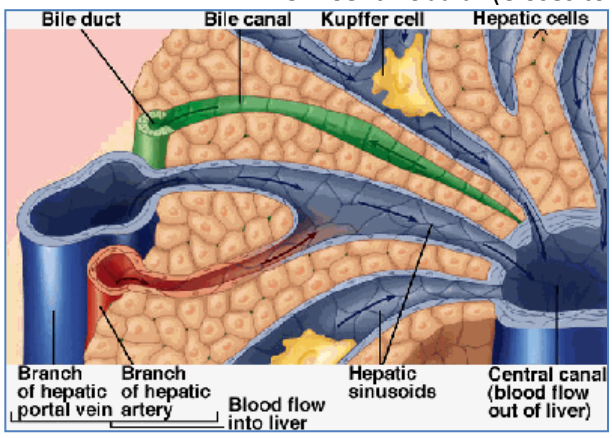
- **Liver Structure:**
  - **General Structure:**
    - Large Gland– 1.5kg
    - Wedge-shaped.
    - 2 Surfaces - Diaphragmatic & Visceral
    - 4 Lobes – Right, Left, Quadrate, Caudate (tail).
    - Dual Blood Supply:
      - Hepatic Artery 25%
      - Portal Vein 75%
    - All Blood *From the Liver* → Inferior Vena Cava

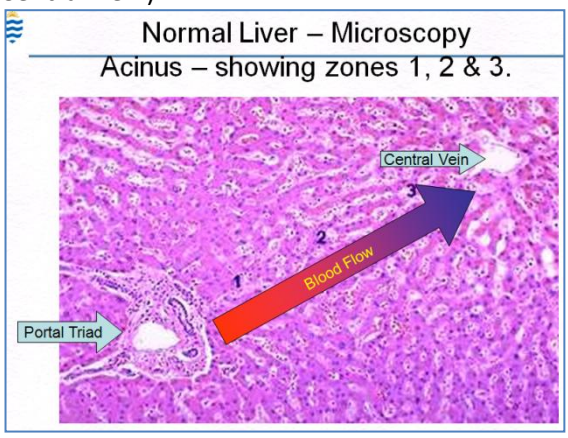




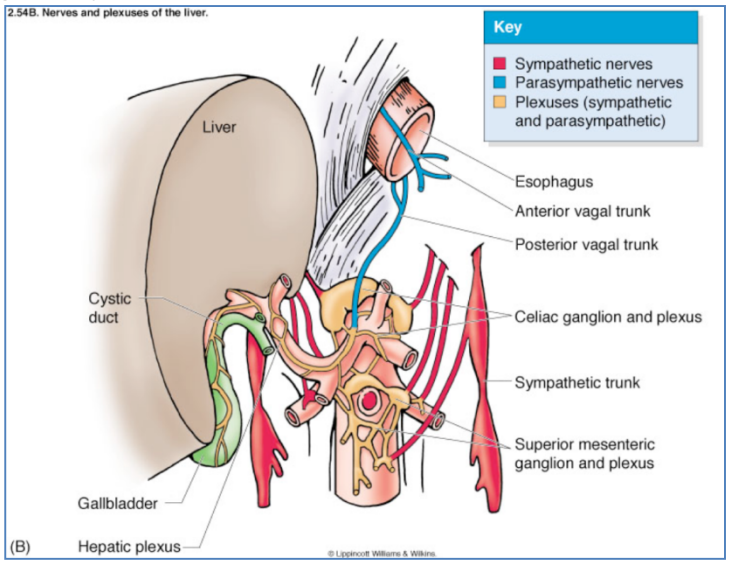
  - **Hepatic Blood Supply**
    - **To Liver:**
      - **Hepatic Artery** (From Celiac Trunk) – 20% - Oxygenated.
      - **Hepatic *Portal* Vein** (Drainage from GIT) – 80% - Nutriated; Deoxygenated.
    - **From Liver:**
      - **Central Veins (In each Lobule) → Hepatic Vein** → IVC

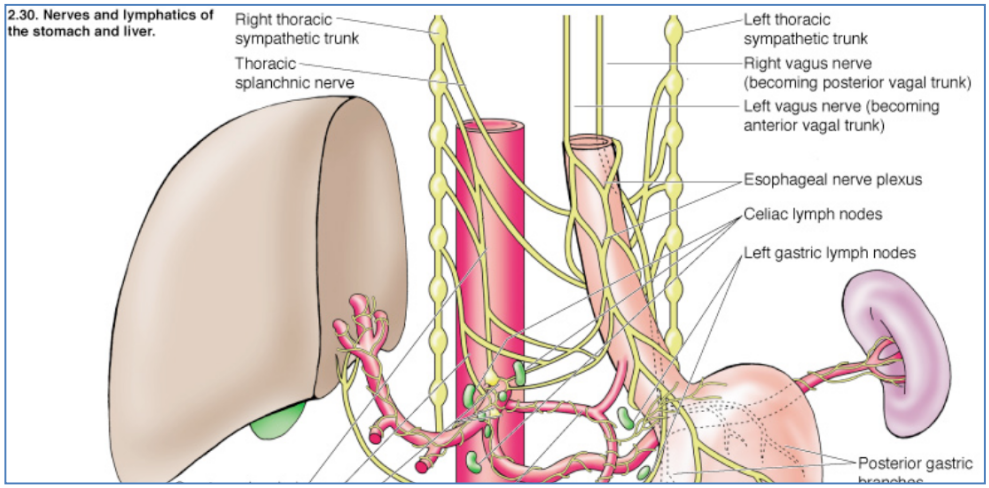
  - **Microscopic Structure – Liver Lobules:**
    - **Portal Triad:**
      - Bile Duct
      - Branch of Portal Vein
      - Branch of Hepatic Artery
    - **Zones:**
      - 1 – Peripheral (Closest to Portal Triad)
      - 2 – Middle
      - 3 – Centrilobular (Closes to Central Vein)



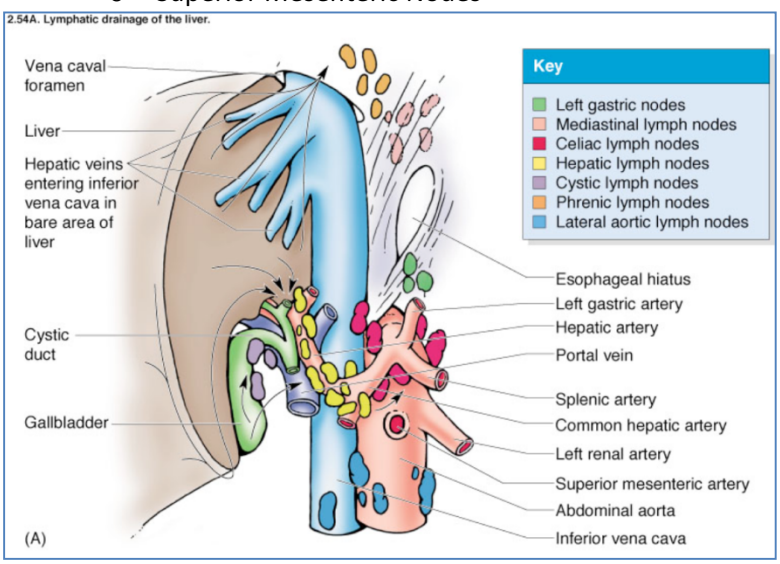


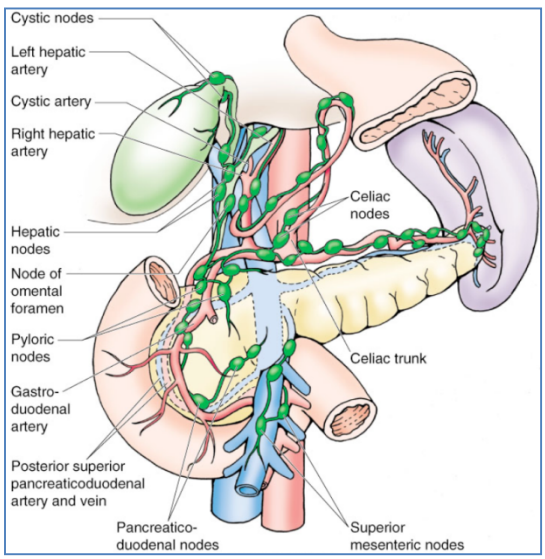
- Nerves:
  - Sympathetic – From L & R Sympathetic Trunk
  - Parasympathetic – From extensions of Vagus Cranial Nerve
  - Various ganglion & plexuses.





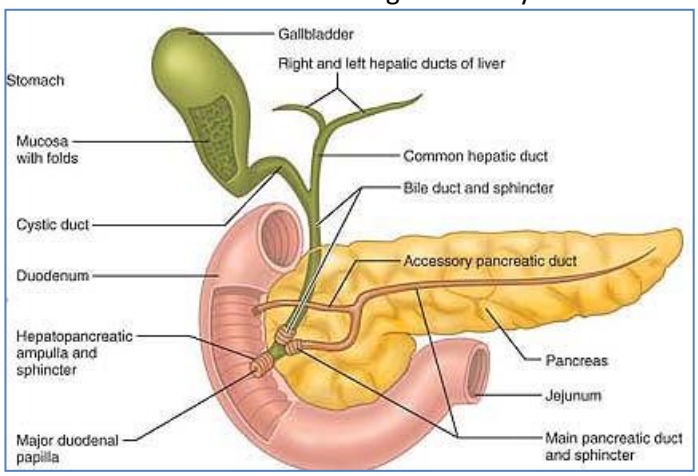
- Lymph:
  - Celiac Nodes
  - Gastric Nodes
  - Hepatic Nodes
  - Cystic Nodes
  - Pyloric Nodes
  - Superior Mesenteric Nodes



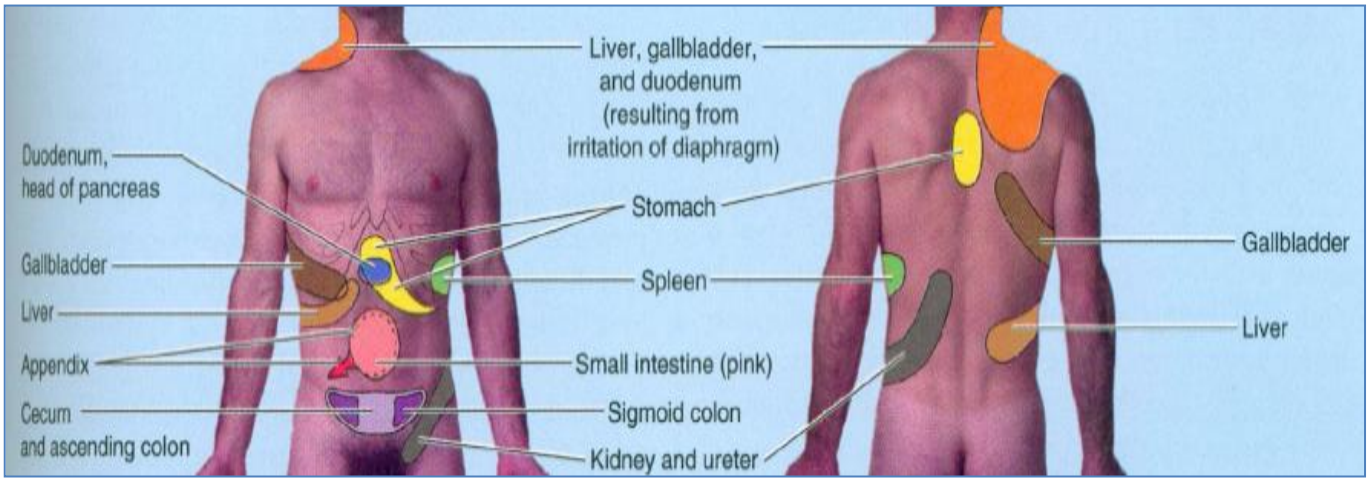


- **Biliary Tree:**
  - **Structures Within the Liver:**
    - Hepatocytes secrete bile into **Bile Canaliculi** → Drain into Larger **Bile Ducts**
    - Many Bile Ducts converge → eventually →**Common Bile Duct**.
  - **Structures Exiting The Liver:**
    - **R & L Hepatic ducts** of liver → **Common Hepatic Duct**
      - → **Cystic Duct** → Gallbladder
      - → **Common Bile Duct**
    - Pancreas → **Pancreatic Duct**
    - **Common Bile Duct + Pancreatic Duct** → **Hepatopancreatic Ampulla**.

- **Gallbladder:**
  - **Function:** Storage & Concentration of Bile
    - Greenish-yellow fluid
    - Alkaline – neutralises stomach acid in duodenum
    - Composed of cholesterol, bile salts (emulsifiers) & metabolic wastes of liver (Incl. Bilirubin).
  - **Regulation:** Hormone = CCK Cholecystokinin: ("move the bile-sac")
    - Secreted by duodenum → Contracts Gall Bladder & Relaxes Hepatopancreatic Sphincter
      - →Causes release of Bile & digestive enzymes



- **Referred Pain:**
  - **Liver:**
    - R-Hypochondrium → R-Flank
    - R-Shoulderblade → R-Neck (Due to Diaphragm Irritation)
  - **Gallbladder:**
    - R-Hypochondrium → R-Back
    - R-Shoulderblade → R-Neck (Due to Diaphragm Irritation)



Physiology:

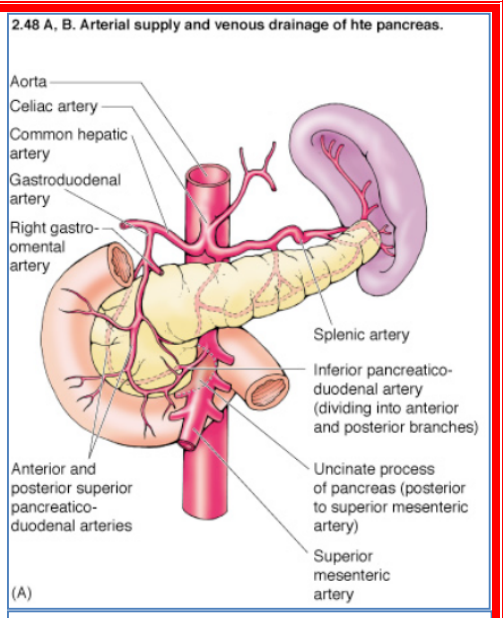
- **Normal Bilirubin Metabolism:**
  - **Where Bilirubin Comes From:**
    - Metabolism of Protoporphyrin, a Breakdown product of Heme in Haemoglobin in RBCs.
  - **Spleen's Role:**
    - Primary organ of RBC sequestration & breakdown.
  - **Process of Haemoglobin Breakdown & Bilirubin Formation:**
    - Haemoglobin → Heme & Globin.
    - Heme → Iron & Protoporphyrin
    - Protoporphyrin → Biliverdin (Green) → Unconjugated Bilirubin (Yellow)
  - **Bilirubin Metabolism:**
    - 1. Unconjugated Bilirubin in Spleen is NOT Water-Soluble
      - :. Transported to Liver via Albumin → Uptake into Hepatocytes.
    - 2. Hepatocytes Conjugate Bilirubin with Sugar Residues → Water Soluble
    - 3. Conjugated Bilirubin is Excreted with Bile into Gut.
      - Most is Excreted as Stercobilin in Faeces.
      - Some is Reabsorbed but Excreted as Con-Bilirubin and Urobilinogen in Urine.
  - **Jaundice:**
    - Jaundice occurs when a fault in the above sequence → ↑↑Bilirubin in the Blood
- **Other Liver Functions:**
  - **Bile Synthesis**
  - **Protein Metabolism** (Synthesis, Storage & Degradation[transamination])
  - **Carbohydrate Metabolism** (Synthesis, Storage & Metabolism).
  - **Lipid Metabolism & Transport** (VLDL Synthesis, HDL Synthesis
  - **Vitamin A production & storage**
  - **Makes Heparin** – blood thinner (anti-clotting agent)
  - **Drug Detoxification/Activation**
  - **Immunological Function** (Kupffer Cells – Macrophages attached to endothelium)

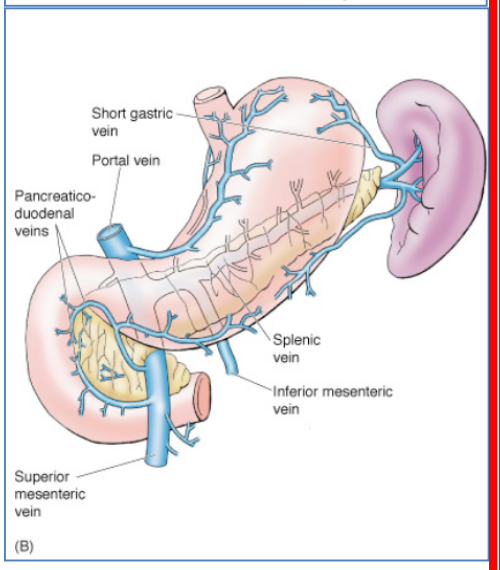
Liver "Function" Tests – What they Mean:

- **Serum BIlirubin:**
  - NB: *Serum* Bilirubin is almost always *Unconjugated*.
  - ↑Unconjugated Bilirubin = (Prehepatic Jaundice)
  - ↑Conjugated Bilirubin = (Posthepatic Jaundice)
- **Serum Albumin/Total Protein/Prothrombin Time:**
  - (Measures of Liver's Synthetic Function)
    - **↓Serum Albumin** = Synthesis/function defect (Eg. Chronic liver disease)
    - **↓Total Protein** = Synthesis/function defect (Eg. Chronic liver disease)
    - **↑Prothrombin Time** (In the presence of *Normal Vit.K*) = Indicates Liver Disease
- **Transaminases:**
  - (Measures of Hepatocyte Injury)
  - **AST (Aspartate Amino Transferase):**
    - A Mitochondrial Enzyme found in Liver, Heart, Kidney & Brain. (Ie. Non-Specific)
    - ↑AST = **Hepatocellular Injury/Inflammation** (Leak into the Blood with Liver Cell Damage)
  - **ALT (Alanine Amino Transferase)**
    - A Cytosolic Enzyme found ONLY in Liver (Ie. More Specific to Liver)
    - ↑ALT = **Hepatocellular Injury/Inflammation** (Leak into the Blood with Liver Cell Damage)
- **ALP (Serum Alkaline Phosphatase):**
  - (Measure of Bile Obstruction)
  - Enzyme found in Canalicular & Sinusoidal Epithelium of the Liver (Also Bone, GIT & Placenta)
    - NB: Non-Specific; but if ↑GGT as well, the ↑ALP is presumed to be Hepatic.
  - ↑ALP = **Reflects Cholestasis (Ie. Bile Obstruction)** (of any cause)
- **GGT (Gamma Glutyl-Transferase):**
  - (Measure of Bile Obstruction/Alcohol Consumption)
  - Enzyme found in Liver (ad many other tisues)
  - ↑GGT (with normal ALP) = **Reflects Alcohol Consumption**
  - ↑GGT (with ↑ALP) = **Reflects Cholestasis**

Spleen

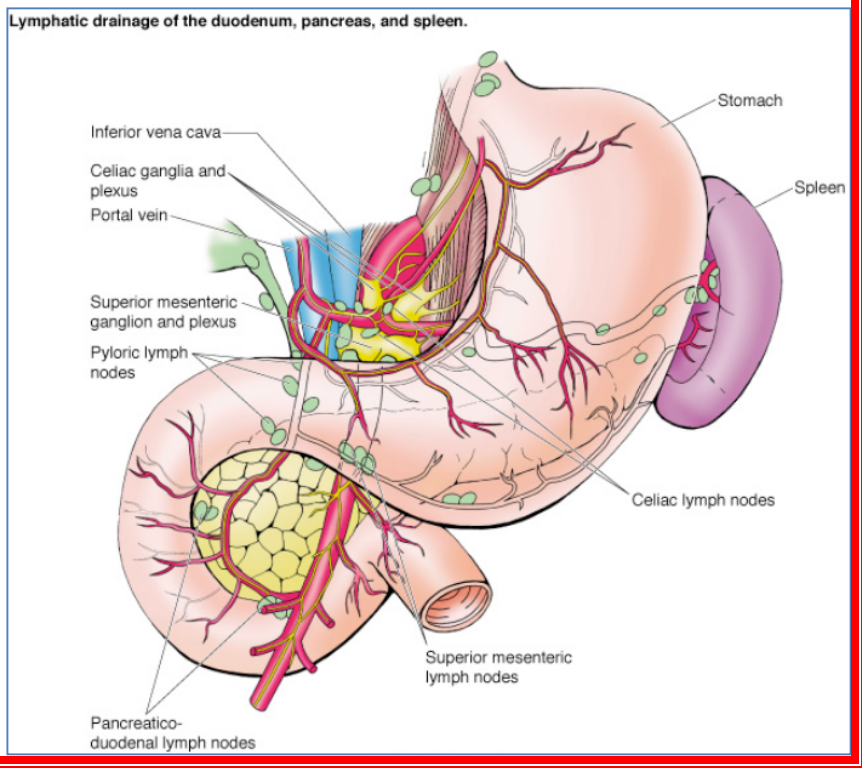
- Size of fist
- Notches – reminants of lobular development
- 3 Areas:
  - Gastric
  - Renal
  - Colic
- Hylum
- Sits roughly under the 10th rib.
- Surrounded in peritoneum
- Ligaments to stomach &…….
- Blood Supply:
  - Splenic artery
  - Splenic vein
- Lymph:
  - Celiac Nodes
- Nerves:
  - Celiac Plexus





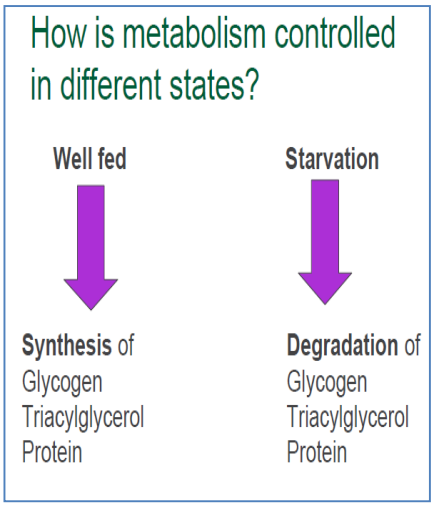
Pancreas

- Defines the foregut-midgut junction
- Elongated & horizontal
- Head –Cupped by the Duodenum
- Neck – just anterior to Portal Vein
- Body – just anterior to Aorta
- Tail – abuts the spleen
- Exocrine:
  - Pancreatic Juice
  - Drains from the centrally-located **Main Pancreatic Duct**
  - Secretes digestive enzymes into duodenum
  - Enzymes degrade proteins, fats
  - Also secretes bicarbonate ions
    - Helps neutralise acid.
    - Environment is more optimal for enzymes
- Endocrine:
  - Secrete Hormones
  - Insulin + Glucagon
  - Regulates Blood Sugar Levels
  - Islets of Langerhans
- Blood Supply:
  - Pancreatico-Duodenal Artery
  - Branches of Splenic Vein →Portal Vein
- Lymph:
  - Celiac Nodes
  - Pyloric Nodes
  - Superior Mesenteric Nodes
- Nerves:
  - Sympathetic Fibres
  - Parasympathetic Fibres
  - Various ganglia & plexuses



Metabolism in the Liver

Liver Metabolism Overview:



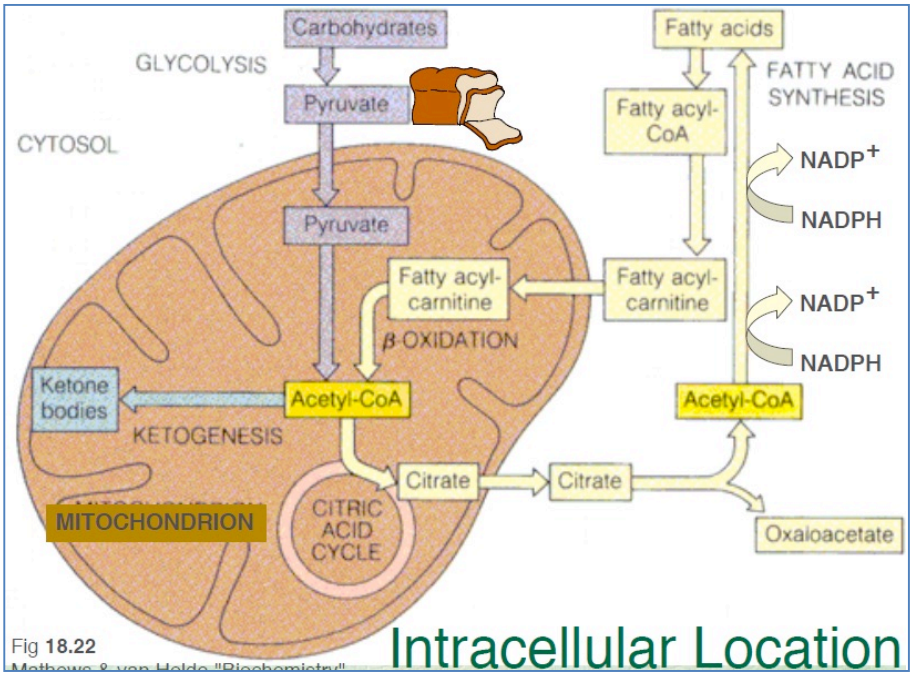


Fig 18.22

Excretion & Detox:

- **Bile Acid Secretion**
- **Bilirubin Secretion**
- **Excretion of Cholesterol**
- **Drug Detoxification**
- **Drug Excretion**
- **Steroid Hormone Inactivation**
- **Steroid Hormone Excretion**

Miscellaneous:

- **Iron Storage**
- **Vitamin (A, D, E, & B12) Storage & Metabolism**

Drug Metabolism – See Week 7 GIMN Notes for full details.

- **Phase I Reactions – Biotransformation:**
  - Catabolic
  - Adds/Exposes a Functional Group
  - Most are catalysed by CP450-Mono-Oxygenases
  - Occur on the Smooth ER in Hepatocytes
- **Phase II Reactions – Conjugation:**
  - Anabolic
  - Drug is Merged with a Polar Compound to **Increase Solubility** → **excretion** through **kidneys**.
    - Glucuronide Conjugation – Most Common
    - Others: Glutathione/Amino Acid/Sulphate/Acetylation/Methylation
  - Occurs in Hepatocytes.
  - Forms **Inactive, Soluble** Products

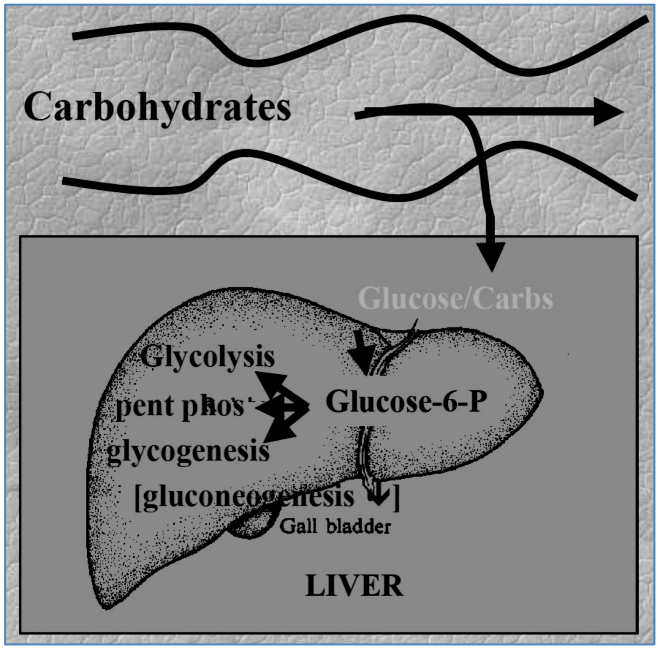
Carbohydrate (Glucose) Homeostasis:

- **Glucose is Required by:**
  - Brain
  - Glycolytic Cells:
    - Eg. Erythrocytes
    - Eg. Anaerobic Cells
    - Eg. Muscles
- **60% of Bodily Carbohydrates Reside in the Liver.**

- **When Blood-Glucose is High:**
  - Glycogenesis/Glycogen Storage
  - Glycolysis
- **When Blood-Glucose is Low:**
  - Gluconeogenesis
  - Glycogenolysis

- **After A Meal → Metabolism (Times of Plenty):**
  - Carbohydrate Absorption in Small Intestines → Blood (Portal Vein) → Increased Blood-Glucose
  - Glucose in Blood→ Increased Insulin →Uptake by Liver →
    - Phosphorylation (one-way ticket) by High Km Glucokinase → Glucose-6-P Accumulates→
      - Activates Glycogen-Synthase + Inactivates Glycogen-Phosphorylase
        - Glycogenesis Increases
    - Insulin Activates Phosho-Fructo Kinase & Pyruvate Kinase →
      - Free Glucose → Glycolysis (Doesn't Enter TCA-Cycle)
    - Decreased Fructose-1-6-Bisphosphatase Activity → Decreased Gluconeogenesis

- **Gluconeogenesis (Times of Scarcity):**
  - From Glycerol (from lipolysis)
  - From Glucogenic Amino Acids
  - From Lactate (Anaerobic Metabolism)



- **Fates of Glucose-6-Phosphate (IN LIVER):**
  1. **Glycogen Synthesis:**
     a. Stored in Liver & Muscle
  2. **Fatty Acid Synthesis:**
     a. Transported & Stored away from Liver.
  3. **Pentose Phosphate Pathway →NADPH →FA-Synthesis:**
     a. Glucose-6-P → Ribose-5-P + 2 NADPH
     b. NADPH needed for FA-Synthesis
  4. **Hydrolysis to Glucose:**
     a. Hydrolysis of Phosphate → Releases Glucose → Bloodstream
  5. (**NB:** LIVER RARELY ENTERS TCA-CYCLE – Only high CHO diets)

Lipid Metabolism:

- **Lipolysis:**
  - Times of Scarcity
  - Oxidation of Triglycerides → Energy
- **Fatty Acid Metabolism**
  - Fatty Acid Breakdown →Acetyl-CoA → Ketogenesis → Ketones in blood for Brain & Heart....
  - **NB:** Most of the liver's ATP requirements comes from β-Oxidation of FAs
  - **NB:** FAs CANNOT produce Glucose. Instead they produce ketones.

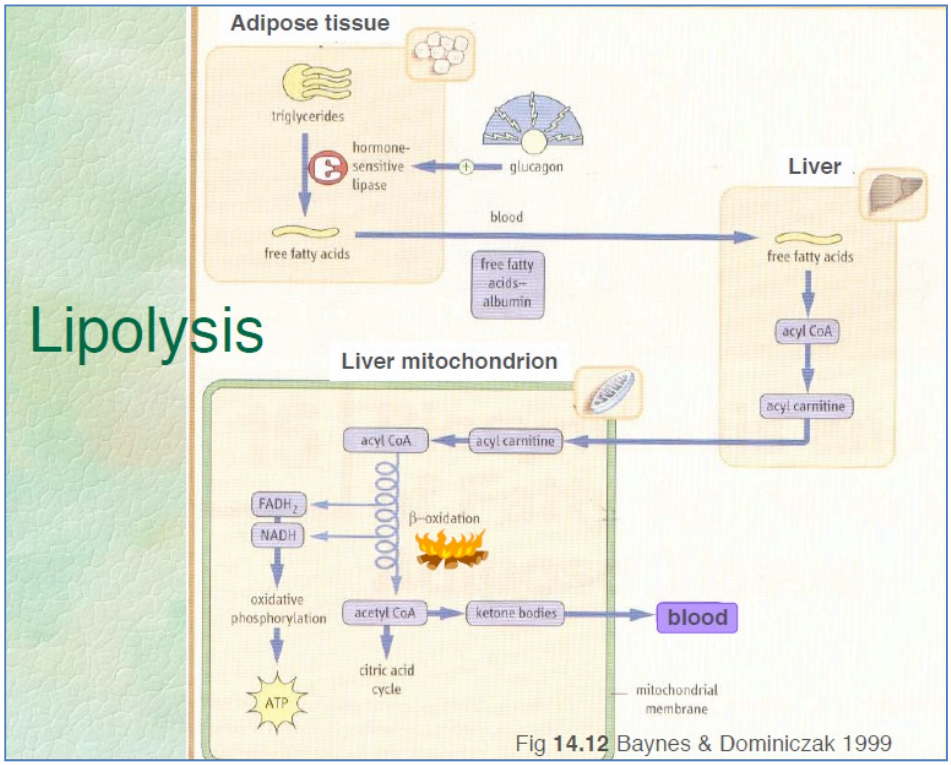
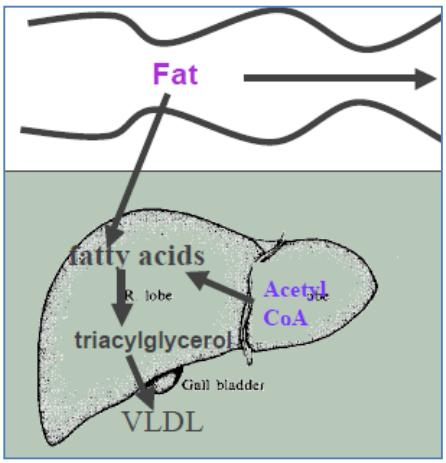


Fig 14.12 Baynes & Dominiczak 1999

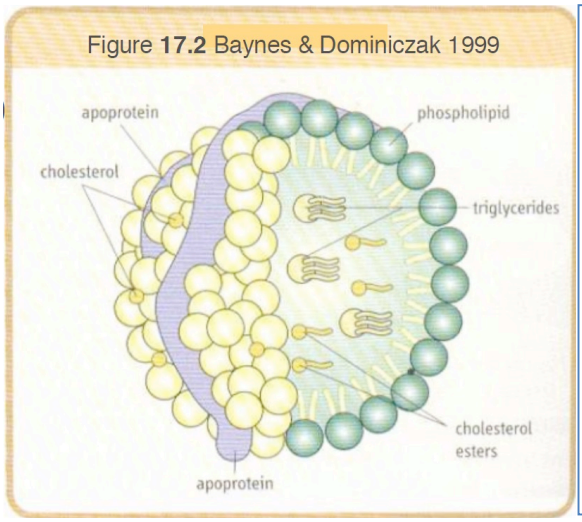
- **Lipogenesis:**
  - Times of Plenty
  - Metabolism of Carbs & Proteins → Increased Substrates: Acetyl CoA →
  - Activates Acetyl-CoA-Carboxylase → Increases Fatty Acid Synthesis
  - Free Fatty Acids Accumulate + Glycerol-3-P → Triglycerides
- **Cholesterol & Phospholipid Synthesis**
  - Needed constantly
- **Lipoprotein Synthesis**
  -

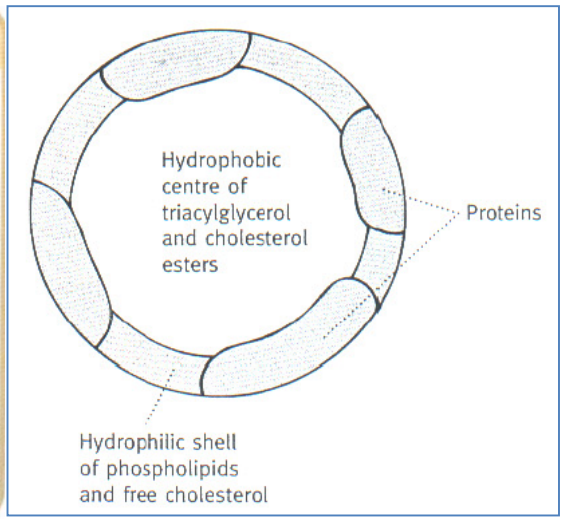


- **Bile Acid Synthesis**
  - See previous weeks

Lipid Transport - Lipoproteins:

- **Made of:**
  - **Amphipathic Shell:**
    - ApoProteins
    - Phospholipids
    - Cholesterol
  - **Hydrophobic Core:**
    - Cholesterol Esters
    - Triglycerides



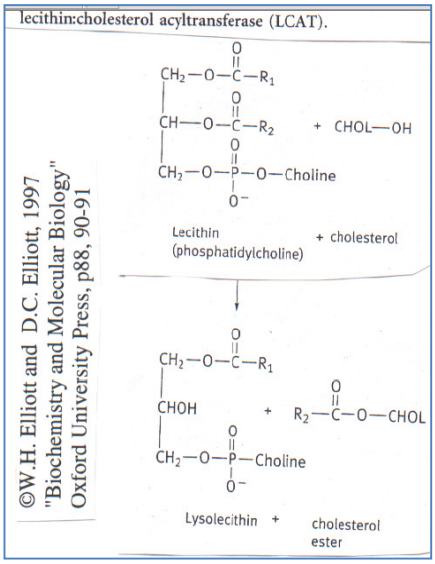


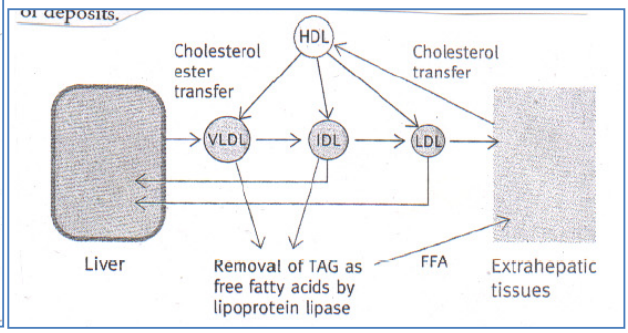
- **Types:**
  - **Chylomicrons**
    - Very, very Low Density Lipoproteins
    - Synthesised by Enterocytes of S. Intestine.
    - Exocytosed into basal interstitial space below Enterocytes→lacteal (lymph vessel in villus)
    - Transport **dietary** lipids from Intestine → Lymph →Liver
    - Apoproteins target chylomicrons to specific tissues
  - **VLDLs**
    - Very Low Density Lipoproteins
    - Synthesised on the ER of the Hepatocytes of Liver
    - 90% Lipid, 10% Protein
    - Export Triglycerides from Liver → Peripheral Tissues
    - As tissues absorb lipids, VLDLs become 'denser' → LDLs
  - **LDLs**
    - Low Density Lipoproteins
    - Tissue absorbs more lipids, LDLs become 'denser' → IDLs
  - **IDLs**
    - Intermediate Density Lipoproteins
    - Fats removed → HDLs
  - **HDLs**
    - High Density Lipoproteins
    - Synthesised in Liver
    - Contain little triglyceride/cholesterol
    - Mostly Proteins & Esterified (hydrophobic) Cholesterol
    - Disc-like structures
    - Role: Pick up Lipids from Peripheral Tissues → Liver
      - When they accumulate with TAG & Cholesterol, they expand into a sphere.

  - **NB:** The higher the **Fat : Protein** ratio in the lipoprotein, the lower the density.
  - **NB:** The higher the **HDL : LDL** ratio, the 'healthier' the person.
  - **NB:** Cholesterol & Fat are absorbed from diet & transported in the same way → via lipoproteins.
  - **NB:** Free Fatty Acids are transported by Serum Albumin in Blood Stream.

Why don't HDLs have a source of ATP?

- Cholesterol esterification *in cells* require ATP.
- But in HDLs, a fatty acyl group of lecithin (in the hydrophobic shell) is transferred to cholesterol in an energy-neutral reaction by the enzyme: **Lecithin:cholesterol-acyltransferase (LCAT)**





What type of molecule is lecithin & where is it found?

- A Fatty Acyl Group
- Found in the hydrophilic shell of the lipoprotein.

What does CETP (cholesterol ester transfer protein) do?

- Cholesterol Ester Transfer Protein
- Transfers the cholesterol esters from HDLs to Chylomicrons, VLDLs, IDLs, & LDLs

Steps:

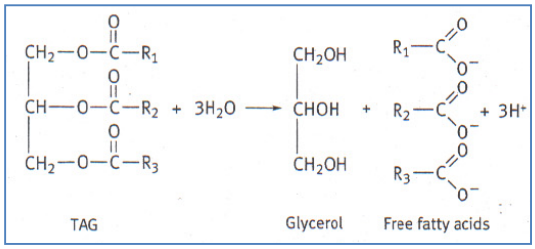
1. Cholesterol is transferred from extrahepatic cell membranes to HDL.
2. The cholesterol is esterified by LCAT and the ester migrates to the centre of the HDL.
3. Cholesterol ester is transferred from HDL to chylomicrons (when present), VLDL, IDL, and LDL.
4. A proportion of the latter two lipoproteins recycle back to the liver, thus delivering cholesterol from extrahepatic cells to that organ (Fig. 6.14). When present after a meal, chylomicron remnants also participate in this reverse flow.

"Good" & "Bad" Cholesterol:

LDL in popular medical terms is regarded as 'bad cholesterol' because excessive levels of cholesterol occur in a proportion of the population in this form, and these are associated with increased risk of atherosclerosis. The latter involves development of plaques in blood vessels, a complex process in which cholesterol deposition is involved. These block blood flow and, if present in coronary arteries, are the cause of heart attacks.

Patients with the genetic disease, familial hypercholesterolemia, are deficient in functional LDL receptors on cells, resulting in impaired removal of LDL from the blood and very high levels of circulating LDL-associated cholesterol. This leads to early cardiovascular disease. By contrast, HDL is popularly known as 'good cholesterol' because high levels are associated with decreased risk of atherosclerosis, possibly related to its role in reverse cholesterol flow and its resultant elimination from the liver, but the protective effect is incompletely understood. There is also the possibility, not proven, that HDL may reverse atherosclerosis by removing cholesterol from vascular cholesterol deposits.

- **FA Uptake in Tissues:**
  - After fatty meal, blood is loaded with chylomicrons
  - Fat (in chylomicrons) transported to Adipose cells (storage), Lactating Mammary Glands, Muscle & other tissue (energy) & also the Liver.
  - HOWEVER: unlike free fatty acids, triglycerides cannot readily pass through cell membranes.
    - Therefore **triglycerides** (in chylomicrons) must first be **hydrolysed** (by **lipoprotein lipase)** in the blood capillaries
      - → glycerol & free fatty acids
    - The liberated FFAs immediately diffuse out of the chylomicron → adjacent cells.



- **Factors Determining FA Uptake by Tissues:**
  - **Lipoprotein Lipase Activity:**
    - lipase activity present in capillaries of that particular tissue
    - Adipose/mammary glands – rich in lipase
    - Other tissues – have less of the enzyme in the capillaries.

      NB: capillary lipase = lipoprotein lipase
  - **Insulin:**
    - Causes increases in the amount of the enzyme.
  - **Glucagon:**
    - Causes decreases in the amount of the enzyme.

  - **Hormone-Sensitive Lipase IN Adipose CELLS:** (different to Lipoprotein Lipase)
    - **Glucagon** - Acticates
    - **Epinephrine -** Activates
    - **Insulin** - Inhibits
    - Ie. After a meal when Blood-Glucose is high, the release of FFAs must be inhibited.
    - But – During fasting, Glucagon in blood Activates $Lipase_{(Adipose)}$, releasing FFAs.
      - NB: FFAs in blood – bound to Serum Albumin.

- **Chylomicron Re-Uptake into Liver:**
  - As chylomicrons circulate the body, Lipids are removed → reduces them in size & increases density.
  - Eventually, they become **Chylomicron Remnants**
  - Ch-Remnants are taken up → Liver – via **receptor-meditated endocytosis.**
  - Liver destroys them & liberates left-over Fat & Cholesterol to the Hepatocytes.

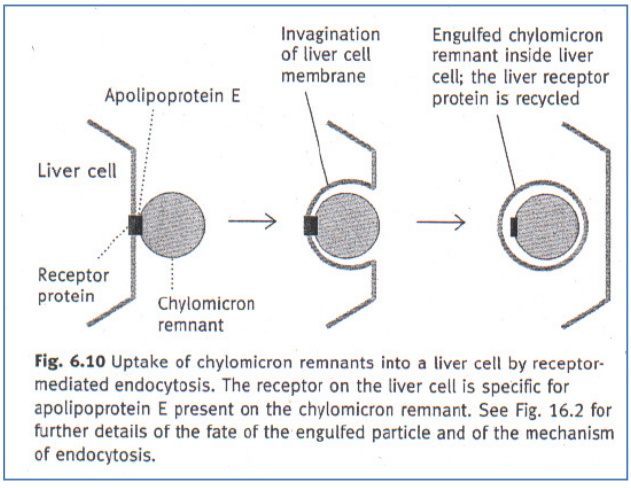
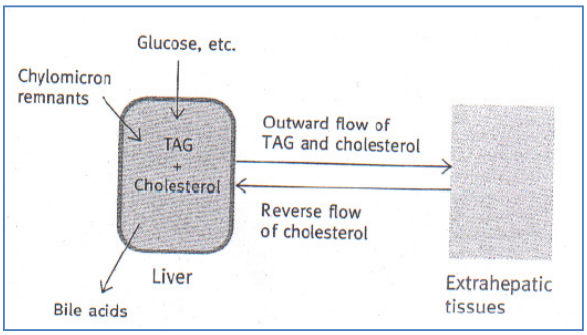


Fig. 6.10 Uptake of chylomicron remnants into a liver cell by receptor-mediated endocytosis. The receptor on the liver cell is specific for apolipoprotein E present on the chylomicron remnant. See Fig. 16.2 for further details of the fate of the engulfed particle and of the mechanism of endocytosis.

- **The Liver: TAG Distribution, Not Storage:**
  - The liver is one of the major sources of blood lipid & cholesterol – in the form of **lipoproteins.**
    - (as well as the intestine→chylomicrons)
  - It synthesises triglycerides (from glucose & other metabolites) & cholesterol, plus fats from chylomicron remnants.
  - It then exports TAGs & cholesterol in lipoproteins (VLDLs) to other tissues.
  - However, it is not responsible for storage. – Actually, a 'fatty' liver is pathological. (**Fatty Liver)**



- **Alcoholic Fatty Liver – Why?:**
  - Metabolism of alcohol produces increased amounts of $NADH^+$
  - Increased NADH Inhibits Fatty Acid Oxidation
  - Fatty acids reaching the liver (from dietary sources or adipose tissue) reform to triglycerides.
  - Eventually the liver fails to produce the apolipoproteins to export the fat as VLDLs & therefore fats in the liver accumulate.

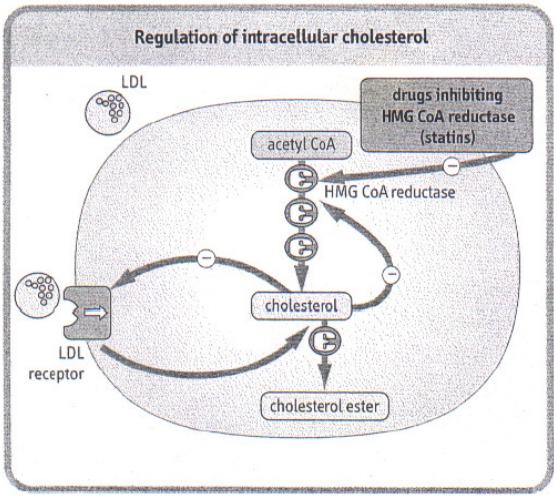
- **The 'Grocery-Bag' Model of Lipid Circulation:**
  - Postulates that cholesterol's purpose may actually be as a structural component of lipoproteins needed for TAG transport to & from the Liver.

<u>Cholesterol:</u>

- Cholesterol is absorbed from diet & transported in the same way as Fats→ via lipoproteins.
- Excess Cholesterol is Excreted via Bile

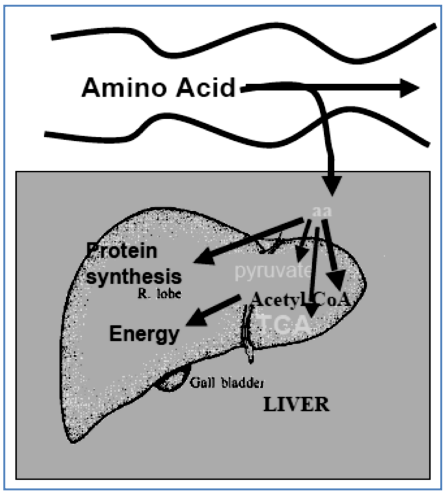
- **The 2 Major Sites of Cholesterol Synthesis:**
  - Most cells of the body are capable of cholesterol synthesis.
  - However the liver & the intestines are the most active cholesterol synthesisers.

- **Cholesterol Synthesis:**
  - Synthesised from Acetyl-CoA
  - HMG-CoA Reductase is a major enzyme in this process.
  - Drugs which Inhibit this enzyme are useful in Treating patients with High Cholesterol.

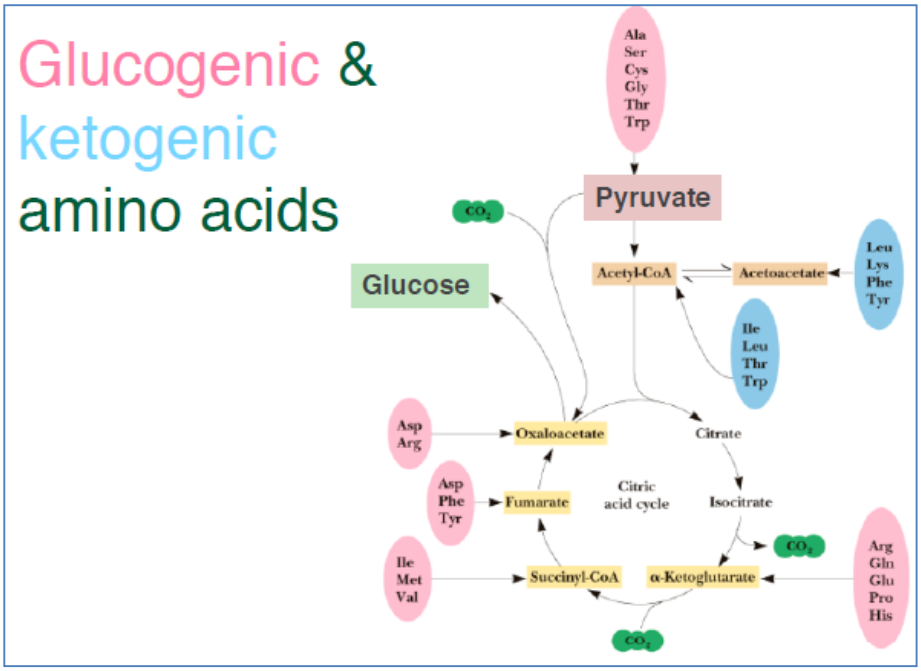


Protein Metabolism:

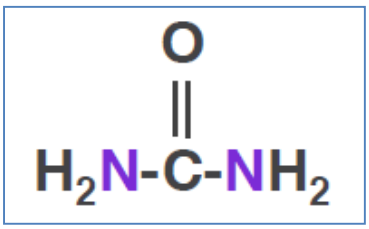
- **Synthesis:**
  - Liver is the major Plasma-Protein manufacturer. (ie. Blood-Proteins)
    - Eg. Albumin, Coagulation Factors, Transferrin, Globins
    - **Albumin:**
      - Most concentrated blood-protein
      - Carrier protein for Hormones, Calcium, Iron, Magnesium, Bilirubin, FAs & Drugs.
      - Amino Acid Store – Most abundant & mobile source of Amino Acids
- **Amino Acid Metabolism:**
  - **After a Meal – Times of Plenty:**
    - Amino Acids absorbed into blood → Liver
    - AAs Metabolised for production of energy
    - Metabolism of AAs to either:
      - Pyruvate
      - TCA Intermediates....or
      - Acetyl CoA
    - Protein Synthesis Increases
    - **NB:** Amino Acids cannot be stored, except as protein.



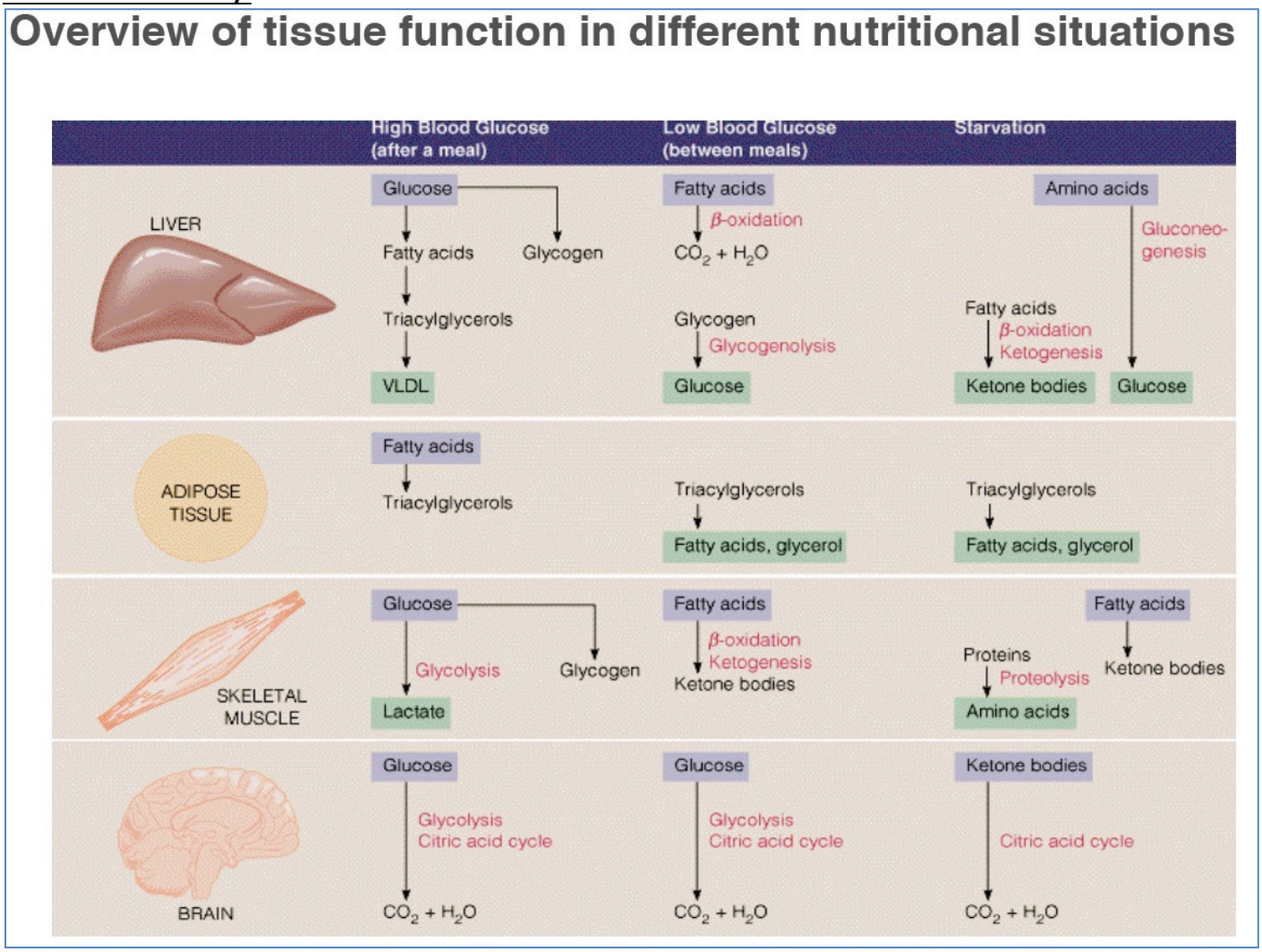
  - **Starvation – Times of Scarcity:**
    - Amino acids are an important source of glucose (Glucogenic)
    - Some AAs form ketone-bodies and are Ketogenic.



- **Urea Synthesis**
  - Urea is synthesised to remove excess Nitrogen.
  - Prevents build-up of Ammonia = Toxic.
  - Eliminated through urine.



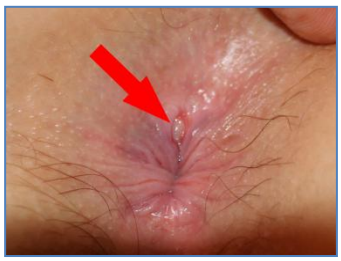
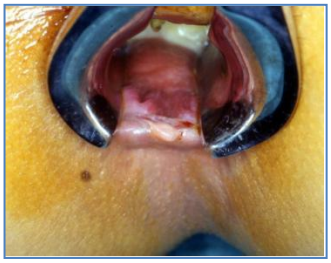
Metabolism Summary:



GASTROINTESTINAL Pathology:
ANAL FISSURES

ANAL FISSURES:

- **Anal Fissure =** Crack/Tear in the skin of the anal canal.
- **Aetiology:**
  - **Over-Stretching of the Anal Mucosa:**
    - **In adults:** Constipation/Prolonged Diarrhea/Crohn's Disease/Post-partum/Anal sex.
    - **Older adults:** Relative Ischaemia.
- **Morphology:**
  - 80% are Posterior
  - Extend Outwards from Anal Opening
  - May be Superficial or Deep
- **DDxs:**
  - Crohn's Ulcer
  - Syphilis
  - Herpes
  - Cancer
- **Clinical Features (In Order of Frequency):**
  - ***Pain**
  - ****Bleeding**
  - ***Itch**
  - Constipation
  - Discharge
- **Management:**
  - Topical Moisturisers
  - If Chronic → Surgery → Lateral Internal Sphincterotomy

- ❑ external hemorrhoids = below dentate line
  - plexus of inferior hemorrhoid veins —> systemic circulation
  - not to be confused with a perianal skin tag = residual excess skin after thrombosis of prior external hemorrhoid
  - dilated venules usually mildly symptomatic unless thrombosed, in which case they are very painful
  - usually present with pain after bowel movement
  - treatment
    - medical therapy: dietary fiber, stool softeners, avoid prolonged straining
    - thrombosed hemorrhoids resolve within 2 weeks
    - hemorrhoidectomy when patient presents within the first 48 hours of thrombosis, otherwise treat conservatively

ANAL FISSURES

- ❑ tear of anal canal below dentate line (very sensitive squamous epithelium)
- ❑ 90% posterior midline, 10% anterior midline
- ❑ if off midline: IBD, STDs, TB, leukemia or anal carcinoma
- ❑ repetitive injury cycle after first tear
- ❑ spasm occurs preventing edges from healing and leads to further tearing
- ❑ ischemia may ensue and contribute to chronicity

Etiology

- ❑ large, hard stools and irritant diarrheal stools
- ❑ tightening of anal canal secondary to nervousness/pain
- ❑ others: habitual use of carthartics, childbirth

Acute Fissure

- ❑ very painful bright red bleeding especially after bowel movement
- ❑ treatment is conservative: stool softeners, sitz baths

Chronic Fissure

- ❑ triad: fissure, sentinel skin tags, hypertrophied papillae
- ❑ treatment = surgery
  - objective is to relieve sphincter spasm —> increases blood flow and promotes healing
  - lateral subcutaneous internal sphincterotomy at 3 o'clock position
  - anal dilation (4 fingers)
- ❑ alternative treatment: topical nitro – increases local blood flow, promoting healing
- ❑ botulinum toxin – inhibits release of acetylcholine (ACh), stops sphincter spasm

ANORECTAL ABSCESS

- ❑ infection in one (or more) of the anal spaces
- ❑ usually a bacterial infection of a blocked anal gland at the dentate line
- ❑ E. *Coli*, *Proteus*, *Streptococci*, *Staphylococci*, *Bacteriodes*, anaerobes
- ❑ constant pain, may not be associated with bowel movement
- ❑ abscess can spread vertically downward (perianal), vertically upward (supralevator) or horizontally (ischiorectal)
- ❑ treatment: incision and drainage are curative in 50% of cases, 50% develop anorectal fistulas
  - may also require antibiotics

Perianal Abscess

- ❑ travels distally in the intersphincteric groove
- ❑ unremmiting pain, indurated swelling

Ischiorectal Abscess

- ❑ penetrate through the external anal sphincter
- ❑ in fatty fossa, can spread readily: necrotizing fasciitis, Fournier's gangrene
- ❑ pain, fever and leukocytosis prior to red, fluctuant mass

Intersphincteric

- ❑ between the internal and external sphincters
- ❑ fluctuant mass palpated in DRE

Supralevator Abscess

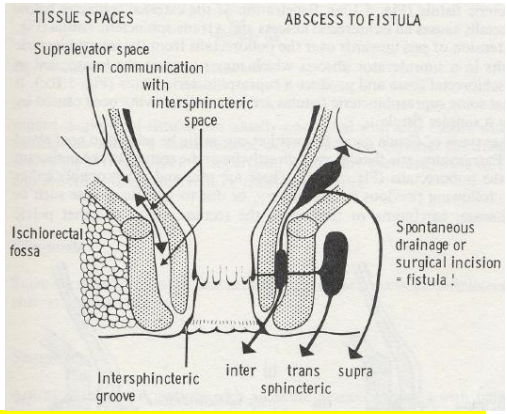
- ❑ difficult to diagnose, rectal mass and swelling detectable with exam under anesthesia

FISTULA IN ANO

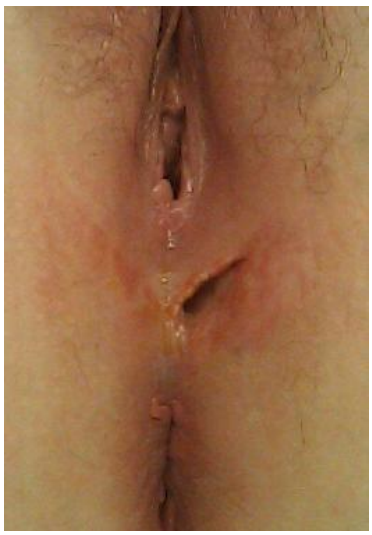
- ❑ a connection between two epithelial lined surfaces, one must be the rectum or anus
- ❑ an inflammatory tract with internal os at dentate line, external os on skin
- ❑ same perirectal process as anal abscess therefore usually associated with abscess
- ❑ other causes: post-op, trauma, arising from anal fissure, malignancy, radiation proctitis
- ❑ intermittent or constant purulent discharge from para-anal opening, pain palpable cord-like tract

GASTROINTESTINAL Pathology:
ANAL FISTULAE

ANAL FISTULAE

- **Aetiology:**
  - "Cryptogenic" – Extensions of the Anal Crypts
- **Pathogenesis:**
  - 

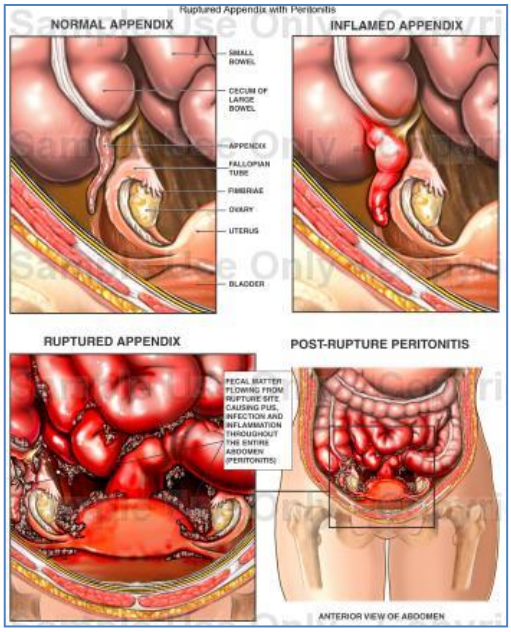
  - ***(Inter-Sphincteric Route is Commonest!)***
- **Clinical Features:**
  - Pain
  - "Incontinence"
  - Discharge
  - Fever
- **Complications:**
  - **ANORECTAL SEPSIS**
- **Diagnosis:**
  - Clinical Examination
- **Management:**
  - **Surgical – (Fistulotomy)**

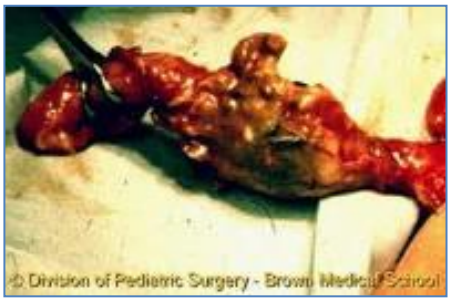


GASTROINTESTINAL Pathology:
APPENDICITIS

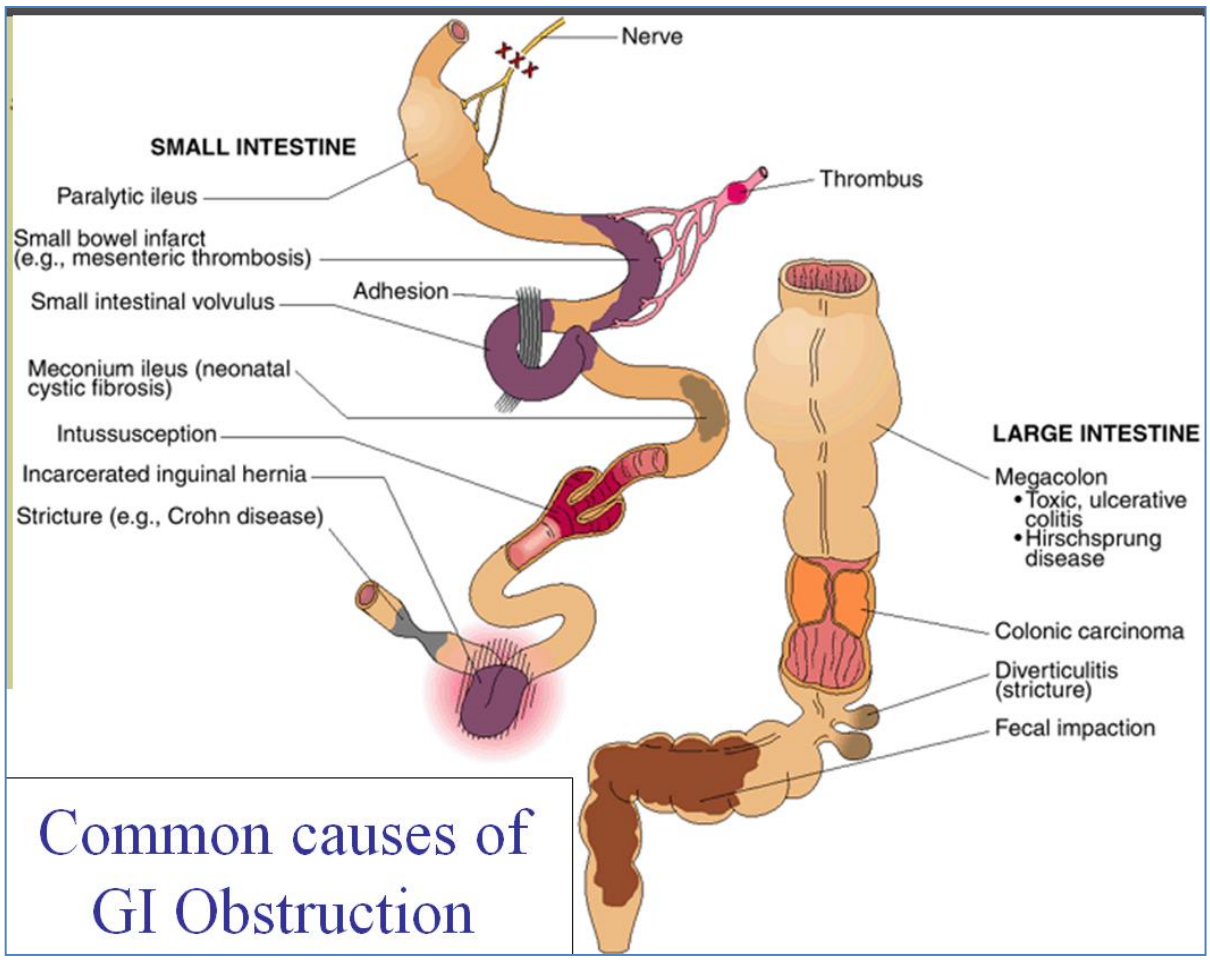
APPENDICITIS:

- **Aetiology:**
  - Idiopathic
- **Pathogenesis:**
  - *'Faecolith'* → Obstruction of Appendix → Stasis → Infection → Gangrene → Perforation
- **Morphology:**
  - Inlarged, Inflamed Appendix
- **Clinical Features:**
  - **Symptoms/Signs:**
    - **Initially Peri-Umbilical Pain** → Classically *Moves to* R-Iliac Fossa
    - **Nausea/Vomiting/Anorexia/Diarrhoea(occasionally)**
    - **R-Iliac Fossa Pain/Tenderness/Guarding**
    - **Rovsing's Sign:** Pain > in RIF than LIF when LIF is Pressed.
    - **Psoas Sign:** Pain on Extension/Flexion/Internal Rotation of the Hip
    - **Mcburney's Sign**: Deep tenderness at McBurney's point
    - **Obturator Sign:** Pain on Rotation of Hip
    - **Referred Rebound Tenderness in L-Iliac Fossa** (Most Painful in R-Iliac Fossa)
- **Diagnosis:**
  - **Ultrasound/CT – (**Enlarged Thickened Appendix**)**
  - **FBC – (**↑WBC - Neutrophilia**)**
  - **↑ESR & CRP**
- **Treatment:**
  - **Haemodynamic Stabilisation – (*Fluids* + *Group & Hold*)**
  - **Prophylactic Antibiotics – (*Ampicillin* + *Gentamicin* + *Metronidazole*)**
  - ****Appendectomy – (*Open or Laparoscopic*)**
- **Complications:**
  - Perforation
  - Sepsis





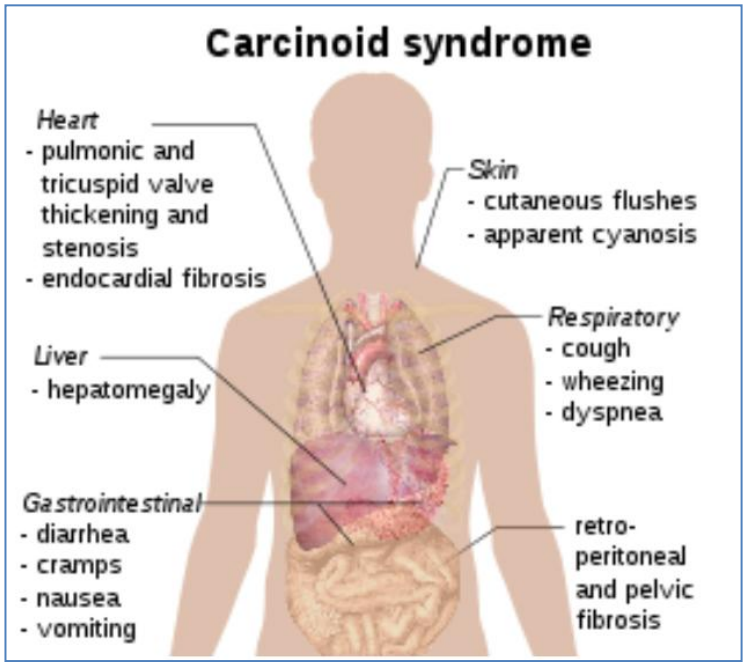
GASTROINTESTINAL Pathology:
BOWEL OBSTRUCTIONS



GASTROINTESTINAL Pathology:
CARCINOID SYNDROME

CARCINOID TUMOUR OF THE INTESTINES

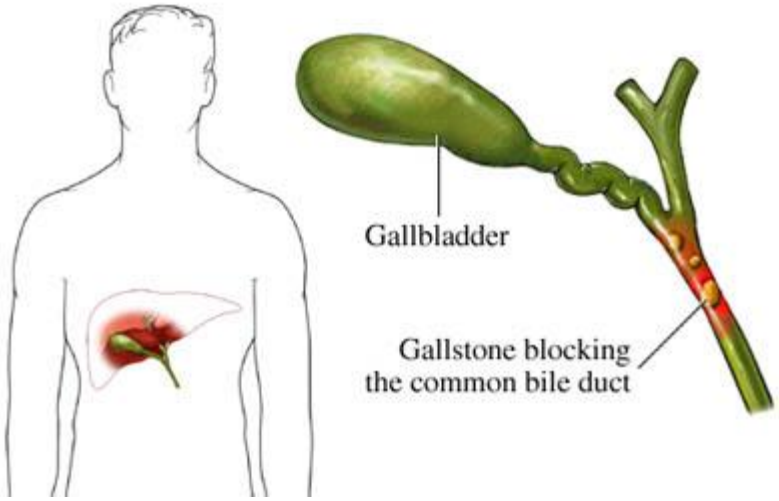
- **Aetiology:**
  - Neuroendocrine Serotonin-Secreting Tumour
- **Pathogenesis:**
  - Neuroendocrine Carcinoid Tumour → Secretes ***Serotonin*, Bradykinin, Histamine & Prostaglandin** → Diarrhoea & Cardiac Complications
- **Morphology:**
  - **3 Common Sites** = Appendix, Terminal Ileum, Rectum.
- **Clinical Features:**
  - **Asymptomatic Unless Metastasis → Carcinoid Syndrome:**
    - Hot Flushes
    - Chronic Watery Diarrhoea/Abdo Pain
    - **R-Sided Cardiac Abnormalities** – Pulmonary Stenosis or Tricuspid Regurgitation
    - Hepatomegaly
- **Diagnosis:**
  - **CT**
  - **Ultrasound** - ?Liver Metastases
  - **Echo – (**Carcinoid Heart Disease - Valvular Disease**)**
  - **Urine 5HIAA** (Metabolite of 5HT/Serotonin)
- **Treatment:**
  - **Somatostatin Analogues** (Symptomatic) → ↓Flushing/Diarrhoea
  - **Tumour Resection**
  - **+/- Cardiac Valvuloplasty/Reapri**
- **Complications:**
  - Metastasis



HEPATOBILIARY Pathology:
CHOLANGITIS

ACUTE CHOLANGITIS:

- **Aetiology:**
  - Choledocholithiasis
  - Bacterial Infection (*E.Coli* or *Klebsiella*)
- **Pathogenesis:**
  - Biliary Stasis (Obstruction / Anorexia / TPN) → Ascending Infection From GIT (E.Coli)
- **Clinical Features:**
  - ***Charcot's Triad*:**
    - **1.** Fever
    - **2.** Jaundice
    - **3.** Abdo Pain
  - ***Renold's Pentad*:**
    - **1.** Fever
    - **2.** Jaundice
    - **3.** Abdo Pain
    - **4.** Hypotension
    - **5.** Confusion
- **Investigations:**
  - **FBC – (↑WCC)**
  - **LFT – (Obstructive)**
  - **Amylase ↑ - (?Pancreatitis)**
  - ****Blood Cultures**
  - ****USS – (Stones in the Duct?)**
- **Management:**
  - *******ERCP/MRCP*** **– (To Confirm Diagnosis + Therapeutic → *Stenting* / *Stone Extraction*)**
  - **Antibiotics – (AGM – *Ampicillin* + *Gentamicin* + *Metronidazole*)**
  - ***IV Fluids***
  - **(+/- Cholecystectomy)**
- **Complications:**
  - **Sepsis**



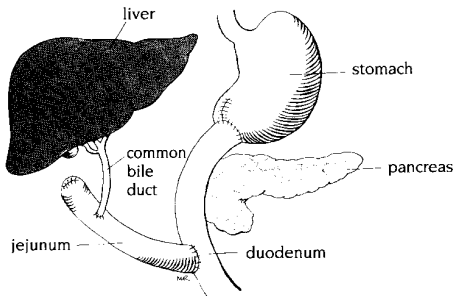


Figure 12. Roux-en-Y Choledochojejunostomy

Drawings by Myra Rudakewich

ACALCULOUS CHOLECYSTITIS

- ❑ acute or chronic cholecystitis in the absence of stones (5%)
- ❑ typically due to gallbladder stasis
- ❑ usually diabetic, immunosuppressed, post-op or in intensive care unit (ICU)
- ❑ etiology
  - dehydration, prolonged fasting, TPN
  - systemic disease (e.g. MOSF)
  - generalized sepsis, trauma
  - kinking or fibrosis of the gallbladder
  - thrombosis of the cystic artery
  - sphincter spasm with obstruction of the biliary and pancreatic ducts
  - collagen vascular disease, DM, immunosuppressed
- ❑ treatment
  - cholecystectomy or cholecystostomy

CHOLEDOCHOLITHIASIS

- ❑ stones in common bile duct (CBD)
- ❑ signs and symptoms
  - 50% asymptomatic
  - often have history of biliary colic
  - tenderness in RUQ or epigastrium
  - pale stool, dark urine
  - intermittent chills, fever or fluctuating jaundice
  - complications include biliary colic, cholangitis, pancreatitis, late benign biliary stricture, and biliary cirrhosis
- ❑ diagnostic investigations
  - increased bilirubin (> 10), ALP, 5'-NTD
  - leukocytosis often > 20 x 109/L
  - U/S – intra/extra-hepatic duct dilatation, does not detect CBD stones
  - endoscopic retrograde cholangiopancreatography (ERCP) (if no previous cholecystectomy) otherwise percutaneous transhepatic cholangiography (PTC) appropriate
  - intra-operative cholangiography
- ❑ treatment
  - antibiotics, NG tube (with abdo distention or vomiting), IV hydration
  - if no improvement in 2-4 days then ERCP/PTC+sphincterotomy or surgery with CBD exploration and laparoscopic cholecystectomy

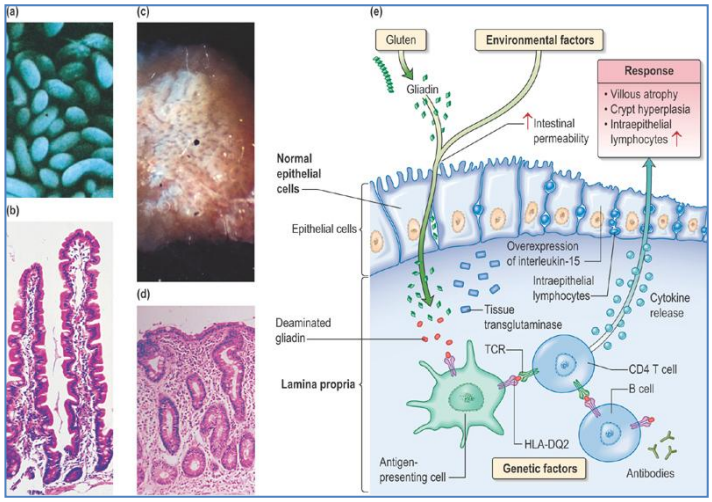
ACUTE CHOLANGITIS

- ❑ mechanism: obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration, and biliary sepsis - life threatening
- ❑ etiology
  - choledocholithiasis (60%)
  - post-operative stricture
  - pancreatic or biliary neoplasms
- ❑ organisms: E. *coli*, K*lebsiella*, P*seudomonas*, E*nterococci*, B. *fragilis*, P*roteus*
- ❑ signs and symptoms
  - Charcot's triad (50-70% of cases): fever, jaundice, RUQ pain
  - Reynold's pentad: Charcot's triad + mental confusion + hypotension leading to renal failure
- ❑ diagnostic investigations
  - elevated WBC
  - elevated liver enzymes (ALP mild increase AST,ALT) and conjugated bilirubin
  - U/S shows stones in gallbladder +/– stones seen in bile ducts +/– dilated extrahepatic or intrahepatic bile ducts
- ❑ treatment
  - immediate goal is to decompress the biliary tree
  - initially hydration, electrolyte correction, broad-spectrum antibiotics
  - urgent ERCP - diagnostic and therapeutic with papillotomy to remove stones
  - if ERCP unavailable or unsuccessful, then PTC
  - if ERCP, PTC unavailable, surgery to decompress CBD —> T-tube
- ❑ prognosis
  - suppurative cholangitis – mortality rate = 50%

GASTROINTESTINAL Pathology:
COELIAC DISEASE

COELIAC DISEASE

- **= Allergic Inflammation of the Proximal Small Bowel due to Gluten.**
- **Aetiology:**
  - Immunological Sensitivity to Gluten and Prolamins in Wheat, barley & Rye.
- **Pathogenesis:**
  - Allergy → Chronic Inflammation → Villous Atrophy & Crypt Hyperplasia
- **Morphology:**
  - **Primarily in Proximal Small Bowel**
  - **Villous Atrophy** (Often Absence of Villi, with Flattened Mucosa)
- **Clinical Features:**
  - **Epidemiology:**
    - Can Present at ANY Age (Peaks = Infancy, in 50's)
    - F>M
  - **Symptoms/Signs:**
    - Fatigue, Malaise
    - Diarrhoea/Steatorrhoea/Constipation
    - Abdo Pain/Discomfort/Bloating
    - Weight Loss
    - Angular Stomatitis/Mouth Ulcers
- **Investigations:**
  - **** Duodenal Biopsy - (*Villous Atrophy*)**
  - **Immunological Testing – (*Anti-Transglutaminase Antibodies*)**
- **Treatment:**
  - **Vitamin Supplements** (Vits, Iron, Folate, Ca, VitD)
  - ****Gluten Free Diet for Life**.
  - **(Future Enzyme Replacement Therapy)**
- **Complications:**
  - **Ulcerative Jejunitis** (Fever, Abdo Pain, Perforation, Bleeding)
  - **↑Risk of GI Malignancies**
  - **↑Risk of Inflammatory Bowel Diseases**
  - **Osteomalacia → Osteoporosis**

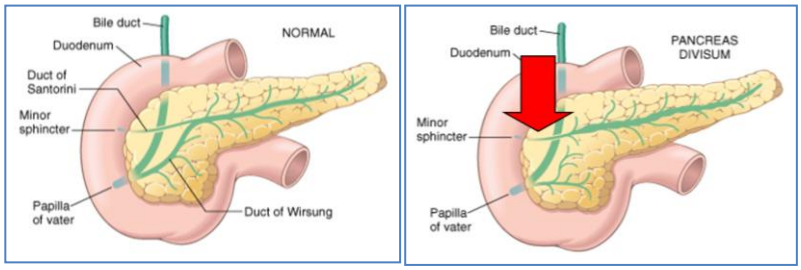


(A, B = Normal Histology; C, D = Coeliac Histology – NB: Flattened Mucosa & Villous Atrophy)

HEPATOBILIARY Pathology:
CONGENITAL PANCREATIC ABNORMALITIES

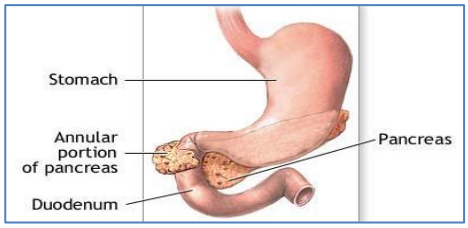
Pancreatic Divism:

- **Common Bile Duct & Pancreatic Duct FAIL TO FUSE**
  - :. CBD exits through Ampulla of Vater
  - :. Pancreatic Duct exits through the Minor Sphincter ONLY – (Narrower & Shorter)
- **→→ Predisposes to Chronic Pancreatitis**



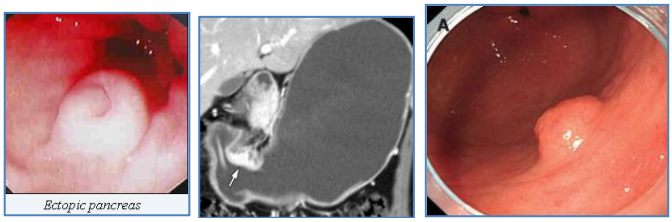
Annular Pancreas:

- **Head of Pancreas Encircles the Duodenum →→ Duodenal Obstruction**



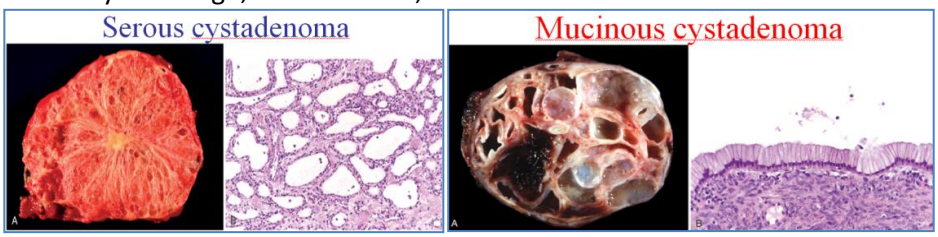
Ectopic Pancreas:

- **= A *Choristoma* = benign tumour of Normal Tissue but in an Abnormal Location.**
- **Exocrine (Acinar) Pancreatic Tissue *Ouside* the Normal Pancreas –**
  - May be in Stomach/Duodenum/Jejunum/Meckel's Diverticulum.
  - (<1cm mass)
- **→→ Typically Asymptomatic; Malignancy is RARE.**



Pancreatic Cysts:

- **What? -** Collections (pools) of fluid within the head, body, or tail of the pancreas
- **Aetiology:** Congenital
- **Types:**
  - ***Serous Cystadenoma***
  - ***Mucinous Cystadenoma***
- **Morphology:**
  - Epithelial Lined
  - **Micro:** Epithelial Lined
  - **Contents:** Fluid Filled
- **Symptoms/Signs:**
  - If Small → Asymptomatic
  - If Large → Abdo Pain/Back Pain/Jaundice (If Head.of.Panc)/Duodenal Obstruction
  - If Infected → Fever/Chills/Sepsis
- **Complications:** May be Benign, Precancerous, or Cancerous.



CONSTIPATION

Definition
❑ passage of infrequent, or hard stools with straining (stool water < 50 mL/day)

Etiology
❑ in the absence of other clinical problems, most commonly due to lack of fiber in diet, change of diet, or poorly understood gut motility changes
❑ organic causes
- medication side effect (antidepressants, codeine) most common
- left sided colon cancer (consider in older patients)
- metabolic
  - diabetes mellitus (DM)
  - hypothyroidism
  - hypercalcemia
- neurological
  - intestinal pseudo-obstruction
  - Parkinson's disease
  - multiple sclerosis (MS)
- collagen vascular disease
  - scleroderma
  - amyloid

Investigation
❑ swallow radio-opaque markers to quantitate colonic transit time (normal: 70 hours)
- normal = misperception of normal defecation
- prolonged ="colonic inertia"
- prolonged plus abnormal anal manometry = outlet obstruction

Treatment (in order of increasing potency)
❑ surface acting (soften and lubricate)
- docusate salts, mineral oils

❑ bulk forming
- bran, psyllium seed

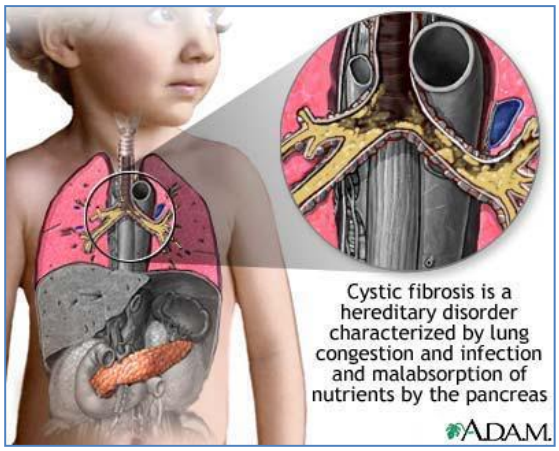
❑ osmotic agents
- lactulose, sorbitol, magnesium citrate, magnesium sulfate, magnesium hydroxide, sodium phosphate.

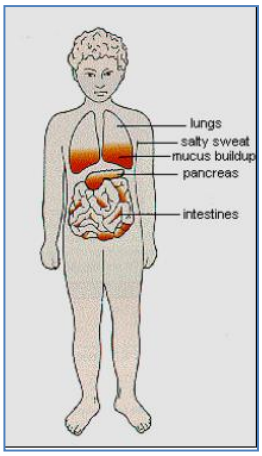
❑ cathartics
- castor oil, senna (watch out for melanosis)

HEPATOBILIARY Pathology:
CYSTIC FIBROSIS

CYSTIC FIBROSIS (CF):

- **Aetiology:**
  - **Simple Autosomal Recessive CFTR Gene Mutation (Chromosome 7)**
    - ≈1/25 people are carriers.
- **Pathogenesis:**
  - **CFTR** – Encodes for Active-Chloride Channels (Which Normally Regulates [Salt] in Secretions)
  - → Thick, Salty Exocrine Secretions → Mostly Affects **Lungs, Pancreas, Intestines & Skin.**
- **Clinical Features:**
  - **Lungs:**
    - Thicker Mucus & ↓Clearance → **Frequent Lung Infections**
  - **Pancreas:**
    - Obstructed Pancreatic Duct → Chronic Subclinical Pancreatitis → **Pancreatic Failure**
  - **Intestines:**
    - Poor Digestion & Malabsorption → **Malnutrition**
  - **Reproductive Ducts:**
    - Obstructed Vas-Deferens → Infertility
  - **Sweat Glands:**
    - Salty Sweat → **Hyponatraemia** if not replaced.





- Crepitations (Crackling) & Rhonchi (Rattling/Whistling) – Heard through stethoscope

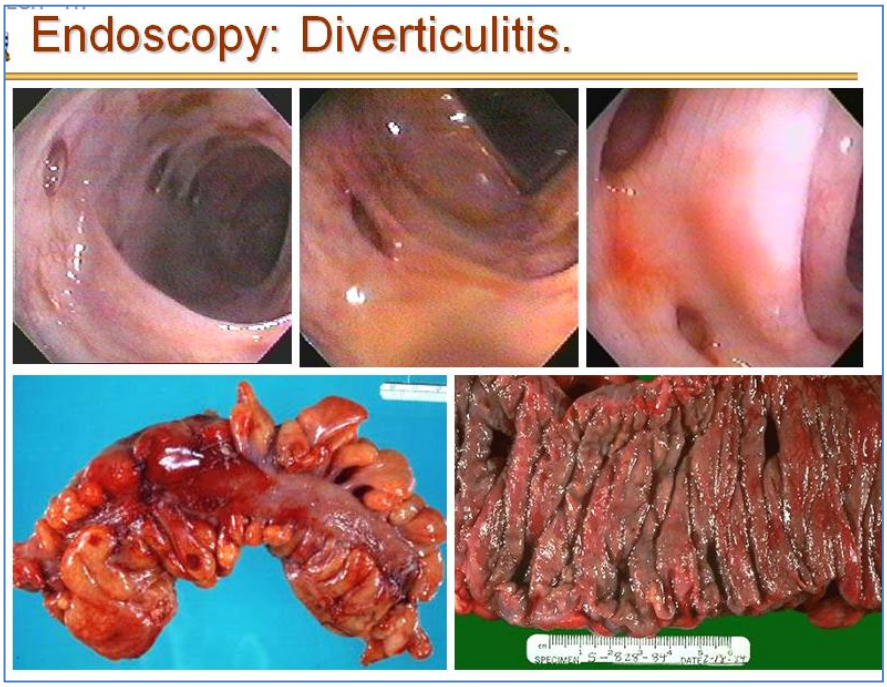
- **Investigation:**
  - **Spirometry – (Obstructive Pattern -** ↓FEV_1**)**
  - **CXR – (**Gas Trapping & Hyperinflated**)**
  - **Genetic Testing – (Definitive)**
- **Management:**
  - **Enzyme Replacement – (“*Creon Forte*”)**
  - **Salt Replacement – (Salt Tablets)**
  - **Fat-Sol. Vitamins – (ADEK)**
  - **Chest Physio – (**Percussion, Postural Drainage**)**
  - **Mucolytics -** (Eg. DNAse → Destroys Extracellular DNA → ↓Mucous Viscosity)
  - **Antibiotics for Recurrent Infections – (*Tobramycin*)**
- **Prognosis:**
  - **40yr Life Expectancy**

GASTROINTESTINAL Pathology:
DIVERTICULOSIS & DIVERTICULITIS

DIVERTICULOSIS/DIVERTICULITIS:

- **DIVERTICULOSIS =** "Presence of Diverticula"
- **DIVERTICULITIS =** "Inflammation of Diverticula"

- **Aetiology:**
  - Straining on Stool, Chronic Constipation, Age.
  - (Or Congenital - "*Meckel's Diverticulum*")
- **Pathogenesis:**
  - **Diverticulosis:** Weakening in Intestinal/Colonic Wall + ↑Intraluminal Pressure (Ie. Straining/Constipation) → Herniation of Mucosa through the Weakening.
  - **Diverticulitis:** Faeces Obstruct the Neck of the Diverticulum → Stagnation → Bacterial Overgrowth → Inflammation → →Complications
- **Morphology:**
  - Pouches/Pockets of bowel in the Intestinal Wall – ***(Typically in LIF)***
- **Clinical Features:**
  - **95% Asymptomatic**
  - **Rectal Bleeding Common**
  - **If Symptomatic** → Intermittent **LIF Pain** + **Erratic Bowel Habit**.
  - **If Diverticulitis** → Severe **LIF Pain** + **Fever** ***(Like appendicitis, but on the Left)***, Tachycardia,
  - **If Perforation** → **Peritonitis** + **Sepsis** .
- **Diagnosis:**
  - **Colonoscopy**
  - **FBC**
- **Treatment:**
  - **High Fibre Diet**
  - **Non-Perforated Diverticulitis → Antibiotics – (AGM – Ampicillin + Gentamicin + Metronidazole).**
  - **Perforated Diverticulitis → As Above + *Surgery***
- **Complications:**
  - **Rectal Bleeding – (Commonest)**
  - **Perforation → Sepsis**
  - **Generalised Peritonitis**
  - **Abscess**
  - **Fistulae into Adjacent Organs**



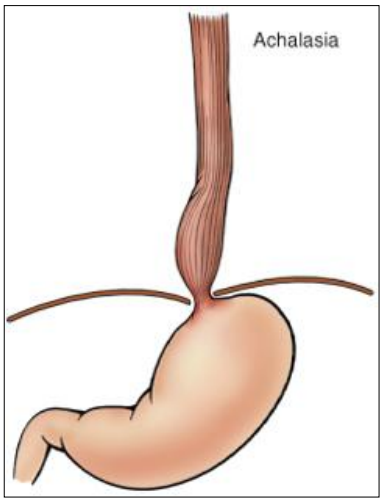
GASTROINTESTINAL Pathology:
DYSPHAGIA & ACHALASIA

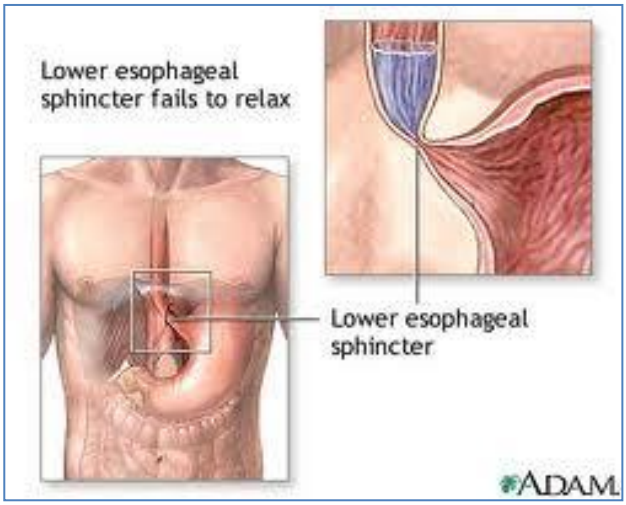
DYSPHAGIA – Symptom NOT Disease:

- **Definition =** "Difficulty Swallowing"
  - NB: Odynophagia = "Painful Swallowing"
- **4 Possible Sites:**
  1) Oropharyngeal
  2) Oesophageal
  3) Gastro-Oesophageal
  4) Para-Oesophageal.
- **Differential Dxs:**
  - **With Solids Only** **= Mechanical Obstruction** – (Strictures/Tumours)
  - **With Solids & Liquids** **= ↓Motility** – (Achalasia/Neural[Vagus Nv])
  - **With Liquids Only** **= Pharyngeal Disorders** – (Globus Pharyngeus)

ACHALASIA:

- **Aetiology:**
  - Unknown – Proposed: Autoimmune, Neurodegenerative, Viral.
- **Pathogenesis:**
  - Vagus Nerve Dysfunction → Oesophageal *Aperistalsis* & Impaired Sphincter Relaxation.
- **Clinical Features:**
  - **Dysphagia -** Long Hx, Intermittent, BOTH Liquids & Solids *FROM THE ONSET*.
  - **Reflux –** Particularly at Night → Can cause Aspiration Pneumonia
  - **Chest Pain** (Oesophageal Spasm)
- **Investigations:**
  - **Barium Swallow**
  - **Endoscopy**
- **Management:**
  - **Palliative Treatment**





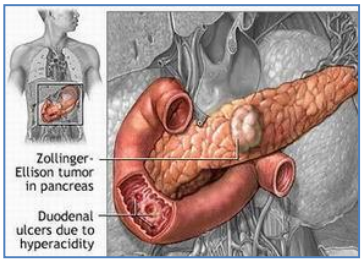
HEPATOBILIARY Pathology:
ENDOCRINE PANCREATIC TUMOURS

Tumours of the Endocrine Pancreas (AKA: Islet Cell Tumours):

- Majority are Benign
- **Treatment:**
  - Monitoring
  - Surgery
  - Hormone Therapy (If not surgically viable)
  - Radiation Therapy/Nuclear Medicine/Radiofrequency Ablation

Pancreatic Adenomas:

- **GASTRINOMA (Zollinger-Ellison Syndrome):**
  - **Pathogenesis:**
    - **"*Gastrinoma*"** → Secretes Gastrin → Hyperacidity → Peptic Ulcers
  - **Morphology:**



  - **Clinical Features:**
    - Abdominal Pain
    - Dyspepsia
    - Chronic Diarrhoea (Due to Inactivation of Pancratic Enzymes – Lipase, & Mucosal Damage)
  - **Diagnosis:**
    - Fasting Serum Gastrin
    - Endoscopic Ultrasound & CT (Tumour Imaging & Staging)
  - **Treatment:**
    - Proton Pump Inhibitors (Omeprazole)
    - Surgery – Remove Gastrinoma – 80% 5yr Survival
  - **Complication:**
    - Malignant Potential

- **INSULINOMA:**
  - **Aetiology:**
    - Tumours of the pancreas that produce too much insulin
  - **Pathogenesis:**
    - Unregulated Insulin Production (even when your blood sugar drops too low) → hypoglycemia
  - **Morphology:**
    - Usually single, small tumors in adults.
  - **Clinical Features:**
    - **Mild Hypoglycaemia** → Anxiety, Tachycardia, Sweating, Hunger, Headache
    - **Severe Hypoglycaemia** → Seizures, Coma, even Death
  - **Diagnosis:**
    - BSL/Insulin Level
    - CT/MRI Abdo
    - Endoscopic Ultrasound
  - **Treatment:**
    - Surgery – Curable (Rarely Malignant)

- **Multiple Endocrine Neoplasia (MEN) Syndromes (Types 1 & 2)**
    - **MEN1 – Wermer's Syndrome:**
        - **NB: 60% of Wermer's Pts have >2x of the Following:**
            - Pituitary Adenoma → Bilateral Hemianopia
            - *Pancreatic Gastrinoma → Peptic Ulcer Disease
            - *Pancreatic Insulinoma → Hypoglycaemia
            - Parathyroid Adenomas → Primary Hyperparathyroidism
        - **Aetiology:**
            - Genetic Mutation in MEN1 Tumour Suppressor Gene.
    - **MEN2 – Sipple's Syndrome:**
        - **NB: .....% of Sipple's Pts have:**
            - 100% Medullary Thyroid Cancer – (Thyroid Hormone Secreting Tumour)
            - 50% Phaeochromocytoma – (Adrenaline Secreting Tumour)
            - 30% Parathyroid Hyperplasia/Adenoma – (PTH Secreting Tumour)
        - **Aetiology:**
            - Genetic Mutation in MEN2 Tumour Suppressor Gene.

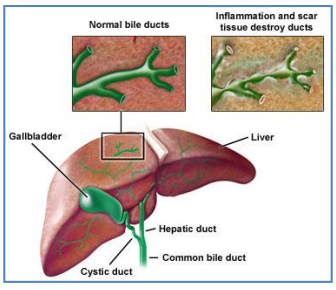
HEPATOBILIARY Pathology:
FAMILIAL LIVER DISEASES

AUTOIMMUNE HEPATITIS:

- **Aetiology:**
  - (Association with other AI-Conditions – Ie. Pernicious Anaemia/Thyroiditis/Coeliacs/AHA)
- **Pathogenesis:**
  - →Inflammation → Progressive Necrosis→ Fibrosis → → Cirrhosis.
- **Clinical Features:**
  - **Symptoms:**
    - May be Asymptomatic – Incidental Diagnosis.
    - Or - Fatigue, Fever, Polyarthritis, Pleurisy.
  - **Signs:**
    - Jaundice
    - Signs of Cirrhosis – Striae, Ascites, Acne.
- **Lab Tests:**
  - **LFT – (**↑↑ALT/AST**)**
  - **ANA+**
  - **Anti-Liver Antibodies**
- **Treatment:**
  - **Corticosteroids – (***Prednisolone***)**
  - **Chemotherapy Drugs – (***Azothioprine***)**
  - **Liver Transplant** if Treatment Fails
- **Prognosis:**
  - **80% Remission** (with Lifelong Steroids + Azothioprine)

PRIMARY BILIARY SCLEROSIS (AKA: "*Chronic, Non-Suppurative Destructive Cholangitis*"):

- ****(NB: *Primary* BC– Due to Autoimmune; *Secondary* BC – Due to Chronic Biliary Obstruction)**
- **Aetiology:**
  - Autoimmune – Specifics Unknown
- **Pathogenesis:**
  - Autoimmune – AMA's & ANA's present, but Pathogenesis is Unclear.
  - →Chronic, Progressive *Destruction of* *Intra-Hepatic Bile Ducts* →→Cirrhosis
- **Clinical Features:**
  - **Signs/Symptoms:**
    - Insidious Onset
    - Then (Cholestatic) Jaundice, Fatigue
    - Hepatomegaly
- **Lab Tests:**
  - **LFTs – (↑Bilirubin, ↑ALP & ↑GGT)**
  - **Autoantibodies (ANA+/AMA+)**
- **Complications:**
  - **Chirrosis** → Liver Failure
- **Treatment:**
  - **Supportive:**
    - **Ursodeoxycholic** – (Improves Bilirubin & AST/ALT levels)
    - **Corticosteroids – (*Prednisone*)**
    - **Fat-Vitamins Supps** – (ADEK)
  - **Liver Transplant – (Definitive)**



GILBERT'S SYNDROME

- **Aetiology:**
  - Familial/Genetic
- **Pathogenesis:**
  - *Benign*
  - Deficiency in Enzyme involved in Bilirubin Glucoronidation (Conjugation).
  - → Conjugation is ≈30% of normal
  - → A *Pre-Hepatic/Unconjugated Jaundice*.
- **Morphology:**
  - No Visible Disease
- **Clinical Features:**
  - **Signs/Symptoms:**
    - Asymptomatic
    - Occasional Mild Jaundice (*Associated with Fasting/Infection /Stress/Exertion)*.
- **Lab Tests:**
  - ↑Bilirubin (Unconjugated)
  - All other LFTs are normal.
  - Normal Reticulocyte Count (Ie. No Haemolysis)
- **Treatment:**
  - NO Treatment (Not necessary)

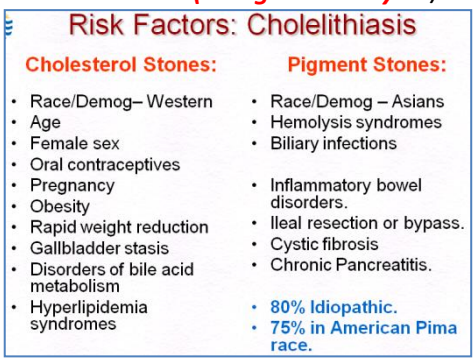
HAEMOCHROMATOSIS – (Simplified):

- **Aetiology:**
  - **(Iron Overload in the Body Due to hyper-absorption iron):**
    - **Primary** (Congenital – HFE Gene Mutation)
    - **Secondary** (Acquired – Transfusions/Supplements/Haemolysis)
- **Pathogenesis:**
  - ↑ Excess Iron → Iron Deposition in Organs (**Liver/Heart**/Endocrine Organs/Joints/Skin)
- **Clinical Features:**
  - **Symptom Profile:**
    - **Initially Asymptomatic**
    - **Early Symptoms – (**Fatigue, Arthralgia, Loss of Libido)
    - **Later Symptoms –** (Skin Bronzing, Abdo Pain, Hepatomegaly, Liver Cirrhosis, Heart Disease)
  - **Long-Term Effects:**
    - Arthritis/Liver Dis/Heart Dis/Impotence/Early Menopause/Bronze complexion/ Diabetes
- **Diagnosis:**
  - **Iron Studies** - (↑Ferritin, ↑Transferrin, ↑LFTs, HFE Gene)
- **Treatment:**
  - **Venesection**
  - **↓Iron Diet**
- **Complications:**
  - **Liver** - Cirrhosis
  - **Heart** - Cardiomyopathy
  - **Endocrine Glands –** Failure of gland**:**
  - **Joints** - Arthritis (Iron Deposition in the Joints)

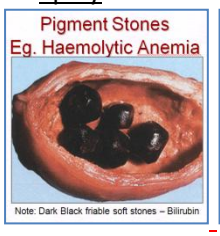
HEPATOBILIARY Pathology:
GALLSTONES & CHOLECYSTITIS

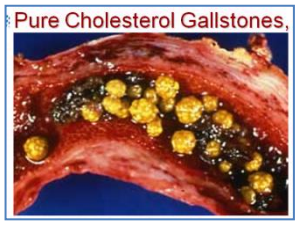
CHOLELITHIASIS – ("Biliary Colic") (Biliary Pain for <3hrs):

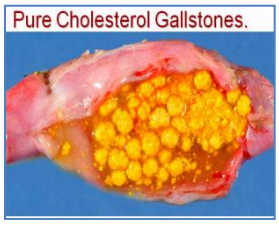
- **Aetiology:**
  - ***Mixed*** *- **80%** -* ***(Cholesterol + Ca^{+} + Bile + Blood)***
  - ***Pure*** *- **20%** -* ***(**Pigment Only**** */ Cholesterol Only)*



- **Pathogenesis – 4x Mechanisms:**
  - **1.** *Supersaturation (Excess Cholesterol)* &/Or *Low Bile Salt* to dissolve it.
  - **2.** *Calcium Microprecipitation*
  - **3.** *Biliary Stasis → Mucus Traps Crystals → Aggregation*
  - **4.** *Stone Growth*
- **Morphology (Types):**
  - **Mixed** - Multiple, Faceted, Yellow-Grey, 20% Radio-Opaque
    - **High % Calcium** - 100% Radio-Opaque
  - **Pigment Only** - Dark Brown/Black, Friable, Soft Stones, 50% Radio-Opaque
  - (Rare) **Cholesterol Only** - Yellow & Spiky







- **Clinical Features:**
  - **80% Asymptomatic**
  - **20% Symptomatic → Biliary Colic/Acute Cholecystitis/Chronic Cholecystitis.**
    - → Severe, Colicky Upper-Abdo Pain → to R-Shoulder (OFTEN after a Fatty Meal)
    - Fat Intolerance → Clay Stools
- **Lab Tests:**
  - ↑Conjugated Bilirubin (Extrahepatic Obstruction)
  - ↑Alk Phos
- **Management:**
  - Nil By Mouth (Bowel Rest)
  - IV Rehydration
  - Analgesia
  - IV-ABs
- **Complications:**
  - **Cholangitis**
  - **Pancreatitis**
  - Cholecystitis
  - Cholangiocarcinoma

CHOLECYSTITIS – Inflammation of the Gallbladder:

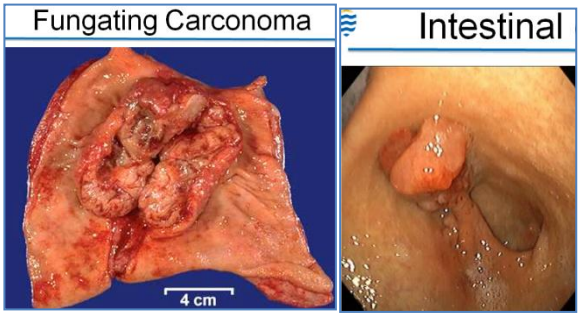
- **ACUTE CHOLECYSTITIS (Biliary Pain for >3hrs):**
  - **Aetiology:**
    - Typically Females
    - **90% - Gallstones in Gallbladder → Blockage of Cystic Duct**
      - (**Risk Factors:** *Age, Female, Obesity, Rapid Weight Loss, Drugs, Pregnancy*)
    - **10% "*Acalculous Cholecystitis*" (Absence of Gallstones)**
      - (**Risk Factors:** *Critical Illness/Sepsis, Major Surgery, Prolonged Fasting*)
  - **Pathogenesis:**
    - **90% - Gallstones** → Blockage of Cystic Duct → Bile Stasis & GB Distension
      - → 2^{o}-Infection by Gut Organisms (E.coli) →Inflammation of Gallbladder
    - **10% - Acalculous:** In Severely Ill Pts, or Trauma Pts.
      - →Prolonged Parenteral Feeding → Bile Stasis & GB Distension
      - → 2^{o}-Infection by Gut Organisms (E.coli) →Inflammation of Gallbladder
  - **Morphology:**
    - Large, Red, Swollen Gallbladder → RUQ "Mass"
  - **Clinical Features:**
    - **Onset:**
      - **RUQ *Colicky* Pain → Radiating to R-Scapula – (**Worse with FOOD**)**
      - Nausea, Vomiting
      - + Fever, Tachycardia,
    - **Later (Hours):**
      - **Severe, *Constant* RUQ Pain + Peritonitis (Rigidity/Guarding/Rebound)**
      - **Murphey's Sign** (Sudden halt of Inspiration)
      - **RUQ Mass** (Swollen Gallbladder)
      - **Jaundice**
  - **Diagnosis:**
    - **↑Alk Phos (Biliary Obstruction)**
    - ****Abdo Ultrasound (Definitive)**
    - **Or ERCP – (Good because Therapeutic as well)**
  - **Complications:**
    - Acute Gangrenous Cholecystitis (↑↑Pressure → Vascular Compromise)
    - 2^{o}-Infection can → Empyema
    - Gallbladder Perforation
    - 30% Require Surgery
  - **Treatment:**
    - Nil By Mouth (Bowel Rest)
    - IV Rehydration
    - Analgesia
    - IV-ABs
    - **Cholecystectomy**

- **RECURRENT/CHRONIC CHOLECYSTITIS:**
  - **Aetiology:**
    - **"*Biliary Gravel*"-** Thick Bile with many Small Gallstones.
  - **Pathogenesis:**
    - →Perpetual cycle of Bile Stasis → Stones Formation →Obstruction →
      - →→*Chronic* Inflammation
      - →→Mild Transient Biliary Obstructions → RUQ Discomfort *Following Meals*.
  - **Clinical Features:**
    - **Chronic Vague RUQ/Upper Abdo Discomfort *Following Meals***
    - Indigestion
    - Upper Abdo Distension
  - **Management:**
    - **Cholecystectomy**

GASTROINTESTINAL Pathology:
GASTRIC CANCER

GASTRIC & DUODENAL CANCERS:

- (NB: "Fungating" = Lesion marked by Ulcerations and Necrosis)
- **Aetiology:**
  - ***90%** H.pylori Metaplasia → **Gastric Adenocarcinoma (Glandular Neoplasm)**
  - **5%** - **MALT Lymphoma**
  - **Rare** - **Carcinoid, GI-Stromal Tumours (GIST), Etc.**
- **Pathogenesis – Fungating Gastric Adenocarcinoma:**
  - **H.pylori → Chronic Gastritis → Metaplasia → Cancer**
- **Morphology - Adenocarcinoma:**
  - **Adenocarcinoma**
  - **"Fungating" → Polypoid, Ulcerating Lesions with Heaped-Up, Rolled Edges.**



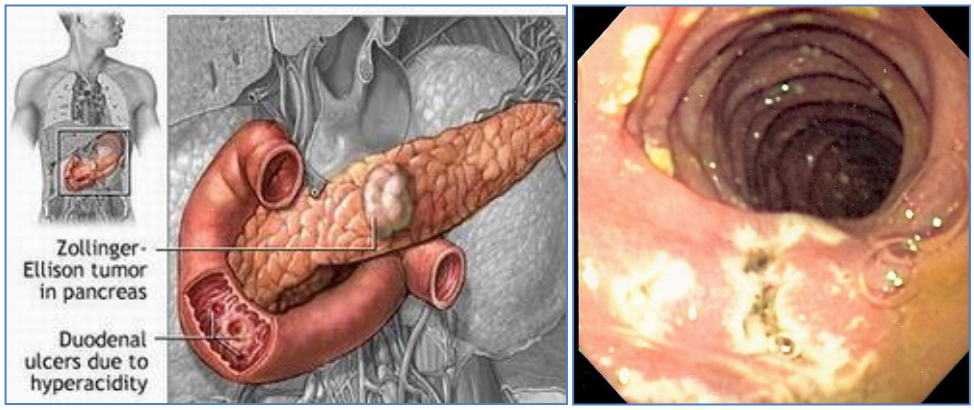
  - **Diffuse ("Leather Bottle") → Fibrotic Scarring → "*Leather Bottle Stomach*"**

- **Clinical Features:**
  - **Asymptomatic until Advanced Disease → *:. Poor Prognosis.***
  - **Early Symptoms:** Epigastric Pain, Nausea, **Haematemesis, Weight Loss**, Adenopathy, Anaemia.
  - **Late Symptoms:** Malignant Ascites/Jaundice, Symptoms of **Brain/Bone/Lung Mets**
- **Investigations:**
  - ****Gastroscopy + Biopsy – (*Grading of Cancer*)**
  - ****CT – (*Grading - ?Metastatic*)**
  - **Tumour Markers – (*Monitoring Only*)**
- **Treatment:**
  - **Surgery – (*Total Gastrectomy & Oesophago-Jejunostomy*)**
    - **+ Sentinal Node Resection**
    - **+/- Splenectomy**
  - **+/- Palliative Chemotherapy**
  - **+/- Palliative Radiotherapy**
- **Prognosis:**
  - **POOR - <30% 5yrs Survival (with surgery)**

GASTROINTESTINAL Pathology:
GASTRINOMA (ZE SYNDROME)

ZOLLINGER ELLISON SYNDROME (Adenoma/GASTRINOMA)

- **Aetiology:**
  - Gastrin-Secreting Neuroendocrine Adenomas ("*Gastrinomas*") in Pancreas/Duodenum/Stomach
- **Pathogenesis:**
  - **Gastrinomas In Pancreas/Duodenum** → Secrete Gastrin → Hyperacidity & ↑Pepsin Secretion → Treatment-Resistant Peptic Ulcers (Gastric & Duodenal)
- **Morphology:**



- **Clinical Features:**
  - Abdominal Pain
  - Dyspepsia
  - PUD → Haematemesis
  - Ruptured Ulcer → Peritonitis / Shock / Death
  - Chronic Diarrhoea (Due to Inactivation of Pancratic Enzymes – Lipase, & Mucosal Damage)
- **Diagnosis:**
  - **Fasting Serum Gastrin**
  - **Endoscopic Ultrasound & CT** (Tumour Imaging & Staging)
- **Treatment:**
  - **PPI – (***Omeprazole***)**
  - **Surgery** – (Remove Gastrinoma – 80% 5yr Survival)
- **Complication:**
  - Malignant Potential

GASTROINTESTINAL Pathology:
GASTRITIS & PUD

Background Info:

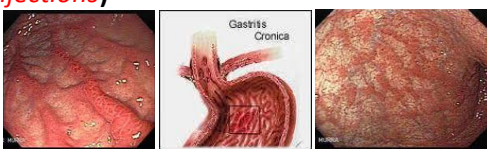
- **Protective Factors:**
  - ***Alkaline Mucus Layer** → Mechanical Barrier
  - ***Prostaglandin** → Stimulates ***Mucin*** Synthesis by Goblet Cells
- **Destructive Factors:**
  - ****Helicobacter Pylori:**
  - ***Acid – (**pH:2**)**
  - ***Pepsin – (**Digestive Proteolytic Enzyme Secreted by Chief Cells.)
  - ***NSAIDs – (Non Steroidal Anti-Inflammatory Drugs) – (Eg. Aspirin/Ibuprofen):**
    - 15-20% of NSAID users develop gastric ulcer.
  - **Stress/Gastrinoma/Zollinger-Ellison Syndrome**

Helicobacter Pylori Background:

- **Common – 75% Prevalence in PUD Pts**
- **Gram Neg Spirochete**
- **Transmission:** Oral → Oral, Faecal → Oral, Vertical
- **Colonises:** 1st Part of duodenum > antrum > G-E junction.
- **Is a Class-I Carcinogen –** (Ie. A Definite Carcinogen)

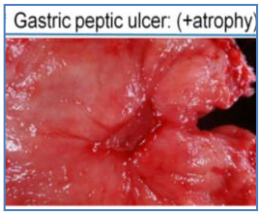
GASTRITIS:

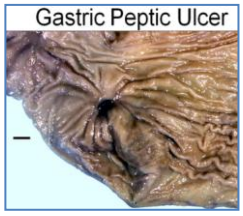
- **= Inflammation of the Stomach Lining**
- **Aetiology & Pathogeneses:**
  - **Acute:**
    - **15% Alcohol**
    - NSAIDs → Inhibits COX → ↓Prostaglandin → Hyperacidity → Inflammation
    - Severe Burns → ↓Plasma Volume → Sloughing of Stomach Mucosa
  - **Chronic:**
    - ****80% Bacterial – Helicobacter Pylori (Most Common)**
  - **Atrophic:**
    - **Autoimmune** –*Pernicious Anaemia* – (Antibodies against Parietal Cell & IF → B12 Deficient)
- **Clinical Features:**
  - **Symptoms:**
    - Abdo Pain
    - Dyspepsia
    - Bloating
    - Nausea/Vomiting
    - +/- Haematemesis (if *PUD*)
    - +/- Anaemia (If *Pernicious B12 Deficiency*)
- **Investigations:**
  - ****C^{13} Urea Breath Test – (*H.Pylori*)**
  - **Serology (IgG) – (*H.Pylori*)**
  - **H.pylori Faecal Antigen Test – (*H.Pylori*)**
  - **Endoscopy + Gastric Biopsy – (*H.Pylori Microscopy + ?Gastric Cancer*)**
- **Treatment:**
  - **Conservative –**(Avoid Precipitating Factors (Alcohol/NSAIDs)**)**
  - **Antacids – (*Mylanta*)**
  - **PPIs – (*Omeprazole*) or H2-Antagonists - (*Ranitidine*)**
  - **H.Pylori Triple Eradication Therapy – (*Clarythromycin* + *Amoxicillin* +/- *Metronidazole*)**
  - **If Pernicious – (*B12 Injections*)**

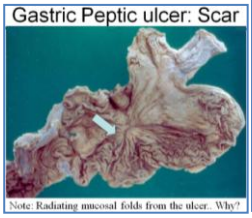


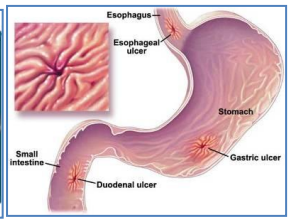
PEPTIC ULCER DISEASE:

- **Aetiology:**
  - ***Either*** **-↑Attack** (Hyperacidity, Zollinger Ellison Syndrome)
  - ***Or*** **- ↓Defence** (****H.pylori**, Stress, **Drugs [NSAIDs & Corticosteroids]**, Smoking)
- **Morphology:**
  - Small, Single, Round, Punched out Ulcer
  - 90% in Duodenum or Lesser-Curve of Stomach.
  - NB: Healing Peptic Ulcers have *Radiating Mucosal Folds* due to scar contraction.

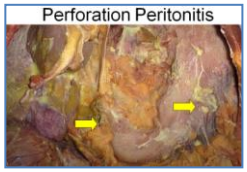


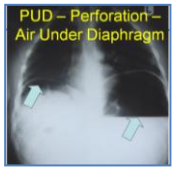






- **Clinical Features:**
  - Burning Epigastric Pain; (Most Severe when Hungry. Relieved by Food)
  - Nausea & Vomiting
  - Anorexia & Weight Loss
  - Haematemesis/Melena
  - **(Perforation → Acute Peritonitis)**
- **Investigation:**
  - **Clinical History**
  - **Endoscopy + Biopsy – (***Ulcer? H.Pylori? Gastric Cancer?***)**
  - ****C^{13} Urea Breath Test - (*H.Pylori?* The Best *NON-Invasive* Diagnosis)**
  - **Serology (IgG) – (H.pylori)**
  - **H.Pylori Faecal Antigen Test – (H.pylori)**
- **Treatment:**
  - **Conservative –(**Avoid Precipitating Factors (Alcohol/NSAIDs)**)**
  - **Antacids – (***Mylanta***)**
  - **PPIs – (***Omeprazole***) or H2-Antagonists - (***Ranitidine***)**
  - **H.Pylori Triple Eradication Therapy – (*Clarythromycin* + *Amoxicillin* +/- *Metronidazole*)**
  - ***Emergency Surgery – (*If Haematemesis / Rupture / Peritonitis / CANCER*)**
- **Complications:**
  - **GI Bleeding** → Anaemia
  - **Perforation** → Haemorrhage/Shock, Peritonitis, or Into Pancreatitis.
  - **Pyloric Stenosis (Scarring)** → Gastric Outlet Obstruction → Vomiting
  - ****GASTRIC CANCER** (NB: H.pylori → 6x Risk of Cancer)





"CURLING'S ULCER"

- **= An Acute Peptic Ulcer of the Duodenum due to ↓Plasma Volume from Severe Burns.**
- **Pathogenesis:**
  - Severe Burns → ↑Fluid Lost &↓Plasma Volume → Sloughing of Gastric Mucosa → Peptic Ulcer.
- **Complications:**
  - High Risk of Perforation/Haemorrhage :. High Mortality Rates.
- **Prevention:**
  - **Conservative:**
    - **TPN – (***Total Parenteral Nutrition***)**
    - **PPI – (***Omeprazole***) / H_2RA – (***Ranitidine***)**
  - **Emergency Surgery – (*If Haematemesis / Rupture / Peritonitis*)**

GASTROINTESTINAL Pathology:
GASTROENTERITIS

Bacterial Gastroenteritis (Food Poisoning):

- **TOXIGENIC DIARRHOEA (FOOD POISONING):**
  - **Aetiology:**
    - **Staph Aureus** (Poor Food Handling)
    - **Bacilis Cereus** (Mostly found in cereal)
  - **Symptoms:**
    - ***Onset Within 4hrs***
    - *Vomiting, *Stomach Cramps, Diarrhoea
  - **Pathogenesis:**
    - **Toxigenic Diarrhoea – (NB: Some toxins are *Heat Stable*)**
  - **Diagnosis:**
    - **History + Clinical Course**
    - **Retrospective Epidemiology** – Find Common Denominator. (Who ate what??)
    - **Stool OCP if worried.**
  - **Treatment:**
    - **Supportive Treatment –** (Fluid & Electrolyte Replacement)
    - **Anti-Diarrhoeals Controversial – (Symptomatic; but ↓Toxin Expulsion)**

- ***ESCHERICHIA COLI – ("TRAVELLER'S DIARRHOEA"):***
  - **ETEC: (Enterotoxigenic E.Coli)**
    - Produces Toxins:
    - **→ Traveller's Diarrhoea**
  - **EIEC: (Enteroinvasive E.Coli)**
    - Active Intestinal Invasion/Destruction
    - **→ Traveller's Dysentery**
  - **EPEC: (Enteropathogenic E.Coli)**
    - →Sporadic disease in babies and children
  - **EHEC: (Entero-Haemorrhagic E.Coli) – The Serious One:**
    - Produce **Verotoxin** → Destroys Platelets & RBCs→***HAEMOLYTIC-UREAMIC SYNDROME***
      - ***→ Kidney Failure + Bleeding + Dysentery***

- **SALMONELLA ("TYPHOID"):**
  - **Aetiology:**
    - *Salmonella typhi:*
  - **Pathogenesis:**
    - **→ Dysentery**
    - **Can → Septicaemia**
    - Also →Fever – rose spots – delirium - perforation of bowel
  - **Management:** ***Ceftriaxone*** ***+/-*** ***Ciprofloxacin***

- **LISTERIOSIS (LISTERIA):**
  - ***Aetiology:***
    - *Listeria Monocytogenes* – (*G-Pos*)
    - (Soft Cheeses & Cold Deli Meats)
  - **Risk to Pregnant Women & Immunocompromised**

- **CHOLERA:**
  - **Aetiology:** Vibrio Cholerae
  - **Symptoms:** Profuse Rice-Water Stools
  - **Management:** Fluid Replacement
  - **Prognosis:** Self-Limiting

- **NB: DYSENTERIC ORGANISMS:**
  - ***Salmonella, Shigella, Entamoeba Histolytica***

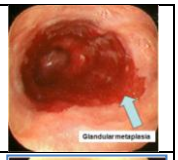
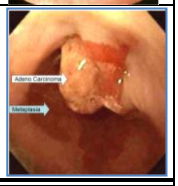
VIRAL GASTROENTERITIS:

- **Aetiology:**
  - ***80% Norovirus* (*Adult Diarrhoea*)**
  - ***Rotavirus* (*Kid Diarrhoea <3yo*) (*Day-Care Centres!!!*)**
  - **(Faecal-Oral Transmission)**
- **Pathogenesis:**
  - →Destruction of Enterocytes→Gastroenteritis
  - → Produces 'Toxic Rotavirus Protein' (NSP4) → Induces Chloride Secretion → Inhibits Water Absorption in gut.
- **Clinical Features:**
  - **Timeframe:**
    - **Incubation Period** ≈ 2 days
    - **Duration of Symptoms** ≈ 6 days
    - **Still infective for** ≈ 2 days after symptoms subside.
    - (:. Any kid with vom/dia should stay home for >1wk to minimise transmission)
  - **Symptoms:**
    - Vomiting (projectile)
    - Diarrhoea
    - + Flu-Like Illness – (Fever, Irritability, Poor Feeding, Myalgia)
- **Diagnosis:**
  - **Clinical Diagnosis of Gastroenteritis**
  - **Definitive Diagnosis via Stool Sample**
    - Enzyme Immunoassay
    - Or RT-PCR
- **Management:**
  - **Supportive Mx**
  - **FLUID REPLACEMENT!**
    - **"421 Rule": *4ml/kg/hr (first 10kg) + 2ml/kg/hr (second 10kg) + 1ml/kg/hr (thereafter)***
  - **Quarantine (Especially for Immunocompromised/Chemo Pts!)**

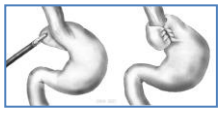
GASTROINTESTINAL Pathology:
GORD , BARRET'S & CANCER

GORD – GASTRO OESOPHAGEAL REFLUX DISEASE, BARRETT'S OESOPHAGUS & OESOPHAGEAL TUMOURS:

- **Aetiology:**
  - ***Defective Lower Oesophageal Sphincter.**
  - **Risk Factors:**
    - ↑Intra-Abdo-Pressure, Hiatus Hernias, Fat/Alcohol/Coffee/Choc/Spices
- **Pathogenesis:**
  - **Sphincter Incompetence → Chronic Regurgitation → Inflammation → (Metaplasia →Dysplasia)**
  - → Inflammation → **Reflux Oesophagitis**
  - → Gastric *Metaplasia* in Oesophagus → ****Barrett's Oesophagus**
  - → Continued Irritation & Regeneration → *Dysplasia* →→**Adenocarcinoma (Cancer)**
- **Morphology:**

BARRETT'S OESOPHAGUS:	**Endoscopic:** Upward Migration of Squamo-Columnar Junction – Looks Darker Pink, Velvety & Inflamed with Irregular Border	
ADENO-CARCINOMA: ***(GORD/ Barrett's)***	**Endoscopic:** Wet, Bulbous, Tumour Surrounded by Gastric Metaplasia (Barrett's) (Lower 1/3 of Oesophagus)	
NB: SQUAMOUS CELL CARCINOMA ***(Smoking/ Alcohol)***	**Endoscopic:** Dry, Keratinized, Ulcerative Tumour (Upper 1/3 of Oesophagus)	

- **Clinical Features:**
  - **Symptoms:**
    - Heartburn (Retrosternal Burning Sensation)
    - Dysphagia (Solids → Liquids)
  - **Complications:**
    - Bleeding/Perforation
    - Stricture/Obstruction
    - **BARRETT'S OESOPHAGUS**
    - **MALIGNANCY → Progressive Dysphagia (Solids → Liquids), Weight Loss, Anorexia, Aspiration**
- **Investigations:**
  - **Gastroscopy + Biopsy – (**Grading from Barret's Metaplasia → Adenocarcinoma**)**
  - **CT – (**Staging if Adenocarcinoma**)**
- **Treatment:**
  - **1. Conservative – (Lifestyle Modification):**
    - ↑Bed-head
    - Avoid Meals Within 3hrs of Bedtime
    - ↓Fat / Alcohol / Caffeine / Spices / Smoking
    - Weight Loss (to → ↓Intra-abdominal Pressure)
  - **2. Medical:**
    - **Antacids - (*Mylanta*).**
    - **Alginates - (*Aluminium Salts*)**
    - **H_2 Histamine Receptor Antagonists - (*Ranitidine*)**
    - **Proton-Pump Inhibitor - (*Omeprazole*)**
  - **3. Surgery:**
    - **Nissen Fundoplication – (**Upper stomach wrapped around Oesophagus**)**



HEARTBURN (Pyrosis) (see GERD section)
❑ most common complaint

CHEST PAIN
❑ may be indistinguishable from angina pectoris, but not predictably elicited by exertion, and often occurs spontaneously
❑ most common esophageal cause of chest pain is GERD

ODYNOPHAGIA
❑ pain on swallowing
❑ causes – usually due to ulceration of esophageal mucosa
- infection - Candida, Herpes, CMV (common only in immunosuppressed, especially AIDS)
- inflammation/ulceration (ex. caustic damage)
- drugs: doxycycline, wax-matrix potassium chloride, quinidine, iron, vitamin C, various antibiotics
- radiation

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Definition
❑ reflux of stomach/duodenal contents severe enough to produce symptoms and/or complications; the most common condition affecting the esophagus

Etiology
❑ LES relaxes inappropriately(most common)
❑ low basal LES tone
❑ hypersecretion of gastric acid
❑ delayed esophageal clearance
❑ delayed gastric emptying from any cause
❑ often associated with sliding hiatus hernia (see General Surgery Chapter)

Signs and Symptoms
❑ acid regurgitation (bitter taste)
❑ waterbrash (sudden hypersalivation)
❑ heartburn (retrosternal burning radiating to mouth)
❑ non-specific chest pain
❑ dysphagia (abnormal motility or esophagitis, reflux-induced stricture)
❑ pharyngitis, laryngitis (with hoarseness)
❑ respiratory (chronic cough, asthma, aspiration pneumonia, wheezing)
❑ symptoms aggravated by
- position (lying or bending)
- increase in intra-abdominal pressure (pregnancy or lifting)
- agents that decrease LES pressure (caffeine, fatty foods, alcohol, peppermint, cigarettes, nitrates, beta-adrenergic agonists, calcium channel blockers (CCB's), theophylline, benzodiazepines, anticholinergics, morphine)
- foods that delay gastric emptying (alcohol, coffee, chocolate)

Investigations
❑ depends on questions being asked
❑ is reflux present?
- 24-hour pH monitoring

❑ has relux damaged the esophagus?
- endoscopy

❑ is relux causing the symptoms?
- acid perfusion (Berstein) test

❑ is stricture present
- barium swallow

Management
❑ see Figure 2

Complications
❑ acid regurgitation —> esophageal inflammation, ulceration and bleeding
—> muscle spasm (DES) and/or stricture (scarring)
—> increased risk of Barrett's esophagus (columnar metaplasia)
—> increased risk of adenocarcinoma

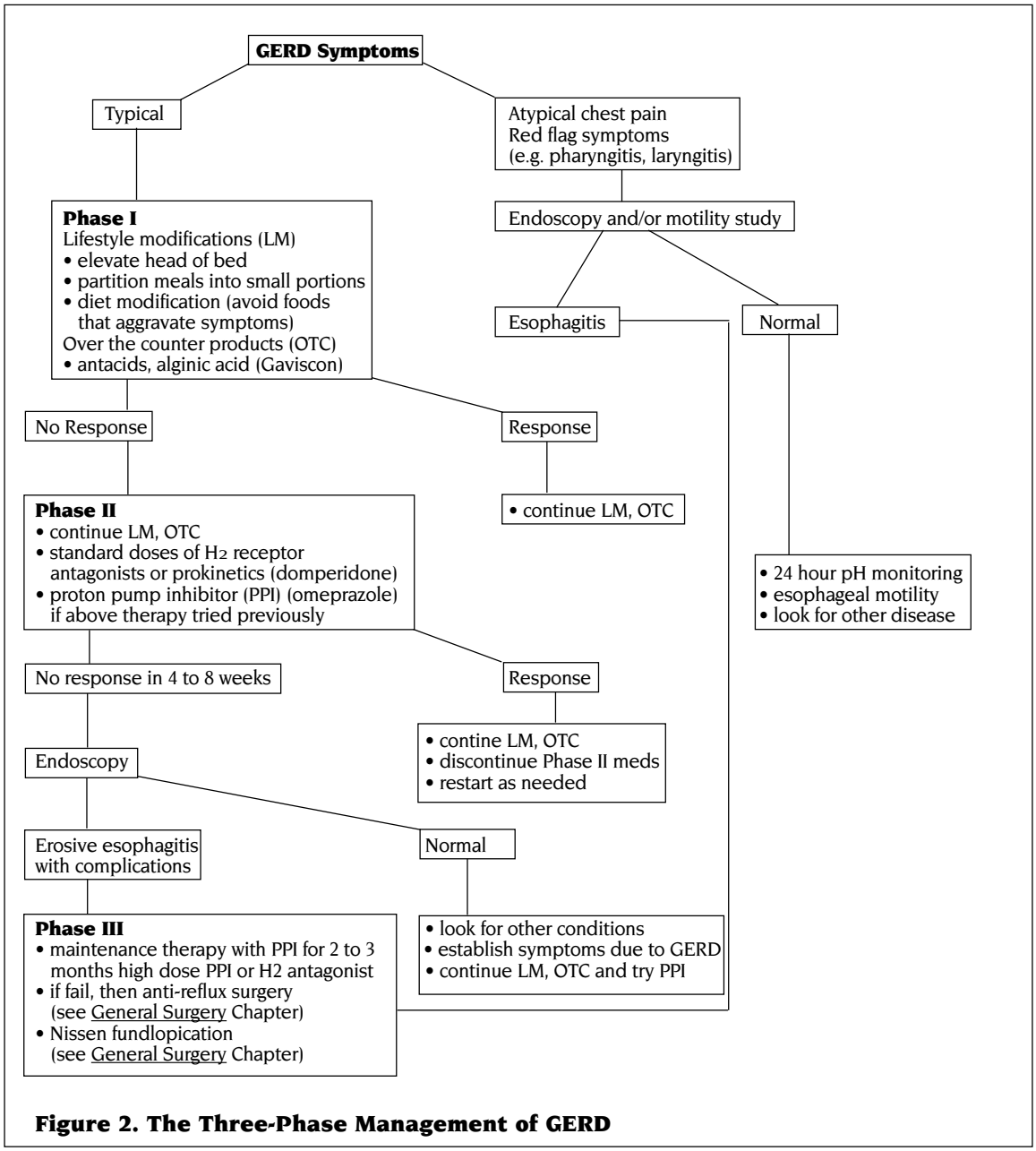
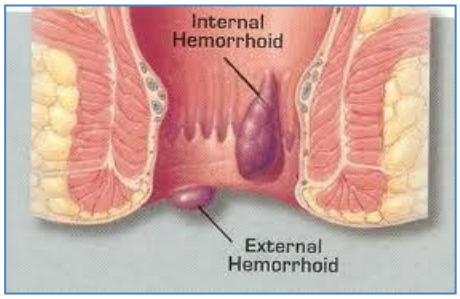


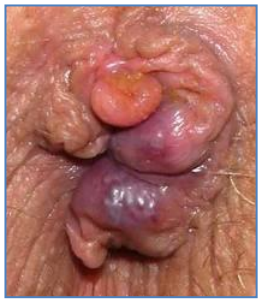
Figure 2. The Three-Phase Management of GERD

GASTROINTESTINAL Pathology:
HAEMORRHOIDS

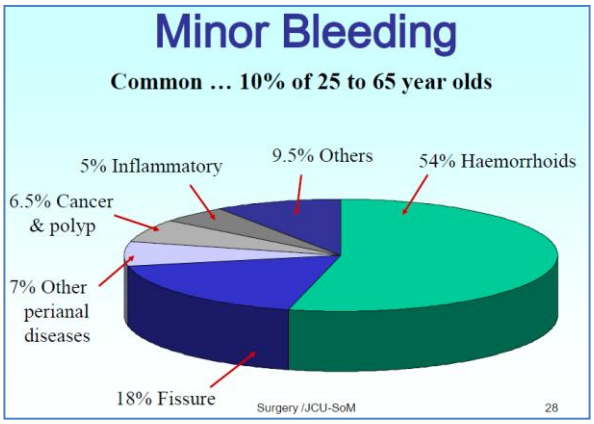
HAEMORRHOIDS (Internal & External)

- **Aetiology:**
  - Incompetent Valves in Rectal Vasculature
- **Pathogenesis:**
  - **Chronic ↑Intra Abdo Pressure** (Eg. Chronic Constipation/Pregnancy/Asthma/Weight Lifting)
    - → Dilation of Lower Abdo Veins & Valves → Incompetent Valves → **Haemorrhoids**
- **Morphology:**



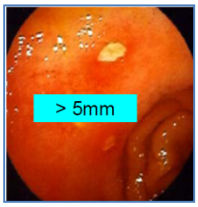


- **Clinical Features:**
  - **Commonest Cause of *MINOR* Rectal Bleeding!! (>50%)**
  - ***Internal*** Haemorrhoids → ***Painless*** Rectal Bleeding
  - ***External*** Haemorrhoids → ***Painful*** Rectal Bleeding
  - **(+/- Itching)**
- **Treatment:**
  - **1st Line:** ↑Dietary Fibre, ↑Fluids, Analgesia, Hygienic Maintenance, Rest.
  - **2nd Line: Surgery**
    - **Banding for Internal Haemorrhoids (Since Painless)**
    - **GA + Excision for External Haemorrhoids (Since Painful)**



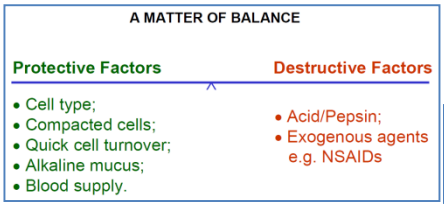
Helicobacter Pylori – The Cause of Gastric Ulcers:

Background on Peptic Ulcer Disease:



- **Where does it Occur?**
  - Duodenum
  - Stomach
  - Oesophagus (a result of GORD)
  - Margins of Gastrojejunostomy (Ie. Sometimes a side effect of surgery)

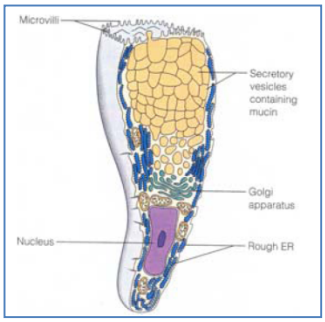
- **Aetiology:**
  - **Matter of imbalance of protective & Destructive factors:**
    - Ie. Breakdown of protective mucosal barrier
    - Or. Excessive Chronic Exposure to Acid/Pepsin

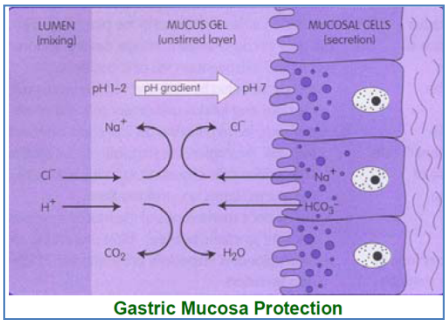


Proposed Mechanisms for Development of PUD

1. Breakdown of protective mucosal barrier;
2. Excessive chronic exposure to acid/pepsin.

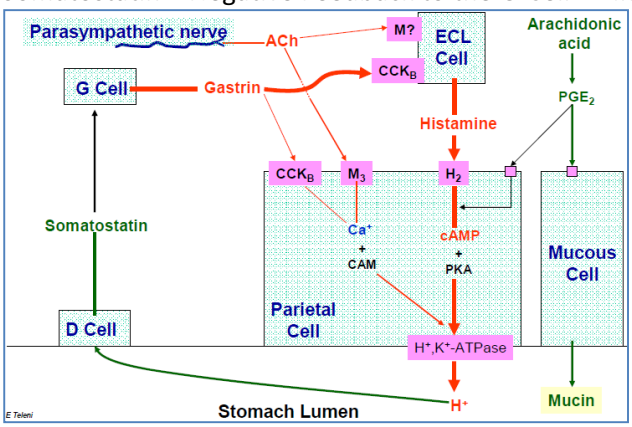
  - **Protective Factors:**
    - ***Thick Alkaline Mucus Lining & Epithelial Barrier:**
      - From Goblet Cells:
        - Mucin Synthesis is stimulated by Prostaglandin
        - Mucin protein synthesized in Endoplasmic Reticulum
        - Mucin is added to water → mucus
      - Unstirred Layer of mucus (closest to stomach lining) is neutral.





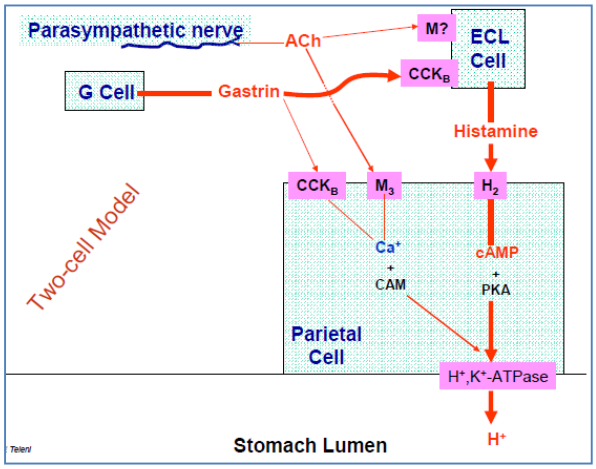
Gastric Mucosa Protection

    - ***Prostaglandin:**
      - → Stimulates ***Mucin*** Synthesis by Goblet Cells
      - → Inhibit *Histamine-Mediated* Acid Secretion by Parietal Cells.
    - ***D-Cells**
      - Detect H^+ in the stomach lumen → Secrete Somatostatin
      - Somatostatin = Negative Feedback to the G-Cell → Inhibits Gastrin Secretion



- **Destructive Factors:**
  - ****Helicobacter Pylori:**
    - Can burrow under the mucus layer (where the ph is neutral) → Survives
    - Also has an enzyme (urease?) which can neutralise the acid.
    - Love Columnar Cells

  - ***Acid:**
    - Two Cell Model: Stimulated by Gastrin → ECL Cell → Parietal Cells via Histamine → Stimulates Hydrogen (Proton) Pump from Parietal Cells.



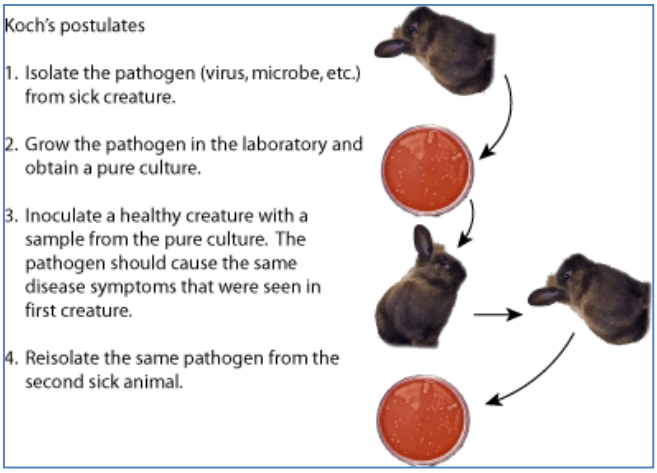
  - ***Pepsin:**
    - Digestive Proteolytic Enzyme Secreted by Chief Cells.
  - ***NSAIDs – (Non Steroidal Anti-Inflammatory Drugs) – (Eg. Aspirin/Ibuprofen):**
    - 15-20% of NSAID users develop gastric ulcer.
    - **Why??**
      - NSAIDs Inhibit Cyclo-oxygenase (→↓Prostaglandin) → - ↓Prostaglandin-Mediated Mucin-Secretion from Goblet Cells; AND - ↓Inhibition of Parietal Cell Acid Secretion.
  - **Stress (Zollinger-Ellison Syndrome):**
    - = A Rare condition characterised by Treatment-Resistant Peptic Ulcers Resulting From 'Gastrinomas' (Acid-Secreting tumour) in the Pancreas/Duodenum → Peptic Ulcers in Duodenum.

- **Pathogenesis – Helicobacter Pylori:**
  - **Gastric Ulcer:**
    - HP → Gastritis → Damage to Epithelial Layer → Exposure to Acid → Gastric Ulcer → ↓Antral D-Cells (&Somatostatin) → Decreased Inhibition of G-Cells → ↑ Gastrin → ↑Histamine-Mediated Acid Secretion by Parietal Cells→ Potentiates Gastric Ulcer.
  - **Duodenal Ulcer:**
    - GORD → ↑Exposure to Acid → Gastric Metaplasia → Colonised by HP → Duodenitis → Duodenal Ulcer.

- **(Therapeutic Management of H.Pylori-*Positive* Peptic Ulcers:)**
  - **Antibiotics** – (To kill the H.Pylori)
  - **Proton Pump Inhibitors** – (To reduce destructive acid)
  - **A Mucosal-Protective Drug: *Bismuth-Containing* Preparation ("Bismuth Chelate")**
    - **–** (Toxic effects on H.Pylori, Inhibits Adherence to Mucosa, & Inhibits Bacterial Proteolytic Enzymes)

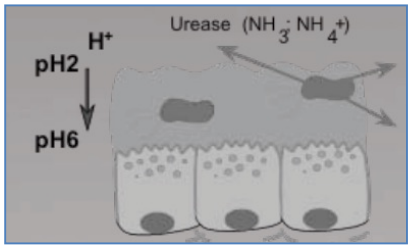
Background on Helicobacter Pylori:

- **H.Pylori Causes Gastric Ulcers – Discovered by Barry Marshal:**
  - Noted spiral bacteria in gastric ulcer biopsies.
  - Proposed that these bacteria cause the ulcers.
  - **Fulfilled Koch's Postulates by Drinking H.Pylori → Gave Himself Gastric Ulcers:**

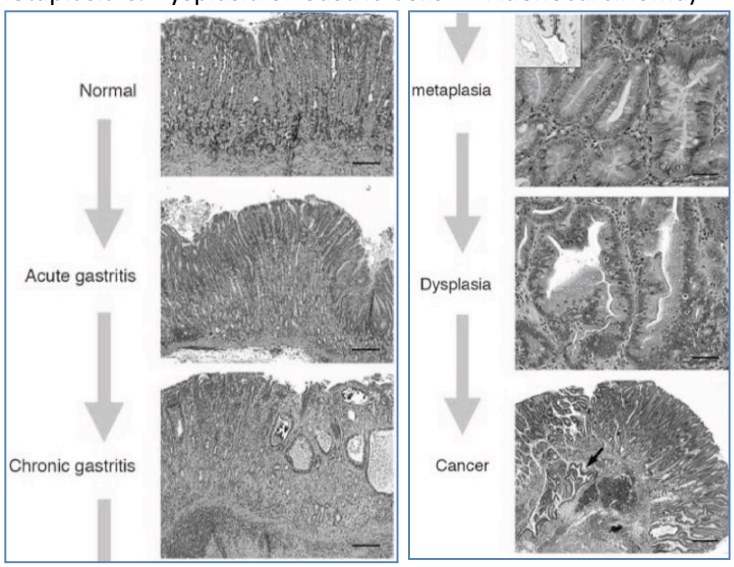


- **What is H.Pylori?**
  - **Gram Neg. Bacteria**
  - **Small, Spiral-Shaped Rod-like Bacteria.**

  - **Has an *'Altered'* LPS –** (Triggers little inflammation)
  - **Produces Urease –** (Produces Ammonia to Neutralise Stomach Acid)

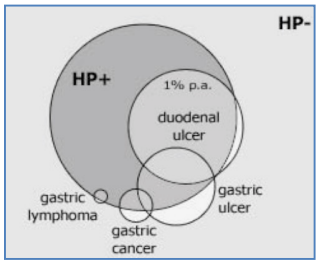


  - **Microaerophillic –** (Ie. Doesn't like too much Oxygen)
  - **Metabolically Fastidious –** (Grows Slowly)
  - **Is a Class-I Carcinogen –** (Ie. A Definite Carcinogen)
    - (Since it causes Chronic Inflammation & Chronic Exposure to Reactive Oxygen Species →Metaplasia & Dysplasia of Gastric Cells → Adenocarcinoma)

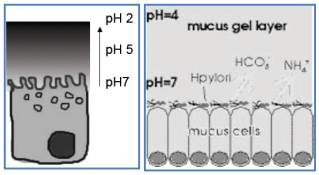


- **Transfer of Infection:**
  - Oral → Oral
  - Faecal → Oral
  - Mother → Child (AKA: "Vertical Transmission")
  - Contaminated Food/Water.

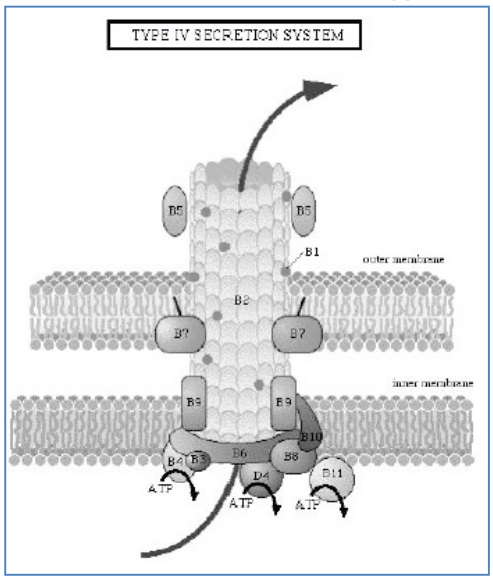
- **H.Pylori Infection:**
  - **Chronic Infection → Ie. Infected for Life.**
  - **Has a Global Distribution:**
    - (Incidence is highest in less developed nations)
    - (Infection correlates with Low SES)
    - (Infection rates high in Elderly)
  - **H.Pylori-Related Diseases:**

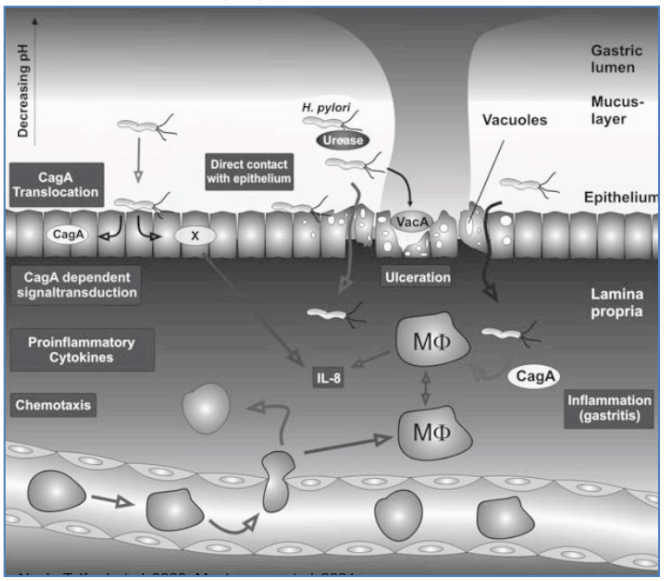


- **Adaptations to a Hostile Envirnoment (& Pathogenicity Factors):**
  - **Adaptations:**
    - Can Metabolise Carbohydrates (Ie. Glucose)
    - Has Pyruvate & Fumerate Pathways
    - Can produce Urease → Neutralise Stomach Acid
      - (Hydrolises Urea → Amonia + Bicarb)
  - **Pathogenicity Factors:**
    - pH Modification Ability (Urease)
    - Motility (Flagellin → Powerful Swimmers)
    - Adherence to Epithelium (Via Adhesins) – (NB: The pH is less acidic @ the epithelium)

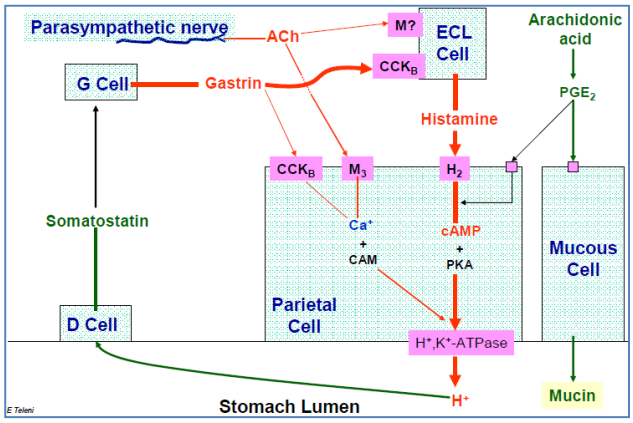


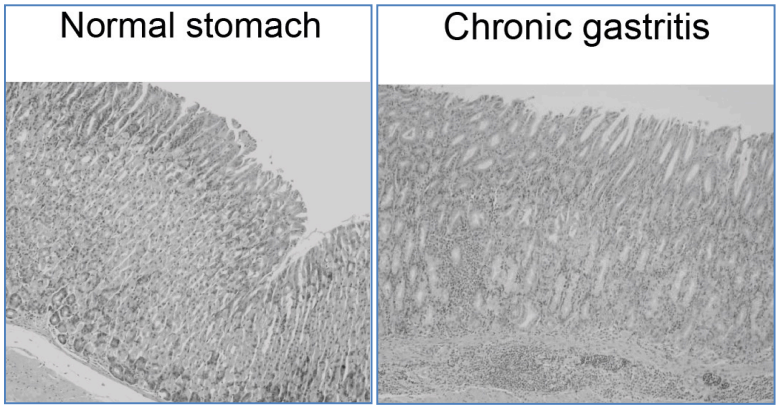
    - Type-IV Secretory System → Secretes Cytotoxins (Eg. "CagA" – a '*molecular syringe*')
      - → interfere with Epithelial Tight-Junctions → Leaky epithelial barrier.
      - → Also induces COX-2 expression → ↑Prostaglandins → Inflammation
      - → Also Trigger release of Inflammatory Cytokines

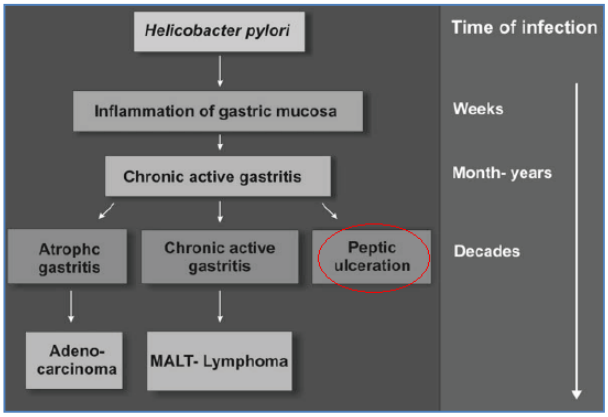


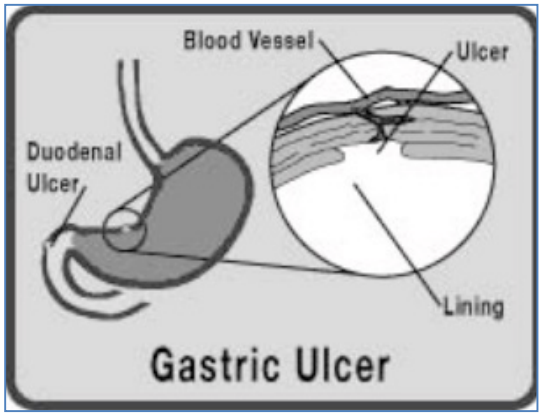


- **How H.Pylori Causes Disease:**
  - **Gastric Ulcer:**
    - HP Colonise the Corpus of the Stomach → **Gastritis** → Damage to Epithelial Layer → Exposure to Acid → Gastric Ulcer → ↓Antral D-Cells (&Somatostatin) → Decreased Inhibition of G-Cells → **↑ Gastrin → ↑Histamine-Mediated Acid Secretion by Parietal Cells→** Potentiates Gastric Ulcer.
  - **Duodenal Ulcer:**
    - ↑Stomach Acid → HP Colonise the Antrum of the Stomach → **Gastritis** →↓Antral D-Cells (&Somatostatin) → Decreased Inhibition of G-Cells → **↑ Gastrin → ↑Histamine-Mediated Acid Secretion by Parietal Cells→** ↑Duodenal Acidity → Duodenal Metaplasia → Colonised by HP → Duodenitis → Duodenal Ulcer.

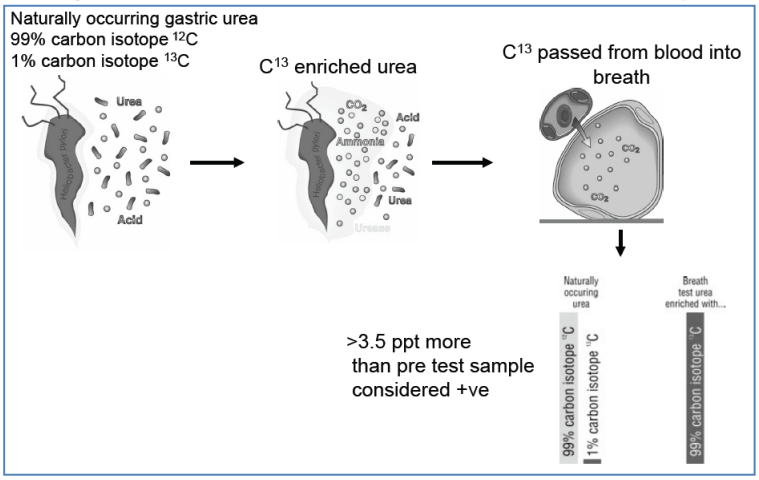








- **Diagnosis:**
  - **Gastric Biopsy:**
    - Histology
    - Culture
  - **Serology:**
    - Gel Electrophoresis
    - - Detects Antibodies against H.Pylori antigens.
  - **C^{13} Urea Breath Test:**
    - Pt. Drinks a C^{13} enriched Urea solution.
    - Urease secreted by H.Pylori splits the C^{13}-Urea → C^{13} is encorporated into CO_2.
    - Detection of the C^{13}-labelled CO_2 in Exhaled Breath indicates that the urea was split → Indicating the Presence of Urease → Hence Presence of H.Pylori.



- **Treatment:**
  - ****Combined Triple Antibiotics + PPI.**
    - **Proton Pump Inhibitors** – (To reduce destructive acid)
    - ****Antibiotics** – (To kill the H.Pylori):
    - (NB: Cure rate is *less* than 80% - Antibiotic resistance is increasing → **Push for vaccine**.)
  - **A Mucosal-Protective Drug: *Bismuth-Containing* Preparation ("Bismuth Chelate")**
    - **–** (Toxic to H.Pylori, Inhibits Adherence to Mucosa, & Inhibits Bacterial Proteolytic Enzymes)

- **Progress towards a Vaccine Against H.Pylori:**
  - Works in some animal models.
  - Poor Results in humans.
  - 100^{+} antigens have been identified.
  - However – Protection isn't due to antibodies. (Ie. We Don't know *how* the vaccine works)
    - We *do know* that CD4-T-Cells are implicated.
  - **Take Home Message:**
    - Still don't know whether a Safe Vaccine is Feasible.
    - Post-Immunisation Gastritis is an issue.
    - Little evidence of Efficacy in Humans.

HEPATOBILIARY Pathology:

HEPATITIS

(NB: The link between Hepatitis, Cirrhosis & Hepatic Cancers):

Hepatitis (Except A/E) → Cirrhosis → Hepatic Cancers

Non-Viral Hepatitis:

- **ALCOHOLIC HEPATITIS (Alcoholic Liver Disease):**
  - **Aetiology:**
    - "High Risk" Alcohol Consumption
      - Males >50std/week
      - Females >35std/week
  - **Pathogenesis:**
    - **Ethyl-Alcohol** → Metabolised to **Acetaldehyde** (Hepatotoxic)
    - → Severe Inflammation → Fibrosis!
  - **Clinical Features:**
    - Jaundice
    - Hepatomegaly (Fatty Liver)
    - Splenomegaly (If Portal Hypertension)
    - Dupuytren's Contracture, Hepatic Flap, Truncal Ataxia
    - **Wernicke/Korsakoff** Syndrome – ***GIVE THIAMINE + B12***
    - **Delerium Tremens** – ***GIVE DIAZAPAM***
  - **Investigations:**
    - ↑AST/ALT
    - **↑GGT:ALP**
  - **Management:**
    - **Avoid Alcohol & Hepatotoxic Drugs**
    - **If Wernicke/Korsakoff** Syndrome – ***GIVE THIAMINE + B12***
    - **If Delerium Tremens** – ***GIVE DIAZAPAM***
    - **Fluid Management**

- **PARACETAMOL-INDUCED HEPATITIS:**
  - **Aetiology:**
    - Paracetamol Overdose
  - **Pathogenesis:**
    - Paracetamol = Directly Hepatotoxic & depletes *Glutathione* (conjugator) stores → ↑↑Free Paracetamol → Toxin-Mediated Centrilobular Necrosis
  - **Clinical Features:**
    - Acute Hepatitis – Jaundice, Confusion, ALOC
  - **Lab Tests:**
    - ↑AST/ALT (Necrosis)
    - ↑Bilirubin (Unconjugated)
  - **Outcomes:**
    - 1 → Acute Hepatic Failure → Death
    - 2→ Spontaneous Recovery
    - 3→ N-Acetyl Cystiene → Recovery
  - **Management:**
    - **N-Acetyl Cystiene - (***A Precursor to Glutathione – A Conjugator for Paracetamol**)**
      - **NB: Titrated to ~Paracetamol Dose on Nomogram**

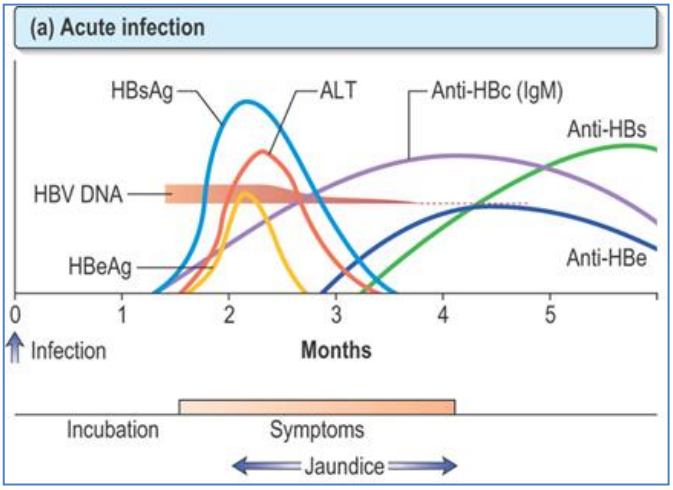
Viral Hepatitises – (A&E=*Acute*, B&D=*Acute & Chronic*, C=*Chronic*):

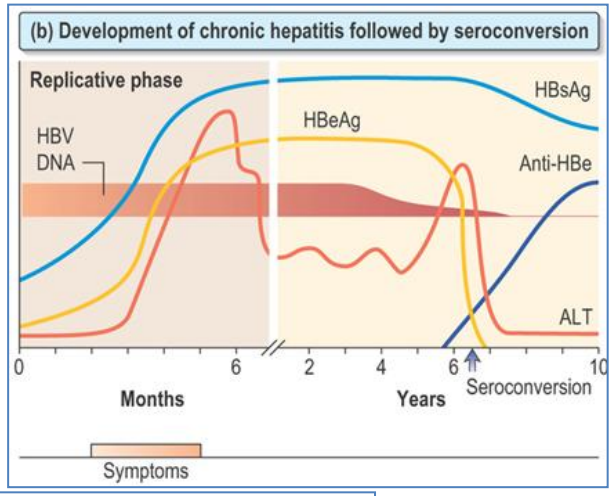
- **HEP A (Acute):**
  - **Aetiology:**
    - Hepatitis A Virus (NB: The commonest *Viral Hepatitis* Worldwide)
  - **Pathogenesis:**
    - **Faecal-Oral Transmission**
      - 2-6wk Incubation
    - **Virus is *Directly Cytopathic to the Liver* – But Does NOT lead to Cirrhosis**
  - **Clinical Features:**
    - ***NB: Acute Syx ONLY; No Chronic*.**
      - **Viraemia** → Fever, Malaise, Anorexia, Nausea, Arthralgia
    - **Signs:**
      - Jaundice (After 1-2wks)(Due to *Intrahepatic Cholestasis*)
        - →↑Conjugated Bilirubin →
          - →Pale Stools
          - →Dark Urine
      - +/- Hepatomegaly
      - +/- Splenomegaly
      - +/- Tender Lymphadenopathy
      - Rarely – Hepatic Encephalopathy & Death.
  - **Investigations**
    - **LFTs – (Everything Raised)**
    - **Hep A Serology**
    - **Hep A PCR**
  - **Prognosis:**
    - Usually Self-Limiting with *Supportive Treatment Only*.
- **HEP E (Acute):**
  - (Very Similar to Hep A; But HIGH MORTALITY in PREGNANCY [20% → DIC in 3rd Trimester])
  - **Aetiology:**
    - Hepatitis E Virus (A Herpesvirus)
  - **Pathogenesis:**
    - **Virus is *Directly Cytopathic to the Liver***
  - **Clinical Features:**
    - **Faecal-Oral Transmission** (Incl. Vectors: Dogs/Pigs/Rodents)
    - **Clinical Picture -** (Same as Hep A)
  - **Investigaitons:**
    - LFTs – (Everything Raised)
    - Hep A Serology
    - Hep A PCR
  - **Prognosis:**
    - 1-2% Mortality (From Fulminant Hepatic Failure)
    - *20% Mortality in Pregnancy* (From DIC in 3rd Trimester)

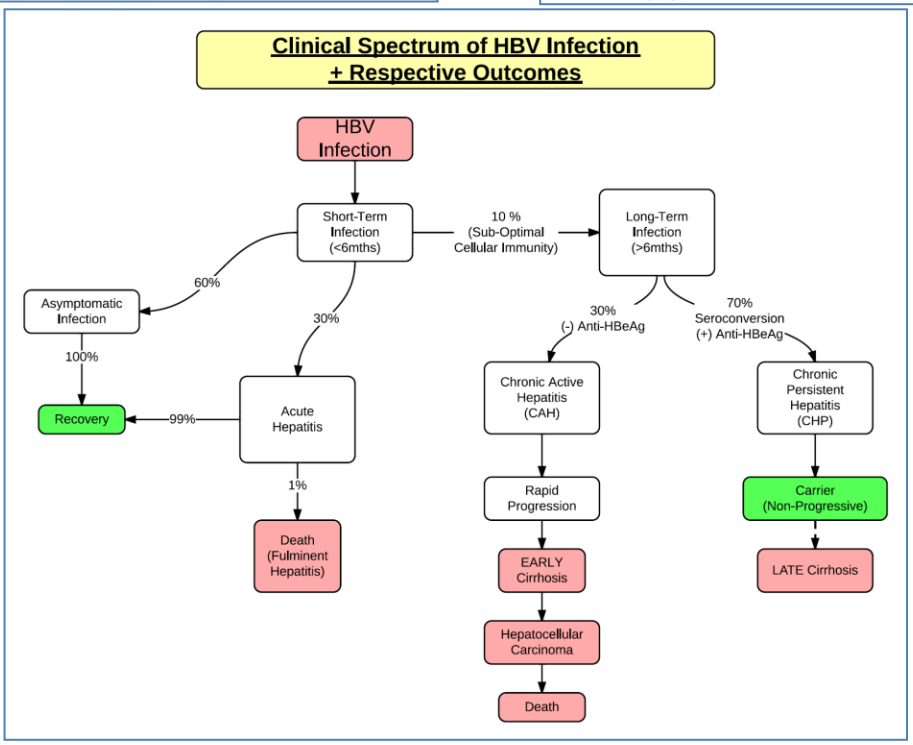
- **HEP B (Acute/Chronic)**
  - **Aetiology:**
    - Hepatitis B Virus
  - **Pathogenesis:**
    - **Acute Hepatitis** → Hepatocyte Injury is due to CD8-T-Cell Attack.
      - ***NB: IF Immunocompetent…Virus is Cleared → Recovery***
    - **30% →Chronic Active Hepatitis – (**Immune Response is Sub-Optimal):
      - **→Chronic Inflammation → Fibrosis → *EARLY* Cirrhosis→HCC / Death**
    - **70% →Chronic Persistent Hepatitis -** (Virtually NO Immune Response)
      - → Very little Inflammation :. Minimal Pathology → ***LATE*** **Cirrhosis**
      - NB: *Sporadic Acute Episodes*.
  - **Clinical Features:**
    - **Transmission:**
      - **Horizontal** - Sexual/Blood/Ingestion/Innoculation (HIGHLY INFECTIOUS)
      - **& Vertical** – Mother→Baby (20% Chance)
        - **Infected Mums Require *Anti-HepB-IVIg* + Oral *Antivirals*.**
    - **Vaccine Preventable – (HBsAg (Surface-Ag) Innoculation).**
      - :. A pt with Anti-HBsAg, but *no* Anti-HBcAg, has been *Vaccinated*.
      - :. A pt with Anti-HBsAg, *AND* Anti-HBcAg, has been *Infected*.
      - **Administered @ Birth, 2/4/6mths, & year 8.**
    - **Carrier State** Exists if Acute → *Chronic Persistent Hepatitis.*

	Symptoms:	**Signs:**	**Lab Tests:**	**Prognosis:**
Acute Hep B	Non-Specific Viral: - Fever - Anorexia - Naus/Vom - Myalgia	Jaundice (Conjugated) - Dark Urine - Pale Stools - Pruritis	(+) HBsAg (-) Anti-HBsAg (+) HBcAg (+) Anti-HBcAg (+) HBeAg (-) Anti-HBeAg ↑ AST/ALT/Bili	>90% →Recover Fully <10% →Chronic Hepatitis - 70% → CPH - 30% → **CAH**
Immunity:	Nil	Nil	(-) HBsAg **(+) Anti-HBsAg = Immunity/Recovery** (-) HBcAg **(-) Anti-HBcAg (If Vaccinated) **(+) Anti-HBcAg (If Previously Infected) **(+) Anti-HBeAg (If Previously Infected) Normal AST/ALT/Bili	
30%-CAH: (Active/ Replicative)	Non-Specific Viral: - Fever - Anorexia - Naus/Vom - Myalgia	Jaundice (Both Types) Small, Nodular Liver Signs of Portal HTN: - Telangiectasias - Caput Medusa - Ascites - Pedal Oedema - Splenomegaly - Gynaecomastia Hep. Encephalopathy	(+) HBsAg (-) Anti-HBsAg (+) HBeAg (-) Anti-HBeAg ↑ AST/ALT/Bili	**100% →Cirrhosis** **↑Risk of Hepatocellular Ca (200x)**
70%-CPH: (Inactive/ Carrier)	May be Asymptomatic	None	(+) HBsAg (-) Anti-HBsAg (-) HBeAg **(+) Anti-HBeAg** Normal LFTs	**Carrier for Life** Minimal Progression - LATE Cirrhosis - ↓Hepato-Ca. *Sporadic Acute Episodes*

  - **Treatment:**
    - ***IFNα***
    - **Long-Term Antivirals (Eg. *Ganciclovir*)** (but remission rate ≈ only 20-40%)
    - **+ Maternal Prophylaxis – (*Anti-HepB-IVIg* + Oral *Antivirals*)**

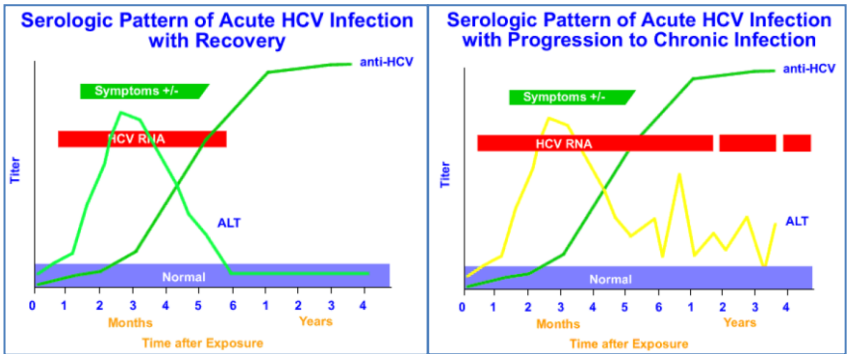






- **HEP D – (Concomitant with Hep B):**
  - **Aetiology:**
    - Hepatitis D Virus – CO-INFECTION with HEP-B.
  - **Pathogenesis:**
    - HDV is *UNABLE* to Replicate on its own; *REQUIRES Hep-B*.
    - Same as Hep.B – (Ie. Immune-Mediated Hepatocyte Injury) – But More Severe.
      - → Quicker Progression to Cirrhosis
  - **Clinical Features:**
    - **Signs/Symptoms:**
      - Indistinguishable from Acute Hep.B – (Ie. Non-Specific Viral Symptoms)
  - **Diagnosis:**
    - ↑AST/ALT
    - IgM Anti-HDV
    - IgM Anti-HBc
  - **Complications:**
    - ↑Risk of Fulminant Hepatitis - (As opposed to *just* Hep.B)
    - Chronic Hep.D → ↑Risk of Cirrhosis (70%) - (As opposed to *just* Hep.B)

- **HEP C (**Acute**/Chronic)**
  - **Aetiology:**
    - Hepatitis C Virus
  - **Transmission:**
    - **Blood (Eg. IVDU):** As little as 0.0001 mL of blood can transmit the infection
    - **Body fluids (Eg. Sexual):** (Incl. Cervical Secretions and Semen)
    - **Vertical** (Uncommon)
  - **Pathogenesis:**
    - **Virus is NOT directly Cytopathic; Damage is due to Immune Response.**
    - → ***Chronic, Low-Grade Inflammation*** → **Eventually leads to Fibrosis → Cirrhosis**
  - **Clinical Features:**
    - **Symptoms:**
      - **10% →Acute with Recovery –** (Mild Viral Illness + Jaundice)
      - **90% →Chronic with Extrahepatic & Intrahepatic Manifestations:**
        - Asymptomatic for years (Usually Incidental Diagnosis)
        - May have Sporadic Mild Viral Illnesses + Jaundice
      - **END STAGE (CIRRHOSIS):**
        - 20-30% → *Cirrhosis* (within 10-30yrs)
        - 5% → *Hepatocellular Carcinoma* – (Hep C Directly inactivates P53)



  - **Investigations:**
    - **Usually discovered on Routine LFTs – (**Mildly ↑ ALT/AST**)**
    - **Hep C Serology – (**(+) Anti-HCV**)**
    - **Hep C PCR – (**(+) HCV-RNA**)**
  - **Treatment:**
    - **Post-Exposure/Acute (Eg. Needlestick):**
      - ***IFN***
      - ***Ribavirin***
    - **Supportive Treatment:** in established disease.

- **Acute Hepatitis due to *Other Infectious Agents*: (NB: This is simply from the *LIVER PERSPECTIVE!*)**
  - **EBV (Epstein Barre Virus/Infectious Mononucleosis/Glandular Fever):**
    - **Morphology:**
      - Acute Hepatitic Changes within 5days (Degeneration/Swelling/Necrosis/Inflamm)
      - **Periportal Inflammation with Large, Mononuclear Cells*.
    - **Clinical Features:**
      - **Common:**
        - Mild Jaundice
        - Mild ↑AST/ALT
      - **Uncommon:**
        - Clinical Hepatitis

  - **CMV (Cytomegalovirus):**
    - **Morphology:**
      - Liver Biopsy:
        - Intranuclear Inclusions
        - Giant Cells
    - **Clinical Features:**
      - Particularly in Immunocompromised

  - **Yellow Fever Virus:**
    - **Pathogenesis:**
      - Virus causes *Acute Hepatic Necrosis*
    - **Morphology:**
      - Acute Hepatitic Changes (Degeneration/Swelling/Necrosis/Inflamm)
      - + Significant Necrosis
    - **Clinical Features:**
      - Jaundice
      - ↑↑AST/ALT

  - **Herpes Simplex Virus:**
    - **Morphology:**
      - Liver Biopsy – Massive Necrosis
    - **Clinical Features:**
      - Particularly in Immunocompromised, or Pregnancy
      - ↑↑AST/ALT
      - Treated with Aciclovir.

  - **Toxoplasmosis (Parasite):**
    - **Clinical Features:**
      - Similar Clinical Picture as EBV (Infectious Mononucleosis)
        - Ie. Mild Jaundice
        - + Mild ↑AST/ALT

GASTROINTESTINAL Pathology:
HIATUS HERNIA

HIATUS HERNIA:

- **Aetiology:**
  - Weakness/Tear in the Diaphragmatic Hiatus
  - +/- ↑Intraabdominal Pressure
- **Pathogenesis:**
  - **1. 95% - Sliding:**
    - Gastro-Oesophageal Junction AND Stomach *Slides* through Hiatus → Above Diaphragm.
    - → Incompetent Lower Oesophageal Sphincter
    - 30% Prevalence >50yrs
    - Symptoms of GORD
  - **2. 5% - Rolling:**
    - Part of the Fundus of the Stomach *Prolapses* through the Hiatus → Above Diaphragm → Alongside the Oesophagus → Can Strangulate/Twist the Oesophagus.
    - → Lower Oesophageal Sphincter *Remains* Competent.
    - Symptoms = Pain due to Oesophageal Strangulation/Twisting.
- **Clinical Features:**
  - **Symptoms:**
    - Mostly Asymptomatic
    - GORD – (Heartburn, Reflux)
    - Relief when Upright
    - Pain due to Oesophageal Strangulation/Twisting
    - Shortness of Breath (Affect on Diaphragm)
    - Heart Palpitations (Irritation of Vagus Nerve)
- **Investigations:**
  - **Gastroscopy + Biopsy – (**Rule out Barrett's / Oesophageal Cancer**)**
  - **Oesophageal Manometry – (**Detects Sphincter Incompetence**)**
  - **Barium Swallow / CT**
- **Complications:**
  - **Barrett's Oesophagus → Oesophageal Cancer**
  - **Strangulation of Stomach** (in Rolling Hernias) → Ischaemia & Necrosis
- **Treatment:**
  - **Conservative – (**Weight Loss, Dietary, Positional, Smaller Meals, No Alcohol/Caffeine**)**
  - **Medical – (**Antacids [***Mylanta***] + [***Omeprazole***] + Antiemetics [***Metoclopromide***]**)**
  - **Surgery –(**Nissen Fundoplication – Open/Laparoscopic**)** if Severe.

HIATUS HERNIA (HH)

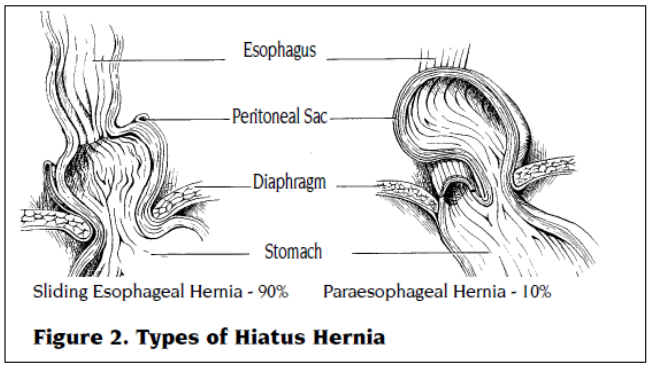
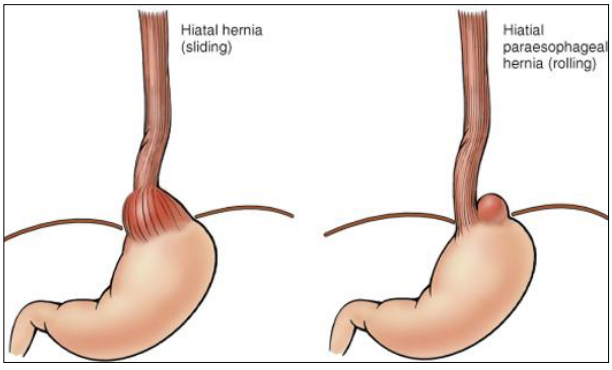


Figure 2. Types of Hiatus Hernia



ESOPHAGUS

HIATUS HERNIA (HH)

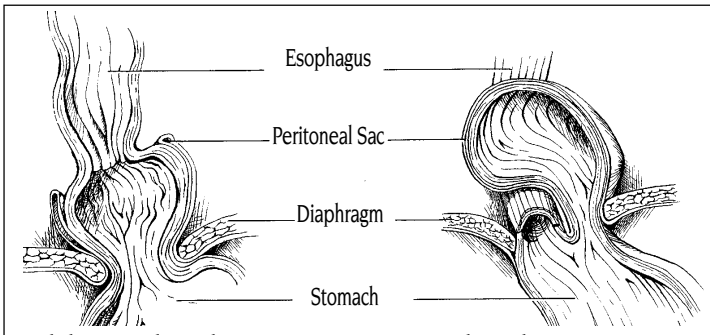


Figure 2. Types of Hiatus Hernia

Illustrations by Bryce Hough

Sliding Hiatus Hernia (Type I)

- ❑ herniation of both the stomach and the gastroesophageal (GE) junction into thorax
- ❑ > 90% of esophageal hernias
- ❑ risk factors: aging, weakening of musculofascial structure, and increased intra-abdominal pressure (e.g. obesity, pregnancy)
- ❑ differential diagnosis: cholelithiasis, diverticulitis, peptic ulcer, achalasia, MI, angina, pancreatitis, gastroesophageal reflux disease (GERD), gastritis, pericarditis
- ❑ clinical presentation
  - majority are asymptomatic
  - GERD (heartburn 1 + 3 hrs post-prandial, chest pain, regurgitation)
  - relief with sitting, standing, water, antacids
- ❑ complications
  - reflux, esophagitis, chronic occult GI blood loss with anemia, ulceration, dysphagia, esophageal stricture, Barrett's esophagus, adenocarcinoma, aspiration pneumonia, bleeding
- ❑ investigation
  - gastroscopy with biopsy —> document type and extent of tissue damage, rule out esophagitis, Barrett's esophagus and cancer
  - 24 hour esophageal pH monitoring —> often used if atypical presentation, gives information about frequency and duration of acid reflux, correlation of symptoms with signs
  - esophageal manometry —> detects decreased lower esophageal sphincter (LES) pressure; may also diagnose motility disorder
  - upper GI series or barium swallow
  - CXR globular shadow with air-fluid level over cardiac silhouette, visible shadow posterior mediastinum on lateral view
- ❑ treatment
  - conservative
    - stop smoking
    - weight loss
    - elevate head of bed
    - no nocturnal meals (< 3 hrs prior to sleeping)
    - smaller and more frequent meals
    - avoid alcohol, coffee, fat
  - medical
    - antacids
    - H_2 antagonists (e.g. cimetidine, ranitidine)
    - proton pump inhibitor (e.g. Losec, Pentaloc, Prevacid) x 8-12 weeks for esophagitis
    - adjuvant prokinetic agents may play a role (metoclopromide, motilium)
  - surgical (< 15%)
    - Nissen fundoplication (laparoscopic or open) where fundus of stomach is wrapped around the LES and sutured in place
    - 90% success rate
    - indications for surgery
      - complications of sliding hernia or GERD (especially stricture, severe ulceration, fibrosis, bleeding, Barrett's)
      - symptoms refractory to conservative and medical treatment

Paraesophageal Hiatus Hernia (Type II) (see Figure 2)
- ❑ herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced gastroesophageal (GE) junction
- ❑ <10 % of esophageal hernias
- ❑ clinical presentation
  - asymptomatic
  - heartburn/reflux uncommon (because normal GE junction)
  - pressure sensation in lower chest, dysphagia
- ❑ complications
  - hemorrhage
  - incarceration, obstruction, strangulation, gastric stasis ulcer
  - palpitations rarely
- ❑ treatment
  - surgery in almost every case to prevent severe complications
  - procedure: reduce hernia, suture to posterior rectus sheath (gastropexy), close defect in hiatus
  - excellent results

Mixed Hiatus Hernia (Type III)
- ❑ a combination of Types I and II

ESOPHAGEAL CARCINOMA
- ❑ epidemiology
  - 1% of all malignant lesions
  - male:female = 3:1
  - 50-60 years of age (onset)
  - squamous cell carcinoma (SCC) 5x more common in blacks
- ❑ risk factors
  - physical agents: alcohol, tobacco, nitrosamines, lye, radiation
  - structural: diverticula, hiatus hernia, achalasia, GERD
  - Barrett's epithelium (8-10% risk of adenocarcinoma, monitor every 1-2 years by endoscopy and biopsy)
  - chronic iron deficiency (Plummer-Vinson syndrome)
- ❑ pathology
  - upper 20-33%, middle 33%, lower 33-50%
  - squamous cell carcinoma: 80-85% (esophagus)
  - adenocarcinoma: 5-10% (GE junction) - associated with Barrett's esophagus
- ❑ differential diagnosis
  - leiomyoma, metastases, lymphoma, benign stricture, achalasia, GERD, spasm
- ❑ clinical presentation
  - frequently asymptomatic - late presentation
  - often dysphagia, first solids then liquids
  - weight loss, weakness, systemic symptoms
  - regurgitation and aspiration (aspiration pneumonia)
  - hematemesis, anemia
  - odynophagia then constant pain
  - tracheoesophageal (TE), bronchoesophageal fistula
  - spread directly or via blood and lymphatics - trachea (coughing), recurrent laryngeal nerves (hoarseness, paralysis), aorta, liver, lung, bone, celiac and mediastinal nodes
- ❑ investigations and diagnosis
  - barium swallow first - narrowing site of lesion (shelf or annular lesion) – localizes tumor
  - esophagoscopy - biopsy for tissue diagnosis and resectability/extent of tumour
  - bronchoscopy - for upper and mid esophageal lesions due to high incidence of spread to tracheobronchial tree
  - CT scan (chest/abdomen): for staging - adrenal, liver, lung, bone metastases
  - trachesophageal U/S
  - CXR, bone scan, LFTs - for metastases staging (see Table 3)

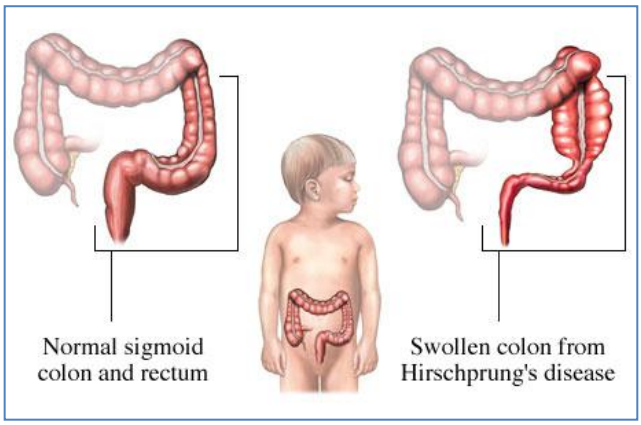
Table 3. Staging of Esophageal Carcinoma

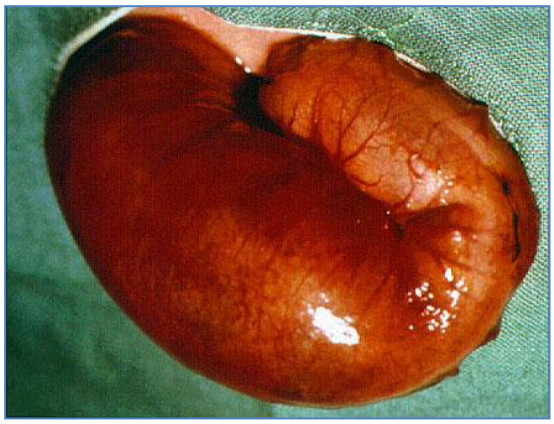
Stage	Criteria	Prognosis (5 year survival)
I	Lamina propria or submucosa	80%
II	Extension to muscularis propria	33%
III	Extension to regional nodes	15%
IV	Distant metastases or involvement of continuous structures	0%

GASTROINTESTINAL Pathology:
HIRSCHPRUNGS DISEASE

HIRSCHSPRUNG'S DISEASE ("*CONGENITAL AGANGLIONIC MEGACOLON*"):

- **= *Functional* Large Bowel Obstruction due to Atonic Bowel.**
- **Aetiology:**
  - Congenital
- **Pathogenesis:**
  - Section of Large Bowel is NOT Innervated → :. Paralysed/Atonic → Bowel Obstruction
- **Morphology:**
  - Typically in the Descending Colon <30cm Long. **(:. Distal Bowel Obstruction)**
  - Atonic Section is ***Narrowed***
  - Proximal Bowel is ***Dilated*** (Due to Functional Obstruction)
- **Clinical Features:**
  - **Presentation:**
    - **If Severe:**
      - Presentation within 2-3days after Birth
      - →Delayed Meconium (>48hrs) Defecation @ Birth
      - → Abdo Distension
      - →Vomiting
    - **If Mild:**
      - Presentation in Late Infancy
      - → Abdo Distension
      - → Constipation & Diarrhoea
- **Diagnosis:**
  - Barium Enema
  - Anorectal Manometry (Used to measure contractility in the Anus & Rectum)
  - Rectal Biopsy - for Lack of Ganglion Cells
- **Treatment:**
  - **Surgery** – Resection of Aganglionic Bowel & Reanastomosis of Normal Bowel to Anus.
- **Complications:**
  - Enterocolitis
  - Death





GASTROINTESTINAL Pathology:
INFLAMMATORY BOWEL DISEASES

INFLAMMATORY BOWEL DISORDERS (CROHN'S DISEASE/ULCERATIVE COLITIS):

- **Aetiology:**
  - **Genetic + Autoimmunity (15% FamHx)**

Risk Factors	Protective Factors
*Smoking (For Crohn's) Western Lifestyle (For Both)	*Smoking (For Ulcerative Colitis) Appendectomy (For Ulcerative Colitis) Breastfeeding (For Crohns)

- **General Pathophysiology:**
  - **Genetic + Autoimmunity → Exaggerated Inflammation to Gut Flora → ↑↑Inflammation:**

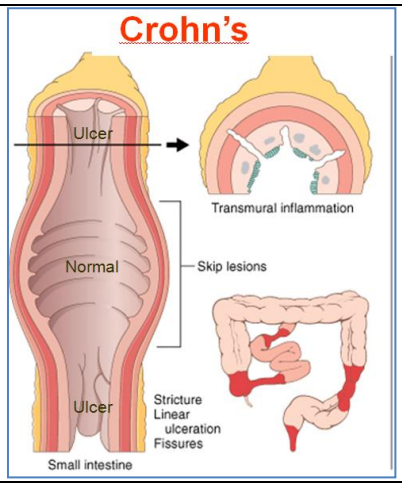
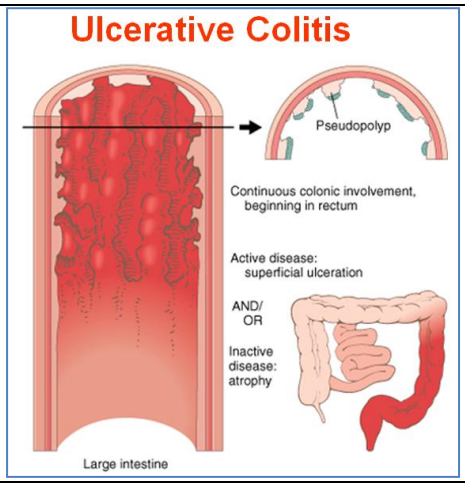
- **Common Features:**

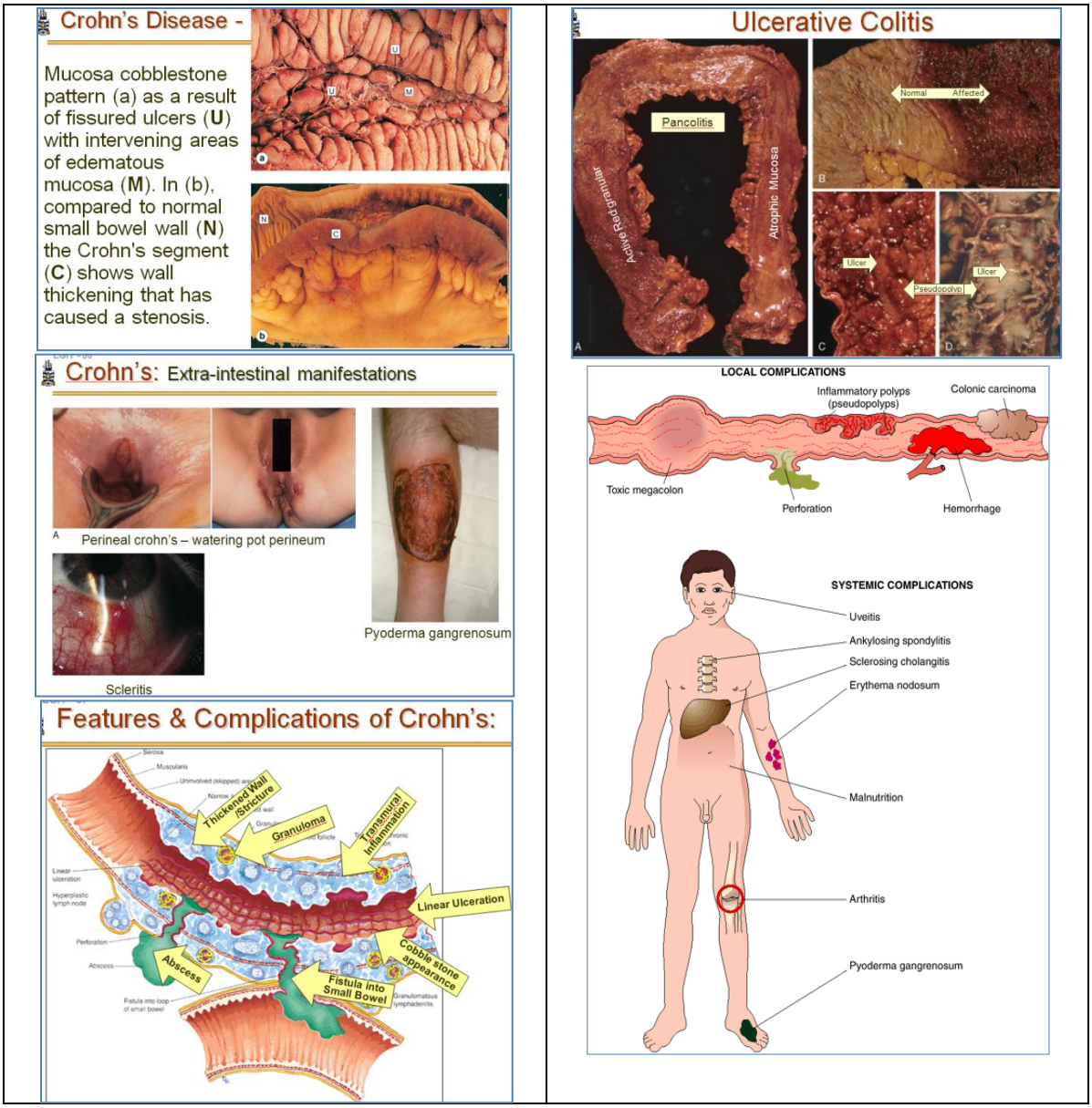
Extra-Intestinal Manifestations	Primary Sclerosing Cholangitis (Primary Biliary Cirrhosis) Arthritis Skin – Pyoderma Gangrenosum Eye Problems
Common Intestinal Symptoms	****Abdominal Pain/Severe Internal Cramps** ****Vomiting/Diarrhoea** ****Rectal Bleeding**

- **Distinguishing Features:**

	Crohn's Disease (CD)	Ulcerative Colitis (UC)
Location of Onset	Starts @ Terminal Ileum	Starts @ Rectum. Spreads Proximally
Location in GIT	*Anywhere* in GIT (Mouth-Anus)	Colon ONLY
Anus Involvement	YES	NO
Distribution	Patchy (Skip Lesions)	Continuous Area of Inflammation
Inflammation Depth	Can be FULL Thickness	Epithelial Lining ONLY
Defecation	Porridge-Like. Sometimes Steatorrhoea	Mucous-Like. +Blood
Tenesmus	NO	**YES**
Fever	**YES**	NO
Fistulae	**YES**	NO
Weight Loss	**YES**	NO

  - **Morphology:**

Crohn's Disease	Ulcerative Colitis
	

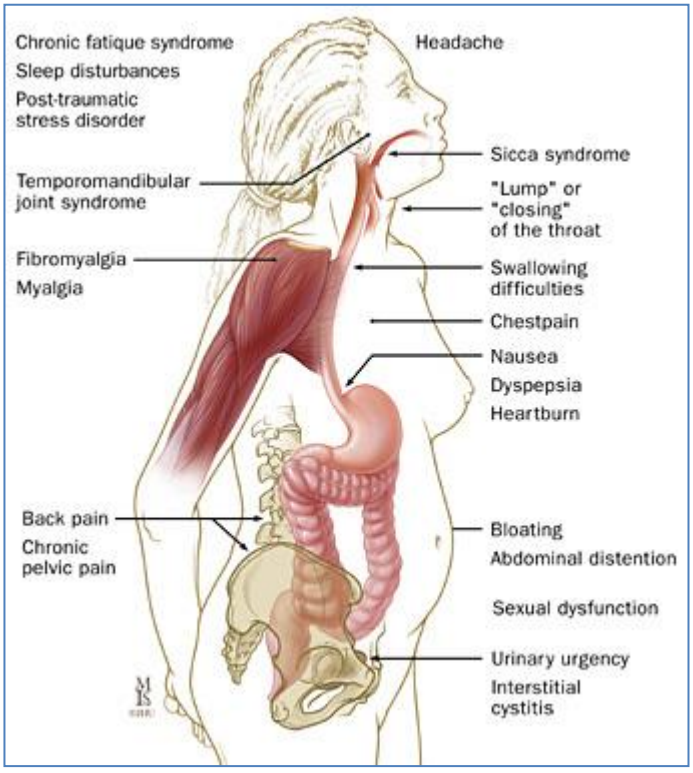


- **Diagnosis:**
  - **Colonoscopy + Biopsy**
- **General Treatment:**
  - **Corticosteroids – (*Prednisone*)**
  - **DMARDs – (*Infliximab*)**
  - **Or Chemotherapy Drugs – (*Sulfasalazine* / *Azathioprine* / *Methotrexate*)**.
  - **Surgery – (Indicated in** 75% of Crohn's; & 20% of Ulcerative Colitis**)**
  - **Yearly Colonoscopy Surveillance –(Colon Cancer)**
- **Complications:**
  - **Toxic Megacolon –** (Common in UC; Rare in Crohns → Dilation, Stasis & Gangrene)
  - **Bowel Perforation – (**Typically Crohns**)**
  - **Fistulae – (**Typically Crohns**)**
  - **Anal Fissures– (**Typically Crohns**)**
  - **↑Risk of Colorectal Cancer**

GASTROINTESTINAL Pathology:
IRRITABLE BOWEL SYNDROME

IRRITABLE BOWEL SYNDROME/'SPASTIC COLON'

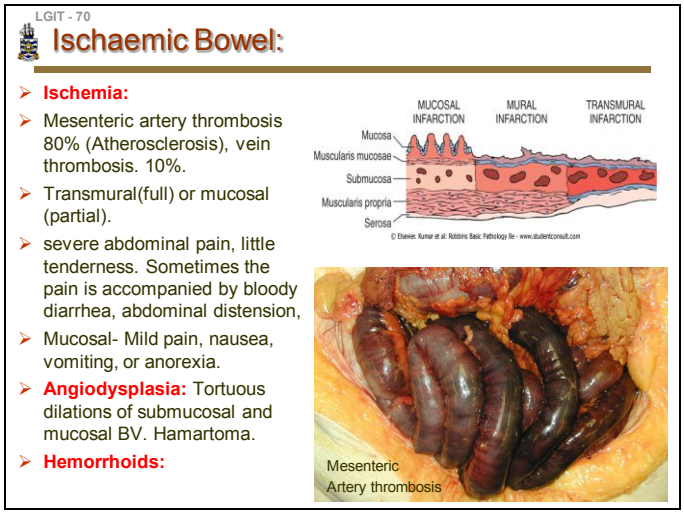
- **Aetiology:**
  - **Unknown – IBS = An *'Umbrella Term'* / Diagnosis of *Exclusion*.**
  - **Triggers:**
    - Stress/Anxiety/Depression
    - Pain
    - Autonomic Irregularities
    - Gut Hypersensitivity
- **Pathogenesis:**
  - **A Functional Disorder – NO PATHOLOGY!**
  - NB: ANY RED FLAGS (Acute Onset/Anaemia/Fever/Blood/Wt Loss) SUGGEST OTHER PATHOLOGY.
- **Morphology:**
  - NO PATHOLOGY!
- **Clinical Features:**
  - Abdominal Pain/Discomfort/Bloating Related to Defecation
  - Chronic Duration >3mths
  - Alternating Bowel Habits (Diarrhoea or Constipation) +/- Tenesmus
- **Investigations – Normal**
  - ***Need to Exclude Other DDxs:**
    - **Stool OCP – (**Parasites**)**
    - **Stool Culture – (**SI-Bacterial Overgrowth**)**
    - **Allergy Testing – (**Lactose Intolerance**)**
    - **Duodenal Biopsy – (**Coeliac Disease**)**
  - **IF >50yrs – Colonoscopy – (*Bowel Cancer*)**
- **Management:**
  - **Diet** – Avoid Foods if Intolerant. Add Fibre
  - **Anti-Diarrhoeals - (*Loperamide*)**
  - **Probiotics – (*Yoghurts, Tablets, Etc*)**



GASTROINTESTINAL Pathology:
ISCHAEMIC BOWEL

ISCHAEMIC BOWEL:

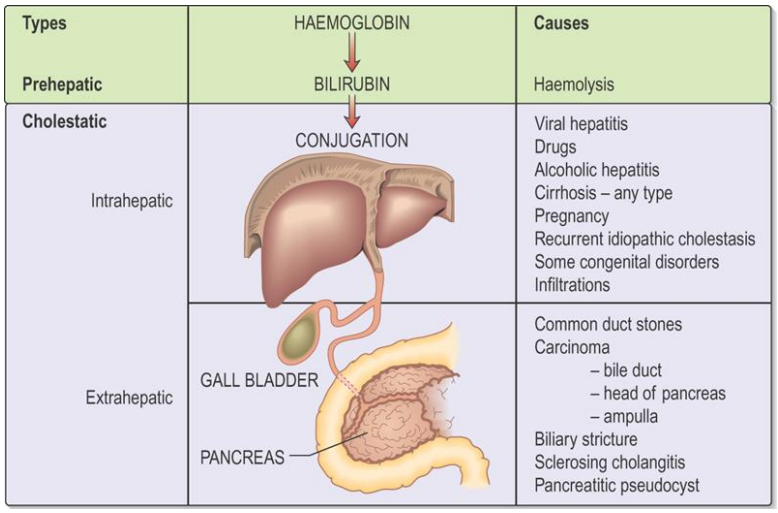
- **Aetiology:**
  - **Mesenteric Thromboembolism – (Eg. AF, Atherosclerosis)**
  - **Aortic Dissection → Occlusion of Coeliac Trunk/SMA/IMA**
  - **Segmental Strangulation (Hernia/Volvulus)**
- **Pathogenesis:**
  - **Mesenteric Thromboembolism → Mesenteric Ischaemia → Bowel Infarction**
- **Clinical Features:**
  - **Early:**
    - Rapid-Onset Severe *Peri-Umbilical Pain*.
    - Nausea & Vomiting
    - Forcefull Defecation
    - Haematochezia (If Large Bowel)
  - **Later:**
    - **Peritonitis – (**Guarding, Rigidity & Rebound Tenderness**)**
    - **Abdo Distension**
    - **Absent Bowel Sounds**
- **Investigations:**
  - **ECG – (**AF**)**
  - **Coags – (**Hypercoaguability**)**
  - **Abdo XRay – (**Thickened Bowel Wall, Pneumatosis Intestinalis**)**
  - **CT – (Definitive)**
  - **Mesenteric Angiogram – (Definitive)**
  - **ABG – (**Metabolic Acidosis**)**
- **Management:**
  - **Reperfusion Reperfusion Reperfusion!!**
    - **Anticoagulation - (*Warfarin* with *Heparin* Cover)**
    - **Thrombolysis – (*TPA*)**
  - **Decompression:**
    - ***NG-Tube* Insertion**
  - **Antibiotics:**
    - ***AGM* – *Ampicillin* + *Gentamicin* + *Metronidazole***
  - **Surgery – If Late Signs/Perforation:**
    - ***Bowel Resection & Colostomy***
  - **(+/- B-Blockers – (*Carvedilol*))**
  - **(+/- *Digoxin* (If AF))**
- **Complications:**
  - **Perforation**
  - **Sepsis**
  - **Lactic Acidosis**



HEPATOBILIARY Pathology:
JAUNDICE

JAUNDICE:

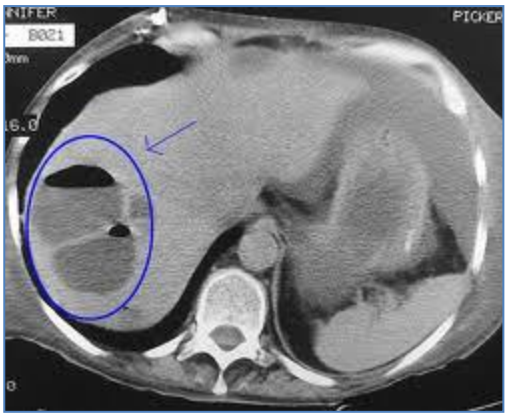
- **Definition:**
  - Jaundice = "Icterus" = Yellow Pigentation of the skin/sclera due to *EXCESS BILIRUBIN in the Blood*.
  - **2 Types of Hyperbilirubinaemia:**
    - ***Unconjugated* (Prehepatic/Haemolytic) Hyperbilirubinaemia**
    - ***Conjugated* (Posthepatic) Hyperbilirubinaemia**
- **Aetiology – Many Diseases Cause Jaundice:**
  - **Hepatitis – (Viral, Alcoholism, Cancer, Gall Stones, Cholangitis)**
- **Pathophysiology:**
  - ***Unconjugated* Hyperbilirubinaemia (Pre-Hepatic/Haemolytic Jaundice):**
    - **Defective *Upstream Conjugation*.**
    - **Common Causes – (Haemolysis, Gilbert's, Physiological Jaundice of Newborn)**
    - **LFT – (↑Unconjugated Bilirubin)**
    - **Clinical Picture – (PALE Urine; DARK Stools)**
  - ***Conjugated* Hyperbilirubinaemia (Cholestatic/Obstructive/Post-Hepatic Jaundice):**
    - **Defective *Downstream of Conjugation***
    - **Common Causes – (Gallstones, H.Of.Pancreas Tumour, Primary Biliary Sclerosis, Sclerosing Cholangitis, Liver Tumours):**
    - **LFTs – (↑Conjugated Bilirubin)**
    - **Clinical Picture – (DARK Urine; PALE Stools)**
- **Differentiating Between Causes:**
  - **Jaundice + Young + Malaise** → Hepatitis
  - **Jaundice + Elderly + Weight Loss** → Carcinoma
  - **Jaundice + Abdo Pain** → Biliary Obstruction (Gallstones)
  - **Jaundice Epidemic** → Hep A Virus
  - **Jaundice + Recent Shellfish Consumption** → Hep A Virus
  - **Jaundice + Hx of IVDU/Injections/Tattoos** → Hep B/C Viruses
  - **Jaundice + Sodomy/Prostitution** → Hep B Virus
  - **Jaundice + Family Hx of Jaundice** → Gilbert's Disease.
  - **Jaundice + Fevers/Rigors** → Cholangitis or Liver Abscess.

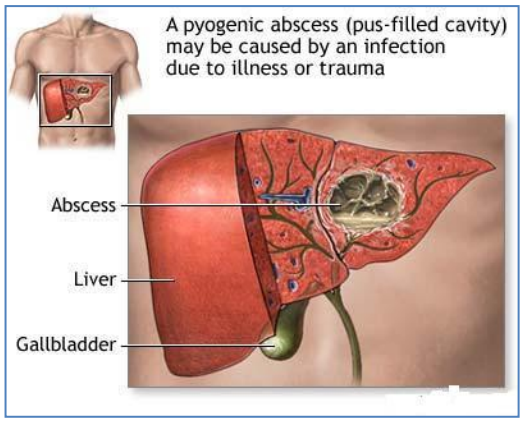


HEPATOBILIARY Pathology:
LIVER ABSCESSES & CYSTS

LIVER ABSCESSES:

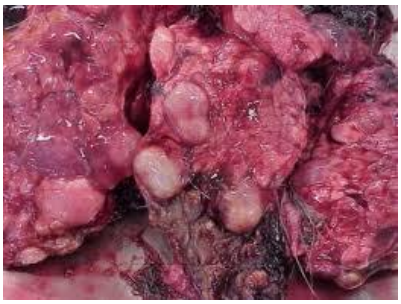
- **Aetiology:**
  - Infection – Typically E-Coli (or other Anaerobes):
    - Intra-Abdominal Sepsis
    - Biliary Sepsis (in Elderly)
- **Pathogenesis:**
  - Abscess formation
- **Morphology:**
  - Pyogenic Abscess
- **Clinical Features:**
  - Broad Spectrum – Asymptomatic → Acute Illness.
  - **Symptoms:**
    - Malaise, Fever, Rigors
    - Anorexia, Weight Loss
    - Vomiting
    - Abdo Pain
  - **Signs:**
    - Pt may be Septic, Jaundiced, and/or Febrile.
    - Tender, Enlarged Liver
- **Investigations:**
  - ↑Alk/Phos
  - ↑Bilirubin
  - Blood Cultures +
  - **Abdo USS – (Definitive)**
  - **Abdo CT – (Rule out HCC)**
- **Treatment:**
  - ***USS-Guided Aspiration***.
  - **Antibiotics – (*Metronidazole* + *Gentamicin*)**
- **Prognosis:**
  - If Single, good Prognosis.
  - If Multiple – 80% Mortality.

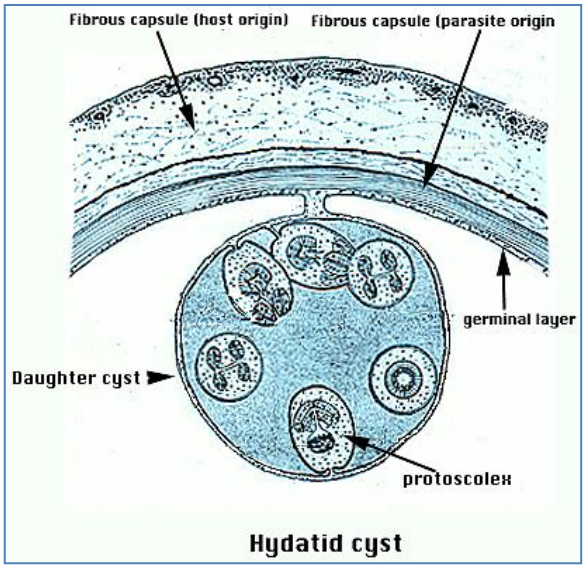




HYDATID DISEASE OF THE LIVER ("*Hydatid Cysts*"):

- **Aetiology:**
  - *Echinococcus Granulosus* Infection (**Parasite**)
    - Spread by dogs and sheep.
- **Pathogenesis:**
  - Cyst Formation (Single or Multiple) – Typically in Lower R-Lobe
- **Morphology:**
  - **3-Layered Cysts:**
    - Outer – Derived from Host
    - Intermediate – Laminated Layer
    - Inner – Germinal Layer that buds off "brood capsules" to form *Daughter Cysts*.
- **Clinical Features:**
  - May be Asymptomatic
  - May have Dull Ache in RUQ
- **Treatment:**
  - ***Albendazole*** (Antiparasitic)
  - **Surgical Aspiration – (Fine Needle or Open Surgery)**.

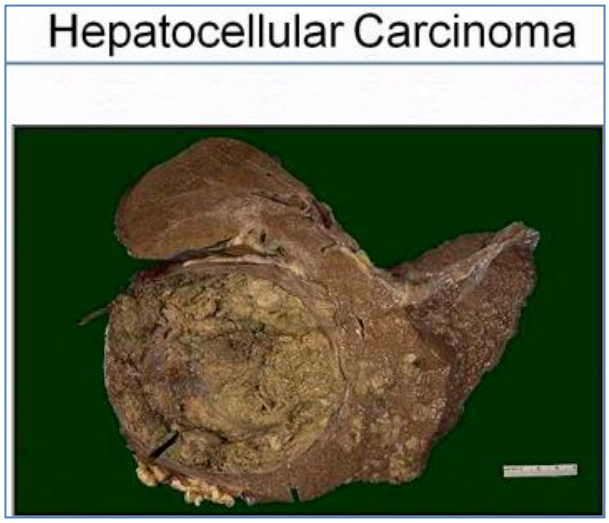




HEPATOBILIARY Pathology:
LIVER CANCERS

HEPATOCELLULAR CARCINOMA – Primary Liver Tumour:

- **Aetiology:**
  - EXTREME RISK in Chronic HepB & C
  - EXTREME RISK in Cirrhotics
- **Pathogenesis:**
  - ****1. Cirrhosis ALWAYS Precedes Hepatocellular Carcinoma:**
    - Eg. Alcoholic/Viral Hepatitis/Haemochromatosis
  - → ***Malignant*** **Neoplasm Formation**
- **Morphology:**
  - Single or Multiple.
  - Cells Resemble Hepatocytes
- **Clinical Features:**
  - **Symptoms:**
    - Fever, Night Sweats
    - Anorexia, Weight Loss
    - RUQ Pain
    - Jaundice, Itch
  - **Signs:**
    - Hepatic Encephalopathy / Flap
    - Small, Nodular Liver (Cirrhosis)
    - Ascites
    - NB: Suspect HCC if you see these signs in a Cirrhotic.
- **Investigations:**
  - **↑Serum a-Fetoprotein**
  - **LFTs – (*Everything's Raised*)**
  - **FBC – (↑MCV?, Infection?, Haemolysis/Retics)**
  - **USS Liver – (*Homogenous Mass*)**
    - **+/- FNA & Biopsy – (*For Grading*)**
  - **CT/MRI – (Staging)**
- **Treatment:**
  - **Surgery**
  - **NB: Chemo/Radio - *Unhelpful***
- **Complications - Metastasis:**
  - - Via Hepatic or Portal Veins
  - - Via Lymphatics
  - → Bones & Lungs
- **Prognosis:**
  - **POOR –** Average Survival 6mths.

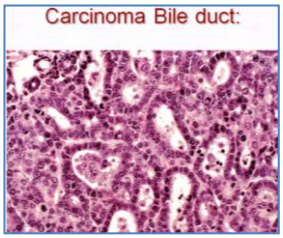


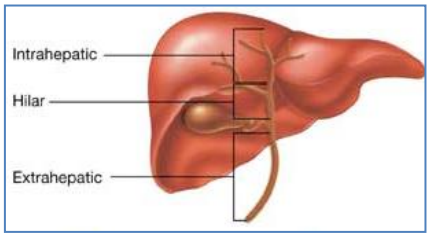
LIVER METASTASES – Secondary Liver Tumours (Most Common):

- **Aetiology:**
  - Metastasis from a Primary Tumour somewhere else.
  - Most Commons = Breast/Colorectal/Lung/Melanoma
- **Pathogenesis:**
  - Cancer @ Distant Site → Haematological/Direct Seeding → Metastasis
- **Morphology:**
  - **Macro:**
    - Multiple, Clearly-Demarcated Masses
- **Clinical Features:**
  - **Signs:**
    - Fever, Night Sweats
    - Anorexia, Weight Loss
    - RUQ Pain
    - Jaundice, Itch
  - **Symptoms:**
    - Cachexia
    - Hepatic Encephalopathy
    - Fevers/Sweats
    - Nausea
    - RUQ Pain
- **Investigations:**
  - **CT – (*Prognostic Purposes Only*)**
  - **LFTs – (*Everything Raised*)**
  - **FNA – (If 1^{o} Unknown – May be chemoresponsive)**
- **Management:**
  - **Palliative Chemotherapy**
  - **Analgesia**

CHOLANGIOCARCINOMA (Bile Duct Carcinoma):

- **= Malignant neoplasm of the Bile Ducts**
- **Aetiology:**
  - **Risk Factors:**
    - Bile Duct Cysts
    - Chronic Biliary Irritation:
      - Primary Sclerosing Cholangitis
      - Ulcerative Colitis
    - Hx of Parasitic Worm Infection
  - **(NOT ass'd with Hepatitis or Cirrhosis)**
- **Pathogenesis:**
  - **Malignant neoplasm of the Bile Ducts – May start anywhere along the Bile Ducts.**
    - → Biliary Obstruction
- **Morphology:**
  - **"*Adenocarcinoma*"**

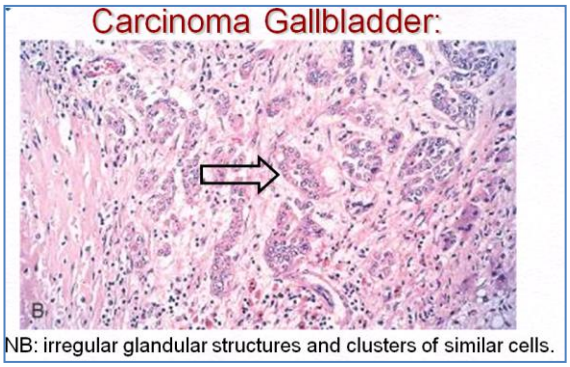




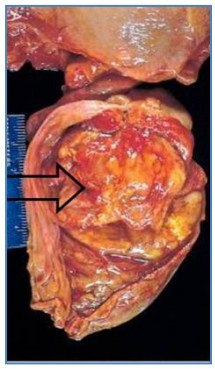
- **Clinical Features:**
  - **Signs/Symptoms:**
    - Fever, Chills
    - Anorexia, Weight Loss
    - **Posthepatic (Obstructive) Jaundice** – (Jaundice, Dark Urine, Pale Stools)
- **Investigations:**
  - **↑ALP/GGT; May have mild ↑ALT/AST**
  - **↑Conjugated Bilirubin**
  - **CT – (Dx & Staging)**
- **Treatment:**
  - **Surgery if Extrahepatic**
  - **If large, Liver Transplant**
- **Prognosis:**
  - **Poor -** 30% 5-year Survival

GALLBLADDER CARCINOMA:

- **Aetiology:**
  - Chronic Cholelithiasis (Gallstones)
- **Pathogenesis:**
  - Chronic Irritation/Inflammation of Gallbladder → Neoplasm
- **Morphology:**
  - Adenocarcinoma
- **Clinical Features:**
  - Females Common
  - **Symptoms:**
    - Vague Abdominal Pain
    - Anorexia
    - Weight Loss
- **Investigations:**
  - **LFT – (↑ALP/GGT)**
  - **CT – (Diagnosis & Staging)**
- **Management:**
  - **Surgical Resection if <Stage 3.**
  - **Palliative Chemotherapy if Metastatic**
- **Prognosis:**
  - Typically Late Diagnosis → Poor Prognosis



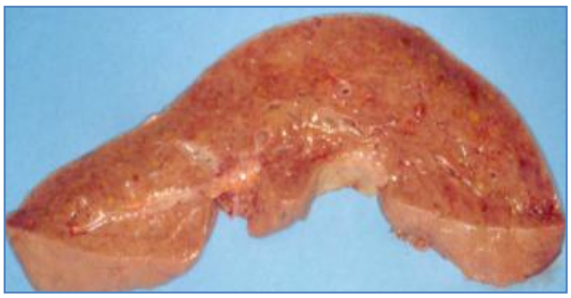
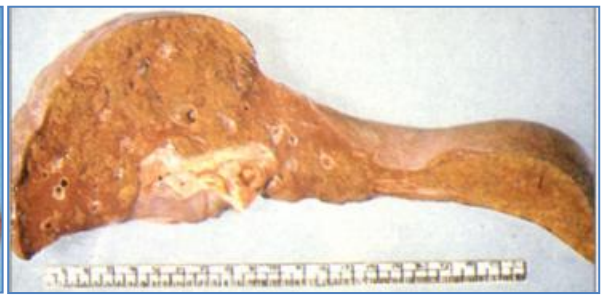
NB: irregular glandular structures and clusters of similar cells.



HEPATOBILIARY Pathology:
LIVER FAILURE & CIRRHOSIS

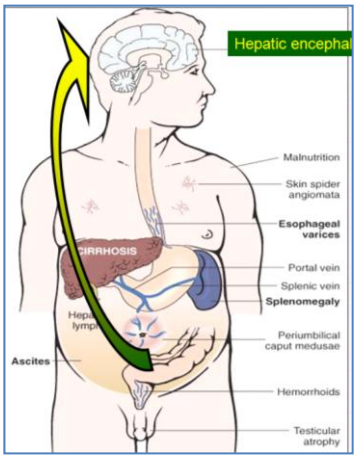
FULMINANT HEPATIC FAILURE:

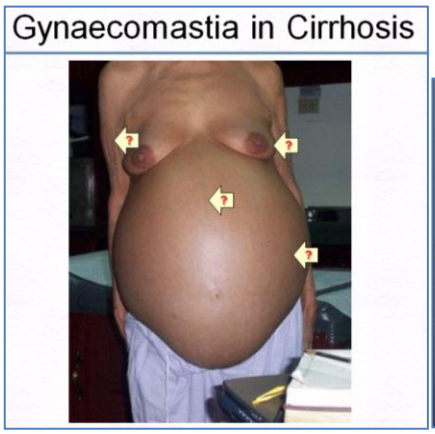
- **= Severe hepatic failure**
- **Aetiology:**
  - **Complication of Acute Hepatitis - Many Causes:**
    - **Viruses** – AB(D)E
    - **Drugs** – Paracetamol/Halothane/Antiepileptics/Ecstasy
    - **Toxins** – Amanita (Poison Mushrooms)
    - **Wilson's Disease**
    - **Autoimmune** Hepatitis
- **Morphology:**
  - Massive, Diffuse Necrosis throughout the Liver
- **Clinical Features:**
  - **Signs/Symptoms:**
    - Jaundice
    - Small Liver
    - Signs of Hepatic Encephalopathy (Within 2wks)
    - Fetor Hepaticus
    - Fever, Vomiting, Cerebral Oedema
- **Investigations:**
  - **FBC – (**?Aetiology**)**
  - **LFTs – (**↑Bilirubin, ↑ALT/AST**)**
  - **Coags – (**↓Coag Factors (Incl. Protrhombin & Factor V**)**
  - **Liver USS**
- **Treatment/Prognosis:**
  - **Treat Underlying Cause**
  - **Supportive Therapy.**
  - **If Coagulopathy – IV Vit.K, Platelets, Blood, or FFP.**
  - **Liver Transplant = Only Definitive Treatment**

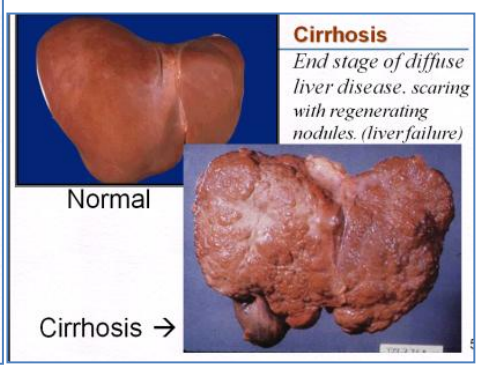



HEPATIC CIRRHOSIS

- **Aetiologies – Multiple Possible:**
  - Toxins – **Alcohol**/Drugs 60-70%
  - Infectious - Chronic **Viral** Hepatitis 10%
  - Biliary Disease (Eg. Obstruction/PBC) 10%
  - Congenital – 1° Haemochromatosis 5%
  - Cryptogenic Cirrhosis 5%
  - (Others – Rare: Wilson's [↑Copper], a1AT-Deficiency)
- **Pathogenesis:**
  - **(Cirrhosis = End-Stage of Diffuse Liver Disease → Liver Failure.)**
  - ***CHRONIC* Hepatocyte Injury → Necrosis → Nodular Fibrosis → Loss of Normal Function.**
- **Morphology:**
  - **Macro:**
    - Shrunken Liver
    - Nodules (Micro or Macro-Nodular depending on Aetiology)
    - Fibrous Septa
- **Clinical Features:**
  - **Signs & Symptoms:**
    - **Hepatic Encephalopathy (↑↑Ammonia in Bloodstream due to ↓↓Liver Breakdown)**
      - → Forgetfulness/Confusion/Irritability
      - → Tremor/Asterixis (Due to ↓Proprioception)
      - → Seizures/Coma
    - **Portal Hypertension:**
      - → Caput Medusae, Oesophageal Varices, & Haemorrhoids
      - → Splenomegaly
      - → Ascites, Peripheral Oedema
    - **Hyper-Oestrogen Secretion:**
      - → Spider Naevi (on chest. >3 is significant)
      - → Gynaecomastia
      - → Palmar Erythema (↑Vascularity of hands)
- **Lab Tests:**
  - **↓Serum Albumin**
  - **↑Prothrombin Time**
  - **↑ALT/AST – (Marked if decompensated)**
  - **↓Sodium (Hyponatraemia**
  - (NB: **Test Serum Copper & a1-AT in *Young Cirrhotics*** – [Screen for Wilson's and a1-AT-Def])
- **Treatment:**
  - **Eliminate/Treat Underlying Cause**
  - **Definitive Treatment = Liver Transplant.**
- **Prognosis:**
  - Irreversible
  - Death without Transplant

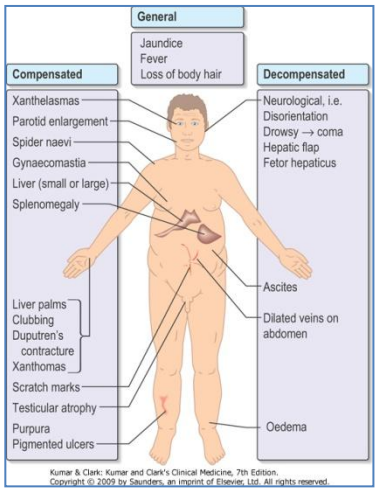






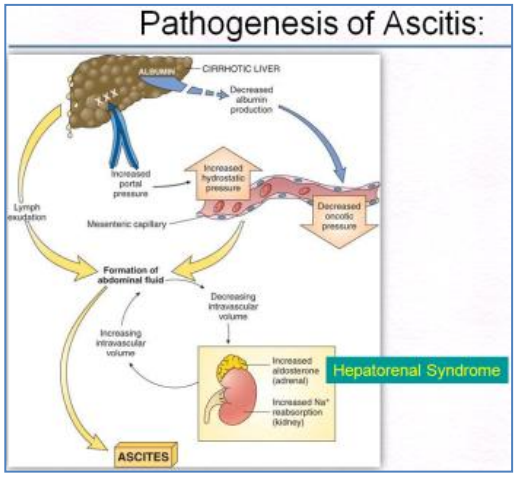
Signs & Symptoms of Acute & Chronic Liver Disease:

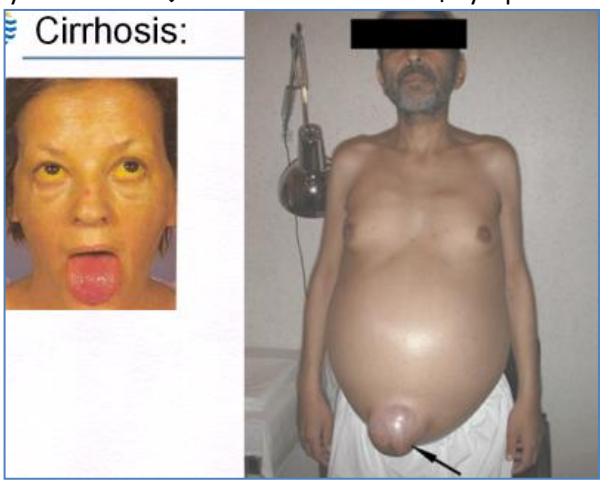
- **Acute liver Disease:**
  - **Symptoms:**
    - May be Asymptomatic
    - If Viral:
      - Malaise
      - Fever
      - Anorexia
  - **Signs:**
    - May be An-Icteric (No Jaundice)
    - May be Icteric (Jaundice)
    - Hepatomegaly
    - If Cholestatic – Pale Stools (No biliverdin) & Dark Urine (High urobilirubin).
- **Chronic Liver Disease:**
  - **Symptoms:**
    - May be Asymptomatic
    - Right Hypochondrial Pain (Hepatomegaly)
    - Abdominal Distension (Ascites) & Ankle Swelling (Fluid Retention)
    - Pruritis (Due to Jaundice)
    - Gynaecomastia, ↓Libido, Amenorrhoea (Endocrine Dysfunction)
    - Confusion/Drowsiness (Hepatic Encephalopathy)
  - **Signs:**
    - Jaundice
    - Fever
    - Loss of Body Hair
    - **Compensated:**
      - Spider Naevi on Chest
      - Gynaecomastia
      - Hepatomegaly/Splenomegaly (Portal Hypertension)
      - Clubbing
      - Duputren's Contracture (Alcoholic Cirrhosis)
      - Xanthelasmas (Eyes) & Xanthomas (Hands)
      - Striae
      - Testicular Atrophy
      - Purpura
    - **Decompensated:**
      - CNS Signs of Hepatic Encephalopathy (Drowsiness → Coma, Hepatic Flap)
      - Ascites
      - "Caput Medusa" (Dilated Abdo Veins due to Portal Hypertension)
      - Peripheral Oedema



ASCITES:

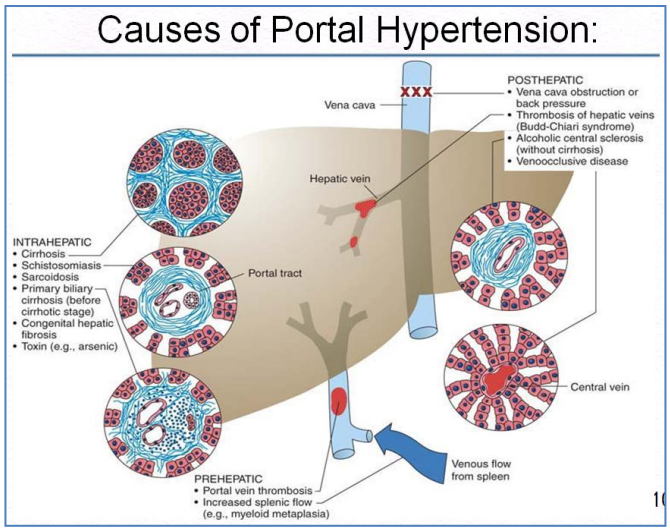
- **Pathogenesis:**
  - **Cirrhotic Liver →**
    - 1. Portal Hypertension → ↑Hydrostatic Pressure →↑Lymph Exudate
    - 2. Hypoalbuminaemia → ↓Oncotic Pressure → ↑Lymph Exudate
  - **+ Hepatorenal Syndrome:**
    - Ascites formation →↓Intravascular Volume → ↑Aldosterone → ↑Fluid Retension → ↑Intravascular Volume → ↑Hydrostatic & ↓Oncotic Pressure → ↑Lymph Exudate.





PORTAL HYPERTENSION:

- **Pre-Hepatic:**
  - Portal Vein Thrombosis/Occlusion → Backup into Mesenteric Veins
- **Intra-Hepatic:**
  - Cirrhosis (Alcoholic/Viral/Biliary/Congenital)
  - Primary Biliary Cirrhosis
  - Schistosomiasis
- **Post-Hepatic:**
  - IVC Obstruction → Backup into Hepatic Vein
  - Thrombosis in Hepatic Veins
  - Alcoholic Central-Vein Sclerosis (without Cirrhosis)



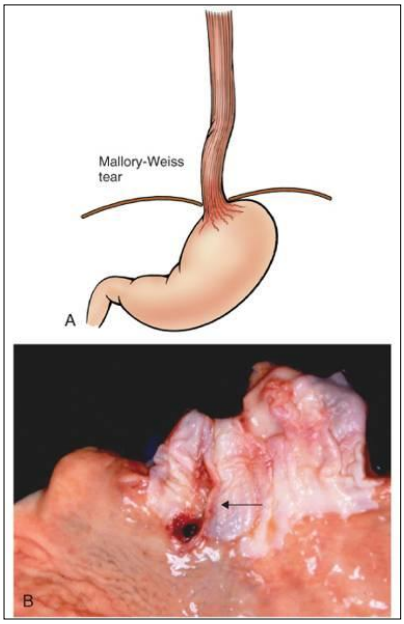
HEPATIC ENCEPHALOPATHY (Hepatic Coma)

- **Aetiology:** Azotaemia (↑↑Ammonia in Bloodstream due to ↓↓Liver Breakdown)
  - → Forgetfulness/Confusion/Irritability
  - → Tremor/Asterixis (Due to ↓Proprioception)
  - → Seizures/Coma

GASTROINTESTINAL Pathology:
MALLORY WEISS TEAR

Mallory Weiss Syndrome:

- **= Oesophageal laceration – (Longitudianl tear)**
- **Aetiology:**
  - **↑Intra-Abdominal Pressure** (Eg. Coughing/Severe/forced vomiting)
  - **Over Eating** - Boerhaave syndrome (Pacific Islands)
  - **Hiatas Hernia** in 75%.
- **Pathogenesis:**
  - ↑Intra-Abdominal Pressure → Tears Mucosa @ the Gastro-Oesophageal Junction → Minor Bleeding
- **Morphology:**
  - Linear Mucosal Tear @ the Gastro-Oesophageal Junction
- **Clinical Features:**
  - Dysphagia
  - Pain
  - Haematemesis
- **Diagnosis:**
  - **Endoscopy**
- **Treatment:**
  - **Typically Self-Limiting**
  - **Rarely – Surgery**.
- **Complication:**
  - **Minor Upper GI Bleeding**



MALLORY WEISS TEAR

Definition
❑ tear in gastric mucosa on lesser curvature near gastroesophageal junction (20% straddle junction, 5% in distal esophagus)

Etiology
❑ due to rapid increases in gastric pressure (i.e. retching)
❑ most patients alcoholics

Signs and Symptoms
❑ hematemesis +/– melena, classically following an episode of retching

Management
❑ 90% stop spontaneously; NG (if needed) and replacement of lost volume
❑ if persistent: endoscopy with electrocautery or surgical repair

LOWER GI BLEEDING

Definition
❑ bleed distal to ligament of Treitz

Signs and Symptoms
❑ hematochezia (see Figure 8)
❑ anemia
❑ occult blood in stool
❑ rarely melena

Differential Diagnosis
❑ massive bleed: diverticulosis, angiodysplasia, occasional UGI site duodenal ulcer (DU), aortoenteric fistula
❑ intermittent bleed: hemorrhoid, colitis, anorectal lesions
❑ occult bleed: neoplasms, colon cancer
❑ systemic diseases (always consider in cases of UGI or LGI bleeding)
- blood dyscrasias (e.g. thrombocytopenia)
- coagulation disorders (e.g. disseminated intravascular coagulation (DIC))
- vascular malformations (e.g. Osler-Weber-Rendu syndrome)
- vasculitides (e.g. Henoch, polyarteritis)

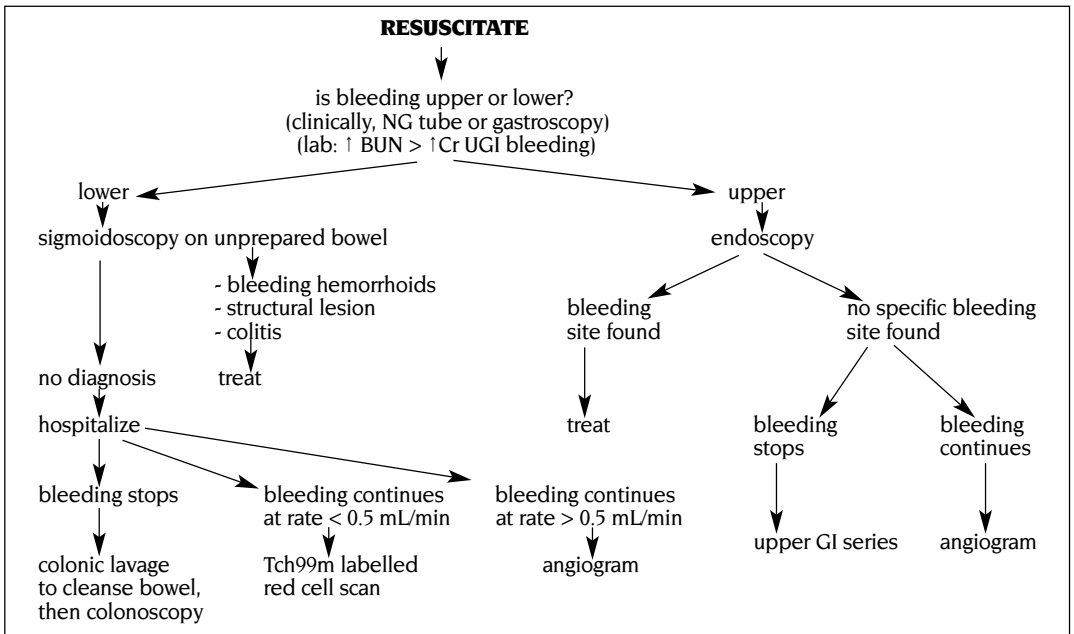
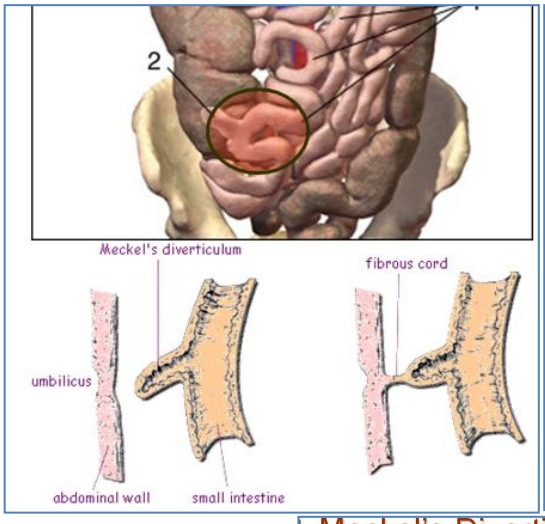


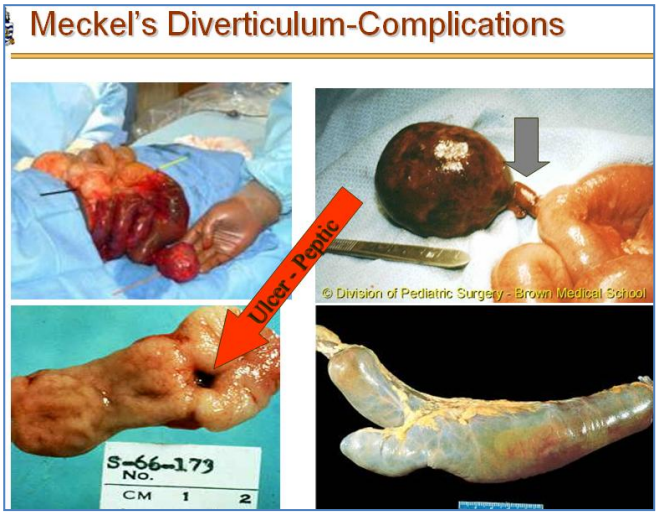
Figure 8. Approach to Hematochezia

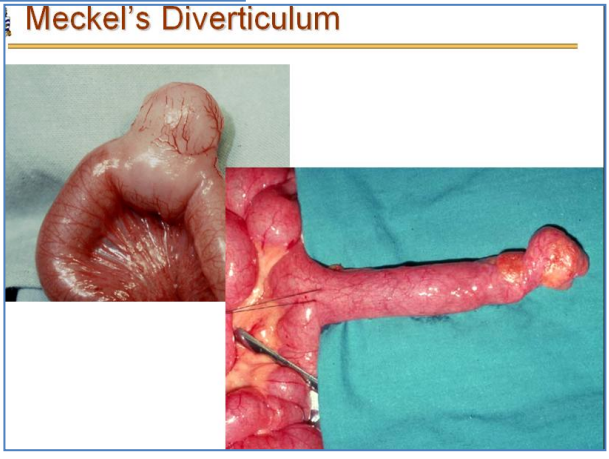
GASTROINTESTINAL Pathology:
MECKEL'S DIVERTICULUM

MECKEL'S DIVERTICULUM:

- **Aetiology:**
  - Congenital Malformation of the Small Intestine
- **Pathogenesis:**
  - Defect in Embryogenesis → Single Diverticulum in SI just deep to the Umbilicus.
- **Morphology:**
  - **A "True" Diverticulum – Ie. All Layers**
  - **"Rule of Twos":**
    - 2cm Long
    - <2ft from Ileocaecal Valve
    - 2 Tissues – (Pancreatic & Gastric)
- **Clinical Features:**
  - **"Rule of Twos":**
    - 2% of Population
    - Presents at 2yrs old
  - **Presentation @ 2yrs Old:**
    - Majority are Asymptomatic
    - **Initially:** Malena
    - **Then:** Severe Upper Abdo Pain (Small Bowel Obstruction/Volvulus/Intussusception)
    - **May present like Appendicitis**
- **Complications:**
  - Bleeding, Peptic Ulceration, Infection, Torsion, Ischaemia, Necrosis, Herniation, Obstruction.
- **Diagnosis:**
  - **Clinical Dx**
  - **Ultrasound/CT**
- **Treatment:**
  - **Surgery**



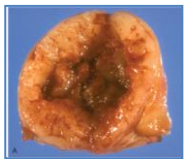




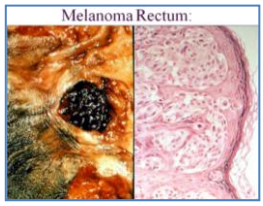
GASTROINTESTINAL Pathology:
MISCELLANEOUS GI TUMOURS

GISTS – GI STROMAL TUMOURS (AKA: LEIOMYOMAS):

- (Smooth Muscle/Mesenchymal Tumours) – (Can Occur in GIT/Liver/Peritoneum/Lungs)
- **Macro:** Mesenchymal/SM Popypoid or Solid Mass
- **Micro:** Mixed Stromal Elements (Ie. Smooth Muscle "Spindle Cells"/Neuronal/Mixed)
- Some Malignant Potential



MELANOMA:

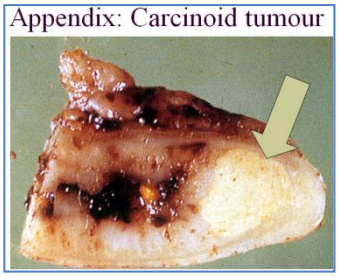


INTESTINAL LYMPHOMA

- MALT Lymphoma

CARCINOID TUMOUR (ALREADY COVERED)

- Neuroendocrine Serotonin-Secreting Tumour of the Enterochromaffin Cells
- **3 Common Sites =** Appendix, Terminal Ileum, Rectum.
- **Asymptomatic Unless Metastasis → "Carcinoid Syndrome":**
    - Hot Flushes
    - Bronchoconstriction/Cyanosis
    - Watery Diarrhoea/Abdo Pain
    - Cardiac Abnormalities – Pulmonary Stenosis or Tricuspid Regurgitation
    - Hepatomegaly

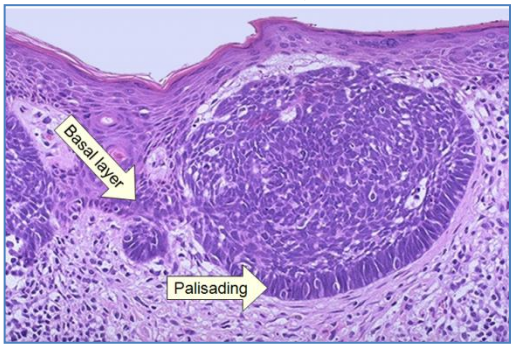


SQUAMOUS CELL CARCINOMA (PERI ANAL):

- Rectum & Anal Canal

BASALOID CARCINOMA:

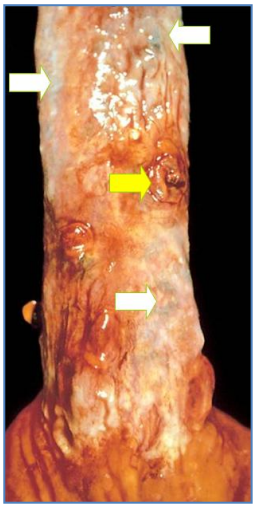
- Rectum & Anal Canal
- Like BCC of Skin appearance
- Tumour Grows *Down* – Locally Invasive (But NOT Metastatitc)
- **Micro:** Palisading (Ie. Linearly Arranged Cells – Like a *Palace Wall*) Cells around Tumour Nests.



GASTROINTESTINAL Pathology:
OESOPHAGEAL VARICES

OESOPHAGEAL VARICES (Due to Portal Hypertension):

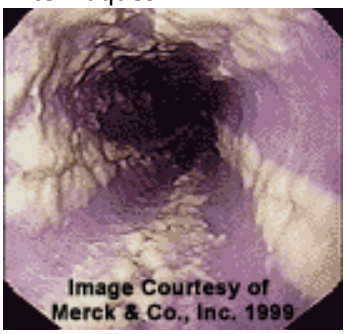
- **= Engorged Veins in Lower Oesophagus**
- **Aetiology:**
  - **Portal Hypertension:**
    - **Prehepatic –** Portal Vein Thrombosis
    - **Intrahepatic –** Cirrhosis
    - **Posthepatic –** Hepatic Vein Obstruction)
- **Pathogenesis:**
  - Portal Hypertension → Porta-Systemic Shunt → Varices of Lower Oesophageal Veins
- **Morphology:**
  - Like Varicose Veins, but of the Oesophagus (Tortuous, Engorged Veins)
- **Clinical Features:**
  - **Hematemesis**
  - **Malena**
  - **Anaemia – (**Dyspnoea, Dizziness, Light-Headed, Syncope**)**
  - **Cirrhotic Symptoms:**
    - Jaundice
    - Confusion
    - Hepatic Flap
    - Small, Nodular Liver
  - **Alcoholic Symptoms:**
    - Intoxication
    - Dupuytrens Contraction
- **Investigations:**
  - **LFTs – (**↑*Transaminases*, ↓*Albumin*, ↑ALP/GGT**)**
  - **FBC – (***Anaemia***)**
  - **B12/Folate – (**Deficiency if Alcoholic**)**
  - **UEC – (**Electrolyte Disturbances**)**
  - ****Endoscopy – (Definitive Dx)**
- **Management:**
  - **Thiamine Replacement + B12/Folate**
  - **PPI – (*Omeprazole*)**
  - **+/- Surgery – (*Endoscopic Band Ligation*) – If Severe or Active Bleeding**
- **Complications:**
  - **Rupture → Massive GI-Bleeding → Shock / Death**



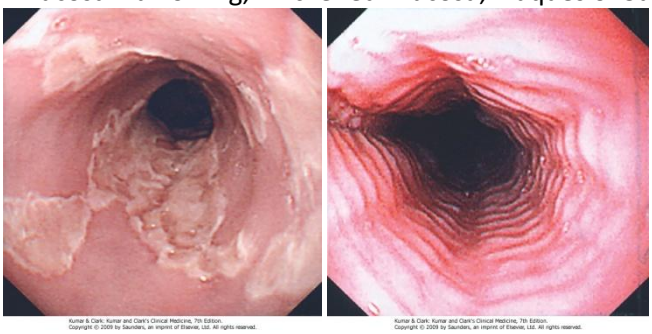
GASTROINTESTINAL Pathology:
OESOPHAGITIS

OESOPHAGITIS:

- **Aetiology:**
  - **Oesophageal Infections – Immunocompromised** → Candida/Herpes/CMV
  - **Allergic Oesophagtitis** – Food Allergy
  - **GORD**
- **Morphology:**
  - **Candida** → Characteristic White Plaques



  - **Eosinophilic** → Mucosal Furrowing, Thickened Mucosa, Plaques of Surface Exudate

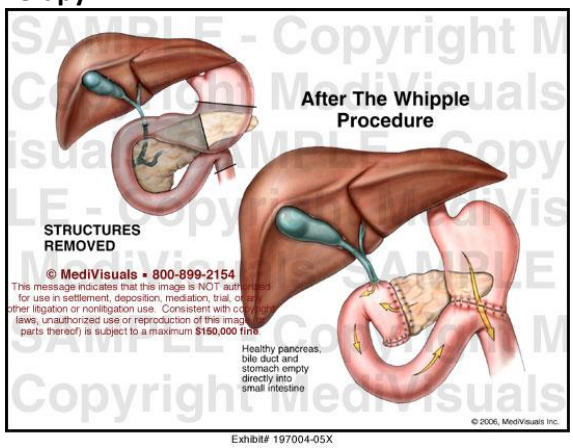


- **Clinical Features:**
  - Dysphagia
  - Heartburn
  - Oesophageal Pain
- **Investigation:**
  - **Endoscopy + Biopsy MCS**
  - **FBC + Diffs – (*Eosinophilia* if Allergic)**
  - **HIV Screen**
- **Management:**
  - **If Candida – (Oral *Fluconazole*)**
  - **If Allergic – (*Inhaled Fluticasone* / *Budesonide*)**

HEPATOBILIARY Pathology:
PANCREATIC CANCER

PANCREATIC ADENOCARCINOMA (Exocrine/Ductal Tumour):

- **Aetiology:**
  - Risk Factors – (Smoking, Alcohol, Chronic Pancreatitis, Diabetes, Familial Syndromes)
- **Pathogenesis:**
  - Carcinogenesis → ***Adeno*carcinoma** Arises from Exocrine Glands
- **Clinical Features:**
  - **60% - Head of Pancreas → Presents with Syx of CBD Obstruction (Eg. Jaundice)**
  - **Typically in Older Age (60-80yrs)**
  - **Signs/Symptoms:**
    - **NB: Asymptomatic until Advanced Diasease**
    - Pain – Mid Epigastrium → Back
    - Obstructive Jaundice
    - Steatorrhoea
    - Palpable *Gallbladder* (Courvoisers Sign)
    - Migratory Thrombophlebitis (Trousseau Syndrome)
    - Diabetes
    - **Anorexia & Weight Loss
    - **Extreme Fatigue
    - **Depression
- **Investigations:**
  - **CT / USS**
  - **CEA (Carcino-Embryonic Antigen) –** (Used to Monitor Treatment).
- **Treatment:**
  - **Surgery - (*"Whipple Procedure"*** if H.O.P. Tumour; of ***Distal Pancreatectomy*** if Tail)
  - **Palliative Chemotherapy**



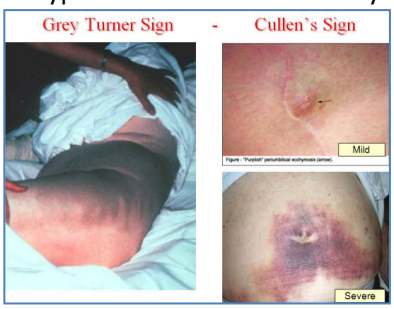
- **Complications:**
  - Metastases
  - Obstructive Jaundice

- **Prognosis:**
  - **Very Poor – Advanced @ Diagnosis**
  - **25% 1yr Survival; 5% 5yr Survival**

HEPATOBILIARY Pathology:
PANCREATITIS

ACUTE PANCREATITIS:

- **Aetiology:**
  - **50% - Gallstones (Cholelithiasis) → Ampulla/Common Bile Duct Obstruction**
  - **40% - Alcohol Abuse**
  - 10% - Infections/Metabolic(↑Ca[hyperparathyroidism], DKA, Uraemia, Pregnancy)/ Trauma/Ischaemia/Duodenal Ulcer/Scorpion Venom/Drugs/Unidentified
- **Pathogenesis:**
  - ***Autodigestion of Pancreas → Reversible Inflammation* → +/- Necrosis**
  - **Can → *'Systemic Inflammatory Response Syndrome'*→**
    - →Shock
    - →Acute Renal Failure
    - →Acute Respiratory Distress Syndrome
- **Clinical Features – *Acute Medical Emergency*:**
  - **Signs/Symptoms:**
    - **Epigastric/Abdo Pain** – Precipitated by *Large Meal OR Alcohol*
    - **Peritonitis – (**Guarding + Rigidity)
    - **Vomiting**
    - **If Haemorrhage** → Hypotension & Shock → Grey Turner's & Cullen's Signs



  - **Local Complications:**
    - Pancreatic Abscess/Infection
    - Pseudocysts
    - Duodenal Obstruction
  - **Systemic Complications:**
    - Jaundice
    - DIC (Diss.Iv.Coag)
    - ARDS (Resp. Distress)
    - Acute Renal Failure
- **Diagnosis:**
  - **1. Rule out Other Causes of "Acute Abdomen"**
    - #Appendix/#Diverticulitis/#Peptic Ulcer/#Cholecystitis/Isch.Bowel/ Bowel Obstruction.
  - **↑Serum Amylase (Within 24hrs)**
  - **↑Serum Lipase (After 72hrs/3days)**
  - **FBC – Neutrophil Leukocytosis**
  - **↑Alk Phos (If Biliary Stasis)**
  - **↑Bilirubin**
  - **(ERCP/MRCP if Indicated)**
  - **!!NOT Biopsy!!! – *HAZARDOUS.***
- **Prognosis:**
  - **80% - Self-Limiting with Supportive Treatment**
  - 20% - Life Threatening & 1/More-Organ Failure (Requires ICU)
- **Treatment:**
  - **Supportive – (**NBM, Fluids, Electrolytes, Analgesia**)**
  - **Aggressive – If Severe Pancreatitis +/- Organ Failure:**
    - ICU Admission
    - +/- Prophylactic Antibiotics (If Necrosis)
    - +/- Surgery (Rarely)

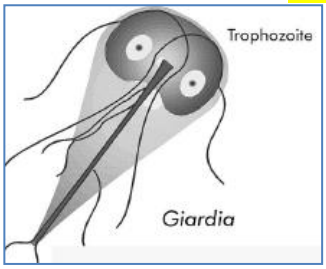
CHRONIC PANCREATITIS

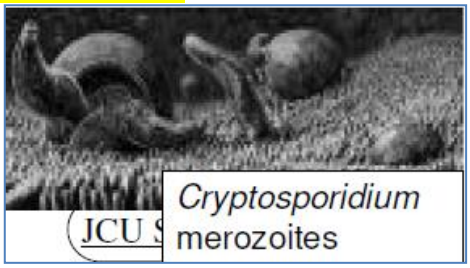
- *= "Repeated Bouts of **Mild-Moderate Pancreatitis** with **Exocrine Atrophy** & **Fibrosis**"*
- **Aetiology:**
  - ****Alcohol Abuse**
  - Also...Biliary Disease/Hypercalcaemia/Pancreatic Divism/Familial Pancreatitis/Cyst.Fibrosis.
- **Pathogenesis:**
  - Chronic Alcoholism/Other → Ductal Obstruction → ***Autodigestion of Pancreas → Pancreatitis***
- **Clinical Features:**
  - **Signs/Symptoms:**
    - Intermittent Pain
    - Weight Loss
    - Steatorrhea
    - Jaundice
    - Secondary Diabetes
  - **Diagnosis:**
    - **1. Rule out Other Causes of "Acute Abdomen"**
    - ↑Serum Amylase (Within 24hrs)
    - ↑Serum Lipase (After 72hrs/3days)
    - FBC – Neutrophil Leukocytosis
    - ↑Alk Phos (If Biliary Stasis)
    - ↑Bilirubin
  - **Complications:**
    - **Progressive Destruction of the Pancreas → ↓↓Pancreatic Function:**
      - **↓Exocrine Functions:** ↓Pancreatic Enzymes → **Nutritional Malabsorption**
      - **↓Endocrine Functions:** ↓Insulin & Glucagon → **Diabetes Mellitis**
    - **Pseudocysts**
    - **Duct Obstruction**
    - **Pancreatic Cancer**
  - **Treatment:**
    - **Supportive – (**NBM, Fluids, Electrolytes, Analgesia**)**
    - **Aggressive – If Severe Pancreatitis +/- Organ Failure:**
    - **Manage Bile-Duct Disease if Present**
    - **If Pancreatic Failure – (*Creon Forte + Insulin*)**

GASTROINTESTINAL Pathology:
PARASITIC GUT INFECTIONS

PARASITIC GUT INFECTIONS (Protozoa & Helminths):

- **Transmission:**
  - Faecal-Oral – (Ingestion of Dormant Cysts in Contaminated Food/Water)
- **Diagnosis:**
  - Stool Samples (Looking for cysts) under Direct Microscopy
  - Antigen Testing
- **Prevention:**
  - Boiling Water to Eliminate Cysts
  - Good Hygiene
  - Avoiding Faecal Contact
- **Examples:**
  - ***GIARDIA*:**
    - **Pathogenesis:**
      - Not Toxigenic; Rather, it covers the brush border → Malabsorption
    - **Diagnosis:**
      - Cysts in Stools
    - **Complications:**
      - Chronic Infection
      - Malabsorption
        - → Malnutrition
        - → Fatty Stools
    - **Treatment:**
      - ***Metronidazole***
  - ***CRYPTOSPORIDIUM:***
    - **Transmission:**
      - Ingestion of oocysts (Contaminated Drinking Water/Public Pools)
      - Can survive Chlorination
    - **Pathogenesis is mostly unknown.**
      - Possibly induces inflammatory response → Disrupts absorptive surface
      - Damages Villi → Crypt Cells Replicate faster to replace them → Immature cells in the villus → Poor absorption.
    - **Treatment:**
      - ***Nitazoxanide*** (Normally Self-Limiting if Immunocompetent)
    - **Long term Effects:**
      - AIDs patients don't recover → Chronic Infection
    - **Diagnosis:**
      - Cysts in Stools
  - ***ENTAMOEBA HISTOLYTICA* - (The Amoebic Dysentery):**
    - **Transmission:**
      - Ingestion of oocysts (Faecal Oral)
    - **Pathogenesis:**
      - Intestinal Invasions → Ulcerations → Dysentery (Bloody Diarrhea)
    - **Diagnosis:**
      - Cysts in Stools
    - **Management:**
      - ***Metronidazole***



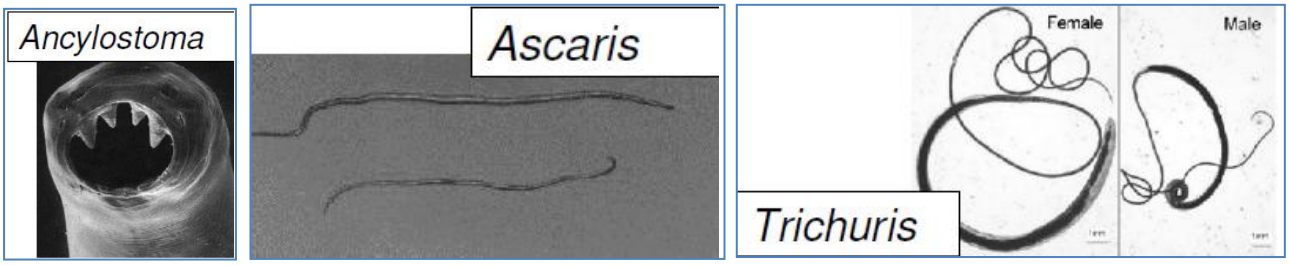


HELMINTHIC INFECTIONS

- (NB: Clinically most important group are the 'soil transmitted helminths')

1. **Infection via swallowing infected eggs**
    a. *Ascaris lumbricoides* (roundworm)
    b. *Trichuris trichiura* (whipworm)
2. **Infection via Active skin penetration**
    a. *Strongyloides stercoralis* (threadworm)
    b. *Ancylostoma duodenale* (hookworm)

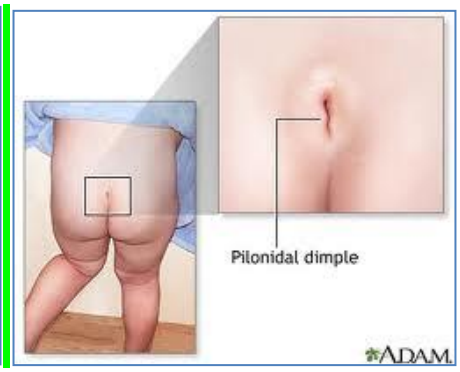
- **Management:**
    - ***Albendazole***



GASTROINTESTINAL Pathology:
PILONIDAL SINUS

Pilonidal Sinuses/Cyst/Abscess:

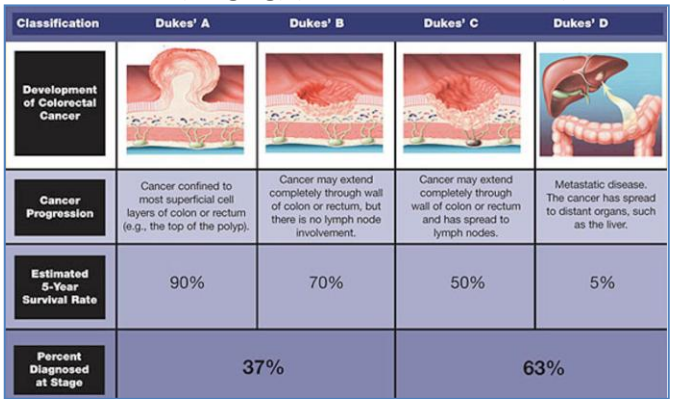
- **= a cyst or abscess near/on the natal cleft of the buttocks that often contains hair and skin debris**
  - (NB: Pilonidal = "nest of hair")
- **Aetiology:**
  - Ingrown Hair/Excessive Sitting/Excessive Sweating
- **Clinical Features:**
  - Very Painful. Men>Women.
  - ++Adolescents.
- **Management:**
  - Excision



GASTROINTESTINAL Pathology:
POLYPS & COLON CANCER

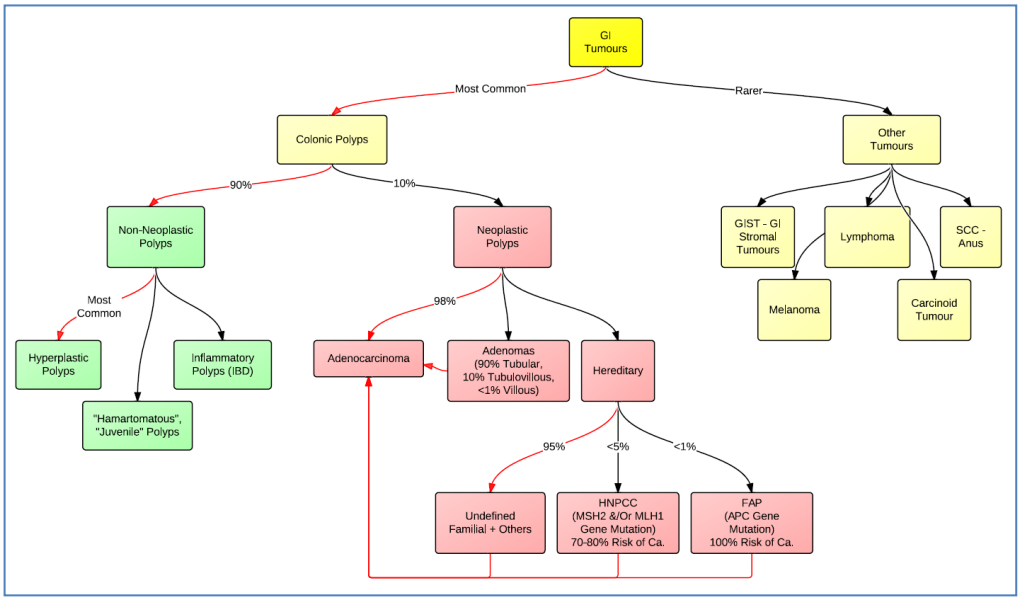
COLONIC TUMOURS – General Information:

- (NB: 98% of *Neoplastic* Colonic Tumours are Adenocarcinomas)
- **Aetiology – Risk Factors for Colonic Neoplasia:**
  - **Age (50yrs +) –** 90% of CRC is diagnosed over age 50yrs.
  - **Pre-Existing Polyps** – Most are Benign; Others (Adenomas) can become Malignant.
  - **Genetics/FamHx**– (**HNPCC** & **FAP** are best known) – 80-100% Lifetime Risk of Cancer
  - **Inflammatory Bowel Disease – Eg. CROHN'S DISEASE or ULCERATIVE COLITIS:**
  - **Diet – (**High Fat/Low Fibre /Low Calcium/Low Folate)
  - **Smoking**
- **Sporadic Vs. Inherited:**
  - **>95% Sporadic CRCs – (**Typically **LEFT/Descending (Distal) Colon** - (↑Toxin/Carcinogen Exposure))
  - **<5% Inherited CRCs – (**Typically **RIGHT/Ascending (Proximal) Colon)**
- **General Pathogenesis:**
  - **Mutation (Inherited/Sporadic) → Cell-Cycle Dysregulation →Dysplasia→Carcinoma**
- **Clinical Features:**
  - **Asymptomatic in Early Stages.**
  - **Alternating in Bowel Habit**
  - **Change in Stool Shape –** (Eg. Thin, Ribbon-like Stool)
  - **Cramping/Colicky Pains/Discomfort/Bloating**
  - **Rectal Bleeding – (NB:** Detected by a '*Faecal Occult Blood Test*' **[FOBT]**)
    - **Left Sided (Sporadic) Ca:** Frank GI-Bleeding
    - **Right Sided (Familial) Ca:** Occult Bleeding, Anaemia
  - **Red Flags – Anorexia, Fever, Night-Sweats, Weight Loss, Fatigue, Anaemia**
- **Complications:**
  - Perforation, Peritonitis, Abscess, or Fistula
  - Metastasis → Death
- **Investigations:**
  - Faecal Occult Blood Test
  - Colonoscopy – (Polypectomy/Biopsy)
  - Imaging – CT/PET/Barium Swallow
  - Genetic Testing – (IF FamHx)
  - FBC – (Anaemia)
- **Management:**
  - **Colonoscopic Polypectomy/Biopsy – (Grading)**
  - **CT/PET/MRI – (Staging) (TNM or "Duke's A-D")**



  - **Bowel Resection & Colostomy**
  - **Targeted Therapy –** *Cetuximab/Panitumumab* (Anti Epi.Growth.Fac.Receptor Ab.)
  - **+/- Chemotherapy**
  - **+/- Radiotherapy**
- **Prevention:**
  - **Screening -** FOBT or Regular Colonoscopies (1-2yrs) if 'At Risk', Polypectomy
  - **Diet -** ↓Fat, ↑Fruits/Veg, ↑Unprocessed Fibre, ↑Calcium.
  - **Lifestyle -** ↑Physical Activity, ↓Alcohol, øSmoking

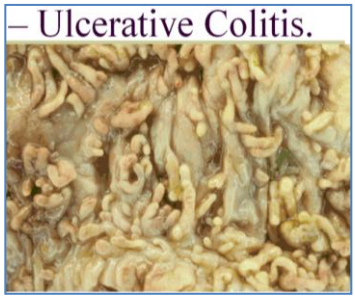
Colonic Tumours Specifics – POLYPS = *Most Common*:



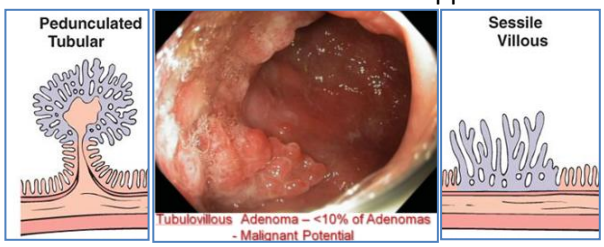
- **90% = Non-Neoplastic Polyps (Low Malignant Potential):**
  - **HYPERPLASTIC POLYPS:**
    - Most Common Non-Neoplastic Polyps
    - Descending Colon
    - **Macro:** Multiple, Small, *Sessile* (No Stalk – cf. *'Pedunculated'*) polyps. – "Nipple-Like"
    - **Micro:** Deeper Crypts, ++Goblet Cells (:. ++Mucous Secretion), No Dysplasia. – "Saw-Tooth"
    - **Benign**

  - **HAMARTOMATOUS/JUVENILE POLYPS:**
    - **"Hamartomas" =** Non-Malignant; Grows at the *Same Rate* as Surrounding Tissues
    - **Common in Peutz-Jegers Syndrome – (Autosomal Dominant)**
    - **Macro:** Large, Irregular,
    - **Micro:** Dilated Glands, Normal Cells; Abnormal Arrangement, No Dysplasia
    - **Benign**, BUT can → Obstruction

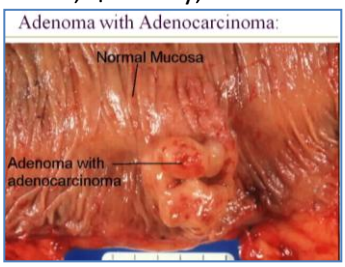
  - **INFLAMMATORY POLYPS/PSEUDOPOLYPS**
    - **In Inflammatory Bowel Disease** (Crohn's/Ulcerative Colitis)



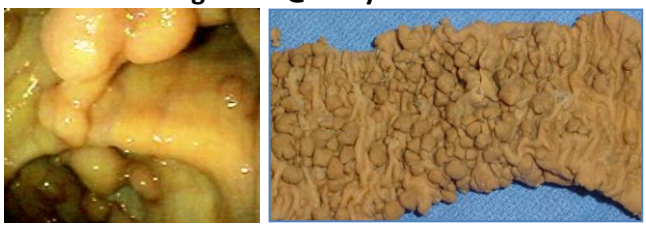
- **10% = Neoplastic Polyps (High Malignant Potential):**
  - **ADENOMAS:**
    - (Pedunculated):
      - **90% - 'Tubular':** - Look like Smooth Mushrooms
      - **<10% - 'Tubulovillous':** - Mixed Morphology
    - (Sessile):
      - **<1% - 'Villous':** - Wart-like Appearance



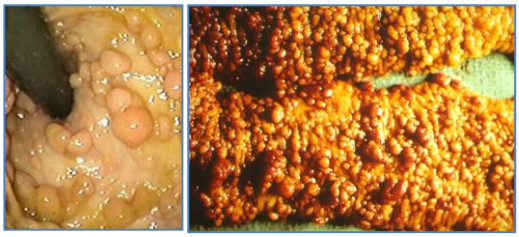
  - **98% - ADENOCARCINOMA OF THE COLON**
    - May start as Adenomas (Sporadic) or as Heriditary (HNPCC/FAP).
    - **Epidemiology:** ↑Western, ↑Elderly, 2nd Most Common Internal Malignancy.



  - **<1% - HERIDITARY NON-POLYPOSIS COLON CANCER – (HNPCC):**
    - **Autosomal Dominant** → 70-80% Lifetime Risk of Cancer
      - →A Few Adenomatous Polyps (With Cancerous Potential)
    - **HNPCC Also Increases Lifetime-Risk of many other *Non-Colonic* Cancers.**
      - (Ie. CRC/Endometrial/Gastric/Ovarian/Intestinal/Ureter/Renal Pelvis)
    - ***"Amsterdam II Criteria"* – To meet a Diagnosis of HNPCC:**
      - **1. 3+ Relatives with HNPCC**
      - **2. >1 Relative must be 1st-Degree of the other 2.**
      - **3. FamHx spans >2 Generations**
      - **4. >1 cases diagnosed @ <50yo.**



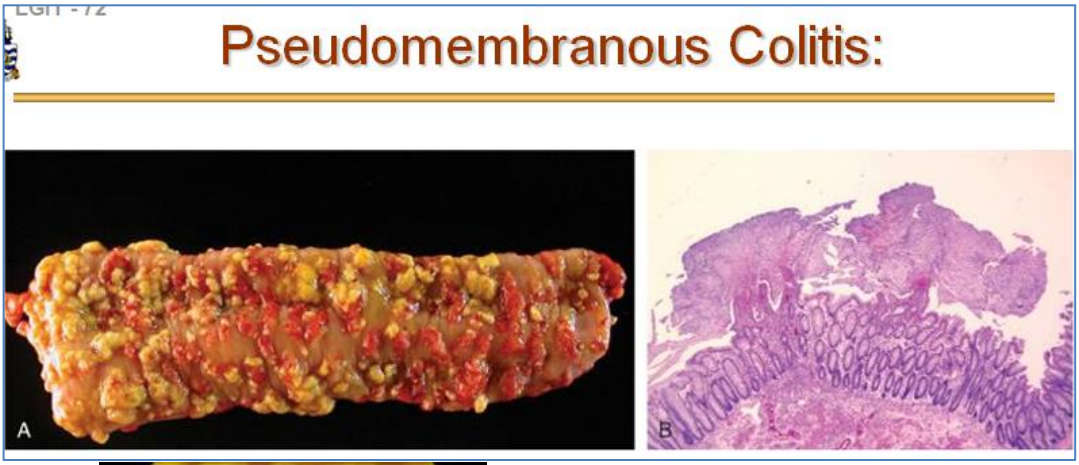
  - **RARE 1% - FAMILIAL ADENOMATOUS POLYPOSIS – (FAP):**
    - **Autosomal Dominant** → THOUSANDS of Adenomatous Polyps → 100% Risk of Cancer
      - NB: ≈90% are benign; but there's too many to cut out.
    - **FAP Also Increases Lifetime-Risk of many other *Non-Colonic* Cancers.**
      - (Ie. CRC/Endometrial/Gastric/Ovarian/Intestinal/Ureter/Renal Pelvis)

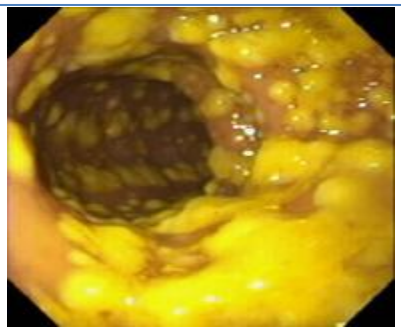


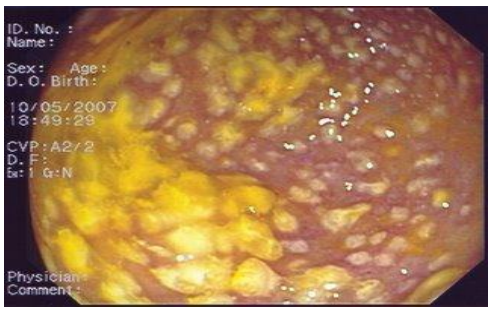
GASTROINTESTINAL Pathology:
PSEUDOMEMBRANOUS COLITIS

PSEUDOMEMBRANOUS COLITIS

- **Aetiology:**
  - Antibiotics
  - Clostridium Difficile Overgrowth (Directly Cytotoxic)
- **Pathogenesis:**
  - **Clostridium Difficile** – (Normally Controlled by Commensal Bacteria)
    - **Antibiotics kill Commensal Bacteria** → C.difficile Overgrowth → Produce *Enterotoxins*
    - **Inflammation** → Forms a Fibrous Pseudomembrane
- **Morphology:**
  - Mucosal Inflammation, Ulceration & Bleeding
  - Pseudomembranes – Fibrous Sacs full of Purulent Debris. They adhere strongly to Mucosa.
- **Clinical Features:**
  - **Symptoms:**
    - Onset Usually within 2days of taking Antibiotic; Persists for 2wks after ceasing Antibiotic.
    - Fever
    - Abdo Cramps
    - Profuse Watery Diarrhoea (<10x/day)
    - Haematochezia
- **Diagnosis:**
  - **Colonoscopy – (***Pseudomembrane,* + Screen for DDx [Crohns/UC/Cancer]**)**
  - **Stool Sample – (**Clostridium Difficile Assay**)**
- **Treatment:**
  - **Stop Causative Antibiotic**
  - **Anti-Clostridial Antibiotic - (*Metronidazole* / *Vancomycin*)**
  - **Pro-Biotics**
  - **+ Supportive Rehydration/Electrolytes**
- **Complications:**
  - Dehydration/Electrolyte Imbalance
  - Perforation
  - Toxic Megacolon



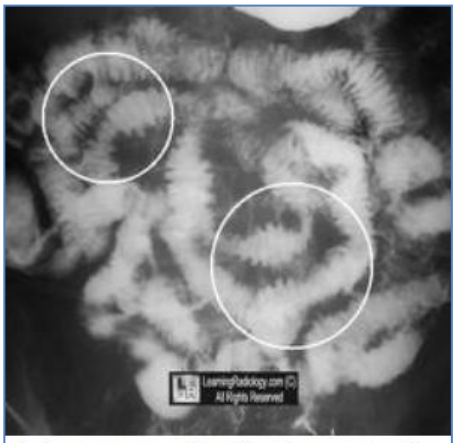




GASTROINTESTINAL Pathology:
RADIATION ENTERITIS

RADIATION ENTERITIS

- **Aetiology:**
  - Chronic Radiotherapy Side Effect
  - (NB: Often Pelvic Irradiation :. Ileum & Rectum are Most Common)
- **Pathogenesis:**
  - >40Gray of Radiation → Damages the Intestine
    - → Muscle Fibre Atrophy
    - →Ischaemia & Ulcerative Changes
    - → Fibrotic Strictures → Obstruction
- **Morphology:**
  - Muscle Atrophy
  - Ulcerative Changes
  - Fibrotic Strictures
- **Clinical Features:**
  - **Acute Sx** – Nausea, Vomiting, Diarrhoea, Abdo Pain. (Improves within 6wks of Radiation)
  - **Chronic Sx** – Symptoms for >3mths.
    - Primarily Pain due to Obstruction.
    - Malabsorption may occur
    - Bowel Frequency, Tenesmus
- **Treatment:**
  - Symptomatic (Self-Limiting)
  - Surgery ONLY for Obstruction/Perforation.
- **Complications:**
  - May → *Chronic Irritable Bowel Syndrome*

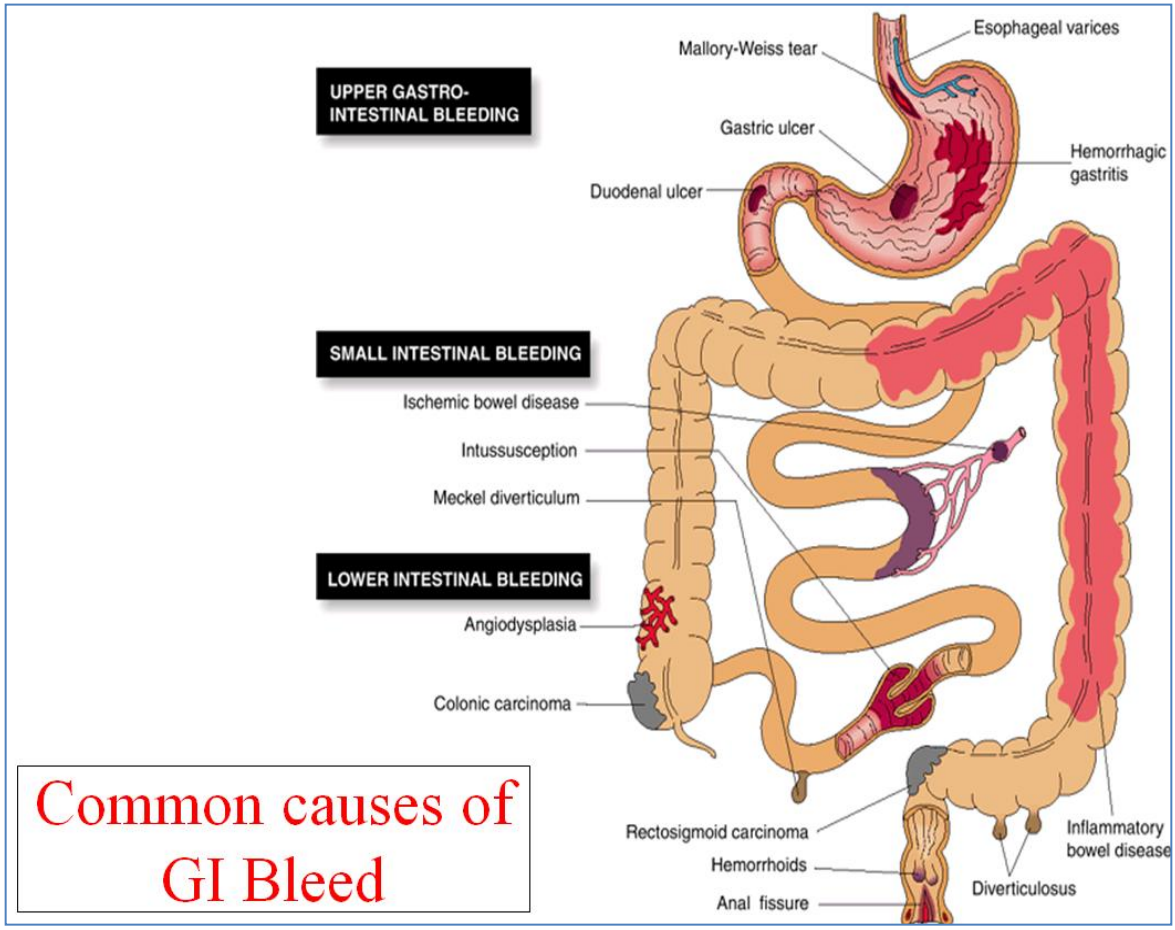


picket fence-Radiation enteritis

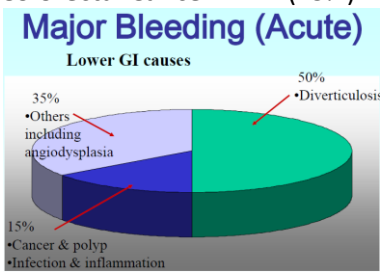
GASTROINTESTINAL Pathology:
RECTAL BLEEDING DDX

GI BLEEDING:

- A common problem – most people will have some form of GI bleeding during their life time!
- Can be Trivial/life-threatening
- May be painful or painless
- Underlying pathology may or may not be serious
- **Terms:**
  - **Haematemesis**
    - Vomiting blood – may be fresh or denatured (dark)
    - Can be VERY SERIOUS
    - Usually Implies bleeding from the ***Stomach***
    - **Priority** = Get Large-Bore IV Access & Cross-Match Blood type (Because people can bleed out very quickly from the stomach)
  - **Haematochezia**
    - Rectal Bleeding
    - The passage of bloody stools
    - Major implies ***Upper GIT Bleeding***
    - Minor implies ***Lower GIT Bleeding***
  - **Melaena**
    - black tar-like stool (usually from upper GI bleeding)
    - Usually implies ***Upper GIT Bleeding***
- **Occult (Hidden) GI Bleeding:**
  - GI tract bleeding may result in *occult blood loss* (occult = hidden)
  - An important cause of Chronic Anaemia
  - Detected by testing stool for 'faecal occult blood'

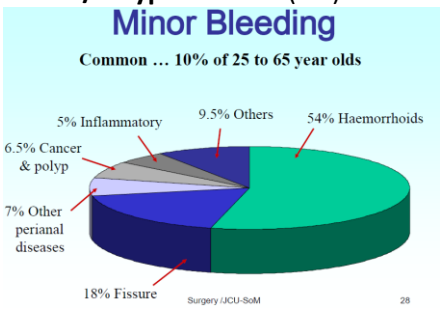


MAJOR RECTAL BLEEDING:

- **= "IF the Pt Requires Resuscitation as a Result" – (Ie. Tachy, Hypotensive, Pale, Dyspnoea, ALOC)**
- **Commonest Aetiologies - *Upper GI-Bleeding*:**
  - **Peptic Ulcer**
  - **Duodenal Ulcer**
  - **Oesophageal Varices**
- **Also Some Lower GI:**
  - **Diverticulosis** (50%)
  - **Angiodysplasia** (35%)
  - **Colorectal Cancer** (15%)
  - 

- **TIP: *Colour of Blood Determines Rate of Bleeding, & Often its Location*:**
  - **Eg. Frank Blood = Massive Bleeding, Or More Distal Origin.**
  - **Eg. Blackened Blood = Slower Bleeding, Or Stomach/Oesophageal Origin.**

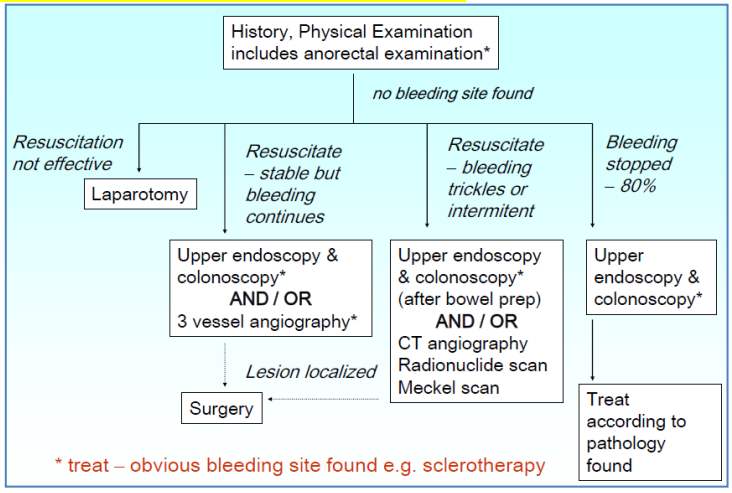
MINOR RECTAL BLEEDING:

- **= "IF the Pt is Haemodynamically Stable"**
- **Commonest Aetiology – *Lower GI-Bleeding*:**
  - **Haemorrhoids** (54%)
  - **Fissure** (18%)
  - **Fistulae** (7%)
  - **Cancer/Polyp** (6%)
  - 

Management:

- **FBC – (↓Hb, ↑Retics, ↓Platelets, ↑/↓MCV)**
- **Coags – (↑PTT)**
- **PPI – (If ?PUD)**
- **G&H & X-Match if Severe!! + IV Fluids**
- **Endoscopy/Colonoscopy – (Definitive)**

LFTs – (?Alcoholic Liver Disease)
EUCs



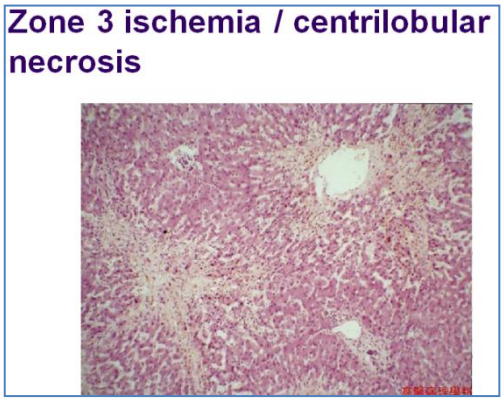
HEPATOBILIARY Pathology:
SECONDARY LIVER DISEASES

Other Random Liver Disorders:

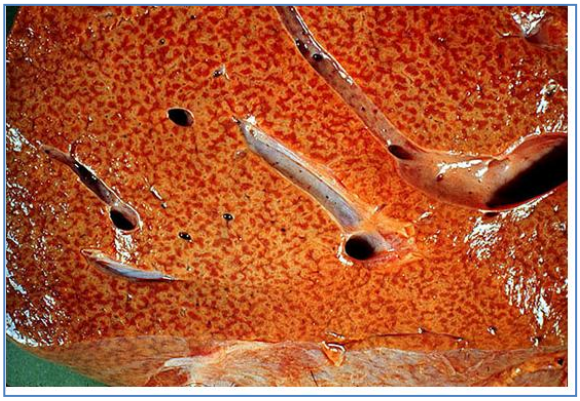
- **REYE SYNDROME:**
  - **Aetiology:**
    - Disease of Childhood (4-12yrs)
    - ***Aspirin + Viral URTI's***:
  - **Pathogenesis:**
    - Unknown Path → Acute Encephalopathy & Liver Failure
  - **Morphology:**
    - Fatty Liver & Hepatomegaly
    - Cerebral Oedema & Encephalopathy
  - **Clinical Features:**
    - **Symptoms:**
      - Persistent Vomiting
      - Lethargy/Irritability/Aggression/Confusion
      - Seizures/Coma
      - NO jaundice.
  - **Treatment:**
    - No Specific Treatment – Only Supportive
  - **Prognosis:**
    - Most make full Recovery.
  - **Complications:**
    - Severe Brain Damage
    - Respiratory Arrest
    - Multi-Organ Failure

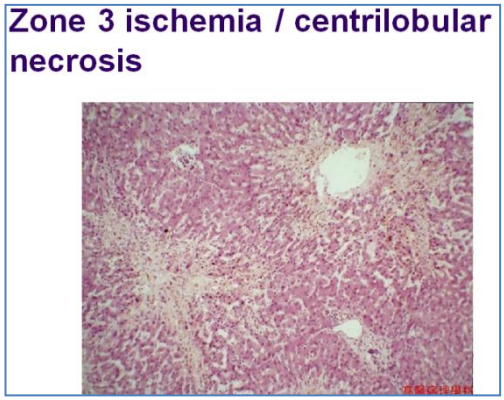
- **TOXAEMIA OF PREGNANCY (AKA: PRE-ECCLAMPSIA/ECCLAMPSIA):**
  - **Aetiology:**
    - Pregnancy
  - **Pathogenesis:**
    - Placental Vasoconstrictors → Endothelial Dysfunction in Blood Vessels → HTN
  - **Clinical Features:**
    - ***Pre-Eclampsia*:**
      - Hypertension (>140/90)
      - Proteinuria
      - Oedema (Face & Hands)
    - ***Eclampsia*:**
      - SEIZURES
      - Stroke/Coma/Death
  - **Complications:**
    - Poor Foetal Growth
    - **Fulminant Hepatic Failure** (Hepatocellular Necrosis)
    - **HELLP Syndrome** – Haemolysis, Elevated Liver Eenzymes, Low Platelets
      - → Jaundice, Epigastric Pain, Vomiting.
  - **Treatment:**
    - **Supportive = Bedrest**
    - **Anti-Hypertensives – (*Labetalol*)**
    - **Vasodilators – (*Magnesium Sulfate*, *Nifedipine*)**
    - **Antenatal Corticosteroids – (*Betamethasone*)**
    - ****Definitive = Birth (Early *Induction of Labour*)**

- **NUTMEG LIVER (AKA: Congestive Hepatopathy):**
  - **Aetiology:**
    - Congestive Heart Failure (RH-Failure)
  - **Pathogenesis:**
    - R-Heart Failure → IVC Venous Stasis → Chronic Passive Congestion of Liver
      - → Hypoperfusion → Necrosis
      - → Congestion → Haemorrhage
  - **Morphology:**
    - **Macro:**
      - Mottled Appearance (Nutmeg)
    - **Micro:**
      - Centrilobular (zone 3) Congestion (Haemorrhagic – RBCs)
      - Centrilobular (Zone 3) Necrosis
  - **Clinical Features:**
    - **Symptoms:**
      - Often Asymptomatic (Detected incidentally via LFTs)
      - RUQ Pain (due to stretching of liver capsule)
    - **Signs:**
      - Hepatomegaly (Firm, Smooth Liver Edge)
      - Ascites (Due to Portal Hypertension), Pedal Oedema
      - Juggular Venous Distension
      - Jaundice (Unconjugated – due to 1. Hepatocellular Dysfunction, 2. Haemolysis, & 3. Biliary Canalicular Obstruction.)
      - Hepatic Encephalopathy
    - **Lab Tests:**
      - ↑AST/ALT
    - **Outcomes:**
      - If Severe/Chronic → Fibrosis → "*Cardiac Cirrhosis*"
      - Rarely, *Fulminant Liver Failure*.



- **BUDD-CHIARI SYNDROME:**
  - **Aetiology:**
    - Venous Outflow Obstruction of the Liver (Occlusion of the Hepatic Vein) Due to:
      - Hypercoagulability (Eg. Polycythaemia)
      - Thrombophilia
      - Leukaemia
      - Compressive Tumour
  - **Pathogenesis – (Similar to Nutmeg Liver/Congestive Hepatopathy):**
    - Occlusion of the Hepatic Vein → Portal Hypertension & Hepatic Congestion
      - → Hypoperfusion → Necrosis
      - → Congestion → Haemorrhage
  - **Morphology – (Similar to Nutmeg Liver/Congestive Hepatopathy):**
    - Centri-Zonal Congestion & Haemorrhage
    - Centri-Zonal Fibrosis & Cirrhosis
    - **NB: Caudate lobe is spared due to Independent Blood Supply & Drainage
  - **Clinical Features:**
    - **Signs/Symptoms:**
      - Abdominal Pain
      - Nausea/Vomiting
      - Hepatomegaly
      - Ascites
      - Negative Hepatojugular Reflux
      - Signs of Portal Hypertension
    - **Treatment:**
      - Treat underlying Cause.
      - Liver Transplant if Chronic/Fulminant.





SPECIFIC SURGICAL NOTES:
ACUTE ABDOMEN

Clinical Evaluation of a Pt with an "Acute Abdomen":

- **Conditions Requiring Laparotomy:**
  - **Organ Rupture (Spleen/Aorta/Ectopic)**
    - → Shock
  - **Peritonitis (Perf'd PUD/DUD/Diverticulum/Appendix/Bowel/Gallbladder)**
    - → Prostration, Shock, Lying Still, Tenderness (Guarding/Rebound/Percussion), Abdo Rigidity, No Bowel Sounds.
- **Conditions NOT Requiring Laparotomy:**
  - **Local Peritonitis (Diverticulitis, Cholecystitis, Salpingitis, Appendicitis)**
    - →Lying Still, Tenderness (Guarding/Rebound/Percussion), Abdo Rigidity
  - **Colic**
    - → Restlessness, Regularly Waxing/Waning Pain.
- **Tests to Perform:**
  - U&E, FBC, Amylase, LFT, CRP, ABG, Urinalysis
  - Erect CXR (look for Air under Diaphragm)
- **Immediate Priorities:**
  - Resuscitation Before Surgery!! – NB: Anaesthesia compounds shock!!
- **Differentials:**

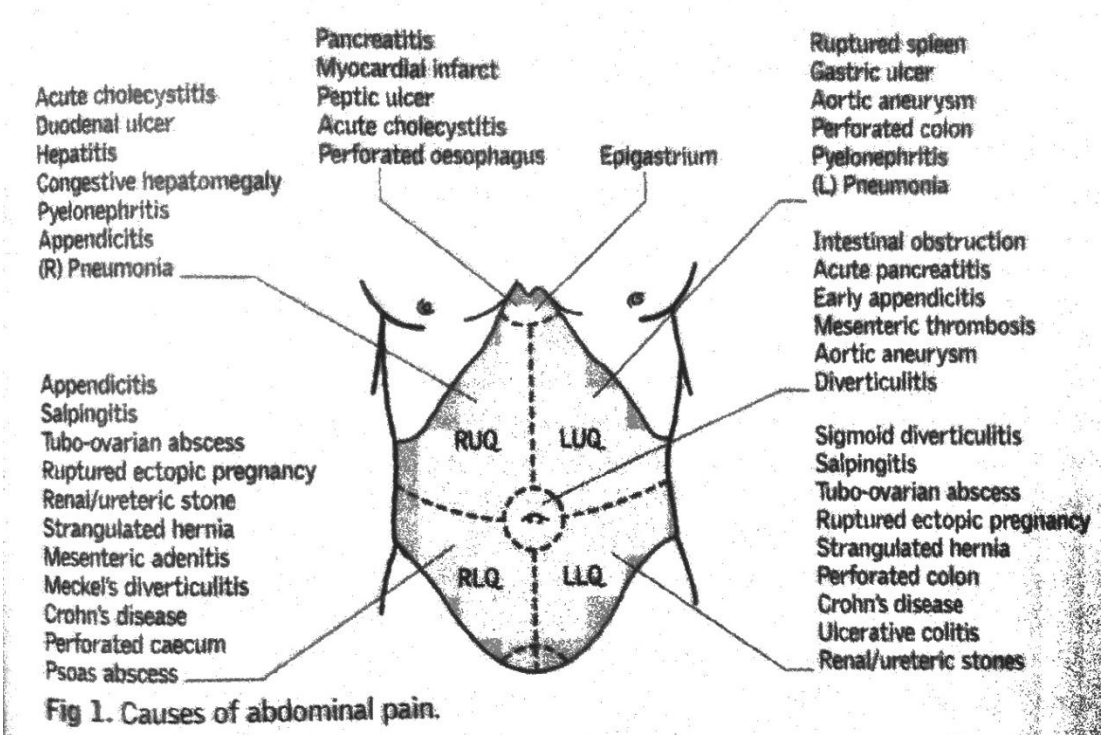


Fig 1. Causes of abdominal pain.

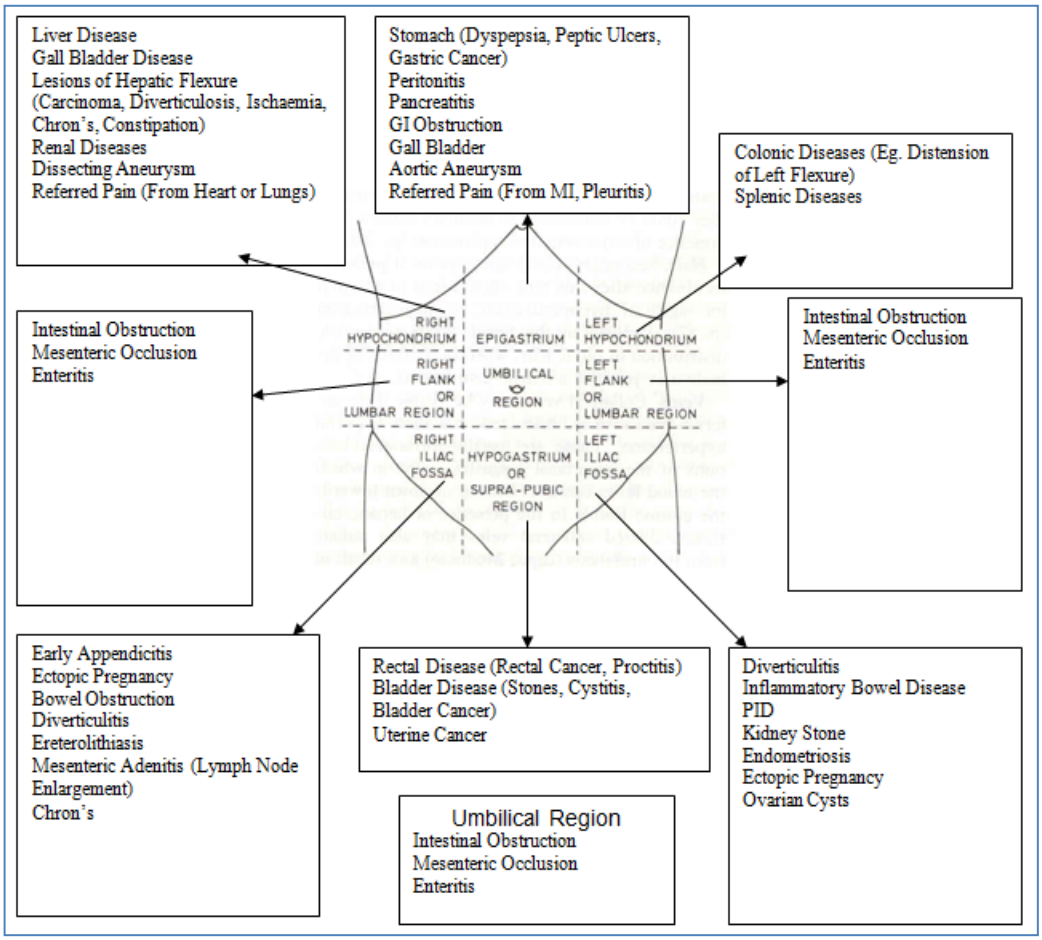
Clinical Features of Intestinal Perforation:

- Severe Abdominal Pain
- Referred Shoulder Pain (Diaphragm Irritation)
- Haemorrhage → Shock
- Sepsis → Fever, Shock
- Peritonitis → Pain, Guarding & Rebound Tenderness
- Pancreatitis

- **Abdominal Pain:**
  - A very common reason for patients to come to the Emergency Department
  - **We will focus on the *GIT causes of Abdominal Pain*:**
    - Almost endless!
    - Think of an organ then apply the 'surgical sieve'
      - Infection
      - Trauma
      - Neoplasia
      - Haemorrhage
      - Toxins/Drugs
  - **3 Types of Abdominal Pain:**
    - **1. Visceral ('Colicky') Pain:**
      - Pain Arising from abdominal *viscera*
        - *Typically due to Pressure*
        - *Typically Diffuse Pain* (Poorly localised – often, but not always, felt in periumbilical region)
        - Fluctuating in Intensity (Comes & Goes)
      - Transmitted by autonomic nerve fibres
      - Often associated with nausea and autonomic symptoms (e.g. sweating)
      - Pts tend to move around a lot (Can't get comfortable)
    - **2. Somatic/Parietal Pain:**
      - Pain due to Inflammation/Irritation of the Parietal ***Peritoneum***
        - *Typically Very Localised*
        - *Sharp Pain (Hurts to Move, Cough, Breathe*)
        - *Irritated by Movement*
      - Usually implies involvement of the (parietal) peritoneum
      - Transmitted via somatic nerves
      - ***Well localised***
    - **3. Referred Pain:**
      - Pain referred to one location from pathology in a different location
      - Usually associated with Embryonic Dermatome Origins of the Affected Structures
      - Eg. Diaphragmatic Pain felt at the Shoulder Tip
      - **Beware of extra-abdominal pain referred *to the abdomen***
        - ***Eg. Myocardial ischaemia*/Infarction:**
          - Inferior Infarcts often $\rightarrow$ Epigastric pain
        - ***Eg. Testicular pathology***
          - Eg. Testicular Torsion $\rightarrow$ hypogastric pain

- **Assessing Pain:**
  - **Pain Qualities:**
    - **Poorly defined or well localised**
    - **What does the pain make you do?**
      - **If Move around (can't get comfortable) – Somatic**
      - **If Can't move – Visceral**
    - **Waxing and waning (typical of colicky pain)**
      - Pain comes & goes
      - Usually an obstruction of something
    - **Constant – sharp or dull**
      - **Sharp implies peritoneal pain**
      - **Dull implies Visceral Pain**
    - **Exacerbating or mitigating factors (e.g. movement)**
      - Better when you eat?
      - Worse when you eat? (Eg. Gastric/duodenal ulcer)
      - Worse when you move?
    - **Progression from visceral to parietal as pathology progresses (e.g. appendicitis:**
      - Begins as Visceral
      - → Irritates Peritoneum → Somatic/Parietal Pain
  - **What does the patient do?**
    - **Visceral Pain - Colic- can't get comfortable, moves around.**
      - Biliary colic
      - Renal colic
    - **Parietal Pain - worse with movement, tend to keep still**
      - Bleeding or infection
  - **Radiation?**
    - Where does the pain go?

Potential Sources of Pain in Each Abdominal Quadrant:



Continue Reading For Bonus Supplementary Study Materials…

G Gastroenterology

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Anatomy Review

Overview of Gastrointestinal Tract

- the gastrointestinal tract runs from mouth to anus ("gum to bum")

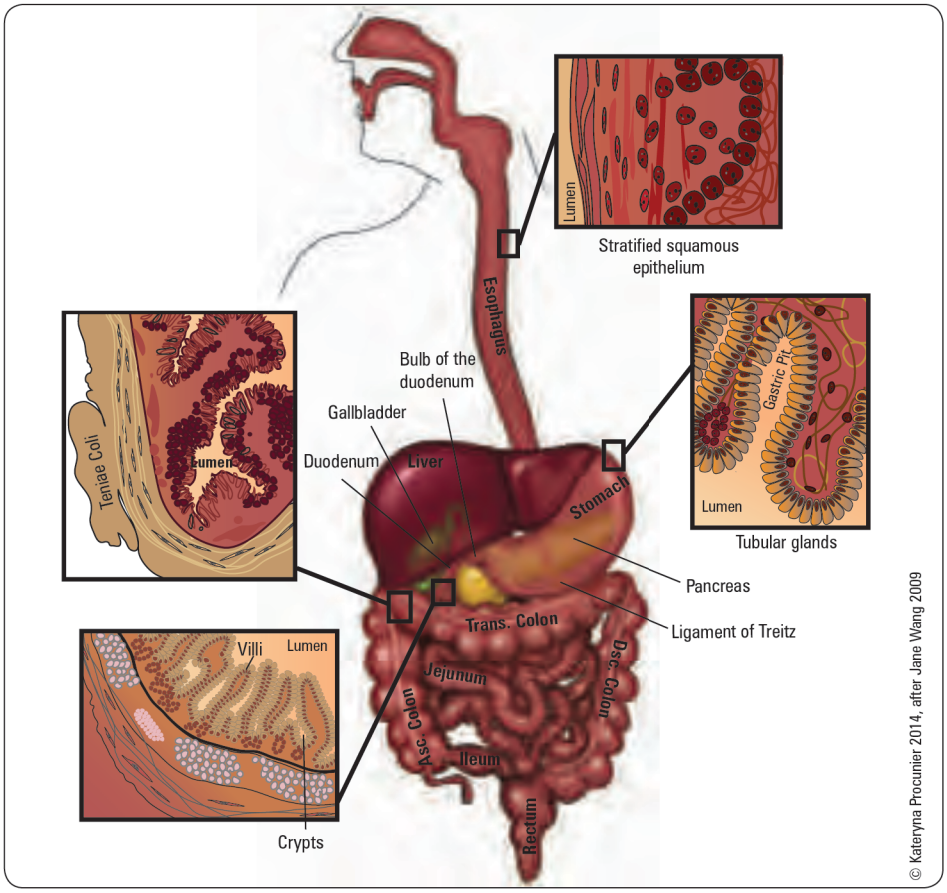

Figure 1. Overview of gastrointestinal tract

Table 1. Summary of Gastrointestinal Tract Structure and Function

Organ	Function	Blood Supply	Innervation	Histology and Structural Features

Esophagus	• Muscular tube approximately 25 cm long with a diameter of 2 cm
	• Extends from pharynx to the stomach
		• Arterial: left gastric artery and left inferior phrenic artery
		• Venous:
		  • Left gastric vein → portal venous system
		  • Esophageal veins → azygos vein → IVC (systemic)
			• Parasympathetic innervation via anterior and posterior gastric nerves (vagal trunks)
			• Sympathetic innervation via thoracic trunks of the greater splanchnic nerves
				• Mucosa: stratified squamous epithelium
				• Submucosa: connective tissue, lymphocytes, plasma cells, nerve cells
				• Muscularis propria (muscularis externa): inner circular, outer longitudinal muscle
				  • Upper 1/3: striated muscle
				  • Middle 1/3: transition zone
				  • Lower 1/3: smooth muscle

Stomach	• Delivers food to intestine for digestion and absorption
	• Secretes acid, probably to reduce enteric infections/pneumonia; facilitate digestion of protein/iron/B_{12}
	• Secretes intrinsic factor to facilitate B_{12} absorption
	• Minor contribution to initial protein digestion via pepsin
		• Lesser curvature
		  • Right and left gastric arteries (from celiac trunk)
		• Greater curvature
		  • Right and left gastro-omental (gastroepiploic) arteries (from gastroduodenal and splenic arteries respectively)
		• Fundus: short and posterior gastric arteries (from the splenic artery)
			• Parasympathetic innervation via vagus nerve
			• Sympathetic innervation via celiac plexus (from T6-T9)
				• 5 parts
				  • Cardia
				  • Fundus
				  • Body
				  • Antrum
				  • Pylorus

Duodenum	• Modulates enteral pH via secretin → decreased gastric acid secretion, increased bicarbonate secretion
	• Secretes CCK to stimulate bile secretion
	• Site of iron absorption
		• Branches of celiac artery and superior mesenteric artery	• Parasympathetic innervation via vagus nerve
			• Sympathetic innervation via greater and lesser splanchnic nerves
				• 4 parts
				  • Superior (5 cm)
				  • Descending (7-10 cm)
				  • Horizontal (6-8 cm)
				  • Ascending (5 cm)
				• 1st part is intraperitoneal; rest is retroperitoneal

Acronyms

ALF	acute liver failure
BE	Barrett's esophagus
BT	biologic therapy
CCK	cholecystokinin
CD	Crohn's disease
DES	diffuse esophageal spasm
EIM	extraintestinal manifestation
EN	enteral nutrition
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
EVL	endoscopic variceal ligation
FAP	familial adenomatous polyposis
GE	gastroesophageal
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HAV	hepatitis A virus
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HNPCC	hereditary non-polyposis colorectal cancer
HRS	hepatorenal syndrome
HVPG	hepatic venous pressure gradient
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
INH	isoniazid
LES	lower esophageal sphincter
MRCP	magnetic resonance cholangiopancreatography
NAC	N-acetylcysteine
NAFLD	non-alcoholic fatty liver disease
NERD	non-erosive reflux disease
NMS	neuroleptic malignant syndrome
OGD	oesophagogastroduodenoscopy
PBC	primary biliary cirrhosis
PN	parenteral nutrition
PPI	proton pump inhibitor
PSC	primary sclerosing cholangitis
PTC	percutaneous transhepatic cholangiography
PUD	peptic ulcer disease
SBP	spontaneous bacterial peritonitis
TIPS	transjugular intrahepatic portosystemic shunt
TPN	total parenteral nutrition
UC	ulcerative colitis

Table 1. Summary of Gastrointestinal Tract Structure and Function (continued)

Organ	Function	Blood Supply	Innervation	Histology and Structural Features
Jejunum	• Absorption of sodium, water, and nutrients (protein, carbohydrates, fat, folic acid, and vitamin A, B, C, D, E, K)	• Superior mesenteric artery	• Parasympathetic innervation via fibers of the posterior vagal trunk • Sympathetic innervation via fibers of T8-T10	• Deep red colour • 2-4 cm in thickness • Thick and heavy wall • Plicae circulares are large, tall, and closely packed • Has long vasa recta • Scant fat in mesentery • Scant Peyer's patches
Ileum	• Absorption of sodium, water, nutrients, soluble vitamins (only site of vitamin B_{12} absorption), and bile salts (entero-hepatic circulation)	• Superior mesenteric artery	• Same as jejunum	When compared to jejunum • Paler pink colour • 2-3 cm in thickness • Thin and light walls • Plicae circulares are small and sparse • Contains more mesenteric fat • Many Peyer's patches
Large Bowel	• Absorption of water (5-10% of total water) • Bacteria: further digestion of chyme and metabolism of undigested CHO to short chain fatty acids • Formation and storage of feces	• Branches of superior and inferior mesenteric arteries • Rectal blood supply: sigmoid, right pudendal, and rectal arteries	• Parasympathetic innervation via vagus nerve • Sympathetic innervation via greater and lesser splanchnic nerves	• Consists of cecum, colon (ascending, transverse, descending, and sigmoid), rectum and anal canal • Features include teniae coli, haustra, and omental appendices

Liver	• Glucose homeostasis
	• Plasma protein synthesis
	• Lipid and lipoprotein synthesis
	• Bile acid synthesis and secretion
	• Vitamin A, D, E, K, B_{12} storage
	• Biotransformation, detoxification
	• Excretion of compounds
		• 2 sources
		  • Portal vein (75-80%)
		  • Hepatic artery (20-25%)
			• Sympathetic innervation via fibers of the celiac plexus
			• Parasympathetic innervation via fibers of the anterior and posterior vagal trunks
				• Largest internal organ
				• Composed of 4 lobes (left, right, caudate, quadrate), and divided into 8 segments

Biliary Tract	• Gallbladder functions to store and release bile that is produced in the liver • Bile is used to emulsify fat and is composed of cholesterol, lecithin, bile acids, and bilirubin • CCK stimulates gallbladder emptying while trypsin and chymotrypsin inhibit bile release	• Cystic artery	• Parasympathetic innervation via vagus nerve • Sympathetic and visceral innervation via celiac nerve plexus • Somatic afferent fibers via right phrenic nerve	• Consists of the hepatic ducts (intrahepatic, left, right and common), gallbladder, cystic duct, common bile duct, and ampulla of Vater
Pancreas	• Endocrine function: islets of Langerhans produce glucagon, insulin, and somatostatin (from the α, β, and δ cells, respectively) • Exocrine function: digestive enzymes are produced including amylase, lipase, trypsin, chymotrypsin, and carboxypeptidase	• Anterior superior pancreaticoduodenal artery (from the celiac trunk) • Anterior inferior pancreaticoduodenal artery (from the superior mesenteric artery) • Dorsal pancreatic artery (from the splenic artery) • Pancreatic veins drain into the portal, splenic, and superior mesenteric veins	• Parasympathetic innervation via vagus nerve • Sympathetic innervation via abdominopelvic splanchnic nerves	• 4 parts of pancreas: head (includes uncinate process), neck, body, and tail • (Major) pancreatic duct connecting to common bile duct prior to ampulla of Vater • Accessory pancreatic duct connected directly to duodenum

Visualizing the GI Tract

• see Medical Imaging, MI10

Retroperitoneal Structures
Suprarenal glands (adrenal glands)
Aorta/IVC
Duodenum (second to fourth segments)
Pancreas (tail is intraperitoneal)
Ureters
Colon (only the ascending and descending branches)
Kidneys
Esophagus
Rectum

Esophagus, Stomach, Duodenum

- OGD: best visualization of mucosa; also allows for therapeutic intervention (e.g. banding varices, thermal therapy/clipping/injecting bleeding ulcers, and dilatation e.g. treatment of esophageal strictures)
  - consider barium swallow first if dysphagia, decreased level of consciousness (increases risk of aspiration), inability to cooperate (increases risk of pharyngeal trauma during intubation), possibility of fistulas
  - endotracheal intubation first if massive upper GI bleed, acidemia, or inability to protect airway

Small Bowel

- most difficult to visualize, especially if mucosal detail is needed
- CT enterography more accurate than small bowel follow through, but both have low sensitivity
- MRI small bowel imaging increasingly available, especially useful if radiation exposure is an issue (e.g. young patient, mutiple radiological images already done)
  - note: MRI enteroclysis: luminal contrast administered by nasojejunal tube to dilate the small bowel – disliked by both radiologist and patient, but may improve sensitivity
- "double balloon" enteroscopy (enteroscope with proximal and distal balloons to propel endoscope into jejunum from mouth or into jejunum/ileum or into ileus from anus) may be most sensitive but currently available only in selected centres; technically demanding
- wireless endoscopy capsule (26 x 11 mm capsule is swallowed, transmits images to a computer; contraindicated in bowel obstruction) is also accurate in diagnosis but unable to provide any therapeutic intervention

Colon and Terminal Ileum

- colonoscopy, with biopsy if required; contraindicated in perforation, acute diverticulitis, and severe colitis (increased risk of perforation)
- CT colonography ("virtual colonoscopy") more accurate in diagnosing diverticulosis, extrinsic pressure on colon (e.g. ovarian cancer compressing sigmoid colon), and fistulae; increasing evidence for use in colorectal cancer screening, especially for assessment of right side of colon in cases where colonscopy is less sensitive

Only the ileum (not jejunum) can absorb vitamin B_{12} and bile acids

Pancreatic/Biliary Duct

- MRCP almost as sensitive as ERCP in determining if bile duct obstruction present, but less accurate in determining cause of obstruction (tumour, stone, stricture)
- ERCP if endoscopic draining necessary, strong suspicion of stone, obstruction requiring stenting, or if tissue sampling required

Differential Diagnosis of Common Presenting Complaints

See General Surgery, *Acute Abdominal Pain*, GS4

Table 2. Differential Diagnosis of Common Presenting Complaints

CHRONIC/ RECURRENT ABDOMINAL PAIN	Inflammatory	Neoplastic/ Vascular	Toxin	Other
	PUD Biliary colic IBD Chronic pancreatitis	Recurrent bowel obstruction Mesenteric ischemia Sickle cell anemia	Lead poisoning	Mittleschmertz Endometriosis Porphyria IBS Radiculopathy Abdominal wall pain syndrome

ACUTE DIARRHEA	Inflammatory		Non-Inflammatory	
*Causes of bloody diarrhea	**Bacterial** *Shigella** *Salmonella** *Campylobacter** *Yersinia** *E. coli* (EHEC 0157:H7)* *C. difficile*	**Protozoal** *E. histolytica** (amoebiasis) Strongyloides **Others** NSAIDs IBD* Ischemic*	**Bacterial** *S. aureus* *C. perfringens* *B. cereus* *E. coli* (ETEC, EPEC) *Salmonella enteritidis* *Vibrio choiera* **Protozoal** *Giardia lamblia*	**Viral** Rotavirus Norwalk CMV **Drugs** Antibiotics Colchicine Laxatives Antacids (magnesium)

CHRONIC DIARRHEA	Organic				Functional
	Inflammatory	Secretory	Steatorrheic	Osmotic	
*Causes of bloody diarrhea	IBD Infectious (*C. difficile*, TB, CMV, HSV) Ischemic bowel Radiation colitis Neoplasia	Stimulant laxatives Post-ileal resection/ cholecystectomy (bile salts) Bacterial toxins Vasculitis Neoplasia (Colon Ca, Carcinoid, VIPoma) Addison's disease Congenital syndromes	*Giardia lamblia* Celiac sprue Chronic pancreatitis Chronic cholestasis	Osmotic laxatives Lactose intolerance Chewing gum (sorbitol, mannitol)	IBS Constipation (overflow diarrhea) Anal sphincter dysfunction

Acute Upper Abdominal Pain
Remember to rule out thoracic sources, e.g. myocardial infarction, pneumonia, dissecting aneurysm

Obscure But Treatable Causes of Abdominal Pain
- Acute Intermittent Porphyria
- Hereditary Angioedema
- Familial Mediterranean Fever
- Vasculitis (e.g. polyarteritis nodosa)

Inflammatory Diarrhea: Occurs when there is damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids and a decreased ability to absorb these lost fluids. Diarrhea may be profuse or very small In volume. Often associated with abdominal pain ± fever and chills

Non-Inflammatory Diarrhea: No damage to the mucosal lining. N/V may be present. Fever, chills, blood in the stool, severe abdominal pain or tenderness are not present

Rule out IBD when patient presents with bloody diarrhea

Table 2. Differential Diagnosis of Common Presenting Complaints (continued)

CONSTIPATION: if no associated rectal bleeding/weight loss, etc., usually no cause found			
Colorectal cancer Stricture Extrinsic compression Anal disease Rectocele	Medications (narcotics, antidepressants, calcium channel blockers) Metabolic (DM, thyroid, hypercalcemia)	Neurologic (Parkinson's, MS, stroke) Collagen vascular disease (scleroderma, dermatomyositis)	

NAUSEA/ VOMITING	With Abdominal Pain		Without Abdominal Pain	
	Relieved by Vomiting	Not Relieved by Vomiting	Headache/Dizziness	No Other Symptoms
	Gastric outlet obstruction Small bowel obstruction GERD (regurgitation more common)	Gallbladder disease Pancreatitis Myocardial infarction Hepatitis Infectious Gastroenteritis	Cerebral tumour Migraine Vestibular disease Increased ICP	Drugs Uremia Pregnancy Metabolic (e.g. hypercalcemia) Gastroparesis (e.g. DM) Ketoacidosis

Commonly Forgotten Causes of Vomiting
- Drugs
- Uremia
- CNS Disease
- Pregnancy

DYSPEPSIA	Common	Uncommon	Rare
	Functional dyspepsia Drug side effect Peptic ulcer GERD	Angina Crohn's disease Cancer Gallstones Aerophagia	*Giardia lamblia* Malabsorption (celiac sprue)

UPPER GI BLEED	Common	Uncommon	Rare
	Ulcers (*H. pylori*, ASA, NSAIDs) Esophageal varices Mallory-Weiss tears Erosive esophagitis Erosive gastritis	Tumours Arteriovenous malformation Dieulafoy's lesion (arterial) Gastric antral vascular ectasia (GAVE) Portal hypertensive gastropathy	Aorto-enteric fistulas Hemobilia

LOWER GI BLEED	Common	Uncommon	Rare
	Diverticulosis Ischemia Angiodysplasia (elderly) Infectious Anorectal (hemorrhoids, fissure, ulcer)	Upper GI bleed (brisk) Post-polypectomy Radiation colitis IBD	Intussusception Vasculitides Stercoral ulcer Coagulopathies

DYSPHAGIA	Mechanical (Solids)	Motility (Solids and Liquids)	Other
	Peptic stricture/cancer Eosinophilic esophagitis Extrinsic compression Schatzki ring/esophageal web Zenker's diverticulum	Achalasia Diffuse esophageal spasm Scleroderma	Foreign body Eosinophilic esophagitis

Difference Between Dysphagia and Odynophagia
- **Dysphagia**: Difficulty swallowing. May suggest difficulty in the passage of solids or liquids from the mouth to the stomach, lack of pharyngeal sensation, or other inadequacy of the swallowing mechanism
- **Odynophagia**: Pain when swallowing

ODYNOPHAGIA	Infection	Inflammation/ Ulceration	Drugs	Other
	Candida Herpes CMV (common in those who are immunosuppressed)	Caustic damage Eosinophilic esophagitis	Quinidine Iron Vitamin C Antibiotics (e.g. tetracycline) Bisphosphonates	Radiation

Table 2. Differential Diagnosis of Common Presenting Complaints (continued)

ABDOMINAL DISTENTION	Fluid (Ascites)		Flatulence	Feces	Other
	Portal HTN	Normal Portal Pressure			
	Cirrhosis Cardiac failure Hepatic vein thrombosis	Cancer (especially ovarian) Pancreatitis TB	Functional bowel disease (e.g. IBS) Fibre Lactose intolerance Chewing gum (e.g. sorbitol, mannitol)	Constipation Colonic obstruction Dysmotility	Pregnancy (fetus) Obesity (fat) Blood Large tumours (fatal growth)

JAUNDICE (UNCONJUGATED BILIRUBIN)	Overproduction	Decreased Hepatic Intake	Decreased Conjugation
	Hemolysis Ineffective erythropoiesis (e.g. megaloblastic anemias)	Gilbert's syndrome Drugs (e.g. rifampin)	Drug inhibition (e.g. chloramphenicol) Crigler-Najjar syndromes type I and II Gilbert's syndrome Neonatal jaundice

JAUNDICE (CONJUGATED BILIRUBIN)	Common	Uncommon
	Hepatocellular disease Drugs Cirrhosis (any cause) Inflammation (hepatitis, any cause) Infiltrative (e.g. hemochromatosis) Familial disorders (e.g. Rotor syndrome, Dubin-Johnson syndrome, cholestasis of pregnancy) PBC PSC Sepsis Post-operative/TPN	**Intraductal obstruction** Gallstones Biliary stricture Parasites Malignancy (cholangiocarcinoma) Sclerosing cholangitis **Extraductal obstruction** Malignancy (e.g. pancreatic cancer, lymphoma) Metastases in peri-portal nodes **Inflammation (e.g. pancreatitis)**

Differential Diagnosis of Abdominal Distention

6 Fs
Fat
Feces
Fetus
Flatus
Fluid
Fatal Growth

Esophagus

Gastroesophageal Reflux Disease

Definition

- condition in which the stomach contents (most characteristically acid) moves backwards from the stomach into the esophagus (the tube from the mouth to the stomach)

Dyspepsia = postprandial fullness, early satiety, epigastric pain, or burning

Etiology

- inappropriate transient relaxations of LES – most common cause
- low basal LES tone (especially in scleroderma)
- contributing factors include: delayed esophageal clearance, delayed gastric emptying, obesity, pregnancy, acid hypersecretion (rare) from Zollinger-Ellison syndrome (gastrin-secreting tumour)
- hiatus hernia worsens reflux, does not cause it (see General Surgery, GS13)

Foods/Substances that Aggravate GERD Symptoms
- EtOH
- Caffeine
- Tobacco
- Fatty/fried foods
- Chocolate
- Peppermint
- Spicy foods
- Citrus fruit juices

Clinical Features

- "heartburn" (pyrosis) and acid regurgitation (together are 80% sensitive and specific for reflux) ± sour regurgitation, water brash, sensation of a lump in the throat (globus sensation), and frequent belching
- non-esophageal symptoms (see G7) are increasingly recognized of being poor predictors of reflux

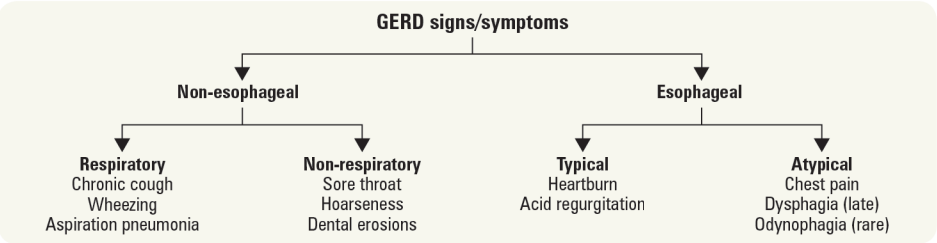

Figure 2. Signs and symptoms of GERD

Investigations
- usually, a clinical diagnosis is sufficient based on symptom history and relief following a trial of pharmacotherapy (PPI: symptom relief 80% sensitive for reflux)
- gastroscopy indications (*Ann Intern Med* 2012;157:808-816)
  - absolute indications
    - heartburn accompanied by red-flags (bleeding, weight loss, etc.)
    - persistent reflux symptoms or prior severe erosive esophagitis after therapeutic trial of 4-8 wk of PPI 2x daily
    - history of esophageal stricture with persistent dysphagia
- repeat endoscopy after 6-8 wk of PPI therapy is indicated if: 1) severe esophagitis (because it can mask Barrett's esophagus) or 2) known Barrett's esophagus or 3) recurrence of symptoms
- esophageal manometry (study of esophageal motility)
  - may be done to diagnose abnormal peristalsis and/or decreased LES tone, but cannot detect presence of reflux; indicated before surgical fundoplication to ensure intact esophageal function
  - surgical fundoplication (wrapping of gastric fundus around the lower end of the esophagus) more likely to alleviate symptoms if lower esophageal pressure is diminished; less likely to be successful if abnormal peristalsis
- 24 h pH monitoring: most accurate test for reflux, but not required or performed in most cases
  - most useful if PPIs do not improve symptoms

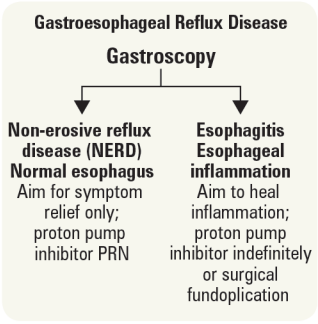

Figure 3. Classification and gastroscopic findings of GERD

Treatment
- PPIs are the most effective therapy and usually need to be continued as maintenance therapy
- on-demand: antacids ($Mg(OH)_2$, $Al(OH)_3$, alginate), H_2-blockers, or PPIs can be used for NERD
- diet helps symptoms, not the disease; avoid alcohol, coffee, spices, tomatoes, and citrus juices
- only beneficial lifestyle changes are weight loss (if obese) and elevating the head of bed (if nocturnal symptoms)
- symptoms may recur if therapy is discontinued

Esophageal damage from reflux is most severe at first gastroscopy, therefore gastroscopy is necessary only once for patients with NERD

Complications
- esophageal stricture disease – scarring can lead to dysphagia (solids)
- ulcer
- bleeding
- Barrett's esophagus and esophageal adenocarcinoma – gastroscopy is recommended for patients with chronic GERD or symptoms suggestive of complicated disease (e.g. anorexia, weight loss, bleeding, dysphagia)

Up to 25% of patients with Barrett's esophagus do not report symptoms of GERD

Barrett's Esophagus

Definition
- metaplasia of normal squamous esophageal epithelium to abnormal columnar epithelium containing-type intestinal mucosa (intestinal metaplasia)

Etiology
- thought to be acquired via long-standing GERD and consequent damage to squamous epithelium

Epidemiology
- in North America and Western Europe, 0.5-2.0% of adults are thought to have Barrett's esophagus
- up to 10% of GERD patients will have already developed BE by the time they seek medical attention
- more common in males, age >50, Caucasians, smokers, overweight, hiatus hernia, and long history of reflux symptoms

Pathophysiology
- endoscopy shows erythematous epithelium in distal esophagus; diagnosis of BE relies on biopsy demonstrating the presence of specialized intestinal epithelium of any length within the esophagus
- BE predisposes first to premalignant changes characterized as low or high-grade dysplasia, which then progresses to adenocarcinoma

Should Patients with Barrett's Esophagus Undergo Periodic Upper GI Endoscopy for Esophageal Cancer Screening?
Impact of Endoscopic Surveillance on Mortality From Barrett's Esophagus - Associated Esophageal Adenocarcinomas
Gastroenterology 2013;145:312-319

There is no question that Barrett's esophagus (BE) increases the incidence of esophageal adenocarcinoma, which can be recognized early on with a safe procedure, endoscopy. Indeed, because early cancer is often asymptomatic and curable, most clinicians recommend period upper endoscopy. Yet Corley et al. found no difference in endoscopy rates in BE patients who died of esophageal adenocarcinoma compared to BE patients who died of other diseases. Perhaps this result is due to statistics, but as the accompanying editorial emphasizes (*Gastroenterology* 2013; 145:273-6) at the very least this finding should question the value of a screening program. In fact, there are multiple other lines of evidence indicating that endoscopic surveillance is of marginal benefit at most. Possible explanations for this disappointing finding include: most esophageal adenocarcinomas may not arise from BE, esophageal carcinoma is too rare a cause of death in BE, morbidity from esophageal cancer treatments, or that endoscopic screening is just not that effective in the real world. The situation is analogous to the disappointing value of serum PSA screening for prostate cancer. Therefore, adoption of screening programs require more than theoretical calculations.

Significance
- rate of malignant transformation is approximately 0.12% per yr for all BE patients prior to dysplasia
- risk of malignant transformation in high-grade dysplasia is significantly higher; studies have reported a 32-59% transformation rate over 5-8 yr of surveillance
- increased gastric acid secretion is more frequently associated with Barrett's esophagus as opposed to reflux alone

Treatment
- acid suppressive therapy with high-dose PPI indefinitely (or surgical fundoplication)
- endoscopy every 3 yr if no dysplasia
- high grade dysplasia: regular and frequent surveillance with intensive biopsy, endoscopic ablation/resection, or esophagectomy produce similar outcomes; however, evidence increasingly favouring endoscopic ablation with mucosal resection or radiofrequency ablation
- if low grade dysplasia, both surveillance and endoscopic ablation/resection are satisfactory options

Dysphagia

Definition
- difficulty swallowing, globus sensation

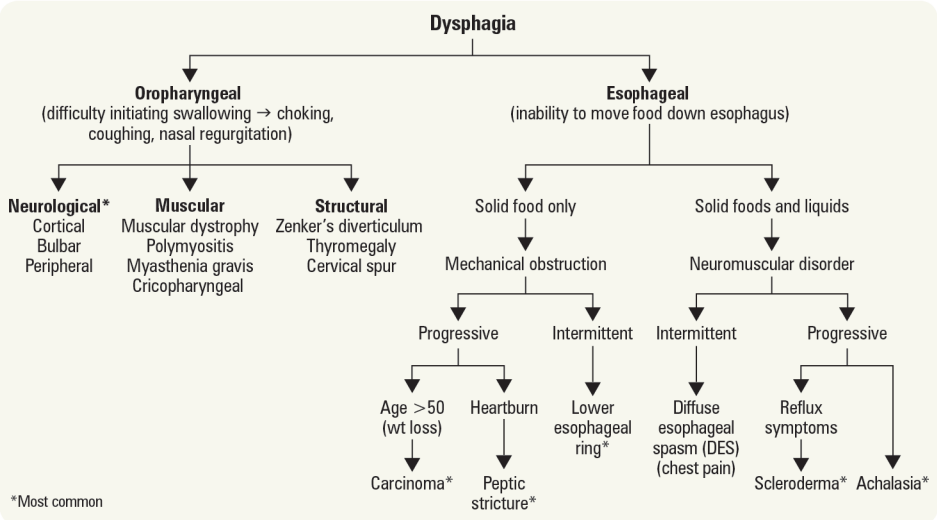

Figure 4. Approach to dysphagia (eosinophilic esophagitis omitted)

Remember:
Dysphagia = Difficulty in swallowing
Odynophagia = Pain on swallowing

Key Questions in Dysphagia
- Difficulty in starting swallowing?
- Associated symptoms? (regurgitation, change in voice pitch, weight loss)
- Solids, liquids, or both?
- Intermittent or progressive?
- History of heartburn?
- Change in eating habits/diet?

Esophageal Motor Disorders

Symptoms
- dysphagia with solids and liquids
- chest pain (in some disorders)

Diagnosis
- motility study (esophageal manometry)
- barium swallow sometimes helpful

Causes (see Table 3)
- idiopathic
- achalasia (painless)
- scleroderma (painless)
- DM
- DES: rare and can be difficult to diagnose due to intermittent presentation

Table 3. Esophageal Motor Disorders

Disorder	Achalasia	Scleroderma	Diffuse Esophageal Spasm
Definition	• Failure of smooth muscle relaxation at LES • Increased LES pressure • Progressive loss of peristaltic function	• See Rheumatology, RH13 • Systemic disease characterized by vasculopathy and tissue fibrosis (especially skin thickening)	• Normal peristalsis interspersed with frequent, repetitive, spontaneous, high pressure, non-peristaltic waves (tertiary peristalsis)
Etiology	• Usually idiopathic • 2º or pseudo-achalasia: e.g. malignancy, Chagas disease (*Trypanosoma cruzi*)	• Involves autoimmune, genetic, hormonal, and environmental factors • Dysphagia: caused by reflux, dysmotility, or both	• Idiopathic
Pathophysiology	• Inflammatory degeneration of Auerbach's plexus → increase in LES pressure, incomplete relaxation of LES with swallowing, aperistalsis	• Blood vessel damage → intramural neuronal dysfunction → distal esophageal muscle weakening → aperistalsis and loss of LES tone → reflux → stricture → dysphagia	• Potential mechanisms include impaired inhibitory innervation to esophageal body, malfunction in endogenous nitric oxide synthesis
Diagnosis	• CXR: no air in stomach, dilated esophagus • Barium studies: esophagus terminates in narrowing at LES ("bird's beak") • Endoscopy: normal mucosa • Manometry: definitive diagnosis (signs listed above)	• Clinical features of scleroderma • Manometry: decreased pressure in LES, decreased peristalsis in body of esophagus	• Barium x-ray: "Corkscrew pattern" • Manometry: >30% (but <100%) of esophageal contractions are aperistaltic • Endoscopy: normal mucosa
Treatment	• Dilatation of LES with balloon, ± GERD prophylaxis, 50% good response, can repeat, risk of perforation (5%) • Injection of botulinum toxin into LES (temporary) • Surgery (myotomy)	• Medical: aggressive GERD therapy (PPIs bid) • Surgery: anti-reflux surgery (gastroplasty, last resort)	• Reassurance not cardiac pain • Medical: nitrates, calcium channel blockers, anticholinergics have variable benefit • Surgical: long esophageal myotomy if unresponsive to above treatment (rarely helpful); balloon dilatation

Esophageal Diverticula

Definition
- outpouchings of one or more layers of the esophageal tract

Clinical Features
- commonly associated with motility disorders
- dysphagia, regurgitation, retrosternal pain, intermittent vomiting, may be asymptomatic

Classification
- classified according to location
  - pharyngoesophageal (Zenker's) diverticulum
    - most frequent form of esophageal diverticulum
    - posterior pharyngeal outpouching most often on the left side, above cricopharyngeal muscle and below the inferior pharyngeal constrictor muscle
    - symptoms: dysphagia, regurgitation of undigested food, halitosis
    - treatment: endoscopic or surgical myotomy of cricopharyngeal muscle ± surgical excision of sac
  - mid-esophageal diverticulum
    - secondary to mediastinal inflammation ("traction" diverticulae), motor disorders
    - usually asymptomatic; no treatment required
  - just proximal to LES (pulsatile type)
    - usually associated with motor disorders
    - usually asymptomatic; no treatment required

Peptic Stricture (from Esophagitis)

- presents as dysphagia alongside a long history of reflux symptoms, but reflux symptoms may disappear as stricture develops
- diagnosed with endoscopy or barium study if endoscopy contraindicated or unavailable

Treatment
- endoscopic dilatation and indefinite PPI
- anti-reflux surgery (fundoplication) if above treatment unsuccessful

Esophageal Carcinoma

- see General Surgery, GS15

Webs and Rings

- web = partial occlusion (upper esophagus)
- ring = circumferential narrowing (lower esophagus)

Clinical Features
- asymptomatic with lumen diameter >12 mm, provided peristalsis is normal
- dysphagia with large food boluses
- Schatzki ring
  - mucosal ring at squamo-columnar junction above a hiatus hernia
  - causes intermittent dysphagia with solids
  - treatment involves disrupting ring with endoscopic bougie

Plummer-Vinson Syndrome Triad
- Iron deficiency anemia
- Dysphagia
- Esophageal webs

Infectious Esophagitis

Definition
- severe mucosal inflammation and ulceration as a result of a viral or a fungal infection

Risk Factors
- DM
- chemotherapeutic agents
- immunocompromised states

Symptoms
- characteristically odynophagia, less often dysphagia
- diagnosis is via endoscopic visualization and biopsy

Appearance
- Candida (most common): whitish-yellow plaques without visible ulceration or inflammation
- Herpes (second most common), CMV: focal ulcers

Treatment
- Candida: nystatin swish and swallow, ketoconazole, fluconazole
- Herpes: often self-limiting; acyclovir, valacyclovir, famciclovir
- CMV: IV gancyclovir, famciclovir, or oral valganciclovir

Eosinophilic Esophagitis
- Eosinophils infiltrate the epithelium of the esophagus
- Causes odynophagia, dysphagia, common cause of bolus food impaction
- Usually primary, but can be part of the spectrum of eosinophilic gastroenteritis, secondary to drugs, parasites etc.
- Often associated with allergies
- most characteristically occurs in young men
- Diagnosis established by endoscopic biopsy, suggested by mucosal rings seen in the esophageal mucosa at endoscopy
- Treatment: (a)diet (b)swallow corticosteroid nasal spray (fluticasone),(c)swallow viscous corticosteroid (budesonide mixed with sucralase)

Stomach and Duodenum

Dyspepsia

Definition
- group of symptoms characterized by discomfort, location in the upper epigastrium, usually following meals; most characteristic symptom is fullness, but can also be a burning, true pain
- multiple causes: esophagitis, peptic ulcer, stomach cancer, drugs, but overall functional disease is most common

History and Physical Exam
- history: most important are age, associated symptoms (such as weight loss and vomiting), and drugs (especially NSAIDs)
- physical exam: adenopathy, abdominal mass/organomegaly, Carnett's sign (if pain is due to abdominal wall muscle problem then the pain will increase during muscle contraction, such as during a sit-up)

Investigations
- laboratory: usual (CBC, liver enzymes, glucose, Cr, etc.), amylase, albumin, calcium, protein electrophoresis, TSH, Helicobacter serology
- consider trial of empiric anti-secretory drug therapy, non-invasive testing for *H. pylori* infection, endoscopy, barium radiography (rarely done nowadays)

The most common cause of dyspepsia is functional (idiopathic) dyspepsia

Red Flags of Dyspepsia
(raise suspicion of gastric malignancy):
- Unintended weight loss
- Persistent vomiting
- Progressive dysphagia
- Odynophagia
- Unexplained anemia or iron deficiency
- Hematemesis
- Jaundice
- Palpable abdominal mass or lymphadenopathy
- Family history of upper GI cancer
- Previous gastric surgery

Stomach

- primary function is mechanical grinding of food facilitating early enzymatic digestion into chyme and propulsion into duodenum (motor function), but also releases secretions

Table 4. Cells of the Gastric Mucosa

Cell Type	Secretory Product	Important Notes
Parietal cells	Gastric acid (HCl) Intrinsic factor	Stimulated by histamine, ACh, gastrin
Chief cells	Pepsinogen	Stimulated by vagal input and local acid
G-cells	Gastrin	Stimulates H^+ production from parietal cells
Superficial epithelial cells	Mucus, HCO_3^-	Protect gastric mucosa
Neuroendocrine cells	Multiple (e.g. somatostatin, inhibits cell secretion)	Involved in neural, hormonal, and paracrine pathways

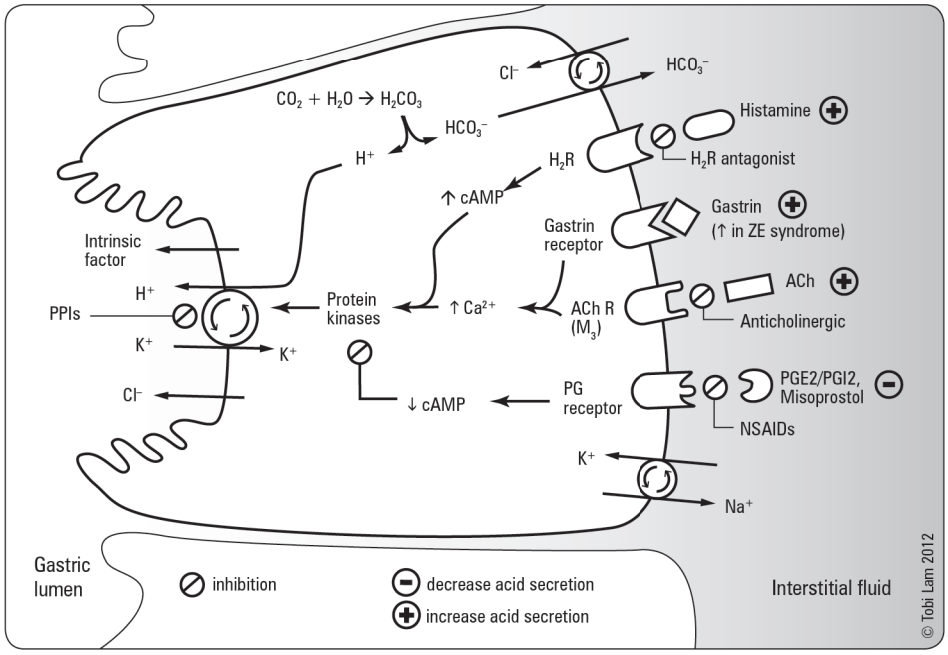

Figure 5. Stimulation of H^+ secretion from the parietal cell

Gastritis

Definition

- defined histologically: inflammation of the stomach mucosa

Etiology

- some causative agents may play a role in more than one type of gastritis and an individual patient may have histopathological evidence of more than one type of gastritis

Table 5. Updated Sydney Classification of Gastritis

Type	Common Etiology
Acute Gastritis	
Hemorrhagic/erosive gastritis	Alcohol*, Aspirin®/NSAID*, shock/physiological stress* (seen in ICU patients)
Helicobacter gastritis	*H. pylori**
Chronic Gastritis	
Non-atrophic	*H. pylori**
Atrophic	*H. pylori**, dietary, environmental factors (multi-focal), autoimmunity
Chemical	NSAID*, bile
Radiation	Radiation injury
Lymphocytic	Celiac disease, drug
Eosinophilic	Food allergies
Non-infectious granulomatous	Crohn's disease, sarcoidosis
Other infectious gastritides	Bacteria, viruses, fungi, parasite, TB, syphilis

*Most common causes

Clinical Features
- non-erosive gastritis is asymptomatic (except in certain rare causes like Crohn's disease); difficult to diagnose clinically or endoscopically – requires biopsy for diagnosis
- erosive gastritis can cause bleeding (pain only if progresses to ulcers – rare); can be seen endoscopically

Treatment
- determined by etiology (see *H. pylori*, G13, *NSAID*, G14 and *Stress-Induced Ulceration*, G14)
- non-pharmacological: avoidance of mucosal irritants such as alcohol, NSAIDs, and foods that trigger symptoms

Peptic Ulcer Disease

Definition
- focal defects in the mucosa that penetrate the muscularis mucosal layer results in scarring (defects superficial to the muscularis mucosa have erosions and no scarring)
- peptic ulcer disease includes defects located in the stomach (gastric ulcers) and duodenum (duodenal ulcers)

Etiology

Table 6. Etiology of Peptic Ulcer Disease

	Duodenal	Gastric
H. pylori infection	90%	60%
NSAIDs	7%	35%
Physiologic stress-induced	<3%	<5%
Zollinger-Ellison (ZE) syndrome	<1%	<1%
Idiopathic	15%	10%

- NSAID negative, *H. pylori* negative ulcers becoming more commonly recognized
- others: CMV, ischemic, idiopathic
- alcohol: damages gastric mucosa but rarely causes ulcers
- peptic ulcer associated with tobacco, cirrhosis of liver, COPD, and chronic renal failure

Cigarette Smoking and PUD
- Increased risk of ulcer
- Increased risk of complications
- Increased chance of death from ulcer
- Impairs healing

Clinical Features
- dyspepsia: most common presenting symptom
  - only 5% of patients with dyspepsia have ulcers, while most have functional disease
- may present with complications
  - bleeding 10% (severe if from gastroduodenal artery)
  - perforation 2% (usually anterior ulcers)
  - gastric outlet obstruction 2%
  - penetration (posterior) 2%; may also cause pancreatitis
- duodenal ulcers: 6 classical features, but history alone cannot distinguish from functional dyspepsia
  - epigastric pain; may localize to tip of xiphoid
  - burning
  - develops 1-3 h after meals
  - relieved by eating and antacids
  - interrupts sleep
  - periodicity (tends to occur in clusters over wk with subsequent periods of remission)
- gastric ulcers: more atypical symptoms; a biopsy is necessary to exclude malignancy

Investigations
- endoscopy (most accurate)
- upper GI series
- *H. pylori* tests (see Table 7)
- fasting serum gastrin measurement if Zollinger-Ellison (ZE) syndrome suspected

Gastric vs. Duodenal Ulcers
Gastric ulcers must always be biopsied to rule out malignancies; duodenal ulcers are rarely malignant

Treatment
- specific management depends on etiology; (see *H. pylori*, G13, *NSAID-Induced Ulceration*, G14 and *Stress-Induced Ulceration*, G14)
- eradicate *H. pylori* if present; chief advantage of triple therapy over PPI is to lower ulcer recurrence rate
- stop NSAIDs if possible
- start PPI: inhibits parietal cell H^+/K^+-ATPase pump which secretes acid
  - heals most ulcers, even if NSAIDs are continued
- other medications (e.g. histamine H_2-antagonists) less effective
- discontinue tobacco
- no diet modifications required but some people have fewer symptoms if they avoid caffeine, alcohol, and spices

Approach to PUD
- Stop NSAIDs
- Acid neutralization
- *H. pylori* eradication
- Quit smoking

Management of Bleeding Peptic Ulcers

- OGD to explore upper GI tract
- IV pantoprazole continuous drip
- establish risk of rebleeding/continuous bleed (since most ulcers stop bleeding spontaneously)
  - clinical risk factors: increased age (>60), bleeding diathesis, history of PUD, comorbid disease, hemodynamically unstable
  - endoscopic signs of recurrent bleeding (active bleeding, visible vessel, clot, red spot) more predictive than clinical risk factors
    - if high risk, consider ICU admission

Bleeding Peptic Ulcers
Risk Factors for Increased Mortality
- Co-existent illness
- Hemodynamic instability
- Age >60 yr
- Transfusion required

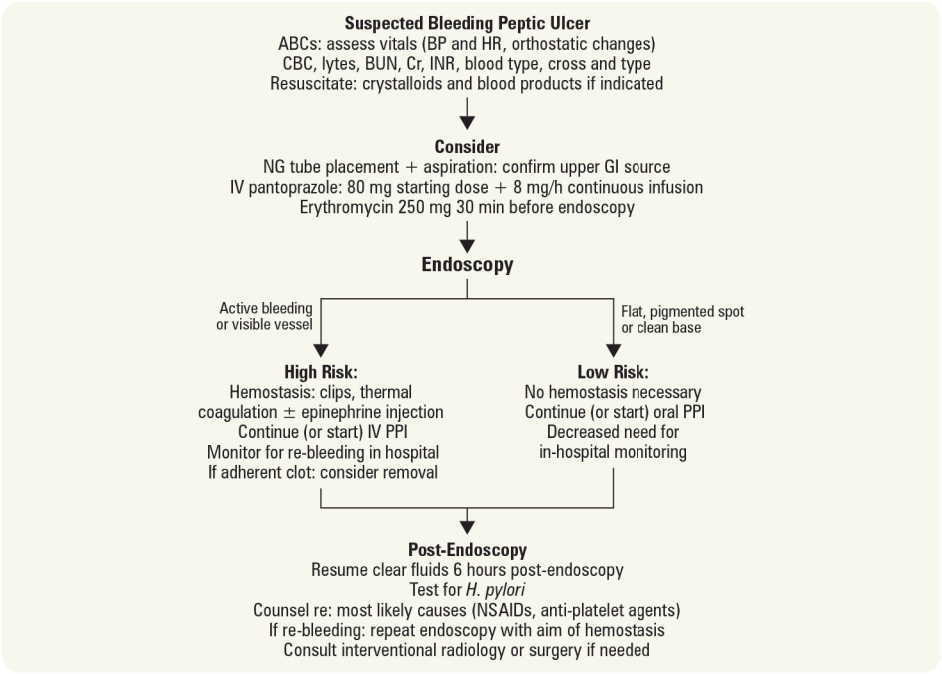

Figure 6. Approach to management of suspected bleeding peptic ulcer
Adapted from: Gralnek I, Barkun A, Bardou M. Management of acute bleeding from a peptic ulcer. *NEJM* 2008;359:928-937

Intragastric pH with Oral vs. Intravenous Bolus Plus Infusion Proton-Pump Inhibitor Therapy in Patients with Bleeding Ulcers
Gastroenterology 2008;134:1836-1841
Study: Randomized control trial.
Participants: Patients presenting with overt bleeding from an ulcer.
Intervention: Patients received either IV lansoprazole (90 mg bolus followed by 9 mg/h infusion; n=32) or oral lansoprazole (120 mg bolus followed by 30 mg every 3 h; n=34).
Primary Outcome: 24 h pH.
Results: Intragastric pH was >6 for >60% of the study period in 22 (68.8%) patients receiving IV and 22 (64.7%) patients receiving oral PPI. At 1 h, mean pHs for IV and oral were 5.3 and 3.3, respectively (difference 2.0; p=0.001). After 1.5 h, there were no differences in mean pH between the groups. Mean pH rose above 6 after 2-3 h of IV PPI and 3-4 h of oral PPI.
Conclusion: Frequent oral PPI may be able to replace the currently recommended IV bolus plus infusion PPI therapy in patients with bleeding ulcers. However, IV PPI has a more rapid increase in pH, reaching mean pH of 6 approximately 1 h sooner than oral PPI.

H. pylori-Induced Peptic Ulceration

Pathophysiology

- *H. pylori*: Gram-negative flagellated rod that resides on but does not invade the gastric mucosa
- acid secreted by parietal cells (stimulated by vagal acetylcholine, gastrin, histamine) necessary for most ulcers
- acid secreted by parietal cells (stimulated by vagal acetylcholine, gastrin, histamine) necessary for most ulcers
- theories of how *H. pylori* causes ulcers: none satisfactory, but pattern of colonization correlates with outcome
  - gastritis only in antrum (15% of patients), high gastric acid, associated with duodenal ulcer, may progress to gastric metaplasia of duodenum where ulcer forms
  - gastritis throughout stomach ("pangastritis" – 85% of patients), low gastric acid, associated with stomach ulcer and cancer

Epidemiology

- *H. pylori* is found in about 20% of all Canadians
  - highest prevalence in those raised during 1930s
- infection most commonly acquired in childhood, presumably by fecal-oral route
- high prevalence in developing countries, low socioeconomic status (poor sanitation and overcrowding)

Outcome

- gastritis (non-erosive) in 100% of patients but asymptomatic
- peptic ulcer in 15% of patients
- gastric malignancy (gastric carcinoma and mucosal associated lymphomatous tissue [MALT] lymphoma in 0.5% of patients)
- most are asymptomatic but still worthwhile eradicating to lower future risk of peptic ulcer/gastric malignancy and prevent spread to others (mostly children <5 yr of age)

Diagnosis

Table 7. Diagnosis of *H. pylori* Infection

Test	Sensitivity	Specificity	Comments
Non-invasive Tests			
Urea breath test	90-100%	89-100%	Affected by PPI therapy (false negatives)
Serology	88-99%	89-95%	Can remain positive after treatment
Invasive Tests (require endoscopy)			
Histology	93-99%	95-99%	Gold standard; affected by PPI therapy (false negatives)
Rapid urease test (on biopsy)	89-98%	93-100%	Rapid
Microbiology culture	98%	95-100%	Research only

Treatment: *H. pylori* Eradication

- triple therapy for 7-14 d (Hp-Pac®): PPI bid (e.g. lansoprazole 30 mg bid) + amoxicillin 1 g bid + clarithromycin 500 mg bid
  - 80% success rate
- quadruple therapy for 10-14 d: PPI bid + bismuth 525 mg qid + tetracycline 500 mg qid + metronidazole 250 mg qid
  - only recommended as first line therapy if resistance to clarithromycin or metronidazole is high, or in patients with recent or repeated exposure to these drugs
  - levofloxacin can replace metronidazole or tetracycline
- sequential therapy
  - days 1-5: PPI bid + amoxicillin 1 g bid
  - days 6-10: PPI bid + clarithromycin 500 mg bid + tinidazole (generally substitute with metronidazole as tinidazole not available in Canada) 500 mg bid
- 5-15% of cases are resistant to all known therapies

NSAID-Induced Ulceration

- NSAID use causes gastric mucosal petechiae in virtually all, erosions in most, ulcers in some (25%)
  - erosions bleed, but usually only ulcers cause significant clinical problems
- most NSAID ulcers are clinically silent: dyspepsia is as common in patients with ulcers as in patients without ulcers; NSAID-induced ulcers characteristically present with complications (bleeding, perforation, obstruction)
- NSAIDs more commonly cause gastric ulcers than duodenal ulcers
- may exacerbate underlying duodenal ulcer disease

Pathophysiology

- direct: erosions/petechiae – are due to local (direct) effect of drug on gastric mucosa
- indirect: systemic NSAID effect (intravenous NSAID causes ulcers, but not erosions), inhibits mucosal cyclooxygenase, leading to decreased synthesis of protective prostaglandins, thus leading to ulcers

Risk Factors For NSAID Causing Peptic Ulcer

- previous peptic ulcers/UGIB
- age
- high dose of NSAID/multiple NSAIDs being taken
- concomitant corticosteroid use
- concomitant cardiovascular disease/other significant diseases

Treatment

- prophylactic cytoprotective therapy with a PPI is recommended if any of the above risk factors exist concomitantly with ASA/NSAID use
- lower NSAID dose or stop all together and replace with acetaminophen
- combine NSAID with PPI or misoprostol in one tablet
- enteric coating of Aspirin® (ECASA) provides minor benefit since this decreases incidence of erosion, not incidence of ulceration

If at high risk for development of ulcers, prophylaxis with PPI indicated

Stress-Induced Ulceration

Definition

- ulceration or erosion in the upper GI tract of ill patients, usually in ICU
- lesions most commonly in fundus of stomach

Pathophysiology

- unclear: likely involves ischemia; may be caused by CNS disease, acid hypersecretion, Cushing ulcers
- physiological stress (e.g. fever, severe illness, complex post-operative course) causes ulcers and erosions

Risk Factors
- mechanical ventilation
- anti-coagulation
- multi-organ failure
- septicemia
- severe surgery/trauma
- CNS injury ("Cushing's ulcers")
- burns involving more than 35% of body surface

Clinical Features
- UGIB (see *Upper Gastrointestinal Bleeding*, G25)
- painless

Treatment
- prophylaxis with gastric acid suppressants (H_2-blockers or PPI) decreases risk of UGIB, but may increase risk of pneumonia
- treatment same as for bleeding peptic ulcer but often less successful

Curling's and Cushing's Ulcers
- **Curling's ulcer**: acute peptic ulcer of the duodenum resulting as a complication from severe burns when reduced plasma volume leads to ischemia and cell necrosis (sloughing) of the gastric mucosa (think BURN from a CURLing iron)
- **Cushing's ulcer**: peptic ulcer produced by elevated intracranial pressure (may be due to stimulation of vagal nuclei secondary to elevated ICP which leads to increased secretion of gastric acid)

Gastric Carcinoma

- see General Surgery, GS19

Small and Large Bowel

Classification of Diarrhea

Definition
- clinically: diarrhea defined as stools that are looser and/or more frequent than normal; physiologically: 24 h stool weight >200 g (less useful clinically)

Classification
- acute vs. chronic
- small volume (tablespoons of stool; typical of colonic diseases) vs. large volume (>1/2 cup stool; typical of small bowel diseases)
- watery vs. steatorrhea
- secretory (diarrhea persists with fasting) vs. osmotic (diarrhea stops with fasting)

Stool Osmotic Gap
Stool osmolality is normally about 290 mOsm/kg and can be approximated by the calculated stool osmolality
$(2 \times [Na^+]_{stool} + [K^+]_{stool})$
In osmotic diarrhea, measured stool osmolality > calculated stool osmolality
In secretory diarrhea measured stool osmolality = calculated stool osmolality

Acute Diarrhea

Definition
- passage of frequent unformed stools for <14 d

Etiology
- most commonly due to infections
- most infections are self-limiting and resolve within 7 d

Risk Factors
- food (seafood, chicken, turkey, eggs, beef)
- medications: antibiotics, laxatives
- others: high risk sexual activity, infectious outbreaks, family history (IBD)

Useful Questions in Acute Diarrhea

Those Fads Wilt
Travel
Homosexual contacts
Outbreaks
Seafood
Extra-intestinal signs of IBD
Family history
Antibiotics
Diet
Steatorrhea
Weight loss
Immunosuppressed
Laxatives
Tumour history

Table 8. Classification of Acute Diarrhea

	Inflammatory	Non-Inflammatory
Definition	Disruption of intestinal mucosa	Intestinal mucosa intact
Site	Usually colon	Usually small intestine
Mechanism	Organisms and cytotoxins invade mucosa, killing mucosal cells, and further perpetuating the diarrhea	Stimulation of intestinal water secretion and inhibition of water absorption (i.e. secretory problem)
Sigmoidoscopy	Usually abnormal mucosa seen	Usually normal
Symptoms	Bloody (not always) Small volume, high frequency Often lower abdominal cramping with urgency ± tenesmus May have fever ± shock	Watery, little or no blood Large volume Upper/periumbilical pain/cramp ± shock
Investigations	Fecal WBC and RBC positive	Fecal WBC negative
Etiology	See *Differential Diagnosis of Presenting Complaints*, G4	See *Differential Diagnosis of Presenting Complaints*, G4
Differential Diagnosis	Acute presentation of idiopathic inflammatory bowel disease	Acute presentation of non-inflammatory chronic diarrhea (e.g. celiac disease)
Significance	Higher yield with stool C&S Can progress to life-threatening megacolon, perforation, hemorrhage Antibiotics may benefit	Lower yield with stool C&S Chief life-threatening problem is electrolyte disturbances/ fluid depletion Antibiotics unlikely to be helpful

Infectious Causes of Inflammatory Diarrhea

Your Stool Smells Extremely Crappy
Yersinia
Shigella
Salmonella
E. coli (EHEC 0157:H7), ***E. histolytica***
Campylobacter, ***C. difficile***

Investigations
- stool cultures/microscopy (C&S/O&P) are required only if diarrhea is inflammatory, severe, or for epidemiological purposes (day care worker, nursing home resident, community outbreaks, e.g. Walkerton, etc.)
  - C&S only tests Campylobacter, Salmonella, Shigella, *E. coli*
    - other organisms must be ordered separately
- flexible sigmoidoscopy (without bowel preparation): useful if inflammatory diarrhea suspected
  - biopsies are the most useful method of distinguishing idiopathic IBD (Crohn's disease and ulcerative colitis) from infectious colitis or acute self-limited colitis
- *C. difficile* toxin: indicated when recent/remote antibiotic use, hospitalization, nursing home, or recent chemotherapy

Treatment
- fluid and electrolyte replacement orally in most cases, intravenous if severe extremes of age/coma
- anti-diarrheals
  - antimotility agents: diphenoxylate, loperamide (Imodium®); contraindicated in mucosal inflammation
    - side effects: abdominal cramps, toxic megacolon
  - absorbants: kaolin/pectin (Kaopectate®), methylcellulose, activated attapulgite
    - act by absorbing intestinal toxins/micro-organisms, or by coating intestinal mucosa
    - much less effective than antimotility agents
  - modifiers of fluid transport: bismuth subsalicylate (Pepto-Bismol®) may be helpful (but should not be used in the presence of bloody diarrhea or fever)
- antibiotics: rarely indicated
  - risks
    - prolonged excretion of enteric pathogen (especially *Salmonella*)
    - drug side effects (including *C. difficile* infection)
    - development of resistant strains
    - renal failure/hemolysis (enterohemorrhagic *E. coli* O157:H7)
  - indications for antimicrobial agents in acute diarrhea
    - septicemia
    - prolonged fever with fecal blood or leukocytes
    - clearly indicated: Shigella, *V. cholerae, C. difficile*, traveller's diarrhea (enterotoxigenic *E. coli* [ETEC]), Giardia, *Entamoeba histolytica,* Cyclospora
    - situational: Salmonella, Campylobacter, Yersinia, non-enterotoxigenic *E. coli*
    - Salmonella: always treat *Salmonella typhi* (typhoid or enteric fever); treat other Salmonella only if there is underlying immunodeficiency, hemolytic anemia, extremes of age, aneurysms, prosthetic valve grafts/joints, sickle cell disease

Finally: A Role for Bacteriotherapy Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*
NEJM 2013; 368:407-15

For centuries, out-of-the-box thinkers have speculated that the colonic bacteria all of us have, but which differs among individuals, play a role in disease. More recently, the colonic microbiome has become the hottest area of research in gastroenterology. The best documented medical indication for manipulating the colonic bacteria is recurrent *C. difficile* infection. In this randomized study of this disease, infusion of donor feces via a nasoduodenal tube resolved diarrhea in 81% of patients, without side-effects, compared to 31% given the standard treatment of oral vancomycin, and 23% of patients given oral vancomycin plus bowel lavage. It takes little prescience to predict an onslaught of future studies investigating the therapeutic potential of altering the human microbiome.

S. typhi has a rose spot rash (transient maculopapular rash on anterior thorax, upper abdomen), and a prodrome of high fever, bradycardia, headache, and abdominal pain. Diarrhea is not the initial presentation

Traveller's Diarrhea

- see Infectious Diseases, ID13

Chronic Diarrhea

Definition
- passage of frequent unformed stool for >14 d
- approach is similar to that of acute diarrhea except that the majority of cases are non-infectious

Etiology/Classification
- see *Differential Diagnosis of Common Presenting Complaints*, G4

Investigations
- guided by history
- stool analysis for: *C. difficile* toxin, C&S, O&P ± fecal fat, WBC
- blood for: CBC, electrolytes, CRP, TSH, celiac serology (IgA anti-tTG; ask for serum protein electrophoresis or immunoglobulin quantitation to rule out IgA deficiency which has an increased frequency in celiac disease)
- colonoscopy and ileoscopy with biopsy
- upper GI endoscopy with duodenal biopsy
- wireless small bowel endoscopy capsule (low yield)
- trial of lactose free diet
  - caveat: may delay diagnosis of IBD and celiac disease

Maldigestion and Malabsorption

Definition
- **maldigestion:** inability to break down large molecules in the lumen of the intestine into their component small molecules
- **malabsorption**: inability to transport molecules across the intestinal mucosa into circulation
- **malassimilation:** encompasses both maldigestion and malabsorption

Etiology
- **maldigestion**
  - inadequate mixing of food with enzymes (e.g. post-gastrectomy)
  - pancreatic exocrine deficiency
  - primary diseases of the pancreas (e.g. cystic fibrosis, pancreatitis, cancer)
  - bile salt deficiency
    - terminal ileal disease (impaired recycling), bacterial overgrowth (deconjugation of bile salts), rarely liver disease (cholestatic, e.g. primary biliary cirrhosis)
  - specific enzyme deficiencies (e.g. lactase)
- **malabsorption**
  - inadequate absorptive surface
    - infections/infestations (e.g. Whipple's disease, Giardia)
    - immunologic or allergic injury (e.g. celiac disease)
    - infiltration (e.g. lymphoma, amyloidosis)
    - fibrosis (e.g. systemic sclerosis, radiation enteritis)
    - bowel resection (length, site, location, presence/absence of ileocecal valve are important)
    - extensive ileal Crohn's disease
  - drug-induced
    - cholestyramine, ethanol, neomycin, tetracycline, and other antibiotics
  - endocrine
    - DM (complex pathogenesis)

Clinical Features
- symptoms usually vague unless disease is severe
- weight loss, diarrhea, steatorrhea, weakness, fatigue
- manifestations of malabsorption/deficiency

Fat Soluble Vitamins: **ADEK**
vitamin A, vitamin D, vitamin E, vitamin K

Table 9. Absorption of Nutrients and Fat Soluble Vitamins

Deficiency	Absorption	Clinical Disease and/or Features	Investigations
Iron	Duodenum, upper jejunum	Hypochromic, microcytic anemia, glossitis, koilonychia (spoon nails), pica	↓ Hb, ↓ serum Fe, ↓ serum ferritin
Calcium	Duodenum, upper jejunum (binds to Ca^{2+} binding-protein in cells; levels increased by Vit D)	Metabolic bone disease, may get tetany and paresthesias if serum calcium falls (see Endocrinology, E37)	↓ serum Ca^{2+}, ↓ serum Mg^{2+}, and ↑ ALP Evaluate for ↓ bone mineralization radiographically (DEXA)
Folic Acid	Jejunum	Megaloblastic anemia, glossitis, ↓ red cell folate (may see ↑ folic acid with bacterial overgrowth)	↓ serum folic acid
Vitamin B_{12}	B_{12} ingested and bound to R proteins mainly from salivary glands; stomach secretes intrinsic factor (IF) in acidic medium; in basic medium, proteases from the pancreas cleave R protein and B_{12}-IF complex forms, protecting B_{12} from further protease attack; B_{12} absorbed in ileum and binds to transcobalamin (TC)	Subacute combined degeneration of the spinal cord, peripheral/optic neuropathy, dementia, megaloblastic anemia, glossitis	Differentiate causes by nuclear Schilling test (when available) Positive anti-intrinsic factor antibodies and atrophic gastritis point toward pernicious anemia (see Hematology, H24)
Carbohydrate	Complex polysaccharides hydrolyzed to oligosaccharides, and disaccharides by salivary and pancreatic enzymes Monosaccharides absorbed in duodenum/jejunum	Generalized malnutrition, weight loss, flatus, and diarrhea	Hydrogen breath test Trial of carbohydrate-restricted diet D-xylose test
Protein	Digestion at stomach, brush border, and inside cell Absorption occurs primarily in the jejunum	General malnutrition and weight loss, amenorrhea, and ↓ libido if severe	↓ serum albumin (low sensitivity)
Fat	Lipase, colipase, phospholipase A (pancreatic enzymes), and bile salts needed for digestion Products of lipolysis form micelles which solubilize fat and aid in absorption Fatty acids diffuse into cell cytoplasm	Generalized malnutrition, weight loss, and diarrhea Foul-smelling feces + gas Steatorrhea	Small bowel biopsy MRCP, ERCP, pancreatic function tests (not routinely available) Quantitative stool fat test (72 h) May start with qualitative stool fat test (Sudan stain of stool) C-triolein breath test (not routinely available)
Vitamin A	Dietary sources (e.g. milk, eggs, liver, carrots, sweet potatoes)	Night blindness Dry skin Keratomalacia	
Vitamin D	Skin (via UV light) or diet (e.g. eggs, fish oil, fortified milk)	Osteomalacia in adults Ricketts in children	
Vitamin E	Dietary sources (e.g. vegetable oils, nuts, leafy green vegetables)	Retinopathy, neurological problems	
Vitamin K	Synthesized by intestinal flora ↑ risk of deficiency after prolonged use of broad spectrum antibiotics and/or starvation	Prolonged INR may cause bleeding	

* Calcium malabsorption more commonly causes decreased bone density rather than hypocalcemia because serum calcium levels are protected by leaching calcium from the bone

Investigations
- transglutaminase antibody serology/immunoglobulin quantitation and abdominal imaging are most useful because celiac disease and chronic pancreatitis are the two most common causes of steatorrhea
- 72 h stool collection (weight, fat content) documents steatorrhea (gold standard)
- fecal elastase (not routinely available) to screen for pancreatic insufficiency and/or consider empiric trial of pancreatic enzymes based on clinical context
- serum carotene (precursor to vitamin A), folate, Ca^{2+}, Mg^{2+}, vitamin B_{12}, albumin, ferritin, serum iron solution, INR/PTT
- stool fat globules on fecal smear stained with Sudan (rarely used)
- other tests specific for etiology (e.g. CT scan/MRI to visualize pancreas)

Treatment
- dependent on underlying etiology

Celiac Disease (Gluten Enteropathy/Sprue)

Definition
- abnormal small intestine mucosa due to intestinal reaction to gliadin, a component of gluten found in cereal grains

Etiology
- only autoimmune disease in which antigen (a peptide in α-gliadin) is recognized
- associated with other autoimmune diseases, especially Sjögren's, thyroid disease
- gluten, a protein in cereal grains, is broken down to gliadin, which is the toxic factor
- HLA-DQ2 (chromosome 6) found in 80-90% of patients compared with 20% in general population; celiac also associated with HLA-DQ8 (note: up to 40% of Caucasians carry the HLA alleles, but will never develop celiac disease)

Epidemiology
- more common in women
- family history: 10-15% of first-degree relatives
- may present any time from infancy (when cereals introduced) to elderly
- peak presentation in infancy

Clinical Features
- classic presentation: diarrhea, weight loss, anemia, symptoms of vitamin/mineral deficiency, failure to thrive; more common current presentation: bloating, gas, iron deficiency
- improves with gluten-free diet, deteriorates when gluten reintroduced
- disease is usually most severe in proximal bowel
  - thus iron, calcium, and folic acid deficiency (proximal absorption) more common than vitamin B_{12} deficiency (absorbed in ileum)
- gluten enteropathy may be associated with dermatitis herpetiformis skin eruption, epilepsy, myopathy, depression, paranoia, infertility, bone fractures/metabolic bone disease

Investigations
- small bowel mucosal biopsy (usually duodenum) is diagnostic with
  - increased intraepithelial lymphocytes (earliest pathologic finding)
  - crypt hyperplasia
  - villous atrophy
  - note: villous atrophy also seen in small bowel overgrowth, Crohn's, lymphoma, Giardia, HIV
- consider CT enterography to visualize small bowel to rule out lymphoma
- evidence of malabsorption (localized or generalized)
  - steatorrhea
  - low levels of ferritin/iron saturation, Ca^{2+}, Fe, albumin, cholesterol, carotene, B_{12} absorption
- improvement with a gluten-free diet; should not be started before anti-tTG and biopsy
- serological tests
  - serum anti-tTG antibody, IgA, is 90-98% sensitive, 94-97% specific
  - IgA deficient patients have false-negative anti-tTG
    - therefore, measure serum IgA concomitantly (via serum quantitative protein electrophoresis)
- fecal fat >7%

Treatment
- dietary counseling
  - gluten free diet; avoid barley, rye, wheat (as these grains are related and also have toxic factor, similar to gliadin)
    - oats allowed if not contaminated by other grains (grown in soil without cross-contamination)
  - rice and corn flour are acceptable
  - iron, folate supplementation (with supplementation of other vitamins as needed)

Gluten Found in BROW

Barley
Rye
Oats (controversial)
Wheat

- if poor response to diet change, consider
  - alternate diagnosis
  - non-adherence to gluten-free diet
  - concurrent disease (e.g. microscopic colitis, pancreatic insufficiency)
  - development of intestinal (enteropathy-associated T-cell) lymphoma (abdominal pain, weight loss, palpable mass)
  - development of diffuse intestinal ulceration, characterized by aberrant intraepithelial T-cell population (precursor to lymphoma)

Prognosis
- associated with increased risk of lymphoma, carcinoma (e.g. small bowel and colon; slight increase compared with general population), autoimmune diseases
- risk of lymphoma may be lowered by dietary gluten restriction

Inflammatory Bowel Disease

Definition
- Crohn's disease (CD), ulcerative colitis (UC), indeterminate colitis or IBD-unclassified (IBDU)

Pathophysiology
- poorly understood
- sustained response of the immune system, perhaps to enteric flora in a genetically predisposed individual
- current hypothesis: lack of appropriate down-regulation of immune responsiveness

Genetics
- increased risk of both UC and CD in relatives of patients with either disease, especially siblings, early onset disease
  - familial risk greater if proband has CD rather than UC
- likely polygenomic pattern: 9 gene loci are associated
- CARD15/NOD2 gene mutation associated with CD (relative risk in heterozygote is 3, in homozygote is 40), especially Ashkenazi Jews, early onset disease, ileal involvement, fistulizing and stenotic disease
  - CARD15 gene product modulates NFκB, which is required for the innate immune response to microbial pathogens, best expressed in monocytes-macrophages

Clinical Features

Table 10. Clinical Differentiation of Ulcerative Colitis from Crohn's Disease

	Crohn's Disease	Ulcerative Colitis
Location	Any part of GI tract • Small bowel + colon: 50% • Small bowel only: 30% • Colon only: 20%	Isolated to large bowel Always involves rectum, may progress proximally
Rectal Bleeding	Uncommon	Very common (90%)
Diarrhea	Less prevalent	Frequent small stools
Abdominal Pain	Post-prandial/colicky	Less common
Fever	Common	Uncommon
Urgency/Tenesmus	Uncommon (unless rectum involved)	Common
Palpable Mass	Frequent (25%), RLQ	Rare (if present, often related to cecum full of stool)
Recurrence After Surgery	Common	None post-colectomy
Endoscopic Features	Ulcers (aphthous, stellate, linear), patchy lesions, pseudopolyps, cobblestoning	Continuous diffuse inflammation, erythema, friability, loss of normal vascular pattern, pseudopolyps
Histologic Features	Transmural distribution with skip lesions Focal inflammation ± noncaseating granulomas, deep fissuring + aphthous ulcerations, strictures Glands intact	Mucosal distribution, continuous disease (no skip lesions) Architectural distortion, gland disruption, crypt abscess Granulomas absent
Radiologic Features	Cobblestone mucosa Frequent strictures and fistulae AXR: bowel wall thickening "string sign"	Lack of haustra Strictures rare; need to rule out complicating cancer
Complications	Strictures, fistulae, perianal disease	Toxic megacolon
Colon Cancer Risk	Increased if >30% of colon involved	Increased except in proctitis

Table 11. Extraintestinal Manifestations (EIM) of IBD

System	Crohn's Disease	Ulcerative Colitis
Dermatologic		
Erythema nodosum	15%	10%
Pyoderma gangrenosum	10%	Less common
Perianal skin tags	75-80%	Rare
Oral mucosal lesions	Common	Rare
Psoriasis	Statistically associated in 5-10% of those with IBD but not an EIM	
Rheumatologic		
Peripheral arthritis	15-20% of those with IBD (CD>UC)	
Ankylosing spondylitis	10% of those with IBD (CD>UC)	
Sacroiliitis	Occurs equally in CD and UC	
Ocular (~10% of IBD)		
Uveitis (vision threatening)		
Episcleritis (benign)	3-4% of IBD patients (CD>UC)	
Hepatobiliary		
Cholelithiasis	15-35% of patients with ileal Crohn's	
PSC	1-5% of IBD cases involving colon	
Fatty liver		
Urologic		
Calculi	Most common in CD, especially following ileal resection	
Ureteric obstruction		
Fistulae	Characteristic of Crohn's	
Others		
Thromboembolism		
Vasculitis		
Osteoporosis		
Vitamin deficiencies (B_{12}, Vit ADEK)		
Cardiopulmonary disorders		
Pancreatitis (rare)		

Crohn's Disease


Definition

- chronic transmural inflammatory disorder potentially affecting the entire gut from mouth to perianal region ("gum to bum")

Epidemiology

- incidence 1-6/100,000; prevalence 10-100/100,000
- bimodal: onset before 30 yr, second smaller peak age 60; M=F
- incidence of Crohn's increasing (relative to UC) especially in young females
- more common in Caucasians, Ashkenazi Jews
  - risk in Asians increases with move to Western countries
- smoking incidence in Crohn's patients is higher than general population

Pathology

- most common location: ileum + ascending colon
- linear ulcers leading to mucosal islands and "cobblestone" appearance
- granulomas are found in 50% of surgical specimens, 15% of mucosal biopsies

Clinical Features

- natural history unpredictable; young age, perianal disease, and need for corticosteroids have been associated with poor prognosis, but associations are not strong enough to guide clinical decisions
- most often presents as recurrent episodes of abdominal cramps, diarrhea, and weight loss
- ileitis may present with post-prandial pain, vomiting, RLQ mass; mimics acute appendicitis
- extra-intestinal manifestations are more common with colonic involvement
- fistulae, fissures, abscesses are common
- deep fissures with risk of perforation into contiguous viscera (leads to fistulae and abscesses)
- enteric fistulae may communicate with skin, bladder, vagina, and other parts of bowel

Investigations

- colonoscopy with biopsy to visualize (less often gastroscopy)
- CT/MR enterography to visualize small bowel
- CRP elevated in most new cases, useful to monitor treatment response (especially acutely in UC)
- bacterial cultures, O&P, *C. difficile* toxin to exclude other causes of inflammatory diarrhea

Management (see Figure 7)

Table 12. Management of Crohn's Disease

Management	Notes
Lifestyle/Diet	Smoking cessation Fluids only during acute exacerbation Enteral diets may aid in remission only for Crohn's ileitis, not colitis No evidence for any non-enteral diet changing the natural history of Crohn's disease, but may affect symptoms Those with extensive small bowel involvement or extensive resection require electrolyte, mineral, and vitamin supplements (vit D, Ca^{2+}, Mg^{2+}, zinc, Fe, B_{12})
Antidiarrheal Agents*	Loperamide (Imodium®) > diphenoxylate (Lomotil®) > codeine (cheap but addictive) All work by decreasing small bowel motility CAUTION if colitis is severe (risk of precipitating toxic megacolon), therefore avoid during flare-ups
5-ASA	Efficacy controversial: most evidence for mild colonic disease Sulfasalazine (Salazopyrin®): 5-ASA bound to sulfapyridine Hydrolysis by intestinal bacteria releases 5-ASA (active component) Dose-dependent efficacy Mesalamine (Pentasa®): coated 5-ASA releases 5-ASA in the ileum and colon
Antibiotics	e.g. metronidazole (20 mg/kg/d, bid or tid dosing) or ciprofloxacin Best described for perianal Crohn's, although characteristically relapse when discontinued
Corticosteroids	Prednisone: starting dose 40 mg OD for acute exacerbations; IV methylprednisolone if severe No proven role for steroids in maintaining remissions; masks intra-abdominal sepsis
Immunosuppressives	6-mercaptopurine (6-MP), azathioprine (Imuran®); methotrexate (used less often) More often used to maintain remission than to treat active inflammation Most commonly used as steroid-sparing agents i.e. to lower risk of relapse as corticosteroids are withdrawn May require >3 mo to have beneficial effect; usually continued for several years May help to heal fistulae, decrease disease activity Side effects: vomiting, pancreatitis, bone marrow suppression, increased risk of malignancy
Biologics	Infliximab IV (Remicade®) or adalimumab SC (Humira®): both = antibody to TNF-α Proven effective for treatment of fistulae and patients with medically refractory CD First-line immunosuppressive therapy with inflixmab + azathioprine more effective than using either alone
Surgical/ Experimental	Surgical treatment (see General Surgery, GS29) Surgery generally reserved for complications such as fistulae, obstruction, abscess, perforation, bleeding, and for medically refractory disease If <50% or <200 cm of functional small intestine, risk of short bowel syndrome At least 50% clinical recurrence within 5 yr; 85% within 15 yr; endoscopic recurrence rate even higher 40% likelihood of second bowel resection, 30% likelihood of third bowel resection Complications of ileal resection <100 cm resected → watery diarrhea or cholorrhea (impaired bile salt absorption) Treatment: cholestyramine or anti-diarrheals e.g. loperamide >100 cm resected → steatorrhea (reduced mucosal surface area, bile salt deficiency) Treatment: fat restriction, medium chain triglycerides

*Cholestyramine: a bile-salt binding resin; for watery diarrhea with <100 cm of terminal ileum diseased or resected; however, non-specific anti-diarrheals are more convenient and often more potent

Prognosis

- highly variable course
- 10% disabled by the disease eventually, spontaneous remission also described
- increased mortality, especially with more proximal disease, greatest in the first 4-5 yr
- complications include
  - intestinal obstruction/perforation
  - fistula formation
  - malignancy (lower risk compared to UC)
- surveillance colonoscopy same as ulcerative colitis (see *Ulcerative Colitis*, G22) if more than 1/3 of colon involved

Traditional Medical Management of Crohn's

	Induction of Remission	Maintenance
5-ASA	?	?
Steroids	+	
Immunosuppressive	+	+
Antibiotics	+	
MTX	+	+
Infliximab	+	+

Note: Starting with immunosupressives plus immunomodulators ("bottom-up approach") increasingly being used (*Lancet* 2008;371:660-667). Combination of azathioprine and infliximab has the highest remission rate yet described with medical treatment (*NEJM* 2010;362;1383-1395). Characteristically more than 1 yr between onset of symptoms and diagnosis of Crohn's disease.

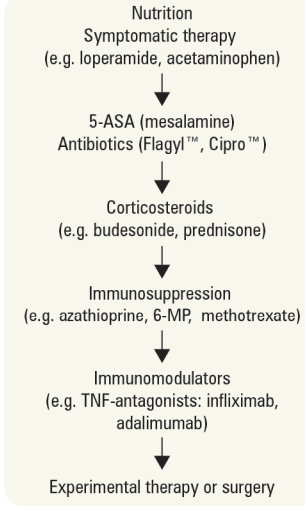

Figure 7. Traditional graded approach to induction therapy in Crohn's disease

Ulcerative Colitis

Definition
- inflammatory disease affecting colonic mucosa anywhere from rectum (always involved) to cecum

Epidemiology
- incidence 2-10/100,000; prevalence 35-100/100,000 (more common than Crohn's)
- 2/3 onset by age 30 (with second peak after 50); M=F
- small hereditary contribution (15% of cases have 1st degree relative with disease)
- risk is less in smokers
- inflammation limited to rectum or left colon is more common than pancolitis

Pathology
- disease can involve any portion of lower bowel ranging from rectum only (proctitis) to entire colon (pancolitis)
- inflammation is diffuse, continuous and confined to mucosa

Clinical Features
- rectal bleeding is the hallmark feature, however diarrhea may be present if more than the rectum is involved
  - can also have abdominal cramps/pain, especially with defecation
- severity of colonic inflammation correlates with symptoms (stool volume, amount of blood in stool)
- tenesmus, urgency, incontinence
- systemic symptoms: fever, anorexia, weight loss, fatigue in severe cases
- extra-intestinal manifestations (see Table 11)
- characteristic exacerbations and remissions; 5% of cases are fulminant

In UC, non-bloody diarrhea is frequently the initial presentation; eventually progressing to bloody diarrhea

Investigations
- sigmoidoscopy with mucosal biopsy (to exclude self-limited colitis) without bowel prep often sufficient for diagnosis
- colonoscopy helpful to determine extent of disease; contraindicated in severe exacerbation
- CT colonography (formerly barium enema) if colonoscopy cannot be done; contraindicated in severe disease
- stool culture, microscopy, *C. difficile* toxin assay necessary to exclude infection
- no single confirmatory test

Treatment
- mainstays of treatment: 5-ASA (mesalamine) derivatives (only in mild to moderate disease) and corticosteroids, with azathioprine used in steroid-dependent or resistant cases
- diet of little value in decreasing inflammation but may alleviate symptoms
- anti-diarrheal medications generally not indicated in UC
- 5-ASA
  - topical (suppository or enema): very effective for distal disease (distal to splenic flexure), preferable to corticosteroids
  - oral: effective for mild to moderate, but not severe colitis (e.g. sulfasalazine 3-4 g/d, mesalamine 4 g/d)
  - commonly used in maintaining remission (decreases yearly relapse rate from 60% to 15%)
  - may decrease rate of colorectal cancer
- corticosteroids
  - to remit acute disease, especially if severe or first attack; may need maximum dose IV steroids initially (e.g. methylprednisolone 30 mg IV q12h)
  - limited role as maintenance therapy for mild to moderate disease
  - use suppositories for proctitis, enemas for proctosigmoiditis
  - topical steroids (e.g. hydrocortisone foam, budesonide enemas) for inflammation distal to splenic flexure
- immunosuppressants (steroid-sparing)
  - in hospitalized patients with severe UC – add IV infliximab if no response to IV methylprednisolone within 3 days; then colectomy if inadequate response to drugs or no response to corticosteroids + infliximab
  - biologics (infliximab, adalimumab, golimumab) can also be used for outpatients with moderate-severe disease, particularly those that are steroid-unresponsive or steroid-dependent
  - azathioprine and 6-mercaptopurine: too slow to rapidly resolve acute relapse
    - most commonly used to maintain remission as corticosteroids withdrawn
- surgical treatment curative
  - aim for cure with colectomy; bowel continuity can be restored with ileal pouch-anal anastamosis (IPAA)
  - indications: failure of adequate medical therapy, toxic megacolon, uncontrollable bleeding, pre-cancerous changes detected either by endoscopy or endoscopic biopsies (dysplasia), inability to taper corticosteroids, overt malignancy

Medical Management of Ulcerative Colitis

	Induction of Remission	Maintenance
5-ASA	+	+
Steroids	+	
Immunosuppressive	±	+

Complications
- similar to CD, except
  - more liver problems (especially PSC in men)
  - greater risk of colorectal cancer
    - risk increases with duration and extent of disease (5% at 10 yr, 15% at 20 yr for pancolitis; overall relative risk is 8%)
    - risk also increases with active mucosal inflammation and sclerosing cholangitis
    - thus, regular colonoscopy and biopsy in pancolitis of ≥8 yr is indicated
  - toxic megacolon (transverse colon diameter >6 cm on abdominal x-ray) with immediate danger of perforation (see General Surgery, GS30)

When Considering Complications of IBD, Think: ULCERATIVE COLITIS

Urinary calculi
Liver problems
Cholelithiasis
Epithelial problems
Retardation of growth/sexual maturation
Arthralgias
Thrombophlebitis
Iatrogenic complications
Vitamin deficiencies
Eyes

Colorectal cancer
Obstruction
Leakage (perforation)
Iron deficiency
Toxic megacolon
Inanition (wasting)
Strictures

Prognosis
- chronic relapsing pattern in most patients
- 10-15% chronic continuous pattern
- >1 attack in almost all patients
- more colonic involvement in the 1st yr correlates with increased severity of attacks and increased colectomy rate
  - colectomy rate = 1% for all patients after the 1st yr; 20-25% eventually undergo colectomy
- normal life expectancy
- if proctitis only, usually benign course

Irritable Bowel Syndrome

Definition
- a form of functional bowel disease; more than just a label for GI symptoms unexplained after normal investigations

Epidemiology
- 20% of North Americans
- onset of symptoms usually in young adulthood
- F>M

Pathophysiology
- associated with either abnormal perception of intestinal activity or abnormal intestinal motility
- abnormal motility: multiple abnormalities described; unclear if associations or if causative
- psychological: stress may increase IBS symptoms but does not cause IBS
- types of IBS: IBS with diarrhea, IBS with constipation, IBS-mixed type (both diarrhea and constipation)

Diagnosis

Table 13. Rome III Criteria for Diagnosing Irritable Bowel Syndrome

IBS Rome III Criteria

• ≥12 wk in the past 12 mo of abdominal discomfort or pain that has 2 out of 3 features
  • Relieved with defecation
  • Associated with a change in frequency of stool
  • Associated with a change in consistency of stool

• The following are supportive, but not essential to the diagnosis:
  • Abnormal stool frequency (>3/d or <3/wk)
  • Abnormal stool form (lumpy/hard/loose/watery) >1/4 of defecations
  • Abnormal stool passage (straining, urgency, feeling of incomplete evacuation) >1/4 of defecations
  • Passage of mucus >1/4 of defecations
  • Bloating

Diagnosis of IBS Less Likely in Presence of "Red Flag" Features • Weight loss • Anemia • Fever • Blood or pus in stool • Nocturnal defecation • Abnormal gross findings on flexible sigmoidoscopy
Normal Physical Exam

Investigations
- if history consistent with Rome III criteria, no alarm symptoms, and no family history of IBD or colorectal cancer, limited investigations required
- aim is to rule out diseases which mimic IBS, particularly celiac disease and IBD
- investigations can be limited to CBC, inflammatory markers (ESR, CRP) and celiac serology
- if available, fecal calprotectin is likely more reliable test to rule out IBD
- consider TSH, stool cultures depending on clinical circumstances
- consider colonoscopy (e.g. if alarming features present, family history of IBD or age > 50)

IBS Mimickers
- Enteric infections e.g. *Giardia*
- Lactose intolerance/other disaccharidase deficiency
- Crohn's disease
- Celiac sprue
- Drug-induced diarrhea
- Diet-induced (excess tea, coffee, colas)

Treatment
- reassurance, explanation, support, aim for realistic goals
- relaxation therapy, biofeedback, hypnosis, stress reduction
- no therapeutic agent consistently effective, pain most difficult to control
- symptom-guided treatment
  - pain predominant
    - antispasmodic medication before meals (e.g. hyoscine, pinaverium, trimebutine)
    - increase dietary fibre (bran or psyllium)
    - tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI)
  - IBS with diarrhea (IBS-D)
    - increase dietary fibre (bran or psyllium) to increase stool consistency
    - loperamide (Imodium®)
    - diphenoxylate (Lomotil®)
    - cholestyramine 4 g QID
  - IBS with constipation (IBS-C)
    - exercise and increase fibre in diet
    - osmotic or other laxatives
  - mixed (alternating constipation and diarrhea) (IBS-M)

Prognosis
- 80% improve over time
- most have intermittent episodes
- normal life expectancy

Rifaximin Therapy for Patients with Irritable Bowel Syndrome Without Constipation
NEJM 2011;364:22-32
Purpose: Previous evidence suggests that gut flora may play an important role in the pathophysiology of IBS. This study evaluated rifaximin, a minimally absorbed antibiotic, in treating IBS without constipation.
Methods: Two phase 3, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2). 1,260 patients who had IBS without constipation were randomly assigned to rifaximin (550 mg dose) or placebo, 3 times daily for 2 wk, with a follow-up of 10 wk. The primary endpoint was adequate self-reported relief of global IBS symptoms.
Results: Significantly more patients in the rifaximin group had adequate self-reported relief of global IBS symptoms compared to the placebo group during the first 4 wk after treatment (40.8% vs. 31.2% respectively). Also, more patients in the rifaximin group had adequate relief of bloating compared to the placebo group (39.5% vs. 28.7% respectively).
Conclusions: Rifaximin therapy for 2 wk provided significant relief of symptoms, bloating, abdominal pain, and stool consistency associated with IBS without constipation.

Constipation

Definition
- passage of infrequent or hard stools with straining (stool water <50 mL/d); bowel frequency <3 times/wk

Epidemiology
- increasing prevalence with age; F>M
- rare in Africa and India where stool weight is 3-4x greater than in Western countries

Etiology
- most common: idiopathic attributed to colon dysmotility but this is difficult to measure
- organic causes
  - medication side effects (narcotics, antidepressants) are the most common
  - intestinal obstruction, left sided colon cancer (consider in older patients), and fecal impaction
  - metabolic
    - DM
    - hypothyroidism
    - hypercalcemia, hypokalemia, uremia
  - neurological
    - intestinal pseudo-obstruction
    - Parkinson's disease
    - MS
  - collagen vascular disease (e.g. scleroderma)
  - painful anal conditions (e.g. fissures)

Causes of Constipation

DOPED
Drugs
Obstruction
Pain
Endocrine dysfunction
Depression

Clinical Presentation
- overlaps with IBS
- stool firm, difficult to expel, passed with straining, abdominal pain relieved by defecation, flatulence, overflow diarrhea, tenesmus, abdominal distension, infrequent BMs (<3/wk)

Investigations
- underlying disease rarely found if constipation is the only presenting symptom
  - only test indicated in this situation is a CBC (2013 recommendation of American Gastroenterology Association), but also consider TSH, calcium, and glucose
- colon visualization if concomitant symptoms such as rectal bleeding, weight loss, or anemia (colonoscopy, CT colonography)
- if refractory to treatment, consider classification based on colon transit time; can measure colonic transit time with radio-opaque markers that are ingested and followed with a series of plain film abdominal x-rays (normal: 70 h)
  1. normal = misperception of normal defecation (IBS)
  2. prolonged throughout = "colonic inertia" (infrequent bowel movements with gas/bloating, tends to occur in youth)
  3. outlet obstruction = inability to coordinate pelvic floor muscles to empty rectum, straining, stool in rectum on digital exam, tends to occur in old age
- combination of 1 and 3 common

Treatment (In order of Increasing Potency)
- dietary fibre
  - useful if mild or moderate constipation, but not if severe
  - aim for 30 g daily, increase dose slowly
- surface-acting (soften and lubricate)
  - docusate salts, mineral oils
- osmotic agents (effective in 2-3 d)
  - lactulose, sorbitol, magnesium salts (e.g. magnesium hydroxide, i.e. milk of magnesia), lactitol, polyethylene glycol 3350
- cathartics/stimulants (effective in 24 h)
  - castor oil, senna (avoid prolonged use to prevent melanosis coli), bisacodyl
- enemas and suppositories (e.g. saline enema, phosphate enema, glycerin suppository, bisacodyl suppository)
- prokinetic agents (prucalopride)
- linaclotide (increases water secretion of bowel)

Upper Gastrointestinal Bleeding

Definition
- bleeding proximal to the ligament of Treitz, see *Gastrointestinal Tract*, G2 (75% of GI bleeds)
  - ligament of Treitz: suspensory ligament where fourth portion of the duodenum transitions to jejunum

Etiology
- above the GE junction
  - epistaxis
  - esophageal varices (10-30%)
  - esophagitis
  - esophageal cancer
  - Mallory-Weiss tear (10%)
- stomach
  - gastric ulcer (20%) (see *Peptic Ulcer Disease*, G12)
  - gastritis (e.g. from alcohol or post-surgery) (20%)
  - gastric cancer
  - gastric antral vascular ectasia (rare, associated with cirrhosis and CTD)
  - Dieulafoy's lesion (very rare)
- duodenum
  - ulcer in bulb (25%)
  - aortoenteric fistula: usually only if previous aortic graft (see sidebar, G25)
- coagulopathy (drugs, renal disease, liver disease)
- vascular malformation (Dieulafoy's lesion, AVM)

Clinical Features
- in order of decreasing severity of the bleed: hematochezia > hematemesis > coffee ground emesis > melena > occult blood in stool

Treatment (initial)
- stabilize patient (1-2 large bore IVs, IV fluids, monitor)
- send blood for CBC, cross and type, platelets, PT, PTT, electrolytes, BUN, Cr, LFTs
- keep NPO
- consider NG tube to determine upper vs. lower GI bleeding in some cases
- endoscopy (OGD): establish bleeding site + treat lesion
  - if bleeding peptic ulcer: most commonly used method of controlling bleeding is injection of epinephrine around bleeding point + thermal hemostasis (bipolar electrocoagulation or heater probe); less often thermal hemostasis may be used alone, but injection alone not recommended
  - endoclips
  - hemospray
- IV PPI: decrease risk of rebleed if endoscopic predictors of rebleeding seen (see prognosis section)
  - given to stabilize clot, not to accelerate ulcer healing
  - if given before endoscopy, decreases need for endoscopic therapeutic intervention
- for variceal bleeds, octreotide 50 µg loading dose followed by constant infusion of 50 µg/h
- consider IV erythromycin (or metoclopramide) to accelerate gastric emptying prior to gastroscopy to remove clots from stomach

Prognosis
- 80% stop spontaneously
- peptic ulcer bleeding: low mortality (2%) unless rebleeding occurs (25% of patients, 10% mortality)
- endoscopic predictors of rebleeding: spurt or ooze, visible vessel, fibrin clot
- can send home if clinically stable, bleed is minor, no comorbidities, endoscopy shows clean ulcer with no predictors of rebleeding
- H_2-antagonists have little impact on rebleeding rates and need for surgery
- esophageal varices have a high rebleeding rate (55%) and mortality (29%)

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding
NEJM 2013;368:11-21
Study: Prospective, unblinded, RCT, follow-up up to 45 d.
Populations: 921 patients with hematemesis, bloody nasogastric aspirate, melena, or both. Exclusion criteria included massive bleed, ACS, stroke/TIA or transfusion within previous 90 d; recent trauma/surgery; lower GI bleed.
Intervention: Patients randomized to restrictive (<70 g/L) or liberal (<90 g/L) transfusion.
Outcome: Mortality, further bleeding, adverse events.
Results: Fewer patients in the restrictive group required transfusion (51% vs. 15%; p<0.001). The hazard ratio for death for restrictive compared to liberal transfusion was 0.55; 95% CI 0.33-0.92; p=0.02. Further bleeding occurred in 10% vs. 16% (p=0.01) of patients, while adverse effects occurred in 40% vs. 48% (p=0.02) of patients in the restrictive and liberal strategies, respectively. The restrictive strategy had a better survival rate in patients with bleeding associated with cirrhosis Child-Pugh class A or B (HR: 0.30; 95% CI 0.11-0.85), but not in cirrhosis Child-Pugh class C (HR: 1.04; 95% CI 0.45-2.37) or a peptic ulcer (HR: 0.70; 95% CI 0.26-1.25).
Conclusions: Transfusing patients with an acute upper GI bleed at hemoglobin of <70 g/L rather than 90 g/L is associated with fewer transfusions, better survival, and fewer adverse events.

Always ask about NSAID/Aspirin® or anticoagulant therapy in GI bleed

Aortoenteric Fistula is a rare and lethal cause of GI bleed, most common in patients with a history of aortic graft surgery. Therefore, perform emergency endoscopy if suspected, emergency surgery if diagnosed
Note: The window of opportunity is narrow. Suspect if history of aortic graft, abdominal pain associated with bleeding

Review Article: Improved Survival with Patients with Variceal Bleeds
Int J Hepatol 2011;doi:10.461/2011/356919
General Measures: Resuscitation to achieve hemodynamic stability (Hb >70-80 g/L) but avoid fluid overload as it can precipitate or worsen ascites.
Antibiotic Prophylaxis: IV ceftriaxone or postendoscopic norfloxacin reduces bacterial infection, rebleeding rates, length of hospitalization, and all-cause mortality.
Splanchnic Vasoconstriction: Somatostatin, Octreotide, Terlipressin.
Therapeutic Endoscopy: Band ligation is superior to injection sclerotherapy in initial control of bleeding, incidence of rebleeding, side effects, time, and survival.
Recommendations: Combination therapy with vasoactive drug plus endoscopic band ligation is recommended for Child-Pugh A and if combined therapy fails (HVPG >20 mmHg within 24 h after start of bleed is the best predictor failure); TIPS is then recommended for patients with Child-Pugh B or C, early TIPS is recommended over combined therapy.

Forrest Classification of Bleeding Peptic Ulcers

Forrest Class	Type of Lesion	Risk of Rebleed (%)
I	Arterial bleeding (oozing/spurting)	55-100
IIa	Visible vessel	43
IIb	Sentinel clot	22
IIc	Hematin covered flat spot	10
III	No stigmata of hemorrhage	5

Lancet 1974;2:394-397

Approach to Iron Deficiency Anemia

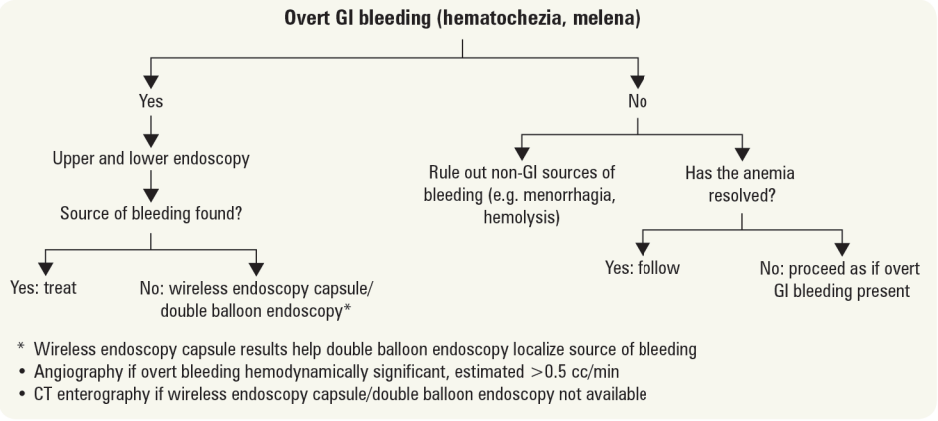

Figure 8. Approach to iron deficiency anemia

Esophageal Varices

Etiology
- almost always due to portal HTN
- often accompanied by varices in stomach

Clinical Features
- characteristically massive upper GI bleeding

Prognosis
- risk of bleeding: 30% in 1st yr
- risk of rebleeding: 50-70% (20% mortality at 6 wk)

Investigations
- endoscopy

Management

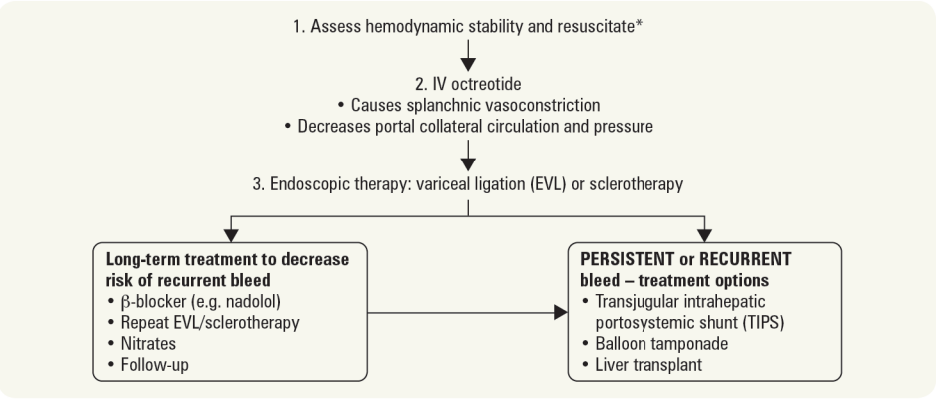

Figure 9. Management of bleeding esophageal varices
Not depicted: Intravenous ceftriaxone (lowers risk of sepsis, especially spontaneous bacterial peritonitis)

If varices isolated to stomach, think of splenic vein thrombosis

Gastric varices best treated by endoscopic injection of cyanoacetate ("crazy glue")

Mallory-Weiss Tear

Definition
- longitudinal laceration in gastric mucosa on lesser curvature near GE junction (20% straddle junction, 5% in distal esophagus)

Etiology
- due to rapid increases in gastric pressure from retching/vomiting against a closed glottis
- hiatus hernia usually present

Clinical Features
- hematemesis ± melena, classically following an episode of retching without blood
- can lead to fatal hematemesis

Management
- 90% stop spontaneously
- if persistent: endoscopy with epinephrine injection ± clips or surgical repair

Lower Gastrointestinal Bleeding

Definition
- bleed distal to ligament of Treitz

Etiology
- if blood per rectum with hemodynamic instability, rule out upper GI source
- diverticular (60% from right colon)
- vascular
  - angiodysplasia (small vascular malformations of the gut)
  - anorectal (hemorrhoids, fissures)
- neoplasm
  - cancer
  - polyps
- inflammation
  - colitis (ulcerative, infectious, radiation, ischemic)
- post-polypectomy

Lower GI Bleed

CHAND
Colitis (radiation, infectious, ischemic, IBD [UC > CD])
Hemorrhoids/fissure
Angiodysplasia
Neoplastic
Diverticular disease

Clinical Features
- hematochezia (see Figure 10)
- anemia
- occult blood in stool
- rarely melena

Treatment
- treat underlying cause

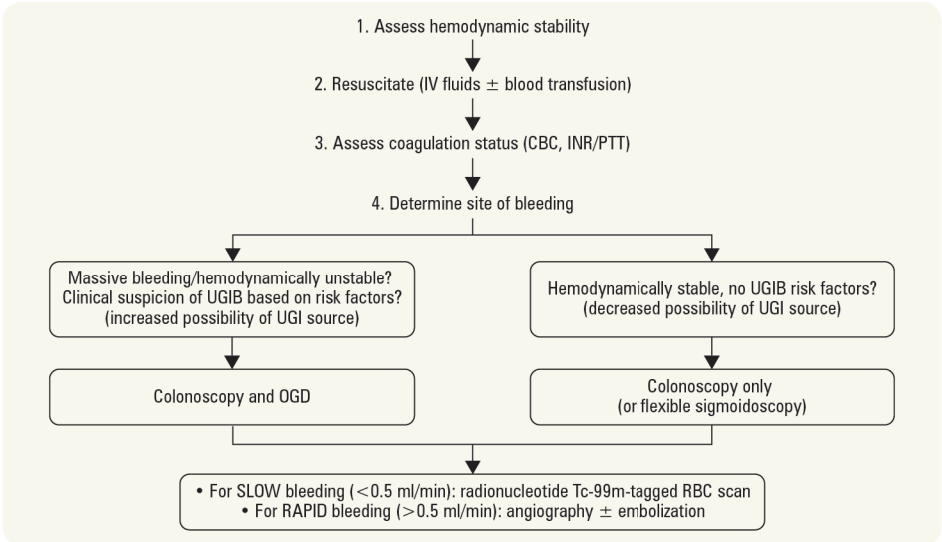

Figure 10. Approach to hematochezia

Always exclude upper GI lesion before localizing the site of the bleeding to the lower GI tract

Colorectal Carcinoma

- see General Surgery, GS35

Colorectal Polyps

- see General Surgery, GS34

Familial Colon Cancer Syndromes

- see General Surgery, GS34

Benign Anorectal Disease

- see General Surgery, GS39

Liver

Investigations of Hepatobiliary Disease

A. TESTS OF LIVER FUNCTION

Table 14. Tests of Liver Function

Test	What Do Levels Correlate With?	Increased by	How to Interpret
Prothrombin Time (PT or INR)	Hepatic protein synthesis All coagulation factors except VIII	Hepatocellular dysfunction Vitamin K deficiency (due to malnutrition, malabsorption, etc.)	PT/INR will promptly correct if vitamin K is administered, so increased PT/INR in absence of vitamin K deficiency is a reliable marker of hepatocellular dysfunction
Serum Albumin	Hepatic protein synthesis (and other causes listed in next column)	Hepatocellular dysfunction Malnutrition Renal or GI losses Significant inflammation Malignancy	Rule out potential causes other than hepatocellular dysfunction
Serum Direct Bilirubin*	Hepatic excretion from hepatocyte to biliary system	Liver dysfunction	Conjugation is preserved even in end stage liver failure, thus increased direct bilirubin indicates liver dysfunction

*Serum Bilirubin
- canaliculus breakdown product of hemoglobin; metabolized in the reticuloendothelial system of liver, transported through biliary system, excreted via gut
- direct bilirubin = conjugated; indirect = unconjugated bilirubin

All clotting factors except factor VIII and von Willebrand factor are exclusively synthesized in the liver. Factor VIII is also produced in the endothelium

B. TESTS OF LIVER INJURY

- disproportionately increased AST or ALT = hepatocellular damage
  - ALT more specific to liver; AST from multiple sources (especially muscle)
  - elevation of both highly suggestive of liver injury
  - most common cause of elevated ALT is fatty liver
- disproportionately increased ALP (and GGT) = cholestasis (stasis of bile flow)
  - if ALP is elevated alone, rule out bone disease by fractionating ALP and/or checking GGT
  - if ALP elevation out of proportion to ALT/AST elevation, consider
    1. obstruction of common bile duct (extraluminal = pancreatic Ca, lymphoma; intraluminal = stones, cholangiocarcinoma, sclerosing cholangitis, helminths)
    - 2. destruction of microscopic ducts (e.g. PBC)
    - 3. bile acid transporter defects (drugs, intrahepatic cholestasis of pregnancy)
    - 4. infiltration of the liver (liver metastases, lymphoma, granulomas, amyloid)

ALT > AST = most causes of hepatitis
AST > ALT = alcoholic liver disease or other causes of hepatitis (i.e. non-alcoholic liver disease) that have progressed to advanced cirrhosis

Acute Viral Hepatitis (General)

Definition
- viral hepatitis lasting <6 mo

Clinical Features
- most are subclinical
- flu-like prodrome may precede jaundice by 1-2 wk
  - N/V, anorexia, taste/smell disturbance, headaches, fatigue, myalgia, low-grade fever
  - arthralgia and urticaria (especially HBV)
- only some progress to icteric (clinical jaundice) phase, lasting days to weeks
  - pale stools and dark urine 1-5 d prior to icteric phase
  - hepatomegaly and RUQ pain
  - splenomegaly and cervical lymphadenopathy (10-20% of cases)

Serum Transaminases >1000 due to
- Viral hepatitis
- Drugs
- Autoimmune hepatitis
- Hepatic ischemia
- Less often, common bile duct stone

Investigations
- AST and ALT (>10-20x normal in hepatocellular necrosis)
- ALP minimally elevated
- viral serology, particularly the IgM antibody directed to the virus

Treatment
- supportive (hydration, diet)
- usually resolves spontaneously, but if severe HBV infection, treatment with entecavir should be considered; in anicteric hepatitis C, anti-viral treatment should be considered (see hepatitis C)
- indications for hospitalization: encephalopathy, coagulopathy, severe vomiting, hypoglycemia

Prognosis
- poor prognostic indicators: comorbidities, persistently high bilirubin (>340 mmol; 20 mg/dL), increased INR, decreased albumin, hypoglycemia

Complications
- cholestasis (most commonly associated with HAV infection)
- hepatocellular necrosis: AST, ALT >10-20x normal, ALP and bilirubin minimally increased, increased cholestasis

Alcoholic hepatitis: history of recent alcohol, RUQ abdominal pain, AST/ALT>2, AST usually <300, low grade fever, mildly elevated WBC

Major Sources of ALP
- Hepatobiliary tree
- Bone
- Placenta

Hepatitis A Virus

- RNA virus
- fecal-oral transmission; incubation period 4-6 wk
- diagnosed by elevated transaminases, positive anti-HAV IgM
- in children: characteristically asymptomatic
- in adults: fatigue, nausea, arthralgia, fever, jaundice
- can cause acute liver failure and subsequent death (<1-5%)
- can relapse, but never becomes chronic

DDx for Hepatitis
- Viral infection
- Alcohol
- Drugs
- Immune-mediated
- Toxins

Hepatitis B Virus

Table 15. Hepatitis B Serology

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc	Liver Enzymes
Acute HBV	+	–	+	–	IgM	
Chronic (e-Ag positive) HBV (generally high HBV DNA)	+	–	+	–	IgG	ALT, AST elevated
Chronic (e-Ag negative) HBV (generally low HBV DNA)	+	–	–	+	IgG	ALT, AST normal
Resolved infection	–	±	–	±	IgG	
Immunization	–	+	–	–	–	

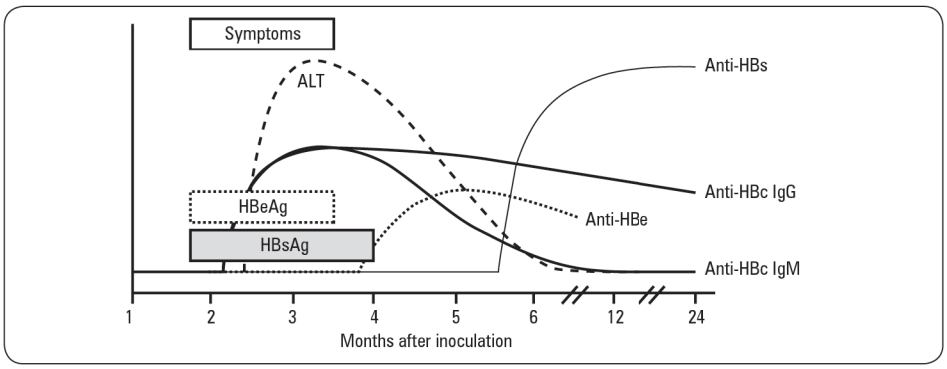

Figure 11. Time course of acute hepatitis B infection

Causes of Elevated Serum Transaminases in Chronic Hepatitis B
- Ongoing immune-mediated liver injury without immune control of HBV
- Reactivation from prior immune control due to lack of adequate immune control
- Seroconversion (HBeAg converting to anti-HBe; spontaneously or with Rx)
- Hepatitis D
- Other liver insult (fatty liver, alcohol, drugs, hepatitis A)

Epidemiology
- 4 phases of chronic hepatitis B: not all carriers will go through all 4 phases, but all carriers will have positive HBsAg
  1. **immune tolerance:** extremely high HBV-DNA (>20,000 IU/mL), HBeAg positive, but normal ALT/AST; due to little immune control and minimal immune-mediated liver damage; characteristic of perinatal infection (or 'incubation period' in adult with newly-acquired HBV)

DDx for Hepatomegaly
- Congestive (right heart failure, Budd-Chiari syndrome)
- Infiltrative
  - Malignant (primary, secondary, lymphoproliferative, leukemia)
  - Benign (fatty liver, cysts, hemochromatosis, extramedullary hematopoiesis, amyloid)
- Proliferative
  - Infectious (viral, tuberculosis, abscess, echinococcus)
  - Inflammatory (granulomas [sarcoid], histiocytosis X)

2. **immune clearance** (or immunoactive): falling but still elevated HBV-DNA levels (>20,000 IU/mL), HBeAg positive; due to immune attack on the virus and immune-mediated liver damage; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment
3. **immune control:** lower HBV-DNA (<20,000 IU/mL), HBeAg negative, anti-HBe positive, ALT/AST normal; due to immune control without immune-mediated liver damage; risk of reactivation to phase 2 (clinically resembles acute hepatitis B), especially with immunosuppression e.g. corticosteroids or chemotherapy
4. **immune escape** ("core or precore mutant"): elevated HBV-DNA (>2,000 IU/mL), HBeAg negative because of pre-core or core promoter gene mutation, anti-HBe positive, ALT/AST high; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment

Treatment

- counselling: 40% of men and 10% of women with perinatal infection will die from HBV-related complications
- prolonged immune-mediated damage leads to higher risk of liver fibrosis
- hepatocellular carcinoma screening with ultrasound q6mo, especially if high serum HBV-DNA levels, cirrhosis, men, (age >40 in Asian men, >50 in Asian women, and >20 in African descent)
- consider pharmacological therapy if
  - 1. HBeAg positive + HBV-DNA >20, 000 IU/mL + elevated ALT ; or
  - 2. HBeAg negative + HBV-DNA >2,000 IU/mL + elevated ALT ± stage ≥2 fibrosis on liver biopsy
  - 3. treat to prevent flare when placed on immunosuppressive therapy such as prednisone, chemotherapy, biologics, etc.
- treatment goal: reduce serum HBV-DNA to undetectable level
- treatment options: interferon, tenofovir, entacavir, lamivudine
- vaccinate against HAV if serology negative (to prevent further liver damage)
- follow blood and sexual precautions

Hepatitis D

- defective RNA virus requiring HBsAg for entry into hepatocyte, therefore infects only patients with HBV; causes more aggressive disease than hepatitis B virus alone
- coinfection: acquire HDV and HBV at the same time
- better prognosis than superinfection (acute HDV infection on pre-existing HBV infection)
- HDV can present as ALF and/or accelerate progression to cirrhosis
- treatment: low-dose interferon (20% response) and liver transplant for end-stage disease

Risk Factors for Progression
- EtOH
- HIV coinfection
- Old age at diagnosis

In acute hepatitis B, HDV coinfection increases severity of hepatitis but does not increase risk of progression to chronic hepatitis. However in the context of chronic hepatitis B, superinfection with HDV increases progression to cirrhosis

Without treatment, 8-20% of those with ongoing immunoactive chronic hepatitis can develop cirrhosis within 5 yr. In contrast, those in the immune tolerant phase (with extremely high HBV-DNA levels) are at minimal risk for liver fibrosis as they do not have immune-mediated liver injury

Risk of hepatocellular carcinoma in HBV increases with increasing age, which is likely a surrogate for increasing liver fibrosis/cirrhosis

Risk of hepatocellular carcinoma in HCV increases only after cirrhosis develops

Hepatitis C Virus

- RNA virus (7 genotypes; genotype 1 is most common in North America)
- blood-borne transmission; sexual transmission is "inefficient"
- major risk factor: injection drug use
- other risk factors: blood transfusion received before 1992 (or received in developing world), tattoos, intranasal cocaine use
- clinical manifestation develops 6-8 wk after exposure
  - symptoms mild and vague (fatigue, malaise, nausea) therefore not commonly diagnosed in acute stage

Diagnosis

- suspected on basis of elevated ALT/AST and positive serum anti-HCV
- diagnosis established by detectable HCV-RNA in serum
- virus genotype correlates with response to treatment but not prognosis
  - serum HCV-RNA inversely correlates with response to treatment
- normal transaminases can have underlying cirrhosis on biopsy, but otherwise excellent prognosis

Treatment

- blood-borne precautions; vaccinate for hepatitis A and B if serology negative; avoid alcohol
- clearest indication for treatment is in subgroup likely to develop clinically significant liver disease
  - persistently elevated transaminases, liver biopsy shows fibrosis/cirrhosis and at least moderately severe necrosis/inflammation
- previous standard of care was pegylated interferon-α + ribavirin + a direct-acting anti-viral agent aiming to clear HCV infection, but <90% success rate and side effects common
- as of 2015, all oral interferon-free regimens (e.g. sofosbuvir/ledipasvir or ombitasvir/paritaprevir/ritonavir+dasabuvir) are now becoming the standard of care with >90% success rate including those who failed previous interferon-based treatment

HCV treatment lowers the risk of hepatocellular carcinoma

From Description to Cure in One Generation
Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection
NEJM 2014; 370; 1889-1898

If you ever need an example to demonstrate the miraculous advances of modern medicine, consider using chronic hepatitis C. It inflicts about 6 per 1000 of Canadians and is the commonest reason for liver transplant in most studies. Yet until 1989, when the virus was first cloned, this condition was so poorly understood that it was labelled as what it wasn't - it was called hepatitis non-A, non-B because there was insufficient evidence to even appreciate that it was one disease, let alone an infection. Today it can be cured by taking a safe drug regimen for 6 to 24 weeks, depending on the virus strain, previous treatments, and the degree of liver damage. This recent study showed that sofosbuvir (nucleoside polymerase inhibitor) and ledispavir (NS5A inhibitor) led to a 99% cure rate in genotype 1 (the most common) infection with only minimal side-effects. These antiviral drugs are designer drugs: specifically tailored in the laboratory to combat pathogenic features of the hepatitis C virus.

Prognosis

- 80% of acute hepatitis C become chronic (of these 20% evolve to cirrhosis)
- risk of hepatocellular carcinoma increases if cirrhotic
- can cause cryoglobulinemia; associated with membranoproliferative glomerulonephritis, lymphoma

Table 16. Characteristics of the Viral Hepatitides

	HAV	HBV	HCV	HDV	HEV	CMV	EBV	Yellow Fever
Virus Family	*Picornaviridae*	*Hepadnaviridae*	*Flaviviridae*	*Deltaviridae*	*Caliciviridae*	*Herpesviridae*	*Herpesviridae*	*Flavivirus*
Genome	RNA	DNA	RNA	RNA	RNA	DNA	RNA	RNA
Envelope	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Transmission	Fecal-oral	Parenteral/sexual or equivalent Vertical	Parenteral /sexual (transfusion, IVDU, sexual [<HBV]) 40% have no known risk factors	Non-parenteral (close ccntact in endemic areas) Parenteral (blood products, IVDU)-sexual transmission is inefficient	Fecal-oral (endemic: Africa, Asia, central America, India, Pakistan)	Close contacts, most body fluids	Saliva-oral	Vector (mosquito)
Incubation	4-6 wk	6 wk-6 mo	2-26 wk	3-13 wk	2-8 wk	20-60 d	30-50 d	3-6 d
Onset	Usually abrupt	Usually insidious	Insidious	Usually abrupt	Usually abrupt	Variable	Variable	Usually abrupt
Communicability	2-3 wk in late incubation to early clinical phase Acute hepatitis in most adults, 10% of children	HBsAg+ state highly communicable Increased during third trimester or early post-partum	Communicable prior to overt symptoms and throughout chronic illness	Infectious only in presence of HBV (HBsAg required for replication)	Unknown	Variable – dormant or persistent	Communicable highest during year after primary infection but never zero	Variable, vector-dependent
Chronicity	None, although can relapse	5% adults, 90% infants	80%, 20% of which develop cirrhosis	5%	None	Common; latent	Common; latent	Infection confers lifelong immunity
Serology	Anti-HAV (IgM)	See Table 15	HCV-RNA Anti-HCV (IgG/IgM)	HBsAg Anti-HDV (IgG/IgM)	Anti-HEV (IgG/IgM)	Anti- CMV (IgM/IgG)	Monospot; anti-EBV IgM/IgG, EBV DNA quantitation	Anti-YF (IgM/IgG)
Immunity	Yes	Yes	?	Yes	?	?	?	Yes
Vaccine	Havrix, 2 doses q6mo, combined with Twinrix at 0, 7, and 21 d	Recombivax HBTM, age 11-15, 2 doses q6mo	No	No	No	No	No	YF-VAX, 1 dose booster q10yr
Management	General hygiene Treat close contacts (anti-HAV Ig) Prophylaxis for high-risk groups (HAV vaccine ± HAV Ig) unless immune	Prevention: HBV vaccine and/or hepatitis B Ig (HBIG) for needlestick, sexual contact, infants of infected mothers unless already immune Rx: oral antivirals vs interferon if indications met	Prevention: no vaccine Rx: IFN + ribavirin ± protease inhibitor; although all oral anti-viral (IFN-free) therapy now available is highly efficacious	Prevention: HBV vaccine	Prevention: general hygiene, no vaccine	In high risk transplant patients: CMV IG and anti-virals (ganciclovir, valganciclovir)	Supportive treatment post infection	Prevention Supportive treatment post infection
Acute Mortality	0.1-0.3%	0.5-2%	1%	2-20% coinfection with HBV, 30% superinfection Predisposes HBV carriers to more severe hepatitis and faster progression to cirrhosis	1-2% overall, 10-20% in pregnancy	Rare in immunocompetent adults	Rare	20-60% in developing countries
Oncogenicity	No	Yes	Yes	?	No	No	Yes	No
Complications	Can cause acute liver failure and subsequent death (<1-5%)	Hepatocellular carcinoma secondary to cirrhosis, serum sickness-like syndrome, glomerulonephritis, cryoglobulinemia, polyarteritis nodosa, porphyria cutanea tarda	Hepatocellular carcinoma in 2-5% of cirrhosis per yr, cryoglobulinemia, B-cell non-Hodgkin lymphoma	Leukocytoclastic vasculitis, membranous glomerulonephropathy	Mild, except in third trimester (10-20% fulminant liver failure)	5% of newborns with multiple handicaps Immunocomprimised patients at risk of CMV-induced hepatitis, retinitis, colitis, esophagitis, pneumonitis	Associated with Burkitt's lymphoma and nasopharyngeal carcinoma (rare in Western world)	Can cause a recurrent toxic phase with liver damage, GI bleeding, and high mortality rates

Autoimmune Chronic Active Hepatitis

- diagnosis of exclusion: rule out viruses, drugs, metabolic, or genetic causes
- can be severe: 40% mortality at 6 mo without treatment
- extrahepatic manifestations
  - sicca, Raynaud's, thyroiditis, Sjögren's, arthralgias
  - hypergammaglobulinemia
    - anti-smooth muscle antibody elevation is most characteristic; also elevations in
    - anti-LKM elevation (liver kidney microsome), especially in children
      - less specific: elevated ANA, RF
    - can have false positive viral serology (especially anti-HCV)
    - biopsy – periportal (zone 1) and interface inflammation and necrosis
- treatment: corticosteroids (80% respond) ± azathioprine (without this, most will relapse as corticosteroids are withdrawn)

Drug-Induced Liver Disease

Table 17. Classification of Hepatotoxins

	Direct	Indirect
Example	Acetaminophen, CCl_4	Phenytoin, INH
Dose-Dependence	Usual	Unusual
Latent Period	Hours-days	Weeks-months
Host Factors	Not important	Very important
Predictable	Yes	No (idiosyncratic)

Specific Drugs

- acetaminophen
  - metabolized by hepatic cytochrome P450 system
  - can cause ALF (transaminases >1,000 U/L followed by jaundice and encephalopathy)
  - requires 10-15 g in healthy, 4-6 g in alcoholics/anticonvulsant users
  - mechanism: high acetaminophen dose saturates glucuronidation and sulfation elimination pathways → reactive metabolite is formed → covalently binds to hepatocyte membrane
  - presentation
    - first 24 h: N/V (usually within 4-12 h of overdose)
    - 24-48 h: asymptomatic, but ongoing hepatic necrosis resulting in increased transaminases
    - >48 h: continued hepatic necrosis possibly complicated with ALF or resolution
    - note: potential delay in presentation in sustained-release products
  - blood levels of acetaminophen correlate with the severity of hepatic injury, particularly if time of ingestion known
  - therapy
    - gastric lavage/emesis (if <2 h after ingestion)
    - oral activated charcoal
    - N-acetylcysteine (NAC, Mucomyst®) can be given PO or IV (most effective within 8-10 h of ingestion, but should be given no matter when time of ingestion)
      - promotes hepatic glutathione regeneration
    - no recorded fatal outcomes if NAC given before increase in transaminases
- chlorpromazine: cholestasis in 1% after 4 wk; often with fever, rash, jaundice, pruritus, and eosinophilia
- INH (isoniazid)
  - 20% develop elevated transaminases but <1% develop clinically significant disease
  - susceptibility to injury increases with age
- methotrexate
  - causes fibrosis/cirrhosis; increased risk in the presence of obesity, DM, alcoholism (i.e. with underlying risk for pre-existing fatty liver)
  - scarring develops without symptoms or changes in liver enzymes, therefore biopsy may be needed in long-term treatment
- amiodarone: can cause same histology and clinical outcome as alcoholic hepatitis
- others: azoles, statins, methyldopa, phenytoin, propylthiouracil (PTU), rifampin, sulfonamides, tetracyclines
- herbs: chaparral, Chinese herbs (e.g. germander, comfrey, bush tea)

Hy's Law: drug-induced hepatocellular jaundice indicates a mortality of at least 10%

Wilson's Disease

Definition
- autosomal recessive defect in copper metabolism (gene ATP7B)

Etiology
- decreased biliary excretion of copper plus decreased incorporation of copper into ceruloplasmin

Clinical Features
- liver: acute hepatitis, acute liver failure, chronic active hepatitis, cirrhosis, low risk of hepatocellular carcinoma
- eyes: Kayser-Fleischer rings (copper deposits in Descemet's membrane); more common in patients with CNS involvement, present in 50% if only liver involvement
- CNS: basal ganglia (wing flapping tremor, Parkinsonism), cerebellum (dysarthria, dysphagia, incoordination, ataxia), cerebrum (psychosis, affective disorder)
- kidneys: Fanconi's syndrome (proximal tubule transport defects) and stones
- blood: intravascular hemolysis; may be initial presentation in fulminant hepatitis
- joints: arthritis, bone demineralization, calcifications

Clinical Manifestations of Wilson's Disease

ABCD
Asterixis
Basal ganglia degeneration: suspect if parkinsonian features in the young
Ceruloplasmin ↓
Cirrhosis
Corneal deposits (Kayser-Fleischer ring)
Copper
Dementia

Investigations
- suspect if increased liver enzymes with clinical manifestations at young age (<30); especially combination of liver disease with dystonia, psychiatric symptoms
- screening tests
  1. reduced serum ceruloplasmin (<50% of normal)
  2. Kayser-Fleischer rings (usually require slit-lamp examination)
  3. increased urinary copper excretion
- gold standard
  1. increased copper on liver biopsy by quantitative assay
  2. genetic analysis imperfect as many mutations in ATP7B are possible

Treatment
- 4 drugs available
  1. penicillamine chelates copper, poorly tolerated
  2. trientine chelates copper
  3. zinc impairs copper excretion in stool and decreases copper absorption from gut
  4. tetrathiomolybdate preferred if neurological involvement
- screen relatives
- liver transplant in severe cases

Hemochromatosis

Definition
- excessive iron storage causing multiorgan system dysfunction (liver, in particular) with total body stores of iron increased to 20-40 g (normal 1 g)

Etiology
- primary (hereditary) hemochromatosis
  - hepcidin deficiency results in ongoing gut absorption of iron despite adequate iron stores
  - results in ongoing gut absorption of iron despite adequate iron stores
- secondary hemochromatosis
  - parenteral iron overload (e.g. transfusions)
  - chronic hemolytic anemia: thalassemia, pyruvate kinase deficiency
  - excessive iron intake

Epidemiology
- hereditary hemochromatosis most common in Northern European descent
  - primarily due to common recessive gene (HFE, 5%); 1/400 patients are homozygotes

Clinical Features
- usually presents with trivial elevation in serum transaminases
- liver: cirrhosis (30%), HCC (200x increased risk) – most common cause of death (1/3 of patients)
- pancreas: DM, chronic pancreatitis
- skin: bronze or grey (due to melanin, not iron)
- heart: dilated cardiomyopathy
- pituitary: hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea)
- joints: arthralgia (any joint, but especially MCP joints), chondrocalcinosis

Hemochromatosis Clinical Features
ABCD
- arthralgia
- bronze skin
- cardiomyopathy, cirrhosis of liver
- diabetes (pancreatic damage)
- hypogonadism (anterior pituitary damage)

Investigations
- screening for individuals with clinical features and/or family history (1/4 chance of sibling having the disease)
  - transferrin saturation (free Fe^{2+}/TIBC) >45%
  - serum ferritin >400 ng/mL
  - HFE gene analysis: 90% of primary hemochromatosis involves C282Y allele, while H63D and S65C alleles also commonly involved and screened
- liver biopsy (generally used to detect cirrhosis or if potential for other causes of liver disease)
  - markers of advanced fibrosis: if any of the following are present at the time of diagnosis → age >40, elevated liver enzymes, or ferritin >1000
  - considered if compound heterozygote and potential other cause of liver injury (e.g. fatty liver, etc.)
  - if C282Y/C282Y and no markers of advanced fibrosis, then biopsy generally not needed
- HCC screening if cirrhosis

Ferritin may never normalize if other causes of high ferritin present (e.g. fatty liver from metabolic syndrome or alcohol)

Gene mutation not 100% penetrant, so not all with homozygous gene defect have clinically significant iron overload

Treatment
- phlebotomy: weekly or q2wk then lifelong maintenance phlebotomies q2-6mo
- deferoxamine if phlebotomy contraindicated (e.g. cardiomyopathy, anemia)
- primary hemochromatosis responds well to phlebotomy
- secondary hemochromatosis usually requires chelation therapy (administration of agents that bind and sequester iron, and then excreted)

Prognosis
- normal life expectancy if treated before the development of cirrhosis or DM

Alcoholic Liver Disease

Definition
- fatty liver (all alcoholics): always reversible if alcohol stopped
- alcoholic hepatitis (35% of alcoholics): usually reversible if alcohol stopped
- cirrhosis (10-15% of alcoholics): potentially irreversible

Standard Drink Equivalent
1 standard drink = 14 g EtOH
= 12 oz beer (5% alcohol)
= 5 oz wine (12-17%)
= 3 oz fortified wine (17-22%)
= 1.5 oz liquor (40%)

Tip: percentage alcohol multiplied by oz in 1 standard drink roughly equals 60

Pathophysiology
- several mechanisms, poorly understood
- ethanol oxidation to acetaldehyde
  - reduces NAD^+ to NADH; increased NADH decreases ATP supply to liver, impairing lipolysis so fatty acids and triglycerides accumulate in liver
  - binds to hepatocytes evoking an immune reaction
- ethanol increases gut permeability leading to increased bacterial translocation
- alcohol metabolism causes
  - relative hypoxia in liver zone III (near central veins; poorly oxygenated) > zone I (around portal tracts, where oxygenated blood enters)
  - necrosis and hepatic vein sclerosis
- histology of alcoholic hepatitis
  - ballooned (swollen) hepatocytes often containing Mallory bodies, characteristically surrounded by neutrophils
  - large fat globules
  - fibrosis: space of Disse and perivenular

Biopsy + Histology of Alcoholic Hepatitis (triad)
- Hepatocyte necrosis with surrounding inflammation in zone III
- Mallory bodies (intracellular eosinophilic aggregates of cytokeratins)
- Chicken-wire fibrosis (network of intralobular connective tissue surrounding cells and venules)

Clinical Features
- >2-3 standard drinks/d in females and >3-6 standard drinks/d in men for >10 yr leads to cirrhosis, but only in about 10-20% of those who consume this amount daily on a continuous basis; cirrhosis risk increases with amount of alcohol consumed above threshold
- clinical findings do not accurately predict type of liver involvement
- fatty liver
  - mildly tender hepatomegaly; jaundice rare
  - mildly increased transaminases <5x normal
- alcoholic hepatitis
  - variable severity: mild to fatal liver failure
  - mild: stops drinking because feels unwell, resumes when feeling better (if assessed, findings of hepatitis, potentially mild jaundice, and mildly elevated INR)
  - severe: stops drinking but feels unwell, low grade fever, RUQ discomfort, increased white blood cell count – mimics RLL pneumonia and cholecystitis

GI Complications of Alcohol Abuse
- Esophagus
- Mallory-Weiss tear
- Esophageal varices (secondary to portal hypertension)
- Stomach
- Alcoholic gastritis
- Pancreas
- Acute pancreatitis
- Chronic pancreatitis
- Liver
- Alcoholic hepatitis
- Fatty liver
- Cirrhosis
- Hepatic encephalopathy
- Portal hypertension (secondary to cirrhosis)
- Ascites (secondary to cirrhosis)
- HCC (secondary to cirrhosis)

Investigations
- blood tests are non-specific, but in general
  - AST:ALT >2:1 (usually <300)
  - increased GGT
  - CBC: increased MCV, increased WBC

Treatment

- alcohol cessation (see Psychiatry, PS25)
  - Alcoholics Anonymous, disulfiram, naltrexone, acamprosate
- multivitamin supplements (especially thiamine)
- caution with drugs metabolized by the liver
- if icteric alcoholic hepatitis prednisone 40 mg OD x 28 d in subgroup with elevated bilirubin and INR (Maddrey's discriminant function > 32); but contraindicated in GI bleeding, renal failure, infection, pancreatitis
  - response (and subsequent decision to continue treatment) predicted by day 7 bilirubin (Lille score)
- pentoxyfilline reported to be beneficial in one of three studies, but most definitive trial shows no benefit (see *Landmark Trials*, G51)

Prognosis

- Maddrey's discriminant function (based on PT and bilirubin) and MELD predict mortality and guide treatment
- fatty liver: complete resolution with cessation of alcohol intake
- alcoholic hepatitis mortality
  - immediate: 30%-60% in the first 6 mo if severe
  - with continued alcohol: 70% in 5 yr
  - with cessation: 30% in 5 yr

Non-Alcoholic Fatty Liver Disease

Definition

- spectrum of disorders characterized by macrovesicular hepatic steatosis
- most common cause of liver disease in North America

Etiology

- pathogenesis not well elucidated; insulin resistance implicated as key mechanism, leading to hepatic steatosis
- changes indistinguishable from those of alcoholic hepatitis despite negligible history of alcohol consumption

Risk Factors

- likely a component of the metabolic syndrome along with type 2 DM, HTN, hypertriglyceridemia
- rapid weight loss or weight gain

Clinical Features

- often asymptomatic
- may present with fatigue, malaise, and vague RUQ discomfort
- elevated serum triglyceride/cholesterol levels and insulin resistance

Investigations

- elevated serum AST, ALT ± ALP; AST/ALT <1
- presents as echogenic liver texture on ultrasound
- liver biopsy diagnostic, but often necessary only for prognosis

Treatment

- no proven effective therapy other than gradual weight loss
- some evidence for vitamin E (800 U daily) in select groups
  - pioglitazone can be considered if DM concomitantly present, but results in weight gain
- modification of risk factors is generally recommended, especially gradual weight reduction
- optimization of therapy for DM, hyperlipidemia, HTN
- some evidence for benefits of coffee drinking (3 cups per day)

Prognosis

- most die from cardiovascular or cerebrovascular disease
- better prognosis than alcoholic hepatitis
  - <25% progress to cirrhosis over a 7-10 yr period
- risk of progression increases if inflammation or scarring occurs alongside fat infiltration (non-alcoholic steatohepatitis)
- other clinical indicators of unfavourable prognosis: DM, age, metabolic syndrome

Acute Liver Failure (formerly Fulminant Hepatic Failure)

Definition
- severe decline in liver function characterized by coagulation abnormality (INR>1.5) and encephalopathy
- in setting of previously normal liver
- rapid (<26 wk duration)

Etiology
- drugs (especially acetaminophen), hepatitis B (measure anti-HBc, IgM fraction because sometimes HBV-DNA and even HBsAg rapidly becomes negative), hepatitis A, hepatitis C (rare), ischemic, idiopathic

Treatment
- correct hypoglycemia, monitor level of consciousness, prevent GI bleeding with PPI, monitor for infection and multiorgan failure (usually requires ICU)
- consider liver biopsy before INR becomes too high
- chief value is to exclude chronic disease, less helpful for prognosis
- liver transplant (King's College criteria can be used as prognostic indicator): consider early, especially if time from jaundice to encephalopathy >7 d (e.g. not extremely rapid), age <10 or >40, cause is drug or unknown, bilirubin >300 μmol/L, INR >3.5, creatinine >200 μmol/L

Cirrhosis

Definition
- liver damage characterized by diffuse distortion of the basic architecture and replacement with scar tissue and formation of regenerative nodules
- Stage 1 cirrhosis is compensated and asymptomatic, can last for 10-20 yr with almost normal life expectancy
- Stage 2 cirrhosis is the onset of first decompensation, typically development of ascites (most common), variceal bleeding, encephalopathy

Etiology
- fatty liver (alcoholic or non-alcoholic fatty liver disease)
- chronic viral hepatitis (B, B+D, C; not A or E)
- autoimmune hepatitis
- hemochromatosis
- primary biliary cirrhosis
- chronic hepatic congestion
  - cardiac cirrhosis (chronic right heart failure, constrictive pericarditis)
  - hepatic vein thrombosis (Budd-Chiari)
- cryptogenic (i.e. no identifiable cause, although many of these patients may represent "burnt-out NASH")
- rare: Wilson's disease, Gaucher's disease, α1-antitrypsin deficiency

Investigations
- definitive diagnosis is histologic (liver biopsy)
- other tests may be suggestive
  - blood work: fall in platelet count <150 is the earliest finding, followed many years later with rise in INR, fall in albumin, rise in bilirubin, fall in glucose level (pre-terminal event)
  - FibroTest: combination of various clinical and biochemical markers that can predict degree of fibrosis
  - imaging
    - U/S is the primary imaging modality but only finds advanced cirrhosis
    - CT to look for varices, nodular liver texture, splenomegaly, ascites
    - Ultrasound elastography (FibroScan): non-invasive tool using elastography (variable availability)
  - gastroscopy: varices or portal gastropathy

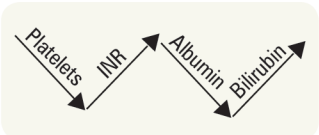

Figure 12. Progression of liver dysfunction based on liver function tests – the "W"

Treatment
- treat underlying disorder
- decrease insults (e.g. alcohol cessation, hepatotoxic drugs, immunize for Hep A and B if non-immune)
- follow patient for complications (esophageal varices, ascites, HCC defines stage 2 cirrhosis)
- prognosis: Child-Pugh Score and MELD score
- liver transplantation for end-stage disease if no alcohol for >6 mo; use MELD score

MELD (Model for End Stage Liver Disease)
- Predicts 3 mo survival and used to stratify patients on transplant list
- Based on creatinine, INR, and total bilirubin

Table 18. Child-Pugh Score and Interpretation

Classification	1	2	3
Serum bilirubin (μmol/L)	<34	34-51	>51
Serum albumin (g/L)	>35	28-35	<28
INR	<1.7	1.7-2.3	>2.3
Presence of ascites	Absent	Controllable	Refractory
Encephalopathy	Absent	Minimal	Severe
Interpretation			
Points	**Class**	**Life Expectancy**	**Perioperative Mortality**
5-6	A	15-50 yr	10%
7-9	B	Candidate for transplant	30%
10-15	C	1-3 mo	82%
Score: 5-6 (Child's A), 7-9 (Child's B), 10-15 (Child's C)			

*Note: Child's classification is rarely used for shunting, (TIPS or other surgical shunts) but is still useful to quantitate the severity of cirrhosis

Complications

- hematologic changes in cirrhosis
  - pancytopenia from hypersplenism: platelets first, then WBC, then hemoglobin
  - decreased clotting factors resulting in elevated INR
  - relationship of INR to bleeding tendency is controversial; some patients may be hypocoagulable, others may be hypercoagulable
- variceal bleeds
  - half of patients with cirrhosis have gastroesophageal varices and one-third of these develop hemorrhage with an overall mortality of >30%
  - hepatic venous pressure gradient (HVPG) ≥10 mmHg is the strongest predictor of variceal development
  - treatment: resuscitation, antibiotic prophylaxis, vasoactive drugs (e.g. octreotide IV) combined with endoscopic band ligation or sclerotherapy, TIPS
- renal failure in cirrhosis
  - classifications
    - pre-renal (usually due to over-diuresis)
    - acute tubular necrosis
    - HRS
      - Type I: sudden and acute renal failure (rapid doubling of creatinine over 2 wk)
      - Type II: gradual increase in creatinine with worsening liver function (creatinine doubling over years)
    - HRS can occur at any time in severe liver disease, especially after
      - overdiuresis or dehydration, such as diarrhea, vomiting, etc.
      - GI bleed
      - sepsis
    - treatment for hepatorenal syndrome (generally unsuccessful at improving long-term survival)
      - for type I HRS: octreotide + midodrine + albumin (increases renal blood flow by increasing systemic vascular resistance)
      - definitive treatment is liver transplant
- hepatopulmonary syndrome
  - majority of cases due to cirrhosis, though can be due to other chronic liver diseases, such as non-cirrhotic portal HTN
  - thought to arise from ventilation-perfusion mismatch, intrapulmonary shunting and limitation of oxygen diffusion, failure of damaged liver to clear circulating pulmonary vasodilators vs. production of a vasodilating substance by the liver
  - clinical features
    - hyperdynamic circulation with cardiac output >7 L/min at rest and decreased pulmonary + systemic resistance (intrapulmonary shunting)
    - dyspnea, platypnea (increase in dyspnea in upright position, improved by recumbency), and orthodeoxia (desaturation in the upright position, improved by recumbency)
    - diagnosis via contrast-enhanced echocardiography: inject air bubbles into peripheral vein; air bubbles appear in left ventricle after third heartbeat (normal = no air bubbles; in ventricular septal defect, air bubbles seen <3 heart beats)
    - only proven treatment is liver transplantation

Cirrhosis Complications

VARICES
Varices
Anemia
Renal failure
Infection
Coagulopathy
Encephalopathy
Sepsis

Usual causes of death in cirrhosis: renal failure (hepatorenal syndrome), sepsis, GI bleed, or HCC

Hepatorenal Syndrome vs. Pre-Renal Failure – Difficult to Differentiate
- Similar blood and urine findings, (see Nephrology, NP17)
- Urine sodium: very low in hepatorenal; low in pre-renal
- Intravenous fluid challenge: giving volume expanders improves pre-renal failure, but not hepatorenal syndrome

Hepatopulmonary Syndrome
Clinical triad
- Liver disease
- Increased alveolar-arterial gradient while breathing room air
- Evidence for intrapulmonary vascular abnormalities

Fibrosis may regress and disappear if cause of liver injury is treated or resolves

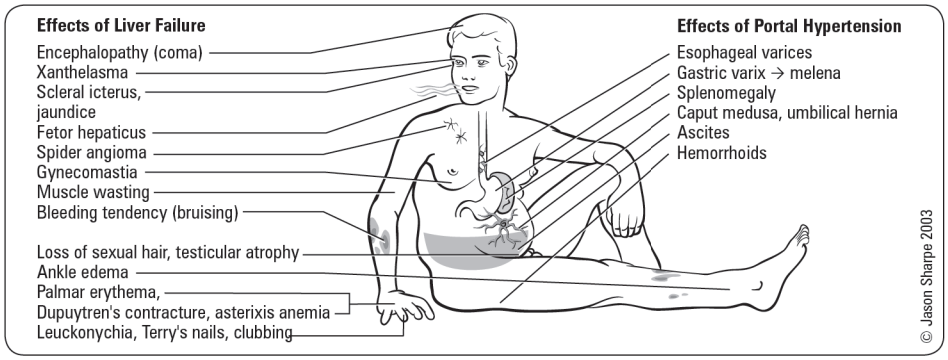

Figure 13. Clinical features of liver disease

Hepatocellular Carcinoma

- see General Surgery, GS45

Liver Transplantation

- see General Surgery, GS46

Portal Hypertension

Definition
- pressure gradient between hepatic vein pressure and wedged hepatic vein pressure (corrected sinusoidal pressure) >5 mmHg

Pathophysiology
- 3 sites of increased resistance (remember pressure = flow x resistance)
  - pre-sinusoidal (e.g. portal vein thrombosis, schistosomiasis, sarcoidosis)
  - sinusoidal (e.g. cirrhosis, alcoholic hepatitis)
  - post-sinusoidal (e.g. right-sided heart failure, hepatic vein thrombosis, veno-occlusive disease, constrictive pericarditis)

Complications
- GI bleeding from varices in esophagus, less commonly in stomach, even less frequently from portal hypertensive gastropathy
- ascites
- hepatic encephalopathy
- thrombocytopenia
- renal dysfunction
- sepsis
- arterial hypoxemia

Treatment
- non-selective β-blockers (propanolol, nadolol) decrease risk of bleeding from varices
- TIPS: to decrease portal venous pressure
  - radiologically inserted shunt between portal and hepatic vein via transjugular vein catheterization and percutaneous puncture of portal vein
  - can be used to stop acute bleeding or prevent rebleeding or treat ascites
  - shunt usually remains open for <1 yr
  - complications: hepatic encephalopathy, deterioration of hepatic function
  - contraindicated with severe liver dysfunction
  - most commonly used as a "bridge" to liver transplant
- other surgically created shunts: portacaval, distal spleno-renal (Warren shunt) - all used only rarely in the modern era

Portal Hypertension

Signs
- Esophageal varices
- Melena
- Splenomegaly
- Ascites
- Hemorrhoids

Management
- β-blockers
- Nitrates
- Shunts (e.g. TIPS)

Hepatic Encephalopathy

Definition
- spectrum of potentially reversible neuropsychiatric syndromes secondary to liver disease diagnosed after ruling out other causes for symptoms (e.g. structural/metabolic)

Pathophysiology
- portosystemic shunt around hepatocytes and decreased hepatocellular function increase level of systemic toxins (believed to be ammonia from gut, mercaptans, fatty acids, amino acids) which go to the brain

Precipitating Factors
- nitrogen load (GI bleed, protein load from food intake, renal failure, constipation)
- drugs (narcotics, CNS depressants)
- electrolyte disturbance (hypokalemia, alkalosis, hypoxia, hypovolemia)
- infection (spontaneous bacterial peritonitis)
- deterioration in hepatic function or superimposed liver disease

Precipitating Factors for Hepatic Encephalopathy

HEPATICS
Hemorrhage in GI tract/**H**ypokalemia
Excess dietary protein
Paracentesis
Alkalosis/**A**nemia
Trauma
Infection
Colon surgery
Sedatives

Stages
- I: apathy, restlessness, reversal of sleep-wake cycle, slowed intellect, impaired computational abilities, impaired handwriting
- II: asterixis, lethargy, drowsiness, disorientation
- III: stupor (rousable), hyperactive reflexes, extensor plantar response (upgoing Babinski)
- IV: coma (response to painful stimuli only)

Investigations
- clinical diagnosis: supported by laboratory findings and exclusion of other neuropsychiatric diseases
- rule out
  - non-liver-related neuropsychiatric disease in a patient with liver problems (e.g. alcohol withdrawal or intoxication, sedatives, subdural hematoma, metabolic encephalopathy)
  - causes of metabolic encephalopathy (e.g. renal failure, respiratory failure, severe hyponatremia, hypoglycemia)
- characteristic EEG findings: diffuse (non-focal), slow, high amplitude waves
- serum ammonia levels increased, but not often necessary to measure in routine clinical use

Treatment
- treat underlying precipitating factors
- decrease generation of nitrogenous compounds
  - routine protein restriction is no longer recommended given patients generally have concurrent malnutrition and muscle wasting; however, vegetable protein is better tolerated than animal protein
  - lactulose: titrated to achieve 2-3 soft stools/d
    - prevents diffusion of NH_3 (ammonia) from the colon into blood by lowering pH and forming non-diffusible NH_4 (ammonium)
    - serves as a substrate for incorporation of ammonia by bacteria, promotes growth in bowel lumen of bacteria which produce minimal ammonia
    - also acts as a laxative to eliminate nitrogen-producing bacteria from colon
- if inadequate response with lactulose may try antibiotics
  - broad-spectrum antibiotics (metronidazole, rifaximin) eliminate ammonia producing bacteria from bowel lumen
  - non-absorbable antibiotic rifaximin probably most effective treatment but not readily available in Ontario
- best acute treatment in comatose patient is lactulose enemas

Ascites

Definition
- accumulation of excess fluid in the peritoneal cavity

Etiology

Table 19. Serum-Ascites Albumin Gradient as an Indicator of the Causes of Ascites

Serum [Alb] – Ascitic [Alb] >11 g/L (1.1 g/dL) Portal Hypertension Related	Serum [Alb] – Ascitic [Alb] <11 g/L (1.1 g/dL) Non-Portal Hypertension Related
Cirrhosis/severe hepatitis	Peritoneal carcinomatosis
Chronic hepatic congestion (right heart failure, Budd-Chiari)	TB
Massive liver metastases	Pancreatic disease
Myxedema	Serositis
	Nephrotic syndrome*

* In nephrotic syndrome: decreased serum [Alb] to begin with therefore gradient not helpful

Pathophysiology
- key factor in pathogenesis is increased sodium (and water) retention by the kidney for reasons not fully understood. Theories include:
  - underfill hypothesis: first step in ascites formation is increased portal pressure and low oncotic pressure (e.g. low serum albumin) driving water out of the splanchnic portal circulation into abdominal cavity; the resulting decreased circulating volume causes secondary sodium retention by the kidney
  - overfill hypothesis: cirrhosis directly causes increased sodium retention by the kidney in the absence of hypovolemia and ascites arises secondarily

- peripheral arterial vasodilation theory (most popular): as portal HTN develops in cirrhosis, production of local mediators such as nitric oxide lead to splanchnic arterial vasodilation which ultimately results in reduction of effective arterial volume and compensatory sodium and fluid retention by the kidneys (i.e. circulation volume is increased, as per overflow hypothesis, but relatively underfilled, as per underfill hypothesis)

Diagnosis
- abdominal ultrasound
- physical exam (clinically detectable when >500 mL)
  - bulging flanks, shifting dullness, fluid-wave test positive
  - most sensitive symptom: ankle swelling

Investigations
- diagnostic paracentesis
  - 1st aliquot: cell count
  - 2nd aliquot: chemistry (especially albumin, but also total protein; amylase if pancreatitis; TG and chylomicrons if turbid and suspect chylous ascites)
  - 3rd aliquot: C&S, Gram stain
  - 4th aliquot: cytology (usually positive in peritoneal carcinomatosis)

Treatment
- non-refractory ascites
  - Na^+ restriction (daily sodium intake <2 g)
  - diuretics: spironolactone, furosemide
  - aim for weight loss 0.5-1 kg/d, more if concomitant peripheral edema (which is mobilized quicker than ascitic fluid); overly rapid weight loss increases risk of renal failure
  - double diuretic dose every 2-4 wk to achieve weight loss target
- refractory ascites (diuretics are inadequate or not tolerated)
  - therapeutic paracentesis with intravenous albumin paracentesis
  - TIPS in an appropriate patient (no contraindications) with potential transplant-free survival advantage
  - liver transplantation should be considered in every case, since development of ascites in patients with cirrhosis are associated with 50% 2 yr mortality

Complication: Primary/Spontaneous Bacterial Peritonitis
- primary/spontaneous bacterial peritonitis (SBP)
  - complicates ascites, but does not cause it (occurs in 10% of cirrhotic ascites); higher risk in patients with GI bleed
  - 1/3 of patients are asymptomatic, thus do not hesitate to do a diagnostic paracentesis in ascites even if no clinical indication of infection
  - fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy, acute kidney injury
  - Gram-negatives compose 70% of pathogens: *E. coli* (most common), Streptococcus, Klebsiella
- diagnosis
  - absolute neutrophil count in peritoneal fluid >$0.25x10^9$ cells/L (250 cells/mm^3)
  - Gram stain positive in only 10-50% of patients
  - culture positive in <80% of patients (not needed for diagnosis)
- prophylaxis: consider in patients with
  - cirrhosis or GI bleed: ceftriaxone IV daily or norfloxacin bid x 7 d
  - previous episode of SBP: long-term prophylaxis with daily norfloxacin or TMP-SMX
- treatment
  - IV antibiotics (cefotaxime 2 g IV q8h or ceftriaxone 2g IV daily is the treatment of choice for 5 d; modify if response inadequate or culture shows resistant organisms)
  - IV albumin (1.5 g/kg at time of diagnosis and 1 g/kg on day 3) decreases mortality by lowering risk of acute renal failure

Secondary bacterial peritonitis (as opposed to primary bacterial peritonitis) usually results from a perforated viscus or surgical manipulation

Primary Prophylaxis of Spontaneous Bacterial Peritonitis Delays Hepatorenal Syndrome and Improves Survival in Cirrhosis
Gastroenterology 2007;133:818-824

Study: RCT, double-blinded study with 1 yr follow-up.
Population: 68 patients with cirrhosis, ascites, ascitic fluid protein <15 g/L, and impaired renal function or severe liver failure.
Intervention: Norfloxacin versus placebo.
Main Outcome: 3-month and 1-year probability of survival
Secondary Outcomes: 1-year probability of SBP and hepatorenal syndrome
Results: There was a significant reduction of patients developing spontaneous bacterial peritonitis (SBP) (6% vs. 30%, p=0.02) and spontaneous bacteremia (0% vs. 12%, p=0.05) with norfloxacin therapy. There were significantly fewer patients who developed all-cause renal failure (7 vs. 16, p=0.03) and hepatorenal syndrome (HRS) with norfloxacin therapy. Probability of survival at 3 mo (94% vs. 62%, p=0.02) and 1 yr (60% vs. 48%, p=0.003) were high in patients treated with norfloxacin.
Conclusion: Primary prophylaxis with norfloxacin in patients with advanced cirrhosis reduced SBP, HRS, and improved 1 yr survival.

Serum Ascites Albumin Gradient
- >11 g/L portal HTN
- <11 g/L unrelated to portal HTN

Biliary Tract

Jaundice

- see Table 2, G6 and Figures 15 and 16, G42

Signs and Symptoms
- dark urine, pale stools: suggests that bilirubin elevation is from direct fraction
- pruritus: suggests chronic disease, cholestasis
- abdominal pain: suggests biliary tract obstruction from stone or pancreatic tumour (obstructive jaundice)
- painless jaundice in the elderly: think of pancreatic cancer, although most patients with pancreatic cancer have pain
- kernicterus: rarely seen in adults due to maturation of blood brain barrier

Investigations
- blood work: CBC, bilirubin (direct and total), liver enzymes (AST, ALT, ALP, GGT), liver function tests (INR/PT, PTT, albumin), amylase
- U/S or CT for evidence of bile duct obstruction (e.g. bile duct dilation)
- direct bile duct visualization
  - magnetic resonance cholangiopancreatography (MRCP): non-invasive
  - endoscopic ultrasound (EUS): sensitive for stones and pancreatic tumours
  - endoscopic retrograde cholangiopancreatography (ERCP): invasive, most accurate, allows for therapeutic intervention
  - percutaneous transhepatic cholangiography (PTC): if ERCP fails (endoscopic access not possible)

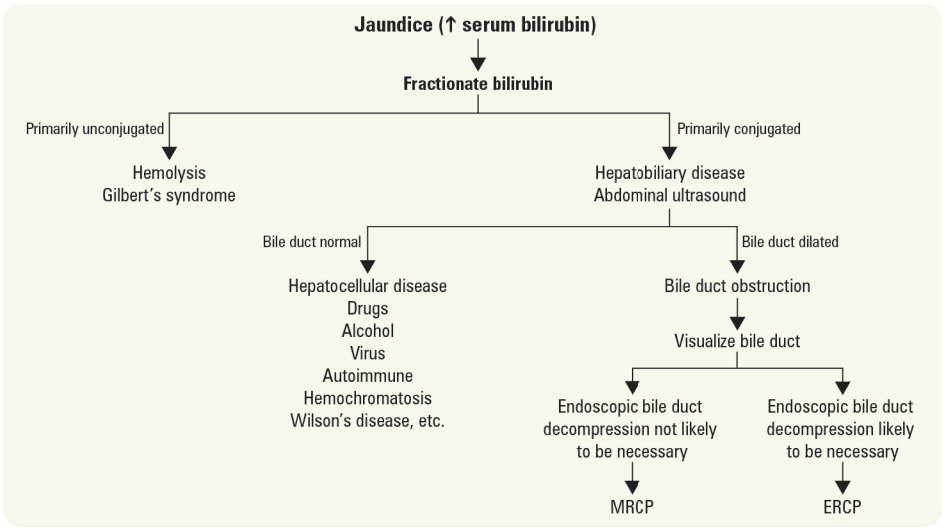

Figure 14. Approach to jaundice

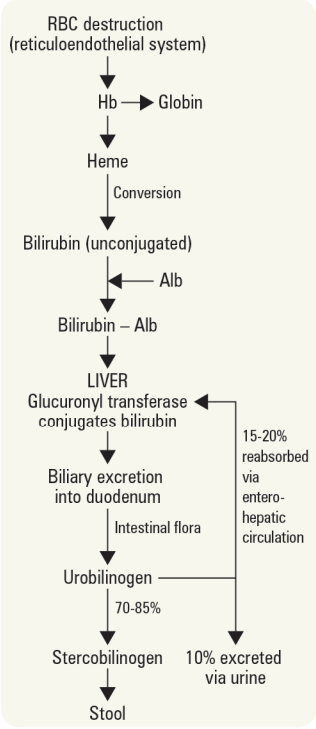

Figure 15. Production and excretion of bilirubin

Gilbert's Syndrome

Definition
- mild decrease in glucuronyltransferase activity leading to defective conjugation of bilirubin
- an abnormality of bilirubin metabolism with no clinical relevance

Etiology/Epidemiology
- some patients have decreased hepatobiliary uptake
- affects 7% of population, especially males
- autosomal dominant, 70% due to a mutation in the UGT gene

Clinical Features
- presents in teens-20s, often an incidental finding
- only manifestation is intermittent jaundice with increased serum unconjugated bilirubin developing most characteristically while fasting, or at times of acute illness; no other clinical implications

Treatment
- none indicated (entirely benign)

Gilbert's Syndrome vs. Crigler-Najjar Syndrome

Gilbert's Syndrome: mild decrease in glucuronyltransferase activity

Crigler-Najjar Syndrome: complete deficiency of glucuronyltransferase

Sclerosing Cholangitis

Definition
- narrowing of biliary tree (intra and/or extrahepatic bile ducts) from scarring

Etiology
- primary/idiopathic (most common)
  - associated with IBD, more commonly UC, in up to 70% of patients (usually male)
  - one of the most common indications for liver transplant

- secondary (less common)
  - long-term choledocholithiasis
  - cholangiocarcinoma
  - surgical/traumatic injury (iatrogenic)
  - contiguous inflammatory process
  - post-ERCP
  - associated with HIV/AIDS ("HIV cholangiopathy")
  - IgG4-related disease

Signs and Symptoms
- often insidious, may present with fatigue and pruritus
- may present with signs of episodic bacterial cholangitis secondary to biliary obstruction

Investigations
- increased ALP (hallmark), less often increased bilirubin
- mildly increased AST, usually <300 U/L
- p-ANCA (30-80%), elevated IgM (40-50%)
- ERCP shows narrowing and dilatations of bile ducts that may result in "beading", both intrahepatic and extrahepatic bile ducts
  - if intrahepatic narrowing only, do anti-mitochondrial antibody to rule out PBC

Complications
- repeated bouts of cholangitis may lead to complete biliary obstruction with resultant secondary biliary cirrhosis and hepatic failure
- increased incidence of cholangiocarcinoma (10-15%): difficult to diagnose and treat

Treatment
- image bile duct (MRCP) at least annually for early detection of cholangiocarcinoma (controversial)
- endoscopic sphincterotomy, biliary stent in selected cases of dominant CBD stricture
- antibiotics for cholangitis
- suppurative cholangitis requires emergency drainage of pus in CBD
- liver transplantation appears to be the best treatment for advanced sclerosing cholangitis (nearly 90% 1-yr survival; mean follow-up from time of diagnosis to need for transplant is 10 yr)
- ursodiol: previously recommended, but studies suggest that at least in high doses it increases mortality

Prognosis
- unfavourable regardless of treatment
- mean survival after diagnosis remains 4-10 yr

Primary Biliary Cirrhosis

Definition
- chronic inflammation and fibrous obliteration of intrahepatic bile ductules

Etiology/Epidemiology
- likely autoimmune (associated with Sjögren's syndrome, scleroderma, CREST syndrome, RA, thyroiditis)
- affects mainly middle-aged women (M:F = 1:9)

Signs and Symptoms
- often asymptomatic
- initial symptoms: pruritus, fatigue
- chronic: jaundice and melanosis (darkening skin) and other signs of cholestasis
- end-stage: hepatocellular failure, portal HTN, ascites
- high incidence of osteoporosis

ERCP
- Absence of narrowing in PBC
- Narrowing of intra and extrahepatic ducts in PSC

Investigations
- increased ALP, GGT; bilirubin rises in later stage
- positive anti-mitochondrial antibodies (AMA; 95% specificity and sensitivity)
- increased serum cholesterol (mild increase in LDL, larger increase in HDL)
  - may have: xanthelasmas, xanthomas
- liver biopsy confirms diagnosis and stages severity
- normal bile duct on MRCP rules out bile duct obstruction which can mimic PBC
- recently described "overlap" syndromes with autoimmune cholangitis, autoimmune hepatitis, sclerosing cholangitis

Treatment
- treat with ursodiol (less frequently colchicine, methotrexate)
- cholestyramine (for pruritus and hypercholesterolemia)
- calcium and vitamin D for low bone density; bisphosphonates if osteoporosis severe
- monitor for thyroid disease
- liver transplant if disease severe, progressive

Prognosis
- can be fatal, although not all asymptomatic patients show progression

Table 20. Primary Sclerosing Cholangitis vs. Primary Biliary Cirrhosis

	Primary Sclerosing Cholangitis	Primary Biliary Cirrhosis
Predominant Gender	Male	Female
Associated Comorbidities	IBD, especially UC	Other autoimmune disorders (Sjögren's, CREST, RA)
Affected Ducts	Both intra- and extra-hepatic	Intrahepatic only
Investigations	ERCP/MRCP (narrowing and dilatations of ducts visualized)	Anti-mitochondrial antibodies, IgM, increased lipids, liver biopsy (absence of duct narrowing on ERCP)

Secondary Biliary Cirrhosis

Definition
- cirrhosis from prolonged partial or total obstruction of major bile ducts

Etiology
- acquired: post-operative strictures, chronic pancreatitis, sclerosing cholangitis, stone in bile duct
- congenital: CF, congenital biliary atresia, choledochal cysts

Investigations
- cholangiography and liver biopsy

Treatment
- treat obstruction, give antibiotics for cholangitis prophylaxis

Biliary Colic, Cholecystitis

- see General Surgery, GS48

Ascending Cholangitis

- see General Surgery, GS50

Definition
- infection of the biliary tree

Etiology
- stasis in the biliary tract due to obstruction or stricture (usually from previous cholecystectomy)
- infection originates in the duodenum or spreads hematogenously from the portal vein
- bacteria
  - *E. coli,* Klebsiella, Enterobacter, Enterococcus
  - co-infection with Bacteroides and Clostridia can occur

Charcot's Triad
- RUQ pain
- Fever
- Jaundice

Reynolds Pentad
- Charcot's triad
- Hypotension
- Altered mental status

Signs and Symptoms
- Charcot's triad: fever, RUQ pain, jaundice (50-70%)
- Reynolds Pentad in patients with suppurative cholangitis: fever, RUQ pain, jaundice, hypotension, altered mental status

Investigations
- increased WBC
- usually increased ALP and bilirubin, ALT variably elevated
- blood culture
- abdominal U/S: CBD dilation, stones

Treatment
- most important is drainage, ideally via ERCP, but if necessary by percutaneous biliary or surgical routes
- antibiotic therapy: broad spectrum to cover Gram-negatives, *Enterococcus*, and anaerobes (especially if CBD manipulation); no clear consensus on antibiotic choice but consider:
  - ampicillin + sulbactam or piperacillin/tazobactam
  - metronidazole + 3rd generation cephalosporin (e.g. ceftriaxone) or fluoroquinolone (e.g. ciprofloxacin or levofloxacin)
  - carbapenem monotherapy (e.g. imipenem or meropenem)

Prognosis
- good with effective drainage and antibiotics in mild to moderate cases
- high mortality (~50%) in patients with Reynolds Pentad

Pancreas

Pancreatic Enzyme Abnormalities

Causes of Increased Serum Amylase
- pancreatic disease
  - pancreatitis, pancreatic duct obstruction (e.g. ampullary cancer), pseudocyst, abscess, ascites, trauma, cancer
- non-pancreatic abdominal disease
  - biliary tract disease, bowel obstruction/ischemia, perforated or penetrating ulcer, ruptured ectopic pregnancy, aneurysm, chronic liver disease, peritonitis
- non-abdominal disease
  - cancer (lung, ovary, esophagus, etc.), salivary gland lesions, bulimia, renal transplant/insufficiency, burns, ketoacidosis
  - macroamylasemia

Pancreatic Enzymes

TALC
Trypsin
Amylase
Lipase
Chymotrypsin

Causes of Increased Serum Lipase
- pancreatic disease: same as above
- non-pancreatic abdominal disease (mild elevations only): same as above
- non-abdominal disease
  - macrolipasemia
  - renal failure

When serum amylase >5x normal, the cause is almost always pancreatitis or renal disease

Acute Pancreatitis

Etiology

Idiopathic: thought to be hypertensive sphincter or microlithiasis
Gallstones (45%)
Ethanol (35%)
Tumours: pancreas, ampulla, choledochocele
Scorpion stings
Microbiological
- bacterial: *Mycoplasma, Campylobacter*, TB, *M. avium intracellulare*, Legionella, leptospirosis
- viral: mumps, rubella, varicella, viral hepatitis, CMV, EBV, HIV, Coxsackie virus, echovirus, adenovirus
- parasites: ascariasis, clonorchiasis, echinococcosis

Autoimmune: SLE, polyarteritis nodosa (PAN), Crohn's disease
Surgery/trauma
- manipulation of sphincter of Oddi (e.g. ERCP), post-cardiac surgery, blunt trauma to abdomen, penetrating peptic ulcer

Hyperlipidemia (TG >11.3 mmol/L; >1000 mg/dL), **H**ypercalcemia, **H**ypothermia
Emboli or ischemia
Drugs/toxins
- azathioprine, mercaptopurine, furosemide, estrogens, methyldopa, H_2-blockers, valproic acid, antibiotics, acetaminophen, salicylates, methanol, organophosphates, steroids (controversial)

When thinking about the causes of acute pancreatitis remember: **I GET SMASHED**, but vast majority due to gallstones or ethanol

Pathophysiology
- activation of proteolytic enzymes within pancreatic cells, starting with trypsin, leading to local and systemic inflammatory response
- in gallstone pancreatitis, this is due to mechanical obstruction of the pancreatic duct by stones

Gallstones only cause acute pancreatitis (not chronic pancreatitis)

- in ethanol-related pancreatitis, pathogenesis is unknown
- in rare genetic diseases, mutations prevent the physiological breakdown of trypsin required normally to stop proteolysis (e.g. mutant trypsin in hereditary pancreatitis or mutation in SPINK 1 gene which normally inhibits activated trypsin); may be model for ethanol-related pancreatitis

Pathology

- mild (interstitial)
  - peri-pancreatic fat necrosis
  - interstitial edema
- severe (necrotic)
  - extensive peri-pancreatic and intra-pancreatic fat necrosis
  - parenchymal necrosis and hemorrhage → infection in 60%
  - release of toxic factors into systemic circulation and peritoneal space (causes multi-organ failure)
- severity of clinical features may not always correlate with pathology
- 3 phases
  - local inflammation + necrosis → hypovolemia
  - systemic inflammation in multiple organs, especially in lungs, usually after IV fluids given → pulmonary edema
  - local complications 2 wk after presentation → pancreatic sepsis/abscess

Signs and Symptoms

- pain: epigastric, noncolicky, constant
- can radiate to back
- may improve when leaning forward (Inglefinger's sign)
- tender rigid abdomen; guarding
- N/V
- abdominal distention from paralytic ileus
- fever: chemical, not due to infection
- jaundice: compression or obstruction of bile duct
- Cullen's/Grey-Turner's signs
- tetany: transient hypocalcemia
- hypovolemic shock: can lead to renal failure
- acute respiratory distress syndrome
- coma

Investigations

- increased serum pancreatic enzymes: amylase, lipase (more specific)
- ALT >150 specific for biliary cause
- increased WBC, glucose, low calcium
- imaging: CT most useful for diagnosis and prognosis
  - x-ray: "sentinel loop" (dilated proximal jejunem), calcification, and "colon cut-off sign" (colonic spasm)
  - U/S: useful for evaluating biliary tree (67% sensitivity, 100% specificity)
  - CT scan with IV contrast: useful for diagnosis and prognosis because contrast seen only in viable pancreatic tissue, non-viable areas can be biopsied percutaneously to differentiate sterile from infected necrosis
  - ERCP or MRCP if cause uncertain, assess for duct stone, pancreatic or ampullary tumour, pancreas divisum

Classification

- interstitial edematous vs. necrotizing
- mild, moderate, severe

Prognosis

- usually a benign, self-limiting course, single or recurrent
- occasionally severe leading to
  - shock
  - pulmonary edema
  - multi-organ dysfunction syndrome
  - GI ulceration due to stress
  - death
  - numerous scales to describe severity: probably most useful is proportion of pancreas not taking up contrast on CT done 48 hours after presentation (necrotic pancreas does not take up the contrast dye)
  - presence of organ failure, particularly organ failure that persists > 48 hours, is associated with worse outcomes

Table 21. Collections in pancreatitis (Revised 2012 Atlanta Classification)

	Liquid	Solid
Acute	Acute peripancreatic fluid collection (APFC)	Acute necrotic collection (ANC)
Chronic	Pancreatic pseudocyst	Walled-off necrosis (WON)

All of these collections are classified as infected or not infected

Ranson's Criteria: Prognostic Indicator of Mortality in Pancreatitis Not Due to Gallstones

At Admission
G: Blood **G**lucose >11 mmol/L (>200 mg/dL) (with no history of hyperglycemia)
A: **A**ge >55
L: Serum **L**DH >350 IU/L
A: **A**ST >250 IU/L
W: **W**BC >16 x 10^9/L (16,000/mm^3)

During First 48 h
C: Serum **C**alcium <2 mmol/L (<8 mEq/L)
H: **H**ematocrit drop >10%
O: Arterial PO_2 <60 mmHg
B: **B**ase deficit >4 mmol/L (>4 mEq/L)
B: **B**UN rise >1.8 mmol/L (>5 mg/dL)
S: Estimated fluid Sequestration >6 L

- Difficult course if 2 criteria present
- High mortality if ≥3 criteria present
- Other prognostic indices available, more accurate than Ranson but difficult to remember (e.g. APACHE)

Cullen's Sign
Periumbilical ecchymosis

Grey-Turner's Sign
Flank ecchymosis

When to call the surgeon in acute pancreatitis? Endoscopic Transgastric vs Surgical Necrosectomy for Infected Necrotizing Pancreatitis: A Randomized Trial
JAMA 2012; 307:1053-61
Once it was recognized that severe acute (necrotizing) pancreatitis had a terrible prognosis because of an exuberant inflammatory response leading to multiorgan failure, pancreatectomy was attempted. However, contrary to the expected favourable results, clinical experience has shown that pancreatectomy is usually not helpful, perhaps because once the inflammatory cascade starts, it persists as a self-perpetuating cycle. The problems caused by acute pancreatitis can be thought of a widespread burn initiated by inflammation in the pancreas, but having little do with ongoing problems within the pancreas itself. Studies suggest that the only compelling indication for surgery is infected necrotizing pancreatitis not responding to antibiotics. As predicted, without removal of such infected pancreatic tissue, death is likely from sepsis.
In this recent randomized trial, transgastric necrosectomy, an endoscopic technique that also removes infected necrotic pancreatic tissue, reduced both a composite end-point of major pancreatitis complications (especially new onset organ failure) and the pro-inflammatory response (as measured by serum IL-6 levels) to a greater extent than surgical necrosectomy. Of course, not all necrotic collections are in areas amenable to endoscopic intervention, and the advice of an experienced surgeon should always be welcomed in severe acute pancreatitis, but the role of surgery in previously considered surgical disease is rapidly diminishing.

Increased Amylase
- Sensitive, not specific

Increased Lipase
- Higher sensitivity and specificity
- Stays elevated longer

Treatment

- goals (only supportive therapy available)
  1. hemodynamic stability
  2. analgesia
  3. oxygen
  4. stop progression of damage (difficult)
  5. treat local and systemic complications
- antibiotics controversial except in documented infection (use cephalosporins, imipenem)
- aspirate necrotic areas of pancreas to diagnose infection; drain if infected
- IV fluids (crystalloid or colloid)
  - beware third spacing of fluid, monitor urine output carefully
- NG suction (lets pancreas rest) if vomiting, stomach very dilated
- endoscopic sphincterotomy if severe gallstone pancreatitis (i.e. cholangitis or ongoing obstruction)
- nutritional support: nasojejunal feeding tube or TPN if cannot tolerate enteric feeds
  - recent evidence supports nasogastric enteral (or oral if feasible) feeds
- no benefit: glucagon, atropine, aprotinin, H_2-blockers, peritoneal lavage
- follow clinically and CT/ultrasound to exclude complications
- chief role of surgery is to excise necrotic tissue (necrosectomy) in the case of infected pancreatic necrosis (try to delay for >2 wk to allow demarcation between viable and necrotic tissue)

Prophylactic Antibiotics Cannot Reduce Infected Pancreatic Necrosis and Mortality in Acute Necrotizing Pancreatitis: Evidence from a Meta-Analysis of Randomized Controlled Trials
Am J Gastroenterol 2008;103:104-110
Purpose: To review the effectiveness of IV antibiotics on pancreatic necrosis.
Study Selection: RCTs comparing antibiotics with placebo or no treatment.
Results: Seven trials (n=467) were included. Antibiotics were not statistically superior to controls in reduction of infected necrosis and mortality.
Conclusion: Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in patients with acute necrotizing pancreatitis.
Note: In practice the temptation to give antibiotics for pancreatitis is mainly in the setting of a sick patient with fever and suggestive pancreatic necrosis on CT scan. It is difficult to determine whether pancreatic necrosis has become infected without aspiration biopsy (see *Curr Gastroenterol Rep* 2009;11:104-110).

Late Complications

- pseudocysts: follow if asymptomatic, drain if symptomatic or growing
  - drain: choice of endoscopic, percutaneous under radiological guidance, or surgical
- infected necrosis/abscesses: antibiotics + percutaneous drainage, endoscopic vs. surgical
- bleeding: (1) gastric varices if splenic vein thrombosis, (2) pseudoaneurysm of vessels in areas of necrosis, especially splenic artery, (3) duodenal ulcer related to compression of duodenum by enlarged pancreas
- splenic and portal vein thrombosis: no effective therapy described, anticoagulation not proven, hazardous
- rare: DM, pancreatic duct damage

Chronic Pancreatitis

Definition

- irreversible damage to pancreas characterized by
  1. pancreatic cell loss (from necrosis)
  2. inflammation
  3. fibrosis

Etiology/Pathophysiology

- alcohol (most common)
  - causes a larger proportion (>90%) of chronic pancreatitis than acute pancreatitis
  - changes composition of pancreatic juice (e.g. increases viscosity)
  - decreases pancreatic secretion of pancreatic stone protein (lithostathine) which normally solubilizes calcium salts
    - precipitation of calcium within pancreatic duct results in duct and gland destruction
  - toxic effect on acinar and duct cells – directly or via increasing free radicals
  - acinar cell injury leads to cytokine release, which stimulates pancreatic stellate cells to form collagen (leading to fibrosis)
  - varying degrees of ductular dilatation, strictures, protein plugs, calcification
  - no satisfactory theory to explain why only a minority of alcoholics develop pancreatitis
- unusual causes
  - CF
  - severe protein-calorie malnutrition
  - hereditary
  - idiopathic

Symptoms of Chronic Pancreatitis
- Abdominal pain
- Diabetes
- Steatorrhea

Etiology = Almost Always Alcohol

Treatment
- Alcohol abstinence
- Pancreatic enzyme replacement
- Analgesics
- Pancreatic resection if ductular blockage

Signs and Symptoms

- early stages
  - recurrent attacks of severe abdominal pain (upper abdomen and back)
  - chronic painless pancreatitis: 10%
- late stages: occurs in 15% of patients
  - malabsorption syndrome when >90% of function is lost, steatorrhea
  - diabetes, calcification, jaundice, weight loss, pseudocyst, ascites, GI bleed

Investigations
- laboratory
  - increase in serum glucose
  - increase in serum ALP, less commonly bilirubin (jaundice)
  - serum amylase and lipase usually normal
- AXR: pancreatic calcifications
- U/S or CT: calcification, dilated pancreatic ducts, pseudocyst
- MRCP or ERCP: abnormalities of pancreatic ducts-narrowing and dilatation
- EUS: abnormalities of pancreatic parenchyma and pancreatic ducts, most sensitive test
- 72-h fecal fat test: measures exocrine function
- secretin test: gold standard, measures exocrine function but difficult to perform, unpleasant for patient, expensive
- fecal pancreatic enzyme measurement (elastase-1, chymotrypsin): available only in selected centres

Treatment
- most common problem is pain, difficult to control
- general management
  - total abstinence from alcohol
  - enzyme replacement may help pain by resting pancreas via negative feedback
  - analgesics
  - celiac ganglion blocks
  - time: pain decreases with time as pancreas "burns out"
- endoscopy: sphincterotomy, stent if duct dilated, remove stones from pancreatic duct
- surgery: drain pancreatic duct (pancreaticojejunostomy) if duct dilated (more effective than endoscopy); resect pancreas if duct contracted
- steatorrhea
  - pancreatic enzyme replacement
  - restrict fat, increase carbohydrate and protein (may also decrease pain)
  - neither endoscopy nor surgery can improve pancreatic function

Autoimmune Pancreatitis

- most commonly presents as a mimicker of pancreatic cancer (pancreatic mass detected because of jaundice ± abdominal pain)

Investigations
- histology: lymphocyte and plasma cell infiltration of pancreas
- imaging: focal or diffuse enlargement of pancreas on CT or MRI, sausage shaped, low density rim around pancreas
- serology: increased serum IgG4
- other organ involvement: sialadenitis, retroperitoneal fibrosis, biliary duct narrowing, nephritis

Treatment
- responds to prednisone

Clinical Nutrition

Determination of Nutritional Status

- corrected weight loss (expressed as body mass index [kg/m^2]) is most important parameter in assessing need for nutritional support
- Subjective Global Assessment: simple bedside tool to assess nutritional status, to help identify those who will benefit from nutritional support

Investigations
- plasma proteins: albumin, pre-albumin (shorter half life than albumin), transferrin
  - decrease may indicate decreased nutritional status or disease state
- thyroid-binding globulin, retinol-binding protein (may be too sensitive)
- anthropometry (e.g. triceps skinfold thickness), grip strength less often used

Table 22. Areas of Absorption of Nutrients

	Fe	CHO	Proteins, Lipids Na^+, H_2O	Bile Acids	Vit B_{12}
Duodenum	+++	+++	+++	+	
Jejunum	+	+	++	+	+
Ileum	+	+	++	+++	+++

Enteral Nutrition

Definition
- enteral nutrition (tube feeding) is a way of providing food through a tube placed in the stomach or the small intestine
- choice of tubes: nasogastric (NG), nasojejunal (NJ), percutaneous endoscopic gastrostomy ("G-tube" or "PEG tube"), percutaneous endoscopic jejunostomy (J-tube) or tubes can be placed radiologically, surgically

Indications
- oral feeding inadequate or contraindicated

Feeds
- polymeric feeds contain whole protein, carbohydrate, fat as a liquid, with or without fibre
- elemental feeds contain protein as amino acids, carbohydrate as simple sugars, fat content low (therefore high osmolarity)
- specific diets: low carbohydrate/high fat solution for ventilated patients (carbohydrate has a high respiratory quotient so minimizes carbon dioxide production), high energy, low electrolyte solutions for dialysis patients

Most Common Indications for Artificial Nutrition Support
- Preexisting nutritional deprivation
- Anticipated or actual inadequate energy intake by mouth
- Significant multiorgan system disease

Relative Contraindications
- non-functioning gut (e.g. intestinal obstruction, enteroenteral or enterocutaneous fistulae)
- uncontrolled diarrhea
- GI bleeding

Complications
- aspiration
- diarrhea
- refeeding syndrome (rare): carbohydrate can stimulate excessive insulin release, leading to cellular uptake and low serum levels of phosphate, magnesium, potassium
- overfeeding syndrome (rare): hypertonic dehydration, hyperglycemia, hypercapnea, azotemia (from excess protein)

Enteral Nutrition Advantages over Parenteral Nutrition
- fewer serious complications (especially sepsis)
- nutritional requirements for enterally administered nutrition better understood
- can supply gut-specific fuels such as glutamine and short chain fatty acids
- nutrients in the intestinal lumen prevent atrophy of the gut and pancreas
- prevents gallstones by stimulating gallbladder motility
- much less expensive

Whenever possible, enteral nutrition is ALWAYS preferable over parenteral nutrition

Parenteral Nutrition

Definition
- parenteral nutrition (PN) is the practice of feeding a person intravenously, bypassing the usual process of eating and digestion

Indications
- short-term (<1 mo)
  - whenever GI tract not functioning
  - only situations where PN has been well shown to increase survival are after bone marrow transplant and in short bowel syndrome, some evidence for benefit in gastric cancer, but often used in ICU, perioperatively, and in difficult to control sepsis
  - pre-operative: only useful in severely malnourished (e.g. loss of >15% of pre-morbid weight, serum albumin <28 g/L or <2.8 g/dL), and only if given for ≥2 wk
  - renal failure: PN shown to increase rate of recovery; no increase in survival
  - liver disease: branched chain amino acids may shorten duration of encephalopathy; no increase in survival
  - IBD: PN closes fistulae and heals acute exacerbations of mucosal inflammation, but effect is transient (EN is equally effective)
  - some evidence for efficacy, but convincing data not available for
    - radiation/chemotherapy-induced enteritis
    - AIDS with wasting diarrhea
    - severe acute pancreatitis
- long-term (>1 mo): can be given at home
  - severe untreatable small bowel disease (e.g. radiation enteritis, extensive CD, high output fistulae)
  - following surgical resection of >70% of small bowel (e.g. small bowel infarction)
  - severe motility diseases (e.g. scleroderma affecting bowel)

Hypomagnesemia may be an initial sign of short bowel syndrome in patients who have undergone surgical bowel resection

Enteral vs. Parenteral Nutrition for Acute Pancreatitis
Cochrane DB of Syst Rev 2010;1:CD002837
Purpose: Compare EN vs. TPN on mortality, morbidity, and hospital stay in patients with pancreatitis.
Study Selection: RCTs of TPN vs. EN in pancreatitis.
Results: Eight trials (n=348) were included. Enteral nutrition decreases RR of death (0.50), multiple organ failure (0.55), infection (0.39), and other local complications (0.70). It also decreased hospital stay by 2.37 d.
Conclusion: EN reduces mortality, organ failure, infections, and length of hospital stay in patients with pancreatitis.

Relative Contraindications
- functional GI tract for enteral nutrition
- active infection; at least until appropriate antibiotic coverage
- inadequate venous access; triple-lumen central venous lines usually prevent this problem
- unreliable patient or clinical setting

Complications of PN
- sepsis: most serious of the common complications
- mechanical pneumothorax from insertion of central line, catheter migration and thrombosis, air embolus
- metabolic: CHF, hyperglycemia, gallstones, cholestasis

Common Medications

Table 23. Common Drugs Prescribed in Gastroenterology

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
Proton Pump Inhibitors (H^+/K^+-ATPase inhibitors)	omeprazole	Losec®/Prilosec®	20 mg PO OD	Inhibits gastric enzymes H^+/K^+-ATPase (proton pump)	Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, reflux esophagitis, symptomatic GERD, dyspepsia, Zollinger-Ellison syndrome, eradication of *H. pylori* (combined with antibiotics)	Hypersensitivity to drug	Dizziness, headache, flatulence, abdominal pain, nausea, rash, increased risk of osteoporotic fracture (secondary to impaired calcium absorption)
	lansoprazole or dexlansoprazole	Prevacid® Dexilant®	Oral therapy: lansoprazole 15-30 mg OD (before breakfast), dexlansoprazole 30-60mg OD (does not need to be taken before breakfast)	Same as above	Same as above	Same as above	Same as above
	pantoprazole	Pantoloc® Protonix®	40 mg PO OD for UGIB: 80 mg IV bolus then 8 mg/h infusion	Same as above	Same as above and UGIB	Same as above	Same as above
	rabeprazole	Pariet®/Aciphex®	40 mg PO OD	Same as above	Same as above	Same as above	Same as above
	esomeprazole	Nexium®	20-40 mg PO OD	Same as above	Same as above	Same as above	Same as above
Histamine H_2-Receptor Antagonists	ranitidine	Zantac®	300 mg PO OD or 150 mg bid IV therapy: 50 mg q8h (but tachyphylaxis a problem)	Inhibits gastric histamine H_2-receptors	Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, ulcer prophylaxis, reflux esophagitis, symptomatic GERD; not useful for acute GI bleeds	Hypersensitivity to drug	Confusion, dizziness, headache, arrhythmias, constipation, nausea, agranulocytosis, pancytopenia, depression
	famotidine	Pepcid®	Oral therapy: duodenal/gastric ulcers: 40 mg qhs GERD: 20 mg bid IV therapy: 20 mg bid	Same as above	Same as above	Same as above	Same as above
Stool Softener	docusate sodium	Colace®	100-400 mg PO OD, divided in 1-4 doses	Promotes incorporation of water into stool	Relief of constipation	Presence of abdominal pain, fever, N/V	Throat irritation, abdominal cramps, rashes
Osmotic Laxatives	lactulose	Lactulose/ Constulose®	Constipation: 15-30 mL PO OD to bid Encephalopathy: 15-30 mL bid to qid	Poorly absorbed in GI tract and is broken down by colonic bacteria into lactic acid in the colon, increases osmotic colonic contents, increases stool volume	Chronic constipation, prevention, and treatment of portal-systemic encephalopathy	Patients who require a low galactose diet	Flatulence, intestinal cramps, nausea, diarrhea if excessive dosage
	PEG3350	Lax-a-day®/ Golytely®	Constipation: 17 g powder dissolved in 4-8 oz liquid PO OD	Osmotic agent causes water retention in stool and promotes frequency of stool	Relief of constipation Colonoscopy prep	Hypersensitivity to drug	Abdominal distension, pain, anal pain, thirst, nausea, rigor, tonic-clonic seizures (rare)

Table 23. Common Drugs Prescribed in Gastroenterology (continued)

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
Stimulant Laxatives	senna	Senokot®	Tablets: 1-4 PO qhs Syrup: 10-15 mL PO qhs	Induce peristalsis in lower colon	Constipation	Patients with acute abdomen	Abdominal cramps, discolouration of breast milk, urine, feces, melanosis coli and atonic colon from prolonged use (controversial)
	bisacodyl	Bisacodyl®	5-30 mg PO OD (start at 10 mg for bowel preparation)	Enteric nerve stimulation and local contact-induced secretory effects. Colonic movements	Constipation Preparation of bowel for procedure	GI obstruction Gastroenteritis	Abdominal colic, abdominal discomfort, proctitis (with suppository use), diarrhea
	metoclopramide	Maxeran®	See anti-emetics	See anti-emetics	See anti-emetics	See anti-emetics	See anti-emetics
Bulk Laxatives	psyllium	Metamucil®	2-6 tabs (1 tab = 0.52 g) PO od-tid prn	Increases stool bulk → water retention in stool	Constipation	Hypersensitivity to drug GI obstruction	GI obstruction, diarrhea, constipation, abdominal cramps
Antidiarrheal Agents	loperamide	Imodium®	Acute diarrhea: 4 mg PO initially, followed by 2 mg after each unformed stool	Acts as antidiarrheal via cholinergic, noncholingeric, opiate, and nonopiate receptor-medicated mechanisms; decreases activity of myenteric plexus	Adjunctive therapy for acute non-specific diarrhea, chronic diarrhea associated with IBD and for reducing the volume of discharge for ileostomies, colostomies, and other intestinal resections	Children <2 yr, known hypersensitivity to drug, acute dysentery characterized by blood in stools and fever, acute ulcerative colitis or pseudomembranous colitis associated with broad-spectrum antibiotics	Abdominal pain or discomfort, drowsiness or dizziness, tiredness, dry mouth, nausea and vomiting, hypersensitivity reaction
	diphenoxylate/ atropine	Lomotil®	5 mg PO tid to qid	Inhibits GI propulsion via direct action on smooth muscle, resulting in a decrease in peristaltic action and increase in transit time	Adjunctive therapy for diarrhea, as above	Hypersensitivity to diphenoxylate or atropine, jaundice, pseudomembranous enterocolitis, diarrhea caused by enterotoxin producing bacteria	Dizziness, drowsiness, insomnia, headache, N/V, cramps, allergic reaction
Anti-Emetics	dimenhydrinate	Gravol®	25-50 mg PO/IV/IM q4-6h prn	Competitive H_1 receptor antagonist in GI tract, blood vessels, and respiratory tract. Blocks chemoreceptor trigger zone. Diminishes vestibular simulation and disrupts labyrinthine function through central anticholinergic action	Motion sickness, radiation sickness, postoperative vomiting, and drug-induced N/V	Hypersensitivity to drug	Xerostomia, sedation
	prochlorperazine	Stemetil®	5-10 mg PO/IV/IM bid-tid prn	D1, D2 receptor antagonist in chemoreceptor trigger zone and α adrenergic and anti-cholinergic effects Depresses reticular activating system (RAS) affecting emesis	Post-operative N/V, antipsychotic, anxiety	Hypersensitivity to drug	Dystonia, EPS, seizure, neuroleptic malignant syndrome (NMS) (rarely)
	metoclopramide	Maxeran®	10 mg IV/IM q2-3h pm, 10-15 mg PO qid (30 min before meals and qhs)	Dopamine and 5-HT receptor antagonist in chemoreceptor trigger zone. Enhances response to ACh in upper GI tract, enhancing motility and gastric emptying. Increases LES tone	GERD, diabetic gastroparesis, post-operative and chemotherapy induced N/V, migraines, constipation	Hypersensitivity to drug, GI obstruction, perforation, hemorrhage, pheochromocytoma, seizures, and EPS	Restlessness, drowsiness, dizziness, fatigue, EPS, some rare serious side effects include NMS, agranulocytosis
	ondansetron	Zofran®	Depends on procedure, generally 8-16 mg PO	Selective 5HT3 receptor antagonist in central chemoreceptor trigger zone and peripherally on vagus nerve	N/V caused by cancer chemotherapy and radiation therapy; multiple off label uses, including gastroenteritis N/V	Morphine, hypersensitivity to drug	Constipation, diarrhea, increased liver enzymes, headache, fatigue, malaise, cardiac dysrhythmia
	granisetron	Kytril®	1 mg PO bid (for nausea from chemotherapy/ radiation)	Same as above	N/V caused by cancer chemotherapy and radiation therapy	Same as above	Constipation, prolonged QT interval (rarely)

Table 23. Common Drugs Prescribed in Gastroenterology (continued)

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
IBD Agents	mesalamine	Pentasa® Salofalk® Asacol® Mesasal®	CD: 1 g PO tid/qid Active UC: 1 g PO qid Maintenance UC: 1.6 g PO divided doses daily also as suppositories and enemas	5-ASA: Blocks arachidonic acid metabolism to prostaglandins and leukotrienes	IBD	Hypersensitivity to mesalamine salicylates; Asacol contains phthalate, potential urogenital teratogenicity for male fetus	Abdominal pain, constipation, arthralgia, headache
	sulfasalazine	Salazopyrin®	3-4 g/d PO in divided doses	Compound composed of 5-ASA bound to sulfapyridine, hydrolysis by intestinal bacteria releases 5-ASA, the active component	Colonic disease	Hypersensitivity to sulfasalazine, sulfa drugs, salicylates; intestinal or urinary obstruction, porphyria	Rash, loss of appetite, N/V, headache, oligospermia (reversible)
	prednisone		20-40 mg PO OD for acute exacerbation	Anti-inflammatory	Mod-severe CD and UC		Complications of steroid therapy
Immuno-suppressive Agents	6-mercaptopurine (6-MP)	Purinethol®	CD: 1.5 mg/kg/d PO	Immunosuppressive	IBD: active inflammation and to maintain remission	Hypersensitivity to mercaptopurine, prior resistance to mercaptopurine or thioguanine, history of treatment with alkylating agents, hypersensitivity to azathioprine, pregnancy	Pancreatitis, bone marrow suppression, increased risk of cancer
	azathioprine	Azasan® Imuran®	IBD: 2-3 mg/kg/d PO	Same as above	Same as above	Same as above	Same as above
Immunomo-dulators	infliximab	Remicade®	5-10 mg/kg IV over 2 h	Antibody to TNFα	Medically refractory CD	Heart failure, moderate to severe, doses >5 mg/kg	Reported cases of reactivated TB, PCP, lymphoma, other infections

Landmark Gastroenterology Trials

Trial	Reference	Results
MELD	*Gastroenterology* 2003;124:91-6	MELD score can be applied for allocation of donor livers as it accurately predicts 3 mo mortality in patients with chronic liver failure
Infliximab, azathioprine, or combination	*NEJM* 2010; 362:1383-95	In moderate-severe Crohn's disease, infliximab + azathioprine was more likely to result in corticosteroid-free remission than infliximab monotherapy. Infliximab monotherapy was more effective than azathioprine monotherapy. Similar results have been reported for ulcerative colitis (*Gastroenterology* 2014; 146:392-400)
Enteral versus parenteral	Cochrane Database Syst Rev 2010;1:	For acute pancreatitis, no trial was convincing alone, but in the congregate, enteral feeds via nasogastric tube is preferable to either no feeding or parenteral nutrition
Rifaximin treatment in hepatic encephalopathy	*NEJM 2010; 362:1071-81*	The most convincing of several articles establishing this non-absorbable antibiotic as the treatment of choice for hepatic encephalopathy for maintaining remission from hepatic encephalopathy and reducing hospitalization associated with the disease
Adenoma detection rate and risk of colorectal cancer and death	*NEJM* 2014; 370:1298-1306	A high miss rate for colorectal cancers has been suggested, chiefly in the right colon. This study demonstrates a method of assessing the competence of endoscopists in detecting cancers using adenoma detection rate (the proportion of colonoscopic exams in which a physician detects one or more adenomas) as a surrogate marker. Adenoma detection rate was associated with lower risk of interval colorectal cancer and has launched quality assurance programs for screening colonoscopies
Prednisolone or pentoxifylline for alcoholic hepatitis	*NEJM* 2015; 372:1619-28	For alcoholic hepatitis, prednisolone improved survival when the Maddrey's discriminant function > 32, but the benefit did not reach statistical significance and pentoxifylline was of no advantage at all. Other studies had shown some benefit with pentoxifylline, but this study was the most definitive

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GS General Surgery

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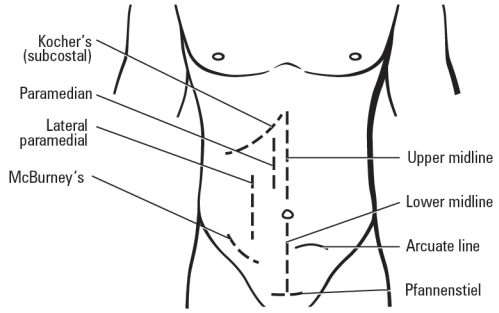
Basic Anatomy Review



Kosher's (subcostal)	Access to RUQ or LUQ contents i.e. gallbladder, spleen
Upper Midline	Access to stomach, duodenum, gallbladder, liver, transverse colon
Paramedian	Can make similar incision in each quadrant for access to each quadrant's contents Not commonly used Post-operative ventral hernias common
Lateral Paramedian	Incision made at outer 1/3 - medial 2/3 border of rectus Modification of paramedian but with lower risk of dehiscence or ventral hernia Not commonly used
Lower Midline	Access to pelvic organs, sigmoid colon, and rectum
Pfannenstiel	Suprapubic incision for access to pelvic cavity
McBurney's	Access to appendix

Figure 1. Abdominal incisions

Lateral Abdominal Wall Layers and their Continuous Spermatic and Scrotal Structures (superficial to deep)

1. skin (epidermis, dermis, subcutaneous fat)
2. superficial fascia
   - Camper's fascia (fatty) → Dartos fascia
   - Scarpa's fascia (membranous) → Colles' superficial perineal fascia
3. muscle (see Figure 2 and Figure 3)
   - external oblique → inguinal ligament → external spermatic fascia and fascia lata
   - internal oblique → cremasteric muscle/fascia
   - transversus abdominis → posterior inguinal wall
4. transversalis fascia → internal spermatic fascia
5. preperitoneal fat
6. peritoneum → tunica vaginalis

Midline Abdominal Wall Layers (superficial to deep)

1. skin
2. superficial fascia
3. rectus abdominis muscle: in rectus sheath, divided by linea alba
   - above arcuate line (midway between symphysis pubis and umbilicus)
     - anterior rectus sheath = external oblique aponeurosis and anterior leaf of internal oblique aponeurosis
     - posterior rectus sheath = posterior leaf of internal oblique aponeurosis and transversus abdominis aponeurosis
   - below arcuate line
     - aponeuroses of external oblique, internal oblique, transversus abdominis all pass in front of rectus abdominis
4. arteries: superior epigastric (branch of internal thoracic), inferior epigastric (branch of external iliac); both arteries anastomose and lie behind the rectus muscle (superficial to posterior rectus sheath above arcuate line)
5. transversalis fascia
6. peritoneum

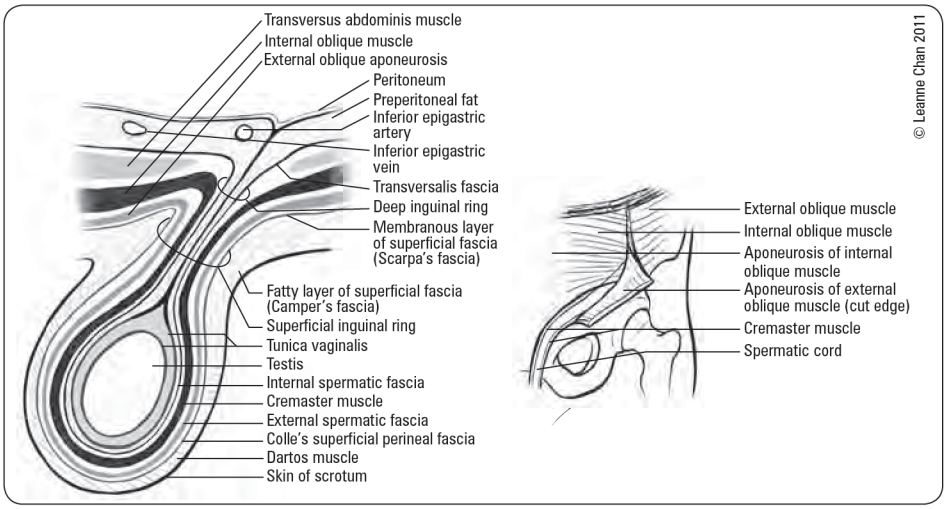


Figure 2. Continuity of the abdominal wall with layers of the scrotum and spermatic cord

Acronyms

5-FU	5-fluorouracil
AAA	abdominal aortic aneurysm
ABG	arterial blood gas
ABI	ankle brachial index
ALND	axillary lymph node dissection
APR	abdominoperineal resection
ARDS	acute respiratory distress syndrome
ATN	acute tubular necrosis
BRBPR	bright red blood per rectum
BCS	breast conserving surgery
CBD	common bile duct
CF	cystic fibrosis
CHF	congestive heart failure
CRC	colorectal cancer
CVA	costovertebral angle
CVP	central venous pressure
DCIS	ductal carcinoma *in situ*
DIC	disseminated intravascular coagulation
DPL	diagnostic peritoneal lavage
DRE	digital rectal exam
EBL	estimated blood loss
ERCP	endoscopic retrograde cholangiopancreatography
EUA	examination under anesthesia
EUS	endoscopic ultrasound
FAP	familial adenomatous polyposis
FAST	focused abdominal sonography for trauma
FNA	fine needle aspiration
FOBT	fecal occult blood test
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GIST	gastrointestinal stromal tumour
GU	genitourinary
HDGC	hereditary diffuse gastric carcinoma
HIDA	hepatobiliary imino-diacetic acid
HNPCC	hereditary nonpolyposis colorectal cancer
I&D	incision and drainage
IPAH	idiopathic pulmonary arterial hypertension
IPF	idiopathic pulmonary fibrosis
LAR	low anterior resection
LBO	large bowel obstruction
LCIS	lobular carcinoma *in situ*
LES	lower esophageal sphincter
LGIB	lower gastrointestinal bleed
LVRS	lung volume reduction surgery
MALT	mucosa-associated lymphoid tissue
MEN	multiple endocrine neoplasia
MIBG	metaiodobenzylguanidine
MIS	minimally invasive surgery
MRCP	magnetic resonance cholangiopancreatography
NGT	nasogastric tube
OGD	oesophagogastroduodenoscopy
POD	post-operative day
PPI	proton pump inhibitor
PTC	percutaneous transhepatic cholangiography
PUD	peptic ulcer disease
SBO	small bowel obstruction
SCC	squamous cell carcinoma
SIADH	syndrome of inappropriate anti-diuretic hormone
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SNLB	sentinel lymph node biopsy
TED	thromboembolic deterrent
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
UGIB	upper gastrointestinal bleed
VATS	video-assisted thorascopic surgery
VIP	vasoactive intestinal peptide

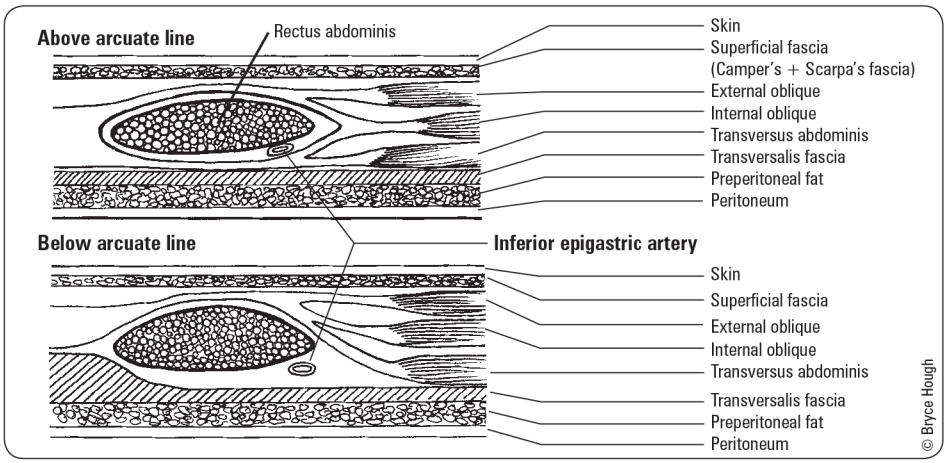


Figure 3. Midline cross-section of abdominal wall

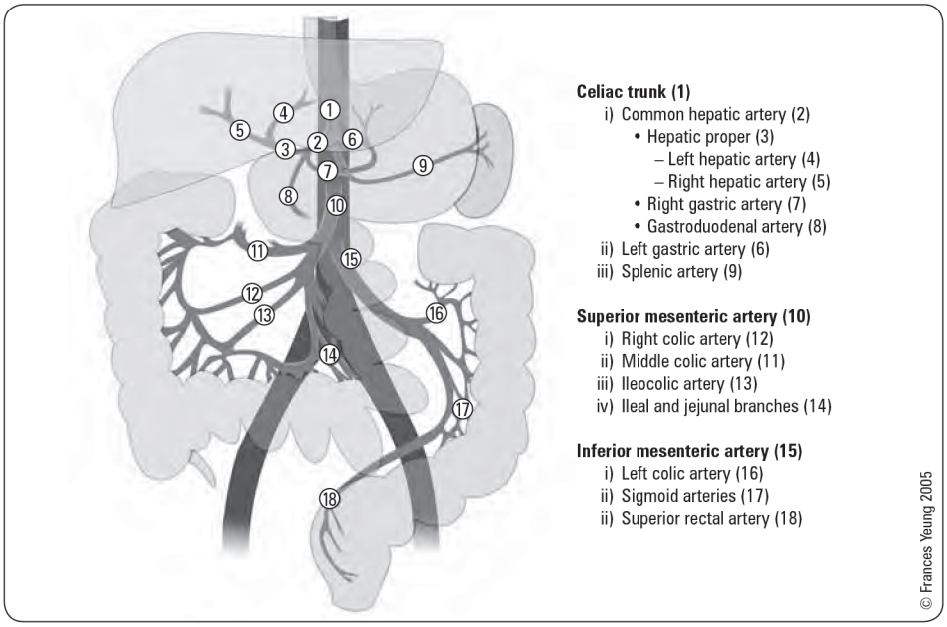


Figure 4. Blood supply to the GI tract

Venous Flow

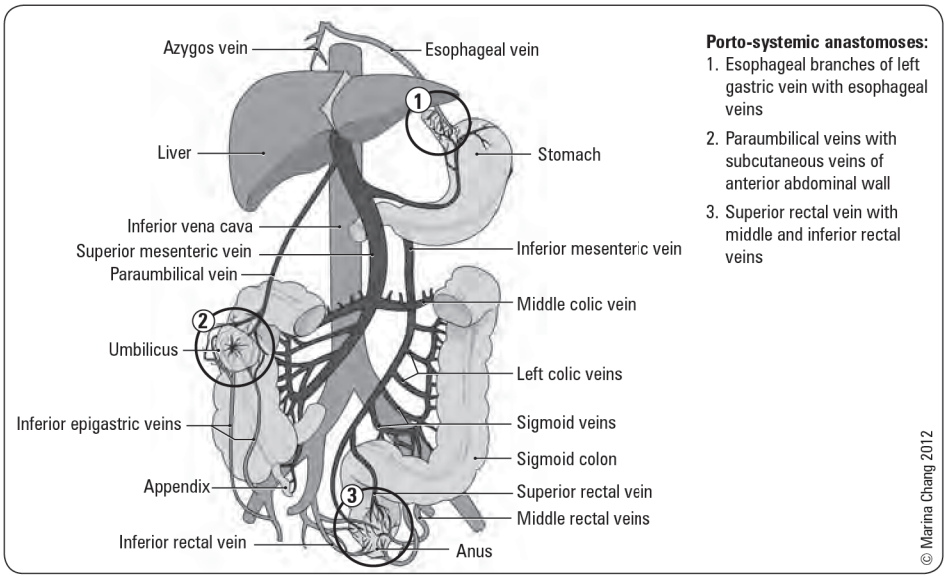


Figure 5. Venous drainage of the GI tract

Organ	Arteries
Liver	Left and right hepatic (branches of hepatic proper)
Spleen	Splenic
Gallbladder	Cystic (branch of right hepatic artery)
Stomach	1. Lesser curvature: right and left gastric 2. Greater curvature: right (branch of gastroduodenal) and left (branch of splenic) gastroepiploic 3. Fundus: short gastrics (branch of splenic)
Duodenum	1. Gastroduodenal 2. Pancreaticoduodenals (superior branch of gastroduodenal, inferior branch of superior mesenteric)
Pancreas	1. Pancreatic branches of splenic 2. Pancreaticoduodenals
Small intestine	1. Superior mesenteric branches: jejunal, ileal, ileocolic
Large intestine	1. Superior mesenteric branches: right colic, middle colic 2. Inferior mesenteric branches: left colic, sigmoid, superior rectal

Differential Diagnoses of Common Presentations

Acute Abdominal Pain

- acute abdomen = severe abdominal pain of acute onset and requires urgent medical attention
- in patients with acute abdominal pain, the first diagnoses that you should consider are those requiring potential urgent surgical intervention
- two main patterns constituting urgent general surgery referrals are peritonitis and obstruction

Table 1. Differential Diagnosis of Acute Abdominal Pain

RUQ

Hepatobiliary
- **Biliary colic**
- **Cholecystitis**
- **Cholangitis**
- **CBD obstruction** (stone, tumour)
- **Hepatitis**
- Budd-Chiari
- Hepatic abscess/mass
- Right subphrenic abscess

Gastrointestinal
- **Pancreatitis**
- Presentation of gastric, duodenal, or pancreatic pathology
- Hepatic flexure pathology (CRC, subcostal incisional hernia)

Genitourinary
- Nephrolithiasis
- Pyelonephritis
- Renal: mass, ischemia, trauma

Cardiopulmonary
- RLL pneumonia
- Effusion/empyema
- CHF (causing hepatic congestion and R pleural effusion)
- MI
- Pericarditis
- Pleuritis

Miscellaneous
- Herpes zoster
- Trauma
- Costochondritis

RLQ

Gastrointestinal
- **Appendicitis**
- **Crohn's disease**
- Tuberculosis of the ileocecal junction
- Cecal tumour
- Intussusception
- Mesenteric lymphadenitis (*Yersinia*)
- Cecal diverticulitis
- Cecal volvulus
- Hernia: femoral, inguinal obstruction, Amyand's (and resulting cecal distention)

Gynecological
- See 'suprapubic'

Genitourinary
- See 'suprapubic'

Extraperitoneal
- Abdominal wall hematoma/abscess
- Psoas abscess

EPIGASTRIC

Cardiac
- **Aortic dissection/ruptured AAA**
- **MI**
- **Pericarditis**

Gastrointestinal
- **Gastritis**
- **GERD/esophagitis**
- **PUD**
- **Pancreatitis**
- Mallory-Weiss tear

DIFFUSE

Gastrointestinal
- **Peritonitis**
- **Early appendicitis, perforated appendicitis**
- **Mesenteric ischemia**
- **Gastroenteritis/colitis**
- **Constipation**
- **Bowel obstruction**
- Pancreatitis
- Inflammatory bowel disease
- Irritable bowel syndrome
- Ogilvie's syndrome

Cardiovascular/Hematological
- Aortic dissection/ruptured AAA
- Sickle cell crisis

Genitourinary/Gynecological
- Perforated ectopic pregnancy
- PID
- Acute urinary retention

Endocrinological
- Carcinoid syndrome
- Diabetic ketoacidosis
- Addisonian crisis
- Hypercalcemia

Other
- Lead poisoning
- Tertiary syphilis

SUPRAPUBIC

Gastrointestinal (see RLQ/LLQ)
- Acute appendicitis
- IBD

Gynecological
- **Ectopic pregnancy**
- **PID**
- **Endometriosis**
- **Threatened/incomplete abortion**
- **Hydrosalpinx/salpingitis**
- Ovarian torsion
- Hemorrhagic fibroid
- Tubo-ovarian abscess
- Gynecological tumours

Genitourinary
- **Cystitis** (infectious, hemorrhagic)
- Hydroureter/urinary colic
- Epididymitis
- Testicular torsion
- Acute urinary retention

Extraperitoneal
- Rectus sheath hematoma

LUQ

Pancreatic
- **Pancreatitis** (acute vs. chronic)
- Pancreatic pseudocyst
- Pancreatic tumours

Gastrointestinal
- **Gastritis**
- **PUD**
- Splenic flexure pathology (e.g. CRC, ischemia)

Splenic
- **Splenic infarct/abscess**
- Splenomegaly
- Splenic rupture
- Splenic aneurysm

Cardiopulmonary (see RUQ and Epigastric)

Genitourinary (see RUQ)

LLQ

Gastrointestinal
- **Diverticulitis**
- Diverticulosis
- Colon/sigmoid/rectal cancer
- Fecal impaction
- Proctitis (ulcerative colitis, infectious; i.e. gonococcus or chlamydia)
- Sigmoid volvulus
- Hernia

Gynecological
- See 'suprapubic'

Genitourinary
- See 'suprapubic'

Extraperitoneal
- Abdominal wall hematoma/abscess
- Psoas abscess

See Gynecology, Urology, and Respirology chapters for further details regarding respective RLQ and suprapubic pain

In all patients presenting with an acute abdomen, order the following:

KEY TESTS FOR SPECIFIC DIAGNOSIS
- ALP, ALT, AST, bilirubin
- Amylase/lipase
- Urinalysis
- β-hCG (in women of childbearing age)
- Troponins
- Lactate

KEY TESTS FOR OR PREPARATION
- CBC, electrolytes, BUN, creatinine, glucose
- CXR + ECG
- INR/PTT

Types of Peritonitis
- Primary peritonitis: spontaneous without clear etiology
- Secondary peritonitis: due to a perforated viscus
- Tertiary peritonitis: recurrent secondary peritonitis more often with resistant organisms

Localization of Pain

Most digestive tract pain is perceived in the midline because of bilaterally symmetric innervation; kidney, ureter, ovary, or somatically innervated structures are more likely to cause lateralized pain

Referred Pain
- Biliary colic: to right shoulder or scapula
- Renal colic: to groin
- Appendicitis: periumbilical to right lower quadrant (RLQ)
- Pancreatitis: to back
- Ruptured aortic aneurysm: to back or flank
- Perforated ulcer: to RLQ (right paracolic gutter)
- Hip pain: to groin

Most Common Presentations of Surgical Pain
- Sudden onset with rigid abdomen = perforated viscus
- Pain out of proportion to physical findings = ischemic bowel
- Vague pain that subsequently localizes = appendicitis or other intra-abdominal process that irritates the parietal peritoneum
- Waves of colicky pain = bowel obstruction

Abdominal Mass

Table 2. Differential Diagnosis of Abdominal Mass

Right Upper Quadrant (RUQ)	Upper Midline	Left Upper Quadrant (LUQ)
Gallbladder: cholecystitis, cholangiocarcinoma, peri-ampullary malignancy, cholelithiasis **Biliary tract:** Klatskin tumour **Liver:** hepatomegaly, hepatitis, abscess, tumour (hepatocellular carcinoma, metastatic tumour, etc.)	**Pancreas:** pancreatic adenocarcinoma, other pancreatic neoplasm, pseudocyst **Abdominal aorta:** AAA (pulsatile) **GI:** gastric tumour (adenocarcinoma, gastrointestinal stromal tumour, carcinoid tumour), MALT lymphoma	**Spleen:** splenomegaly, tumour, abscess, subcapsular splenic hemorrhage, can also present as RLQ mass if extreme splenomegaly **Stomach:** tumour
Right Lower Quadrant (RLQ)	**Lower Midline**	**Left Lower Quadrant (LLQ)**
Intestine: stool, tumour (CRC), mesenteric adenitis, appendicitis, appendiceal phlegmon or other abscess, typhlitis, intussusception, Crohn's inflammation **Ovary:** ectopic pregnancy, cyst (physiological vs. pathological), tumour (serous, mucinous, struma ovarii, germ cell, Krukenberg) **Fallopian tube:** ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour	**Uterus:** pregnancy, leiomyoma (fibroid), uterine cancer, pyometra, hematometra **GU:** bladder distention, tumour	**Intestine:** stool, tumour, abscess (see RLQ) **Ovary:** see RLQ **Fallopian tube:** see RLQ

Pancreatitis can look like a surgical abdomen, but is rarely an indication for immediate laparotomy

Indications for Urgent Operation

IHOP
Ischemia
Hemorrhage
Obstruction
Perforation

Gastrointestinal Bleeding

- see Gastroenterology, G25, G27

Indications for Surgery

- failure of medical management
- exsanguinating hemorrhage: hemodynamic instability despite vigorous resuscitation
- recurrent hemorrhage after initial stabilization procedures with up to two attempts of endoscopic hemostasis
- hypovolemic shock
- prolonged bleeding with transfusion requirement >3 units
- bleeding at rate >1 unit/8 h

Surgical Management of GI Bleeding

- UGIB
  - bleeding from a source proximal to the ligament of Treitz
  - often presents with hematemesis and melena unless very brisk (then can present with hematochezia, hypotension, tachycardia)
  - initial management with endoscopy; if fails, then consider surgery
  - note: PUD accounts for approximately 55% of severe UGIB
- LGIB
  - bleeding from a source distal to the ligament of Treitz
  - often presents with BRBPR unless proximal to transverse colon
    - may occasionally present with melena
  - initial management with colonoscopy to detect and potentially stop source of bleeding
  - 75% of patients will spontaneously stop bleeding, however if bleeding continues barium enema should NOT be performed
  - angiography, RBC scan to determine source as indicated
  - surgery indicated if bleeding is persistent - aimed at removing underlying cause of bleeding
  - obscure bleed may require blind total colectomy if the source is not found

Overt bleeding: obvious hematochezia or melena per rectum visible to naked eye

Occult bleeding: bleeding per rectum is not obvious to naked eye (e.g. positive guaiac test)

Obscure bleeding: overt bleeding with no identifiable source after colonoscopy and endoscopy

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding
NEJM 2013;368:11-21
Recent study by Villanueva et al., demonstrates that a restrictive transfusion strategy (transfusion with hemoglobin below 70 g/L) significantly improves outcomes in patients with acute UGIB, compared to a liberal transfusion strategy (transfusion with hemoglobin below 90 g/L). Refer to study for details.

Table 3. Differential Diagnosis of GI Bleeding

Anatomical Source	Etiology	
Hematological	Excess anticoagulation (coumadin, heparin, etc.) Excess antiplatelet (clopidogrel, ASA)	DIC Congenital bleeding disorders
Nose	Epistaxis	
Esophagus	Esophageal varices Mallory-Weiss tear Esophagitis	Aorto-esophageal fistula (generally post endovascular aortic repair)* Esophageal cancer
Stomach	Gastritis Gastric varices Dieulafoy's lesion	Gastric ulcer Gastric cancer*
Duodenum	Duodenal ulcer Perforated duodenal ulcer*	Duodenal cancer*
Jejunum	Tumours* Polyps Ulcers	

Table 3. Differential Diagnosis of GI Bleeding (continued)

Anatomical Source	Etiology	
Ileum and Ileocecal Junction	Meckel's diverticulum (rare surgical management) Small bowel obstruction	Crohn's disease* Tuberculosis of ileocecal junction
Large Intestine	Colorectal cancer* Mesenteric thrombosis/ischemic bowel* Ulcerative colitis* (subtotal colectomy if failure of medical management) Angiodysplasia Diverticulosis (*if bleeding is persistent)	Crohn's disease (less frequently presents with bleeding)* Pancolitis (infectious, chemotherapy, or radiation induced) Bleeding post-gastrointestinal anastomosis
Sigmoid	Diverticulosis (*if bleeding is persistent) Sigmoid cancer* Bleeding post-polypectomy	Polyps (*if not amenable to colonoscopic polypectomy) Inflammatory bowel disease (IBD)
Rectum and Anus	Hemorrhoids Fissures Rectal cancer* Anal varices	Polyps (*if not amenable to colonoscopic polypectomy) Crohn's or ulcerative colitis* Solitary rectal ulcer syndrome

*Managed surgically in most cases

Biochemical Signs for Differentiating Jaundice
Hepatocellular: Elevated bilirubin + elevated ALT/AST
Cholestatic: Elevated bilirubin + elevated ALP/GGT ± duct dilatation upon biliary U/S
Hemolysis: ↓ haptoglobin ↑ LDH

Note: cholestatic jaundice is usually surgical

Jaundice

- see Gastroenterology, G40

Pre-Operative Preparations

Considerations

- informed consent (see Ethical, Legal, and Organizational Medicine, ELOAM7)
- screening questionnaire to determine risk factors e.g. age, exercise capacity, medication use, allergies
- consider pre-operative anesthesia, medicine consult as indicated to optimize patient status
- NPO according to guidelines (see Anesthesia and Perioperative Medicine, A5)
- IV – balanced crystalloid at maintenance rate (4:2:1 rule → roughly 100-125 cc/h): normal saline or Ringer's lactate; bolus to catch up on estimated losses including losses from bowel prep
  - appropriate use of fluids perioperatively decreases risk of cardiorespiratory complications
- patient's regular medications including with the exception of hypoglycemic agents, diuretics and ACE-inhibitors
- prednisone will require stress dose coverage, anticoagulation medication must be managed to decrease surgical bleeding but not put patient at risk for increased thrombotic events (e.g. switching from warfarin to LMWH)
- hold ASA x 1 wk pre-operative
- prophylactic antibiotics depending on wound class (within 1 h prior to incision): usually cefazolin (Ancef®) ± metronidazole (Flagyl®)
- consider bowel prep: cleans out bowel and decreases bacterial population
  - oral cathartic (e.g. fleet Phosphosoda®) starting previous day
  - in selected cases, current evidence does not support routine use
- consider DVT prophylaxis for all inpatient surgery (heparin)
- do not hold heparin prior to surgery unless epidural is expected
- smoking cessation x 8 or more wk and weight loss pre-operative can significantly decrease post-operative complications
- infection: delay elective surgery until infection controlled including respiratory infection particularly in asthma patients

Investigations

- see Anesthesia and Perioperative Medicine, A3
- routine pre-operative laboratory investigations for **elective** procedures should be **selective**
  - only ASA class and surgical risk have been found to independently predict post-operative adverse effects
- blood components: group and screen or cross and type depending on procedure
- CBC, electrolytes, BUN, creatinine
- INR/PT, PTT
- ABGs if predisposed to respiratory insufficiency
- CXR (PA and lateral) for patients with history of cardiac or pulmonary disease
- ECG as indicated by history or if >69 yr and no risk factors
- β-hCG testing in all women of reproductive age

Bilirubin Levels

	Prehepatic	Intrahepatic	Posthepatic
Serum Bilirubin			
Indirect	↑	↑	N
Direct	N	↑	↑
Urine			
Urobilinogen	↑	↑	–
Bilirubin	–	+	+
Fecal			
Urobilinogen	↑	↑	–

In patients with liver disease and an acute abdomen, spontaneous bacterial peritonitis must be ruled out

Best Practice in General Surgery (BPIGS)
http://www.bpigs.ca/
BPIGS is a University of Toronto initiative with the goal of standardizing care in general surgery. This link contains EBM based guidelines which have been implemented by consensus within all Toronto teaching hospitals. This is a highly recommended source for the most up-to-date pre-operative and general treatment guidelines

Surgical Emergencies: Take an AMPLE History

Allergies
Medications
Past medical/surgical history (including anesthesia and bleeding disorders)
Last meal
Events (HPI and FHx of bleeding disorders/anesthesia complications)

Drains

- NGT
  - indications: gastric decompression, analysis of gastric contents, irrigation/dilution of gastric contents, feeding (only if necessary due to risk of aspiration → naso-jejunal tube preferable)
  - contraindications: suspected basal skull fracture, obstruction of nasal passages due to trauma
- Foley catheter with urometer
  - indications: to accurately monitor urine output, decompression of bladder, relieve obstruction, rapidly expanding suprapubic mass
  - contraindications: suspected urethral injury, difficult insertion of catheter

Drain Size
Measured by the unit French:
French = diameter (mm) x 3

Surgical Complications

- general principles in preventing complications during the post-operative period include
  - frequent examination of the patient (daily or more) and their wound
  - removal of surgical tubes as soon as possible (e.g. Foley catheters and surgical drains)
  - early ambulation
  - monitor fluid balance and electrolytes
  - analgesia - enough to adequately address pain, but not excessive
  - skillful nursing care

Pre and Post-Operative Orders

ADDAVIDS
Admit to ward X under Dr. Y
Diagnosis
Diet
Activity
Vitals (q4h from ED and post-operative is standard)
IV, **I**nvestigations, **I**ns and Outs
Drugs, **D**ressings, **D**rains
Special procedures

Post-Operative Fever

- fever does not necessarily imply infection particularly in the first 24-48 h post-operative
- fever may not be present or is blunted if patient is receiving chemotherapy, glucocorticoids, or immunosuppression
- timing of fever may help identify cause
  - hours after surgery – POD #1 (immediate)
    - inflammatory reaction in response to trauma from surgery; unlikely to be infectious
    - reaction to blood products received during surgery
    - malignant hyperthermia
  - POD #1-2 (acute)
    - atelectasis (most common cause of fever on POD #1)
    - early wound infection (especially *Clostridium*, Group A *Streptococcus* – feel for crepitus and look for "dishwater" drainage)
    - aspiration pneumonitis
    - other: Addisonian crisis, thyroid storm, transfusion reaction
  - POD #3-7 (subacute): likely infectious
    - UTI, surgical site infection, IV site/line infection, septic thrombophlebitis, leakage at bowel anastomosis (tachycardia, hypotension, oliguria, abdominal pain)
  - POD #8+ (delayed)
    - intra-abdominal abscess, DVT/PE (can be anytime post-operative, most commonly POD #8-10), drug fever
    - other: cholecystitis, peri-rectal abscess, URTI, infected seroma/biloma/hematoma, parotitis, *C. difficile* colitis, endocarditis

5 Ws of Post-Operative Fever
Wind POD #1-2 (pulmonary – atelectasis, pneumonia)
Water POD #3-5 (urine – UTI)
Wound POD #5-8 (if earlier think streptococcal or clostridial infection)
Walk POD #8+ (thrombosis – DVT/PE)
Wonder drugs POD #1+ (drug)

Treatment

- treat primary cause
- antipyrexia (e.g. acetaminophen)

Drugs – 7 As

Analgesia
Anti-emetic
Anticoagulation
Antibiotics
Anxiolytics
Anticonstipation
All other patient meds (home meds, stress dose steroids, and β-blockers)

Approach to the Critically Ill Surgical/ Trauma Patient

ABC, I'M FINE
ABC
IV: 2 large bore IVs with NS, wide open
Monitors: O_2 sat, ECG, BP
Foley catheter to measure urine output
Investigations: blood work
NGT if indicated
"**E**x" rays (abdomen 3 views, CXR), other imaging – only when stable

Wound/Incisional Complications

WOUND CARE (see Plastic Surgery, PL8)

- can shower POD #2-3 after epithelialization of wound
- dressings can be removed POD #2 and left uncovered if dry
- examine wound if wet dressing, signs of infection (fever, tachycardia, pain)
- skin sutures and staples can be removed POD #7-10
  - exceptions: incision crosses crease (groin), closed under tension, in extremities (hand) or patient factors (elderly, corticosteroid use, immunosuppressed) removed POD #14, earlier if signs of infection
- negative pressure dressings consist of foam and suction, promote granulation
  - ideal for large (grafted sites) or non-healing wounds (irradiated skin, ulcer)

DRAINS

- sometimes placed intra-operatively to prevent fluid accumulation (blood, pus, serum, bile, urine)
  - can be used to assess quantity of third space fluid accumulation post-operatively
- potential route of infection, bring out through separate incision (vs. operative wound) to decrease risk of wound infection and remove as soon as possible

- types of drains
  - open (e.g. Penrose), higher risk of infection
  - closed: 1) Gravity drainage (e.g. Foley catheter); 2) Underwater-seal drainage system (e.g. chest tube); 3) Suction drainage (e.g. Jackson-Pratt)
  - sump (e.g. NGT)
- monitor drain outputs daily
- drains should be removed once drainage is minimal (usually <30-50 cc/24 h)
- evidence does not support routine post-operative drainage of abdominal cavity
- drains do not guarantee that the patient will not form a collection of fluid
- ridged drains can erode through internal structures, and excessive suction can cause necrosis

SURGICAL SITE INFECTION

Etiology
- *S. aureus, E. coli, Enterococcus, Streptococcus* spp., *Clostridium* spp.

Risk Factors

Table 4. Procedures and Their Impact on Surgical Site Infection

Classification	Clean	Clean-Contaminated	Contaminated	Dirty/Infected
Definition	Incision under sterile conditions; nontraumatic; no entrance of hollow organ	Incision under sterile conditions; ENTRANCE of hollow viscus; no evidence of active infection; minimal contamination	Incision under sterile conditions; MAJOR contamination of wound during procedure (i.e. gross spillage of stool, infection in biliary, respiratory, or GU systems)	Established infection present before wound is made in skin
Example	Wound created to repair hernia	Routine cholecystectomy; colon resection	Bowel obstruction with enterotomy and spillage of contents; necrotic bowel resection; fresh traumatic wounds	Appendiceal abscess; traumatic wound with contaminated devitalized tissue; perforated viscus
Infection Rate	<2%	3-4%	7-10%	30-40%
Wound Closure	Primary closure	Primary closure	Often secondary closure	Secondary closure

- patient characteristics
  - age, DM, steroids, immunosuppression, obesity, burn, malnutrition, patient with other infections, traumatic wound, radiation, chemotherapy
- other factors
  - prolonged pre-operative hospitalization, reduced blood flow, break in sterile technique, multiple antibiotics, hematoma, seroma, foreign bodies (drains, sutures, grafts), skin preparation, hypoxemia, hypothermia

Clinical Presentation
- typically fever POD #5-8 (*Streptococcus* and *Clostridium* can present in 24 h)
- pain, blanchable wound erythema, induration, purulent discharge, warmth
- complications: fistula, sinus tracts, sepsis, abscess, suppressed wound healing, superinfection, spreading infection to myonecrosis or fascial necrosis (necrotizing fasciitis), wound dehiscence, evisceration, hernia

Prophylaxis
- used to reduce the chance of surgical site infections
- pre-operative antibiotics for most surgeries (cefazolin ± metronidazole or if β-lactam allergy, clindamycin ± gentamycin)
  - within 1 h pre-incision; can re-dose at 1-2 half-lives (~q4-8h) in the OR
  - not required for low risk elective cholecystectomy, hemorrhoidectomy, fistulotomy, sphincterotomy for fissure
  - evidence suggests role in breast surgery
- generally no need to continue prophylactic antibiotics post-operatively
  - reserve post-operative antibiotics for treatment of suspected or documented intra-abdominal infection
- normothermia (maintain patient temperature 36-38°C during OR)
- hyperoxygenation (consider FiO_2 of 80% in OR)
- chlorhexidine-alcohol wash of surgical site
- hair removal should not be performed unless necessary; if so, clipping superior to shaving
- consider delayed primary closure of incision for contaminated wounds

Systemic Prophylactic Antibiotics Recommendations
Updated Recommendations for Control of Surgical Site Infections
Ann Surg 2011;253:1082-93
- Choice of routine prophylactic antibiotic depends on the pathogen and patient allergies.
- Vancomycin and fluorquinolones should be administered 1-2 h prior to incision; all other antibiotics should be administered 30 min prior to incision.
- Short-acting antibiotics should be redosed ~3 h after incision.
- Antibiotic administration >24 h after surgery does not appear to add benefits.
- Antibiotics should no longer be routinely administered in three doses.
- The majority of antibiotics are renally excreted hence renal function must be considered in antibiotic administration.
- Obese patients need higher antibiotic doses to achieve therapeutic concentrations.
- Drug half-life and length of operation need to be considered in antibiotic administration.

Treatment
- examination of the wound: inspect, compress adjacent areas, swab drainage for C&S and Gram stain
- re-open affected part of incision, drain, pack, heal by secondary intention in most cases
- for deeper infections, debride necrotic and non-viable tissue
- antibiotics and demarcation of erythema only if cellulitis or immunodeficiency

WOUND HEMORRHAGE/HEMATOMA
- secondary to inadequate surgical control of hemostasis

Risk Factors
- anticoagulant therapy, coagulopathies, thrombocytopenia, DIC, severe liver disease, myeloproliferative disorders, severe arterial HTN, severe cough
- more common with transverse incisions through muscle, due to cutting of muscle

Clinical Features
- pain, swelling, discolouration of wound edges, leakage
- rapidly expanding neck hematoma can compromise airway and is a surgical emergency: consider having a suture kit at bedside in all neck surgery in the event of having to open the wound emergently

Treatment
- pressure dressing
- open drainage ± wound packing (large hematoma only)
- if significant bleeding, may need to re-operate to find source (often do not find a discrete vessel)

SEROMA
- fluid collection other than pus or blood
- secondary to transection of lymph vessels
- delays healing
- increased infection risk

Treatment
- consider pressure dressing ± needle drainage
- if significant may need to re-operate

WOUND DEHISCENCE
- disruption of fascial layer, abdominal contents contained by skin only
- 95% caused by intact suture tearing through fascia

Clinical Features
- typically POD #1-3; most common presentation sign is serosanguinous drainage from wound ± evisceration
- palpation of wound edge: should normally feel a "healing ridge" from abdominal wall closure (raised area of tissue under incision)

Risk Factors
- local: technical failure of closure, increased intra-abdominal pressure (e.g. COPD, ileus, bowel obstruction), hematoma, infection, poor blood supply, radiation, patient not fully paralyzed while closing, transverse incision
- systemic: smoking, malnutrition (hypoalbuminemia, vitamin C deficiency), connective tissue diseases, immunosuppression, pulmonary disease, ascites, poor nutrition, steroids, chemotherapy, obesity, other (e.g. age, sepsis, uremia)
- DM alone is not a risk factor

Treatment
- place moist dressing over wound with binder around abdomen and transfer to OR
- may consider conservative management with debridement of fascial and/or skin margins
- evisceration, also known as 'burst abdomen', is a surgical emergency (mortality rates as high as 45%): take patient for operative closure, use slowly absorbable suture ± retention sutures

Pre-Operative Skin Antiseptics for Preventing Surgical Wound Infections After Clean Surgery
Cochrane DB Syst Rev 2013;3:CD003949
Purpose: To determine if pre-operative skin antisepsis prior to clean surgery prevents surgical-site infection (SSI) and which antiseptic is most effective.
Methods: Systematic review and meta-analysis of randomized-controlled trials (RCTs). Main outcome was SSI. Secondary outcomes included quality of life, mortality, and length of hospital stay.
Results: 13 RCTs (n=2,623 patients) were included that made 11 total comparisons between skin antiseptics. A single study found a statistically significant difference between two antiseptics: 0.5% chlorhexidine solution in methylated spirits prevented SSIs after clean surgery better than alcohol-based povidone-iodine paint. No other statistically significant differences were found.
Conclusions: Insufficient evidence that one antiseptic is better than another. Alcohol-based solutions are probably more effective than aqueous-based solutions.

Systemic Review and Meta-Analysis of Randomized Clinical Trials Comparing Primary vs. Delayed Primary Skin Closure in Contaminated and Dirty Abdominal Incisions
JAMA Surg 2013;148:779-786
Purpose: To compare rates of surgical site infection (SSI) with delayed primary closure (DPC) vs. primary skin closure (PC).
Results/Conclusions: 8 RCTs with 623 patients. Most common diagnosis was appendicitis (77.4%). Although there was significant heterogeneity between studies, DPC (2-5 d time to first review) was found to significantly reduce the chance of SSI (OR 0.65, 95% CI 0.40-0.93). Although current trials are poorly designed, DPC may be a simple and cost-effective way of reducing the rates of SSIs following abdominal surgery with contaminated or dirty wounds.

Urinary and Renal Complications

URINARY RETENTION
- may occur after any operation with general anesthesia or spinal anesthesia
- more likely in older males with history of benign prostatic hyperplasia, patients on anticholinergics

Clinical Presentation
- abdominal discomfort, palpable bladder, overflow incontinence, post-void residual urine volume >100 mL

Treatment
- Foley catheter to rest bladder, then trial of voiding

OLIGURIA/ANURIA (see Nephrology, NP17)

Etiology
- prerenal vs. renal vs. postrenal
  - most common post-operative cause is prerenal ± ischemic ATN
    - external fluid loss: hemorrhage, dehydration, diarrhea
    - internal fluid loss: third-spacing due to bowel obstruction, pancreatitis

Clinical Presentation
- urine output <0.5 cc/kg/h, increasing Cr, increasing BUN

Treatment
- according to underlying cause; fluid deficit is treated with crystalloid (NS or RL)

Post-Operative Dyspnea

- see *Respiratory Complications* below and *Cardiac Complications*, GS11

Etiology
- respiratory: atelectasis, pneumonia, pulmonary embolus (PE), ARDS, asthma, pleural effusion
- cardiac: MI, arrhythmia, CHF
- inadequate pain control

Respiratory Complications

ATELECTASIS
- comprises 90% of post-operative pulmonary complications

Clinical Features
- low-grade fever on POD #1, tachycardia, crackles, decreased breath sounds, bronchial breathing, tachypnea

Risk Factors
- COPD, smoking, obesity, elderly persons
- upper abdominal/thoracic surgery, oversedation, significant post-operative pain, poor inspiratory effort

Treatment
- pre-operative prophylaxis
  - smoking cessation (best if >8 wk pre-operative)
- post-operative prophylaxis
  - incentive spirometry, deep breathing exercise, chest physiotherapy, intermittent positive-pressure breathing
  - selective NGT decompression after abdominal surgery
  - short-acting neuromuscular blocking agents
  - minimize use of respiratory depressive drug, good pain control, early ambulation

PNEUMONIA/PNEUMONITIS
- may be secondary to aspiration of gastric contents during anesthetic induction or extubation, causing a chemical pneumonitis

Risk Factors
- aspiration: general anesthetic, decreased LOC, GERD, full stomach, bowel/gastric outlet obstruction + non-functioning NGT, pregnancy, seizure disorder
- non-aspiration: atelectasis, immobility, pre-existing respiratory disease

Clinical Features
- productive cough, fever
- tachycardia, cyanosis, respiratory failure, decreased LOC
- CXR: pulmonary infiltrate

Treatment
- prophylaxis: see atelectasis prophylaxis, pre-operative NPO/NGT, rapid sequence anesthetic induction
- immediate removal of debris and fluid from airway
- consider endotracheal intubation and flexible bronchoscopic aspiration
- IV antibiotics to cover oral nosocomial aerobes and anaerobes (e.g. ceftriaxone, metronidazole)

PULMONARY EMBOLUS (see Respirology, R18)

Clinical Features
- unilateral leg swelling and pain (DVT as a source of PE), sudden onset shortness of breath, tachycardia, fever
- most commonly POD #8-10, but can occur anytime post-operatively
- diagnosis made by Chest CT scan usually

Treatment
- IV heparin, long-term warfarin (INR = 2-3) for 3 mo
- Greenfield (IVC) filter if contraindications to anticoagulation
- prophylaxis: subcutaneous heparin (5,000 U bid) or LMWH, compression stockings (TED™ Hose)

PULMONARY EDEMA

Etiology
- cardiogenic vs. noncardiogenic
- circulatory overload: excess volume replacement, LV failure, shift of fluid from peripheral to pulmonary vascular bed, negative airway pressure, alveolar injury due to toxins (e.g. ARDS)
  - more common with pre-existing cardiac disease
- negative pressure pulmonary edema due to inspiratory efforts against a closed glottis upon awakening from general anesthesia

New onset "asthma" and wheezing in the elderly is cardiogenic until proven otherwise

Clinical Features
- shortness of breath, crackles at lung bases, CXR abnormal

Treatment (LMNOP)
- **L**asix
- **M**orphine (decreases symptoms of dyspnea, venodilator and afterload reduction)
- **N**itrates (venodilator)
- **O**xygen + non-invasive ventilation
- **P**osition (sit patient up)

RESPIRATORY FAILURE

Clinical Features
- dyspnea, cyanosis, evidence of obstructive lung disease
- earliest manifestations – tachypnea and hypoxemia (RR >25, pO_2 <60)
- pulmonary edema, unexplained decrease in SaO_2

Treatment
- ABCs, O_2, ± intubation
- bronchodilators, diuretics to treat CHF
- adequate blood pressure to maintain pulmonary perfusion
- if these measures fail to keep PaO_2 >60, consider ARDS

Cardiac Complications

- abnormal ECGs common in post-operative period (compare to pre-operative ECG)
- common arrhythmias: supraventricular tachycardia, atrial fibrillation (secondary to fluid overload, PE, MI)

MYOCARDIAL INFARCTION

- see Cardiology and Cardiac Surgery, C26
- surgery increases risk of MI
- incidence
  - 0.5% in previously asymptomatic men >50 yr old
  - 40-fold increase in men >50 yr old with previous MI

Risk Factors

- pre-operative HTN, CHF
- previous MI (highest risk ≤6 mo, but risk never returns to baseline)
- increased age
- intra-operative hypotension
- operations >3 h
- angina

Clinical Features

- majority of cases on day of operation or POD #3-4 (shifting of third space fluid back into intravascular compartment)
- often silent without chest pain, may only present with new-onset CHF (dyspnea), arrhythmias, hypotension

Intra-Abdominal Abscess

Definition

- collection of pus walled-off from rest of peritoneal cavity by inflammatory adhesions and viscera

Etiology

- usually polymicrobial: Gram-negative bacteria, anaerobes
  - consider Gram-positives if coexisting cellulitis

Risk Factors

- emergency, contaminated OR
- GI surgery with anastomoses
- poor healing risk factors (DM, poor nutrition, etc.)
- may occur POD #3 after laparotomy when third space fluid re-distribution occurs

Clinical Features

- persistent spiking fever, dull pain, weight loss
- mass difficult to palpate
- peritoneal signs if abscess perforation and secondary peritonitis
- leukocytosis or leukopenia (immunocompromised, elderly)
- co-existing effusion (pleural effusion with subphrenic abscess)
- common sites: pelvis, Morrison's pouch (space between kidney and liver), subphrenic, paracolic gutters, lesser sac, peri-appendiceal, post-surgical anastomosis, diverticular, psoas

Investigations

- CBC, blood cultures x2
- CT ± water-soluble contrast
- DRE (pelvic abscess)

Treatment

- drain placement by interventional radiology (preferred), laparoscopy, open drainage
- subsequent antibiotic coverage, ciprofloxacin (Cipro®) + metronidazole (Flagyl®)

Paralytic Ileus

- see *Bowel Obstruction,* GS24

Delirium

- see Psychiatry, PS20 and Neurology, N21

Thoracic Surgery

Hiatus Hernia

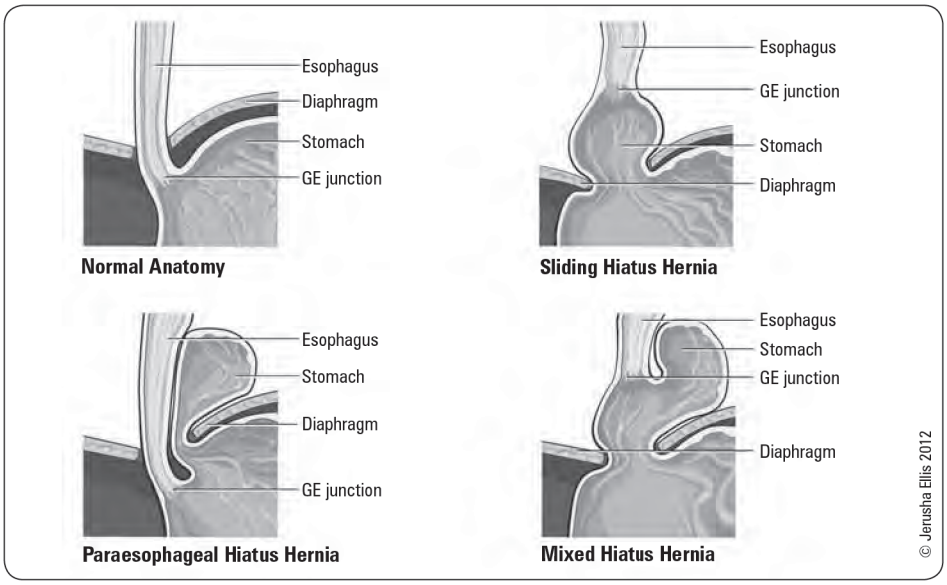


Figure 6. Types of hiatus hernia

Differential Diagnosis of Hiatus Hernia

GI Causes	Non-GI Causes
• Cholelithiasis	• MI
• Diverticulitis	• Angina
• Peptic ulcer	• Pericarditis
• Achalasia	
• Pancreatitis	
• GERD	
• Gastritis	

SLIDING HIATUS HERNIA (Type I)

- see Figure 6
- herniation of both the stomach and the gastroesophageal (GE) junction into thorax
- 90% of esophageal hernias

Risk Factors

- age
- increased intra-abdominal pressure (e.g. obesity, pregnancy, coughing, heavy lifting)
- smoking

Clinical Features

- majority are asymptomatic
- larger hernias frequently associated with GERD due to decreased competence of LES

Complications

- most common complication is GERD
- other complications are rare and are related to reflux
  - esophagitis (dysphagia, heartburn)
  - consequences of esophagitis (peptic stricture, Barrett's esophagus, esophageal carcinoma)
  - extra-esophageal complications (pneumonitis/pneumonia, asthma, cough, laryngitis)

Investigations

- CXR, barium swallow, endoscopy, or esophageal manometry (technique for measuring LES pressure)
- 24 h esophageal pH monitoring to quantify reflux
- gastroscopy with biopsy to document type and extent of tissue damage and rule out esophagitis, Barrett's esophagus, and cancer

Treatment

- lifestyle modification
  - stop smoking, weight loss, elevate head of bed, no meals <3 h prior to sleeping, smaller and more frequent meals, avoid alcohol, coffee, mint, and fat
- medical
  - antacid, H_2-antagonist, PPI, prokinetic agent
- surgical (<15%)
  - if failure of medical therapy, esophageal stricture, severe nocturnal aspiration, Barrett's esophagus
  - anti-reflux procedure (usually laparoscopic) e.g. Nissen fundoplication
    - fundus of stomach is wrapped around the lower esophagus and sutured in place
    - 90% success rate

PARAESOPHAGEAL HIATUS HERNIA (Type II)
- see Figure 6
- herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced GE junction
- least common esophageal hernia (<10%)

Clinical Features
- usually asymptomatic due to normal GE junction
- pressure sensation in lower chest, dysphagia

Complications
- hemorrhage, incarceration, strangulation (gastric volvulus), obstruction, gastric stasis ulcer (Cameron's lesion – causes Fe-deficiency anemia)

Treatment
- surgery to prevent severe complications
  - reduce hernia and excise hernia sac, repair defect at hiatus, and anti-reflux procedure (e.g. Nissen fundoplication)
  - may consider suturing stomach to anterior abdominal wall (gastropexy)
  - in very elderly patients at high surgical risk consider PEG (percutaneous endoscopic gastrostomy)

MIXED HIATUS HERNIA (Type III)
- see Figure 6
- combination of Types I and II

TYPE IV HERNIA
- herniation of other abdominal organs into thorax: colon, spleen, small bowel

Esophageal Perforation

Etiology
- iatrogenic (most common)
  - endoscopic, dilatation, biopsy, intubation, operative, NGT placement
- barogenic
  - trauma
  - repeated, forceful vomiting (Boerhaave's syndrome)
  - other: convulsions, defecation, labour (rare)
- ingestion injury
  - foreign body, corrosive substance
- carcinoma

Boerhaave's syndrome: transmural esophageal perforation

Mallory-Weiss tear: non-transmural esophageal tear (partial thickness tear)

Both are associated with forceful emesis

Clinical Features
- neck or chest pain
- fever, tachycardia, hypotension, dyspnea, respiratory compromise
- subcutaneous emphysema, pneumothorax, hematemesis

Investigations
- CXR: pneumothorax, pneumomediastinum, pleural effusion, subdiaphragmatic air
- CT chest: widened mediastinum, pneumomediastinum
- contrast swallow (water-soluble then thin barium): contrast extravasation

6Ss of SCC

Smoking
Spirits (alcohol)
Seeds (betel nut)
Scalding (hot liquid)
Strictures
Sack (diverticula)

Treatment
- supportive if rupture is contained
  - NPO, vigorous fluid resuscitation, broad-spectrum antibiotics, possible percutaneous drainage
- surgical
  - <24 h
    - primary closure of a healthy esophagus or resection of diseased esophagus
  - >24 h or non-viable wound edges
    - diversion and exclusion followed by delayed reconstruction (i.e. esophagostomy proximally, close esophagus distally, gastrostomy/jejunostomy for decompression/feeding)

Complications
- sepsis, abscess, fistula, empyema, mediastinitis, death
- post-operative esophageal leak
- mortality 10-50% dependent on timing of diagnosis

Esophageal Carcinoma

Epidemiology
- M:F = 3:1
- onset 50-60 yr of age
- upper (20-33%), middle (33%), lower (33-50%)
- main types:
  - most common worldwide: SCC in upper 2/3 of esophagus
  - most common in Western countries: adenocarcinoma in distal 1/3 of esophagus

Risk Factors
- geographic variation in incidence
- SCC
  - underlying esophageal disease such as strictures, diverticula, achalasia
  - smoking, alcohol, hot liquids
  - more common in patients from Asia
- adenocarcinoma
  - Barrett's esophagus (most important), smoking, obesity (increased reflux), GERD

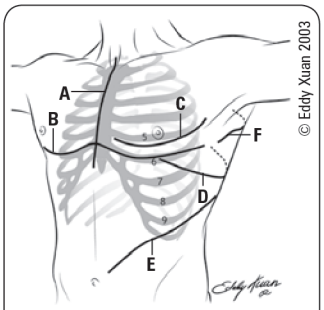
Clinical Features
- frequently asymptomatic: late presentation
- progressive dysphagia (mechanical): first solids then liquids
- odynophagia then constant pain
- constitutional symptoms
- regurgitation and aspiration (aspiration pneumonia)
- hematemesis, anemia
- tracheoesophageal or bronchoesophageal fistula
- direct, hematogenous, or lymphatic spread
  - trachea (coughing), recurrent laryngeal nerves (hoarseness, vocal paralysis), aortic, liver, lung, bone, celiac and mediastinal nodes

Investigations and Staging
- barium swallow: shows narrowing – suggestive but not diagnostic
- esophagoscopy: biopsy and assess resectability
- both SCC and adenocarcinoma use TNM staging system but have separate stage groupings according to histology
- endoscopic U/S (EUS)
  - visualize local disease
  - regional nodal involvement (number of nodes may be more important than location)
- bronchoscopy ± thoracoscopy
  - rule out airway invasion in tumours of the upper and mid esophagus
- full metastatic workup (CXR, bone scan, CT head, CT chest/abdomen/pelvis, LFTs, etc.)
- PET scan more sensitive than CT in detecting metastatic disease

Treatment
- if present with distant metastatic disease
  - treat with systemic therapy and treat symptoms (esophageal stent)
- if locally advanced (locally invasive disease or nodal disease on CT or EUS)
  - multimodal therapy
    - concurrent external beam radiation and chemotherapy (cisplatin and 5-FU)
    - possibility of curative esophagectomy after chemoradiation if disease responds well
  - if unable to tolerate multimodal therapy or if highly advanced disease, consider palliative resection, brachytherapy, or endoscopic dilatation/stenting/laser ablation for palliation
- if early stage (non-transmural and without evidence of nodal disease)
  - esophagectomy (transthoracic or trans-hiatal approach) and lymphadenectomy
    - anastomosis in chest or neck
    - stomach most often used for reconstruction; may also use colon
  - neoadjuvant chemotherapy and radiation are controversial
  - adjuvant chemotherapy ± radiation usually recommended for post-operative node-positive disease

Prognosis
- prognosis usually poor because presentation is usually at advanced stage

OTHER DISORDERS
- esophageal motor disorders (see Gastroenterology, G8)
- esophageal varices (see Gastroenterology, G26)
- Mallory-Weiss tear (see Gastroenterology, G26)



A. Median sternotomy
B. Transverse thoracotomy (clam shell)
C. Anterolateral thoracotomy
D. Lateral thoracotomy
E. Thoracoabdominal thoracotomy
F. Posterolateral thoracotomy

Figure 7. Typical thoracic surgery incisions

Perioperative Chemo(radio)therapy vs. Primary Surgery for Resectable Adenocarcinoma of the Stomach, Gastroesophageal Junction, and Lower Esophagus
Cochrane DB Syst Rev 2013;5:CD008107
Study: Review of RCTs to examine the effect of perioperative chemotherapy for gastroesophageal adenocarcinoma on survival and other clinically relevant outcomes.
Results/Conclusions: 14 RCTs, 2,422 participants.
1) Perioperative chemotherapy was associated with a significantly longer overall survival (HR 0.81, 95% CI 0.73 to 0.89), a relative survival increase of 19% and an absolute increase of 9%.
2) Tumours of the GE junction showed a more pronounced response to perioperative chemotherapy compared to other sites.
3) Combined chemoradiotherapy was more effective for tumours of the esophagus and GE junction compared to chemotherapy alone.
4) Perioperative chemotherapy was more effective in younger patients and is associated with longer disease-free survival, higher rates of R0 resection, and a more favorable tumour stage upon resection.
5) Resection with negative margins is a strong predictor of survival.

Thymoma

Epidemiology
- most common neoplasms in thymus including both thymoma and thymic carcinoma
- patients between 40 and 60 yr
- M > F

Risk Factors
- no known risk factors, strong association with myasthenia gravis and other paraneoplastic syndromes

Clinical presentation
- frequently asymptomatic: incidental finding on imaging
- symptoms related to tumour size and location: chest pain, SOB, cough, phrenic nerve palsy
- ddx includes lymphoma, other anterior mediastinal tumours (see Respirology, R21)

Investigations
- CT chest (and/or MRI)
- Germ cell tumor markers (β-hcg, alpha fetoprotein), thyroid function, PFTs

Treatment
- for patients with resectable disease
- open surgical resection of thymus via median sternotomy
- ± post-operative radiation based on Masaoka staging
- for non-surgical patients
- multimodal therapy including neoadjuvant or palliative chemotherapy and post-operative chemoradiotherapy if de-bulking procedure feasible

Prognosis
- depends upon stage of disease and resectability
- generally slow growing tumours

Pleura, Lung, and Mediastinum

- see Respirology, R22

Tube Thoracostomy

Indications
- to drain abnormal large-volume air or fluid collections in the pleural space
  - hemothorax, chylothorax, empyema
  - pneumothorax, if
    - large or progressive
    - patient is on mechanical ventilation
    - bronchopleural fistula
    - tension pneumothorax
- to treat symptomatic and/or recurrent pleural effusion
  - see Respirology, R22
  - for long-term drainage of malignant effusions
  - via facilitation of pleurodesis (obliteration of the pleural space by instilling talc or doxycycline to cause fibrosis and adherence of parietal and visceral pleura)

Complications
- overall complications are rare (1-3%)
- malposition (most common complication), especially by inexperienced operators
  - tubes may dissect along the external chest wall, or may be placed below the diaphragm
- bleeding (anticoagulation is a relative contraindication)
- local infection, empyema
- perforation of lung parenchyma
- risk of re-expansion pulmonary edema when large volumes of air or fluid are drawn off quickly (>1.0-1.5 L)

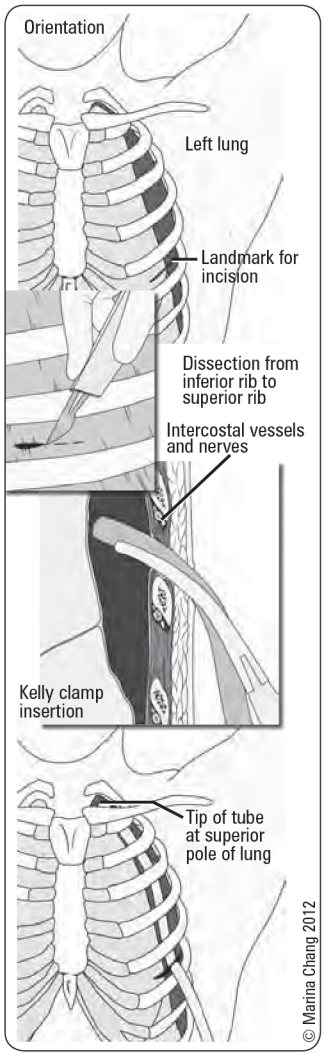


Figure 8. Tube thoracostomy

Tube thoracostomy can be completed under U/S guidance by an interventional radiologist or surgeon

Lung Transplantation

Conditions Leading to Transplantation
- chronic acquired lung disease: COPD
- genetic: CF, emphysema due to α-1 antitrypsin deficiency
- idiopathic interstitial pneumonias: IPF, nonspecific interstitial pneumonitis
- HTN-related: IPAH, secondary pulmonary HTN, Eisenmenger's syndrome
- other: sarcoidosis, lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis

Clinical Indications
- transplantation should be considered for patients with advanced lung disease refractory to maximal medical or surgical therapy
- patients who are symptomatic during activities of daily living and limited expected survival over the next 2 yr

Criteria for Transplantation
- lung allocation score based on: 1) post-transplant survival measure, and 2) waiting list urgency measure
- transplant benefit = post-transplant survival (days) – waitlist survival (days)

Contraindications
- uncontrolled or untreatable pulmonary or extrapulmonary infection
- malignancy in the last 2 yr
- advanced cardiopulmonary disease
- significant chest wall/spinal deformity
- active cigarette smoking
- HIV infection, ongoing HBV or HCV infections

Post-Operative Complications
- primary graft dysfunction: main cause is ischemia-reperfusion injury, graded by PaO_2/FiO_2 ratio and CXR findings
- airway anastomotic complications (focal infection, bronchial necrosis and dehiscence, excess granulation tissue, tracheobronchomalacia, stenosis, fistula)
- chronic graft dysfunction: bronchiolitis obliterans syndrome
- infectious complications (bacterial, fungal, CMV, community-acquired respiratory viruses, mycobacteria)
- malignancy (non-melanoma skin cancer, post-transplant lymphoproliferative disease, colon, breast, Kaposi's sarcoma, bladder)

Prognosis
- median survival for all adult recipients: 5.4 yr
- 1 yr survival: COPD > IPF > IPAH
- 10 yr survival: CF, α-1 antitrypsin deficiency > IPAH > COPD, IPF

Chronic Obstructive Pulmonary Disease

- see Respirology, R9

Treatment
- indications for surgical management
  - dyspnea despite maximal medical therapy and pulmonary rehabilitation
  - CT showing hyperinflation and heterogeneously distributed emphysema predominant in the upper lung zone
  - may be used as a bridging procedure to lung transplantation
- contradindications
  - age >75, cigarette smoking within the prior 6 mo, higher risk of surgical mortality
  - homogeneously distributed emphysematous changes without areas of preserved lung tissue
  - diffusing capacity of lung for carbon monoxide <20% of predicted, $PaCO_2$ >60 mmHg, PaO_2 <45 mmHg
- surgical procedures
  - lung volume reduction surgery: wedge excision of emphysematous tissue
  - bilateral or unilateral, thoracotomy or VATS

Long-Term Survival Analysis of the Canadian Lung Volume Reduction Surgery Trial
Ann Thorac Surg 2013;96:1217-1222
Study: Retrospective observational study assessing the long-term survival of patients enrolled in the CLVRS at 8-10 yr follow-up.
Results/Conclusions: 62 patients total. 52 patients had a median survival time of 4.11 yr. Compared with the best medical care group, patients in the LVRS group showed a 16-mo survival advantage and a 20% reduction in mortality. LVRS may provide long-term benefits in the treatment of end-stage emphysema, however, the results were not statistically significant.

Complications of Treatment
- air leak: may require reintubation and mechanical ventilation
- arrhythmias, pneumonia

Prognosis
- total mortality at 2 yr same as with maximal medical therapy, but better exercise capacity and quality of life with LVRS

Stomach and Duodenum

Peptic Ulcer Disease

GASTRIC ULCERS

- see Gastroenterology, G12

Indications for Surgery

- refractory to medical management (intractability)
- suspicion of malignancy even if biopsy benign
- complications of PUD: obstruction, perforation, bleeding (3x greater risk compared to duodenal ulcers)
- surgical treatment is increasingly rare due to *H. pylori* eradication and medical treatment

Procedures

- ligation of bleeding vessels
- distal gastrectomy with ulcer excision: Billroth I or Billroth II or Roux-en-Y
- vagotomy and pyloroplasty only if acid hypersecretion (rare)
- wedge resection if possible or biopsy with primary repair

DUODENAL ULCERS

- see Gastroenterology, *Bleeding Peptic Ulcer,* G12, and *Peptic Ulcer Disease,* G12
- most within 2 cm of pylorus (duodenal bulb)

Indications for Surgery

- hemorrhage, rebleed in hospital, perforation, gastric outlet obstruction
- refractory to medical management (endoscopy)

Procedures

- Graham patch of perforated ulcer-plication of ulcer and omental patch
- oversewing of bleeding ulcer ± pyloroplasty
- pyloroplasty, gastroduodenostomy, or gastrojejunostomy (improved drainage)
- antrectomy (eliminate hormonal stimulation from the antrum)
- gastric resection (decrease the number of parietal cells)
- vagotomy
  - rarely done now due to *H. pylori* eradication and PPI

Complications of Surgery

- retained antrum
- fistula (gastrocolic/gastrojejunal)
- dumping syndrome, postvagotomy diarrhea, afferent loop syndrome (see *Complications of Gastric Surgery*, GS20)

Table 5. Complications of Duodenal Ulceration

Complication	Clinical Features	Management
Perforated Ulcer (typically on anterior surface)	Sudden onset of pain (possibly in RLQ due to track down right paracolic gutter) Acute abdomen: rigid, diffuse guarding Ileus Initial chemical peritonitis followed by bacterial peritonitis	Investigation CXR – free air under diaphragm (70% of patients) Treatment Oversew ulcer (plication) and omental (Graham) patch – most common treatment
Posterior Penetration	Elevated amylase/lipase if penetration into pancreas Constant mid-epigastric pain burrowing into back, unrelated to meals	
Hemorrhage (typically on posterior surface)	Gastroduodenal artery involvement	Resuscitation initially with crystalloids; blood transfusion if necessary Diagnostic and/or therapeutic endoscopy (laser, cautery, or injection); if recurs, may have second scope Consider interventional radiology: angiography with embolization/coiling Surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy and IR: oversewing of ulcer, pyloroplasty

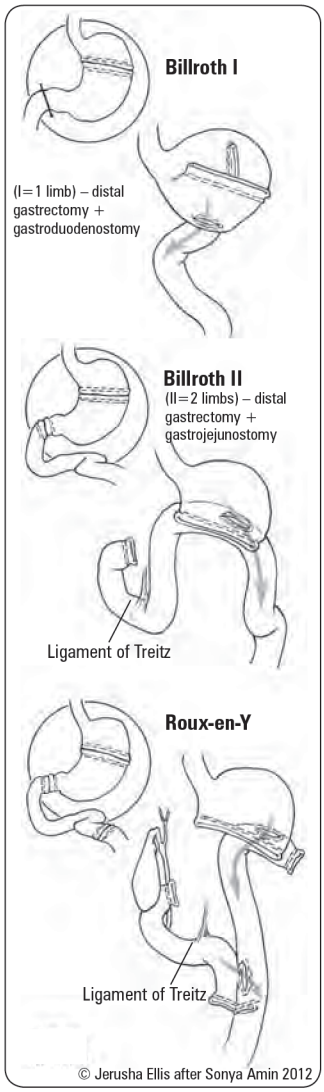


Figure 9. Billroth I and Billroth II with Roux-en-Y reconstruction (gastrojejunostomy)

Kissing Ulcer: combination of perforation and bleeding

Table 5. Complications of Duodenal Ulceration (continued)

Complication	Clinical Features	Management
Gastric Outlet Obstruction	Ulcer can lead to edema, fibrosis of pyloric channel, neoplasm N/V (undigested food, non-bilious), dilated stomach, crampy abdominal pain Succussion splash (splashing noise heard with stethoscope over the stomach when patient is shaken) Auscultate gas and fluid movement in obstructed organ	NGT decompression and correction of hypochloremic, hypokalemic metabolic alkalosis Medical management initially: high dose PPI therapy Surgical resection if obstruction does not resolve: either Billroth I, pyloroplasty, or gastrojejunostomy

Gastric Carcinoma

Epidemiology

- 5th most common cancer in the world
- M:F = 3:2
- incidence of adenocarcinoma <10 (US) vs. 40 (Japan, Korea) per 100,000 (incidence highest in Asia, Latin America, and Caribbean)
- most common age group = 50-59 yr
- incidence has decreased by 2/3 in past 50 yr

Risk Factors

- compensatory epithelial cell proliferation via gastric atrophy from:
  - *H. pylori*, causing chronic atrophic gastritis
  - pernicious anemia associated with achlorhydria and chronic atrophic gastritis
  - previous partial gastrectomy (>10 yr post-gastrectomy)
- host-related factors
  - blood type A
  - hereditary nonpolyposis colorectal cancer (HNPCC), hereditary diffuse gastric carcinoma (HDGC)
  - gastric adenomatous polyps
  - hypertrophic gastropathy
- environmental factors: smoking, alcohol, smoked food, nitrosamines

Signs of Metastatic Gastric Carcinoma

Virchow's node: left supraclavicular node

Blumer's shelf: mass in pouch of Douglas

Krukenberg tumour: metastases to ovary

Sister Mary Joseph node: umbilical metastases

Irish's node: left axillary nodes

Clinical Features

- clinical suspicion
  - ulcer fails to heal
  - lesion on greater curvature of stomach or cardia
- asymptomatic, insidious, or late onset of symptoms
  - postprandial abdominal fullness, vague epigastric pain
  - anorexia, weight loss
  - burping, N/V, dyspepsia, dysphagia
  - hepatomegaly, epigastric mass (25%)
  - hematemesis, fecal occult blood, melena, iron-deficiency anemia
- metastasis
  - peritoneum, liver, lung, brain

Investigations

- OGD and biopsy; EUS to assess pre-operative T-stage and N-stage
- CT chest/abdomen/pelvis (for metastatic workup see Table 7)

Table 6. TNM Classification System for Staging of Gastric Carcinoma (AJCC/IUCC 2010)

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
T0	No evidence of primary tumour	NX	Cannot be assessed	M0	No distant metastasis
Tis	Carcinoma *in situ*	N0	No regional node metastasis	M1	Distant metastasis
T1a	Invasion into lamina propria or muscularis mucosae	N1	Metastasis in 1-2 regional nodes		
T1b	Invasion into submucosa	N2	Metastasis in 3-6 regional nodes		
T2	Invasion into muscularis propria	N3a	Metastasis in 7-15 regional nodes		
T3	Penetration of subserosal connective tissue without tissue invasion of visceral peritoneum or adjacent structures	N3b	Metastasis in ≥16 regional nodes		
T4a	Invasion into serosa				
T4b	Invasion into adjacent structures				

Staging and 5 Yr Survival Rates for Gastric Cancer

Stage	TNM	5-Yr Survival
IA	T1N0M0	71%
IB	T2N0M0 T1N1M0	57%
IIA	T3N0M0 T2N1M0 T1T2M0	45%
IIB	T4aN0M0 T3N1M0 T2N2M0 T1N3M0	33%
IIIA	T4aN1M0 T3T2M0 T2N3M0	20%
IIIB	T4bN0M0 T4bN1M0 T4aN2M0 T3N3M0	14%
IIIC	T4bN2M0 T4bN3M0 T4aN3M0	9%
IV	TxNxM1	4%

Treatment
- adenocarcinoma
  - proximal lesions
    - total gastrectomy and Roux-en-Y esophagojejunostomy
  - distal lesions
    - distal gastrectomy: wide margins, en bloc removal of omentum and lymph nodes
  - palliation
    - gastric resection to decrease bleeding and relieve obstruction, enables the patient to eat
    - radiation therapy
    - studies are showing larger role for chemotherapy
- lymphoma
  - *H. pylori* eradication, chemotherapy ± radiation, surgery in limited cases (perforation, bleeding, obstruction)

Gastrointestinal Stromal Tumour

Epidemiology
- most common mesenchymal neoplasm of GI tract
- derived from interstitial cells of Cajal (cells associated with Auerbach's plexus that have autonomous pacemaker function which coordinate peristalsis throughout the GI tract)
- 75-80% associated with tyrosine kinase (c-KIT) mutations
- most common in stomach (50%) and proximal small intestine (25%), but can occur anywhere along GI tract
- typically present with vague abdominal mass, feeling of abdominal fullness, or with secondary symptoms of bleeding and anemia
- often discovered incidentally on CT, laparotomy, or endoscopy

Risk Factors
- Carney's triad: GISTs, paraganglioma, and pulmonary chondroma
- Type IA neurofibromatosis

Investigations
- pre-operative biopsy: controversial, but useful for indeterminate lesions
  - not recommended if index of suspicion for GIST is high
  - percutaneous biopsy is NOT recommended due to high friability and risk of peritoneal spread

Treatment
- surgical resection if >2 cm; follow with serial endoscopy if <2 cm and resect if growing or symptomatic
- localized GIST
  - surgical resection with preservation of intact pseudocapsule
  - lymphadenectomy NOT recommended, as GISTs rarely metastasize to lymph nodes
  - consider imatinib post-operative for high-risk GIST (large, >4 cm with significant mitotic activity)
- advanced disease (i.e. metastases to liver and/or peritoneal cavity)
  - chemotherapy with imatinib

Prognosis
- risk of metastatic potential depends on
  - tumour size (worse if >10 cm)
  - mitotic activity (worse if >5 mitotic figures or 50/hpf)
  - degree of nuclear pleomorphism
  - location: with identical sizes, extra-gastric location has a higher risk of progression than GISTs in the stomach
- metastases to liver, omentum, peritoneum; nodal metastases rare

Bariatric Surgery
- weight reduction surgery for morbid obesity
- indications: BMI ≥40 without illness or BMI ≥35 with 1+ serious comorbidity (e.g. DM, CAD, sleep apnea, severe joint disease)

Surgical Options
- malabsorptive/restrictive
  - laparoscopic Roux-en-Y gastric bypass (most common – see Figure 9)

Bariatric (Weight Loss) Surgery for Obesity is Considered when Other Treatments have Failed
Cochrane DB Syst Rev 2009;2:CD003641

Benefits
- Greater weight loss in patients with BMI >30 at 2 yr.
- Reduction in comorbidities (type 2 DM, HTN, and medication use).
- Improvement in quality of life at 2 yr (physical function, physical role, general health, vitality, and emotional role).

Risks
- Complications: leaks, hernias, infection, pulmonary embolism, post-operative mortality.
- Side effects specific to type of procedure (i.e. vomiting, dumping syndrome, food intolerance).
- Cholecystitis occurs as a result of rapid weight loss.

  - staple off small gastric pouch (restrictive) with Roux-en-Y limb to pouch (malabsorptive) with dumping syndrome physiology
  - most effective, higher complication rates
- restrictive
  - laparoscopic adjustable gastric banding
    - silicone band around fundus creates pouch, adjustable through port under skin
  - laparoscopic vertical banded gastroplasty
    - vertical stapled small gastric pouch with placement of silastic ring band
- malabsorptive
  - biliopancreatic diversion with duodenal switch
  - gastrectomy, enteroenterostomy, duodenal division closure and duodenoenterostomy

Complications
- perioperative mortality ~1% (anastomotic leak with peritoneal signs, PE)
- obstruction at enteroenterostomy (see *Complications of Gastric Surgery*)
- staple line dehiscence
- dumping syndrome
- cholelithiasis due to rapid weight loss (20-30%)
- band abscess (if long-term)

Complications of Gastric Surgery

- most resolve within 1 yr

Alkaline Reflux Gastritis (see Figure 10A)
- duodenal contents (bilious) reflux into stomach causing gastritis ± esophagitis
- treatment
  - medical: H_2-blocker, metoclopramide, cholestyramine (bile acid sequestrant)
  - surgical: conversion of Billroth I or II to Roux-en-Y

Afferent Loop Syndrome (see Figure 10B)
- accumulation of bile and pancreatic secretions causes intermittent mechanical obstruction and distention of afferent limb
- clinical features
  - early postprandial distention, RUQ pain, nausea, bilious vomiting, anemia
- treatment: surgery (conversion to Roux-en-Y increases afferent loop drainage)

Dumping Syndrome (see Figure 10C)
- early – 15 min post-prandial
  - etiology
    - hyperosmotic chyme released into small bowel (fluid accumulation and jejunal distention)
  - clinical features
    - post-prandial symptoms
    - epigastric fullness or pain, emesis, nausea, diarrhea, palpitations, dizziness, tachycardia, diaphoresis
  - treatment
    - small multiple low carbohydrate, low fat, and high protein meals and avoidance of liquids with meals
    - last resort is interposition of antiperistaltic jejunal loop between stomach and small bowel to delay gastric emptying
- late – 3 h post-prandial
  - etiology: large glucose load leads to large insulin release and hypoglycemia
  - treatment: small snack 2 h after meals

Blind-Loop Syndrome (see Figure 10D)
- bacterial overgrowth of colonic Gram-negative bacteria in afferent limb
- clinical features
  - anemia/weakness, diarrhea, malnutrition, abdominal pain, and hypocalcemia
- treatment: broad-spectrum antibiotics, surgery (conversion to Billroth I)

Postvagotomy Diarrhea (see Figure 10E)
- up to 25%
- bile salts in colon inhibit water resorption
- treatment: medical (cholestyramine), surgical (reversed interposition jejunal segment)

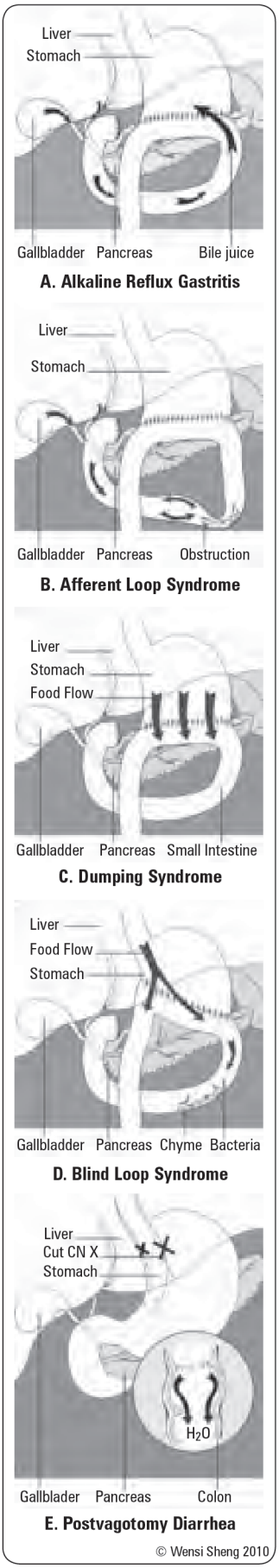


Figure 10. Complications of gastric surgery

SMALL INTESTINE

Small Bowel Obstruction

Mechanical Small Bowel Obstruction

Etiology

Table 7. Common Causes of SBO

Intraluminal	Intramural	Extramural
Intussusception	Crohn's	Adhesions from previous surgeries (75% SBO)
Gallstones	Radiation stricture	Incarcerated hernia
Bezoars	Adenocarcinoma	Peritoneal carcinomatosis

MUST DO
Rule out CRC in constipated patient
Send for TURP in patient with BPH (treat intra-abdominal HTN)

Pathophysiology

- obstruction → gas & fluid (swallowed or GI secretions) accumulate proximal to site of obstruction and distal decompression → intestinal activity increases to overcome obstruction → colicky pain and diarrhea (initially)
- bowel wall edema and disruption of normal bowel absorptive function can lead to increased intraluminal fluid and transudative fluid loss into peritoneal cavity, electrolyte disturbances
- increase intramural pressure can lead to impaired microvascular perfusion leading to intestinal ischemia and necrosis (strangulated bowel obstruction)
- **three types**
  - partial SBO: only a portion of intestine is occluded, allows passage of some gas & fluid, less likely to be strangulated
  - complete SBO: progression of pathophysiologic event is much faster than partial SBO
  - closed-loop obstruction: segment of intestine is obstructed both proximally and distally (e.g. volvulus), leading to rapid rise in intraluminal pressure from gas and fluid that cannot escape and rapid progression to strangulation

Increased Risk of Perforation with Distention as seen on Abdomen Imaging
- Small bowel ≥3 cm
- Distal colon ≥6 cm
- Proximal colon ≥9 cm
- Cecum ≥12 cm

Patients presenting with a SBO in setting of "virgin" abdomen should have surgery ASAP – EXCEPTION: malignant obstruction from history and imaging

Risk Factors

- prior abdominal or pelvic surgery, abdominal wall or groin hernia, history of malignancy, prior radiation

In a non-virgin abdomen – adhesional SBOs resolve spontaneously with NGT decompression 70% of time

Clinical Features

- 1) distinguish mechanical obstruction from ileus; 2) determine etiology of obstruction; 3) recognize partial from complete SBO; 4) differentiate simple from complicated (e.g. strangulated) obstruction
- **symptoms:** colicky abdominal pain, nausea/vomiting, obstipation
  - vomiting is more prominent with proximal than distal
  - more feculent vomitus suggest more established obstruction because of bacterial overgrowth
  - continue passage of gas and/or stool 6-12 h after onset of symptoms suggest partial than complete obstruction
- **signs:** abdominal distention (most prominent if obstruction at distal ileum), hyperactive proceeding to minimal bowel sound
- strangulated obstruction: abdominal pain disproportionate to physical exam findings suggest intestinal ischemia
  - may have tachycardia, localized abdominal tenderness, fever, marked leukocytosis, lactate acidosis

Top 3 Causes of SBO (in order)

ABC
Adhesions
Bulge (hernias)
Cancer (neoplasms)

Causes of SBO

SHAVING
Stricture
Hernia
Adhesions
Volvulus
Intussusception/IBD
Neoplasm
Gallstones

Investigations

- **radiological**
  - abdominal x-ray (3 views): triad of dilated small bowel (>3 cm in diameter), air-fluid levels on upright film, paucity of air in colon (high sensitivity, low specificity as ileus and LBO can present similarly)
  - CT: discrete transition zone with proximal bowel dilation, distal bowel decompression, and intraluminal contrast does not pass the transition zone
    - most importantly to r/o ischemic bowel/strangulation: pneumatosis intestinalis (free air in bowel wall) & thickened bowel wall, air in portal vein, free intraperitoneal fluids, differential wall enhancements (poor uptake of IV contrast into the wall of the affected bowel)
  - other
    - less used: upper GI series/small bowel series (if no cause apparent, i.e. no hernias, no previous surgeries)
    - may consider U/S or MRI in pregnant patients

- **laboratory**
  - may be normal early in disease course
  - BUN, creatinine, hematocrit to assess degree of dehydration
  - fluid, electrolyte abnormalities; metabolic alkalosis due to frequent emesis; amylase elevated
  - if strangulation: leukocytosis with left shift, lactic acidosis, elevated LDH (late signs)

Treatment
- IV isotonic fluid resuscitation + urine output monitoring with catheter
  - SBO related vomiting and decrease PO intake leads to volume depletion
- NG tube in the stomach for gastric decompression; decrease nausea, distention, and risk of aspiration from vomiting
- **partial SBO/Crohn's/Carcinomatosis:** conservative management with fluid resuscitation and NG tube decompression
  - 48 h of watchful waiting; if no improvement or develops complications, surgery
- **SBO with history of abdomen/pelvic surgery:** conservative management
  - 48 h of watchful waiting; if no improvement or develops complications, surgery
- **complete SBO/strangulation:** urgent surgery to prevent irreversible ischemia
- **early post-operative SBO:** if bowel function do not return within 3-5 d after surgery; usually partial, extended conservative therapy (2-3 wk) with bowel rest, fluids, and TPN is appropriate
  - surgery if presence of peritonitis or complete SBO demonstrated

Prognosis
- related to etiology; mortality: non-strangulating <1%, strangulating 8% (25% if >36 h), ischemic = up to 50%

Prevention
- open surgery has four fold increase in risk of SBO in 5 yr compared to laparoscopic surgery

Functional Small Bowel Obstruction: Paralytic Ileus

Pathogenesis
- temporary, reversible impairment of intestinal motility; mostly frequently caused by:
  - abdominal operations, infections & inflammation, medications (opiates, anesthetics, psychotropics), and electrolyte abnormalities
  - passing gas is the most useful indicator
- **NOT** the same as intestinal pseudo-obstruction
  - chronic pseudo-obstruction refers to specific disorders that affect the smooth muscle and myenteric plexus, leading to **irreversible** intestinal dysmotility

Clinical Features
- symptoms and signs of intestinal obstruction without mechanical obstruction
  - bowel sounds are diminished or absent (in contrast to initial hyperactive bowel sounds in SBO)

Investigations
- routine post-operative ileus: expected, no investigation needed
- if ileus persists or occurs without abdominal surgery
  - review patient medications (especially opiates)
  - measure serum electrolyte to monitor for electrolyte abnormalities (including extended lytes like Mg, Ca^{2+}, PO_4)
  - CT scan to rule out abscess or peritoneal sepsis, or to exclude complete mechanical obstruction

Treatment
- most important: NPO + fluid resuscitation
- NGT decompression, correct causative abnormalities (e.g. sepsis, medications, electrolytes), consider TPN for prolonged ileus
- **post-operative:** gastric and small bowel motility returns by 24-48 h, colonic motility by 3-5 d
- current interest in novel therapies such as gum chewing and pharmacologic therapy (e.g. alvimopan, an opioid antagonists)

Intestinal Ischemia

Etiology
- acute
  - arterio-occlusive mesenteric ischemia (AOMI)
    - thrombotic, embolic, extrinsic compression (e.g. strangulating hernia)
  - non-occlusive mesenteric ischemia (NOMI)
    - mesenteric vasoconstriction secondary to systemic hypoperfusion (preserves supply to vital organs)
  - mesenteric venous thrombosis (MVT)
    - consider hypercoagulable state (i.e. rule out malignancy), DVT (prevents venous outflow)
- chronic: usually due to atherosclerotic disease – look for CVD risk factors
- can lead to occlusion in vessels that supplies the small intestine and the large intestine

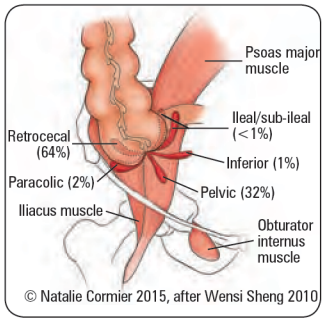


Figure 11. Appendix anatomy

Clinical Features
- acute: severe abdominal pain out of proportion to physical findings, vomiting, bloody diarrhea, bloating, minimal peritoneal signs early in course, hypotension, shock, sepsis
- chronic: postprandial pain (from mesenteric angina), fear of eating, weight loss
- common sites: SMA supplied territory, "watershed" areas of colon – splenic flexure, left colon, sigmoid colon

Pain "out of keeping with physical findings" is the hallmark of early intestinal ischemia

Investigations
- laboratory: leukocytosis (non-specific), lactic acidosis (late finding)
  - amylase, LDH, CK, ALP can be used to observe progress
  - hypercoagulability workup if suspect venous thrombosis
- AXR: portal venous gas, intestinal pneumatosis, free air if perforation
- contrast CT: thickened bowel wall, luminal dilatation, SMA or SMV thrombus, mesenteric/portal venous gas, pneumatosis
- CT angiography is the gold standard for acute arterial ischemia

An acute abdomen + metabolic acidosis is bowel ischemia until proven otherwise

Treatment
- fluid resuscitation, correct metabolic acidosis, NPO, NGT decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
- exploratory laparotomy
- angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, anticoagulation therapy, percutaneous transluminal angioplasty ± stent
- segmental resection of necrotic intestine
  - assess extent of viability; if extent of bowel viability is uncertain, a second look laparotomy 12-24 h later is mandatory

Tumours of Small Intestine

BENIGN TUMOURS
- 10x more common than malignant
- usually asymptomatic until large
- most common sites: terminal ileum, proximal jejunum
- polyps
  - adenomas
  - hamartomas
  - FAP (see *Familial Colon Cancer Syndromes,* GS33)
  - juvenile polyps
- other: leiomyomas, lipomas, hemangiomas

Malignant Tumours – ACLS

Adenocarcinoma	Most common
Carcinoid	↓
Lymphoma	
Sarcoma	Least common

Carcinoid Syndrome Symptoms – FDR

Flushing
Diarrhea
Right-sided heart failure

Table 8. Malignant Tumours of the Small Intestine

	Adenocarcinoma	Carcinoid	Lymphoma	Metastatic
Epidemiology	Usually 50-70 yr M>F	Increased incidence 50-60 yr	Highest incidence in 70s M>F Usually non-Hodgkin's lymphoma	Most common site of GI metastases in patients with metastatic melanoma
Risk Factors	Crohn's, FAP, history of CRC, HNPCC		Crohn's, celiac disease, autoimmune disease, immunosuppression, radiation therapy, nodular lymphoid hyperplasia	Melanoma, breast, lung, ovary, colon, cervical cancer
Clinical Features	Early metastasis to lymph nodes 80% metastatic at time of operation Abdominal pain (common)	N/V, anemia, GI bleeding, jaundice, weight loss (less common) Often slow-growing Usually asymptomatic, incidental finding Obstruction, bleeding, crampy abdominal pain, intussusception Carcinoid syndrome (<10%) • Hot flashes, hypotension, diarrhea, bronchoconstriction, right heart failure • Requires liver involvement: lesion secretes serotonin, kinins, and vasoactive peptides directly to systemic circulation (normally inactivated by liver)	Fatigue, weight loss, fever malabsorption, abdominal pain, anorexia, vomiting, constipation, mass Rarely – perforation, obstruction, bleeding, intussusception	Obstruction and bleeding
Investigations	CT abdomen/pelvis Endoscopy	Most found incidentally at surgery for obstruction or appendectomy Chest thorax/abdomen/pelvis Consider small bowel enteroclysis to look for primary Serum chromogranin A as a tumour marker Elevated 5-HIAA (breakdown product of serotonin) in urine or increased 5-HT in blood Radiolabelled octreotide or MIBG scans to search for metastases and locate tumour	CT abdomen/pelvis	CT abdomen/pelvis
Treatment	Surgical resection ± chemotherapy	Surgical resection ± chemotherapy Carcinoid syndrome treated with steroids, histamine, octreotide Metastatic risk 2% if size <1 cm, 90% if >2 cm	Low grade: chemotherapy with cyclophosphamide High grade: surgical resection, radiation Palliative: somatostatin, doxorubicin	Palliation
Prognosis	5 yr survival 25% (if node positive)	5 yr survival 70%; 20% with liver metastases	5 yr survival 40%	Poor
Origin/Location	Usually in proximal small bowel, incidence decreases distally	Classified based on embryological origin (foregut, midgut, hindgut) Originate from gut enterochromaffin cell Appendix 46%, distal ileum 28%, rectum 17%	Usually distal ileum Proximal jejunum in patients with celiac disease	Hematogenous spread from breast, lung, kidney Direct extension from cervix, ovaries, colon
Staging System	TNM	TNM	Ann Arbor	

Short Gut Syndrome

Definition

- <200 cm of small bowel causing insufficient intestinal absorption leading to diarrhea, malnutrition, and dehydration

Risk Factors

- acute mesenteric ischemia: resection of large amount of bowel at once
- Crohn's disease: cumulative resections
- malignancies

Prognostic Factors

- residual bowel length, residual colon length (reabsorption of water and electrolytes and some reabsorption of nutrients), condition of the remnant small bowel (healthier bowel facilitate better reabsorption), presence of ileocecal valve (delay transition into colon leading to more reabsorption)
- resection of ileum is less tolerated than resection of jejunum (ileum reabsorbs bile salt and vitamin B_{12})

Therapy
- medical
  - TPN: replenish lost fluid and electrolytes in diarrhea
  - HT2R antagonist or PPI to prevent gastric acid secretion
  - antimotility agent to prolong transit time in the small intestine
  - consider octreotide to decrease GI secretion & cholestyramine for bile acid absorption
- surgical: non-transplant
  - to slow transit time: small bowel segmental reversal, intestinal valve construction, or electrical pacing of small bowel
  - to increase intestinal length:
    - LILT (longitudinal intestinal lengthening and tailoring) procedure
    - STEP (serial transverse enteroplasty procedure) in dilated small bowels
- surgical: transplant
  - indication: life-threatening complication from intestinal failure or long-term TPN
    - liver failure, thrombosis of major central veins, recurrent catheter-related sepsis, recurrent severe dehydration

Abdominal Hernia

- see *Hiatus Hernia*, GS12

Definition
- defect in abdominal wall causing abnormal protrusion of intra-abdominal contents

Epidemiology
- M:F = 9:1
- lifetime risk of developing a hernia: males 20-25%, females 2%
- frequency of occurrence: 50% indirect inguinal, 25% direct inguinal, 8-10% incisional (ventral), 5% femoral, 3-8% umbilical
- most common surgical disease of males

Risk Factors
- activities which increase intra-abdominal pressure
  - obesity, chronic cough, asthma, COPD, pregnancy, constipation, bladder outlet obstruction, ascites, heavy lifting
- congenital abnormality (e.g. patent processus vaginalis, indirect inguinal hernia)
- previous hernia repair, especially if complicated by wound infection
- loss of tissue strength and elasticity (e.g. hiatus hernia, aging, repetitive stress)

Clinical Features
- mass of variable size
- tenderness worse at end of day, relieved with supine position or with reduction
- abdominal fullness, vomiting, constipation
- transmits palpable impulse with coughing or straining

Investigations
- physical examination usually sufficient
- U/S ± CT (CT required for obturator hernias, internal abdominal hernias, and Spigelian and/or femoral hernias in obese patients)

Classification
- complete: hernia sac and contents protrude through defect
- incomplete: partial protrusion through the defect
- internal hernia: sac herniating into or involving intra-abdominal structure
- external hernia: sac protrudes completely through abdominal wall
- strangulated hernia: vascular supply of protruded viscus is compromised (ischemia)
  - requires **emergency** repair
- incarcerated hernia: irreducible hernia, not necessarily strangulated
- Richter's hernia: only part of bowel circumference (usually anti-mesenteric border) is incarcerated or strangulated so may not be obstructed
  - a strangulated Richter's hernia may self-reduce and thus be overlooked, leaving a gangrenous segment at risk of perforation in the absence of obstructive symptoms
- sliding hernia: part of wall of hernia sac formed by retroperitoneal structure (usually colon)

Indirect Inguinal Hernias: Rule of 5s
5% lifetime incidence in males
5x more common than direct inguinal hernias
5-10x more common in males than females
Generally occur by 5th decade of life

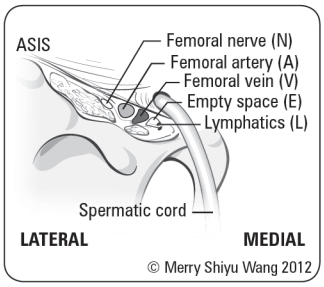


Figure 12. Normal inguinal anatomy

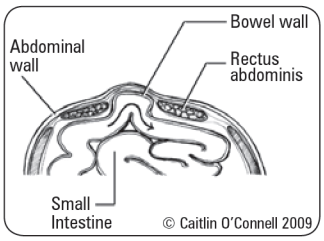


Figure 13. Richter's hernia

Inguinal Hernias – MD's don't LIe
MD: **M**edial to the inferior epigastric a. = **D**irect inguinal hernia
LI: **L**ateral to the inferior epigastric a. = **I**ndirect inguinal hernia

Inguinal canal walls = MALT x 2

2M Roof	2 muscles (internal oblique, transversus abdominis)
2A Ant. wall	2 aponeuroses (external and internal oblique)
2L Floor	2 ligaments (inguinal and lacunar)
2 Ts Post. wall	2T (transversalis fascia, conjoint tendon)

Borders of Hesselbach's Triangle
- Lateral: inferior epigastric artery
- Inferior: inguinal ligament
- Medial: lateral margin of rectus sheath

Shouldice Technique vs. Other Open Techniques for Inguinal Hernia Repair
Cochrane DB Syst Rev 2012;4:CD001543
Purpose: To evaluate the efficacy and safety of the Shouldice technique to other non-laparoscopic techniques.
Results/Conclusions: 16 RCTs or quasi-randomized RCTs with 2,566 hernias (1,121 mesh; 1,608 non-mesh). The recurrence rate with Shouldice was higher than mesh (OR 3.80, 95% CI 1.99-7.26) but lower than non-mesh (OR 0.62, 95% CI 0.45-0.85). There was no difference in chronic pain or complications. In conclusion, with respect to recurrence rates, Shouldice herniorrhaphy is the best non-mesh technique, although inferior to mesh. However, it is also more time consuming and results in slightly longer post-operative hospital stays.

Anatomical Types
- groin (see Tables 9 and 10)
  - indirect and direct inguinal, femoral (see Figure 14)
  - pantaloon: combined direct and indirect hernias, peritoneum draped over inferior epigastric vessels
- epigastric: defect in linea alba above umbilicus
- incisional: ventral hernia at site of wound closure, may be secondary to wound infection
- other: Littre's (involving Meckel's), Amyand's (containing appendix), lumbar, obturator, peristomal, umbilical, Spigelian (ventral hernia through linea semilunaris)

Complications
- incarceration
- strangulation
  - small, new hernias more likely to strangulate
  - femoral >> indirect inguinal > direct inguinal
  - intense pain followed by tenderness
  - intestinal obstruction, gangrenous bowel, sepsis
  - surgical emergency
  - **DO NOT** attempt to manually reduce hernia if septic or if contents of hernial sac gangrenous
    - will cause closed loop SBO – and EMERGENCY

Treatment
- surgical treatment (herniorrhaphy) is only to prevent strangulation and evisceration, for symptomatic relief, for cosmesis; if asymptomatic can delay surgery
- repair may be done open or laparoscopic and may use mesh for tension-free closure
- most repairs are now done using tension free techniques – a plug in the hernial defect and a patch over it or patch alone
- observation is acceptable for small asymptomatic inguinal hernias

Post-Operative Complications
- recurrence (15-20%)
  - risk factors: recurrent hernia, age >50, smoking, BMI >25, poor pre-operative functional status (ASA ≥3 – see Anesthesia and Perioperative Medicine, A4), associated medical conditions: type 2 DM, hyperlipidemia, immunosuppression, any comorbid conditions increasing intra-abdominal pressure
  - less common with mesh/"tension-free" repair
- scrotal hematoma (3%)
  - painful scrotal swelling from compromised venous return of testes
  - deep bleeding: may enter retroperitoneal space and not be initially apparent
  - difficulty voiding
- nerve entrapment
  - ilioinguinal (causes numbness of inner thigh or lateral scrotum)
  - genital branch of genitofemoral (in spermatic cord)
- stenosis/occlusion of femoral vein
  - acute leg swelling
- ischemic colitis

Groin Hernias

Table 9. Groin Hernias

	Direct Inguinal	Indirect Inguinal	Femoral
Epidemiology	1% of all men	Most common hernia in men and women M>F	Affects mostly females
Etiology	Acquired weakness of transversalis fascia "Wear and tear" Increased intra-abdominal pressure	Congenital persistence of processus vaginalis in 20% of adults	Pregnancy – weakness of pelvic floor musculature Increased intra-abdominal pressure
Anatomy	Through Hesselbach's triangle **Medial** to inferior epigastric artery Usually does not descend into scrotal sac	Originates in deep inguinal ring **Lateral** to inferior epigastric artery Often descends into scrotal sac (or labia majora)	Into femoral canal, below inguinal ligament but may override it Medial to femoral vein within femoral canal
Treatment	Surgical repair	Surgical repair	Surgical repair
Prognosis	3-4% risk of recurrence	<1% risk of recurrence	

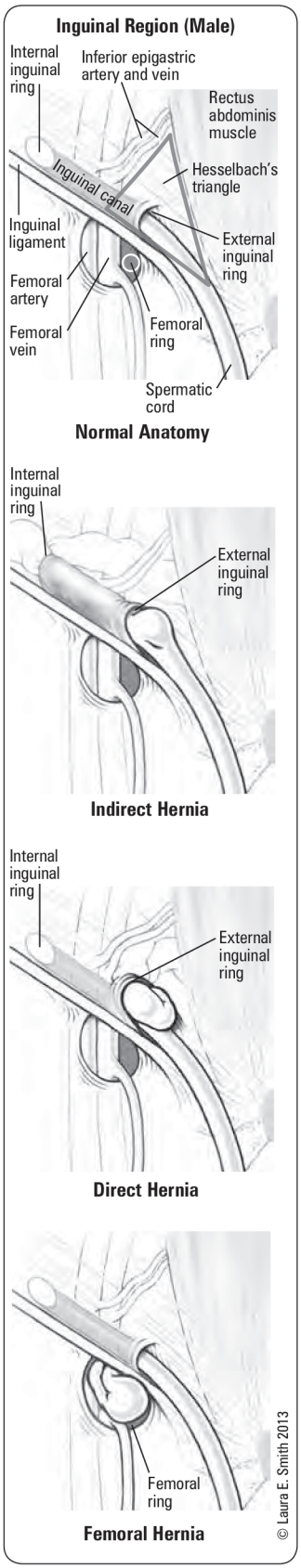


Figure 14. Schematic of inguinal (direct and indirect) and femoral hernias

Table 10. Superficial Inguinal Ring vs. Deep Inguinal Ring*

Superficial Inguinal Ring	Deep Inguinal Ring
Opening in external abdominal aponeurosis; palpable superior and lateral to pubic tubercle	Opening in transversalis fascia: palpable superior to mid-inguinal ligament
Medial border: medial crus of external abdominal aponeurosis	Medial border: inferior epigastric vessels
Lateral border: lateral crus of external oblique aponeurosis	Superior-lateral border: internal oblique and transversus abdominis muscles
Roof: intercrural fibres	Inferior border: inguinal ligament

*see *Basic Anatomy Review*, Figure 2, GS2

Appendix

Appendicitis

Epidemiology
- 6% of population, M>F
- 80% between 5-35 yr of age

Pathogenesis
- luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess (walled off by omentum) or peritonitis
- etiology
  - children or young adult: hyperplasia of lymphoid follicles, initiated by infection
  - adult: fibrosis/stricture, fecolith, obstructing neoplasm
  - other causes: parasites, foreign body

Clinical Features
- most reliable feature is progression of signs and symptoms
- low grade fever (38°C), rises if perforation
- abdominal pain then anorexia, N/V
- classic pattern: pain initially periumbilical; constant, dull, poorly localized, then well localized pain over McBurney's point
  - due to progression of disease from visceral irritation (causing referred pain from structures of the embryonic midgut, including the appendix) to irritation of parietal structures
  - McBurney's sign
- signs
  - inferior appendix: McBurney's sign (see sidebar), Rovsing's sign (palpation pressure to left abdomen causes McBurney's point tenderness). McBurney's sign is present whenever the opening of the appendix at the cecum is directly under McBurney's point; therefore McBurney's sign is present even when the appendix is in different locations
  - retrocecal appendix: psoas sign (pain on flexion of hip against resistance or passive hyperextension of hip)
  - pelvic appendix: obturator sign (flexion then external or internal rotation about right hip causes pain)
- complications
  - perforation (especially if >24 h duration)
  - abscess, phlegmon

Investigations
- laboratory
  - mild leukocytosis with left shift (may have normal WBC counts)
  - higher leukocyte count with perforation
  - β-hCG to rule out ectopic pregnancy
  - urinalysis
- imaging
  - of psoas shadow, RLQ ileus
  - U/S: may visualize appendix, but also helps rule out gynecological causes – overall accuracy 90-94%, can rule in but CANNOT rule out appendicitis (if >6 mm, SENS/SPEC/NPV/PPV 98%)
  - upright CXR, AXR: usually nonspecific – free air if perforated (rarely), calcified fecolith, loss of psoas shadow, RLQ ileus
  - CT scan: thick wall, appendicolith, inflammatory changes – overall accuracy 94-100%, optimal investigation

Watchful Waiting vs. Repair of Inguinal Hernia in Minimally Symptomatic Men: A Randomized Clinical Trial
JAMA 2006;295:285-292
Purpose: To compare pain and the physical component score (PCS) of the Short Form-36 Version 2 survey at 2 yr in men with minimally symptomatic inguinal hernias treated with watchful waiting or surgical repair.
Methods: RCT of 720 men (n=364 watchful waiting, n=356 surgical repair) followed up for 2-4.5 yr. Watchful-waiting patients were followed up at 6 mo and annually and watched for hernia symptoms; repair patients received standard open tension-free repair and were followed up at 3 and 6 mo and annually. The main outcome was pain and discomfort interfering with usual activities at 2 yr and change in PCS from baseline to 2 yr. Secondary outcomes were complications, patient-reported pain, functional status, activity levels, and satisfaction with care.
Results: Primary intention-to-treat outcomes were similar at 2 yr for watchful waiting vs. surgical repair: pain limiting activities (5.1% vs. 2.2%, respectively; p=0.06 [corrected]); PCS (improvement over baseline, 0.29 points vs. 0.13 points; p=0.79). Twenty-three percent of patients assigned to watchful waiting crossed over to receive surgical repair (increase in hernia-related pain was the most common reason offered); 17% assigned to receive repair crossed over to watchful waiting. Self-reported pain in watchful-waiting patients crossing over improved after repair. Occurrence of post-operative hernia-related complications was similar in patients who received repair as assigned and in watchful-waiting patients who crossed over. One watchful-waiting patient (0.3%) experienced acute hernia incarceration without strangulation within 2 yr; a second had acute incarceration with bowel obstruction at 4 yr, with a frequency of 1.8/1,000 patient/yr inclusive of patients followed up for as long as 4.5 yr.
Conclusion: Watchful waiting is an acceptable option for men with minimally symptomatic inguinal hernias. Delaying surgical repair until symptoms increase is safe because acute hernia incarcerations occur rarely.

Outcomes of Laparoscopic vs. Open Repair of Primary Ventral Hernias
JAMA Surg 2013;148:1043-1048
Purpose: To compare outcomes (surgical site infection (SSI), hernia recurrence and bulging) of patients undergoing laparoscopic ventral hernia repair (LVHR) versus open ventral hernia repair (OVHR).
Results/Conclusions: 79 patients with LVHR matched to 79 patients with OVHR with mesh with a median follow-up of 56 mo. LVHR was associated with fewer SSIs (7.6% vs. 34.1%) but more cases of bulging (21.5% vs. 1.3%) and port-site hernia (2.5% vs. 0.0%). No differences in recurrence were observed.

McBurney's Sign
Tenderness 1/3 the distance from the ASIS to the umbilicus on the right side

Treatment
- hydrate, correct electrolyte abnormalities
- surgery (gold standard, 20% mortality with perforation especially in elderly) + antibiotic coverage
- if localized abscess (palpable mass or large phlegmon on imaging and often pain >4-5 d), consider radiologic drainage + antibiotics x 14 d ± interval appendectomy in 6 wk (controversial)
- appendectomy
  - laparoscopic vs. open (see sidebar)
  - complications: spillage of bowel contents, pelvic abscess, enterocutaneous fistula
  - perioperative antibiotics:
    - cefazolin + metronidazole (no post-operative antibiotic unless perforated)
    - other choices: 2nd/3rd generation cephalosporin for aerobic gut organisms
- colonoscopy in the elderly to rule out other etiology (neoplasm)

Prognosis
- mortality rate: 0.08% (non-perforated), 0.5% (perforated appendicitis)

Laparoscopic vs. Open Appendectomy
Cochrane DB Syst Rev 2010;10:CD001546

Laparoscopic Surgery
- Wound infection less likely
- Intra-abdominal abscesses 2x more likely
- Reduced pain on POD #1
- Reduced hospital stay by 1.1 d
- Sooner return to normal activity, work, and sport
- Costs outside hospital are reduced

Open Surgery
- Shorter duration of surgery
- Lower operation costs

Overview
Diagnostic laparoscopy and laparoscopic appendectomy appear to be advantageous over open appendectomy, particularly for young female patients and obese patients.

Inflammatory Bowel Disease

- see Gastroenterology, G19

Principles of Surgical Management
- can alleviate symptoms, address complications, improve quality of life
- conserve bowel: resect as little as possible to avoid short gut syndrome
- perioperative management
  - optimize medical status: may require TPN (especially if >7 d NPO) and bowel rest
  - hold immunosuppressive therapy pre-operative, provide pre-operative stress dose of corticosteroid if patient had recent steroid therapy, taper steroids post-operative
  - DVT prophylaxis: heparin (IBD patients at increased risk of thromboembolic events)

Effect of Delay to Operation on Outcomes in Adults with Acute Appendicitis
Arch Surg 2010;145:886-892
Purpose: To examine the effect of delay to appendectomy on morbidity and mortality among adults with appendicitis.
Method: Retrospective cohort study with the main exposure being time to operation, and main outcomes being 30 d overall morbidity and serious morbidity/mortality.
Results: Of 32,782 patients in the study, 75.2%, 15.1%, and 9.8% underwent surgeries within 6 h, 6-12 h, and >12 h of admission, respectively. Differences in operative duration and length of post-operative stay were statistically significant but not clinically meaningful. No significant differences were observed in adjusted overall morbidity or serious morbidity/mortality. Duration from surgical admission to anesthesia induction was not predictive in regression models for either outcomes.
Conclusions: Delay of appendectomy for acute appendicitis among adults does not adversely affect outcomes.

Crohn's Disease

- see Gastroenterology, G20

Treatment
- surgery is NOT curative, but over lifetime ~70% of Crohn's patients will have surgery
- indications for surgical management
  - failure of medical management
  - SBO (due to stricture/inflammation): indication in 50% of surgical cases
  - abscess, fistula (enterocolic, vesicular, vaginal, cutaneous abscess), quality of life, perforation, hemorrhage, chronic disability, failure to thrive (children), perianal disease
- surgical procedures
  - resection and anastomosis/stoma if active or subacute inflammation, perforation, fistula
    - resection margin only has to be free of gross disease (microscopic disease irrelevant to prognosis)
  - stricturoplasty – widens lumen in chronically scarred bowel: relieves obstruction without resecting bowel (contraindicated in acute inflammation)

Antibiotics vs. Placebo for Prevention of Post-Operative Infection After Appendectomy
Cochrane DB Syst Rev 2005;3:CD001439
Purpose: To determine the effectiveness of antibiotics against post-operative infections after appendectomy.
Method: Meta-analysis of randomized controlled trials (RCTs) and controlled clinical trials (CCTs), on both adults and children, in which any antibiotic regime was compared to placebo in patients undergoing appendectomy for suspected appendicitis. The main outcomes of interest were wound infection, intra-abdominal abscess, length of hospital stay, and mortality.
Results: 45 studies (n=9,576) were included. Treatment with antibiotics decreased wound infection and abscess rates.
Conclusion: Various prophylactic antibiotic regimens are effective in preventing post-operative complications after appendectomy.

Complications of Treatment
- short gut syndrome (diarrhea, steatorrhea, malnutrition)
- fistulas
- gallstones (if terminal ileum resected, decreased bile salt resorption → increased cholesterol precipitation)
- kidney stones (loss of calcium in diarrhea → increased oxalate absorption and hyperoxaluria → stones)

Crohn's 3 Major Patterns
- Ileocecal 40% (RLQ pain, fever, weight loss)
- Small intestine 30% (especially terminal ileum)
- Colon 25% (diarrhea)

Prognosis
- recurrence rate at 10 yr: ileocolic (25-50%), small bowel (50%), colonic (40-50%)
- re-operation at 5 yr: primary resection (20%), bypass (50%), stricturoplasty (10% at 1 yr)
- 80-85% of patients who need surgery lead normal lives
- mortality: 15% at 30 yr

Findings in Crohn's
- "Cobblestoning" on mucosal surface due to edema and linear ulcerations
- "Skip lesions": normal mucosa in between
- "Creeping fat": mesentery infiltrated by fat
- Granulomas: 25-30%

Ulcerative Colitis

- see Gastroenterology, G22

Treatment

- indications for surgical management
  - failure of medical management (including inability to taper steroids)
  - complications: hemorrhage, obstruction, perforation, toxic megacolon (emergency), failure to thrive (children)
  - reduce cancer risk (1-2% risk per yr after 10 yr of disease)
- surgical procedures
  - proctocolectomy and ileal pouch-anal anastomosis (IPAA) ± rectal mucosectomy (operation of choice)
  - proctocolectomy with permanent end ileostomy (if not a candidate for ileoanal procedures)
  - colectomy and IPAA ± rectal mucosectomy
  - in emergency: total colectomy and ileostomy with Hartmann closure of the rectum, rectal preservation

Complications of Treatment

- early: bowel obstruction, transient urinary dysfunction, dehydration (high stoma output), anastomotic leak
- late: stricture, anal fistula/abscess, pouchitis, poor anorectal function, reduced fertility

Prognosis

- mortality: 5% over 10 yr
- total proctocolectomy will completely eliminate risk of cancer
- perforation of the colon is the leading cause of death from ulcerative colitis

Findings in Ulcerative Colitis

- Patients usually present with diarrhea (± blood in their stool)
- Associated symptoms include colicky abdominal pain, urgency, tenesmus, and incontinence
- Presence of extra-intestinal manifestations
- Endoscopically, there is loss of vascular markings, erythema, granularity of mucosa, petechiae, exudates, edema, erosions, and spontaneous bleeding
- Biopsy features included crypt abscesses, crypt branching, shortening and disarray, and crypt atrophy
- Inflammation is continuous and usually involves rectum

LARGE INTESTINE

Large Bowel Obstruction

Mechanical Large Bowel Obstruction

Etiology

Table 11. Common Causes of LBO

Intraluminal	Intramural	Extramural
Constipation Foreign bodies	Adenocarcinoma Diverticulitis IBD stricture Radiation stricture	Volvulus Adhesions Hernias (sigmoid colon in a large groin hernia)

Top 3 Causes of LBO (in order)

- Cancer
- Diverticulitis
- Volvulus

Clinical Features (unique to LBO)

- open loop (10-20%)
  - incompetent ileocecal valve allows relief of colonic pressure as contents reflux into ileum, therefore clinical presentation similar to SBO
- closed loop (80-90%) (dangerous)
  - competent ileocecal valve, resulting in proximal and distal occlusions
  - massive colonic distention → increased pressure in cecum → bowel wall ischemia → necrosis → perforation

In a patient with clinical LBO consider impending perforation when:

- Cecum ≥12 cm in diameter
- Tenderness present over cecum

Treatment

- surgical correction of obstruction (usually requires resection + temporary diverting colostomy)
- volvulus requires sigmoidoscopic or endoscopic decompression followed by operative reduction if unsuccessful
  - if successful, consider sigmoid resection on same admission
- cecal volvulus can be a true volvulus or a cecal 'bascule' (cecum folds anteriorly to the ascending colon producing a flap valve occlusion to cecal emptying) – both need surgical treatment

Prognosis

- overall mortality: 10%
- cecal perforation + feculent peritonitis: 20% mortality

Table 12. Bowel Obstruction vs. Paralytic Ileus

	SBO	LBO	Paralytic Ileus
N/V	Early, may be bilious	Late, may be feculent	Present
Abdominal Pain	Colicky	Colicky	Minimal or absent
Abdominal Distention	+ (prox SBO), ++ (distal SBO)	++	+
Constipation	+	+	+
Bowel Sounds	Normal, increased Absent if secondary ileus (delayed presentation)	Normal, increased (borborygmi) Absent if secondary ileus (delayed presentation)	Decreased, absent
AXR Findings	Air-fluid levels "Ladder" pattern (plicae circularis) Proximal distention (>3 cm) + no colonic gas	Air-fluid levels "Picture frame" appearance Proximal distention + distal decompression No small bowel air if competent ileocecal valve Coffee bean sign (sigmoid volvulus)	Air throughout small bowel and colon

Functional LBO: Colonic Pseudo-obstruction (Ogilvie's Syndrome)

Definition
- acute pseudo-obstruction
- distention of colon without mechanical obstruction in distal colon
- arises in bedridden patients with serious extra-intestinal illness or trauma
- exact mechanism unknown, likely autonomic motor dysregulation → possibly sympathetic deprivation to colon, unopposed parasympathetic tone, and interruption of sacral parasympathetic tone to distal bowel
- first presents with abdominal distention (>90%) ± tenderness
- later symptoms mimic true obstruction

Associations
- most common: trauma, infection, cardiac (MI, CHF)
- disability (long-term debilitation, chronic disease, bed-bound nursing home patients, paraplegia), drugs (narcotic use, laxative abuse, polypharmacy), other (recent orthopedic or neurosurgery, post-partum, electrolyte abnormalities including hypokalemia, retroperitoneal hematoma, diffuse carcinomatosis)

Clinical Features
- Most prominent is abdominal distention (acute or graduate over 3-7 days)
- Abdominal pain, nausea and vomiting, constipation/diarrhea
- Watch out for fever, leukocytosis, and presence of peritoneal signs

Investigations
- AXR: cecal dilatation – if diameter ≥12 cm, increased risk of perforation

Treatment
- treat underlying cause
- NPO, NGT
- decompression: rectal tube, colonoscopy, neostigmine (cholinergic drug), surgical decompression (ostomy/resection) uncommon
- surgery (extremely rare): if perforation, ischemia, or failure of conservative management

Prognosis
- most resolve with conservative management

Diverticular Disease

Definitions
- diverticulum: abnormal sac-like protrusion from the wall of a hollow organ
- diverticulosis: presence of multiple diverticula
- diverticulitis: inflammation of diverticula
- true (congenital) diverticuli: contain all layers of colonic wall, often right-sided
- false (acquired) diverticuli: contain mucosa and submucosa, often left-sided

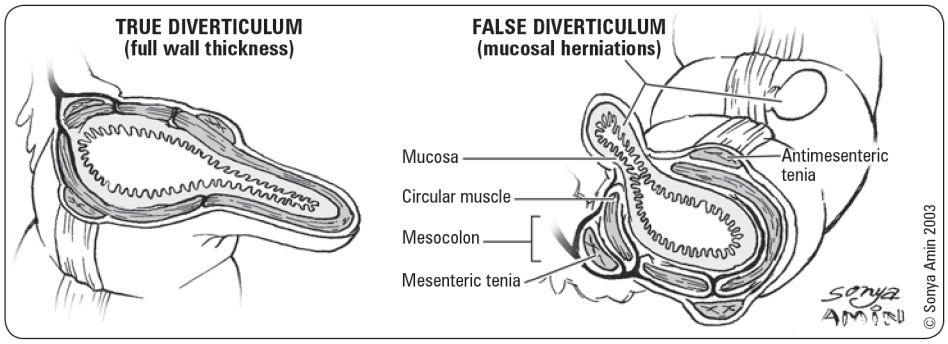


Figure 15. Diverticular disease – cross-sections of true and false diverticuli

Diverticulosis

Epidemiology
- 5-50% of Western population, lower incidence in non-Western countries, M=F
- prevalence is age dependent: <5% by age 40, 30% by age 60, 65% by age 85
- 95% involve sigmoid colon (site of highest pressure)

Pathogenesis
- risk factors
  - lifestyle: low-fibre diet (predispose to motility abnormalities and higher intraluminal pressure), inactivity, obesity
  - muscle wall weakness from aging and illness (e.g. Ehler-Danlos, Marfan's)
- high intraluminal pressures cause outpouching to occur at point of greatest weakness, most commonly where vasa recta penetrate the circular muscle layer, therefore increased risk of hemorrhage

Clinical Features
- uncomplicated diverticulosis: asymptomatic (70-80%)
- episodic abdominal pain (often LLQ), bloating, flatulence, constipation, diarrhea
- absence of fever/leukocytosis
- no physical exam findings or poorly localized LLQ tenderness
- complications
  - diverticulitis (15-25%): 25% of which are complicated (i.e. abscess, obstruction, perforation, fistula)
  - bleeding (5-15%): PAINLESS rectal bleeding, 30-50% of massive LGIB
  - diverticular colitis (rare): diarrhea, hematochezia, tenesmus, abdominal pain

Treatment
- uncomplicated diverticulosis: high fibre, education
- diverticular bleed
  - initially workup and treat as any LGIB
  - if hemorrhage does not stop, resect involved region

Diverticulosis vs. Diverticulitis
Diverticulosis represents the presence of diverticuli (bulging pouches) within the colonic wall, whereas diverticulitis is the inflammation of one or more diverticuli

Diverticulitis

Epidemiology
- 95% left-sided in patients of Western countries, 75% right-sided in Asian populations

Pathogenesis
- erosion of the wall by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro or macroscopic perforation
- usually mild inflammation with perforation walled off by pericolic fat and mesentery; abscess, fistula, or obstruction can ensue
- poor containment results in free perforation and peritonitis

Clinical Features
- depend on severity of inflammation and whether or not complications are present; hence ranges from asymptomatic to generalized peritonitis
- LLQ pain/tenderness (2/3 of patients) often for several days before admission
- constipation, diarrhea, N/V, urinary symptoms (with adjacent inflammation)

- complications (25% of cases)
  - abscess: palpable tender abdominal mass
  - fistula: colovesical (most common), coloenteric, colovaginal, colocutaneous
  - colonic obstruction: due to scarring from repeated inflammation
  - perforation: generalized peritonitis (feculent vs. purulent)
    - recurrent attacks rarely lead to peritonitis
- low-grade fever, mild leukocytosis common, occult or gross blood in stool rarely coexist with acute diverticulitis

Investigations

- AXR, upright CXR
  - localized diverticulitis (ileus, thickened wall, SBO, partial colonic obstruction)
  - free air may be seen in 30% with perforation and generalized peritonitis
- CT scan (test of choice): very useful for assessment of severity and prognosis; usually done with rectal contrast
  - 97% sensitive, 99% specific
  - increased soft tissue density within pericolic fat secondary to inflammation, diverticula secondary to inflammation, bowel wall thickening, soft tissue mass (pericolic fluid, abscesses), fistula
  - 10% of diverticulitis cannot be distinguished from carcinoma
- elective evaluations: establish extent of disease and rule out other diagnoses (polyps, malignancy) after resolution of acute episode
  - colonoscopy or barium enema and flexible sigmoidoscopy

Treatment

- uncomplicated: conservative management
- outpatient: clear fluids only until improvement and antibiotics (e.g. ciprofloxacin and metronidazole) 7-10 d to cover gram negative rods and anaerobes (e.g. *B. fragilis*)
- hospitalize: if severe presentation, inability to tolerate oral intake, significant comorbidities, fail to improve outpatient management
- treat with NPO, IVF, IV antibiotics (e.g. IV ceftriaxone + metronidazole, ampicillin, gentamicin)
- indications for surgery
  - unstable patient with peritonitis
  - Hinchey stage 3-4
  - after 1 attack if immunosuppressed
  - consider after >4 episodes, recent trend is toward conservative management of recurrent mild/moderate attacks
  - complications: generalized peritonitis, free air, abscess, fistula, obstruction, hemorrhage, inability to rule out colon cancer on endoscopy, or failure of medical management
- surgical procedures
  - for emergency or complex cases: Hartmann procedure
    - traditionally, Hartmann procedure was done, with colon resection + colostomy and rectal stump → colostomy reversal in 3-6 mo
    - emerging evidence suggests that for Hinchey stage III acute complicated diverticulitis, laparoscopic peritoneal lavage with drain placement near the affected colon, in addition to IV antibiotics (NO resections), offers lower mortality and morbidity compare to Hartmann procedure. This procedure is gradually becoming standard practice
  - elective cases or minimal contamination of the abdominal cavity: consider colon resection + primary anastomosis

Prognosis

- mortality rates: 6% for purulent peritonitis, 35% for fecal peritonitis
- recurrence rates: 13-30% after first attack, 30-50% after second attack

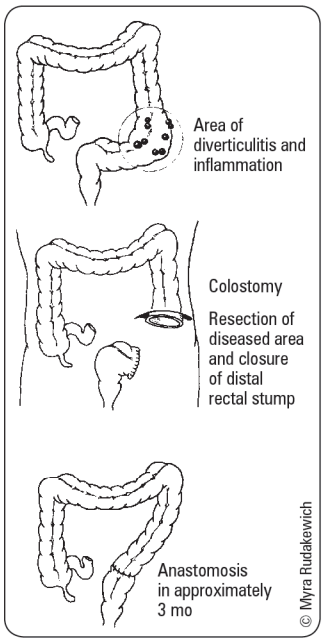


Figure 16. Hartmann procedure

Table 13. Hinchey Staging and Treatment for Diverticulitis

Hinchey Stage	Description	Acute Treatment
1	Phlegmon/small pericolic abscess	Medical
2	Large abscess/fistula	Abscess drainage, resection ± primary anastomosis
3	Purulent peritonitis (ruptured abscess)	Hartmann procedure
4	Feculent peritonitis	Hartmann procedure

Colorectal Neoplasms

Colorectal Polyps

Definition
- polyp: protuberance into the lumen of normally flat colonic mucosa
- sessile (flat) or pedunculated (on a stalk)

Epidemiology
- 30% of the population have polyps by age 50, 40% by age 60, 50% by age 70

Clinical Features
- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, do not typically bleed, tenesmus, intestinal obstruction, mucus
- usually detected during routine endoscopy or familial/high risk screening

Pathology
- non-neoplastic
  - hyperplastic: most common non-neoplastic polyp
  - mucosal polyps: small <5 mm, no clinical significance
  - inflammatory pseudopolyps: associated with IBD, no malignant potential
  - submucosal polyps: lymphoid aggregates, lipomas, leiomyomas, carcinoids
- neoplastic
  - lipomas, leiomyomas, carcinoids
  - hamartomas: juvenile polyps (large bowel), Peutz-Jegher syndrome (small bowel)
    - malignant risk due to associated adenomas (large bowel)
    - low malignant potential → most spontaneously regress or autoamputate
  - adenomas: premalignant, considered carcinoma *in situ* IF high grade dysplasia
  - some may contain invasive carcinoma ("malignant polyp" – 3-9%): invasion into submucosa
    - malignant potential: villous > tubulovillous > tubular

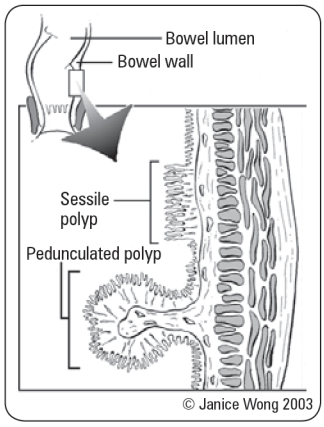


Figure 17. Sessile and pedunculated polyps

Table 14. Characteristics of Tubular vs. Villous Polyps

	Tubular	Villous
Incidence	Common (60-80%)	Less common (10%)
Size	Small (<2 cm)	Large (usually >2 cm)
Attachment	Pedunculated	Sessile
Malignant Potential	Lower	Higher
Distribution	Even	Left-sided predominance

Investigations
- colonoscopy is the gold standard for diagnosis and treatment of colonic polyps
- CT colonography: increasing in availability; patients still require bowel prep and will require colonoscopy if polyps are identified
- other: flexible sigmoidoscopy if polyps are detected, proceed to colonoscopy for examination of entire bowel and biopsy

Treatment
- indications: symptoms, malignancy or risk of malignancy (i.e. adenomatous polyps)
- endoscopic removal of entire growth
- indications for segmental resection for malignant polyps: 1) lymphovascular invasion; 2) tumour budding; 3) positive resection margin; 4) poorly differentiated cells; 5) evidence of regional or distant metastases on staging. Most of these cases are usually discussed at multi-disciplinary tumour boards
- follow-up endoscopy 1 yr later, then every 3-5 yr

Familial Colon Cancer Syndromes

FAMILIAL ADENOMATOUS POLYPOSIS

Pathogenesis
- autosomal dominant inheritance, mutation in adenomatous polyposis coli (APC) gene on chromosome 5q21

Clinical Features
- hundreds to thousands of colorectal adenomas usually by age 20 (by 40s in attenuated FAP)

- extracolonic manifestations
  - carcinoma of small bowel (i.e. polyps in colon), bile duct, pancreas, stomach, thyroid, adrenal, small bowel
  - congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients; 97% sensitivity
  - virtually 100% lifetime risk of colon cancer (because of number of polyps)
- variants
  - Gardner's syndrome: FAP + extra-intestinal lesions (sebaceous cysts, osteomas, desmoid tumours)
  - Turcot syndrome: FAP + CNS tumours (childhood cerebellar medulloblastoma)

Investigations
- genetic testing (80-95% sensitive, 99-100% specific)
- if no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then routine screening
- if polyposis or APC gene mutation found: annual colonoscopy and consider surgery (see Figure 16); consider upper endoscopy to evaluate for periampullary tumours

Treatment
- surgery indicated by age 17-20
- total proctocolectomy with ileostomy or total colectomy with ileorectal anastomosis
- doxorubicin-based chemotherapy
- NSAIDs for intra-abdominal desmoids

Referral Criteria for Genetic Screening for APC
- To confirm the diagnosis of FAP (in patients with ≥100 colorectal adenomas)
- To provide pre-symptomatic testing for individuals at risk for FAP (1st degree relatives who are ≥10 yr old)
- To confirm the diagnosis of attenuated FAP (in patients with ≥20 colorectal adenomas)

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER – LYNCH SYNDROME

Pathogenesis
- autosomal dominant inheritance, mutation in a DNA mismatch repair gene (MSH2, MSH6, MLH1) resulting in microsatellite genomic instability and subsequent mutations
- microsatellite instability account for approximately 15% of all colorectal cancers

Clinical Features
- early age of onset, right > left colon, synchronous and metachronous lesions
- mean age of cancer presentation is 44 yr, lifetime risk 70-80% (M>F)
  - HNPCC I: hereditary site-specific colon cancer
  - HNPCC II: cancer family syndrome – high rates of extracolonic tumours (endometrial, ovarian, hepatobiliary, small bowel)

Diagnosis
- Amsterdam Criteria
  - 3 or more relatives with verified Lynch syndrome associated cancers, and 1 must be 1st degree relative of the other 2
  - 2 or more generations involved
  - 1 case must be diagnosed before 50 yr old
  - FAP is excluded
- genetic testing (80% sensitive) – colonoscopy mandatory even if negative
  - refer for genetic screening individuals who fulfill EITHER the Amsterdam Criteria (as above) OR the revised Bethesda Criteria (see sidebar)
- colonoscopy (starting age 20) annually
- surveillance for extracolonic lesions

Treatment
- total colectomy and ileorectal anastomosis with annual proctoscopy

Revised Bethesda Criteria for HNPCC and Microsatellite Instability (MSI)

Tumours from individuals should be tested for MSI in the following situations:
- Colorectal cancer diagnosed in a patient who is <50 yr
- Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours, regardless of age
- Colorectal cancer with the MSI-H histology diagnosed in a patient who is <60 yr
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed <50 yr
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age

Colorectal Carcinoma

Epidemiology
- 4th most common cancer (after lung, prostate, and breast), 2nd most common cause of cancer death

Risk Factors
- most patients have no specific risk factors
- age >50 (dominant risk factor in sporadic cases), mean age is 70
- genetic: FAP, HNPCC, family history of CRC
- colonic conditions
  - adenomatous polyps (especially if >1 cm, villous, multiple)
  - IBD (especially UC: risk is 1-2%/yr if UC >10 yr)
  - previous colorectal cancer (also gonadal or breast)

Elderly persons who present with iron-deficiency anemia should be investigated for colon cancer

Staging for CRC

I T1,2 N0M0
II T3,4 N0M0
III TxN+M0
IV TxNxM1

- diet (increased fat, red meat, decreased fibre) and smoking
- DM and acromegaly (insulin and IGF-1 are growth factors for colonic mucosal cells)

Pathogenesis
- adenoma-carcinoma sequence; rarely arise *de novo*

Clinical Features
- often asymptomatic
- hematochezia/melena, abdominal pain, change in bowel habits
- others: weakness, anemia, weight loss, palpable mass, obstruction
- 20% patients have distant metastatic disease at time of presentation
- spread
  - direct extension, lymphatic, hematogenous (liver most common, lung, bone, brain; tumour of distal rectum → IVC → lungs)
  - peritoneal seeding: ovary, Blumer's shelf (pelvic cul-de-sac)

Table 15. Clinical Presentation of CRC

	Right Colon	Left Colon	Rectum
Frequency	25%	35%	30%
Pathology	Exophytic lesions with occult bleeding	Annular, invasive lesions	Ulcerating
Symptoms	Weight loss, weakness, rarely obstruction	Constipation ± overflow (alternating bowel patterns), abdominal pain, decreased stool caliber, rectal bleeding	Obstruction, tenesmus, rectal bleeding
Signs	Fe-deficiency anemia, RLQ mass (10%)	BRBPR, LBO	Palpable mass on DRE, BRBPR

Investigations
- colonoscopy (best), look for synchronous lesions (3-5% of patients); alternative: air contrast barium enema ("apple core" lesion) + sigmoidoscopy
- if a patient is FOBT +ve, or has microcytic anemia or has a change in bowel habits, do colonoscopy
- laboratory: CBC, urinalysis, liver enzymes, liver function tests, carcinogenic embryonic antigen (CEA) (pre-operative for baseline, >5 ng/mL have worse prognosis)
- staging (see Table 16 and sidebar GS35): CT chest/abdomen/pelvis; bone scan, CT head only if lesions suspected
- rectal cancer: pelvic MRI or endorectal U/S to determine T and N stage

Table 16. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/IUCC 2010)

Primary Tumour (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
T0 No primary tumour found	N0 No regional node involvement	M0 No distant metastasis
Tis Carcinoma *in situ*	N1 Metastasis in 1-3 regional nodes	M1 Distant metastasis
T1 Invasion into submucosa	N2 Metastasis in 4 or more regional nodes	
T2 Invasion into muscularis propria		
T3 Invasion through muscularis propria and into serosa		
T4 Invasion into adjacent structures or organs		

Treatment
- **colon cancer**
  - wide surgical resection of lesion and regional lymphatic drainage; usually colectomy with primary anastomosis
    - curative: wide resection of lesion (5 cm margins) with nodes and mesentery
    - palliative: if distant spread, local control for hemorrhage or obstruction
    - care is taken to not spread tumour by unnecessary palpation
    - cancer-bearing portion of colon is removed according to vascular distribution of segment
  - adjuvant chemotherapy (5-FU or oral capecitabine with oxaliplatin) for stage III and is considered in select stage II patients
- **rectal cancer**
  - choice of operation depends on individual case; types of operations
    - low anterior resection of rectum (LAR): curative procedure of choice if adequate distal margins; uses technique of total mesorectal excision
    - abdominoperineal resection of rectum (APR): if adequate distal margins cannot be obtained; involves the removal of distal sigmoid colon, rectum, and anus – permanent end colostomy required
    - local excision: for select T1 lesions only
    - palliative procedures involve proximal diversion with an ostomy for obstruction and radiation for bleeding or pain
  - adjuvant therapy
    - combined neoadjuvant chemoradiation therapy followed by post-operative adjuvant chemotherapy for stages II and III

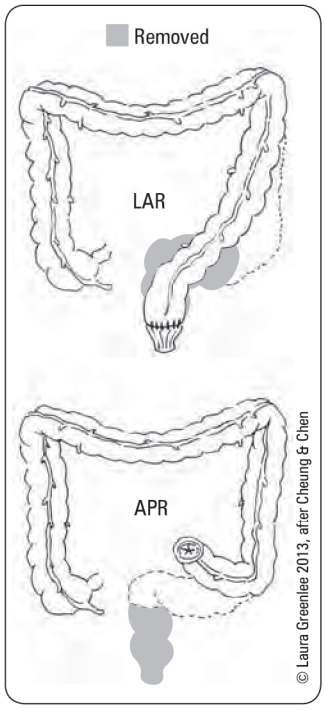


Figure 18. APR vs. LAR

APR removes distal sigmoid colon, rectum, and anus; permanent end colostomy required

LAR removes distal sigmoid and rectum with anastomosis of distal colon to anus

Pre-Operative vs. Post-Operative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial after a Median Follow-Up of 11 Yr

J Clin Oncol 2012;30:1926-1933

Background: The CAO/ARO/AIO-94 trial (published 2004) recommended pre-operative chemoradiotherapy (CRT) as standard treatment for locally advanced rectal cancer. However, no survival benefit was shown after median follow-up of 46 mo, and this study reports long-term effects.

Methods: Patients with stage II to III rectal cancer (n=799) were randomly assigned to pre-operative (n=404) or post-operative CRT (n=395) with fluorouracil (FU), radiation, and adjuvant FU chemotherapy, in addition to total mesorectal excision surgery. Follow-up was designed to assess long-term overall survival as the primary end point; and cumulative incidence of local and distant relapses and disease-free survival as secondary end points.

Results: 10 yr incidence of local relapse was significantly lower in the pre-operative CRT group than in the post-operative group (7.1% vs. 10.1%, p=0.048). Overall survival at 10 yr was similar at ~60% for patients treated with pre-operative or post-operative CRT (p=0.85). Disease-free survival rates at 10 yr was similar at ~68% for patients treated with pre-operative or post-operative CRT (p=0.54). No significant difference was detected for 10-yr incidence of distant metastases (pre-operative CRT 29.8% vs. post-operative CRT 29.6%, p=0.9).

Conclusion: There is long-term reduction in local recurrence of stage II to III rectal cancer with pre-operative chemotherapy, but no improvement in overall survival or distant recurrence of disease.

Follow-Up
- currently there are no data suggesting optimal follow-up
- combination of periodic CT chest/abdomen/pelvis, CEA, and colonoscopy is recommended
- CEA to monitor for initial response to treatment, and to assess for recurrence q3mo (not a screening test)
- intensive follow-up improves overall survival in low-risk patients

5-yr Survival Rates for CRC

Stage	Colon	Rectum
I	74%	74%
IIA	67%	64%
IIB	59%	52%
IIC	37%	32%
IIIA	73%	74%
IIIB	46%	45%
IIIC	28%	33%
IV	6%	6%

Other Conditions of the Large Intestine

Angiodysplasia

Definition
- vascular anomaly: focal submucosal venous dilatation and tortuosity

Clinical Features
- most frequently in right colon of patients >60 yr old
- bleeding typically intermittent, rarely massive, not usually hypotensive (melena, anemia, guaiac positive stools)

Investigations
- colonoscopy: cherry red spots, branching pattern from central vessel
- angiography: early-filling vein, vascular tuft, delayed emptying vein; rarely active bleeding
- RBC technetium-99 scan
- barium enema is contraindicated (obscures other x-rays, i.e. angiogram)

Treatment
- none if asymptomatic
- cautery, right hemicolectomy, embolization, vasopressin infusion, sclerotherapy, band ligation, laser, octreotide, and rarely segmental resection if other treatments fail

Volvulus

Definition
- rotation of segment of bowel about its mesenteric axis
- sigmoid (65%), cecum (30%), transverse colon (3%), splenic flexure (2%)
- 5-10% of large bowel obstruction; 25% of intestinal obstruction during pregnancy

Risk Factors
- age (50% of patients >70 yr: stretching/elongation of bowel with age is a predisposing factor)
- high fibre diet (can cause elongated/redundant colon), chronic constipation, laxative abuse, pregnancy, bedridden, institutionalization (less frequent evacuation of bowels)
- congenital hypermobile cecum

Clinical Features
- symptoms due to bowel obstruction (see *Large Bowel Obstruction*, GS30) or intestinal ischemia (see *Intestinal Ischemia*, GS24)
- colicky abdominal pain, persistence of pain between spasms, abdominal distention, vomiting

Investigations
- AXR (classic findings): "omega", "bent inner-tube", "coffee-bean" signs
- barium/Gastrografin® enema: "ace of spades" (or "bird's beak") appearance due to funnel-like luminal tapering of lower segment towards volvulus
- sigmoidoscopy or colonoscopy as appropriate
- CT

Treatment
- initial supportive management (same as initial management for bowel obstruction (see *Large Bowel Obstruction*, GS30)
- cecum
  - nonsurgical
    - may attempt colonoscopic detorsion and decompression
  - surgical
    - right colectomy + ileotransverse colonic anastomosis

Cecal Volvulus
AXR: Central cleft of "coffee bean" sign points to RLQ

Sigmoid Volvulus
AXR: Central cleft of "coffee bean" sign points to LLQ

Barium enema: "ace of spades" or "bird's beak" sign

- sigmoid
  - nonsurgical
    - decompression by flexible sigmoidoscopy and insertion of rectal tube past obstruction
    - subsequent elective surgery recommended (50-70% recurrence)
  - surgical: Hartmann procedure (if urgent)
    - indications: strangulation, perforation, or unsuccessful endoscopic decompression

Toxic Megacolon

Pathogenesis
- extension of inflammation into smooth muscle layer causing paralysis
- damage to myenteric plexus and electrolyte abnormalities are not consistently found

Etiology
- inflammatory bowel disease (ulcerative colitis > Crohn's disease)
- infectious colitis: bacterial (*C. difficile, Salmonella, Shigella, Campylobacter*), viral (cytomegalovirus), parasitic (*E. histolytica*)

Clinical Features
- infectious colitis usually present for >1 wk before colonic dilatation
- diarrhea ± blood (but improvement of diarrhea may portend onset of megacolon)
- abdominal distention, tenderness, ± local/general peritoneal signs (suggest perforation)
- triggers: hypokalemia, constipating agents (opioids, antidepressants, loperamide, anticholinergics), barium enema, colonoscopy

Diagnostic Criteria
- must have both colitis and systemic manifestations for diagnosis
- radiologic evidence of dilated colon
- **three of:** fever, HR >120, WBC >10.5, anemia
- **one of:** fluid and electrolyte disturbances, hypotension, altered LOC

Investigations
- CBC (leukocytosis with left shift, anemia from bloody diarrhea), electrolytes, elevated CRP, ESR
- metabolic alkalosis (volume contraction and hypokalemia) and hypoalbuminemia are late findings
- AXR: dilated colon >6 cm (right > transverse > left), loss of haustra
- CT: useful to assess underlying disease

Treatment
- NPO, NGT, stop constipating agents, correct fluid and electrolyte abnormalities, transfusion
- serial AXRs
- broad-spectrum antibiotics (reduce sepsis, anticipate perforation)
- aggressive treatment of underlying disease (e.g. steroids in IBD, metronidazole for *C. difficile*)
- indications for surgery (50% improve on medical management)
  - worsening or persisting toxicity or dilation after 48-72 h
  - severe hemorrhage, perforation
  - high lactate and WBC especially for *C. difficile*
- procedure: subtotal colectomy + end ileostomy (may be temporary, with second operation for re-anastomosis later)

Use caution when giving antidiarrheals, especially with bloody diarrhea

Prognosis
- average 25-30% mortality

Fistula

Definition
- abnormal communication between two epithelialized surfaces (e.g. enterocutaneous, colovesical, aortoenteric, entero-enteric)

Etiology
- foreign object erosion (e.g. gallstone, graft)
- inflammatory states (e.g. infection, IBD [especially Crohn's], diverticular disease)
- iatrogenic/surgery (e.g. post-operative anastomotic leak, radiation)
- congenital, trauma
- neoplastic

Investigations
- U/S, CT scan, fistulogram
- measure amount of drainage from fistula

Why Fistulae Stay Open

FRIENDO
Foreign body
Radiation
Infection
Epithelialization
Neoplasm
Distal obstruction (most common)
Others: increased flow; steroids (may inhibit closure, usually will not maintain fistula)

Treatment
- decrease secretion: octreotide/somatostatin/omeprazole
- surgical intervention: dependent upon etiology (for non-closing fistulas); uncertainty of diagnosis

Colostomy/Ileostomy
- Connection of proximal limb of colon or ileum to abdominal wall skin

Mucous Fistula
- Connection of distal limb of colon to abdominal wall skin

Ileal Conduit
- Connection of bowel to ureter proximally and abdominal wall distally to drain urine

Stomas

Definition
- an opening of the GI tract onto the surface of the abdomen wall

Ileostomy
- usually positioned in RLQ; ileum is brought through rectus abdominus muscles
- indications: after protocolectomy for ulcerative colitis, in some cases of Crohn's disease or familial polyposis
- conventional ileostomy: discharges small quantities of liquid material continuously, appliance (plastic bag attached to a sheet of protective material) required at all times
- continent ileostomy: reservoir is constructed from distal ileum, emptied by inserting catheter into stoma several times a day; rarely used, has mostly been replaced by ileal pouch anal anastomosis

Colostomy
- indications: to decompress an obstructed colon, to protect a distal anastomosis after resection, or to evacuate stool after distal colon or rectum is removed
- colostomies can be done by making an opening in a loop of colon (loop colostomy) or by dividing the colon and bringing out one end (end colostomy)
- most common permanent colostomy is a sigmoid colostomy – expels stool once per day, no appliance required
- chronic paracolostomy hernia is a common complication

Complications (10%)
- obstruction: herniation, stenosis (skin and abdominal wall), adhesive bands, volvulus
- peri-ileostomy abscess and fistula
- skin irritation
- prolapse or retraction
- diarrhea (excessive output)

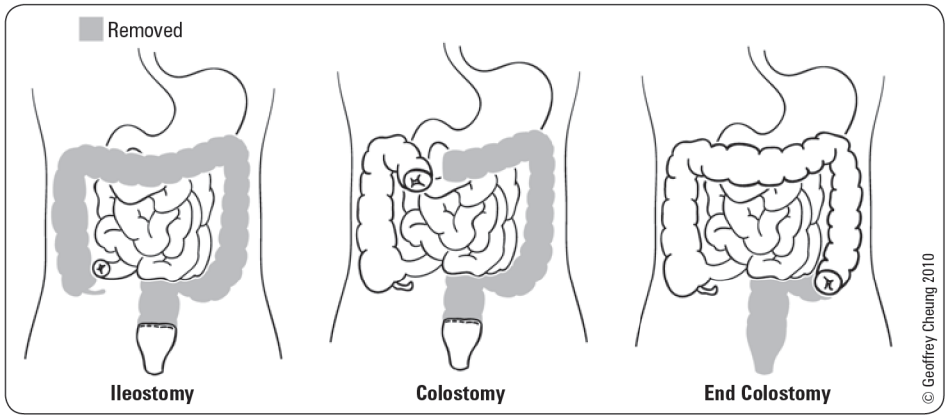


Figure 19. Ostomies

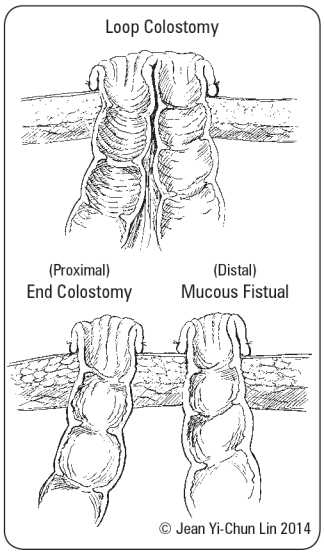


Figure 20. End vs. loop colostomy

Anorectum

Hemorrhoids

Etiology
- vascular and connective tissue complexes form a plexus of dilated veins (cushion)
  - internal: superior hemorrhoidal veins, above dentate line, portal circulation
  - external: inferior hemorrhoidal veins, below dentate line, systemic circulation

Risk Factors
- increased intra-abdominal pressure: chronic constipation, pregnancy, obesity, portal HTN, heavy lifting

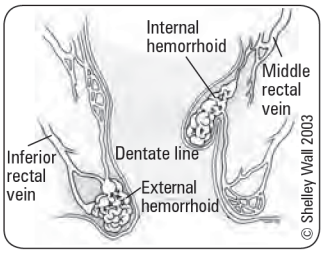


Figure 21. Hemorrhoids

Clinical Features and Treatment

- internal hemorrhoids
  - engorged vascular cushions usually at 3, 7, 11 o'clock positions (patient in lithotomy position)
  - PAINLESS rectal bleeding, anemia, prolapse, mucus discharge, pruritus, burning pain, rectal fullness
    - **1st degree:** bleed but do not prolapse through the anus
      - treatment: high fibre/bulk diet, sitz baths, steroid cream, parmoxine (Anusol®), rubber band ligation, sclerotherapy, photocoagulation
    - **2nd degree:** bleed, prolapse with straining, spontaneous reduction
      - treatment: rubber band ligation, photocoagulation
    - **3rd degree:** bleed, prolapse, requires manual reduction
      - treatment: same as 2nd degree, but may require closed hemorrhoidectomy
    - **4th degree:** bleed, permanently prolapsed, cannot be manually reduced
      - treatment: closed hemorrhoidectomy
- external hemorrhoids
  - dilated venules usually mildly symptomatic
    - PAIN after bowel movement, associated with poor hygiene
    - medical treatment: dietary fibre, stool softeners, steroid cream (short course), parmoxine (Anusol®), avoid prolonged straining
  - thrombosed hemorrhoids are very painful
    - resolve within 2 wk, may leave excess skin = perianal skin tag
    - treatment: consider surgical decompression within first 48 h of thrombosis, otherwise medical treatment

Always rule out more serious causes (e.g. colon CA) in a person with hemorrhoids and rectal bleeding

Band ligation can be done as outpatient

External hemorrhoids will often recur

Table 17. Signs and Symptoms of Internal vs. External Hemorrhoids

Internal Hemorrhoids	External Hemorrhoids
Painless BRBPR	Sudden severe perianal pain
Rectal fullness or discomfort	Perianal mass
Mucus discharge	

Anal Fissures

Definition

- tear of anal canal below dentate line (very sensitive squamous epithelium)
- 90% posterior midline, 10% anterior midline
- if off midline: consider other possible causes such as IBD, STIs, TB, leukemia, or anal carcinoma
- repetitive injury cycle after first tear
  - sphincter spasm occurs preventing edges from healing and leads to further tearing
  - ischemia may ensue and contribute to chronicity

Etiology

- forceful dilation of anal canal: large, hard stools and irritant diarrheal stools
- tightening of anal canal secondary to nervousness/pain leads to further tearing
- others: habitual use of cathartics, childbirth

Clinical Features

- acute fissure
  - very painful bright red bleeding especially after bowel movement, sphincter spasm on limited DRE
  - treatment is conservative: stool softeners, bulking agent, sitz baths (heals 90%)
- chronic fissure (anal ulcer)
  - triad: fissure, sentinel skin tags, hypertrophied papillae
  - treatment
    - stool softeners, bulking agents, sitz baths
    - topical nitroglycerin or nifedipine: increases local blood flow, promoting healing and relieves sphincter spasm
    - lateral internal anal sphincterotomy (most effective): objective is to relieve sphincter spasm → increases blood flow and promotes healing; but 5% chance of fecal incontinence therefore not commonly done
  - alternative treatment
    - botulinum toxin: inhibits release of acetylcholine (ACh), reducing sphincter spasm

Anorectal Abscess

Definition

- infection in one or more of the anal spaces
- usually bacterial infection of blocked anal gland at the dentate line
  - *E. coli, Proteus, Streptococci, Staphylococci, Bacteroides,* anaerobes

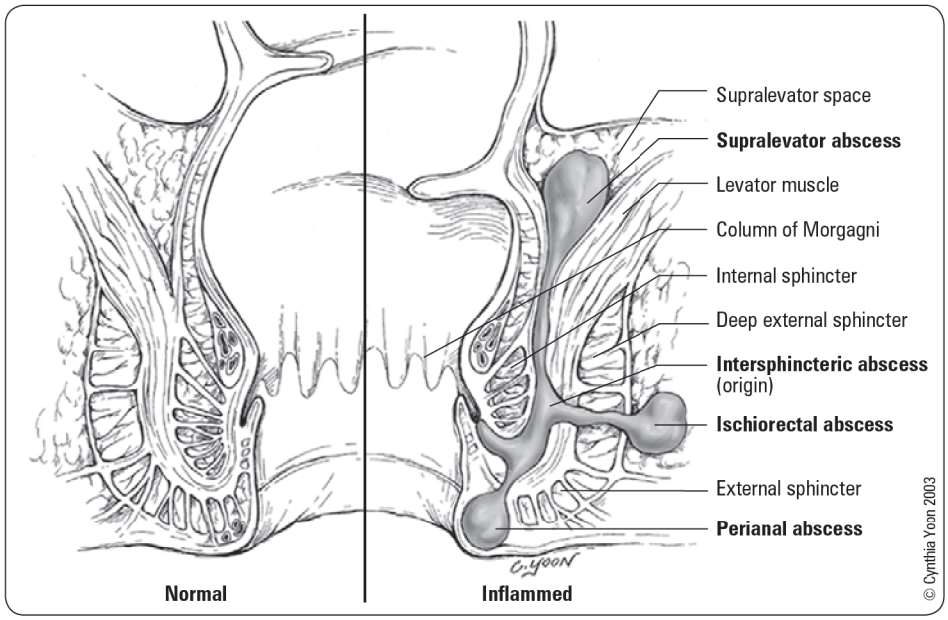


Figure 22. Different types of perianal abscesses

Clinical Features
- throbbing pain that may worsen with straining and ambulation
- abscess can spread vertically downward (perianal), vertically upward (supralevator), or horizontally (ischiorectal)
- tender perianal/rectal mass on exam

Recurrent perianal abscesses is associated with Crohn's disease

Treatment
- I&D
  - curative in 50% of cases
  - 50% develop anorectal fistulas
- may require antibiotics if diabetic, heart murmur, or cellulitis

Antibiotics are not typically helpful in the treatment of perianal abscesses

Fistula-In-Ano

Definition
- anal fistula from rectum to perianal skin
- an inflammatory tract with internal os at dentate line, external os on skin

Etiology
- see *Fistula*, GS38
- same perirectal process as an anal abscess, therefore usually associated with an abscess
- other causes: post-operative, trauma, anal fissure, malignancy, radiation proctitis

Clinical Features
- intermittent or constant purulent discharge from perianal opening
- pain
- palpable cord-like tract

Treatment
- identification
  - internal opening
    - Goodsall's rule
      - fistulas originating anterior to a transverse line through the anus will have a straight course and exit anteriorly, whereas those originating posterior to the transverse line will begin in the midline and have a curved tract
  - fistulous tract
    - probing or fistulography under anesthesia
- surgery
  - fistulotomy: unroof tract from external to internal opening, allow drainage, heals by secondary intention
  - low lying fistula (does not involve external sphincter) → primary fistulotomy
  - high lying fistula (involves external sphincter) → staged fistulotomy with Seton suture placed through tract
    - promotes drainage
    - promotes fibrosis and decreases incidence of incontinence
    - delineates anatomy
    - usually done to spare muscle cutting

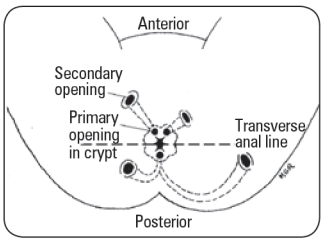


Figure 23. Goodsall's rule

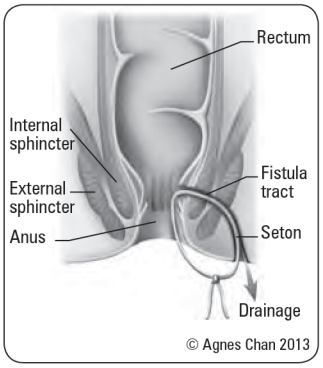


Figure 24. Fistulotomy

Post-Operative
- sitz baths, irrigation, and packing to ensure healing proceeds from inside to outside

Complications
- recurrence
- rarely fecal incontinence

Pilonidal Disease

Definition
- chronic recurring abscess or chronic draining sinus in sacrococcygeal area

Epidemiology
- occurs most frequently in young men age 15-40 yr; rare in >50 yr

Etiology
- obstruction of the hair follicles in this area → formation of cysts, sinuses, or abscesses

Clinical Features
- asymptomatic until acutely infected, then pain/tenderness, purulent discharge, inspissated hair

Treatment
- acute abscess
  - I&D (often performed by primary care doctors)
  - wound packed open
  - 40% develop chronic pilonidal sinuses
- surgery
  - indication: failure of healing after I&D, recurrent disease, complex disease
  - pilonidal cystotomy: excision of sinus tract and cyst; wound closed by secondary intention, primary closure with tissue flap, or marsupialization (cyst edge sewn to surrounding tissue to leave sinus tract open)

Rectal Prolapse

Definition
- protrusion of some or all of rectal mucosa through external anal sphincter

Epidemiology
- extremes of ages: <5 yr old and >5th decade
- 85% women

Etiology
- lengthened attachment of rectum secondary to constant straining
- 2 types
  I. false/partial/mucosal: protrusion of mucosa only, radial furrows at junction with anal skin; most common type of rectal prolapse in childhood
  II. true/complete (most common): full thickness extrusion of rectal wall, concentric folds in:
    - first degree: prolapse includes mucocutaneous junction
    - second degree: without involvement of mucocutaneous junction
    - third degree (internal intussusception): prolapse is internal, concealed, or occult

Risk Factors
- gynecological surgery
- chronic neurologic/psychiatric disorders affecting motility

Clinical Features
- extrusion of mass with increased intra-abdominal pressure
  - straining, coughing, laughing, Valsalva
- difficulty in bowel regulation
  - tenesmus, constipation, fecal incontinence
- permanently extruded rectum with excoriation, ulceration, and constant soiling
- may be associated with urinary incontinence or uterine prolapse

Treatment
- Type I
  - conservative: gentle manual reduction of prolapsed area, especially in children
  - mucosectomy with excision of redundant mucosa, mostly in adults
- Type II
  - conservative: reduce if possible
  - surgery: abdominal, perineal, transsacral approaches

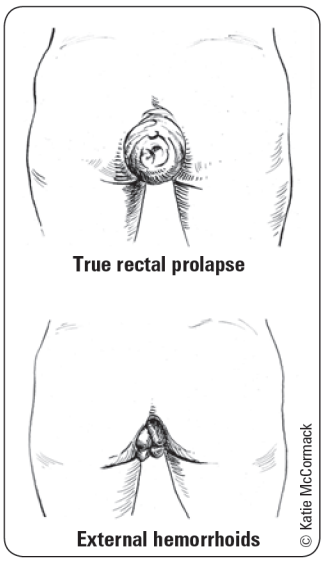


Figure 25. Rectal prolapse (true vs. false)

Anal Neoplasms

ANAL CANAL

Squamous Cell Carcinoma of Anal Canal (Above Dentate Line)

- most common tumour of anal canal (75%)
- anus prone to human papillomavirus (HPV) infection, therefore at risk for anal squamous intra-epithelial lesions (ASIL)
  - high grade squamous intra-epithelial lesion (HSIL) and low grade squamous intra-epithelial lesion (LSIL) terminology used
- clinical features: anal bleeding, pain, mass, ulceration, pruritus; 25% asymptomatic
- treatment: chemotherapy ± radiation ± surgery
- prognosis: 80% 5-yr survival

Malignant Melanoma of Anal Canal

- 3rd most common site for primary malignant melanoma after skin, eyes
- aggressive, distant metastases common at time of diagnosis
- treatment: wide excision or APR ± chemoradiation
- prognosis: <5% 5 yr survival

ANAL MARGIN

- clinical features and treatment as for skin tumours elsewhere
- squamous and basal cell carcinoma, Bowen's disease (SCC *in situ*), and Paget's disease

Liver

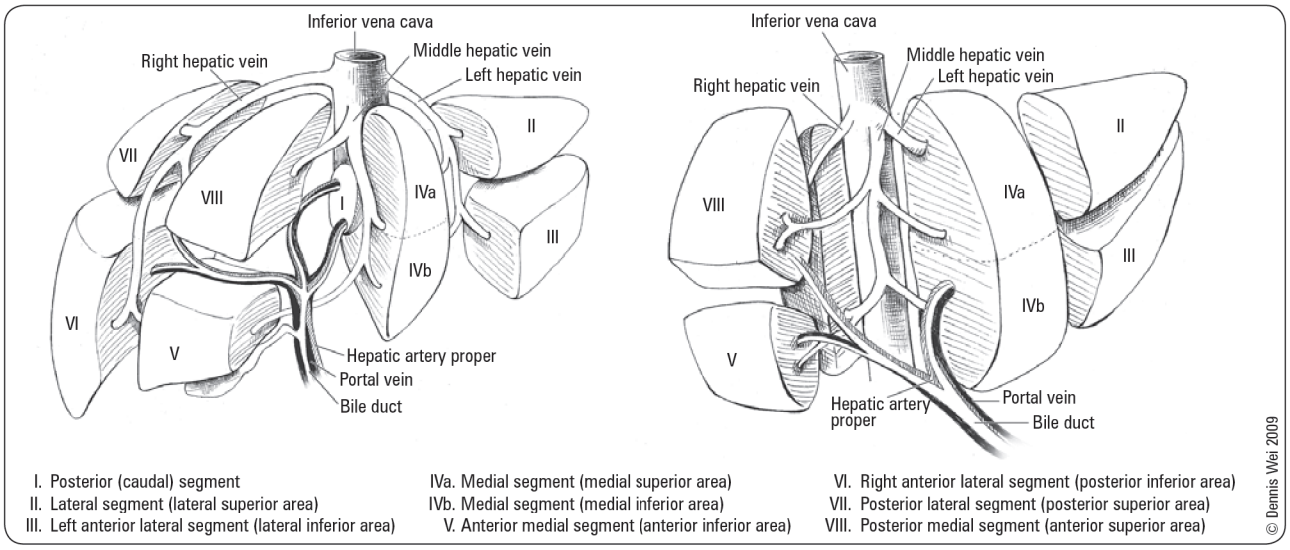


Figure 26. Anatomy of liver

Liver Cysts

Table 18. Characteristics of Liver Cysts

	Simple Cysts	Polycystic Liver Disease	Choledochal Cysts	Hydatid (Cystic Echinococcosis)	Cystadenoma (Premalignant)/ Cystadenocarcinoma
Description	Contain clear fluid that do not communicate with the intrahepatic biliary tree Most common	Several cysts that replace much of the liver	Congenital malformations of pancreaticobiliary tree high risk of malignancy majority present before age 10	Infection with parasite *Echinococcus granulosus* associated with exposure to dogs, sheep, and cattle in Southern Europe, Middle East, Australasia, South America	Rare cystic tumours that occur in the liver parenchyma or the extrahepatic bile ducts Cystadenocarcinoma is an invasive carcinoma
Clinical Features	Usually asymptomatic may have multiple simple cysts	Progressive 50% associated with polycystic kidney disease	Recurrent abdominal pain Intermittent jaundice RUQ mass Cholangitis Pancreatitis	Asymptomatic mass chronic pain Hepatomegaly	Upper abdominal mass Abdominal pain Anorexia

Table 18. Characteristics of Liver Cysts (continued)

	Simple Cysts	Polycystic Liver Disease	Choledochal Cysts	Hydatid (Cystic Echinococcosis)	Cystadenoma (Premalignant)/ Cystadenocarcinoma
Investigations	U/S: Used for diagnosis and follow-up CT: well demarcated lesion that does not enhance with contrast	U/S	U/S CT Transhepatic cholangiography LFTs	Anti-Echinococcus Ab (IgG) U/S CT: calcified mass Needle biopsy	Appear as complex cysts: internal septae, papillary projections, irregular lining Need histology for definite diagnosis
Treatment	Not required unless very large Monitor if >4 cm	Only if symptomatic partial liver resection drainage	Complete excision of cysts liver transplant if cyst involves intrahepatic bile ducts (Caroli's disease)	Albendazole (anti-helminthic) – cure up to 30% Surgical (risk of spillage into abdomen): Conservative: open endocystectomy or PAIR (**P**ercutaneous **A**spiration, **I**njection of protoscolicidal agent, **R**e-aspiration) Radical: partial hepatectomy or total pericystectomy	All complex, multiloculated cysts (except echinococcal) should be excised because of malignancy risk
Complications	Intracystic hemorrhage		Biliary cirrhosis, portal HTN, rupture, cholangiocarcinoma Abnormal pancreaticobiliary junction is associated with increased risk of malignancy	Inferior vena cava compression rupture can cause biliary colic, jaundice, cholangitis, pancreatitis, or anaphylactic reaction	Cystadenocarcinoma can invade adjacent tissues and metastasize

Liver Abscesses

Etiology
- types
  - pyogenic (bacterial): most common etiology; most often polymicrobial – *E. coli, Klebsiella, Proteus, Strep. milleri*
  - parasitic (amoebic): *Entamoeba histolytica*, *Echinococcal* cyst
  - fungal: *Candida*
- sources: direct spread from biliary tract infection, portal spread from GI infection, systemic infection (e.g. endocarditis)

Clinical Features
- fever, malaise, chills, anorexia, weight loss, abdominal pain, nausea
- RUQ tenderness, hepatomegaly, jaundice

Investigations
- leukocytosis, anemia, elevated liver enzymes, hemagglutination titres for *Entamoeba* antibodies
- U/S, CXR (right basilar atelectasis/effusion), CT, cyst aspiration with C&S

Treatment
- treat underlying cause
- generally will treat initially with antibiotics alone, and add surgical or percutaneous drainage and IV antibiotics for larger abscesses (initially ceftriaxone + metronidazole or piperacillin/tazobactam)

Prognosis
- overall mortality 15% – higher rate if delay in diagnosis, multiple abscesses, malnutrition

Neoplasms

BENIGN LIVER NEOPLASMS

Hemangioma (cavernous)
- pathogenesis: most common benign hepatic tumour; results from malformation of angioblastic fetal tissue
- risk factors: F:M = 3:1

- clinical features
  - usually small and asymptomatic
  - consumptive coagulopathy if giant (in children)
- investigations
  - contrast CT (well-demarcated hypodense mass with peripheral enhancement and delayed venous emptying), U/S (homogenous hyperechoic mass), arteriography (rarely used; "cotton wool" appearance), MRI
  - avoid biopsy: may result in hemorrhage
- treatment
  - usually none unless tumour bleeds or is symptomatic, then excision by lobectomy or enucleation

Focal Nodular Hyperplasia

- pathogenesis: unclear, may be regenerative response to hyperperfusion from anomalous arteries at centre of nodule
- risk factors: female, age 20-50
- clinical features: asymptomatic, rarely grows or bleeds, no malignant potential
- investigations: central stellate scar on CT scan; MRI, biopsy may be required
- treatment: may be difficult to distinguish from adenoma/fibrolamellar HCC (malignant potential) → often resected

Adenoma

- definition: benign glandular epithelial tumour
- risk factors: female, age 20-50, estrogen (OCP, pregnancy)
- clinical features: asymptomatic, 25% present with RUQ pain or mass, may present with bleeding
- investigations: CT (well-demarcated masses, often heterogeneous enhancement on arterial phase, isodense on venous phase without washout of contrast), U/S, MRI, biopsy often needed
- treatment
  - stop anabolic steroids or OCP
  - excise, especially if large (>5 cm), due to risk of transformation to hepatocellular carcinoma and spontaneous rupture/hemorrhage

Differential Diagnosis of Metastatic Liver Mass

Some **GU** **C**ancers **P**roduce **B**umpy **L**umps

Stomach
Genito**U**rinary cancers (kidney, ovary, uterus)
Colon
Pancreas
Breast
Lung

MALIGNANT LIVER NEOPLASMS

Primary

- usually hepatocellular carcinoma (HCC)/hepatoma
- others include angiosarcoma, hepatoblastoma, hemangioendothelioma
- epidemiology: 3rd leading cause of cancer death worldwide, 9th in United States; highest in Africa, China, Taiwan
- risk factors
  - chronic liver inflammation: chronic hepatitis B (inherently oncogenic) and hepatitis C, cirrhosis (especially macronodular), hemochromatosis, α_1-antitrypsin deficiency
  - medications: OCPs (3x increased risk), steroids
  - smoking, alcohol, Betel nuts
  - chemical carcinogens (aflatoxin, microcystin, vinyl chloride – associated with angiosarcoma)
- clinical features
  - RUQ discomfort, right shoulder pain
  - jaundice, weakness, weight loss, ± fever (if central tumour necrosis)
  - hepatomegaly, bruit, hepatic friction rub
  - ascites with blood (sudden intra-abdominal hemorrhage)
  - paraneoplastic syndromes – hypoglycemia, hypercalcemia, erythrocytosis, watery diarrhea
  - metastasis: lung, bone, brain, peritoneal seeding
- investigations
  - elevated ALP, bilirubin, and α-fetoprotein (80% of patients)
  - U/S (poorly-defined margins with internal echos), triphasic CT (enhancement on arterial phase and washout on portal venous phase), MRI
  - liver enzyme and liver function tests: AST, ALT, ALP, bilirubin, albumin, INR
- treatment
  - cirrhosis is a *relative* contraindication to tumour resection due to decreased hepatic reserve
  - surgical: resection (10% of patients have resectable tumours)
  - liver transplant; may use bridging therapy while awaiting transplant
    - **absolute contraindications**: extrahepatic disease, vascular invasion
    - **relative contraindications**: dependent on liver transplant protocol based on staging criteria followed by transplant centre
  - non-surgical: radiofrequency ablation, percutaneous ethanol injection, transcatheter arterial chemoembolization (TACE), chemotherapy (consider sorafenib for HCC; pre-operative chemotherapy for hepatoblastoma is standard of care), radiotherapy

Staging Criteria for Hepatocellular Carcinoma

Milan Criteria*	1 tumour ≤5 cm Up to 3 tumours each ≤3 cm
UCSF Criteria*	1 tumour ≤6.5 cm Up to 3 tumours each ≤4.5 cm, total diameter ≤8 cm
Toronto Criteria*	No tumour size of number restrictions No systemic symptoms Not poorly differentiated

*Each criteria assumes no extrahepatic and no macrovascular invasion

Child-Turcotte-Pugh Score (Prognosis of Chronic Liver Disease/Cirrhosis, Including Post-Operatively)

	1 Point	2 Points	3 Points
Albumin (g/L)	>35	28-35	<28
Ascites	Absent	Easily controlled	Poorly controlled
Bilirubin (μmol/L) (mg/dL)	<34 <2.0	34-51 2.0-3.0	>51 >3.0
Coagulation (INR)	<1.7	1.7-2.3	>2.3
Hepatic Encephalopathy	None	Minimal (Grade I-II)	Advanced (Grade III-IV)

Points	Class	One Yr Survival	Two Yr Survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

- prognosis
  - median survival: 6-20 mo
  - 5-yr survival: all patients – 5%; patients undergoing complete resection – 11-40%

Secondary

- metastases to the liver are the most common malignant tumours found in the liver
- etiology
  - GI (colorectal most common), lung, breast, pancreas, ovary, uterus, kidney, gallbladder, prostate
- treatment
  - hepatic resection for metastatic colorectal liver metastases if control of primary is possible, no extrahepatic or extrapulmonary metastases and if possibility of "curative" resection
  - possible chemotherapy
- prognosis: 30-40% 5 yr survival with a "curative" resection; prognosis same if metastases are multilobar compared with confined to one lobe

Secondary liver metastases are common in many cancers, with some studies showing a prevalence of 40-50% amongst patients with extrahepatic cancers. They commonly arise from breast, lung, and colorectal cancers. For metastases secondary to colorectal cancer, surgical resection offers the greatest likelihood of cure

Liver Transplantation

Table 19. Conditions Leading to Transplantation

Parenchymal Disease	Cholestatic Disease	Inborn Errors	Tumours
Chronic hepatitis B or C* Alcoholic cirrhosis Acute liver failure Budd-Chiari syndrome Congenital hepatic fibrosis CF Autoimmune hepatitis Cryptogenic cirrhosis Drug induced hepatotoxicity Non-alcoholic steatohepatitis	Biliary atresia** Primary biliary cirrhosis Sclerosing cholangitis	α_1-antitrypsin deficiency Wilson's disease Hemochromatosis	Hepatocellular carcinoma

*leading cause in adults; **leading cause in children

Clinical Indications

- early referral for transplant should be considered for all patients with progressive liver disease not responsive to medical therapy, especially:
  - decompensated cirrhosis (ascites, esophageal variceal hemorrhage, spontaneous hepatic encephalopathy, coagulopathy, progressive jaundice, severe fatigue)
  - unresectable primary liver cancers
  - fulminant hepatic failure
- end-stage liver disease with life expectancy <1 yr and if no other therapy is appropriate

Criteria for Transplantation

- Model for End-Stage Liver Disease (MELD): prognostic model to estimate 3 mo survival and disease severity if patient does not receive transplant; based on creatinine, bilirubin, INR; MELD scores from 6-40 used to prioritize liver allocation
- Child-Turcotte-Pugh Score: classification system to assess the prognosis and mortality of liver disease; patient must have ≥7 points (Class B)

Contraindications

- active alcohol/substance abuse
- extrahepatic malignancy within 5 yr
- advanced cardiopulmonary disease
- active uncontrolled infection

Post-Operative Complications

- primary non-function (graft failure): urgent re-transplantation is indicated
- acute and chronic rejection, ischemia-reperfusion injury
- vascular: hepatic artery or portal vein thrombosis, IVC obstruction
- biliary complications: fever, increasing bilirubin and ALP
- complications related to immunosuppression: HTN, renal disease, DM, obesity, hyperlipidemia, osteoporosis, malignancy, neurologic complications, infection (leading cause of mortality following transplant)

Prognosis

- patient survival at 1 yr: 85%
- graft survival at 1 yr: >80%, at 5 yr: 60-70%

Living Liver Donors vs. Deceased Liver Donors
The right lobe of a living donor liver is transplanted into the recipient, whereas whole livers from deceased donors are transplanted orthotopically into the recipient

Which Matters Most: Number of Tumours, Size of the Largest Tumour, or Total Tumour Volume?
Liver Transplant 2011;17:S58-66
Purpose: To determine if the size and/or number of hepatocellular carcinoma (HCC) nodules predict disease recurrence and survival after liver transplantation.
Methods: Systematic review and meta-analysis.
Results: 74 studies were included for analysis. Patients beyond the Milan criteria had reduced overall and disease-free survivals and higher recurrence. Patients outside the UCSF criteria had reduced overall and disease-free survivals and higher recurrence. Patients outside the Milan criteria but within the UCSF criteria had reduced overall and disease-free survivals. Overall and disease-free survivals were reduced for patients with larger total tumour diameter, ≥10 cm vs. <10 cm and ≥9 cm vs. <9 cm, respectively. Similarly, patients with higher diameter of largest tumour nodule (≥3 cm vs. <3 cm) had reduced overall survival and higher recurrence. Overall and disease-free survivals were reduced and recurrence higher for patients with tumour size ≥5 cm vs. <5 cm. Mixed results were found regarding number of tumour nodules.
Conclusion: Tumour size and volume are important factors in survival after liver transplantation.

Living Donor Liver Transplantation vs. Deceased Donor Liver Transplantation for Hepatocellular Carcinoma: Comparable Survival and Recurrence
Liver Transplant 2012;18:315-322
Purpose: To compare the overall survival and hepatocellular carcinoma (HCC) recurrence rates after living donor liver transplantation (LDLT) versus deceased donor liver transplantation (DDLT) in a series of patients with HCC.
Methods: Study conducted between 1996 and 2009 at a single centre. 345 patients with HCC undergoing liver transplantation included.
Results: The overall survival rates at 1, 3, and 5 yr did not significantly differ between the LDLT and DDLT groups (p=0.62). Disease free survival at 1, 3, and 5 yr did not differ between the groups (p=0.82). The recurrence rates at 1, 3, and 5 yr also did not differ between the two group (p=0.54).
Conclusion: LDLT and DDLT lead to similar survival and recurrence rates.

Biliary Tract

Cholelithiasis

Definition
- the formation of gallstones

Pathogenesis
- imbalance of cholesterol and its solubilizing agents (bile salts and lecithin)
- excessive hepatic cholesterol secretion → bile salts and lecithin are "overloaded" → supersaturated cholesterol can precipitate and form gallstones
- North America: cholesterol stones (80%), pigment stones (20%)

Risk Factors
- cholesterol stones
  - obesity, age <50
  - estrogens: female, multiparity, OCPs
  - ethnicity: First Nations heritage (especially Pima Indians) > Caucasian > Black
  - terminal ileal resection or disease (e.g. Crohn's disease)
  - impaired gallbladder emptying: starvation, TPN, DM
  - rapid weight loss: rapid cholesterol mobilization and biliary stasis
- pigment stones (contain calcium bilirubinate)
  - cirrhosis
  - chronic hemolysis
  - biliary stasis (strictures, dilation, biliary infection)
- protective factors: statins, vitamin C, coffee, exercise

Risk Factors for Cholesterol Stones

4Fs
Fat
Female
Fertile
Forties

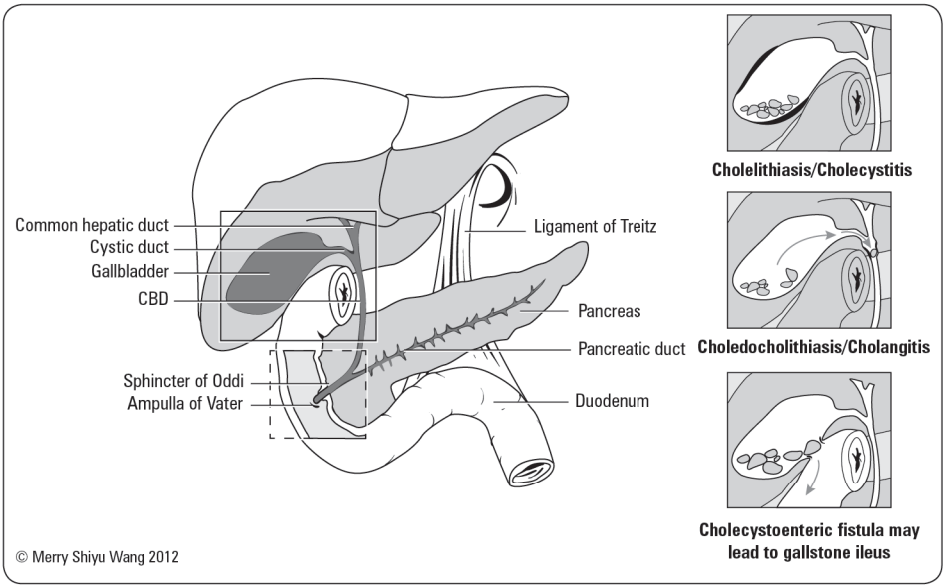


Figure 27. Gallstone disease

Clinical Presentation
- asymptomatic (80%)
  - most do NOT require treatment
  - consider cholecystectomy if: increased risk of malignancy (choledochal cysts, Caroli's disease, porcelain or calcified gallbladder), sickle cell disease, pediatric patient, bariatric surgery, immunosuppression
- biliary colic (10-25%)
- cholecystitis
- choledocholithiasis (8-15%)
- cholangitis
- gallstone pancreatitis (see *Acute Pancreatitis*, GS52)
- gallstone ileus (0.3-0.5%)
- other: empyema of the gallbladder, liver abscess, gallbladder perforation with bile peritonitis

Summary of Biliary Tract Conditions

Gall Bladder	Asymptomatic	Pain Only	Infection + Pain
Cholelithiasis	√ (majority)		
Biliary Colic		√	
Cholecystitis			√
Common Bile Duct	**Asymptomatic**	**Pain Only**	**Infection + Pain**
Choledocholithiasis	√ (majority)	√	
Cholangitis			√ (majority)

Investigations
- Labs
  - CBC, LFTs, amylase, and lipase

- U/S: diagnostic procedure of choice
  - image for signs of inflammation, obstruction, localization of stones
  - 95% specific for detecting stones
  - signs: gallbladder wall thickening >4 mm, edema (double-wall sign), gallbladder sludge, pericholecystic fluid, sonographic Murphy's sign
- ERCP
  - visualization of upper GI tract, ampullary region, biliary and pancreatic ducts
  - method for treatment of CBD stones in periampullary region
  - complications: traumatic pancreatitis (1-2%), pancreatic or biliary sepsis
- MRCP
  - same information gained as ERCP but non-invasive
  - cannot be used for therapeutic purposes
- PTC
  - injection of contrast via needle passed through hepatic parenchyma
  - useful for proximal bile duct lesions or when ERCP fails or not available
  - requires prophylactic antibiotics
  - contraindications: coagulopathy, ascites, peri/intrahepatic sepsis, disease of right lower lung or pleura
  - complications: bile peritonitis, chylothorax, pneumothorax, sepsis, hemobilia
- HIDA scan
  - used less commonly
  - radioisotope technetium-99 injected into a vein is excreted in high concentrations into bile, allowing visualization of the biliary tree
  - does not visualize stones; diagnosis by seeing occluded cystic duct or CBD

Biliary Colic

Biliary colic is a **constant** pain, not colicky

Pathogenesis
- gallstone transiently impacted in cystic duct, no infection

Clinical Features
- steady, severe dull pain in epigastrium or RUQ for minutes to hours, crescendo-decrescendo pattern
- may present with chest pain
- N/V
- frequently occurs at night or after fatty meal, not after fasting
- can radiate to right shoulder or scapula
- patients often restless
- no peritoneal findings, no systemic signs

2 Most Important Lab Tests for Biliary Pain
- Amylase
- Bilirubin

Investigations
- normal blood work: CBC, electrolytes, LFTs, bilirubin, amylase
- U/S shows cholelithiasis, may show stone in cystic duct

Treatment
- analgesia, rehydration during colic episode
- elective cholecystectomy (95% success)
  - complications: CBD injury (0.3-0.5%), hollow viscus injury, bile peritonitis, vessel injury
  - laparoscopic cholecystectomy is the standard of care, no benefit to delaying surgery
  - risk of open cholecystectomy higher in emergency situations

Biliary colic is treated with analgesia and elective cholecystectomy
Acute cholecystitis is treated with antibiotics and early cholecystectomy

Acute Cholecystitis

Pathogenesis
- inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann's pouch
- no cholelithiasis in 5-10% (see *Acalculous Cholecystitis*, GS49)

Clinical Features
- often have history of biliary colic
- severe constant (hours to days) epigastric or RUQ pain, anorexia, N/V, low grade fever (<38.5°C)
- focal peritoneal findings: Murphy's sign, palpable, tender gallbladder (in 33%)
- Boas' sign: right subscapular pain

Investigation
- blood work: elevated WBC and left shift, mildly elevated bilirubin, AST, ALT, and ALP
- U/S: 98% sensitive, consider HIDA scan if U/S negative

Complications
- gallbladder mucocele (hydrops): long-term cystic duct obstruction results in mucous accumulation in gallbladder (clear fluid)
- gangrene (20%), perforation (2%): result in abscess formation or peritonitis
- empyema of gallbladder: suppurative cholecystitis, pus in gallbladder + sick patient

Early vs. Delayed Laparoscopic Cholecystectomy for Uncomplicated Biliary Colic
Cochrane DB Syst Rev 2013;6:CD007196
Study: To assess the benefits and harms of early versus delayed laparoscopic cholecystectomy for patients with uncomplicated biliary colic due to gallstones.
Results: One trial with 75 participants, average age 43 yr. Early laparoscopic cholecystectomy (<24 h) vs. delayed (mean wait period 4.2 mo). The proportion of serious adverse events was lower in the early versus delayed group (0% vs. 22.5%, respectively). There was a shorter hospital stay in the early group (MD -1.25 d, 95% CI -2.05 to -0.45) and a shorter operating time in the early group (MD -14.80 min, 95% CI -18.02 to -11.58). There was no difference in the proportion of patients requiring conversion to open cholecystectomy in the two groups.
Conclusion: Early laparoscopic cholecystectomy (<24 h of diagnosis of biliary colic) decreased morbidity during the waiting period for elective laparoscopic cholecystectomy, hospital stay, and operating time.

- cholecystoenteric fistula, from repeated attacks of cholecystitis, can lead to gallstone ileus
- emphysematous cholecystitis: bacterial gas present in gallbladder lumen, wall, or pericholecystic space (risk in diabetic patient)
- organisms involved in secondary infection: *E. coli, Klebsiella, Enterococcus*
- Mirizzi syndrome: extra-luminal compression of CBD/CHD due to large stone in cystic duct

Treatment
- admit, hydrate, NPO, NGT (if persistent vomiting from associated ileus), analgesics once diagnosis is made
- antibiotics
  - cefazolin if uncomplicated cholecystitis
- cholecystectomy
  - early (within 72 h) vs. delayed (after 6 wk)
    - equal morbidity and mortality
    - early cholecystectomy preferred: shorter hospitalization and recovery time, no benefit to delaying surgery
    - emergent OR indicated if high risk, e.g. emphysematous
  - laparoscopic is standard of care (convert to open for complications or difficult case)
    - laparoscopic: reduced risk of wound infections, shorter hospital stay, reduced post-operative pain, increased risk of bile duct injury
- intra-operative cholangiography (IOC)
  - indications: clarify bile duct anatomy, obstructive jaundice, history of biliary pancreatitis, small stones in gallbladder with a wide cystic duct (>15 mm), single faceted stone in gallbladder, bilirubin >137 μmol/L
- percutaneous cholecystostomy tube: critically ill or if general anesthetic contraindicated

Acalculous Cholecystitis

Definition
- acute or chronic cholecystitis in the absence of stones

Pathogenesis
- typically due to gallbladder ischemia, stasis

Risk Factors
- DM, immunosuppression, ICU admission, trauma patient, TPN, sepsis

Clinical Features
- see *Acute Cholecystitis*, GS48
- occurs in 20% of cases of acute cholecystitis

Investigations
- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see *Acute Cholecystitis*, GS48)
- CT or HIDA scan

Treatment
- broad-spectrum antibiotics, cholecystectomy
- if patient unstable → cholecystostomy

Choledocholithiasis

Definition
- stones in CBD

Clinical Features
- 50% asymptomatic
- often have history of biliary colic
- tenderness in RUQ or epigastrium
- acholic stool, dark urine, fluctuating jaundice
- primary vs. secondary stones
  - primary: formed in bile duct, indicates bile duct pathology (e.g. benign biliary stricture, sclerosing cholangitis, choledochal cyst, CF)
  - secondary: formed in gallbladder (85% of cases in U.S.)

Investigations
- CBC: usually normal; leukocytosis suggests cholangitis
- LFTs: increased AST, ALT early in disease, increased bilirubin (more sensitive), ALP, GGT later
- amylase/lipase: to rule out gallstone pancreatitis
- U/S: intra-/extra-hepatic duct dilatation; differential diagnosis is choledochal cyst
- ERCP, PTC
- MRCP (90% sensitive, almost 100% specific, not therapeutic)

Rouviere's Sulcus
Fissure between right lobe and caudate process of liver; keeping dissection anterior to this landmark prevents bile duct injury

Critical View of Safety
Space between the gallbladder and liver clear of any structures other than the cystic artery

Mirizzi Syndrome
Extrinsic compression of the common hepatic duct by a gallstone in the cystic duct or Hartmann's pouch. Impacted gallstone may erode into the CHD or CBD, creating a cholecystohepatic or cholecystocholedochal fistula; Mirizzi syndrome has an association with gallbladder cancer

Laparoscopic vs. Open Cholecystectomy

Laparoscopic Cholecystectomy
- Shorter operating time
- Shorter length of stay
- Shorter sick leave
- Shorter time to return to daily activities
- Less post-operative pain
- Decreased use of post-operative analgesia
- Decreased reduction in pulmonary function*
- Fewer pulmonary complications
- Decreased acute phase response
- Less impairment in intestinal motility*

Open Cholecystectomy
- Lower conversion rates to open surgery (for mini-laparotomies)

*NOTE:
Pulmonary function = O_2 consumption, spirometric parameters, ABG, and acid-base balance
Intestinal motility = auscultating intestinal peristalsis, abdominal circumference measurement, and time interval to restitution of defecation

American Society of Gastrointestinal Endoscopy 2010 Predictors for Risk of CBD Stones

Very strong
- CBD stone on U/S
- Clinical ascending cholangitis
- Bilirubin >68 μmol/L

Strong
- CBD dilated >6 mm on U/S
- Bilirubin 31-68 μmol/L

Moderate
- Abnormal liver test (besides bilirubin)
- Age >55 yr
- Clinical gallstone pancreatitis

Complications
- cholangitis, pancreatitis, biliary stricture, and biliary cirrhosis

Treatment
- if no evidence of cholangitis: treat with ERCP for CBD stone extraction possibly followed by elective cholecystectomy in 25% of patients

Acute Cholangitis

Pathogenesis
- obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration and biliary sepsis – may be life-threatening, especially in elderly

Etiology
- choledocholithiasis (60%), stricture, neoplasm (pancreatic or biliary), extrinsic compression (pancreatic pseudocyst or pancreatitis), instrumentation of bile ducts (PTC, ERCP), biliary stent
- organisms: *E. coli, Klebsiella, Pseudomonas, Enterococcus, B. fragilis, Proteus*

Charcot's Triad
Fever, RUQ pain, jaundice

Clinical Features
- Charcot's triad: fever, RUQ pain, jaundice
- Reynold's pentad: fever, RUQ pain, jaundice, shock, confusion
- may have N/V, abdominal distention, ileus, acholic stools, tea-coloured urine (elevated direct bilirubin)

Reynolds' Pentad
Fever, RUQ pain, jaundice, shock, confusion

Investigations
- CBC: elevated WBC + left shift
- may have positive blood cultures
- LFTs: obstructive picture (elevated ALP, GGT, and conjugated bilirubin, mild increase in AST, ALT)
- amylase/lipase: rule out pancreatitis
- U/S: intra-/extra-hepatic duct dilatation

Common Bacteria in Biliary Tract

KEEPS
K*lebsiella*
E*nterococcus*
E*. coli, Enterobacter*
P*roteus, Pseudomonas*
S*erratia*

Treatment
- initial: NPO, fluid and electrolyte resuscitation, ± NGT, IV antibiotics (treats 80%)
- biliary decompression
  - ERCP + sphincterotomy: diagnostic and therapeutic
  - PTC with catheter drainage: if ERCP not available or unsuccessful
  - laparotomy with CBD exploration and T-tube placement if above fails
- all patients should also have a cholecystectomy, unless contraindicated

Prognosis
- suppurative cholangitis mortality rate: 50%

Gallstone Ileus

Pathogenesis
- repeated inflammation causing a cholecystoenteric fistula (usually duodenal) → large gallstone enters the gut and impacts at or near the ileocecal valve, causing a true bowel obstruction (note: ileus is a misnomer in this context)

Clinical Features
- crampy abdominal pain, N/V (see *Large Bowel Obstruction*, GS30)

Investigations
- AXR: dilated small intestine, air fluid levels, may reveal radiopaque gallstone, air in biliary tree (pneumobilia) (40%)
- CT: biliary tract air, obstruction, gallstone in intestine
- Rigler's triad: pneumobilia (air in biliary tree), small bowel obstruction (partial or complete), gallstone (usually in right iliac fossa)

Rigler's Triad of Gallstone Ileus
- Pneumobilia
- Small bowel obstruction
- Gallstone

Treatment
- fluid resuscitation, NGT decompression
- surgery: enterolithotomy and removal of stone, inspect small and large bowel for additional proximal stones
- may close fistula surgically or manage expectantly (can resolve spontaneously)
- cholecystectomy either during enterolithotomy or after recovery if patient experiences gallbladder symptoms

Bouveret's Syndrome
Gastric outlet/duodenal obstruction caused by a large gallstone passing through a cholecystogastric or cholecystoduodenal fistula

Carcinoma of the Gallbladder

Risk Factors
- chronic symptomatic gallstones (70% of cases), old age, female, gallbladder polyps, porcelain gallbladder, chronic infection (*Salmonella, Helicobacter*), abnormal pancreaticobiliary duct junction

Clinical Features
- majority are adenocarcinoma
- may be incidental finding on elective cholecystectomy (~1% of elective cholecystectomies)
- many patients are asymptomatic until late
- local: non-specific RUQ pain, ± palpable RUQ mass
- Courvoisier's gallbladder: an enlarged, often palpable gallbladder in a patient with carcinoma of the head of the pancreas; associated with jaundice due to obstruction of the CBD
- systemic: jaundice (50%) due to invasion of CBD or compression of CBD by pericholedochal nodes, weight loss, malaise, anorexia
- early local extension to liver, may extend to stomach, duodenum
- early metastasis common to liver, lung, bone

Investigations
- U/S: mural thickening, calcification, loss of interface between gallbladder and liver, fixed mass
- endoscopic U/S (EUS): good for distinguishing carcinomas from other diagnoses such as polyps, good for staging, allows sampling of bile for cytology
- abdominal CT: polypoid mass, mural thickening, liver invasion, nodal involvement, distant metastases
- MRI/MRCP: good for distinguishing benign and malignant polyps

Treatment
- if carcinoma of the gallbladder is suspected pre-operatively, an open cholecystectomy should be considered to avoid tumour seeding of the peritoneal cavity
- confined to mucosa (rare): cholecystectomy
- beyond mucosa: cholecystectomy, en bloc wedge resection of 3-5 cm underlying liver, dissection of hepatoduodenal lymph nodes

Prognosis
- poor 5 yr survival (10%) as gallbladder carcinoma is often detected late
- better outcomes when detected incidentally following cholecystectomy

Courvoisier's Sign
Palpable, nontender distended gallbladder due to CBD obstruction. Present in 33% of patients with pancreatic carcinoma. The distended gallbladder could not be due to acute cholecystitis or stone disease because the gallbladder would actually be scarred and smaller, not larger

Efficacy of Neoadjuvant Chemoradiation, Followed by Liver Transplantation, for Perihilar Cholangiocarcinoma at 12 US Centers
Gastroenterology 2012;143:88-98
Purpose: To determine the effectiveness of neoadjuvant chemoradiation and liver transplantation for unresectable perihilar cholangiocarcinoma and to determine the appropriateness of the United Network of Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) criteria for model of end-stage liver disease (MELD) exception for patients with this disease.
Methods: Study conducted from 1993-2010 in 12 transplant centers. 287 patients included.
Results: Median follow-up was 2.5 yr. 43% of patients (n=122) died after a median of 1.2 yr from presentation, and of these, 60 died pretransplant. Post-transplant, 43 patients had recurrences and 62 died. Recurrence-free survival at 2, 5, and 10 yr were 78%, 65%, and 59%, respectively. Intention-to-treat survival rates at 2 and 5 yr were 68% and 53%, respectively. 25% of patients left the waiting list after a median of 4.6 mo. The waiting list drop-out rate increased by an average of 11.5% every 3 mo. Patients who received transplantation outside of the criteria for MELD exception or who had a malignancy within 5 yr had significantly worse recurrence-free survival compared to those who met the criteria (HR=2.98, 95% CI 1.79, 4.95). Recurrence-free survival at 5 yr was shorter for patients with tumours >3 cm vs. ≤3 cm (p<0.001).
Conclusions: Neoadjuvant chemoradiation and liver transplantation are effective treatments for unresectable perihilar cholangiocarcinoma. Furthermore, the UNOS/OPTN criteria for MELD exception appear to be appropriate.

Cholangiocarcinoma

Definition
- malignancy of extra- or intrahepatic bile ducts

Risk Factors
- age 50-70, gallstones, ulcerative colitis, primary sclerosing cholangitis, choledochal cyst, *Clonorchis sinensis* infection (liver fluke), chronic intrahepatic stones (hepatolithiasis)

Clinical Features
- majority are adenocarcinomas
- gradual signs of biliary obstruction: jaundice, pruritus, dark urine, pale stools
- anorexia, weight loss, RUQ pain, Courvoisier's sign (if CBD obstructed), hepatomegaly
- early metastases are uncommon, but commonly tumour grows into portal vein or hepatic artery
- Klatskin tumour: cholangiocarcinoma located at bifurcation of common hepatic duct

Investigations
- LFTs show obstructive picture
- U/S, CT: bile ducts usually dilated, but not necessarily
- ERCP or PTC: to determine resectability, for biopsies
- CXR, bone scan: for metastatic workup

Treatment
- if resectable: biliary drainage and wide excision margin
  - upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
  - middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
  - lower third lesions: Whipple procedure
- unresectable lesions: stent or choledochojejunostomy (surgical bypass)
- chemotherapy ± radiotherapy
- role for transplantation in some patients with Klatskins tumours

Prognosis
- radiotherapy useful for additional palliation, chemotherapy may be helpful
- the more proximal to the liver, the worse the prognosis
- overall 5 yr survival: 15%

Obstructive jaundice is the most common presenting symptom for cholangiocarcinoma

Ranson's Criteria

A. At admission
1. Age >55 yr
2. WBC >16 x 10^9/L
3. Glucose >11 mmol/L
4. LDH ≥350 IU/L
5. AST >250 IU/L

B. During initial 48 h
1. Hct drop >10%
2. BUN rise >1.8 mmol/L
3. Arterial PO_2 <60 mmHg
4. Base deficit >4 mmol/L
5. Calcium <2 mmol/L
6. Fluid sequestration >6 L

C. Interpretation
≥2 = difficult course
≥3 = high mortality (≥15%)

Pancreas

Acute Pancreatitis

• see Gastroenterology, G44

GALLSTONE PANCREATITIS (35% of Acute Pancreatitis)

Pathogenesis
- obstruction of pancreatic duct by large or small gallstones and biliary sludge
- backup of pancreatic enzymes can cause autodigestion of the pancreas

Clinical Features (Pancreatitis of Any Etiology)
- pain (epigastric pain radiating to back), N/V, ileus, peritoneal signs, jaundice, fever
- Inglefinger's sign: pain worse when supine, better when sitting forward
- rarely may have coexistent cholangitis or pancreatic necrosis
- Ranson's criteria for determining prognosis of acute pancreatitis (see sidebar)
- physical exam may show: tachypnea, tachycardia, hypotension, abdominal distention and tenderness, Cullen's sign, Grey Turner's sign

Investigations
- high amylase (higher than alcoholic pancreatitis), lipase, leukocytosis
- elevated ALT (>150 IU/L), AST strongly suggest gallstone etiology of pancreatitis
- U/S may show multiple stones (may have passed spontaneously), edematous pancreas
- CXR, AXR, CT (if severe to evaluate for complications)

Treatment
- supportive: e.g. NPO, hydration, analgesia, early enteric nutrition
- antibiotics for severe cases of necrotizing pancreatitis or signs of sepsis
- stone often passes spontaneously (~90%); usually no surgical management in uncomplicated acute pancreatitis
- cholecystectomy during same admission (25-60% recurrence if no surgery)
- may need urgent ERCP + sphincterotomy if failure of conservative management if stone impacted in CBD (benefits of early ERCP controversial)
- early ERCP if concomitant cholangitis
- **surgical indications** in acute pancreatitis (rare):
  - debridement and drain placement for necrotizing pancreatitis if refractory to medical management, if septic or in ICU without other sources of sepsis

Complications
- pseudocyst (collection of pancreatic secretions >4 wk old surrounded by a defined wall of granulation tissue)
- abscess/infection, necrosis
- splenic/mesenteric/portal vessel thrombosis or rupture
- pancreatic ascites/pancreatic pleural effusion
- DM
- ARDS/sepsis/multiorgan failure
- coagulopathy/DIC
- encephalopathy
- severe hypocalcemia

Chronic Pancreatitis

• see Gastroenterology, G46

Surgical Treatment
- treatment is generally medical
- indications for surgery
  - failure of medical treatment
  - debilitating abdominal pain
  - pseudocyst complications: persistence, hemorrhage, infection, rupture
  - CBD obstruction (e.g. strictures), duodenal obstruction
  - pancreatic fistula, variceal hemorrhage secondary to splenic vein obstruction
  - rule out pancreatic cancer (present in 15% of chronic pancreatitis treated surgically)
  - anatomical abnormality causing recurrent pancreatitis
- pre-operative CT and/or ERCP are mandatory to delineate anatomy
- minimally invasive options
  - endoscopic pancreatic duct decompression: less effective than surgery
  - extracorporeal shockwave lithotripsy: if pancreatic duct stones
  - celiac plexus block: lasting benefit in 30% patients, less effective in those <45 yr or with prior pancreatic surgery

The hallmark of chronic pancreatitis is epigastric pain radiating to the back

- surgical options
  - drainage procedures: only effective if ductal system is dilated
    - Puestow procedure (lateral pancreaticojejunostomy): improves pain in 80% of patients
  - pancreatectomy: best option in absence of dilated duct
    - proximal disease: Whipple procedure (pancreaticoduodenectomy) – pain relief in 80%
    - distal disease: distal pancreatectomy ± Roux-en-Y pancreaticojejunostomy
    - total pancreatectomy: refractory disease
  - denervation of celiac ganglion and splanchnic nerves

PSEUDOCYST

- localized fluid collections rich in pancreatic enzymes, with a non-epithelialized wall consisting of fibrous and granulation tissue
- complication of chronic and/or acute pancreatitis
- often resolve spontaneously
- cyst wall must be mature prior to drainage (4-6 wk)
- pseudoaneurysm an absolute contraindication to endoscopic drainage, must embolize first

The lining of pancreatic pseudocysts consists of fibrous and granulation tissue; the lack of an epithelial lining distinguishes pseudocysts from true cystic lesions of the pancreas

Treatment

- surgical drainage (gold standard)
  - cystgastrostomy
  - cystenterostomy
  - resection
- endoscopic drainage
  - cystgastrostomy
  - cystduodenostomy
  - percutaneous catheter drainage
- consider biopsy of cyst wall to rule out cystadenocarcinoma

Pancreatic Cancer

Epidemiology

- fourth most common cause of cancer-related mortality in both men and women in Canada
- M:F = 1.3:1, average age: 50-70

Risk Factors

- increased age
- smoking: 2-5x increased risk, most clearly established risk factor
- high fat/low fibre diets, heavy alcohol use
- obesity
- DM, chronic pancreatitis
- partial gastrectomy, cholecystectomy
- chemicals: betanaphthylamine, benzidine
- African descent

Trousseau's Sign
Spontaneous peripheral venous thrombosis, often associated with pancreatic and other cancers

Clinical Features

- head of the pancreas (70%)
  - weight loss, obstructive jaundice, steatorrhea, vague constant mid-epigastric pain (often worse at night, may radiate to back)
  - painless jaundice (occurs more often with peri-ampullary), Courvoisier's sign (see sidebar GS49)
- body or tail of pancreas (30%)
  - tends to present later and usually inoperable
  - weight loss, vague mid-epigastric pain
  - <10% jaundiced
  - sudden onset DM

Vague abdominal pain with weight loss ± jaundice in a patient over 50 yr old is pancreatic cancer until proven otherwise

Investigations

- serum chemistry is non-specific, can have elevated ALP and bilirubin >300 µmol/L
- CA 19-9 (most useful serum marker of pancreatic cancer)
- U/S, contrast CT (also evaluates metastasis and resectability), ERCP, MRI, MRCP

Pathology

- ductal adenocarcinoma: most common type (75-80%); exocrine pancreas
- intraductal papillary mucinous neoplasm (IPMN)
- other: pancreatic neuroendocrine tumours (non-functional, insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma), mucinous cystic neoplasm (MCN), acinar cell carcinoma
- see *Surgical Endocrinology*, GS61 for functional pancreatic neuroendocrine tumours

Treatment

- resectable (10-20% of pancreatic cancer)
  - no involvement of liver, peritoneum, or vasculature (hepatic artery, SMA, SMV, portal vein, IVC, aorta), no distant metastasis
  - Whipple procedure (pancreaticoduodenectomy) for cure <5% mortality
  - distal pancreatectomy ± splenectomy, lymphadenectomy if carcinoma of midbody and tail of pancreas

Steps of a Whipple Resection (Pancreaticoduodenectomy)

1. Assessment of metastatic disease (all peritoneal surfaces)
2. Mobilization of the duodenum and head of the pancreas
3. Identification of the superior mesenteric vein and mobilization of the pancreatic neck
4. Mobilization of the stomach; dissection of the hepatoduodenal ligament and cholecystectomy
5. Division of the stomach, proximal jejunum, and CBD
6. Transection of the pancreatic neck and dissection of the uncinate process from the retroperitoneum
7. Restoration of gastrointestinal continuity: construction of a pancreaticojejunostomy, hepaticojejunostomy, gastrojejunostomy using a neoduodenum

Removed

- CBD
- Gallbladder
- Duodenum
- Pancreatic head
- Distal stomach (sometimes)

- borderline resectable
  - tumours that abut the SMA, SMV, portal vein, hepatic artery, or celiac artery
- non-resectable (palliative → relieve pain, obstruction)
  - most body/tail tumours are not resectable (due to late presentation)
  - relieve biliary/duodenal obstruction with endoscopic stenting or double bypass procedure (choledochoenterostomy + gastroenterostomy)
  - chemotherapy (gemcitabine, folfirinox), radiotherapy – only slightly increase survival

Prognosis

- most important prognostic indicators are lymph node status, margin status, size >3 cm, perineural invasion (invasion of tumour into microscopic nerves of pancreas)
- overall 5 yr survival for all patients with pancreas cancer is 1%; following surgical resection 5 yr survival is 20%
- median survival for unresectable disease: 3-6 mo if metastatic, 8-12 mo if locally advanced at presentation

Diagnostic Value of Serum Carbohydrate Antigen 19-9 in Pancreatic Cancer: A Meta-Analysis
Tumour Biol 2014 [Epub ahead of print]
Summary: 11 studies with 2,316 patients were included in the analysis. The sensitivity of CA19-9 in the diagnosis of pancreatic cancer was found to be 0.8 (95% CI 0.77-0.82) and the specificity also 80% (95% CI 0.77-0.82) with a diagnostic odds ratio of 14.79 (95% CI 8.55-25.59). Overall, CA19-9 plays an important role in the diagnosis of pancreatic cancer.

Table 20. TNM Classification System for Exocrine and Endocrine Tumours of the Pancreas

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Carcinoma *in situ*	N1	Regional lymph node metastasis		
T1	Tumour limited to pancreas, <2 cm in greatest dimension				
T2	Tumour limited to pancreas, >2 cm in greatest dimension				
T3	Tumour extends beyond pancreas, no involvement of celiac axis or SMA				
T4	Tumour involves celiac axis or SMA (unresectable)				

Table 21. Staging and Treatment of Pancreatic Cancer

Stage	Classification	5 Yr Survival	Treatment
0	Tis, N0, M0		Surgical resection ± chemotherapy
IA	T1, N0, M0	14%	Same as above
IB	T2, N0, M0	12%	Same as above
IIA	T3, N0, M0	7%	Same as above
IIB	T1-3, N1, M0	5%	Same as above
III	T4, any N, M0	3%	Borderline resectable, trial of chemotherapy and radiation
IV	any T, any N, M1	1%	Non-resectable, palliative treatments

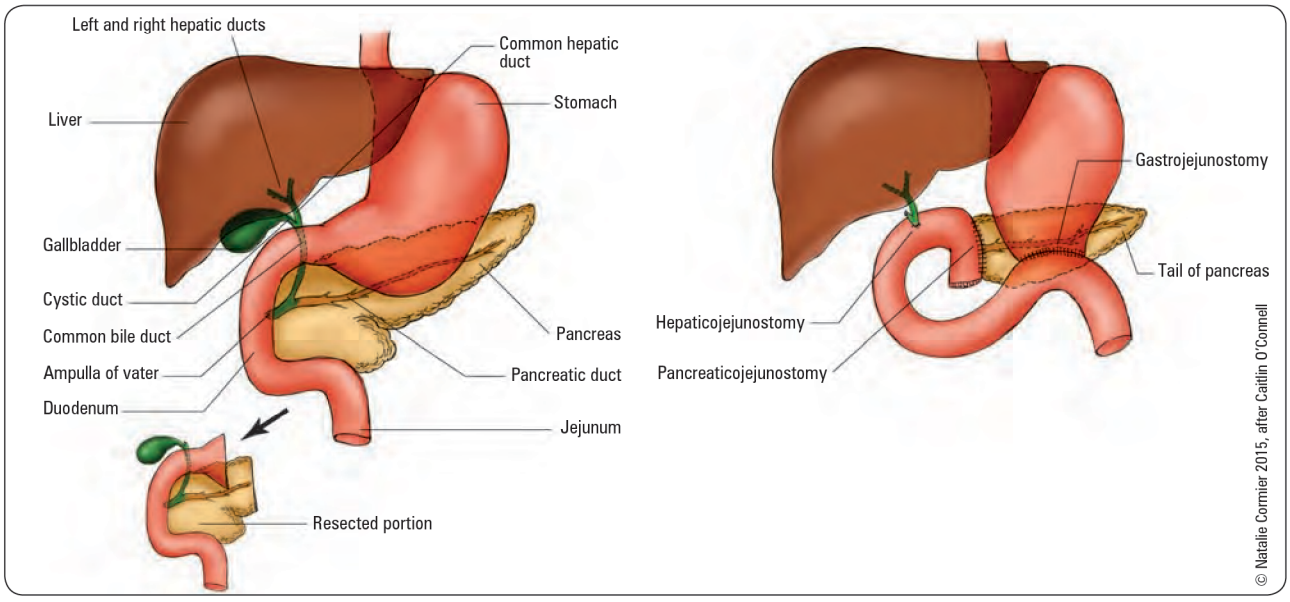


Figure 28. Schematic of Whipple resection, showing the resected components

Spleen

Splenic Trauma

- typically from blunt trauma (especially in people with splenomegaly)
- most common intra-abdominal organ injury in blunt trauma
- may have Kehr's sign

Kehr's Sign
Left shoulder pain due to diaphragmatic irritation from splenic rupture, worsens with inspiration

Treatment

- non-operative
  - in stable patients: extended bed rest with serial hematocrit levels, close monitoring for 3-5 d; pediatric guidelines for days of bed rest is grade plus 1 (i.e. grade 3 splenic laceration requires 4 d of bed rest)
  - hemostatic control
  - splenic artery embolization if patient stable and one of: active contrast extravasation, splenic pseudoaneurysm, hemoperitoneum
- operative
  - splenorrhaphy (suture of spleen) ± splenic wrapping with hemostatic mesh – if patient hemodynamically stable, patient has stopped bleeding and laceration does not involve hilum
  - partial splenectomy, rarely performed due to risk of recurrent hemorrhage
  - total splenectomy if patient unstable or high-grade injury

Splenectomy

Indications

- splenic trauma (most common reason for splenectomy), hereditary spherocytosis, primary hypersplenism, chronic immune thrombocytopenic purpura (ITP), splenic vein thrombosis causing esophageal varices, splenic abscess, thrombotic thrombocytopenic purpura (TTP), sickle cell disease
- does not benefit all thrombocytopenic states (e.g. infection, most malignancies involving the bone marrow, drugs/toxins)
- probability of cure of ITP by splenectomy is 60-70%, may be predicted by response to IVIg

Indication of Splenectomy

SHIRTS
Splenic abscess/splenomegaly
Hereditary spherocytosis
Immune thrombocytopenic purpura
Rupture of spleen
Thrombotic thrombocytopenic purpura
Splenic vein thrombosis

Complications

- short-term
  - injury to surrounding structures (e.g. gastric wall, tail of pancreas)
  - post-operative thrombocytosis, leukocytosis
  - thrombosis of portal, splenic, or mesenteric veins
  - subphrenic abscess
- long-term
  - post-splenectomy sepsis (encapsulated organisms): 4% of splenectomized patients (highest risk in those <16 yr old)
    - 50% mortality
    - prophylaxis with vaccinations, ideally 2 wk pre- or post-operative (pneumococcal, *H. influenzae,* and meningococcus)
    - liberal use of penicillin especially in children <6 yr old
  - splenosis: intra-abdominal "seeding" of splenic tissue during removal

Breast

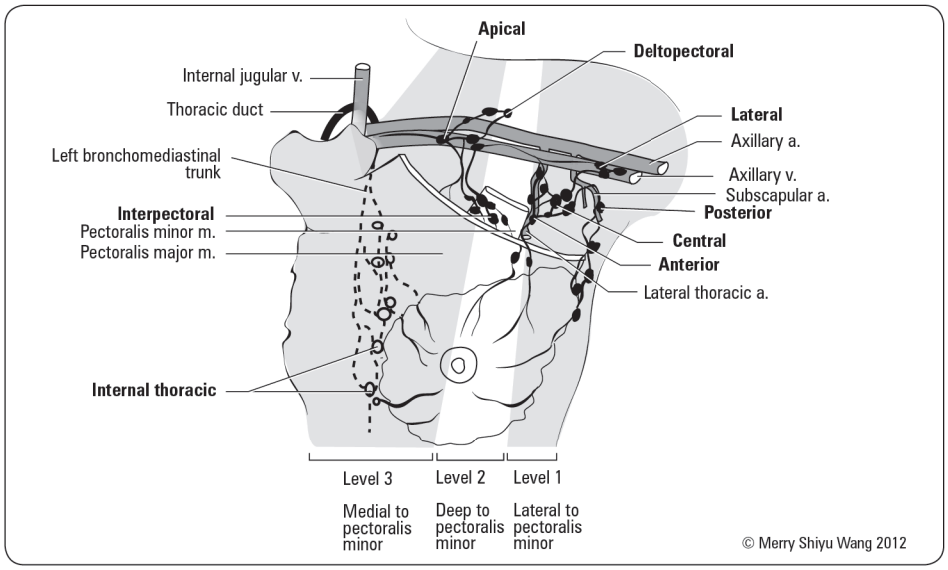


Figure 29. Anatomy of the breast

Levels of Axillary Lymph Nodes
Level I: lateral to pectoralis minor
Level II: deep to pectoralis minor
Level III: medial to pectoralis minor

(higher level of nodal involvement = worse prognosis)

Benign Breast Lesions

Three Categories

1. nonproliferative
2. proliferative without atypia
3. atypical hyperplasia

NONPROLIFERATIVE LESIONS

- benign breast condition characterized by fibrous and cystic changes in the breast
- most common: breast cysts
- other lesions include papillary apocrine change, epithelial-related calcifications and mild hyperplasia of the usual type
- no increased risk of breast cancer
- age 30 to menopause (and after if HRT used)
- clinical features
  - breast pain, focal areas of nodularity or cysts often in the upper outer quadrant, frequently bilateral, mobile, varies with menstrual cycle, nipple discharge (straw-like, brown, or green)
- treatment
  - evaluation of breast mass (U/S, mammography as indicated) and reassurance
  - no strong evidence for avoidance of xanthine-containing products (coffee, tea, chocolate, cola)
  - analgesia (ibuprofen, ASA)
  - for severe symptoms: OCP, danazol, bromocriptine

DDx for Breast Mass

Benign
- Fibrocystic changes
- Fibroepithelial lesions (fibroadenoma most common; benign phyllodes also)
- Fat necrosis
- Papilloma/papillomatosis
- Galactocele
- Duct ectasia
- Ductal/lobular hyperplasia
- Sclerosing adenosis
- Lipoma
- Neurofibroma
- Granulomatous mastitis (e.g. TB, granulomatosis with polyangiitis, sarcoidosis)
- Abscess
- Silicone implant

Malignant
- Breast cancer (likely invasive, DCIS rarely forms a breast mass)
- Malignant phyllodes
- Angiosarcoma (rare)

PROLIFERATIVE LESIONS – WITHOUT ATYPIA

Table 22. Proliferative Lesions - without Atypia

		Clinical Features	Diagnosis	Treatment	Risk of Breast Cancer
Fibroadenoma	Most common breast tumour in women <30y	Nodules: firm, rubbery, discrete, well-circumscribed, non-tender, mobile, hormone-dependent Unlike cysts, needle aspiration yields no fluid	Core or excisional biopsy some times required if concerned about malignancy U/S and FNA alone cannot differentiate fibroadenoma from Phyllodes tumour	Generally conservative: serial observation Consider excision if size 2-3 cm and growing on serial U/S (q6mo x 2 yr is usual follow-up), if symptomatic, formed after age 35, or patient preference or features on core biopsy suggestive a Phyllodes tumour	Increased if complex, adjacent atypia of strong family history of breast cancer
Intraductal Papilloma	Solitary intraductal benign polyp	Can present as nipple discharge (most common cause of spontaneous, unilateral, bloody nipple discharge = pathologic nipple discharge), breast mass, nodule on U/S		Surgical excision of involved duct to ensure no atypia	**Can harbour areas of atypia or DCIS**
Usual Ductal Hyperplasia	Increased number of cells within the ductal space	Incidental finding on biopsy of mammographic abnormalities or breast masses		None required	**Generally low risk, slightly increased if moderate or florid hyperplasia**
Sclerosing Adenosis	Lobular lesion with increased fibrous tissue and glandular cells	Mass or mammographic abnormality		None required	**Low risk**

ATYPICAL HYPERPLASIA

- can involve ducts (ductal hyperplasia with atypia) or lobules (lobular hyperplasia with atypia)
- cells lose apical-basal orientation
- increased risk of breast cancer
- diagnosis: core or excisional biopsy
- treatment: complete resection, risk modification (avoid exogenous hormones), close follow-up

OTHER LESIONS

Fat Necrosis

- uncommon, result of trauma (may be minor, positive history in only 50%), after breast surgery (i.e. reduction)
- firm, ill-defined mass with skin or nipple retraction, ± tenderness
- regress spontaneously, but complete imaging ± biopsy to rule out carcinoma

Mammary Duct Ectasia

- obstruction of a subareolar duct leading to duct dilation, inflammation, and fibrosis
- may present with nipple discharge, bluish mass under nipple, local pain
- risk of secondary infection (abscess, mastitis)
- resolves spontaneously

Montgomery Tubercle

- Montgomery tubercles (or Morgagni tubercles) are papular projections at the edge of the areola
- obstruction of these glands can lead to inflammation or cystic collections (cyst of Montgomery i.e. retroareolar cyst)
- if signs of secondary infection, start treatment for mastitis
- resolves spontaneously in weeks to years

Abscess

- lactational (see Obstetrics, OB48) vs. periductal/subareolar
- unilateral localized pain, tenderness, erythema, subareolar mass, nipple discharge, nipple inversion
- rule out inflammatory carcinoma, as indicated
- treatment: initially broad-spectrum antibiotics and I&D, if persistent total duct excision (definitive)
- if mass does not resolve: U/S to assess for presence of abscess, core biopsy to exclude cancer, consider MRI

Breast Cancer

Epidemiology
- leading cancer diagnosis in women in NA, 2nd leading cause of cancer mortality in women
- 1/8 (12.8% life time risk) women in Canada will be diagnosed with breast cancer in their lifetime
- 1/30 women in Canada will die from breast cancer

Risk Factors
- gender (99% female)
- age (80% >40 yr old)
- personal history of breast cancer and/or prior breast biopsy (regardless of pathology)
- family history of breast cancer (greater risk if relative was first degree and premenopausal)
- high breast density, nulliparity, first pregnancy >30 yr, menarche <12 yr, menopause >55 yr
- decreased risk with lactation, early menopause, early childbirth
- radiation exposure (e.g. mantle radiation for Hodgkin's disease)
- >5 yr HRT use, >10 yr OCP use
- BRCA1 and BRCA2 gene mutations
- alcohol use, obesity, sedentary lifestyle

Gender followed by age are the two greatest risk factors for breast cancer

Male breast cancer (<1%)
- most commonly invasive ductal carcinoma
- often diagnosed at later stages
- stage-for-stage similar prognosis to breast cancer in females
- consider genetic testing: most often hormone receptor positive

Any palpable dominant breast mass requires further investigation

Investigations
- mammography
  - indications
    - screening guidelines (see Family Medicine, FM3)
  - findings indicative of higher risk of malignancy
    - mass that is poorly defined, spiculated border
    - microcalcifications
    - architectural distortion
    - interval mammographic changes
  - normal mammogram does not rule out suspicion of cancer based on clinical findings
- other radiographic studies
  - U/S: differentiate between cystic and solid
  - MRI: high sensitivity, low specificity
  - galactogram/ductogram (for nipple discharge): identifies lesions in ducts
  - metastatic workup indicated in Stage II-IV disease: bone scan, abdominal U/S, CXR (or CT chest/abdomen/pelvis), CT head (if specific neurological symptoms)

Diagnostic Procedures
- needle aspiration: for palpable cystic lesions; send fluid for cytology if blood or cyst does not completely resolve
- U/S or mammography guided core needle biopsy (most common)
- fine needle aspiration (FNA): for palpable solid masses; need experienced practitioner for adequate sampling
- excisional biopsy: only performed as second choice to core needle biopsy; should not be done for diagnosis if possible

Diagnostic mammography is indicated in all patients, even in women <50 yr

Genetic Screening
- consider testing for BRCA1/2 if
  - patient diagnosed with breast AND ovarian cancer
  - strong family history of breast/ovarian cancer
  - family history of male breast cancer
  - young patient (<35 yr)
  - bilateral breast cancer in patients <50 yr

Phyllodes tumours are rare fibroepithelial breast tumours that can be benign or malignant that mostly affect women from 35-55 yr

Staging
- patients are assigned a clinical stage pre-operatively (cTNM); following surgery the pathologic stage is determined (pTNM)
- clinical
  - tumour size by palpation, mammogram, U/S and/or MRI
  - nodal involvement by palpation, imaging
  - metastasis by physical exam, CXR, and abdominal U/S (or CT chest/abdomen/pelvis), bone scan (usually done post-operative if node-positive disease)
- pathological
  - tumour size and type (see Pathology below)
  - grade: modified Bloom and Richardson score (I to III) – histologic, nuclear, and mitotic grade

- number of axillary nodes positive for malignancy out of total nodes resected, extranodal extension, sentinel lymph node biopsy (SLNB) positive/negative
- tumour biology: estrogen receptor (ER), progesterone receptor (PR) and HER2/neu oncogene status
- margins: for invasive breast cancer negative margin is sufficient, for DCIS prefer 2mm margin
- lymphovascular invasion (LVI)
- extensive in situ component (EIC): DCIS in surrounding tissue
- involvement of dermal lymphatics (inflammatory) – automatically Stage IIIb

Table 23. Staging of Breast Cancer (American Joint Committee on Cancer)

Stage	Tumour	Nodes (regional) (clinical)	Metastasis	Survival (5 yr)
0	*in situ*	None	None	99%
I	<2 cm	None	None	94%
II A	<2 cm	Mobile ipsilateral	None	85%
II B	2-5 cm or >5 cm	None or mobile ipsilateral None	None None	70%
III A	Any size	Fixed ipsilateral or internal mammary	None	52%
III B	Skin/chest wall invasion	Any	None	48%
III C	Any size	Ipsilateral infraclavicular/internal mammary plus axillary nodes; ipsilateral supraclavicular node(s) ± axillary nodes	None	33%
IV	Any	Any	Distant	18%

Favourable Features	Unfavourable Features
• <2 cm • Grade I (low grade) • Node negative • ER positive • Mucinous pattern	• >5 cm • Grade III (high grade) • Node positive • ER negative • Inflammatory cancer • Her2Neu positive • Positive margins • LVI • EIC • Dermal lymphatics involved

Pathology

NON-INVASIVE

Ductal Carcinoma *in situ* (DCIS)

- proliferation of malignant ductal epithelial cells completely contained within breast ducts, often multifocal
- 80% non-palpable, detected by screening mammogram
- risk of invasive ductal carcinoma in same breast up to 35% in 10 yr
- treatment
  - lumpectomy with wide excision margins + radiation (5-10% risk invasive cancer)
  - mastectomy if large area of disease, high grade, or multifocal (risk of invasive cancer reduced to 1%)
  - possibly tamoxifen as an adjuvant treatment
  - 99% 5 yr survival

Lobular Carcinoma *in situ* (LCIS)

- neoplastic cells completely contained within breast lobule
- no palpable mass, no mammographic findings, usually incidental finding on breast biopsy for another indication
- LCIS is a risk factor for invasive carcinoma (approximately 1%/yr)
- treatment
  - if diagnosed on core biopsy, excisional biopsy necessary to rule out malignancy
  - if diagnosed on excisional biopsy, wide excision not needed since LCIS if often multicentric and not managed as precursor lesion
  - clinical follow-up and surveillance
  - consider chemoprevention (e.g. tamoxifen)

Diagnosis of Breast Lesions: Fine-Needle Aspiration Cytology or Core Needle Biopsy? A Review
J Clin Pathol 2012;65:287-292

CNB
- High sensitivity (85-100%) and specificity (86-100%).
- High success rates for diagnosis of malignancy for palpable lesions (97%), non-palpable lesions (94%), and lesions <10 mm (90%).
- More accurate for histologic and immunohistochemistry examinations, and differentiation between *in situ* and invasive malignancies.
- Reliable for testing of ER, PR, and HER2 status and proliferation assessment.
- More painful procedure.

FNAC
- Variable sensitivity (35-95%) and specificity (48-100%).
- Quality correlates with skill of aspirator.
- Lower success rates for diagnosis of malignancy for palpable lesions (75-90%), non-palpable lesions (34-58%), and lesions <10 mm (50%).
- High rates of insufficient sampling for lesions >40 mm or calcified lesions.
- Quick to perform.
- Low technical costs.

Conclusions: FNAC is preferable for palpable, low malignancy-risk lesions. However, for potential malignancies, CNB is advantageous with respect to prognostication and prediction and is likely cost-effective in the long-term.

INVASIVE

Invasive Ductal Carcinoma (most common 80%)

- originates from ductal epithelium and infiltrates supporting stroma
- characteristics: hard, scirrhous, infiltrating tentacles, gritty on cross-section

Invasive Lobular Carcinoma (8-15%)

- originates from lobular epithelium
- 20% bilateral (i.e. more often than infiltrating ductal carcinoma)
- does not form microcalcifications, harder to detect mammographically (may benefit from MRI)

Paget's Disease (1-3%)

- ductal carcinoma that invades nipple with scaling, eczematoid lesion

Inflammatory Carcinoma (1-4%)
- ductal carcinoma that invades dermal lymphatics
- most aggressive form of breast cancer
- clinical features: erythema, skin edema, warm, swollen, and tender breast ± lump
- peau d'orange indicates advanced disease (IIIb-IV)

Sarcomas: rare
- most commonly Phyllodes tumour, a variant of fibroadenoma with potential for malignancy
- can also be angiosarcomas – after previous radiation

Lymphoma: rare

Other
- papillary, medullary, mucinous, tubular cancers
- generally better prognosis

Treatment

Table 24. Breast Cancer Treatment by Stage

Stage	Primary Treatment Options	Adjuvant Systemic Therapy
0 *(in situ)*	BCS + radiotherapy BCS alone if margins >1 cm and low nuclear grade Mastectomy* ± SLNB	Consider post-operative tamoxifen for ER+, trastuzumab for HER2+
I	BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB	May not be needed; discuss risks/benefits of chemotherapy and tamoxifen
II	BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB	Chemotherapy for premenopausal women or postmenopausal and estrogen receptor (ER) negative, followed by tamoxifen if ER positive
III	Likely mastectomy + axillary node dissection + radiotherapy after chemotherapy (neoadjuvant)	Neoadjuvant therapy should be considered i.e. pre-operative especially if not resectable chemotherapy and/or hormone therapy. Adjuvant radiation and chemotherapy may also be appropriate (i.e. post-operative)
Inflammatory	Mastectomy + axillary node dissection + radiotherapy	Neoadjuvant therapy
IV	Surgery as appropriate for local control	Primary treatment is systemic therapy i.e. chemotherapy and/or hormone therapy

BCS = breast conserving surgery; SLNB = sentinel lymph node biopsy
*If no reason to select mastectomy, the choice between BCS + radiotherapy and mastectomy can be made according to patient's preference since choice of local treatment does not significantly affect survival if local control is achieved

Analysis of Circulating Tumour DNA to Monitor Metastatic Breast Cancer
NEJM 2013;368:1199-1209
Study: The quantification of circulating tumour DNA, cancer antigen 15-3 (CA 15-3), and circulating tumour cells in 30 women with metastatic breast cancer receiving systemic therapy. The results were compared with radiographic imaging of tumours.
Results/Conclusions: Circulating tumour DNA was detected in 97% of women and showed greater correlation with changes in tumour burden than did CA 15-3 or circulating tumour cells, providing the earliest measure of treatment response in 53% of women. CA 15-3 and circulating tumour cells were detected in 78% and 87% of women, respectively. Circulating tumour DNA may therefore be an informative biomarker for metastatic breast cancer.

PRIMARY SURGICAL TREATMENT

Breast Conservation Surgery (BCS)
- lumpectomy must be combined with radiation for survival equivalent to mastectomy
- contraindications include
  - high risk of local recurrence e.g. extensive malignant-type calcifications on mammogram, multifocal primary tumours
  - failure to obtain tumour-free margins after re-excision
  - not candidate for radiation therapy (pregnancy, previous radiation, collagen vascular disease)
  - large tumour size relative to breast

Breast conserving surgery can be offered to most women with stage I/II disease

Mastectomy
- radical mastectomy (rarely): removes all breast tissue, skin, pectoralis muscle, axillary nodes
- modified radical mastectomy (MRM): removes all breast tissue, skin, and axillary nodes
- simple mastectomy: removes all breast tissue and skin
- see Plastic Surgery, PL33 for breast reconstruction

There is no survival benefit of mastectomy over lumpectomy plus radiation for stage I and II disease

Sentinel Lymph Node Biopsy (SLNB)
- perform in women with clinically node-negative invasive breast cancer and those with extensive DCIS who are undergoing mastectomy
- patients with clinically suspicious nodes should U/S + FNA prior to decision to proceed with SLNB
- technetium-99 ± blue dye injected at tumour site prior to surgery to identify sentinel node(s)
- intra-operative frozen section evaluated can be considered
- proceed with ALND if >3 positive nodes, with 1-3 nodes whole breast radiation therapy may be alternative
- 5% false negative rate

Axillary Lymph Node Dissection (ALND)
- perform in all patients with pathologic confirmation of nodal involvement (including positive SLNB as above)
- risk of arm lymphedema (10-15%) especially if getting radiation therapy, decreased arm sensation, shoulder pain

ADJUVANT/NEOADJUVANT

Radiation
- indications
  - decrease risk of local recurrence; almost always used after BCS, sometimes after mastectomy
  - inoperable locally advanced cancer
  - axillary nodal radiation may be added if nodal involvement

Hormonal
- indications
  - ER positive plus node-positive or high-risk node-negative
  - SERM if premenopausal (e.g. tamoxifen) or aromatase inhibitors if postmenopausal (e.g. anastrozole); optimal duration 5-10 yr
  - ovarian ablation (e.g. goserelin/GnRH agonist, oophorectomy), progestins (e.g. megestrol acetate), androgens (e.g. fluoxymesterone) are other options
  - palliation for metastatic disease

Chemotherapy
- indications
  - ER negative plus node-positive or high-risk node-negative
  - ER positive and young age
  - stage I disease at high risk of recurrence (high grade, lymphovascular invasion)
  - palliation for metastatic disease
  - can consider oncotype DX (21 gene analysis) to provide recurrence score (low, intermediate, high)

FOLLOW-UP

Post-Treatment Follow-Up
- assessment and physical exam q3-6mo x 3 yr, q6-12mo x 2yr, and annually thereafter
- following BCS mammography q6-12mo; can reduce to annual once stable, no other routine imaging unless clinically indicated
- women who receive tamoxifen should have regular gynecologic follow-up (increased risk of endometrial cancer)
- psychosocial support and counselling
- delayed breast reconstruction if underwent a mastectomy

Local/Regional Recurrence
- recurrence in treated breast or ipsilateral axilla
- 1% per yr up to maximum of 15% risk of developing contralateral malignancy
- 5x increased risk of developing metastases

Metastasis
- bone > lungs > pleura > liver > brain
- treatment is palliative: hormone therapy, chemotherapy, radiation
- overall survival of metastatic breast cancer is 36-60 mo

Surgical Endocrinology

Thyroid and Parathyroid

- see Endocrinology, E20 and Otolaryngology, OT35

Thyroidectomy
- indications: thyroid cancer, symptomatic thyroid mass or goitre, medically refractory Graves' or hyperthyroidism
- contraindications: uncontrolled severe hyperthyroidism (i.e. Graves') due to risk of intra-operative or post-operative thyroid storm
- pre-operative workup: thyroid U/S for thyroid nodules, FNA for large nodules, U/S of the neck for lesions suspicious for papillary or medullary thyroid cancer, CT neck useful to rule out extension, vocal cord function
- complications: hypocalcemia secondary to hypoparathyroidism, recurrent/superior laryngeal nerve injury, neck hematoma, infection, thyrotoxic storm

Hypertrophic Pyloric Stenosis
Non-bilious emesis in infant is the classic presentation

Parathyroidectomy
- indications: symptomatic primary hyperparathyroidism due to effects of PTH on bone or kidneys, asymptomatic primary hyperparathyroidism with specific laboratory criteria (elevated serum Ca, marked hypercalciuria, Cr clearance <30% normal, bone density reduction with T score <2.5, <50 yr)
- contraindications: familial hypocalciuric hypercalcemia
- pre-operative workup: ^{99m}Tc sestamibi scanning, ± SPECT or CT, U/S
- complications: recurrent/superior laryngeal nerve injury, post-operative hypocalcemia, infection, bleeding

Adrenal Gland

- see Endocrinology, E29
- functional anatomy
  - cortex: glomerulosa (mineralocorticoids), fasciculata (glucocorticoids), reticularis (sex steroids)
  - medulla: catecholamines (epinephrine, norepinephrine)
- types of adrenal tumours: functional (e.g. Cushing's syndrome, Conn's syndrome) or non-functional

INCIDENTALOMA

- adrenal mass discovered by investigation of unrelated symptoms

Epidemiology

- benign adenoma (38%) > metastases to adrenal (22%) >> cyst, carcinoma, pheochromocytoma, neuroblastoma
- metastasis to adrenal gland from: lung > breast, colon, lymphoma, melanoma, kidney
- peak incidence of carcinoma: females age 50-60, risk decreases with increasing age and male gender

Investigations

- MRI, CT: size >6 cm is best predictor of primary adrenal carcinoma (92% are >6 cm)
- functional studies
  - pheochromocytoma: 24 h urine epinephrine, norepinephrine, metanephrine, normetanephrine, VMA (vanillylmandelic acid)
  - Cushing's: 24 h urine cortisol or 1 mg overnight dexamethasone suppression test
  - aldosteronoma: electrolytes, aldosterone:renin level, saline suppression test if appropriate
  - adrenal androgens: 17-OH progesterone, DHEAS
- FNA biopsy: if suspect metastasis to adrenal (must exclude pheochromocytoma first to prevent a hypertensive crisis)
  - indicated if history of cancer or patient is smoker
- iodocholesterol scintigraphy: may distinguish benign vs. malignant disease

Treatment

- functional tumour: resect
- non-functional tumour
  - >4 cm: resect
  - <4 cm: follow-up imaging in 6-12 mo, resect if >1 cm enlargement

Pancreas

INSULINOMA

- tumour that secretes insulin
- most common pancreatic endocrine neoplasm; 10% associated with MEN1 syndrome

Clinical Features

- Whipple's triad
- palpitations, trembling, diaphoresis, confusion, seizure, personality changes

Whipple's Triad
- Symptomatic fasting hypoglycemia
- Serum glucose <50 mg/dL
- Relief of symptoms when glucose is administered

Investigations

- blood work: decreased serum glucose and increased serum insulin and C-peptide
- U/S, CT: insulinomas evenly distributed throughout head, body, tail of pancreas

Treatment

- only 10% are malignant
- enucleation of solitary insulinomas may be done endoscopically
- tumours >2 cm located close to the pancreatic duct may require pancreatectomy or pancreaticoduodenectomy

GASTRINOMA

- tumour secreting gastrin; cause of Zollinger-Ellison syndrome

Clinical Features

- abdominal pain, PUD, severe esophagitis
- multiple ulcers in atypical locations refractory of antacid therapy

Investigations
- blood work: serum gastrin levels (usually >1,000 pg/mL), secretin stimulation test
- U/S, CT: 70-90% found in Passaro's triangle (head of pancreas medially, 2nd portion of duodenum inferiorly, and the confluence of the cystic and CBD superiorly)
- octreotide scintigraphy scan

Treatment
- 50% are malignant
- surgical resection of tumour dependent on location
- non-surgical treatment: chemotherapy, somatostatin analogues, interferon, chemoembolization
- if inoperable, vagotomy can be performed for symptomatic control

VASOACTIVE INTESTINAL PEPTIDE-SECRETING TUMOUR
- tumour secreting VIP; commonly located in the distal pancreas and most are malignant when diagnosed

Clinical Features
- severe watery diarrhea causing dehydration, weakness, electrolyte imbalance

Investigations
- blood work: serum VIP levels
- U/S, CT

Treatment
- somatostatin analogues
- surgical resection/palliative debulking

Bilious vomiting in infant is a life-threatening emergency secondary to midgut volvulus until proven otherwise

Rule of 2s for Meckel's Diverticulum
- **2%** of the population
- **2**:1 male-to-female ratio
- Symptomatic in **2%** of cases
- Found within **2** feet (10-90 cm) of the ileocecal (IC) valve
- **2** inches in length
- **2** inches in diameter
- **2** types of tissue (gastric, pancreatic)
- Often present by **2** yr of age

Pediatric Surgery

Table 25. Pediatric Surgery

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical Exam	Investigations	Treatment	Prognosis
Hydrocele (see Urology, U29) 	1-2% of live births Present at birth, majority close spontaneous by 1 yr M:F = 6:1 Prematurity	**Communicating hydroceles:** processus vaginalis fails to close with small opening for fluid to move freely between peritoneal cavity through patent processus (if opening progresses to allow passage of intestine, it is a hernia) **Noncommunicating hydroceles**: fluid trapped in tunica vaginalis; in older children, may be secondary to testicular pathology (reactive hydrocele)	Painless scrotal mass Communicating hydroceles increase in size with standing or Valsalva, may be absent in the morning and large in the evening	Transillumination suggests hydrocele Silk glove sign: gently palpating hydrocele sac over pubic tubercle feels like rubbing silk on silk	U/S if suspect pathology	Most resolve spontaneously by 1 yr Surgical repair if: – Persistence >2 yr – Pain – Fluctuating in size which suggests communication – Cosmetic reasons – Infection	<2% recurrence
Hypertrophic Pyloric Stenosis	0.03-1.0% of live births Can present at 1-20 wk, most commonly at 6-8 wk M:F = 4:1 Early erythromycin exposure (<13 d old)	Acquired pyloric circular muscle hypertrophy results in gastric outlet obstruction Hypovolemia caused by emesis of gastric contents causes hypochloremic hypokalemic metabolic alkalosis Electrolyte exchange based volume retention in kidneys results in paradoxical aciduria	Projectile non-bilious vomiting Vomiting 30-60 min after feeds Hungry after vomiting Dehydration (variable severity)	Smooth oblong 1-2 cm mass palpable above umbilicus, "olive" Visible left-to-right gastric contraction "waves" after feeding	Electrolytes (assess hypochloremia, dehydration) U/S shows pyloric length >14 mm, muscle thickness >4 mm Upper GI series necessary only when U/S unavailable or non-diagnostic will show "string sign"	Fluid resuscitate with normal saline, correct electrolyte and acid/base abnormalities with D5, 1/2NS + 20 mEq/L KCl at maintenance rate NGT decompression unnecessary Pyloromyotomy, open (Ramstedt vs. transumbilical or laparoscopic approach) Alternative therapies such as TPN/wait or atropine impractical due to long time course of effect	Pyloromyotomy curative

Table 25. Pediatric Surgery (continued)

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical Exam	Investigations	Treatment	Prognosis
Congenital Diaphragmatic Hernias 3 types: – Posterolateral (Bochdalek) – Left-sided, 85% – Right-sided, 13% – Bilateral, rare, often fatal – Anterior (Morgagni) – Hiatus	1 in 2,000 to 5,000 live births Presents within hours of life although some cases of delayed presentation M=F >10% are associated with other congenital anomalies Prenatal diagnosis common	**Left-sided**: small bowel, large bowel, stomach, and solid viscera (spleen, left lobe of liver) herniate into thorax **Right-sided**: liver, large bowel herniate into thorax Pulmonary hypoplasia Pulmonary HTN	Early respiratory distress Cyanosis Scaphoid abdomen Prenatal diagnosis	Decreased air entry ± bowel sounds in the chest Displaced heart sounds	Prenatal US/MRI ABG CXR (bowel loops in hemithorax, shifted heart) Echocardiography Genetic consultation if warranted	Intubate Orogastric suction Period of respiratory stabilization due to associated pulmonary hypoplasia (may require extracorporeal membrane oxygenation) Surgical repair after stable by hernia reduction and closure of diaphragmatic defect – open vs. thoracoscopic vs. laparoscopic with or without prosthetic or muscular patch depending on size of defect	Later presentations have better outcomes Hearing deficit (40%) Associated GERD MSK defects – chest wall and scoliotic defects a potential complication of thoracotomy Need for long-term surveillance for potential recurrence Failure to thrive Chronic lung disease if severe hypoplasia
Meckel's Diverticulum Most common remnant of vitelline duct that connects yolk sac with primitive midgut	1-3% of population M:F = 3:1 Present most frequently during first 5 yr of life Symptomatic in 2% of cases	Failure of vitelline duct to regress 5-7 wk *in utero*; 50% contain heterotopic tissue (e.g. gastric mucosa, ectopic pancreas); other associated anomalies include omphalomesenteric fistula, umbilical sinus, umbilical cyst, fibrous band	BRBPR (heterotopic gastric mucosa in Meckel's causing mucosal ulceration and bleeding in adjacent small bowel mucosa) Abdominal sepsis (Meckel's diverticulitis ± perforation) Small bowel volvulus around fibrous band	Tenderness (lower abdomen) near umbilicus	AXR Meckel scan: scan for ectopic gastric mucosa with technetium Tc99m pertechnetate IV (sensitivity 85%, specificity 95%)	Stabilize, resection by laparotomy or laparoscopy ± incidental appendectomy	Resection curative
Malrotation	1:500 live births 1/3 present by 1 wk of age, 3/4 by 1 mo of age, 90% by 1 yr of age M:F = 1:1; higher incidence among patients with cardiac anomalies, heterotaxy syndromes	Failure of gut to normally rotate around SMA with associated abnormal intestinal attachments and anatomic positions Represent a spectrum of rotational abnormalities including complete non-rotation (which is not at high risk for volvulus)	Bilious emesis is THE cardinal sign, especially if abdomen nondistended If bilious emesis in ill child with distended abdomen, consider surgical exploration to rule out volvulus Rectal bleed (late/ominous signs) Intermittent symptoms	Bilious drainage from NGT Tachycardic, pale Diaphoretic Flat abdomen Tenderness	AXR: obstruction of proximal small bowel, double-bubble sign, intestinal wall thickened Immediate UGI: dilated duodenum, duodenojejunal segment (Ligament of Treitz) right of midline and not fixed posteriorly over spinal column, "corkscrew" sign indicating volvulus U/S: "whirlpool" sign, abnormal SMA/SMV relationship indicates UGI to rule out rotational anomalies	IV antibiotics Fluid resuscitation EMERGENT LAPAROTOMY Ladd procedure: counterclockwise reduction of midgut volvulus, division of Ladd's bands, division of peritoneal attachments between cecum and abdominal wall that obstruct duodenum, broadening of the mesentery (open folded mesentery like a book and divide congenital adhesions), ± appendectomy Positioning the bowel into non-rotation (small bowel in right abdomen, large bowel in left abdomen)	Mortality related to length of bowel loss: 10% necrosis – 100% survival rate, 75% necrosis – 35% survival rate Recurrence 2-6%
Gastroschisis	1:2,000 live births Antenatal diagnosis common Increases with younger maternal age and associated with IUGR M:F = 1:1	Defect of abdominal wall, with free extrusion of intestine into amniotic cavity No specific environmental factor identified Defect in embryogenesis unclear	Not associated with genetic syndromes 10% with intestinal atresia Some cases associated with short bowel syndrome due to antenatal volvulus and necrosis of herniated bowel	Hollow viscera (stomach, small and large bowels) Defect lateral to cord (usually right) Bowel may be inflamed, thickened, matted, foreshortened Defect size variable	Prenatal U/S Elevated MS-AFP	NGT decompression IV fluids IV antibiotics Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with silo May have bowel dysmotility requiring motility medications	>90% survival rate
Omphalocele	1:5,000 live birth Antenatal diagnosis common Lower gestational age Increased maternal age M:F = 1.5:1	Defect of abdominal wall, with extrusion of sac covered viscera (amnion, Wharton's jelly, peritoneum) Duhamel's theory – failure of body wall morphogenesis	Associated with genetic syndromes 30-70% (e.g. Pentalogy of Cantrell, congenital heart disease, Beckwith-Wiedemann syndrome) Associated pulmonary hypoplasia	Hollow viscera (stomach, small and large bowels, often liver) Cord on the sac	Prenatal U/S Elevated MS-AFP	NGT decompression IV fluids IV antibiotics Small defect (<2 cm): Primary closure Medium (2-4 cm) and large (>4 cm) defects best treated with silver sulfadiazine to promote epithelialization coupled with compression dressing to allow gradual reduction, followed by future repair with or without mesh	40-70% survival rate Higher survival rates most likely related to antenatal mortality of fetuses with giant omphaloceles

Table 25. Pediatric Surgery (continued)

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical Exam	Investigations	Treatment	Prognosis
Umbilical Hernias	Incidence 2-14% Increases with prematurity Decreases with increasing age	Incomplete closure of peritoneal and fascial layers within umbilicus by 5 yr	Majority asymptomatic Majority spontaneously resolve by age 5 Incarceration prior to age 5 very rare Most symptoms occur in late adolescence or adulthood	Protrusion from umbilicus Important to differentiate from less common abdominal wall hernias that do not spontaneously resolve (e.g. epigastric hernias) Most umbilical fascial defects >1.5 cm in infancy will not close spontaneously	None if uncomplicated	Repair if not spontaneously closed by age 5 Earlier repair of large "proboscoid" hernias with extensive skin stretching may be warranted for cosmetic reasons Simple primary closure of fascial defect	Low risk of recurrence
Intestinal Atresia	Incidence 2-14% May be antenatally diagnosed by dilated bowel loops or "double-bubble" sign on x-ray for duodenal atresia Decreasing with increasing age	Duodenal – failure of bowel to recanalize after endodermal epithelium proliferation (wk 8-10) Jejunal/ileal – acquired as a result of vascular disruption → ischemic necrosis → resorption of necrotic tissue → blind distal and proximal ends Colonic – mechanism unknown, thought to be similar to small bowel atresia	Gastric distension and vomiting (usually bilious) Duodenal – may be associated with other anomalies (tracheoesophageal fistula, cardiac, renal, and vertebral anomalies), 24-28% have Down syndrome Jejunal/ileal – within 2 d of birth, may be associated with CF Colonic – within 3 d of birth	Complete physical Special attention to abdominal exam Perineum and anus Include evaluation of respiratory distress and signs of volume depletion Congenital anomalies Jaundice	Contrast enema ± UGI with small bowel follow through (SBFT) Group and screen INR and PTT if for surgery	NPO NGT decompression Fluid resuscitate TPN Broad spectrum antibiotics Duodenal – duodenoduodenostomy or duodenojejunostomy Jejunal/ileal – primary anastomosis; or if atresia associated with short bowel then may create end stoma or defer surgery for bowel lengthening procedures Colonic – primary anastomosis	Long-term survival Duodenal – 86% Jejunal/ileal – 84% Colonic – 100%
Hirschsprung's Disease	1:5,000 births M:F = 3:1 to 4:1, approaches 1:1 when whole colon involved Can have aganglionosis of small bowel as well Familial Hirschsprung's in <5% of cases	Defect in migration of neurocrest cells to intestine resulting in aganglionic bowel that fails to peristalse and internal sphincter that fails to relax (internal anal sphincter achalasia) causing functional and partial mechanical obstruction, respectively; always starts in the rectum and variable involvement proximally; RET mutation	Failure to pass meconium spontaneously within 48 h of life is the classic history (95% of normal children should pass meconium within 24 h, and the remaining 5% within 48 h) Symptoms of bowel obstruction: abdominal distension, constipation, bilious emesis Enterocolitis/sepsis Failure to thrive	± abdominal distension Squirt/blast sign	Rectal biopsy (gold standard) – look for aganglionosis and neural hypertrophy AXR Contrast enema to find narrow rectum and transition zone Anal manometry unreliable in infants – classic finding is absence of rectoanal inhibitory reflex	Surgical resection of aganglionic intestinal segment and anastomosis of remaining intestine to anus Either in newborn period or staged if extensive aganglionosis	Most have normal/near-normal anorectal function Complications: Fecal incontinence and constipation, post-operative enterocolitis (medical emergency if progresses to sepsis)
Cryptorchidism	2-5% of term males – most of these descend spontaneously by 6 mo of age 1% of males do not spontaneously descend	Idiopathic Descent is mediated by descendin which is created in response to testosterone Descent usually begins at 28 wk	Palpable testicle within inguinal canal or testicle which can be milked down into scrotum (called retractile testis) Occasionally no palpable testis as it is intra-abdominal Consider other congenital abnormalities	Bi-annual testicular exam with palpation Distinguish truly undescended testis from retractile testis (which is "high" testis due to hyperactive cremasteric muscles)	Depends on age of presentation U/S or MRI if no palpable testis Older child: LH, FSH, MIS, hCG stimulation test for gonadotropin production Infant: U/S, FSH, LH, karyotype, MIS, 17-hydroxy-progesterone	hCG to stimulate testosterone production and descent Orchidopexy – especially if undescended by age 6 mo-2 yr	Orchidopexy Decreased risk of torsion and blunt trauma to testicle No effect on malignant potential of testicle Descent can preserve spermatogenesis if performed by 1 yr of age 1/1,000 risk for testicular cancer (population risk is 1/4,000)

Table 25. Pediatric Surgery (continued)

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical Exam	Investigations	Treatment	Prognosis
Intussusception	Most common cause of bowel obstruction between the ages of 6-36 mo 26/100,000 newborns M:F = 3:2 Pathologic lead points: enlarged Peyer's patches due to viral infections of the GI tract, polyps, Meckel's diverticulum CF, lymphoma, IBD may increase risk	Idiopathic is most common Usually starts at ileocecal junction Telescoping of bowel into itself causing an obstruction and vascular compromise	Acute onset of abdominal pain which is classic episodic "colicky" pain Vomiting ± bilious Abdominal mass Currant-jelly stool suggests mucosal necrosis and sloughing	Abdominal exam Palpate for masses (especially sausage shaped upper abdominal mass) and tenderness Signs of bowel obstruction: distended abdomen Look for localized peritonitis which suggests transmural ischemia	AXR for signs of bowel obstruction or perforation U/S if suspect pathology	If peritonitis, then consider operative management Non-operative management involves reduction via air contrast enema Operative reduction can be done open or laparoscopically Resection of involved colon if failure to reduce or bowel appears compromised	10% recurrence rate If recurrent = more likely non-idiopathic In successfully reduced by enema in older children allow 2 wk resolution of edema then perform SBFT to rule out pathologic lead points
Tracheoesophageal Fistula (TEF)	1:3,000-1:4,500	Associated anomalies in 50%: VACTERL association (see Pediatrics, P42)	Varies with type of fistula May have history of maternal polyhydramnios May present after several months (if no associated esophageal atresia) of non-bilious vomiting, coughing, cyanosis with feeds, respiratory distress, recurrent pneumonia, frothy bubbles of mucus in mouth and nose that return after suctioning		X-ray: anatomic abnormalities, NGT curled in pouch	Investigate for other congenital anomalies, early repair by surgical ligation to prevent lung damage and maintain nutrition and growth	Complications: pneumonia, sepsis, reactive airways disease Following repair: esophageal stenosis and strictures at repair site, GERD and poor swallowing (i.e. dysphagia, regurgitation)
Inguinal Hernias	5% of all term newborns 2x risk and more likely bilateral if pre-term M:F = 4:1 Low birth weight increases risk 1/5 inguinal hernias will become incarcerated if patient is <1 yr old Incarceration is more common in females Associated with other conditions: androgen insensitivity, connective tissue diseases	All infant hernias are indirect: descent of intra-abdominal contents through the internal inguinal ring through a patent tunica vaginalis	Most common presentation: painless intermittent mass in groin, may also note extension into scrotum (scrotal mass in absence of inguinal mass is a hydrocele) If incarcerated: tender, vomiting, firm mass, erythema then cyanosis of mass may be noted	Palpate for "bag of worms" suggests possible testicular varicocele Biannual testicular exam + palpation along inguinal canal to evaluate for any masses "Silk sign" – palpable thickening of cord Mass palpated at external inguinal ring and reducible through inguinal canal into abdomen Must always try reduction to confirm that hernia is not incarcerated	Physical exam is gold standard U/S only if physical exam uncertain (e.g. in small infants where exam can be difficult)	Manual reduction – to relieve acute symptoms Herniorraphy – definitive treatment by reduction of herniated contents and high ligation of sac for indirect hernias Laparoscopic or open techniques	Risk of recurrence after surgical reduction <3% but higher if repair done in premature infants or if hernia was incarcerated/ strangulated at repair

All inguinal hernias of infancy and childhood require repair at the earliest convenience; emergent repair if incarcerated/strangulated

Skin Lesions

- see Dermatology, D35; Emergency Medicine, ER17; Plastic Surgery, PL5

Common Medications

Antiemetics	• dimenhydrinate (Gravol®) 25-50 mg PO/IV/IM q4-6h prn • prochlorperazine (Stemetil®) 5-10 mg PO/IV/IM bid-tid prn • metoclopramide (Maxeran®) 10 mg IV/IM q2-3h prn, 10-15 mg PO qid (30 min before meals and qhs) • ondansetron (Zofran®) 4-8 mg PO q8h prn • granisetron (Kytril®) 1 mg PO bid (for nausea from chemotherapy/radiation)
Analgesics	• acetaminophen ± codeine (Tylenol® #3/plain) 1-2 tabs q4-6h PO/PR prn • hydromorphone i-ii tabs PO q4h prn, 0.5-2 mg IV q3-4h prn • ibuprofen 200-400 mg PO q4-6h prn • morphine 2.5-10 mg IM/SC q4-6h prn + 1-2 mg IV q1h prn for breakthrough • ketorolac (Toradol®) 30-60 mg IM/IV q6h prn • Percocet® (acetominophen/oxycodone, 325/5 mg) 1-2 tabs PO q4-6h prn
DVT Prophylaxis	• heparin 5,000 units SC bid, if cancer patient then heparin 5,000 units SC tid • dalteparin (Fragmin®) 5,000 units SC daily • enoxaparin (Lovenox®) 40 mg SC daily
Antidiarrheals	• loperamide (Imodium®) 4 mg PO initially, then 2 mg PO after each loose stool up to 16 mg/d • diphenoxylate + atropine (Lomotil®) 2 tabs/10 mL PO qid
Laxatives	• sennosides (Senokot®) 1-2 tabs qhs • docusate sodium (Colace®) 100 mg PO bid • glycerine suppository 1 tab PR prn • lactulose 15-30 mL PO qid prn • milk of magnesia (MOM) 30-60 mL PO qid prn • bisacodyl (Dulcolax®)10-15 mg PO prn
Sedatives	• zopiclone (Imovane®) 5-7.5 mg PO qhs prn • lorazepam (Ativan®) 0.5-2 mg PO/SL qhs prn
Antibiotics	• cefazolin (Ancef®) 1 g IV/IM on call to OR or q8h – GP except *Enterococcus*, GN only *E. coli*, *Klebsiella,* and *Proteus* • cefalexin (Keflex®) 250-500 mg PO qid – *Listeria*, GP except *Enterococcus*, GN only *E. coli*, *Klebsiella,* and *Proteus* • ceftriaxone 1-2 g IM/IV q24h – broad coverage including *Pseudomonas* • ampicillin 1-2 g IV q4-6h – *Listeria*, GP (*Enteroccus*) except *Streptococcus* and *E. coli*, oral anaerobes except *Bacteroides* • gentamicin 3-5 mg/kg/d IM/IV divided q8h; monitor creatinine, gentamicin levels – GN including *Pseudomonas* • ciprofloxacin 400 mg IV q12h, 500 mg PO bid – GN including *Pseudomonas* • metronidazole (Flagyl®) 500 mg PO/IV bid (500 mg PO tid for *C. difficile*) – anaerobes • clindamycin 600-900 mg IV q8h, 150-400 mg PO qid – GP except *Enterococcus*, anaerobes • piperacillin/tazobactam 4.5 mg IV q6h – GP, GN, and anaerobes • vancomycin 1g IV q12h – GP and MRSA • sulfamethoxazole/trimethoprim DS (Septra®) PO bid – GP, GN including norcardia
Over-the-Counter Medications	• Pepto-Bismol® (bismuth subsalicylate) 2 tabs or 30 mL PO q30min-1h up to 8 doses/d side effects: black stools, risk of Reye's syndrome in children • Alka-Seltzer® (ASA + citrate + bicarbonate) 2 tabs in 4 oz water PO q4h prn, max 8 tabs • Maalox® (aluminum hydroxide + magnesium hydroxide) 10-20 mL or 1-4 tabs PO prn • Tums® (calcium carbonate) 1-3 g PO q2h prn • Rolaids® (calcium carbonate and magnesium hydroxide) 2-4 tabs PO q1h prn, max 12 tabs/d

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