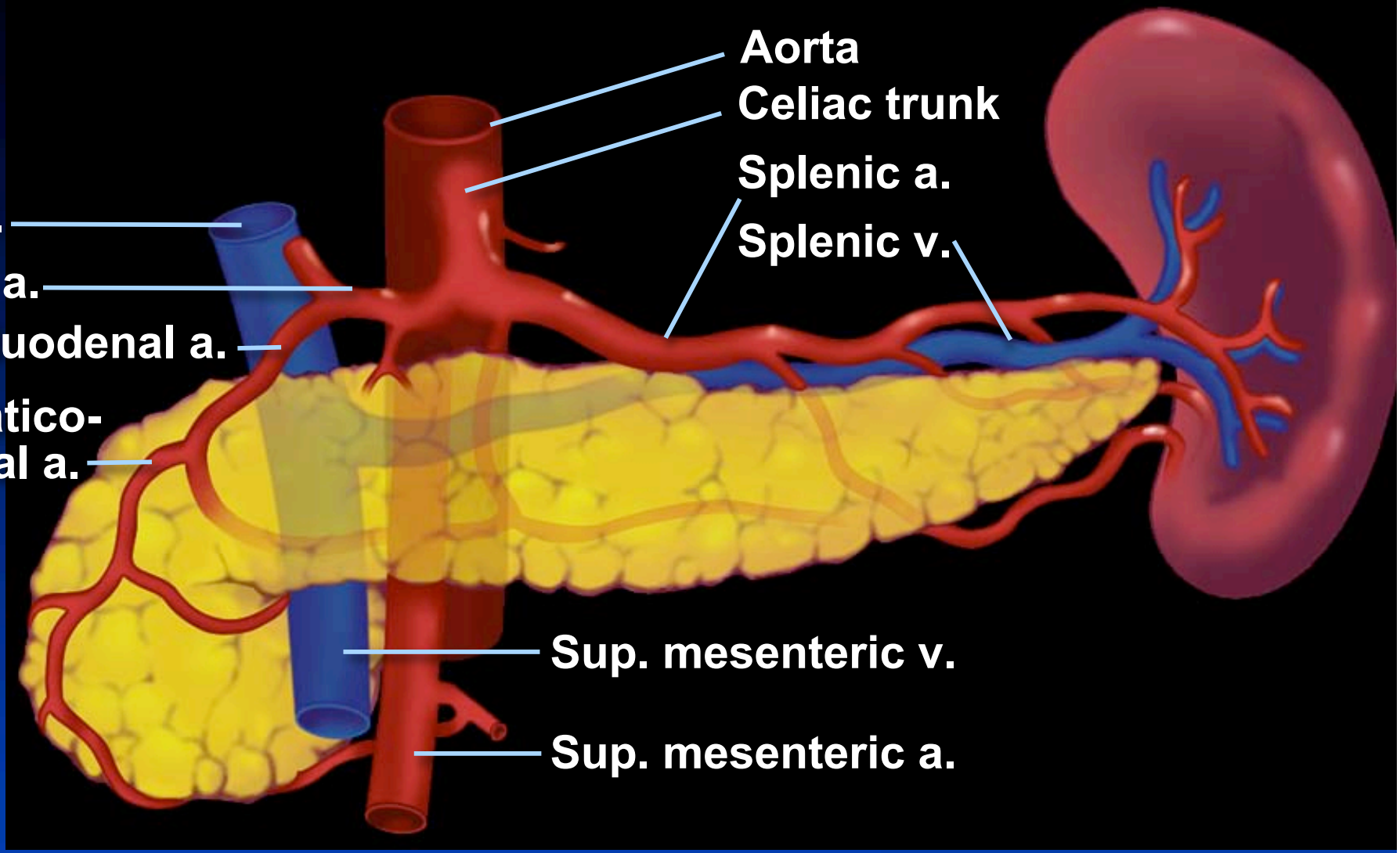
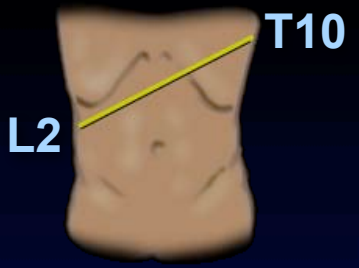
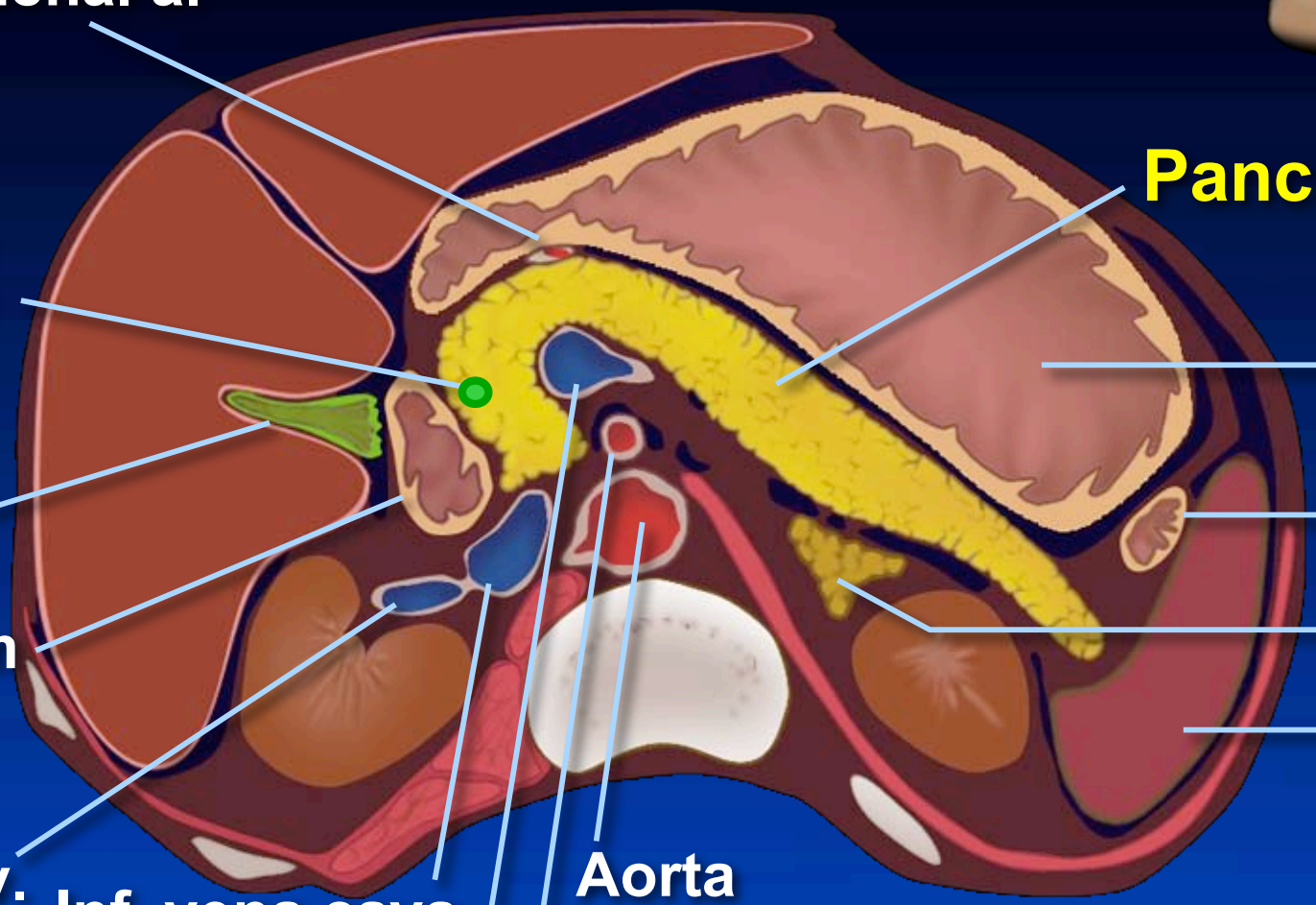
Pancreatic Vascular Supply



Cross-Sectional Anatomy





Gastroduodenal a.

Common bile duct

Gall bladder

Duodenum

R. renal v.

Inf. vena cava

S. mesenteric v.

Aorta

S. mesenteric a.

Pancreas

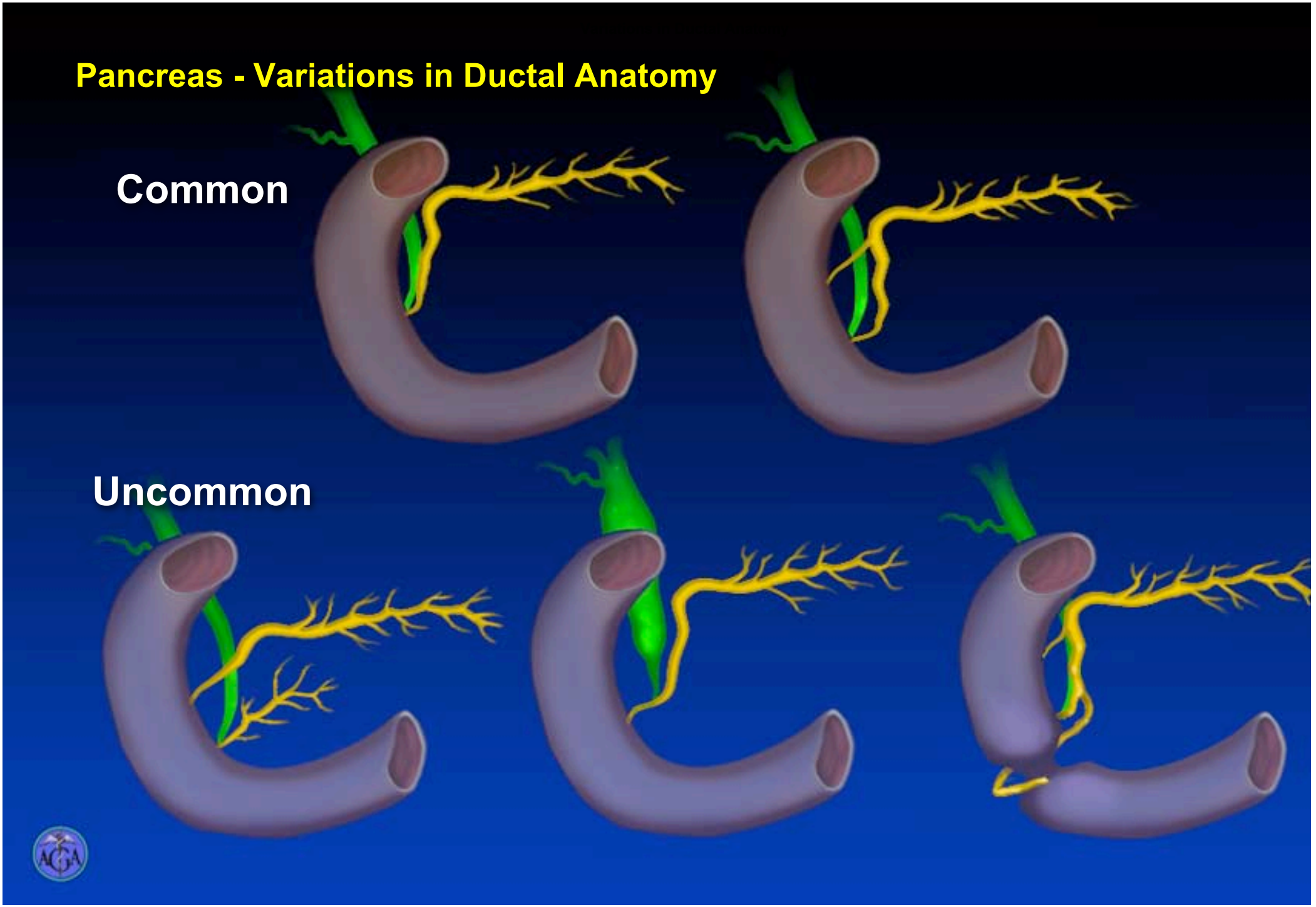
Stomach

Splenic flexure

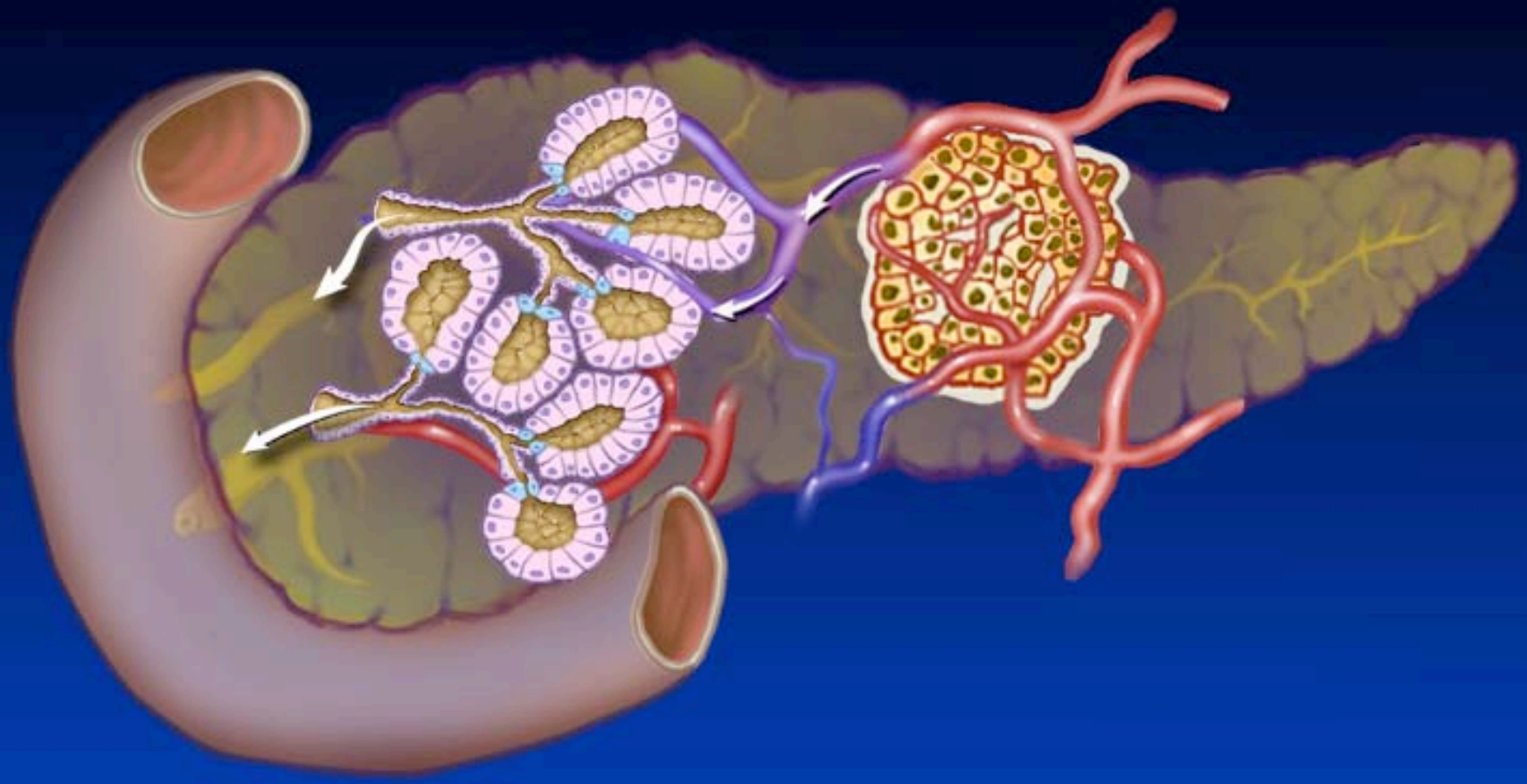
L. adrena

Spleen

Pancreas - Variations in Ductal Anatomy



Endocrine and Exocrine Pancreas Secretion

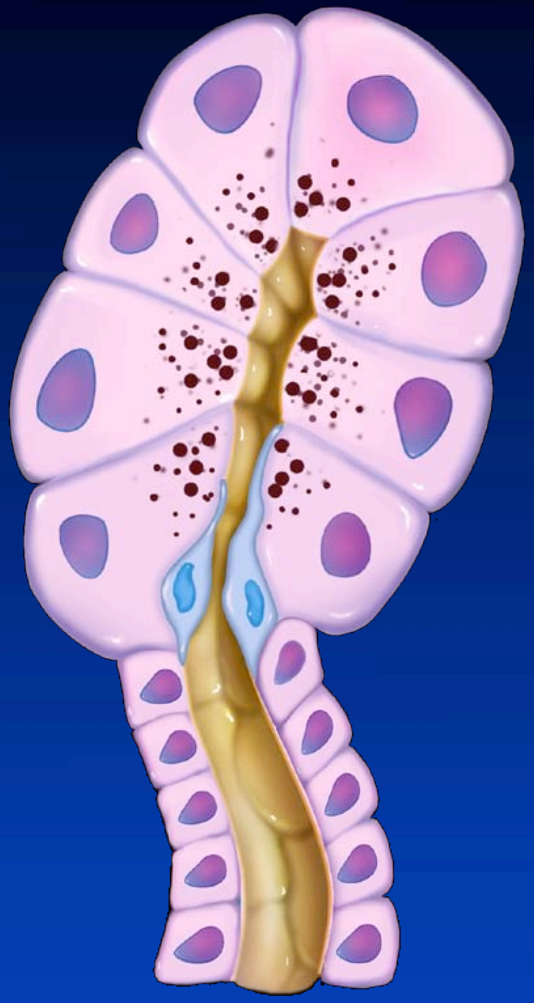


Exocrine Pancreas

Major Functional Units

Acinus

Duct



Secretory products

Proenzymes and enzymes

Secretory products

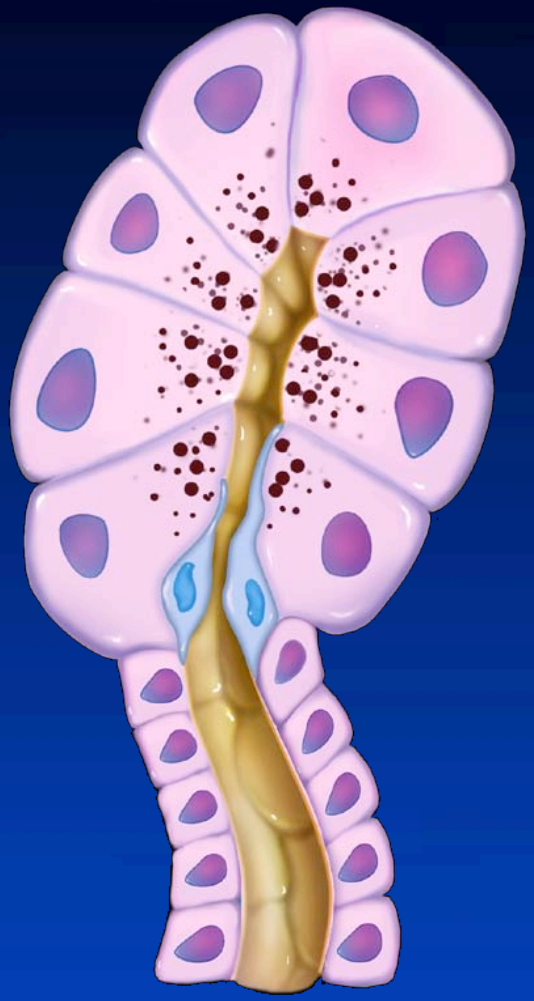
Water and electrolytes

Regulation

Endocrine

CCK
Secretin

Secretin

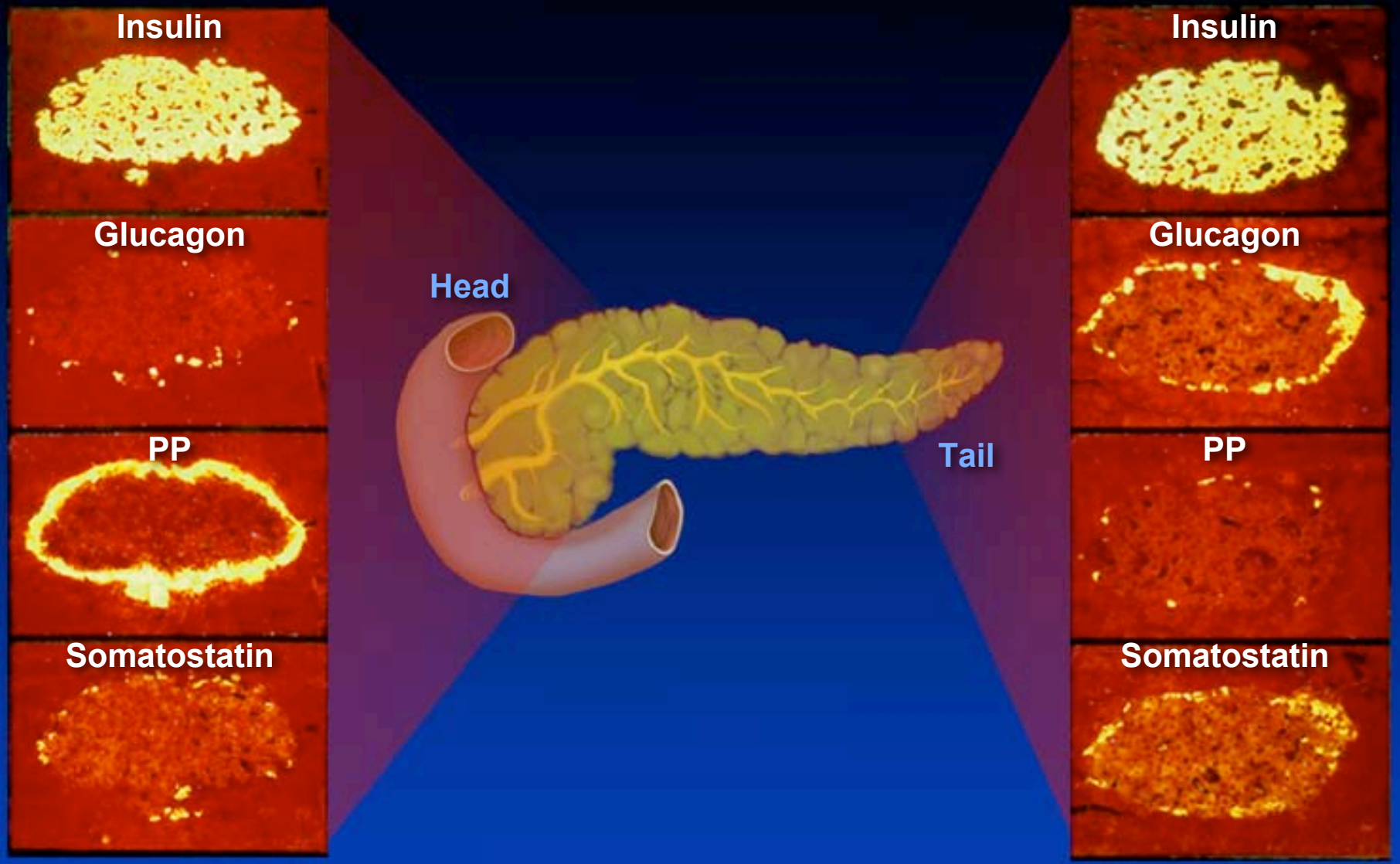


Neurocrine

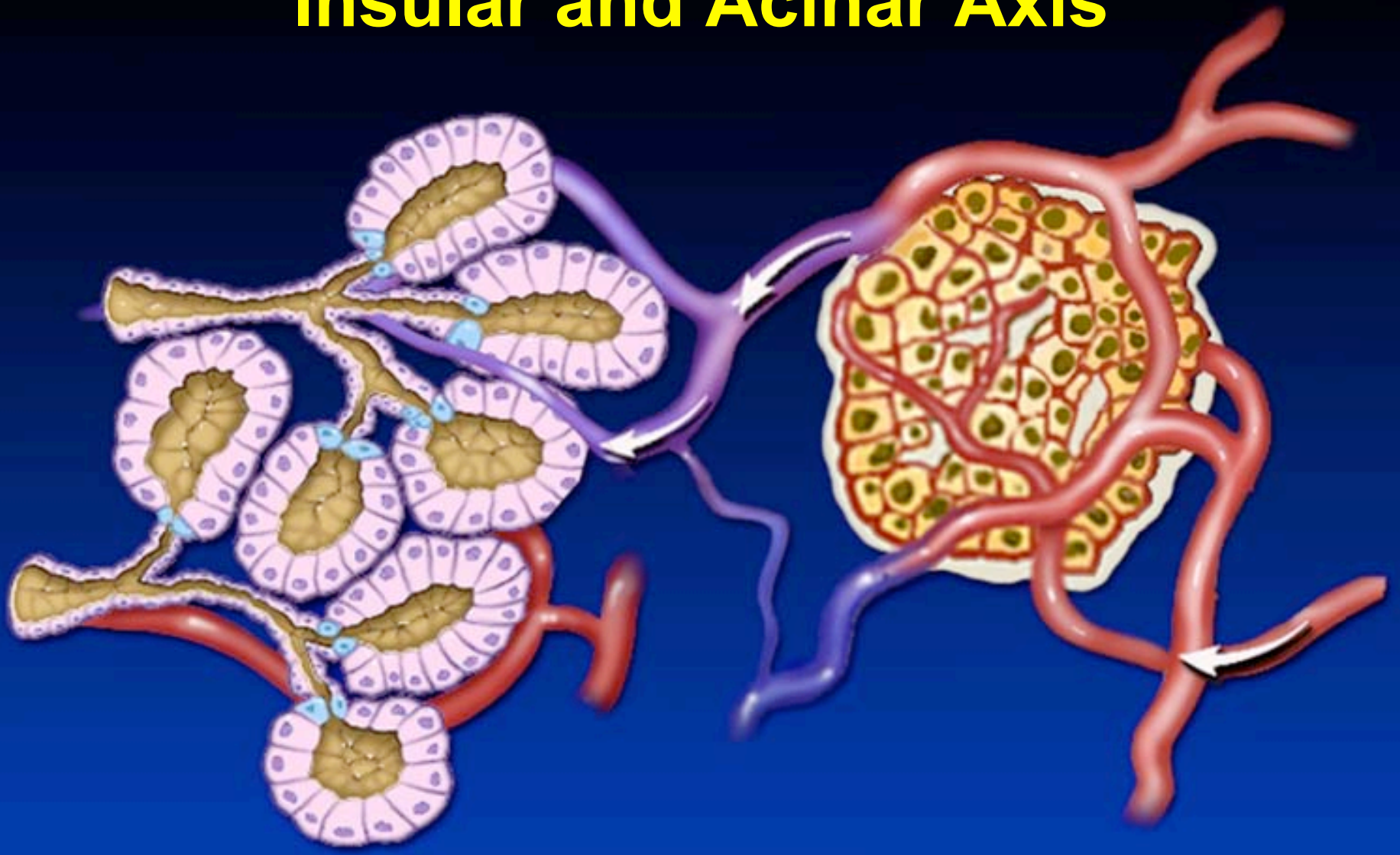
Ach
GRP
VIP
Substance P

Ach

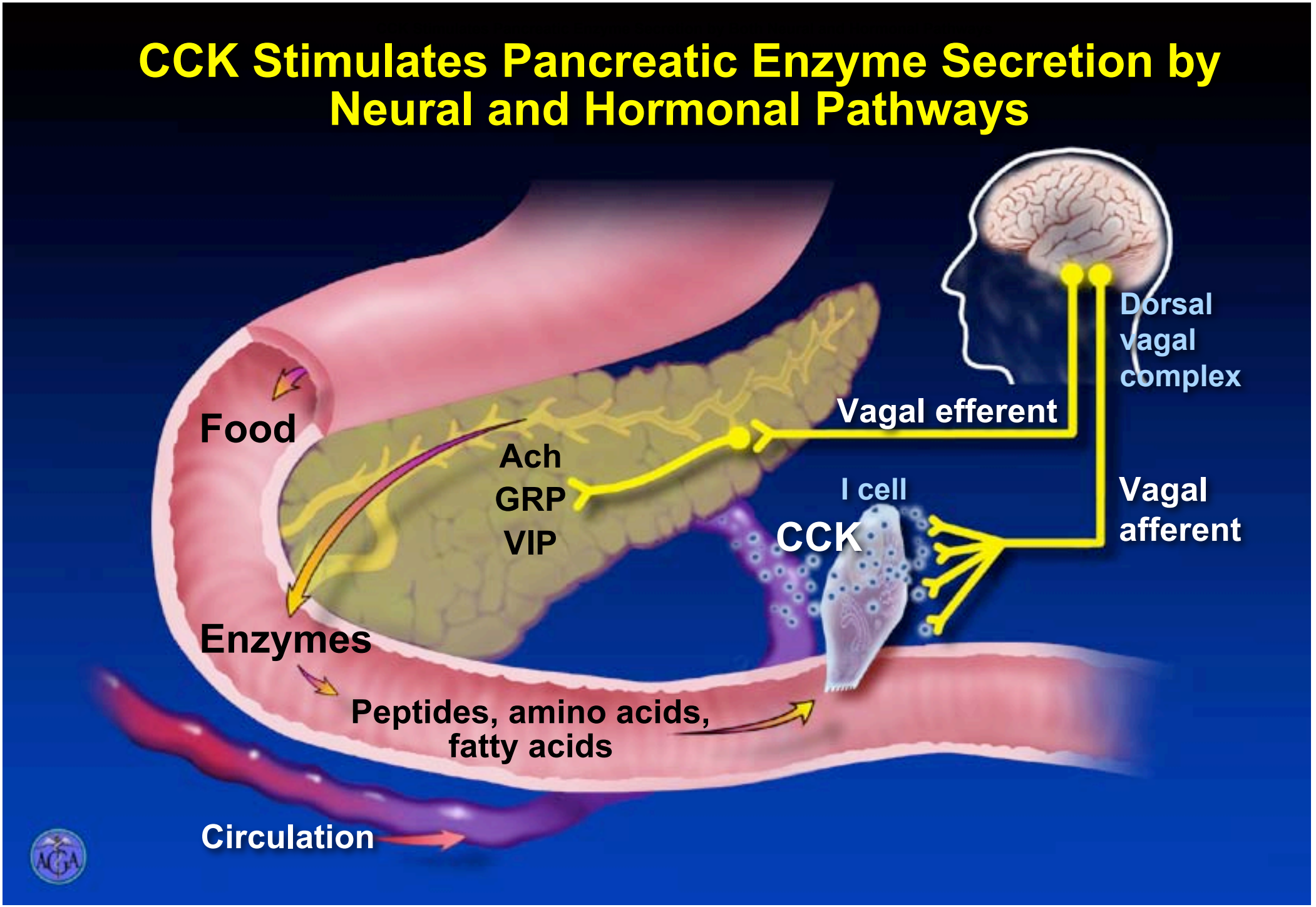
Regional Differences in Islet Hormones



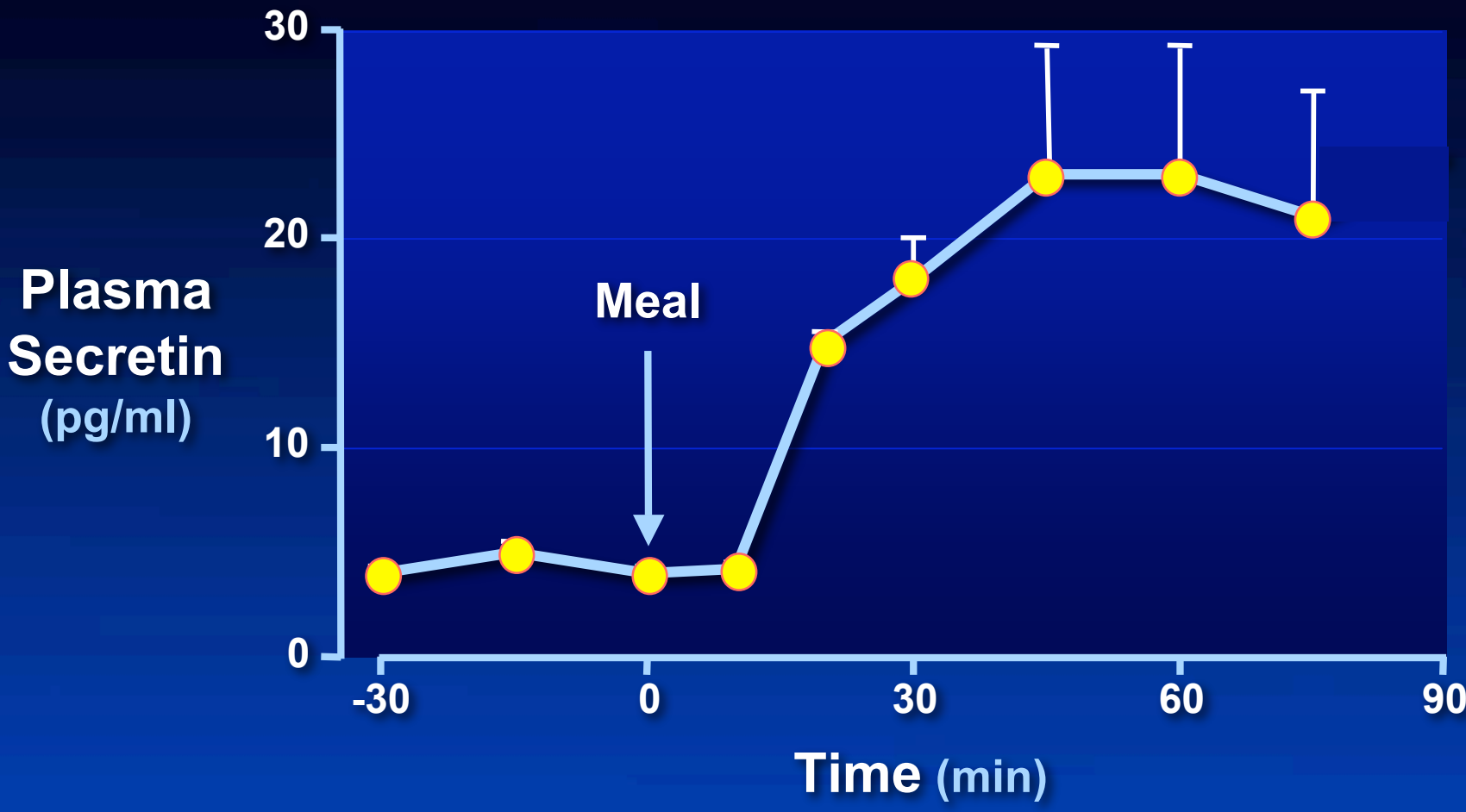
Insular and Acinar Axis



CCK Stimulates Pancreatic Enzyme Secretion by Neural and Hormonal Pathways



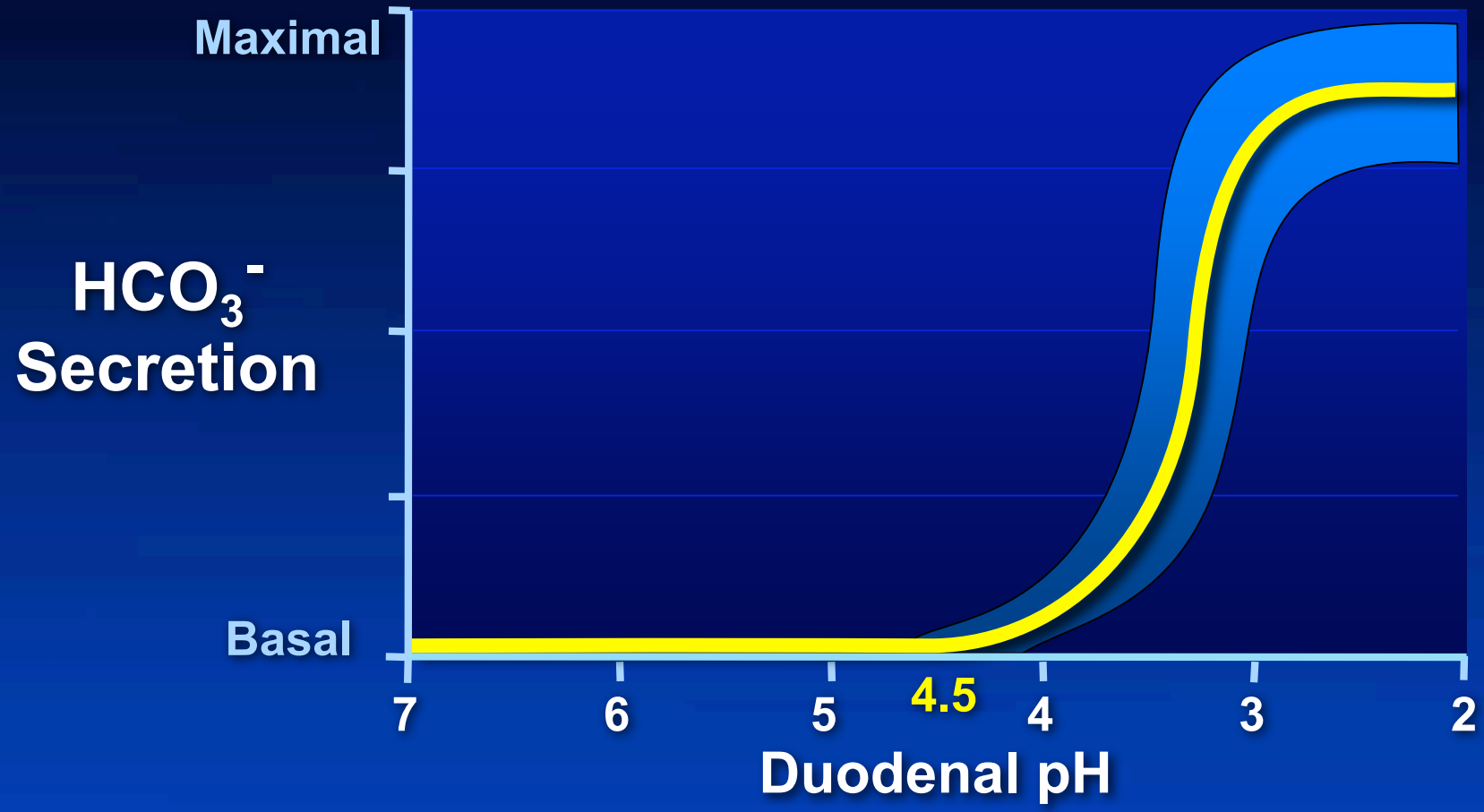
Plasma Secretin Levels



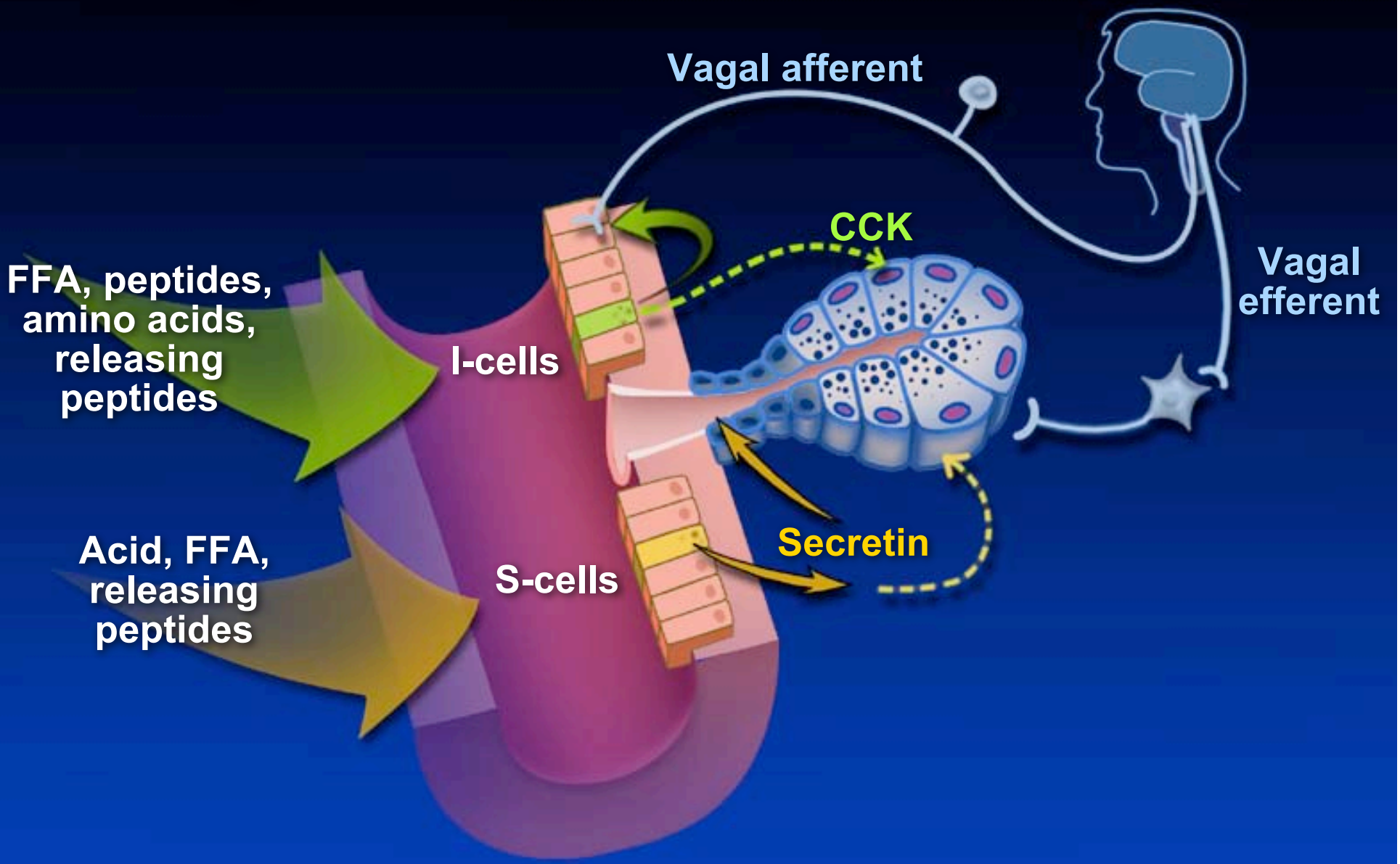
MS Kim, et al., AJP 1979; 236:E359

Pancreas

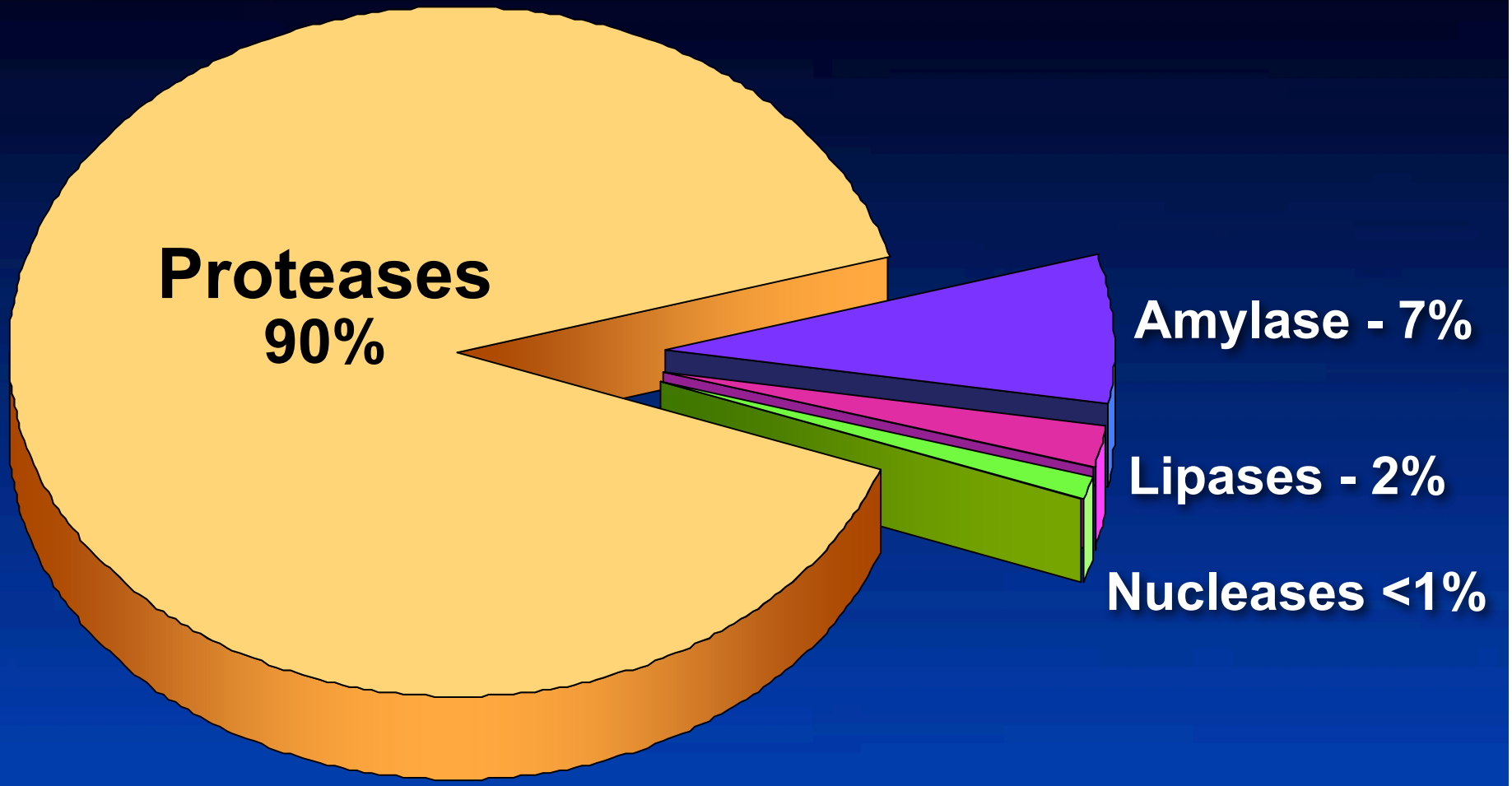
Bicarbonate Secretion is Related to Duodenal pH



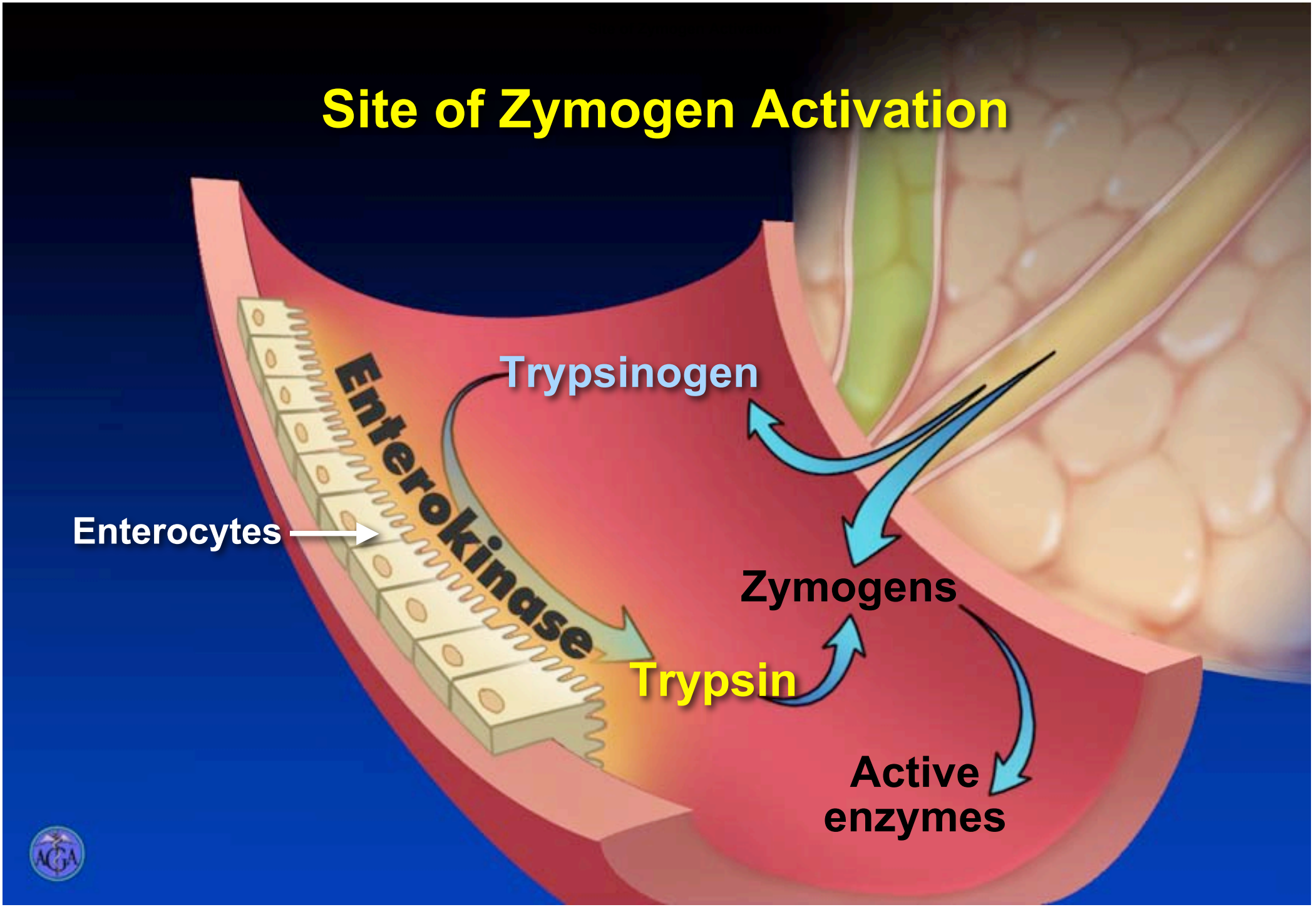
Regulation of Pancreatic Secretion



Classes of Enzymes in Pancreatic Juice

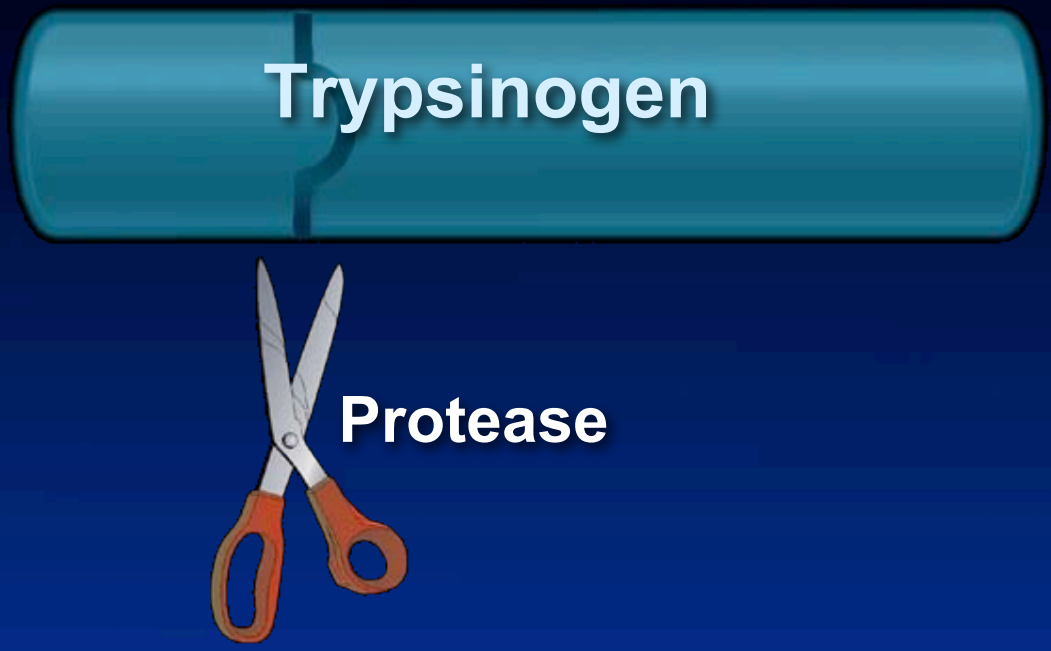


G. Scheele, et al., Gastroenterology 1981; 80:461

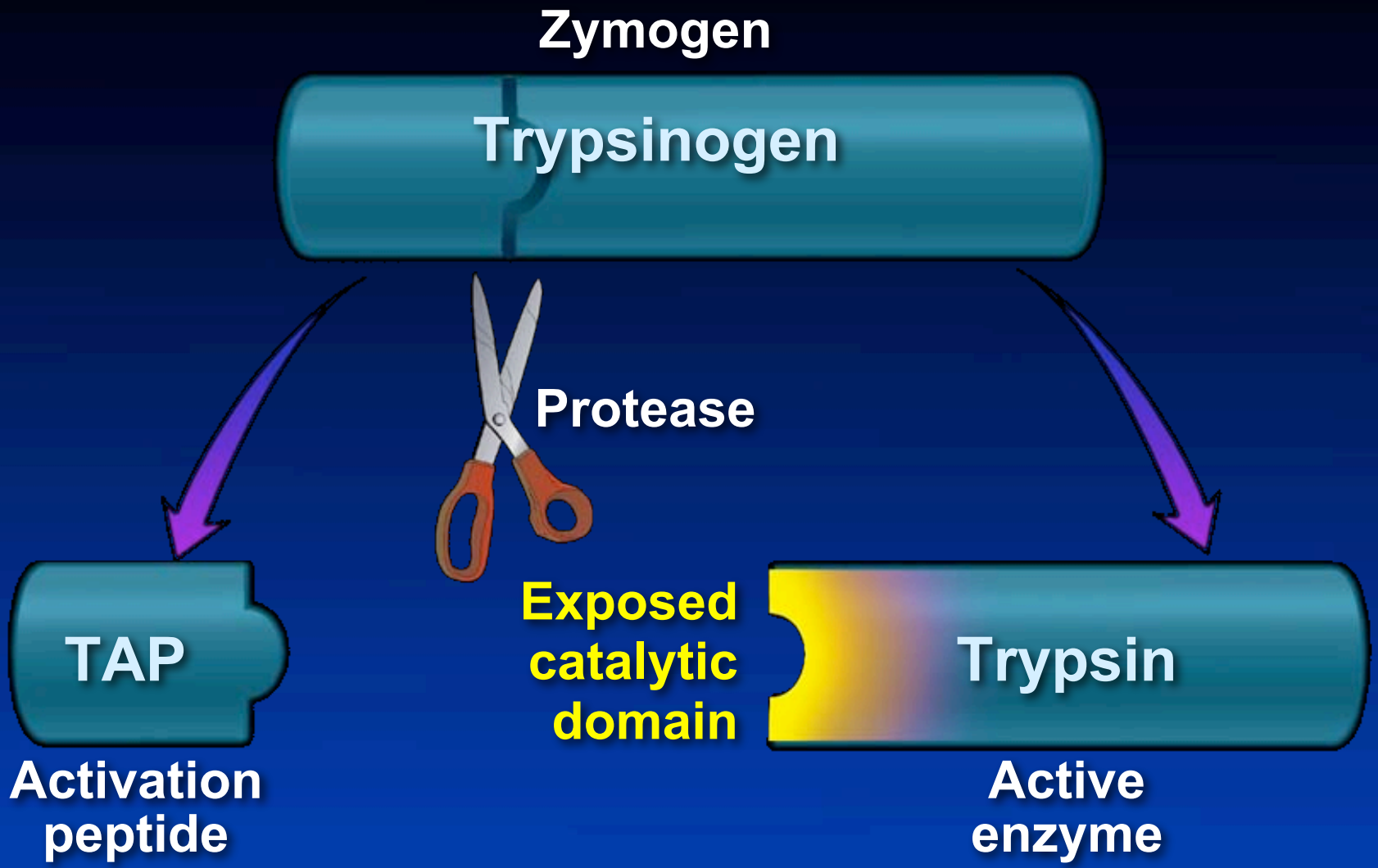

Site of Zymogen Activation
Trypsinogen
Enterokinase
Enterocytes
Zymogens
Trypsin
Active enzymes

Mechanism of Activation

Zymogen

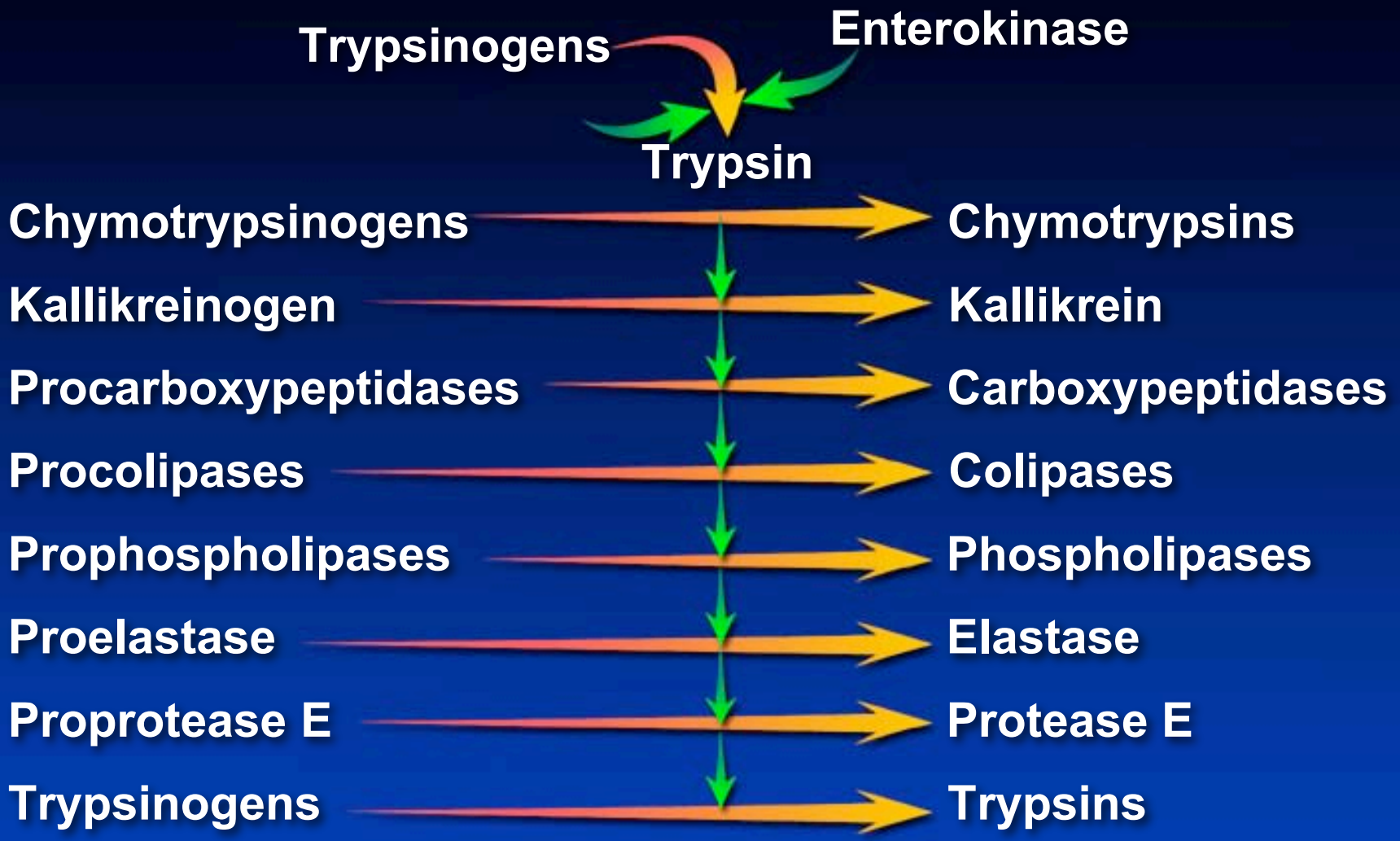


Mechanism of Activation



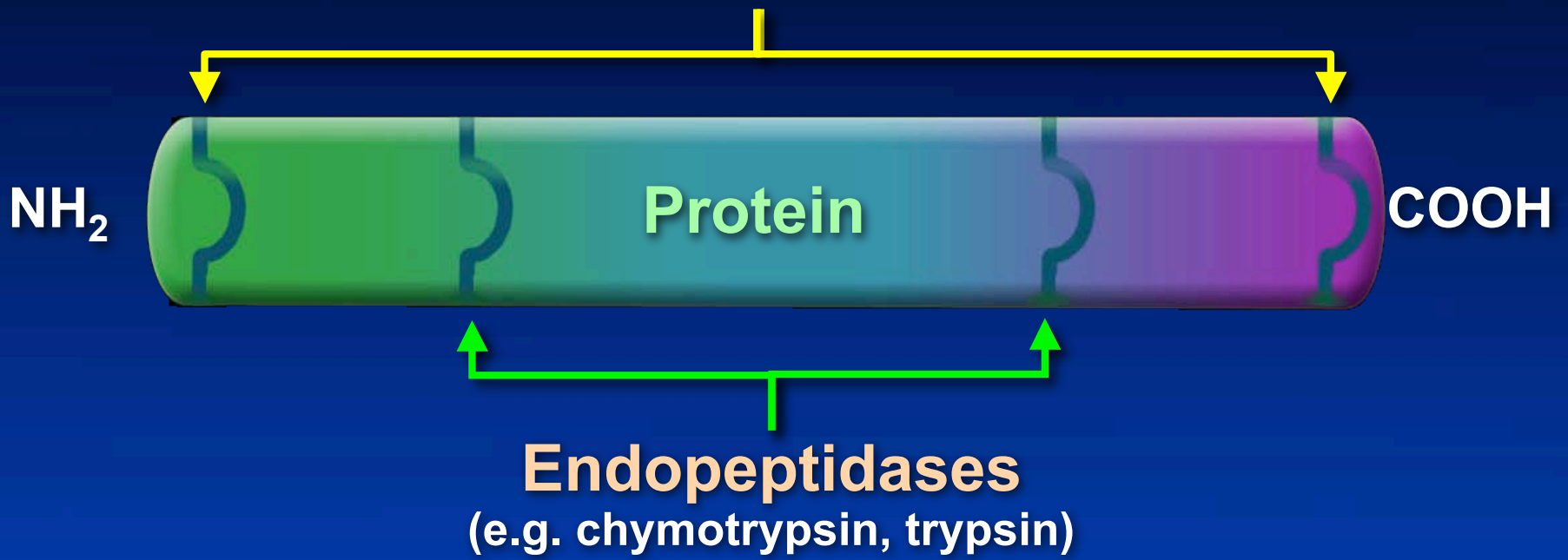
Pancreatic Enzymes

Zymogen Activation Cascade



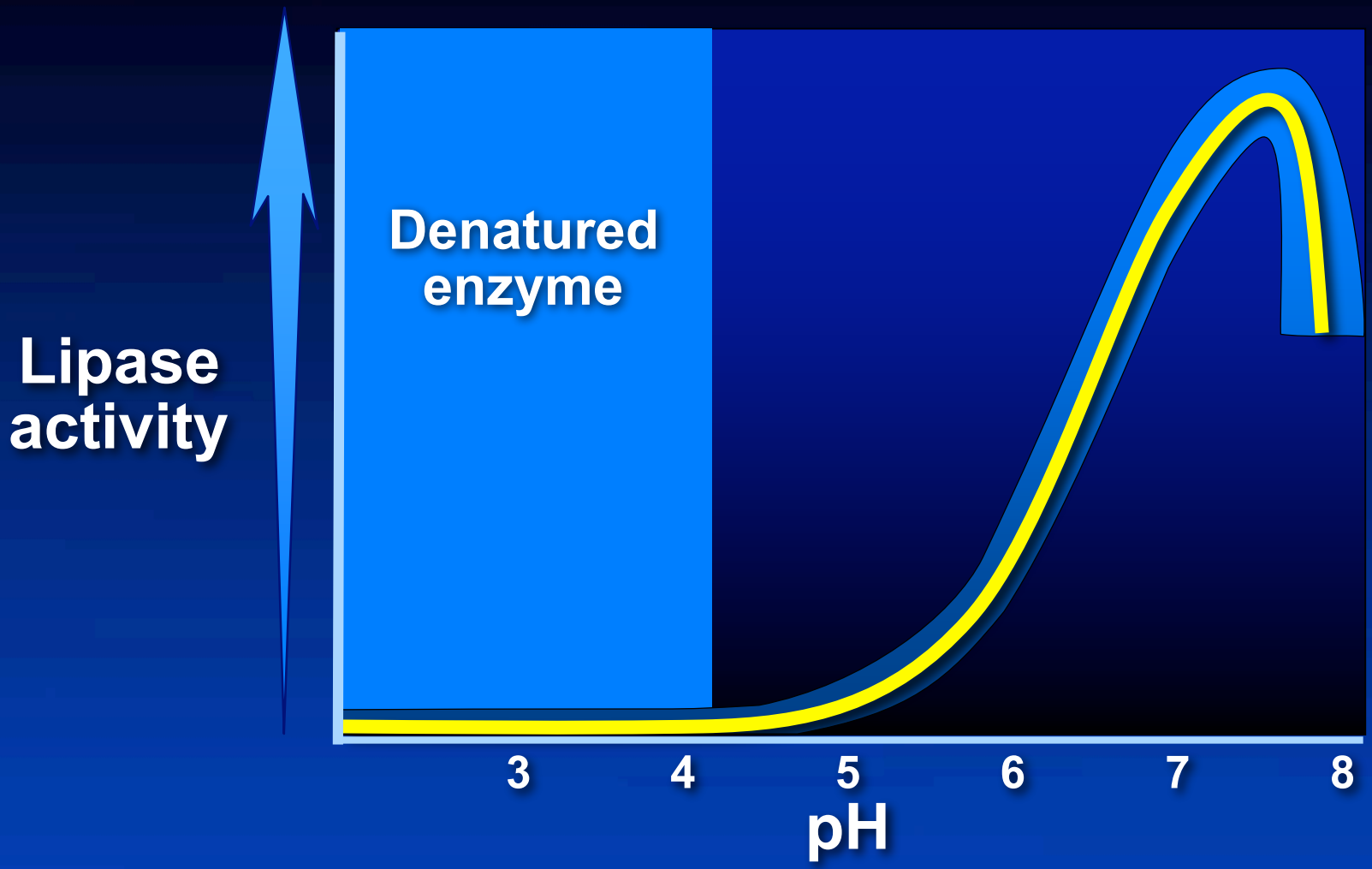
Pancreatic Enzymes

Protease Actions



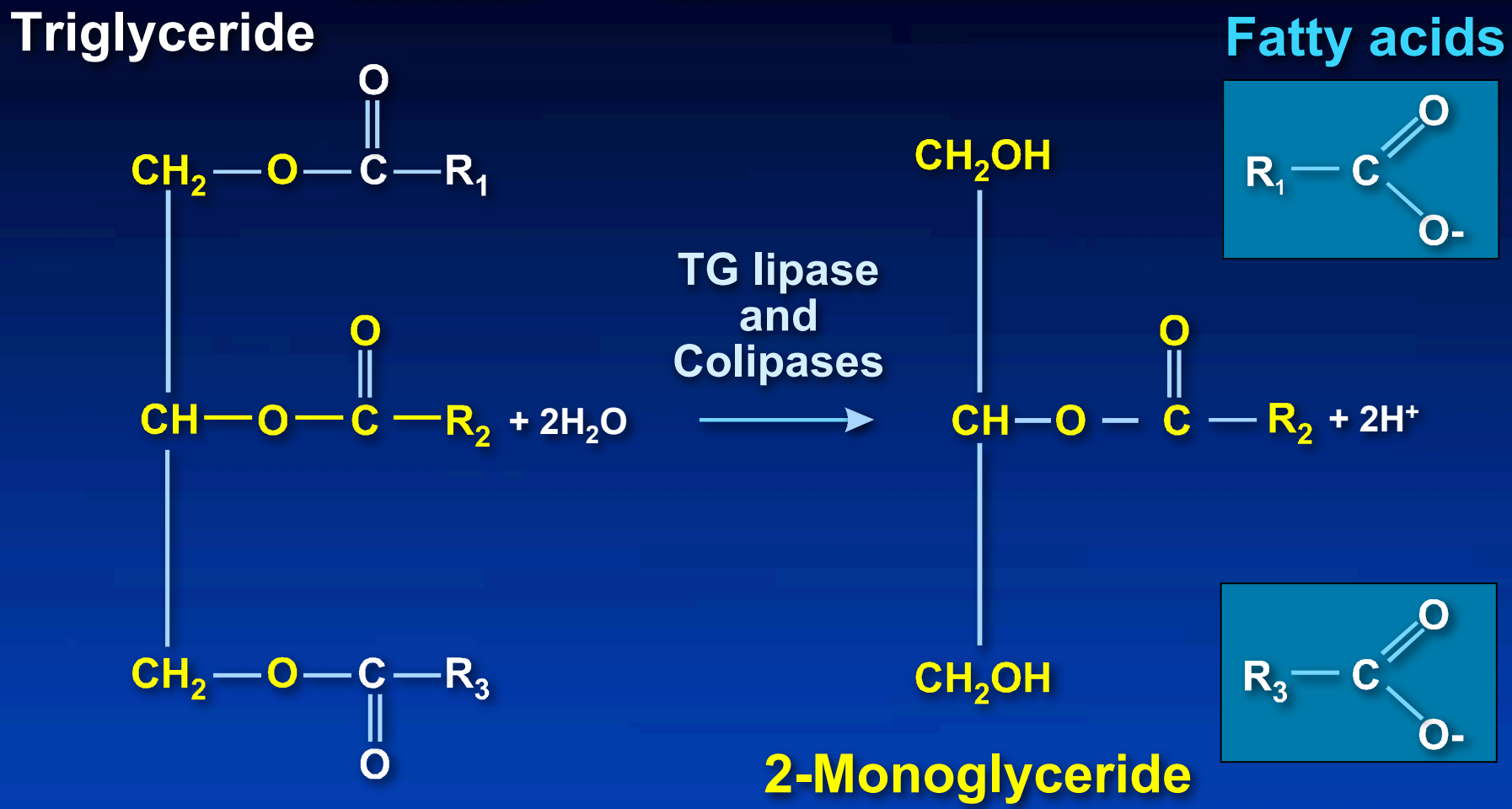
Pancreatic Enzymes

Luminal pH And Lipase Activity



Pancreatic Enzymes

Triglyceride Hydrolysis

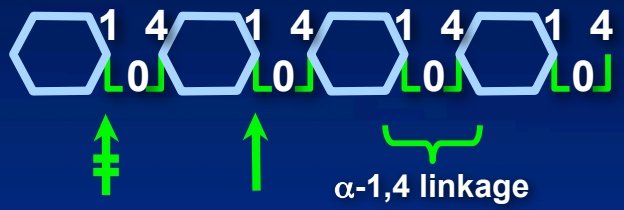


Pancreatic Enzymes

Pancreatic α-Amylase is an Endoglycosidase

Substrate

Amylose

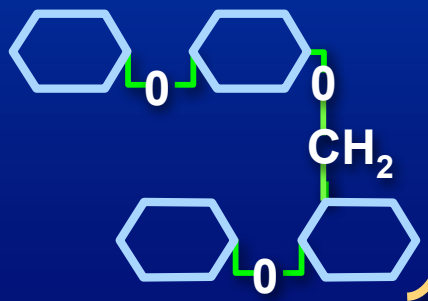


Products

Maltose

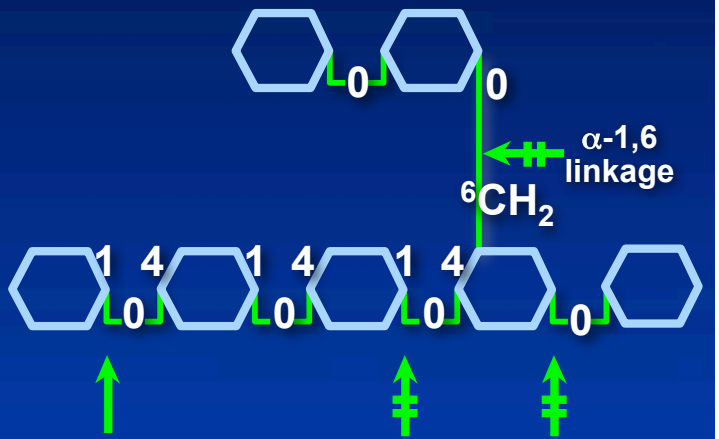
Maltotriose

α-limit-dextrins



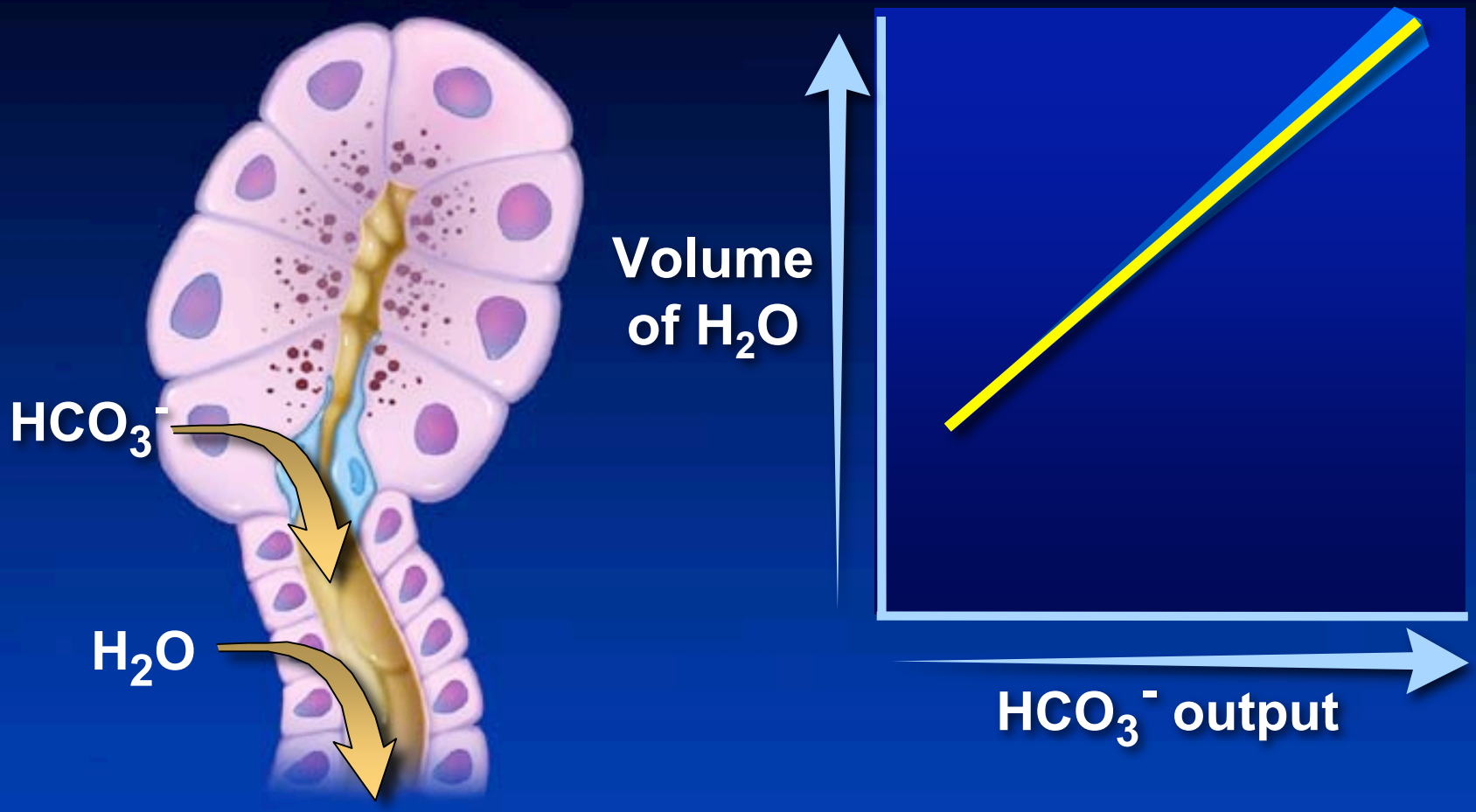
Substrate

Amylopectin and Glycogen

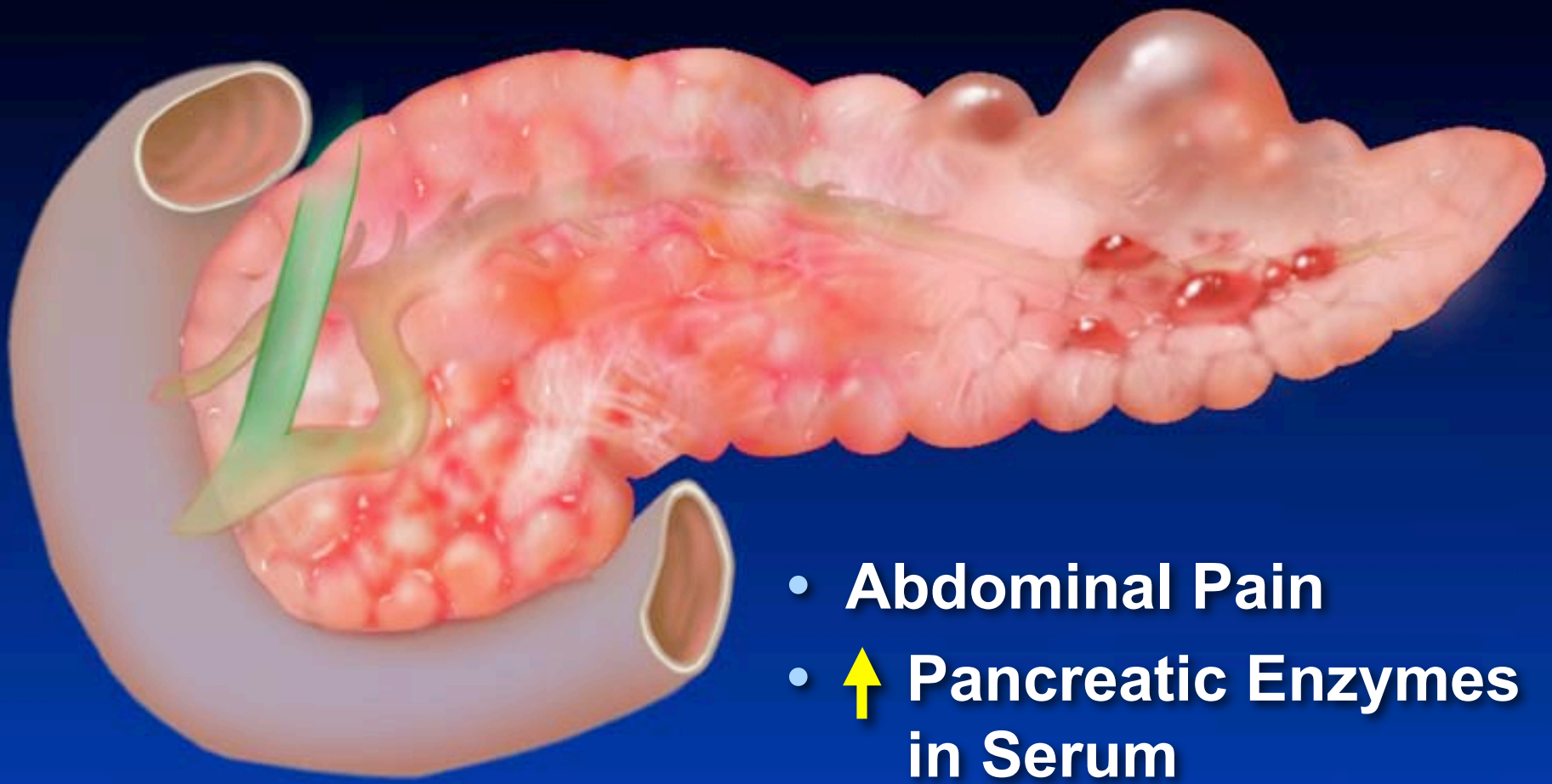


Pancreas

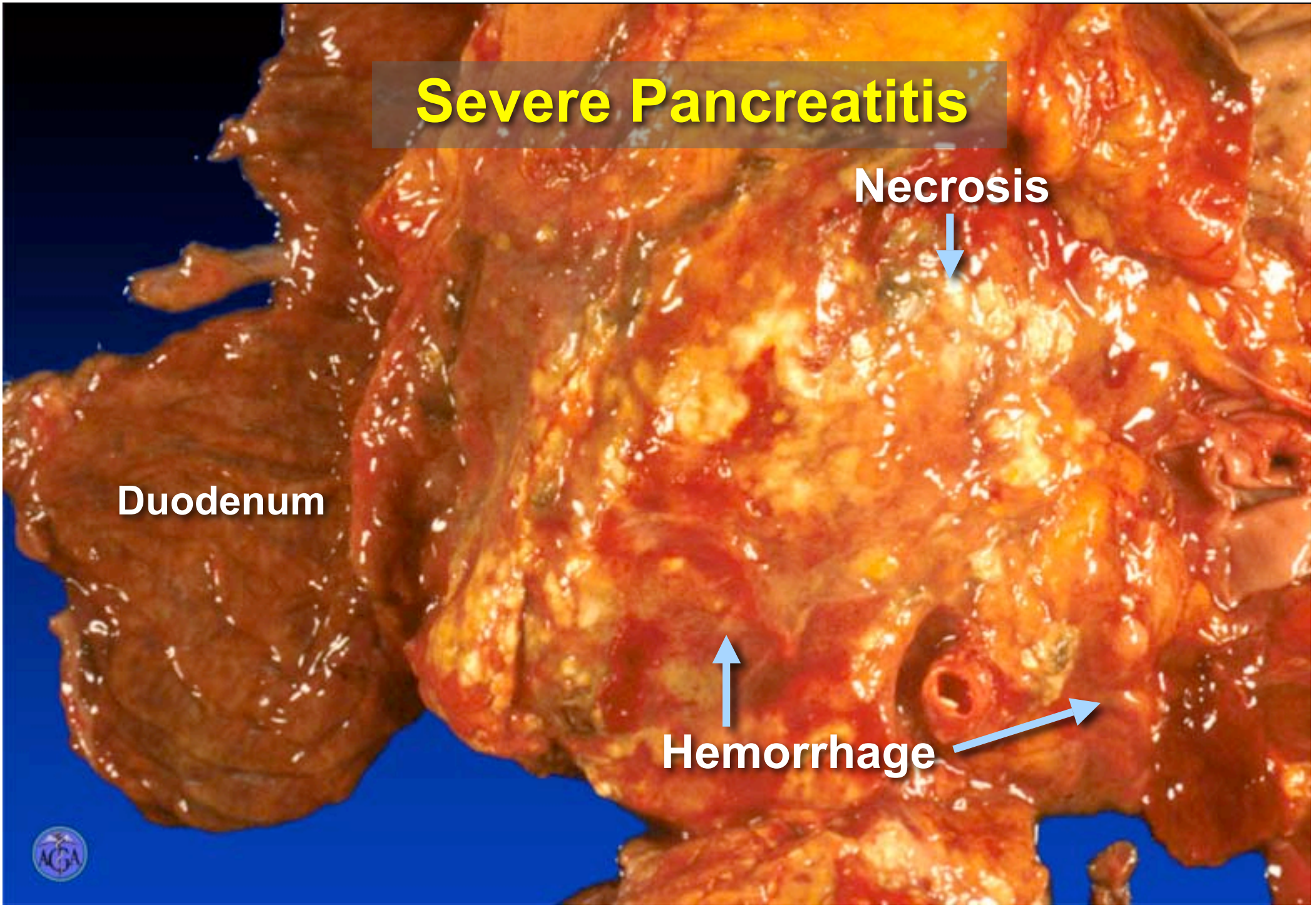
Coupled Water and Bicarbonate Secretion



Acute Pancreatitis

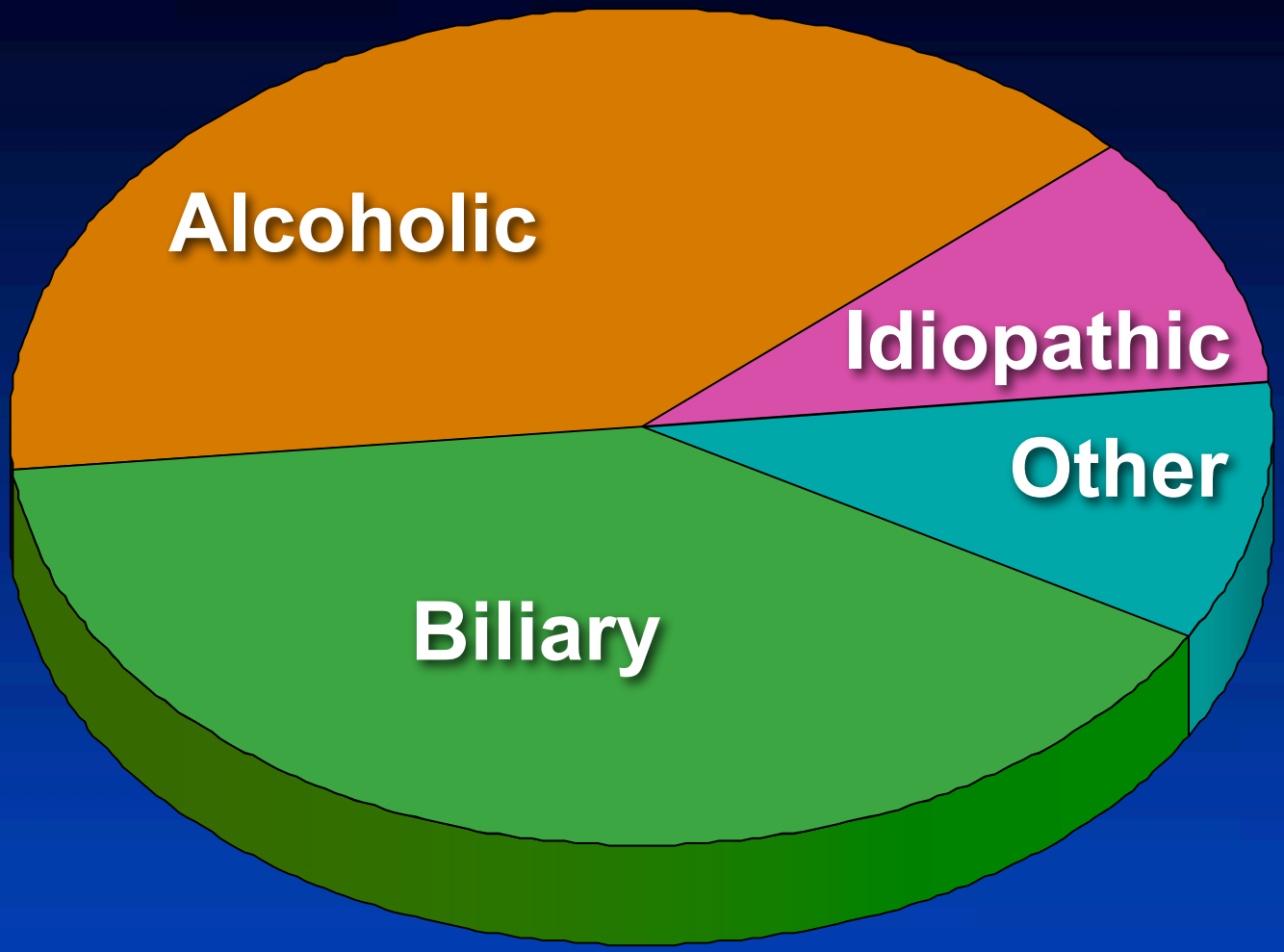


- Abdominal Pain
- ↑ Pancreatic Enzymes in Serum


Severe Pancreatitis
Necrosis
Duodenum
Hemorrhage

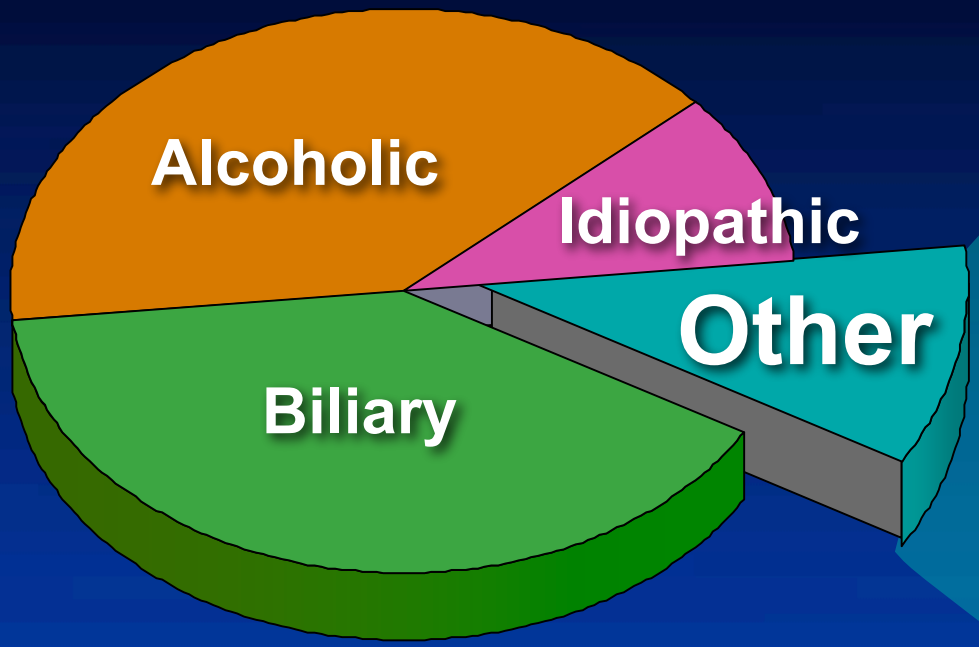
Acute Pancreatitis

Etiologies



Acute Pancreatitis

Etiologies



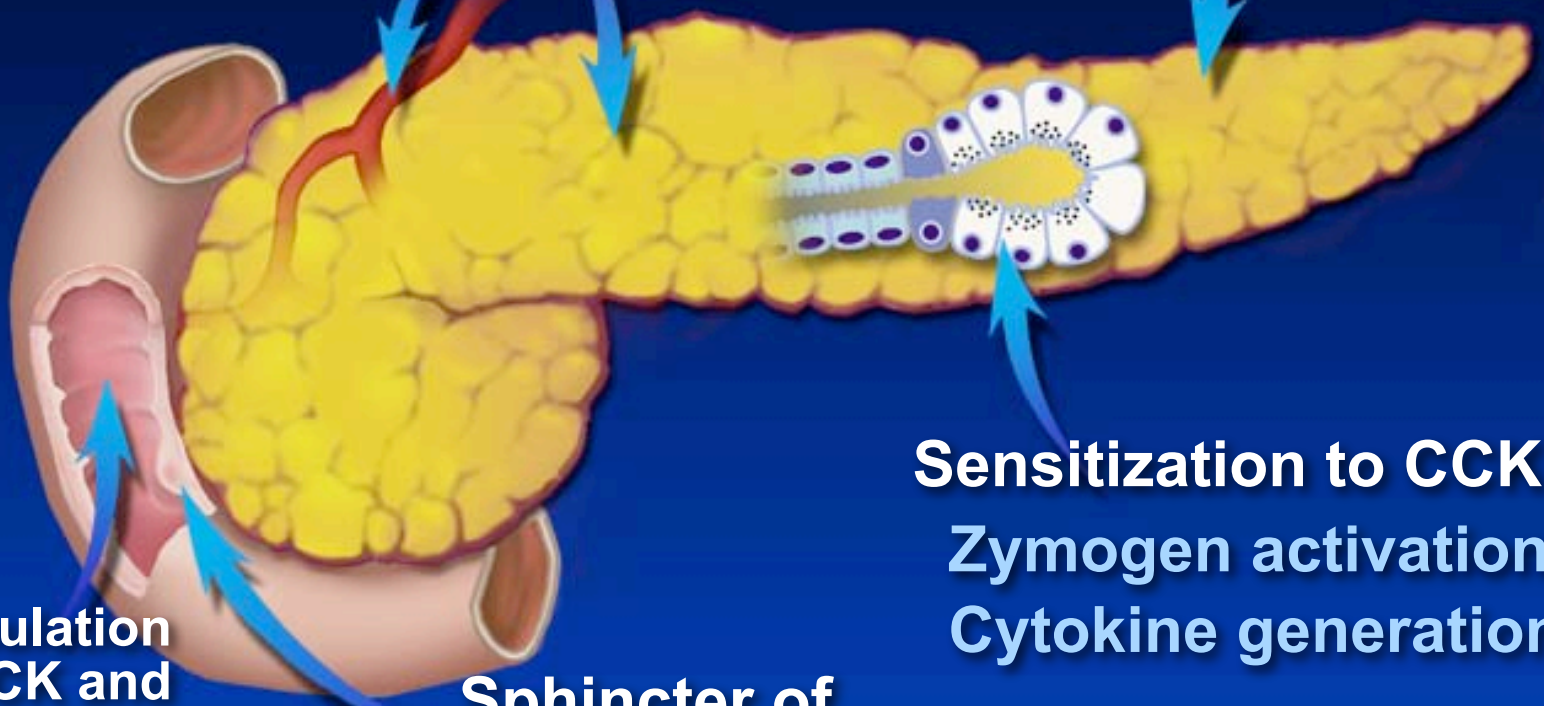
- Autoimmune
- Drug-induced
- Iatrogenic
- IBD-related
- Infectious
- Inherited
- Metabolic
- Neoplastic
- Structural
- Toxic
- Traumatic
- Vascular

Drug Induced Pancreatitis Sorted by Incidence

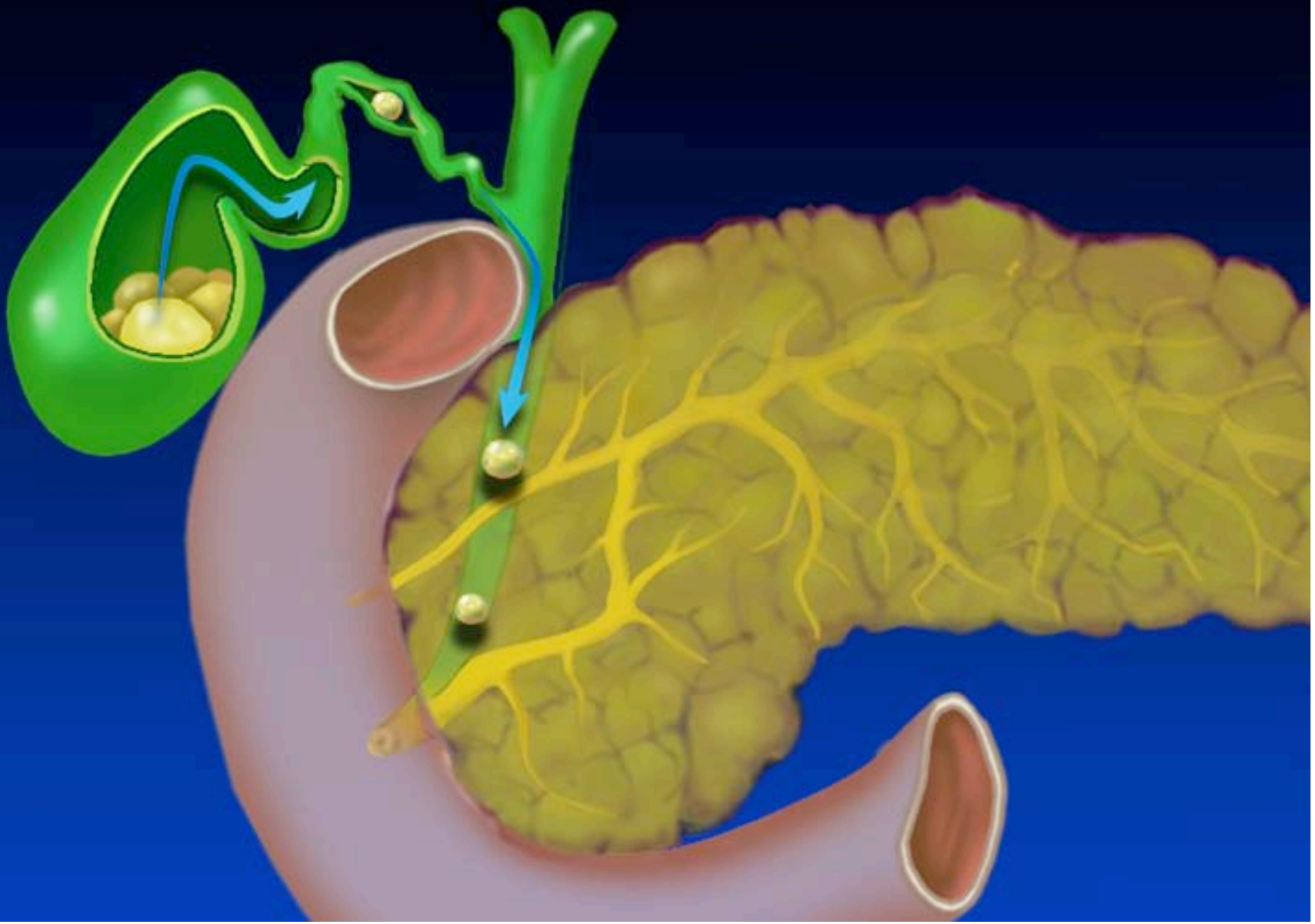
Common	Uncommon	Rare
asparaginase	ACE inhibitors	carbamazepine
azathioprine	acetaminophen	corticosteroids
6-mercaptopurine	5-amino ASA	estrogens
didanosine (DDI)	furosemide	minocycline
pentamidine	sulfasalazine	nitrofurantoin
valproate	thiazides	tetracycline

Pancreatitis

Acute Alcohol Effects

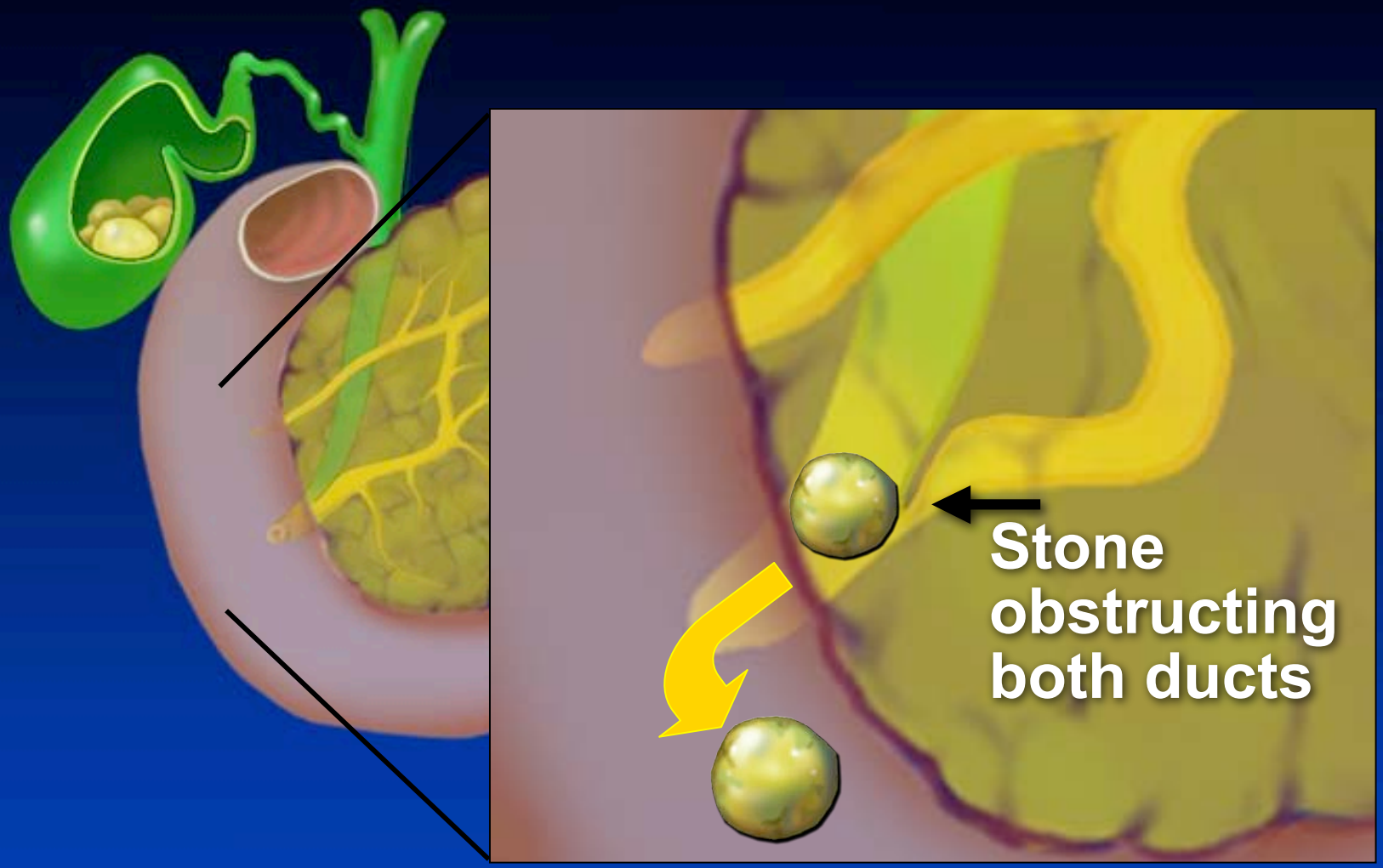


Gallstone Migration

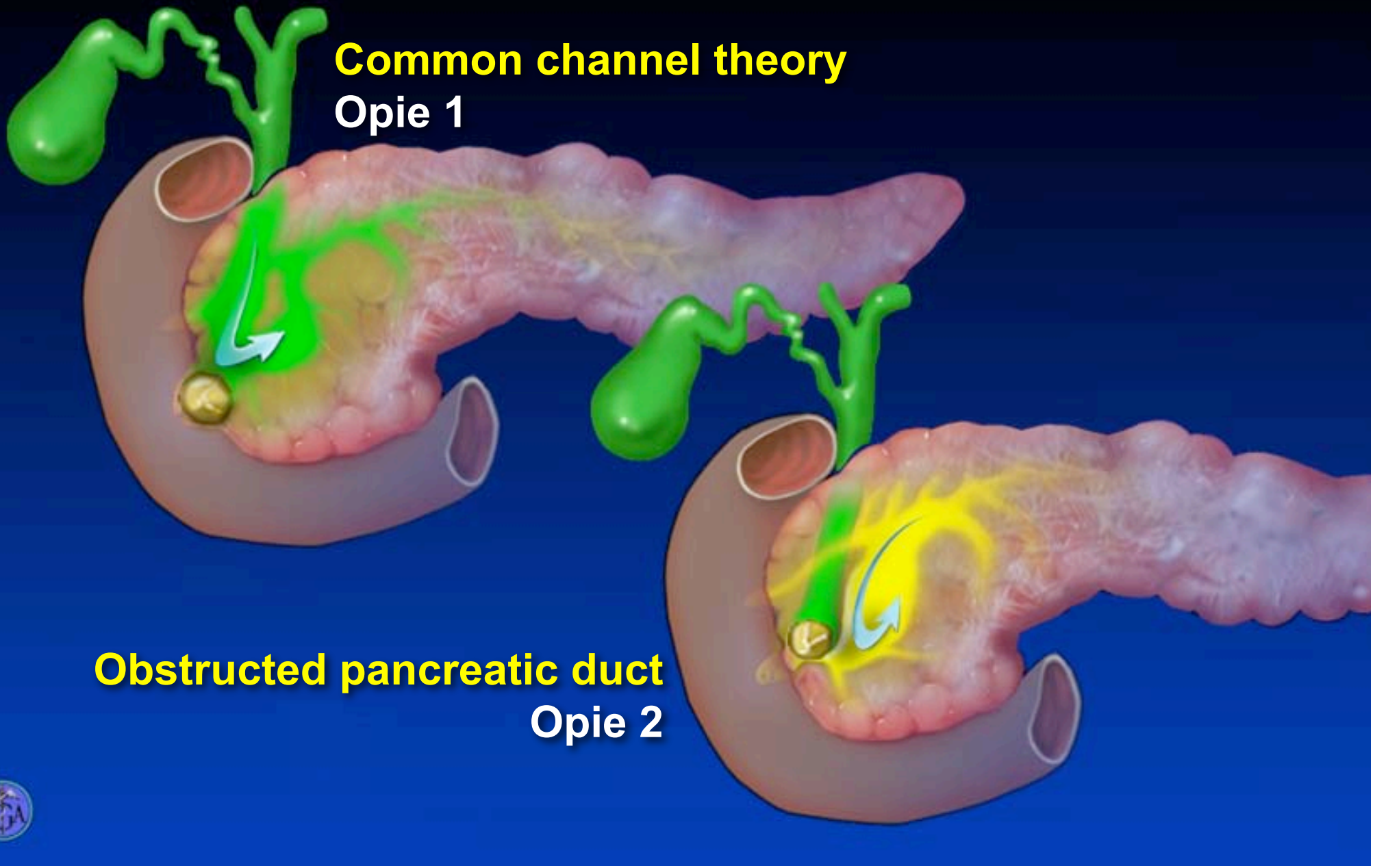


Acute Pancreatitis

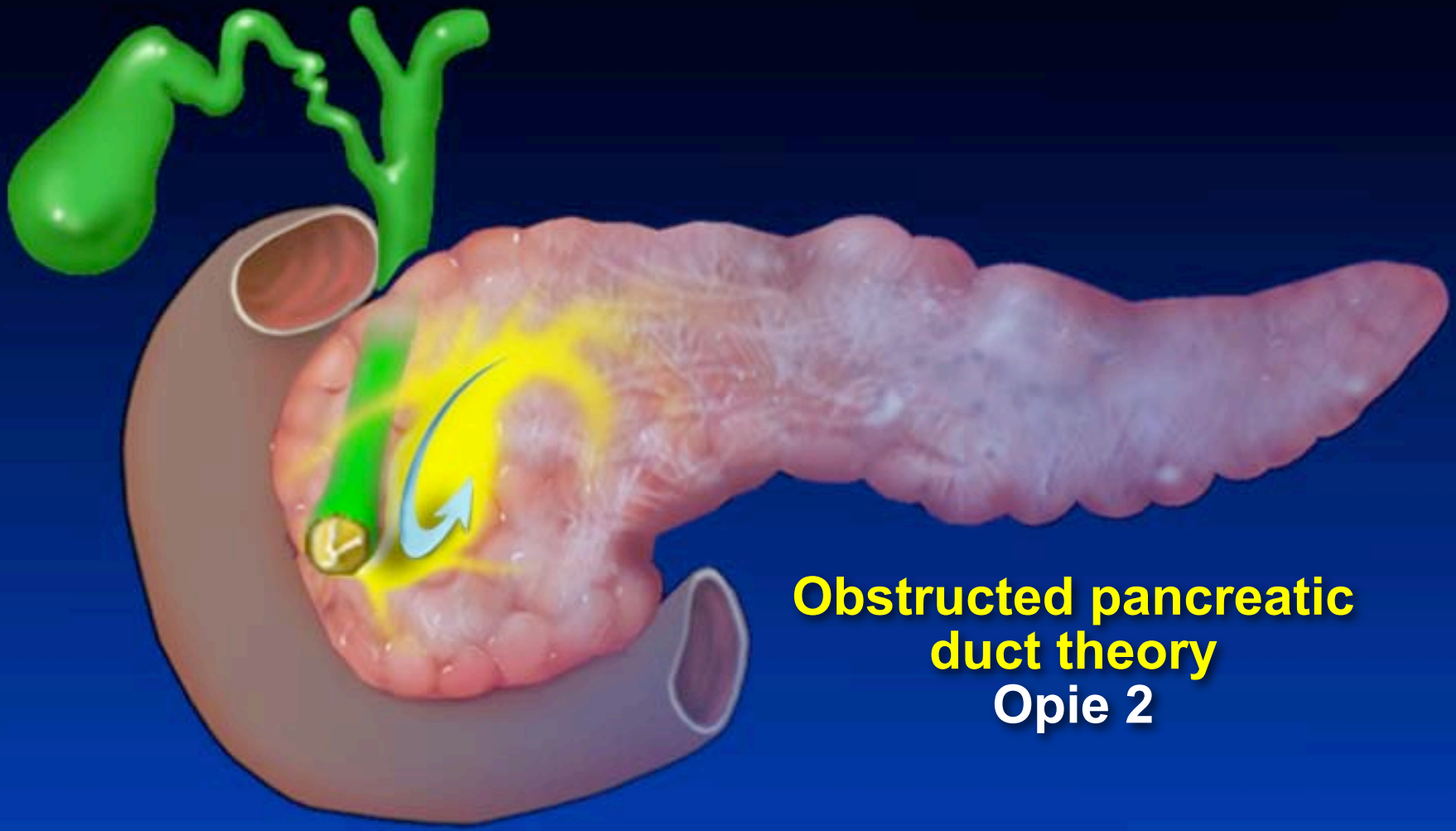
Gallstones



Gallstone Pancreatitis Mechanism



Gallstone Pancreatitis Mechanism



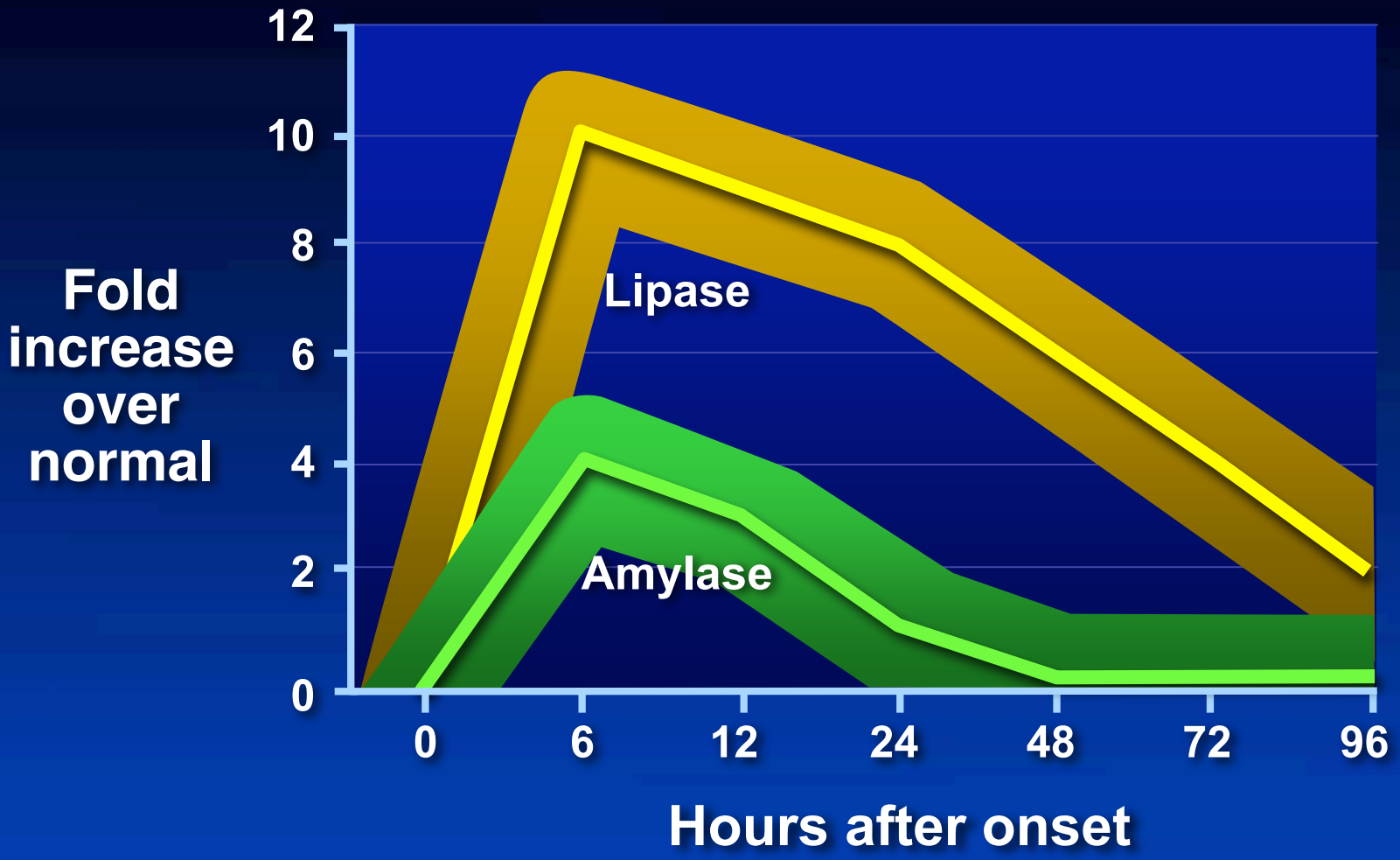
Obstructed pancreatic duct theory
Opie 2

Standard Diagnostic Tests

Test	Sensitivity	Specificity	Comment
Serum enzymes	high	moderate	>3x normal increases specificity
Ultrasound	moderate	high	best for gallbladder stones
CT	moderate	high	detects edema, calcifications, fluid collections
CT with IV contrast	moderate	high	detects necrosis

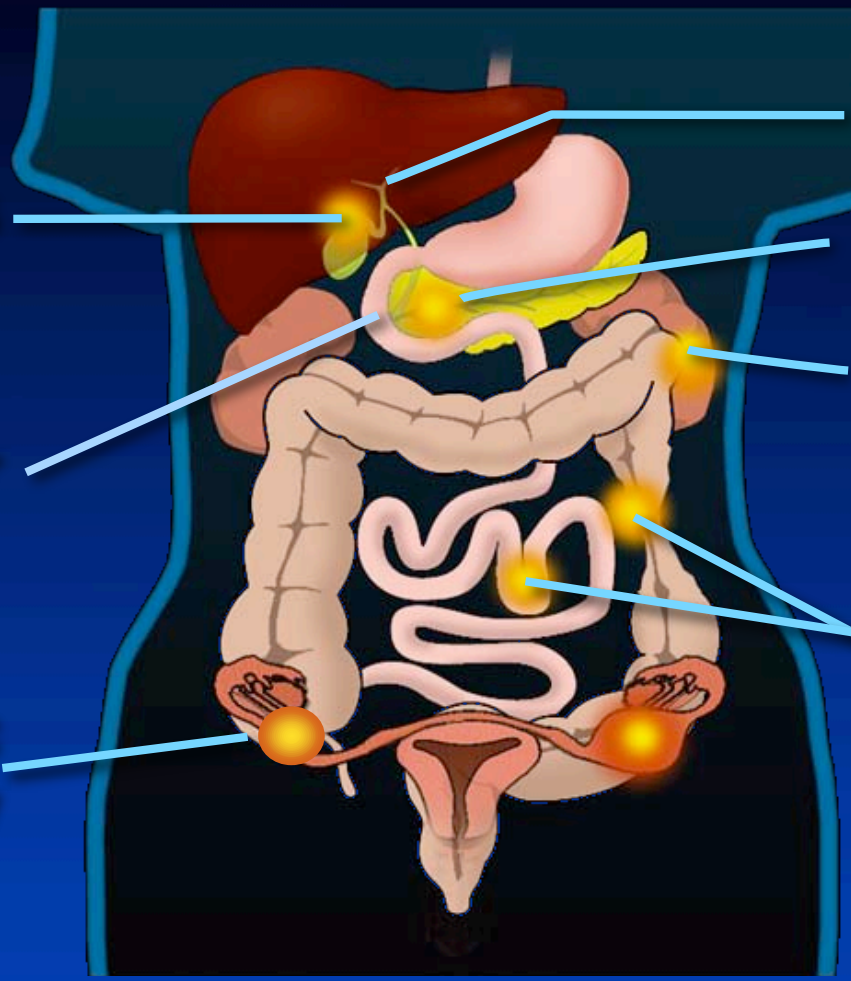
Acute Pancreatitis

Time Course of Enzyme Elevations



Acute Pancreatitis

Elevated Serum Amylase



Cholangitis

Cholecystitis

Pancreatitis

Kidney stone

Peptic ulcer

Intestinal obstruction, ischemia or perforation

Ectopic pregnancy

Conditions Associated with Hyperamylasemia and Hyperlipasemia

	Amylase	Lipase
Paroditis	yes	no
Tumors	yes	no
Biliary disease	yes	slight
Pancreatitis	yes	yes
Renal failure	yes	slight
Intestinal obstruction, ulceration, ischemia	yes	yes
Ectopic pregnancy	yes	no
Macroamylasemia	yes	no
Perforated viscus	yes	yes

Treatment

Supportive care

- Aggressive fluid and electrolyte replacement
- Monitoring
  - Vital signs
  - Urine output
  - O_2 saturation
  - Pain
- Analgesia, anti-emetics

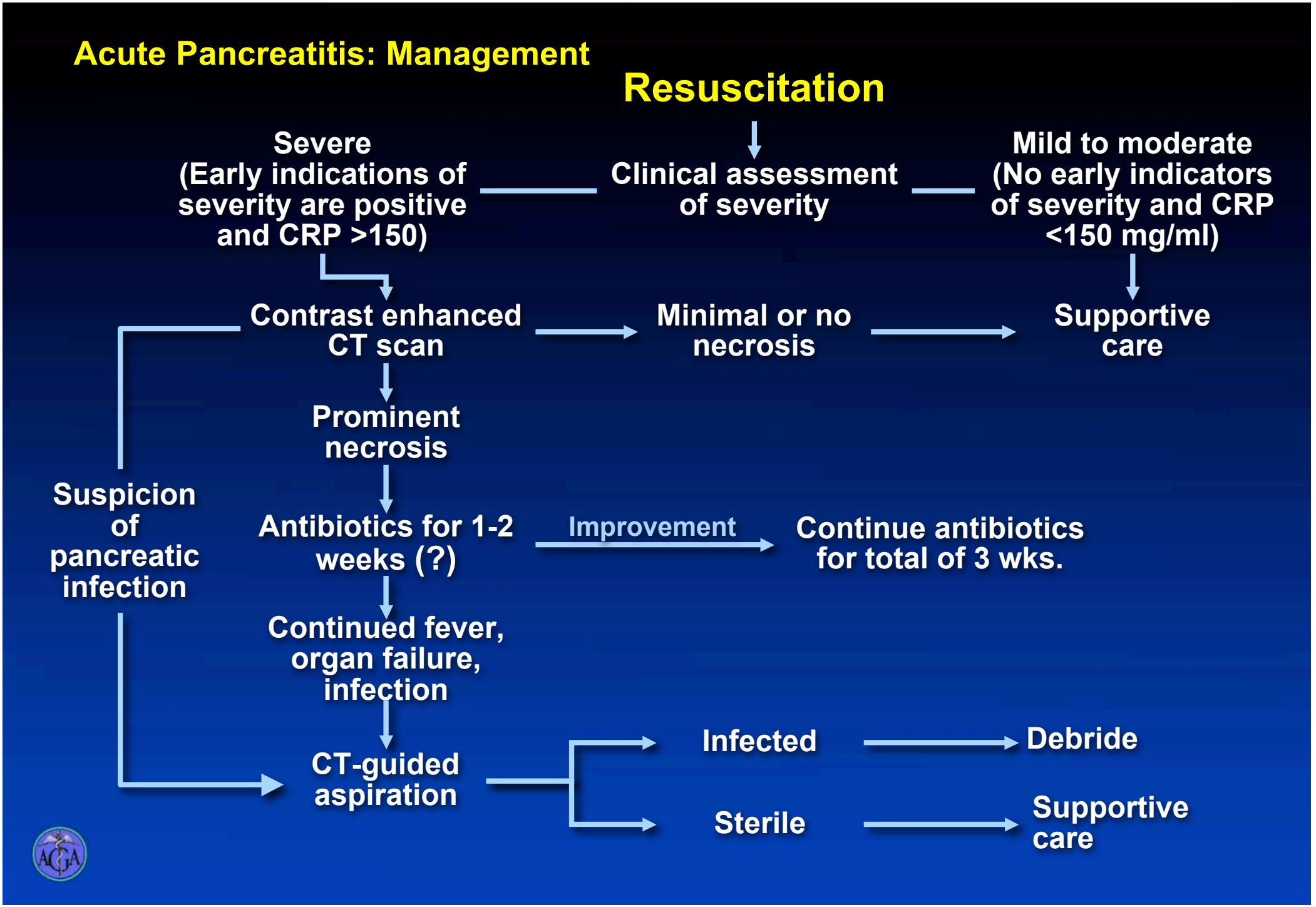
Other treatments

- Acid suppression
- Antibiotics
- NG tube
- Nutritional support
- Urgent ERCP

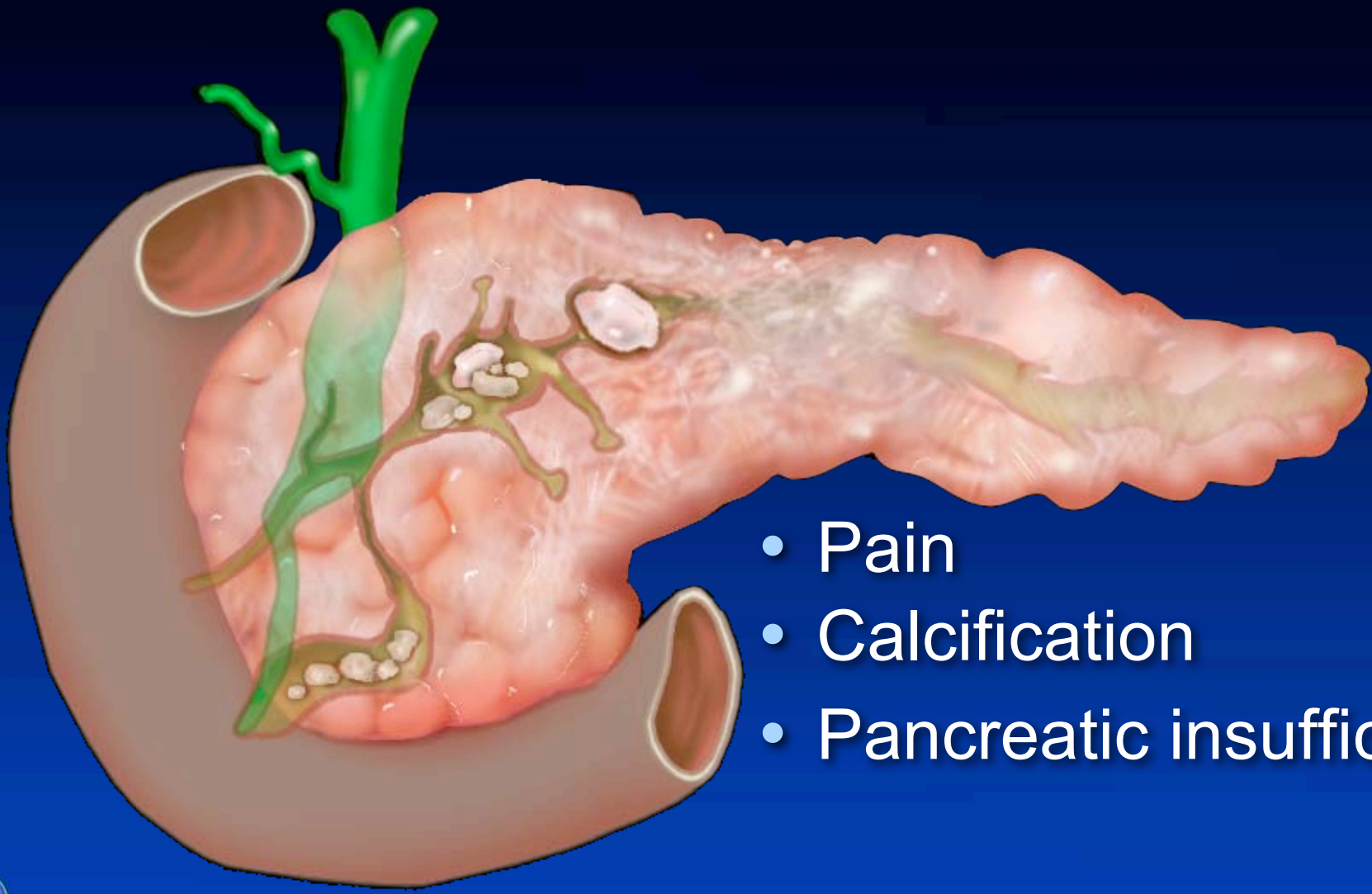
Pain Management

Medication	Initial dose	Frequency	Usual Dose Range
Morphine	2 mg	4 hrs	2-10 mg
Hydromorphone	0.2 mg	4 hrs	0.2-1.5 mg
Fentanyl	25 µg	4 hrs	25-100 µg

Acute Pancreatitis: Management



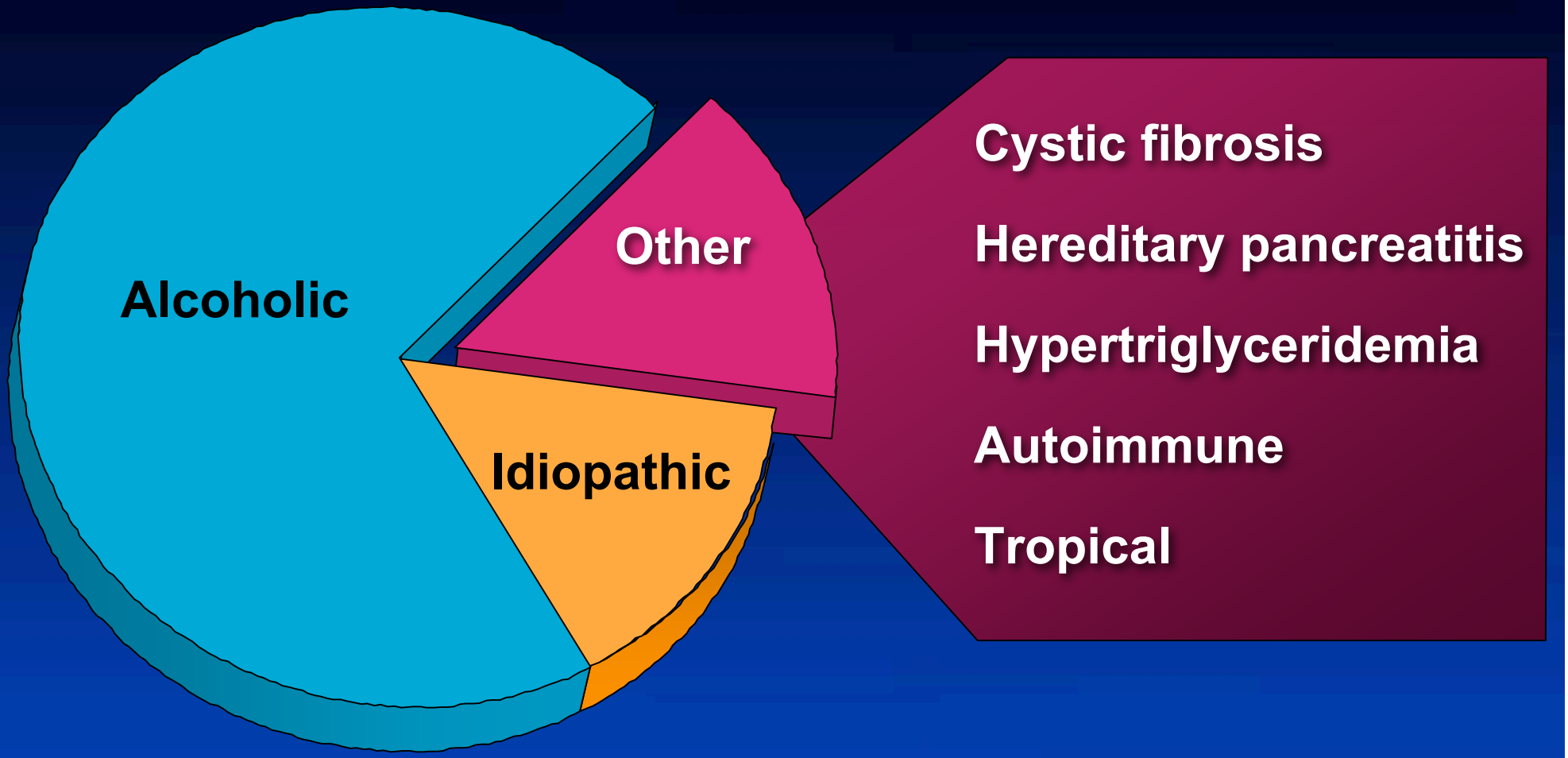
Chronic Pancreatitis



- Pain
- Calcification
- Pancreatic insufficiency

Chronic Pancreatitis

Etiologies



Pancreatic Insufficiency Without Pancreatitis

Non-pancreatic

- Mucosal disease
  - ↓ CCK release
  - Enterokinase deficiency *
- Gastrinoma
- Bilroth II reconstruction

Pancreatic

- Cystic fibrosis *
- Pancreatic tumors
- Shwachman-Diamond syndrome *
- Childhood pancreatic atrophy *
- Johanson-Blizzard syndrome*
- Adult lipomatosis or atrophy
- Protein-calorie malnutrition

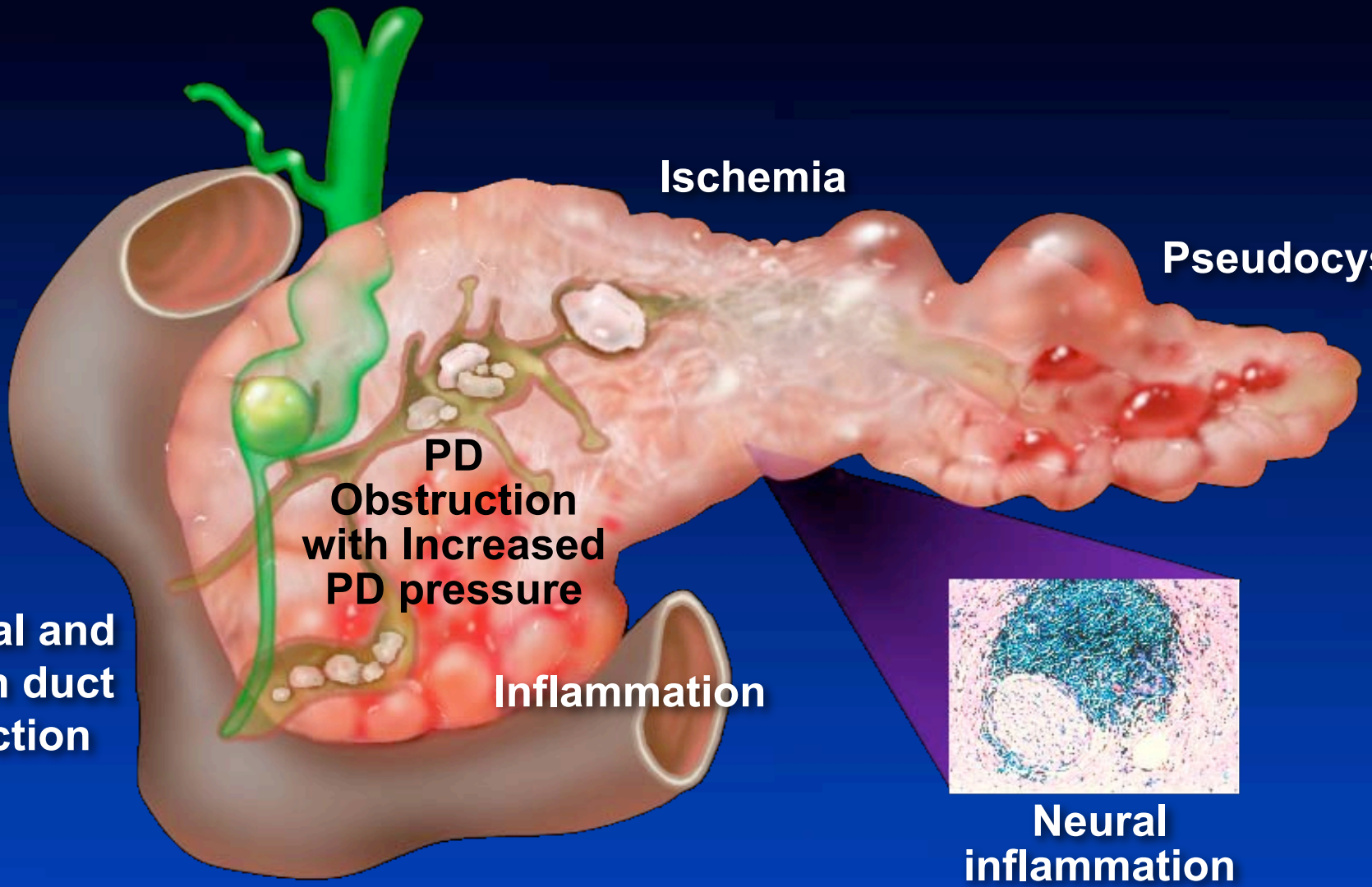
*** inherited**

Clinical Diagnosis

Symptom	Features
Pain	Intermittent or constant Moderate to severe Epigastric with radiation to back
Steatorrhea	Visible oil droplets or grease in stool ↑ volume, light color, foul odor

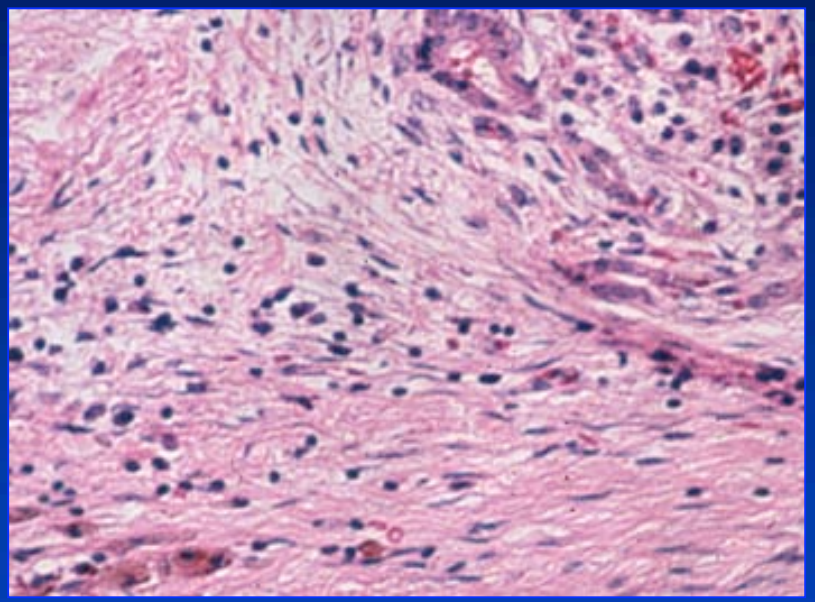
Chronic Pancreatitis

Causes of Pain

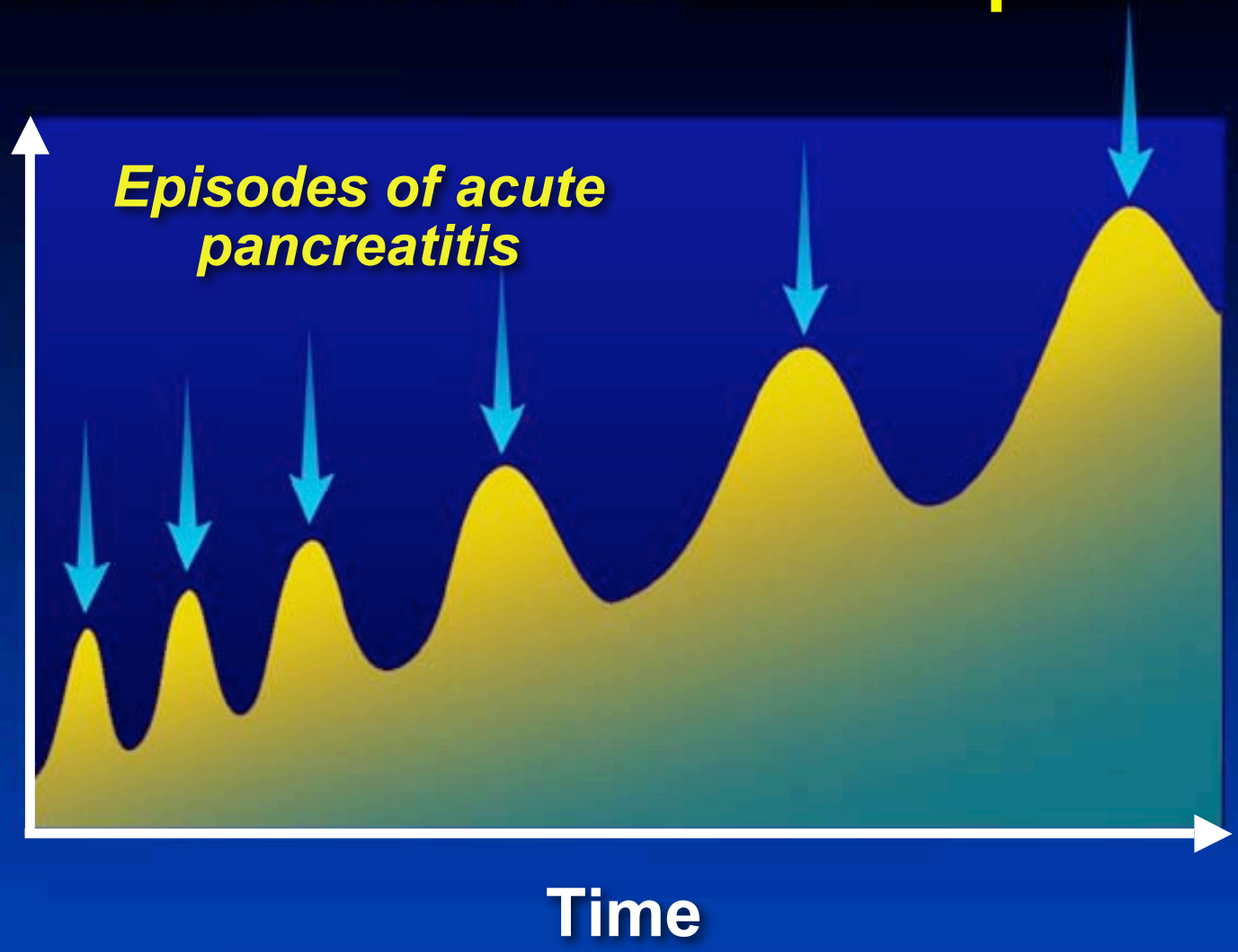


Proposed Pathologic Mechanisms

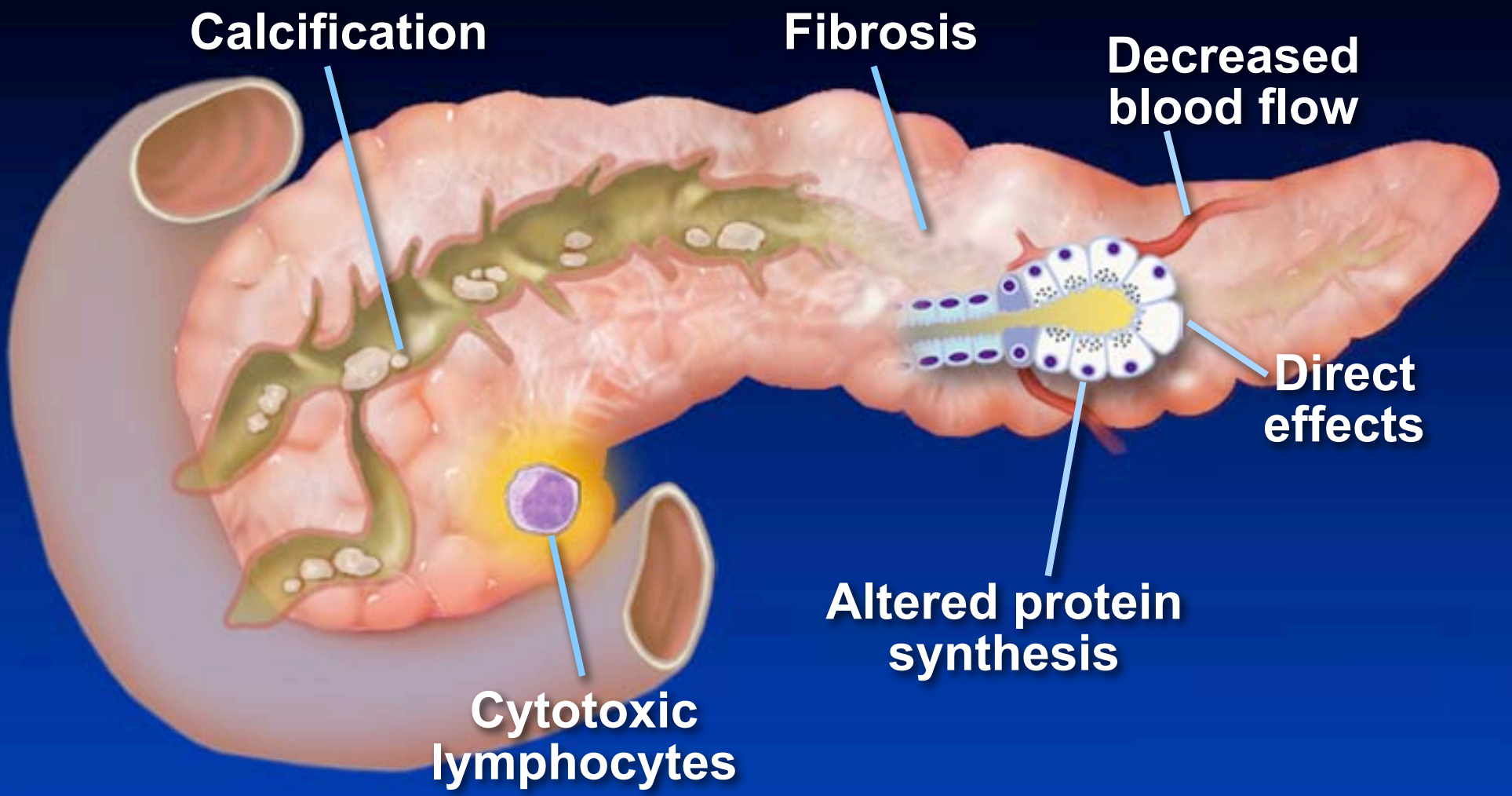
- Intraductal plugging and obstruction
- Direct toxins and toxic metabolites
- Oxidative stress
- Necrosis-fibrosis
- Immune dysregulation



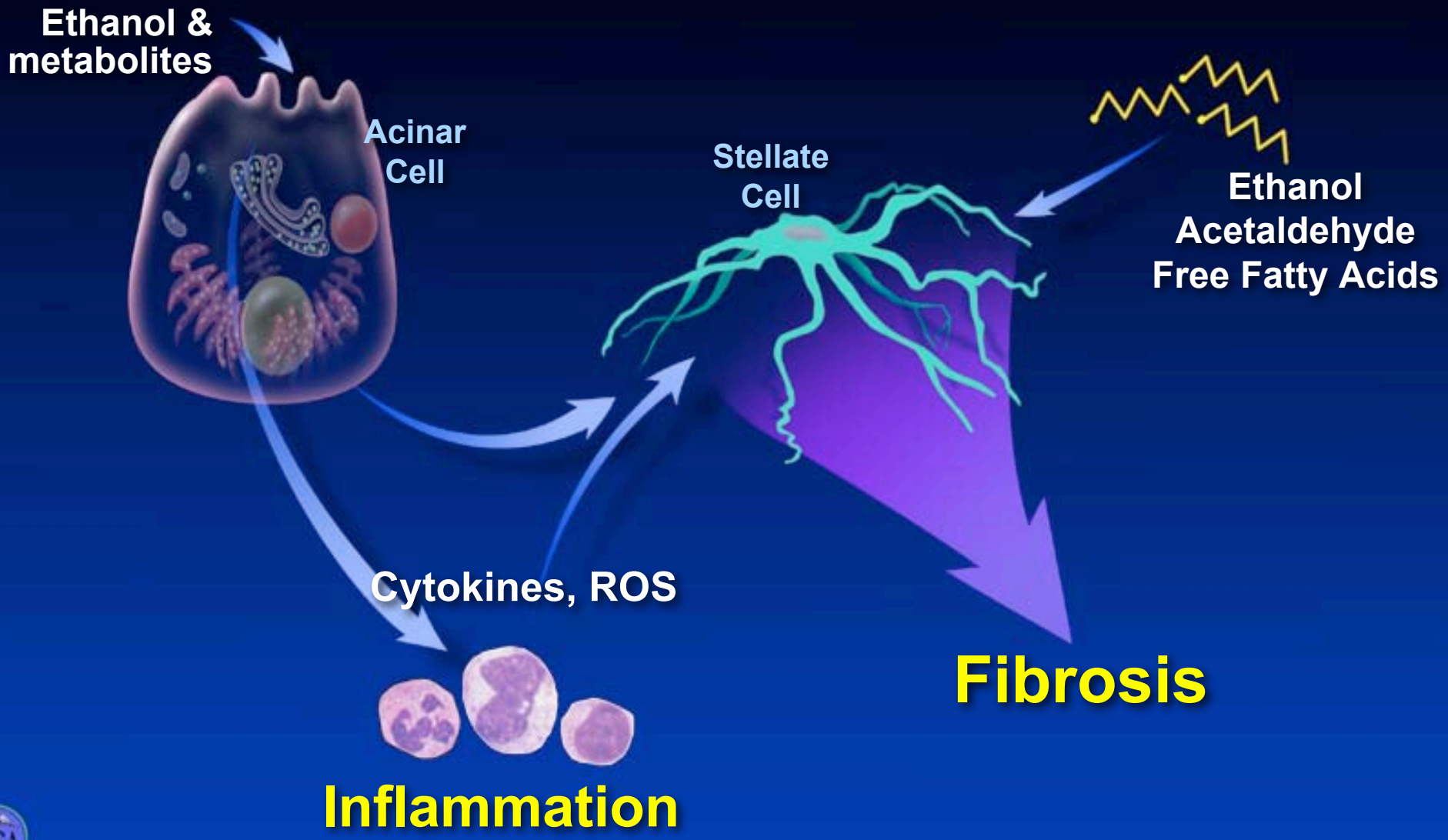
Proposed Necrosis-Fibrosis Sequence



Chronic Effects of Alcohol



Alcohol: Acinar Cell Pathology

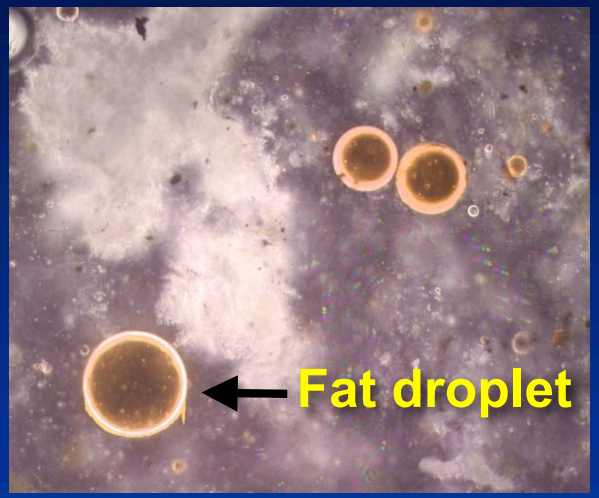


Malabsorption

Lost nutrient	Terminology	Deficient enzymes	Clinical expression
Di/triglycerides	Steatorrhea	Lipase, colipase	Common
Protein/peptides	Azotorrhea	Proteases	Uncommon
Starch fragments	Amylorrhea	Amylase	Rare

Steatorrhea

Stool with excessive fat



Sudan stain

Mechanisms

- Decreased concentration of lipase and colipase
- ↓ Duodenal pH
  - Inactivation of pancreatic lipase pH<4.5
  - Precipitation of bile salts

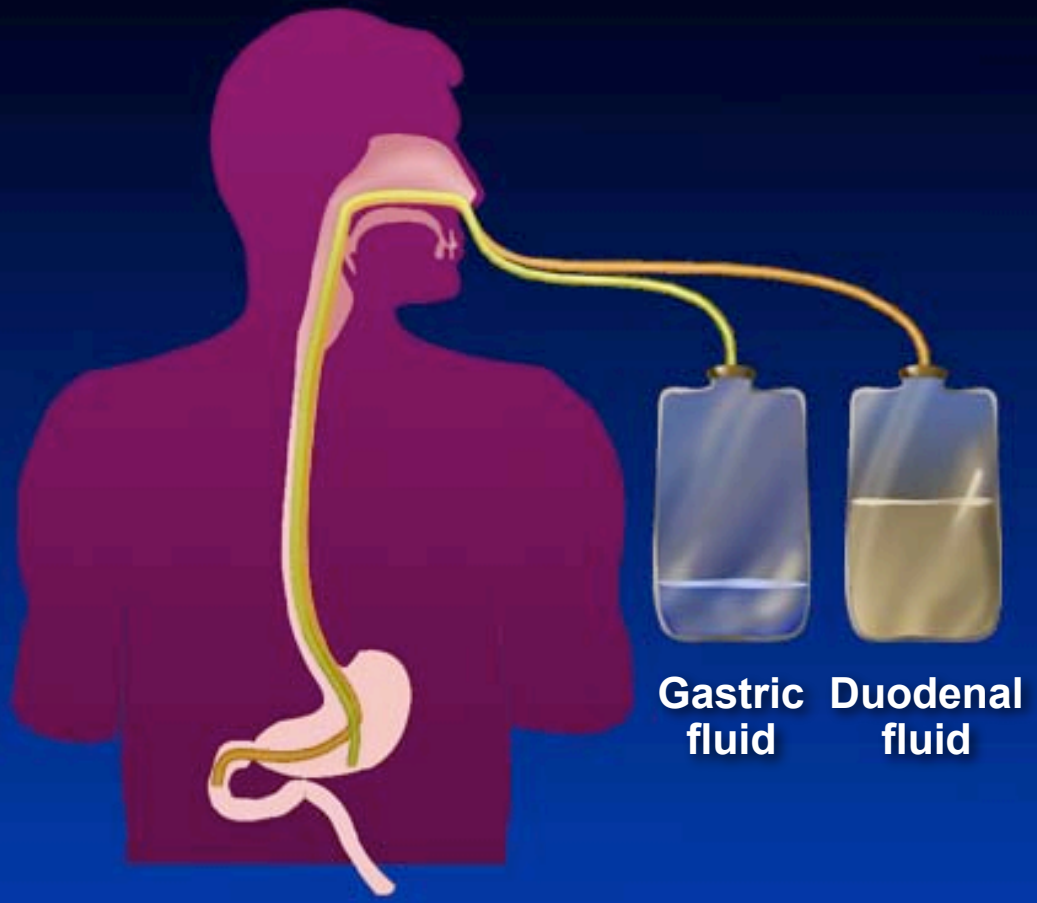
Clinical Assessment

Presentation	Order of evaluation
Pain	Imaging
Malabsorption	Imaging Trial of pancreatic enzymes Tests of pancreatic insufficiency

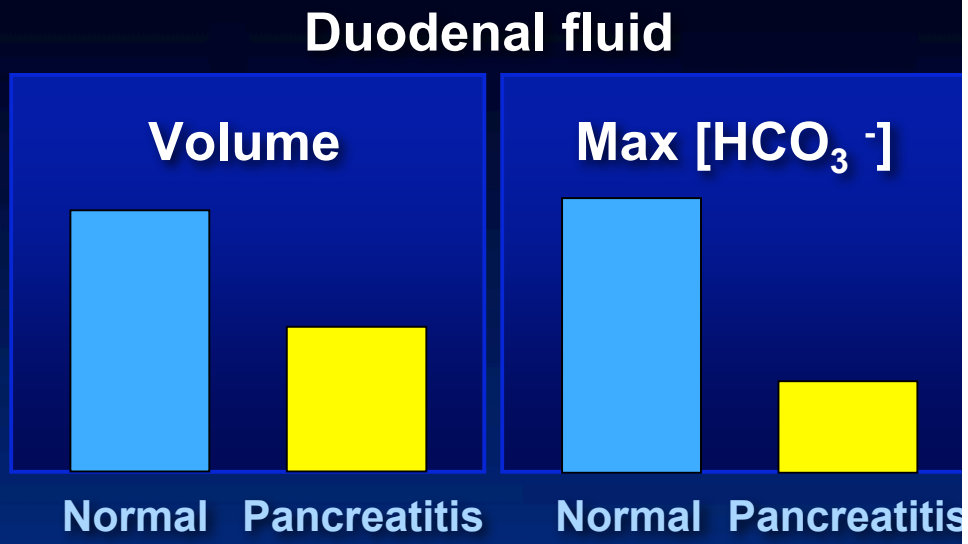
Tests of Exocrine Function

Type	Measured	Assay
Stool	Fat digestion and absorption	Stool fat
Stool	Protease secretion	Stool elastase-1 and chymotrypsinogen
Urine	Protease secretion	Pancreatolauryl test
Duodenal tube / secretin-CCK stimulation	Protease and electrolyte secretion	Volume, enzymes, HCO_3^-

Double Lumen Tube Test



Secretin test

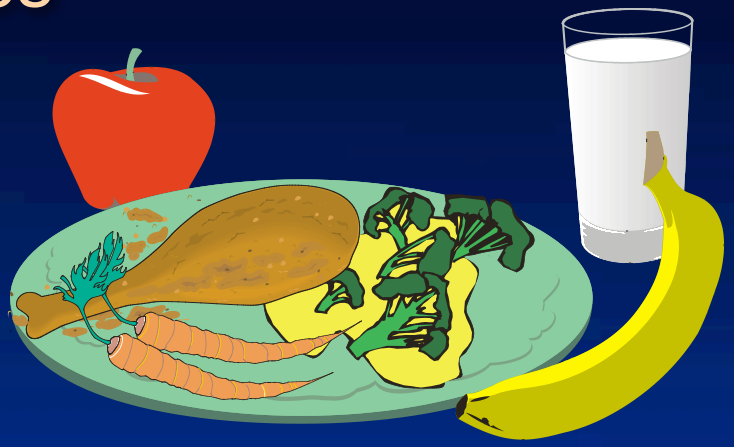


- Sensitive and specific
- Unpleasant
- Time-consuming
- Fluoroscopy needed
- Not readily available

Nutritional Management of Exocrine Insufficiency

Diet and exogenous enzymes

- Modify fat intake
- Medium chain triglycerides
- Enzyme replacement
  - Coated vs uncoated
  - Acid suppression



Vitamins, supplements

- Fat soluble
- Calcium
- Cyanocobalamin (B_{12})

Dietary Management of Exocrine Insufficiency

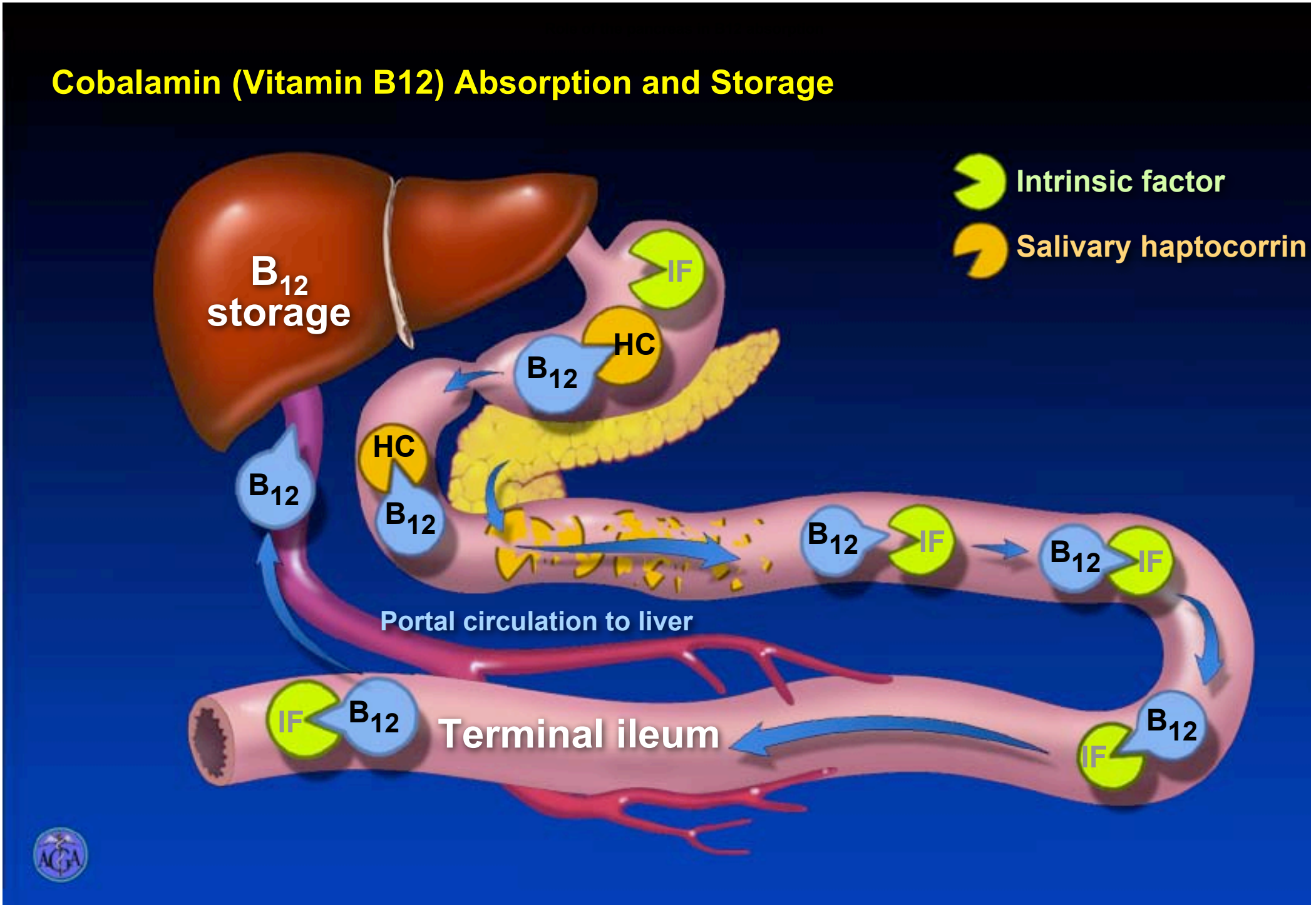
Issue	Comment
Modifying fat intake	Utility unknown
Medium chain triglycerides	With severe insufficiency
Fat soluble vitamins	Occasionally deficient
Cyanocobalamin (B_{12})	Decreased absorption but rarely deficient*

*May develop with proton pump inhibitor use

Use of Pancreatic Enzyme Replacements

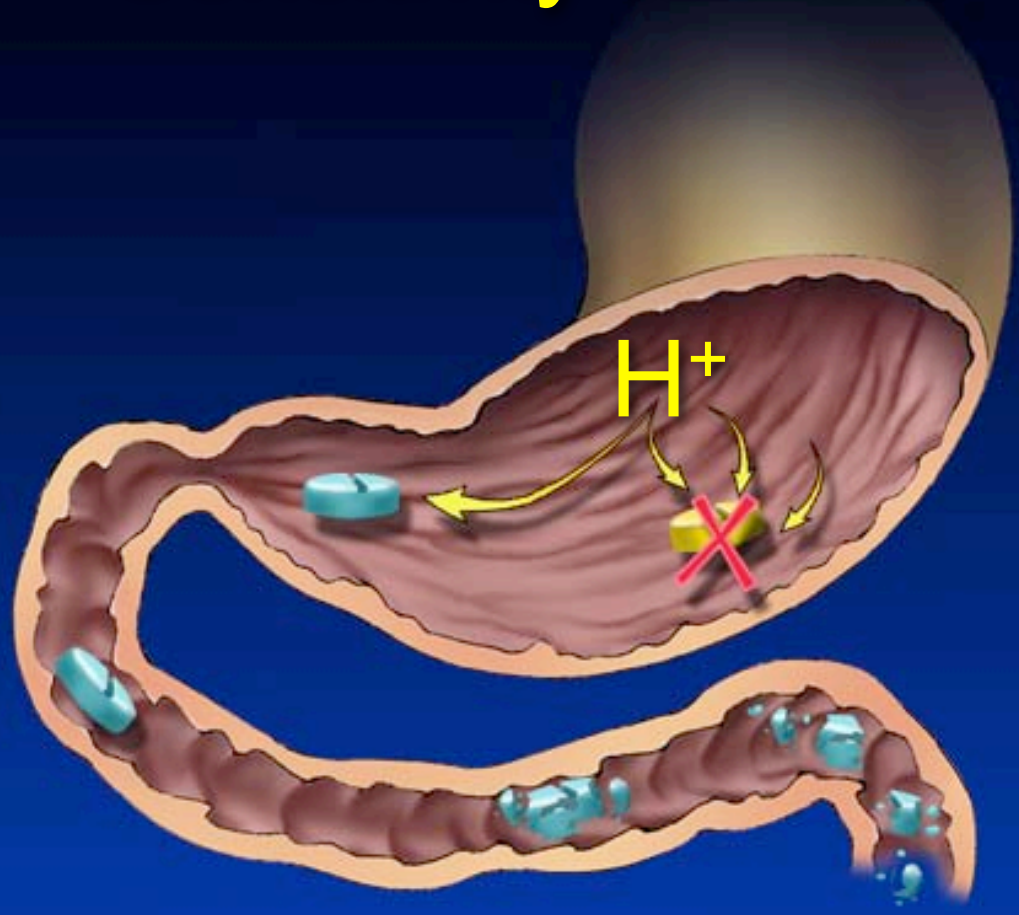
Issue	Example
Type of preparation	Uncoated, coated, microencapsulation
Enzyme content	Levels of lipase vary
Enzyme dosing	Timing with meal
Acid inhibition	Need with uncoated preparations
Side effects	Flatus, colitis, strictures

Cobalamin (Vitamin B12) Absorption and Storage



Chronic Pancreatitis

Sensitivity to Acid



Coated

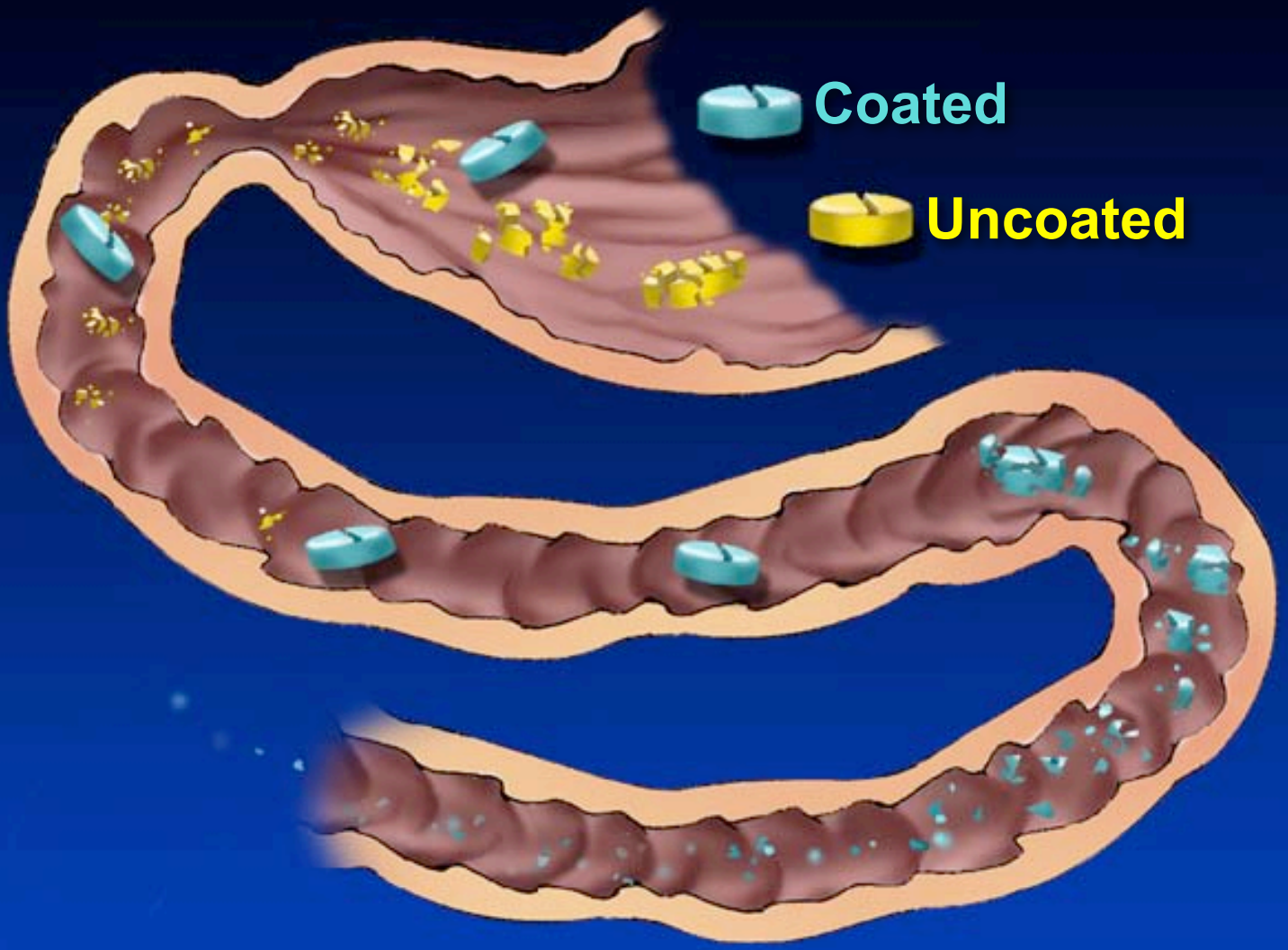
Intact

Uncoated

denatured by gastric acid

Chronic Pancreatitis

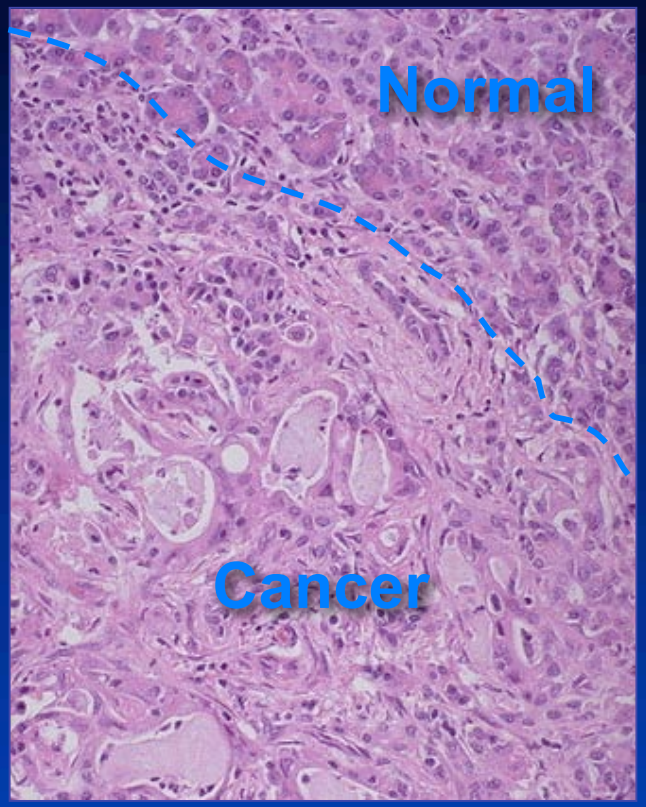
Site of Dissolution

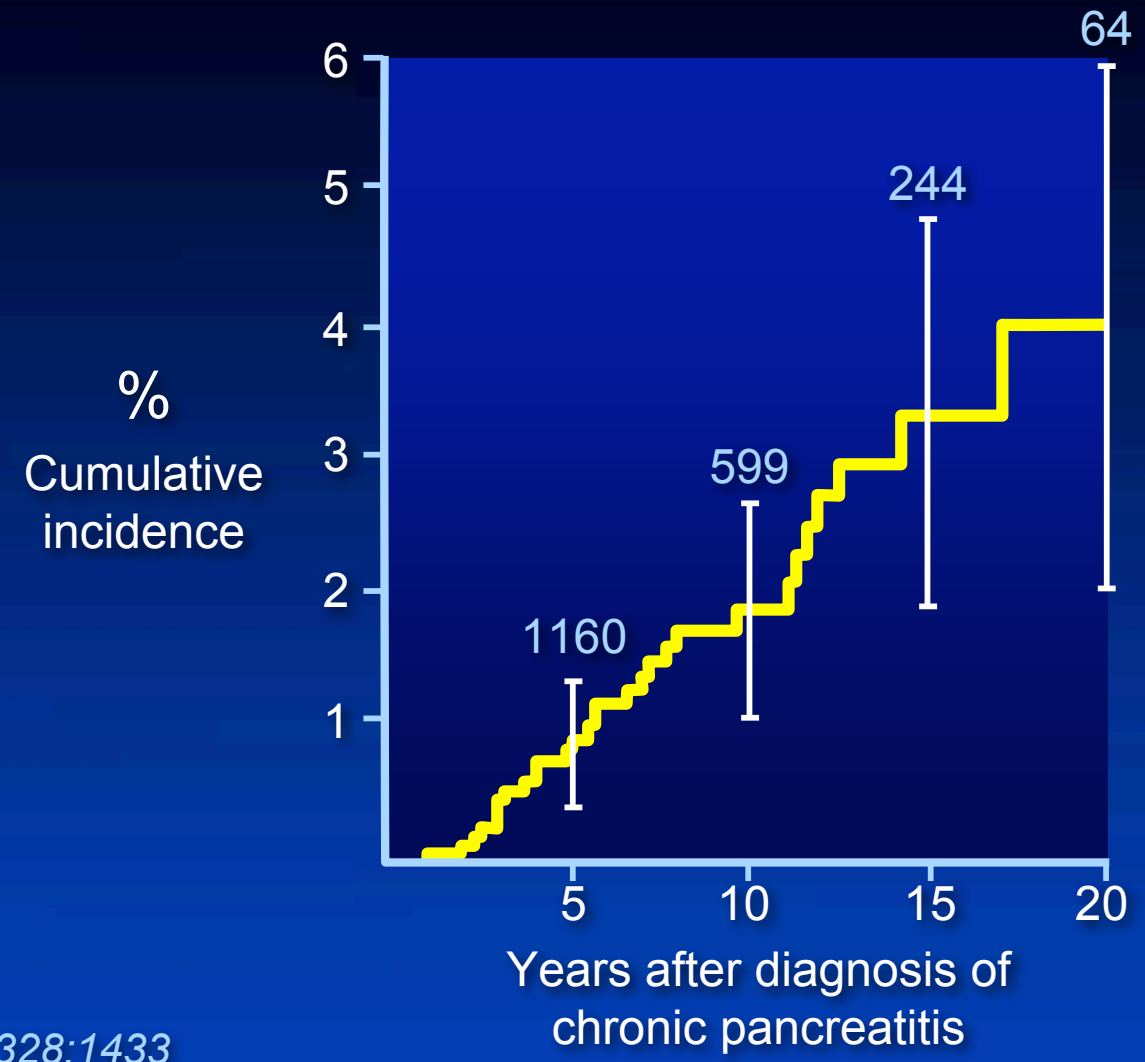


Chronic Pancreatitis

Pancreatic Cancer Risk

3-15 fold increase





Lowenfels, et al., N Engl J Med 1993; 328:1433

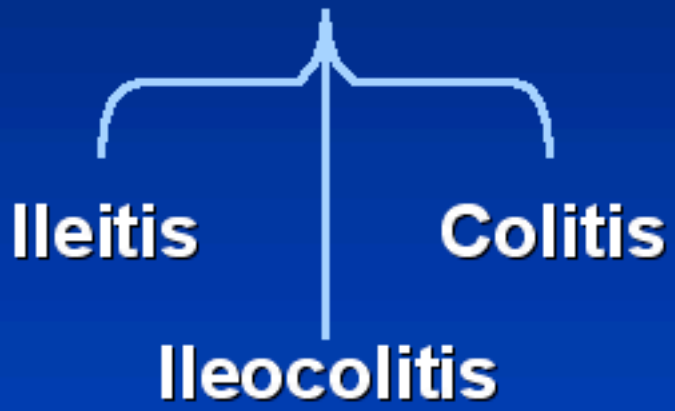
Inflammatory Bowel Diseases

Ulcerative Colitis

Mucosal ulceration in colon

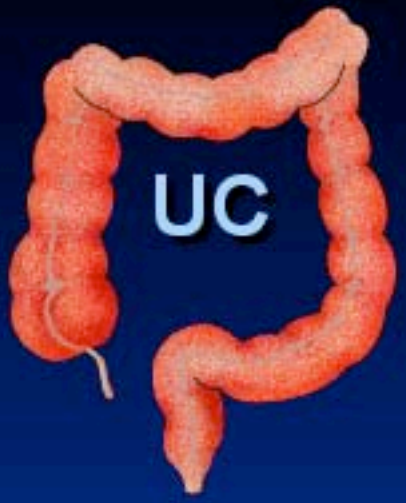
Crohn's Disease

Transmural inflammation

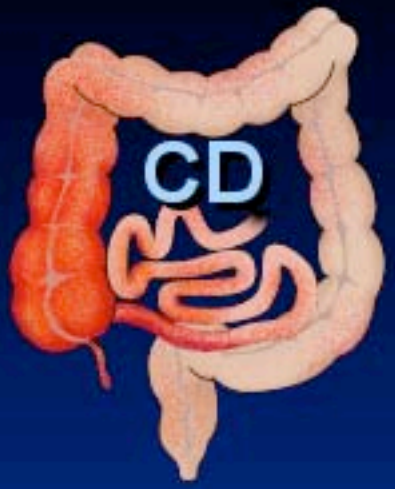


Other Colitides

- Microscopic colitis
- Diversion colitis
- Diverticular colitis
- Pouchitis



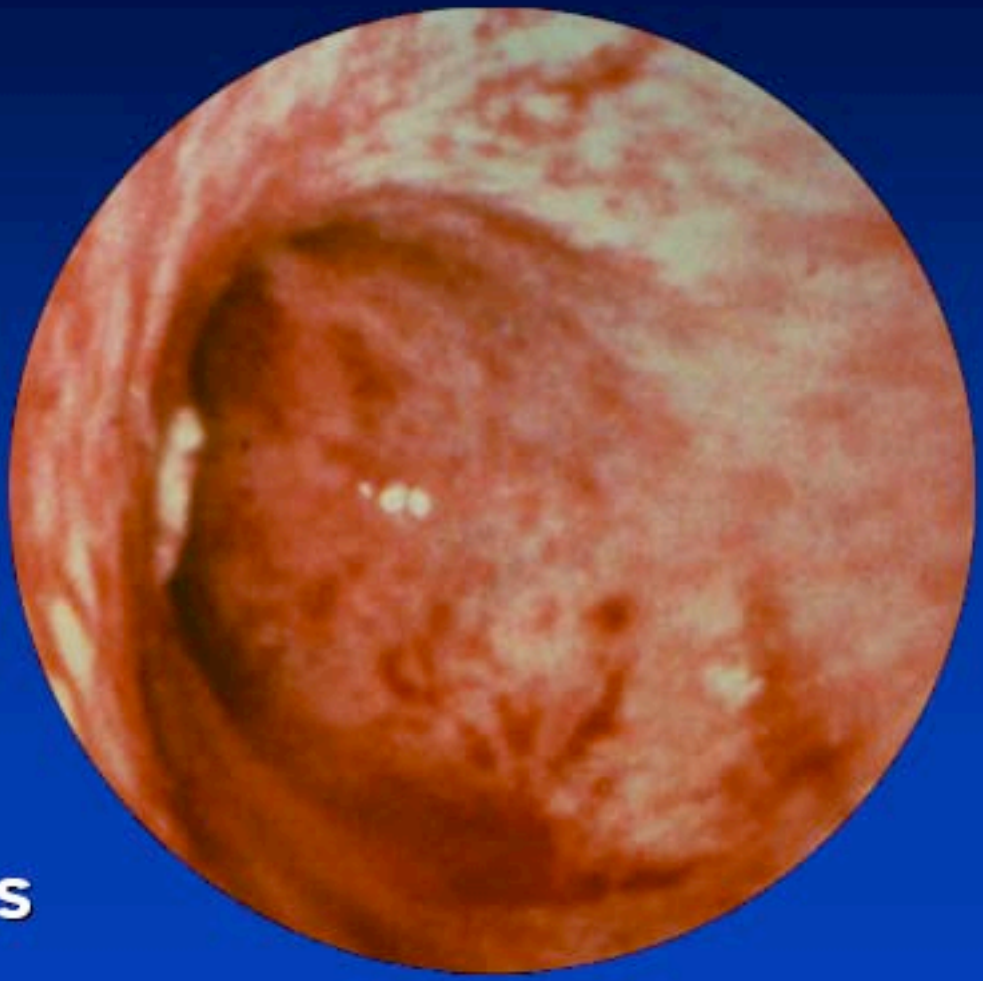
- Diffuse mucosal inflammation limited to colon
- Affects rectum
- May involve all or part of rest of colon



- Patchy transmural inflammation
- May affect any part of GI tract

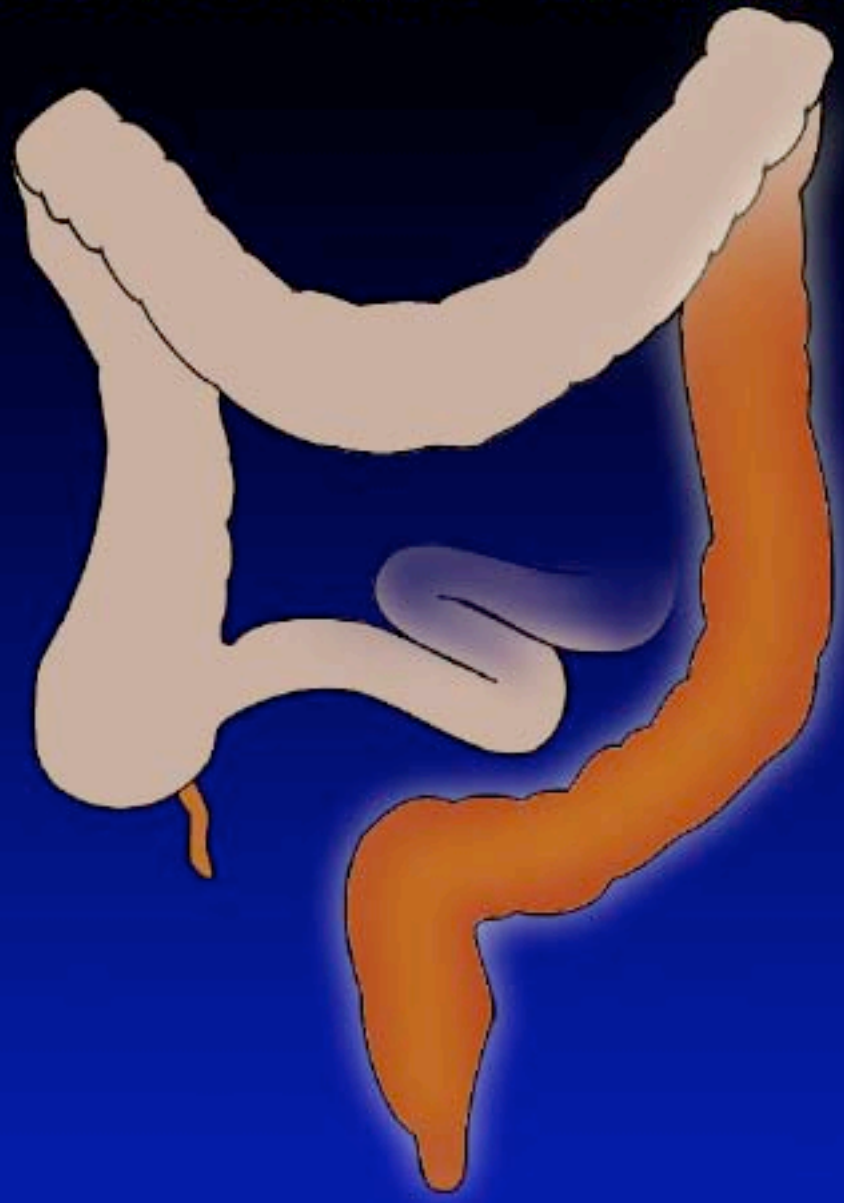
Colitis

- Ulcerative colitis
- Crohn's disease
- Radiation
- Ischemia
- Infections
- Antibiotics
- NSAIDs
- Diversion colitis
- Diverticular colitis



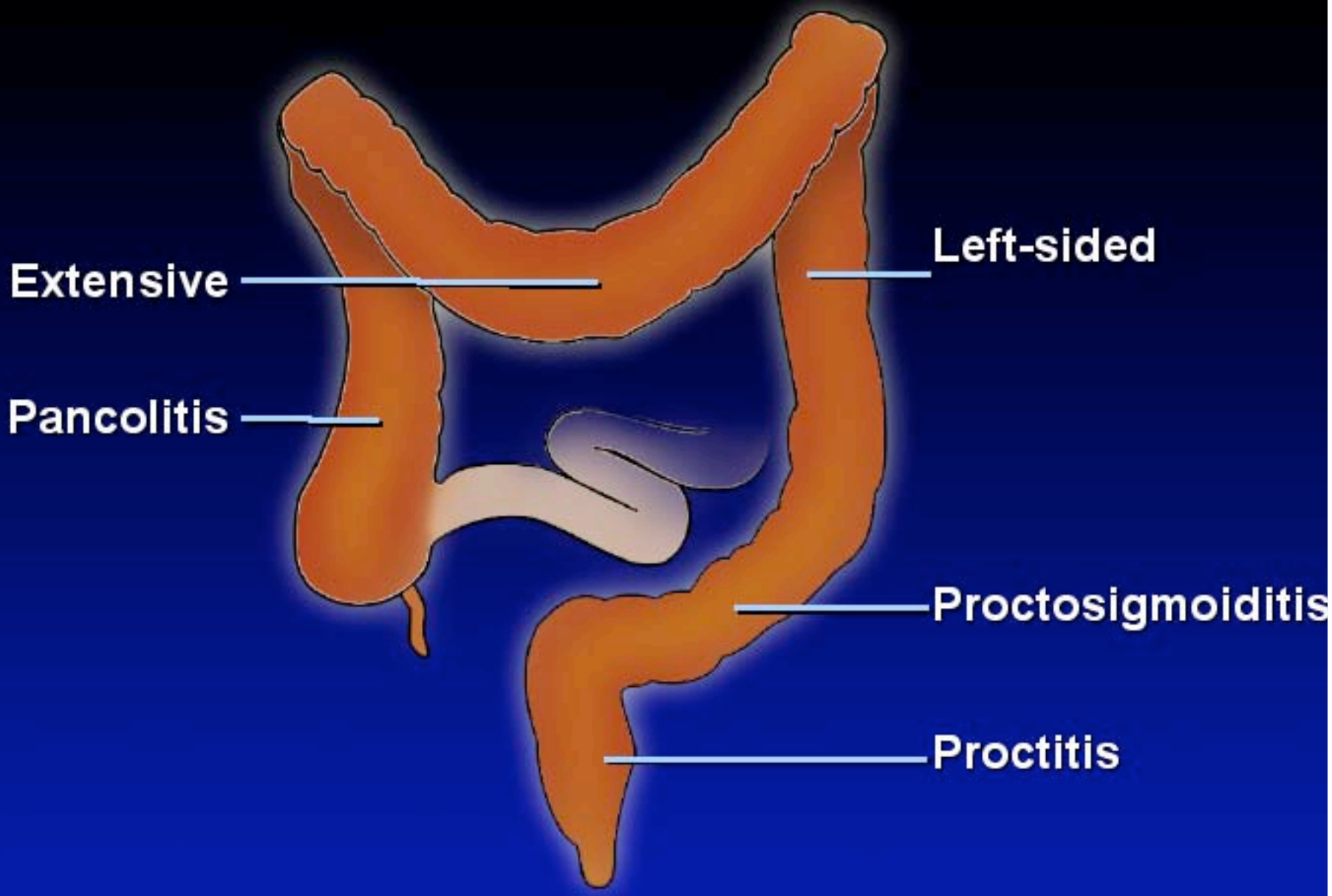
IBD

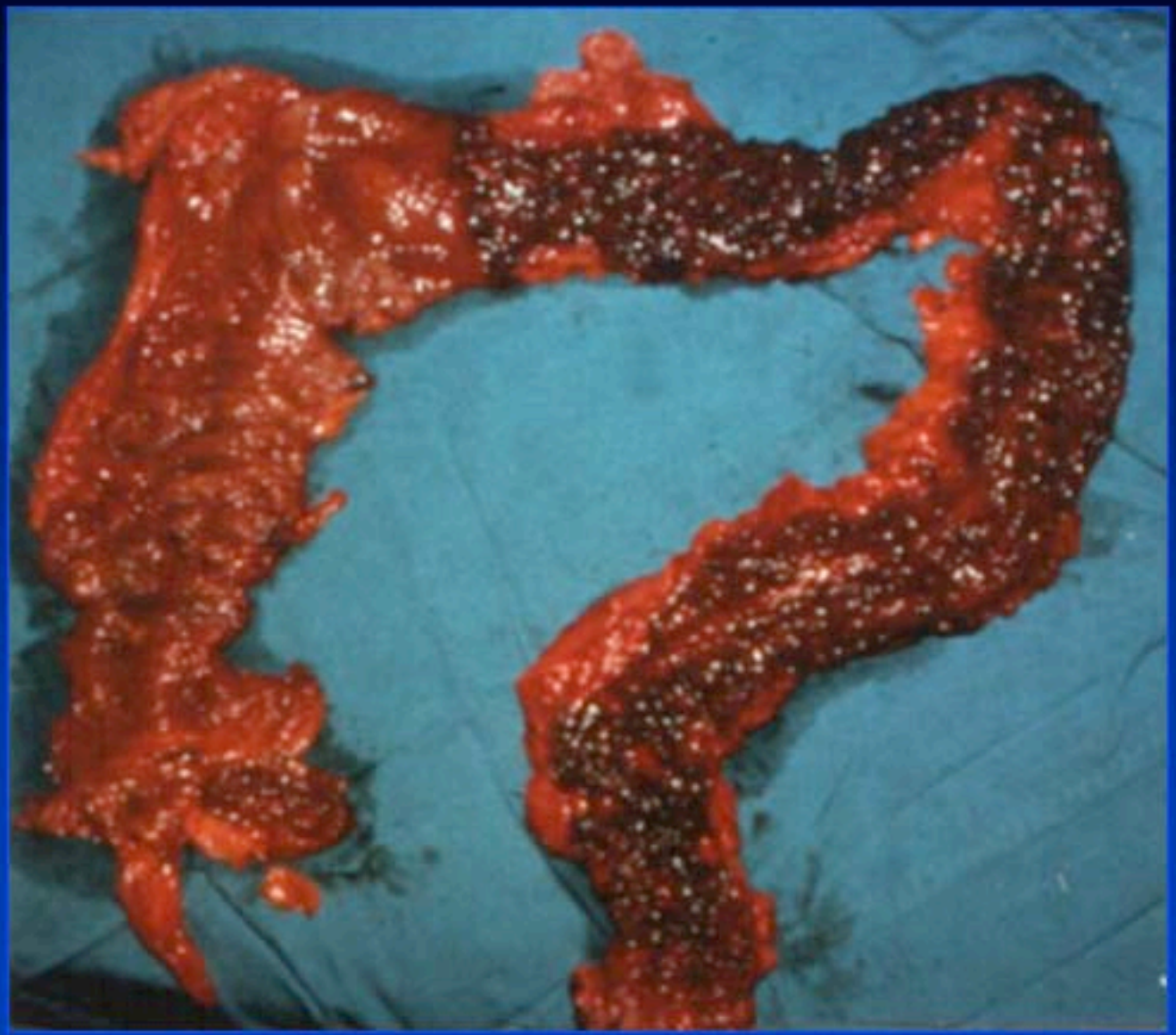
Ulcerative Colitis



- Colon only
- Mucosal inflammation
- Continuous distribution
- Rectal involvement

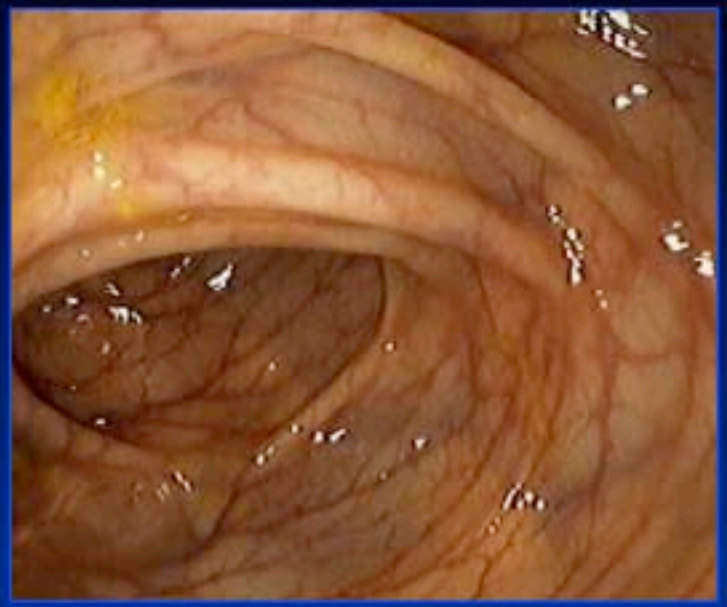
UC - Extent of Disease

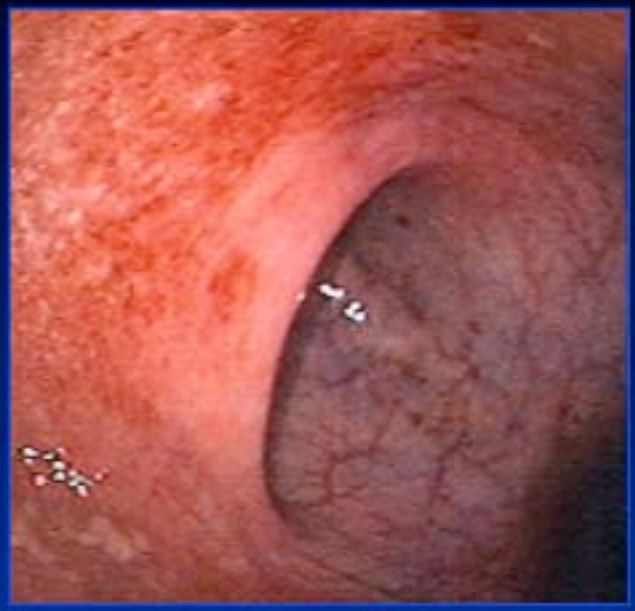




UC - Spectrum of Disease

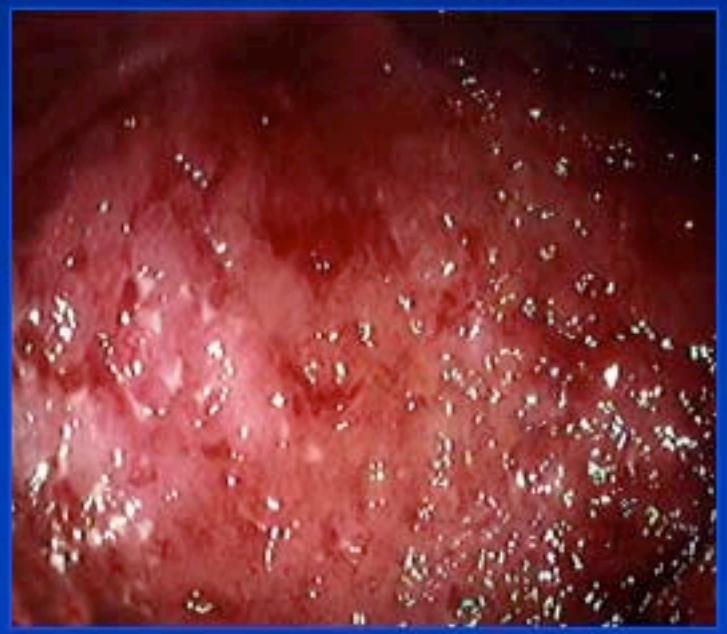
Normal

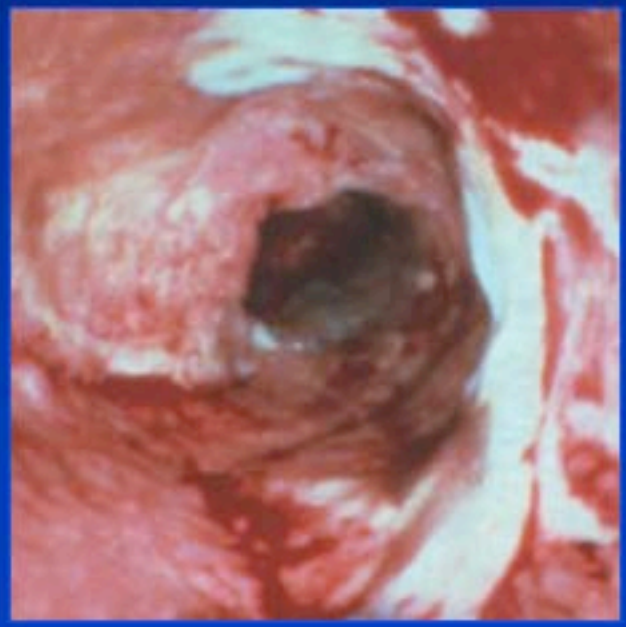




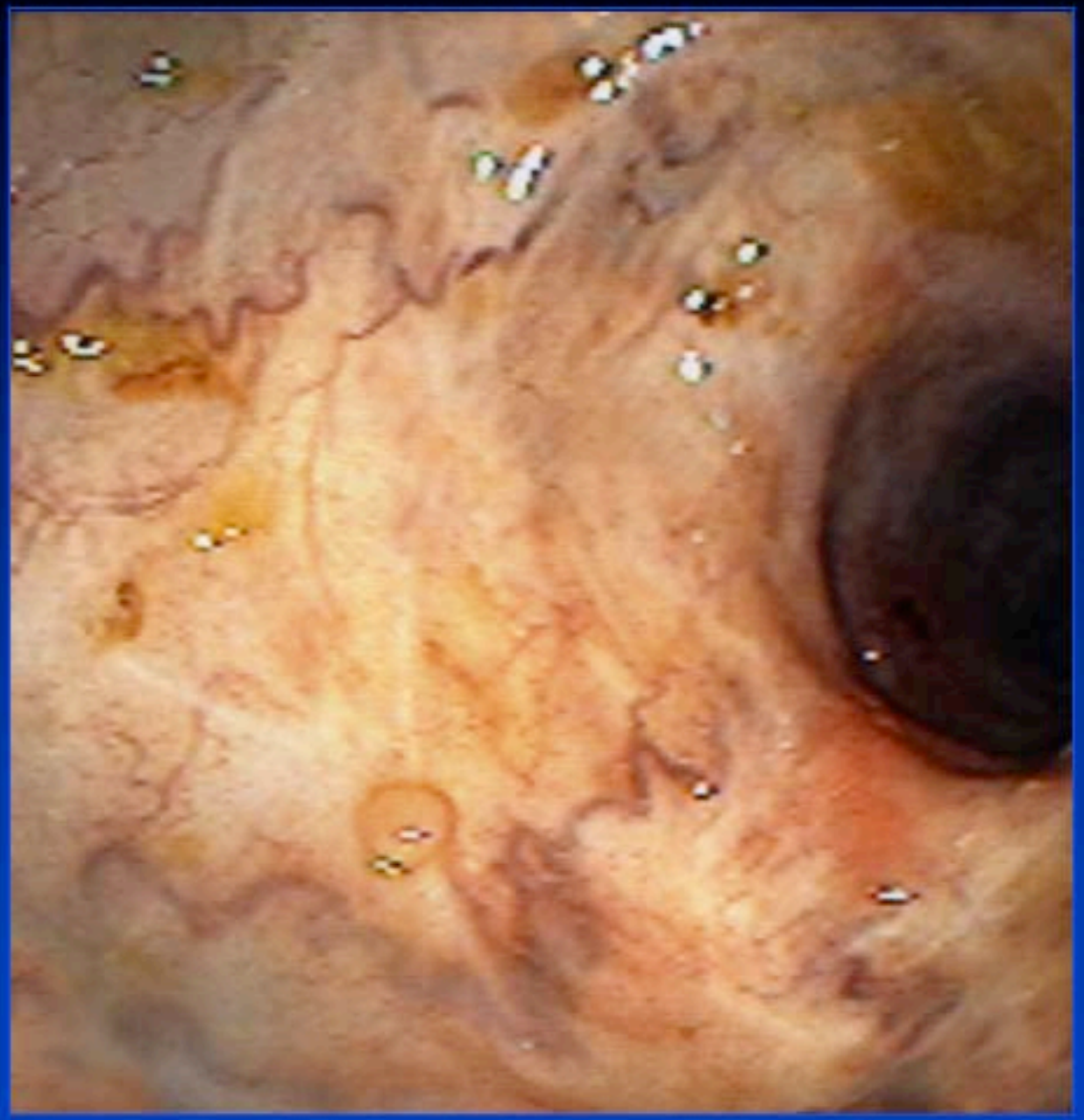
Mild

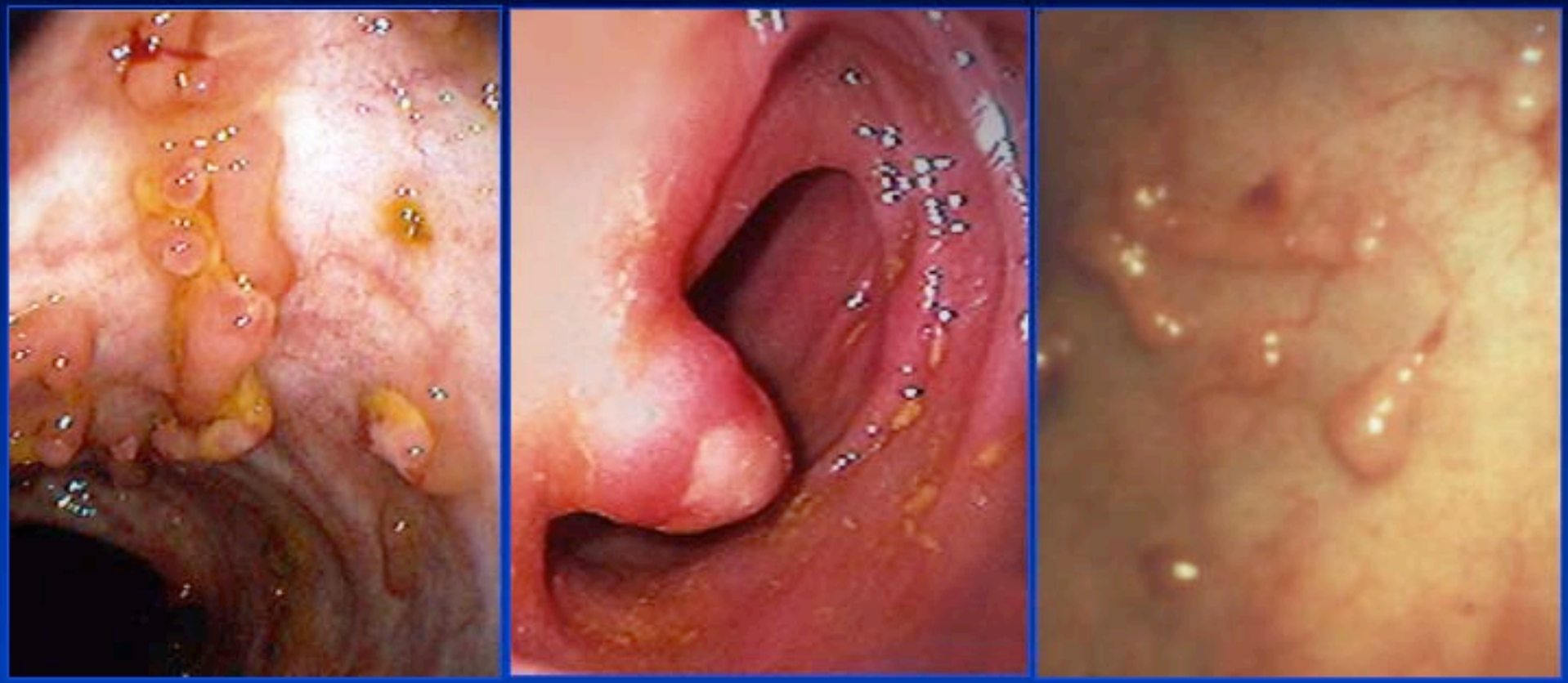
Moderate



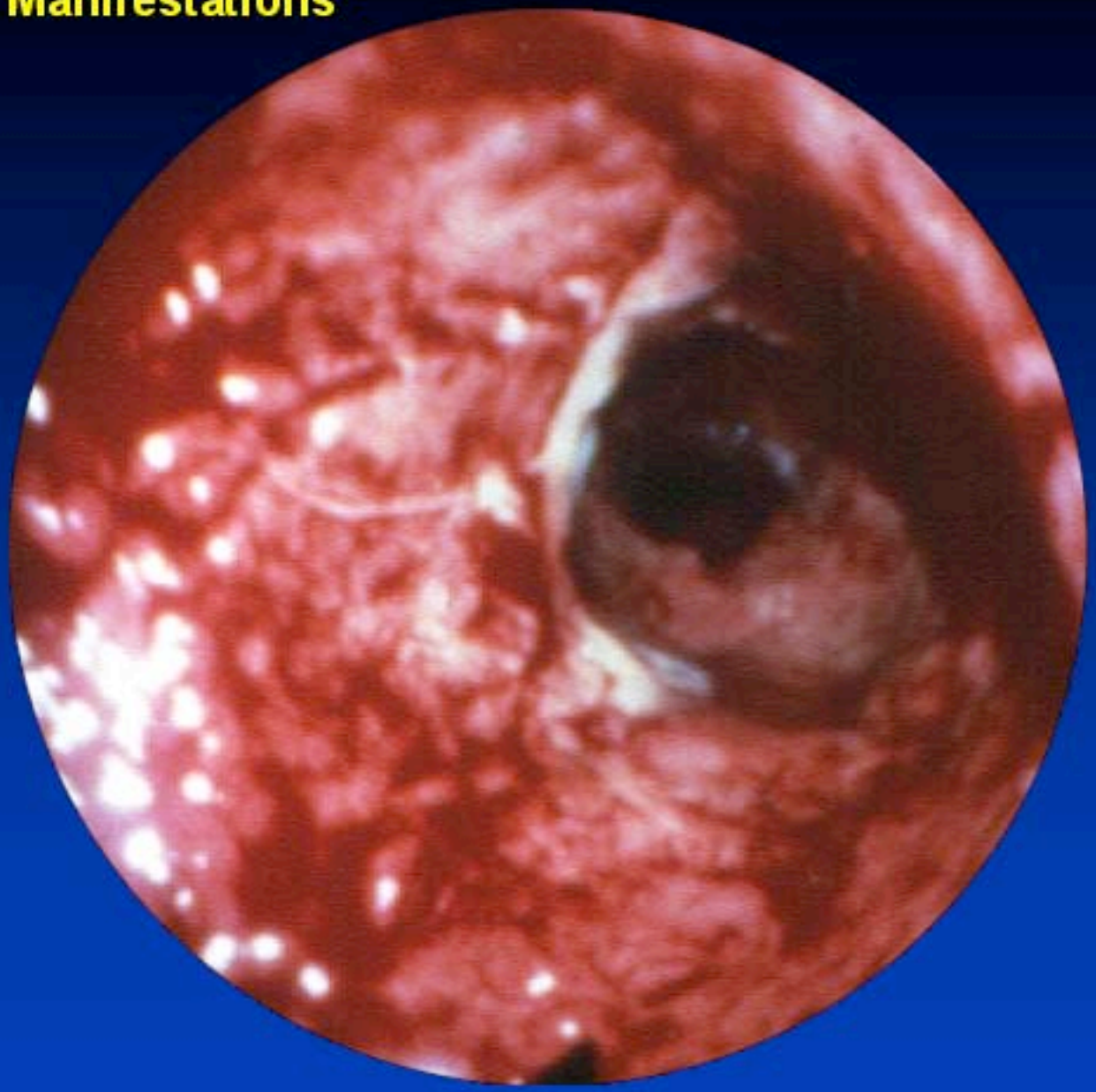


Severe



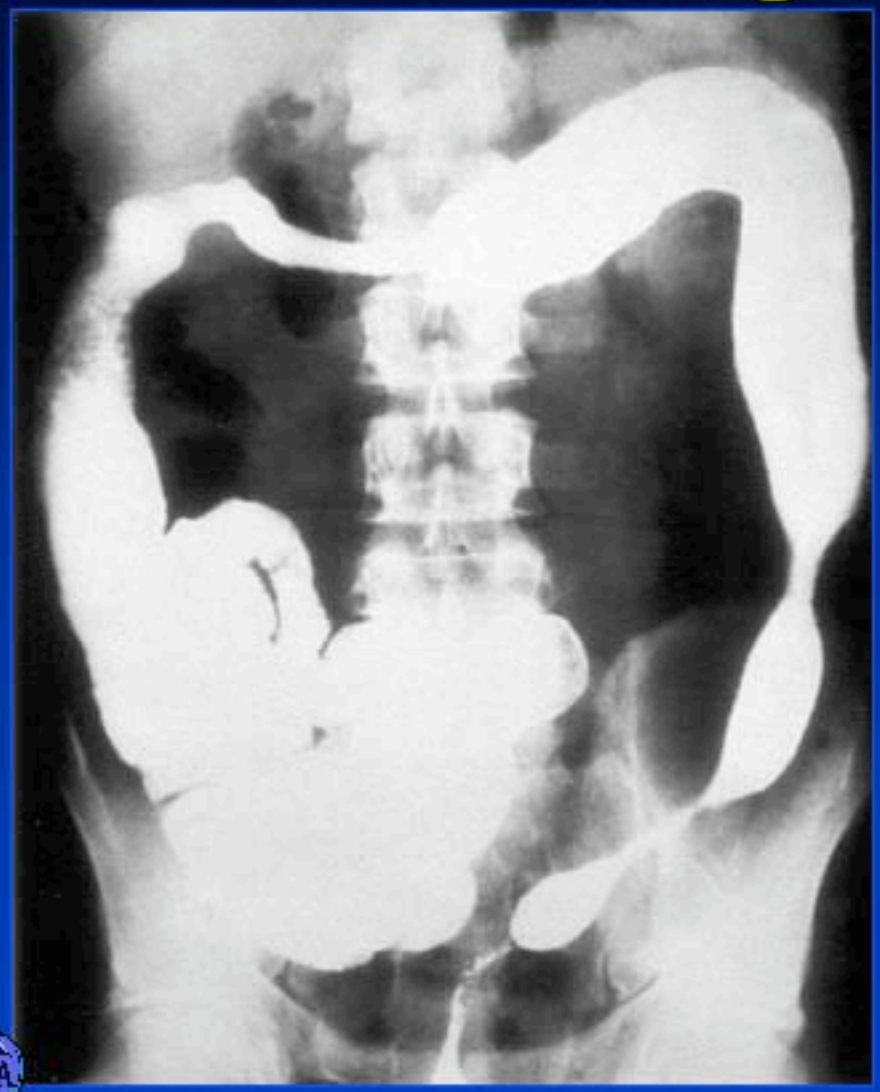


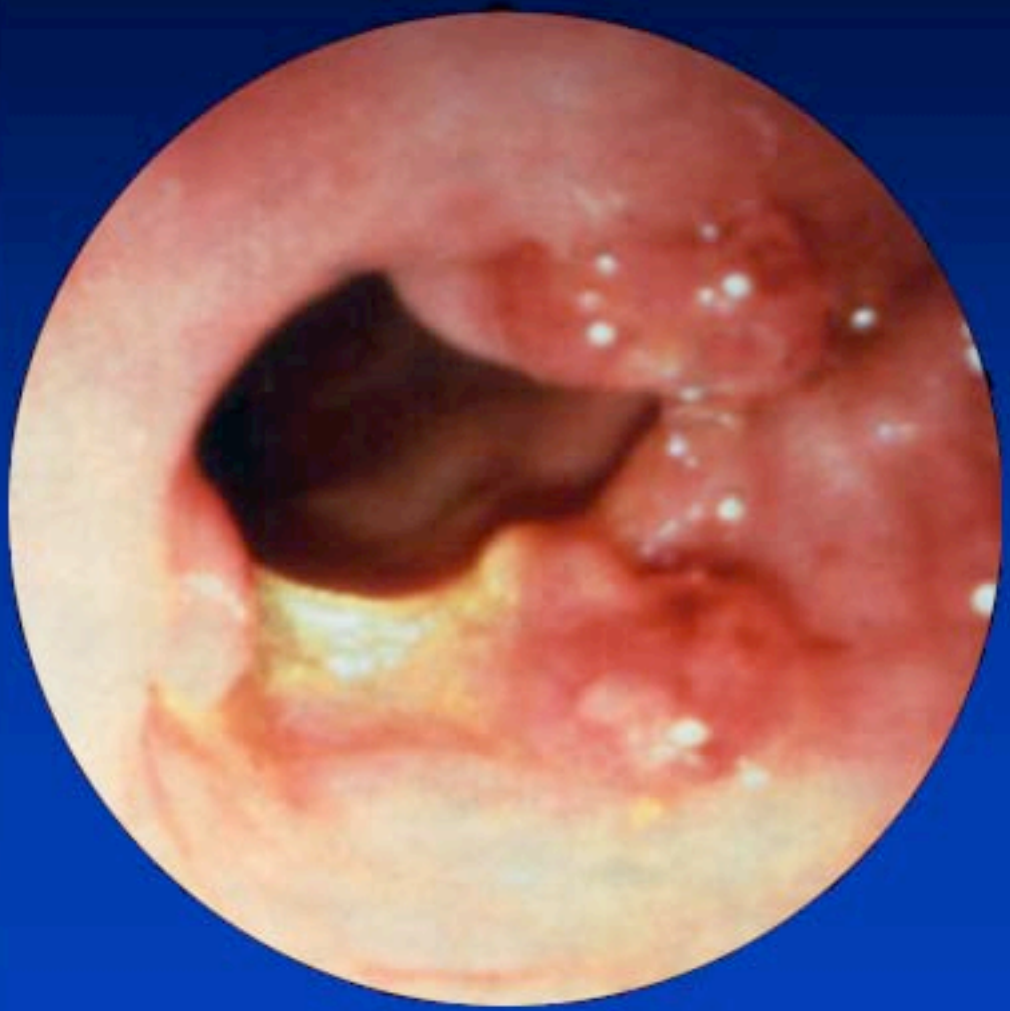
UC - Intestinal Manifestations



UC - Intestinal Complications

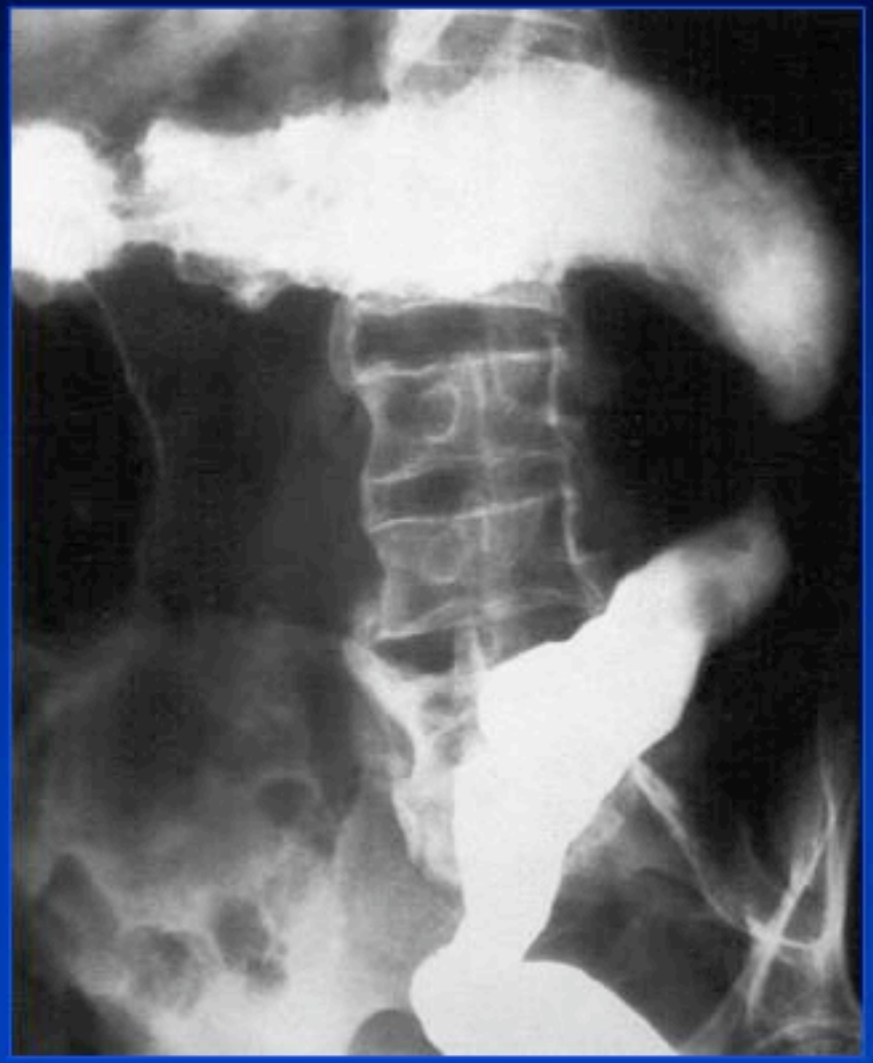
Benign Stricture

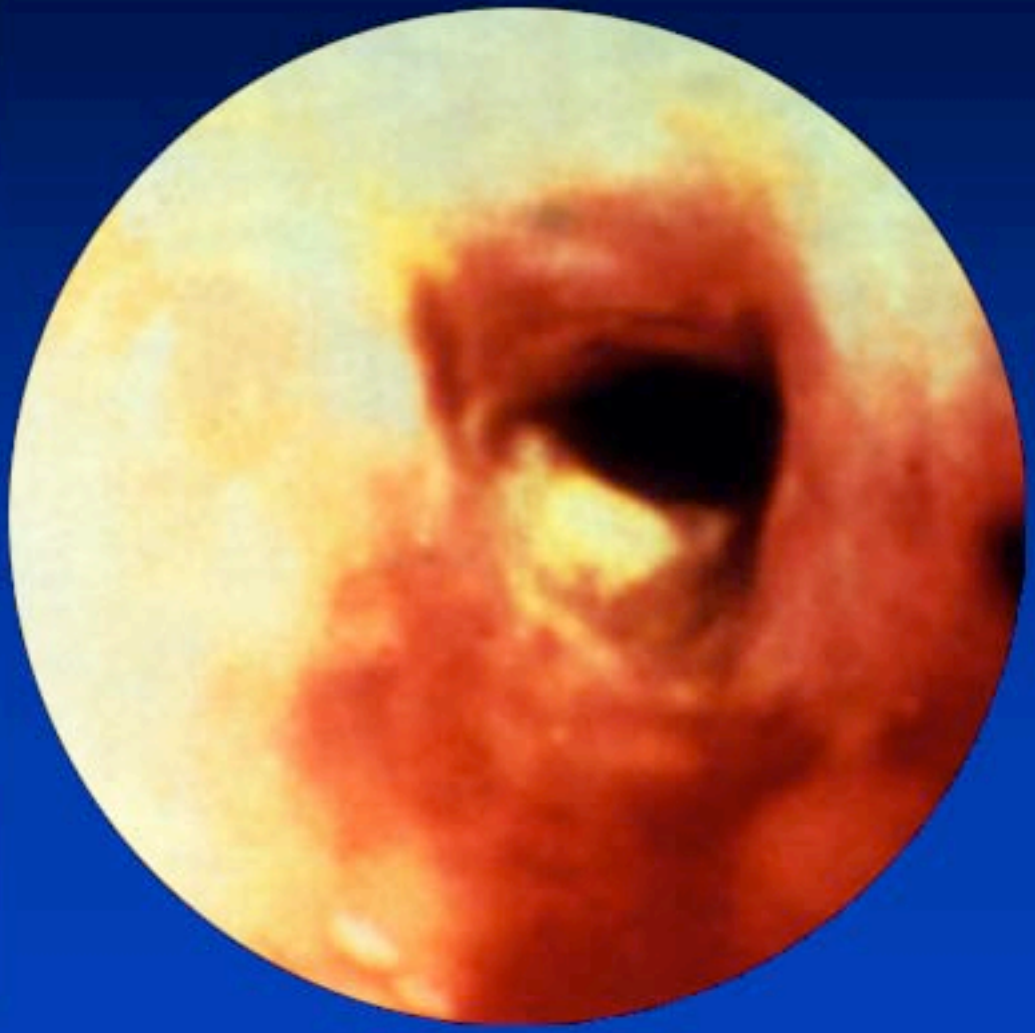


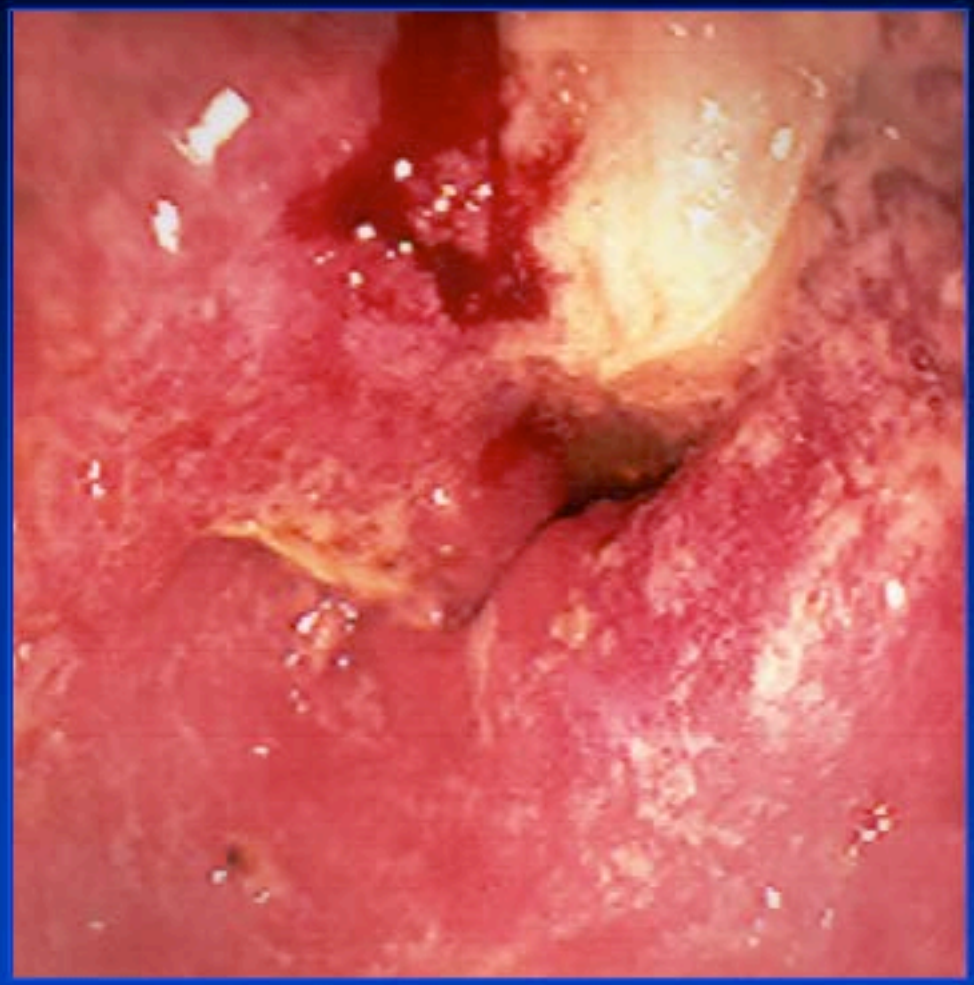


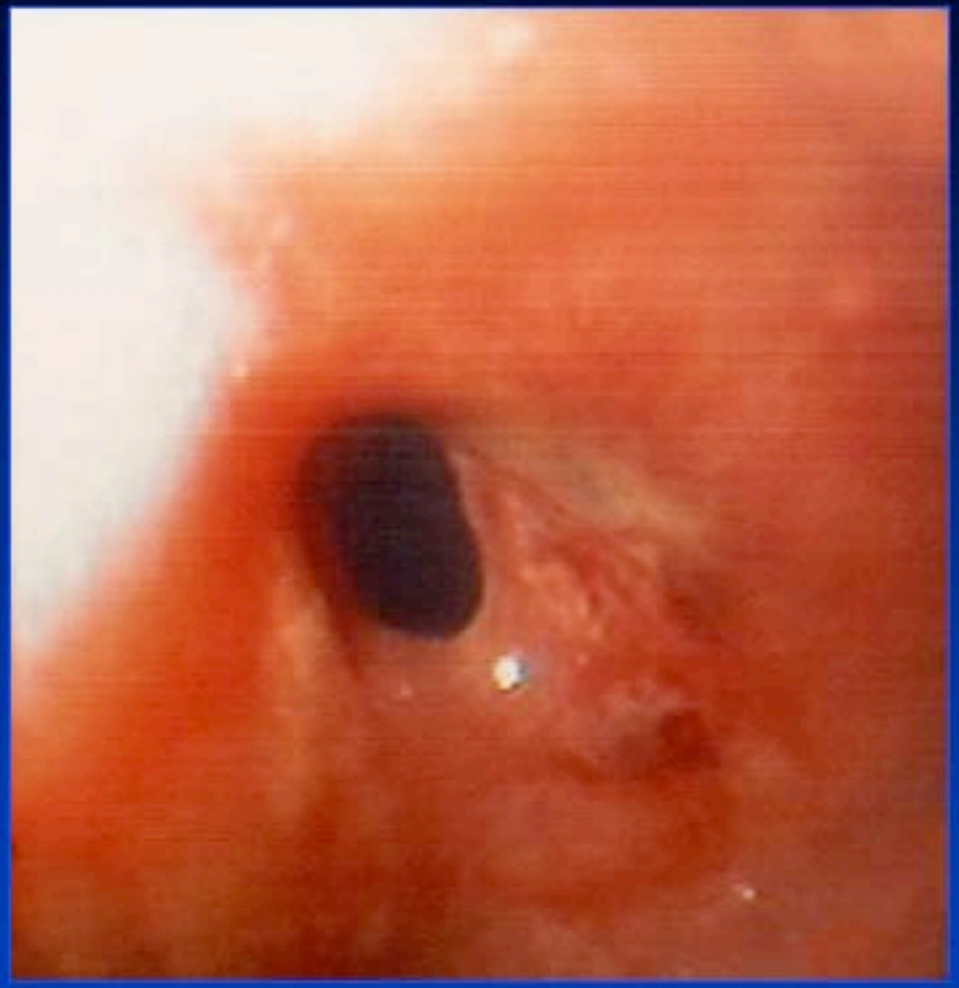
UC - Intestinal Complications

Malignant Stricture









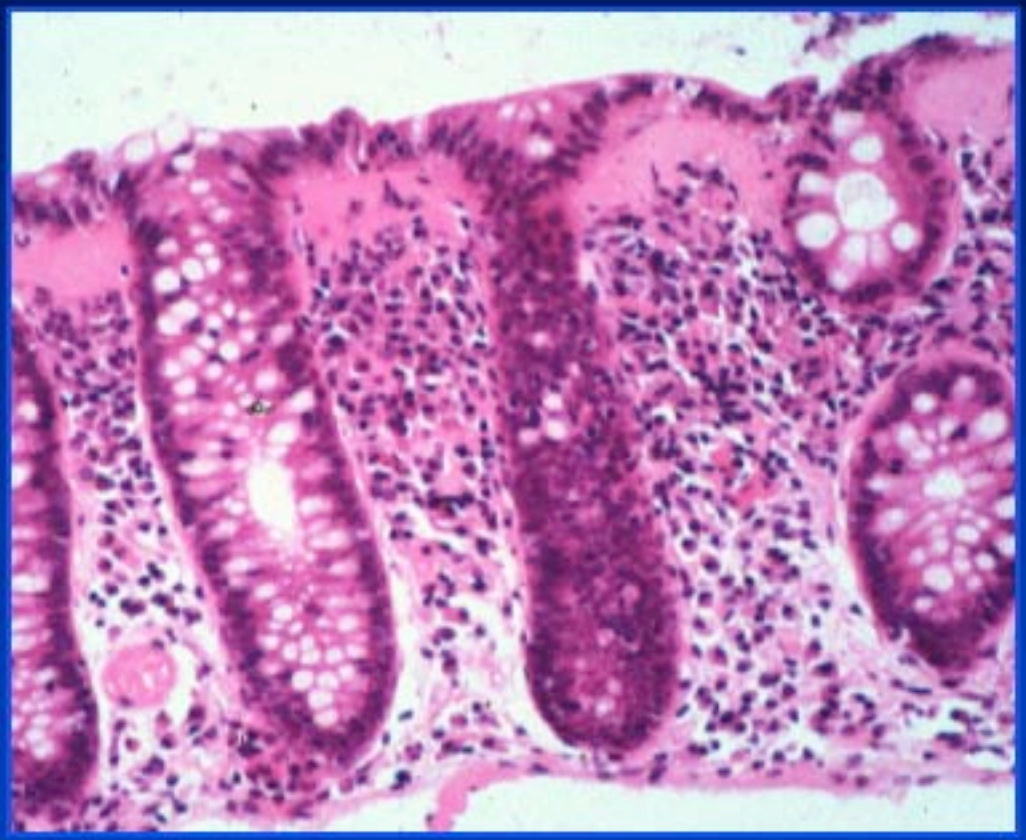
Microscopic Colitis

Collagenous

Lymphocytic

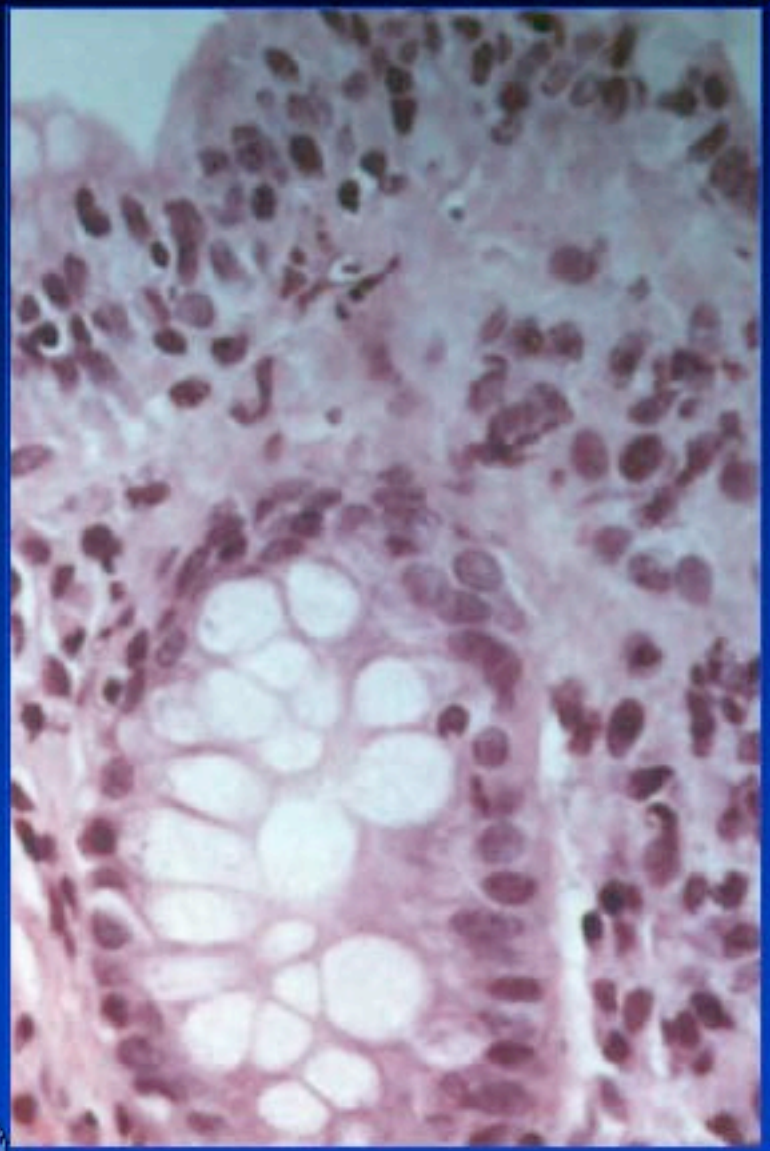
Mucosa usually endoscopically normal but microscopically inflamed

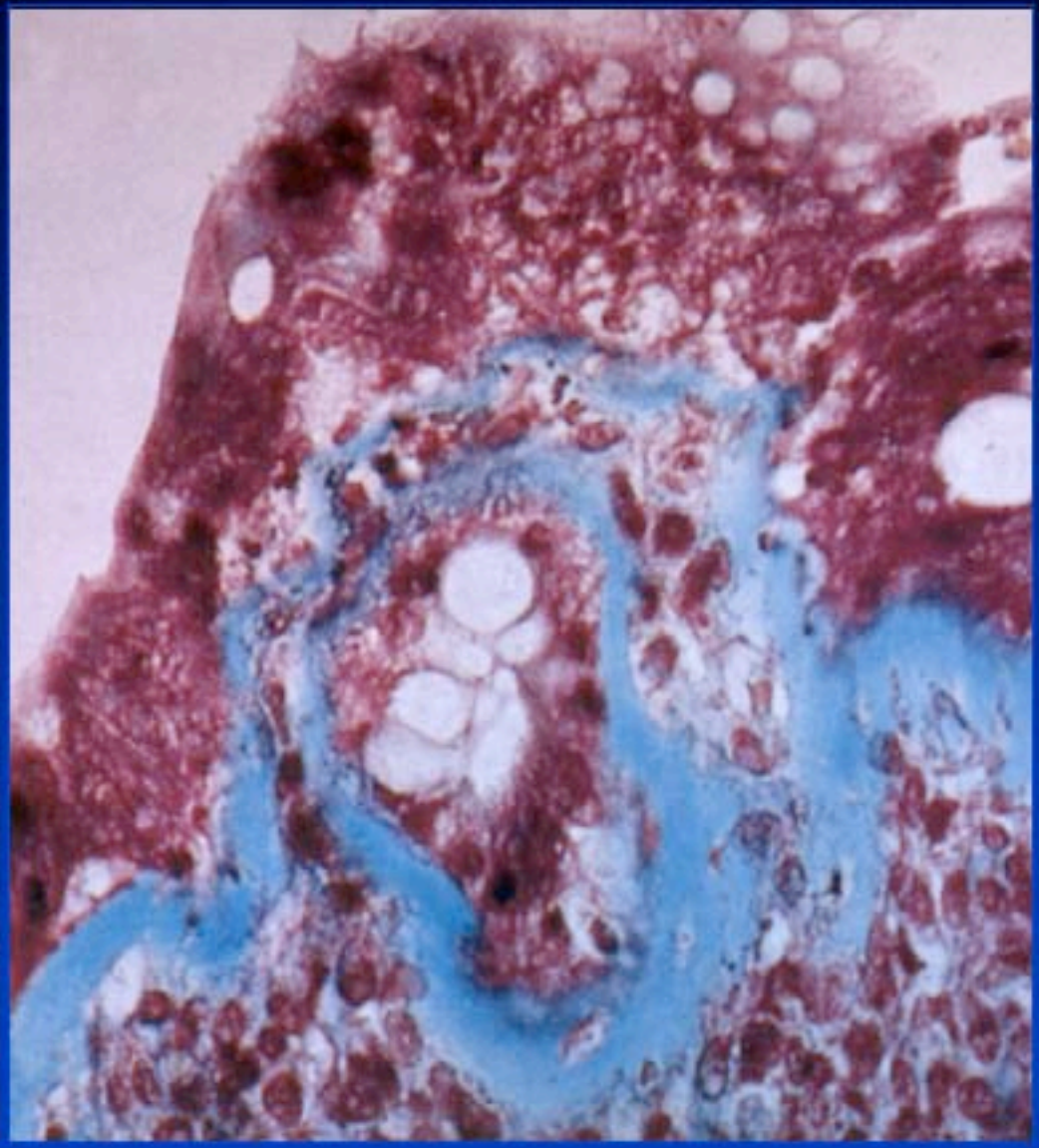
Collagenous Colitis



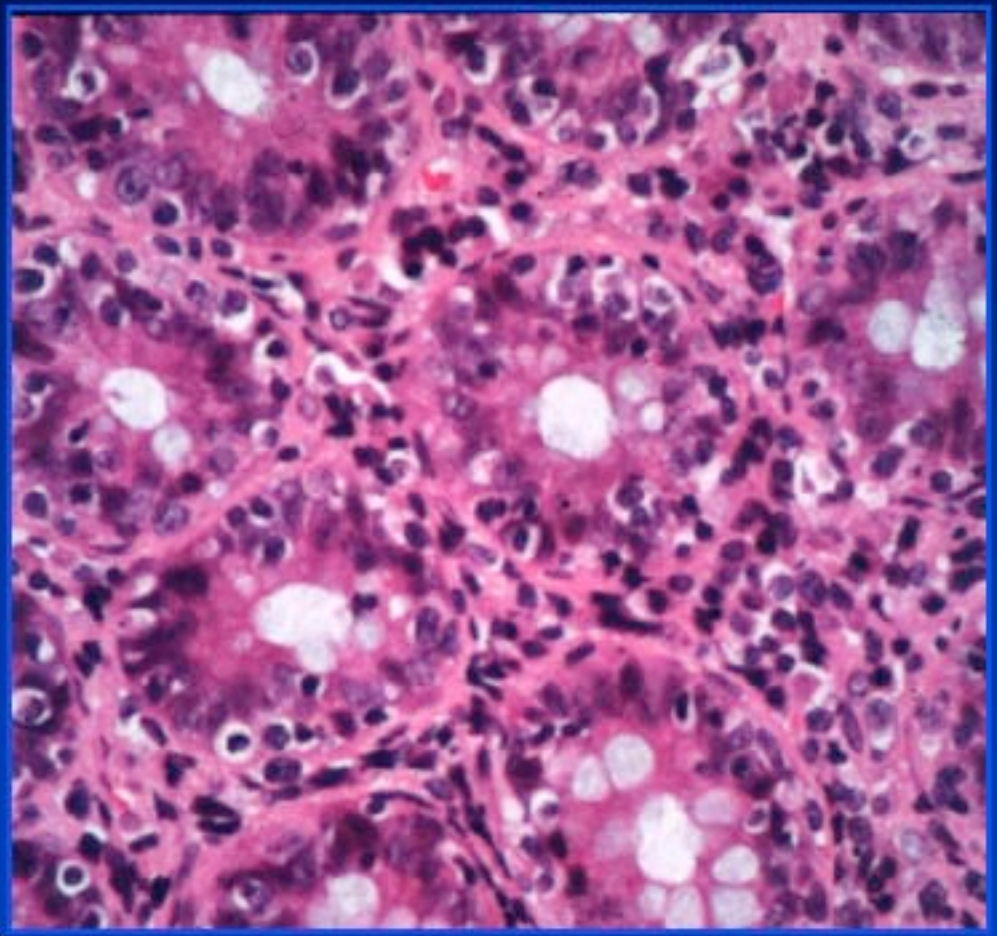
- Watery diarrhea
- No bleeding
- Predominantly older women
- Usually normal endoscopy

IBD - Differential Diagnosis



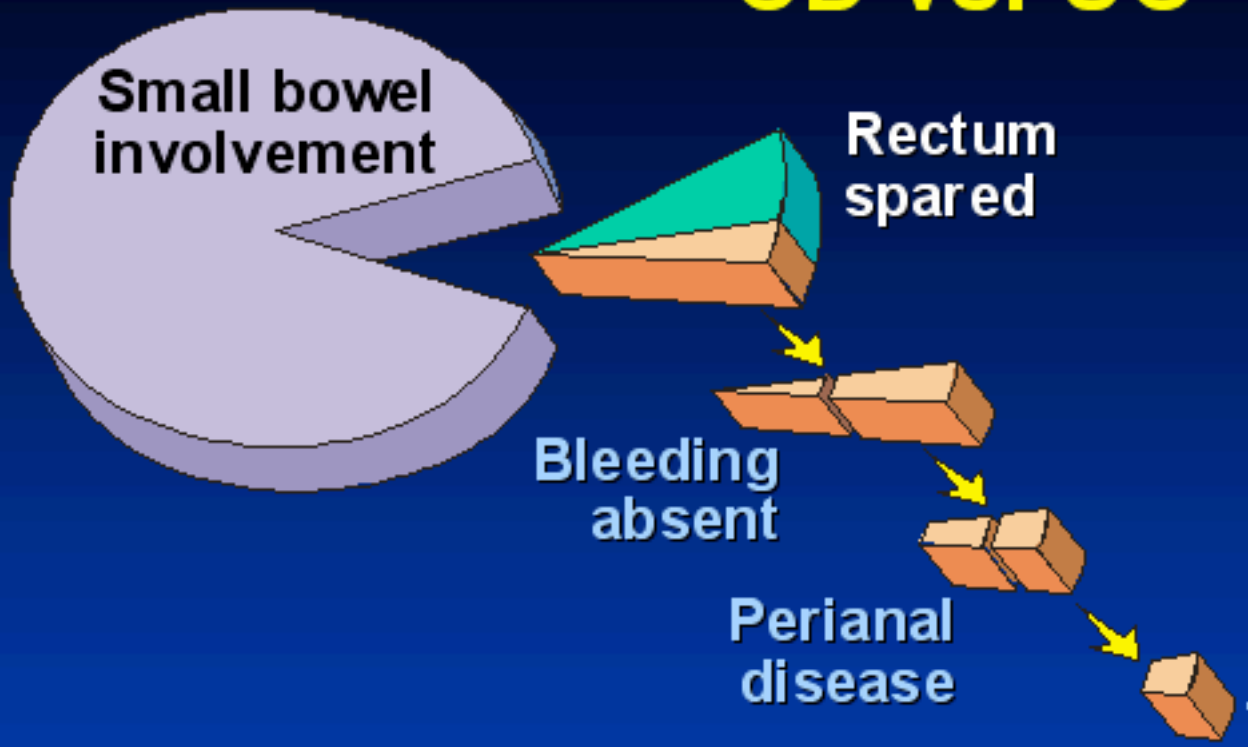


Lymphocytic Colitis



- Watery diarrhea
- Middle aged adults, M = F
- Usually normal endoscopy
- May be associated with celiac disease or autoimmunity

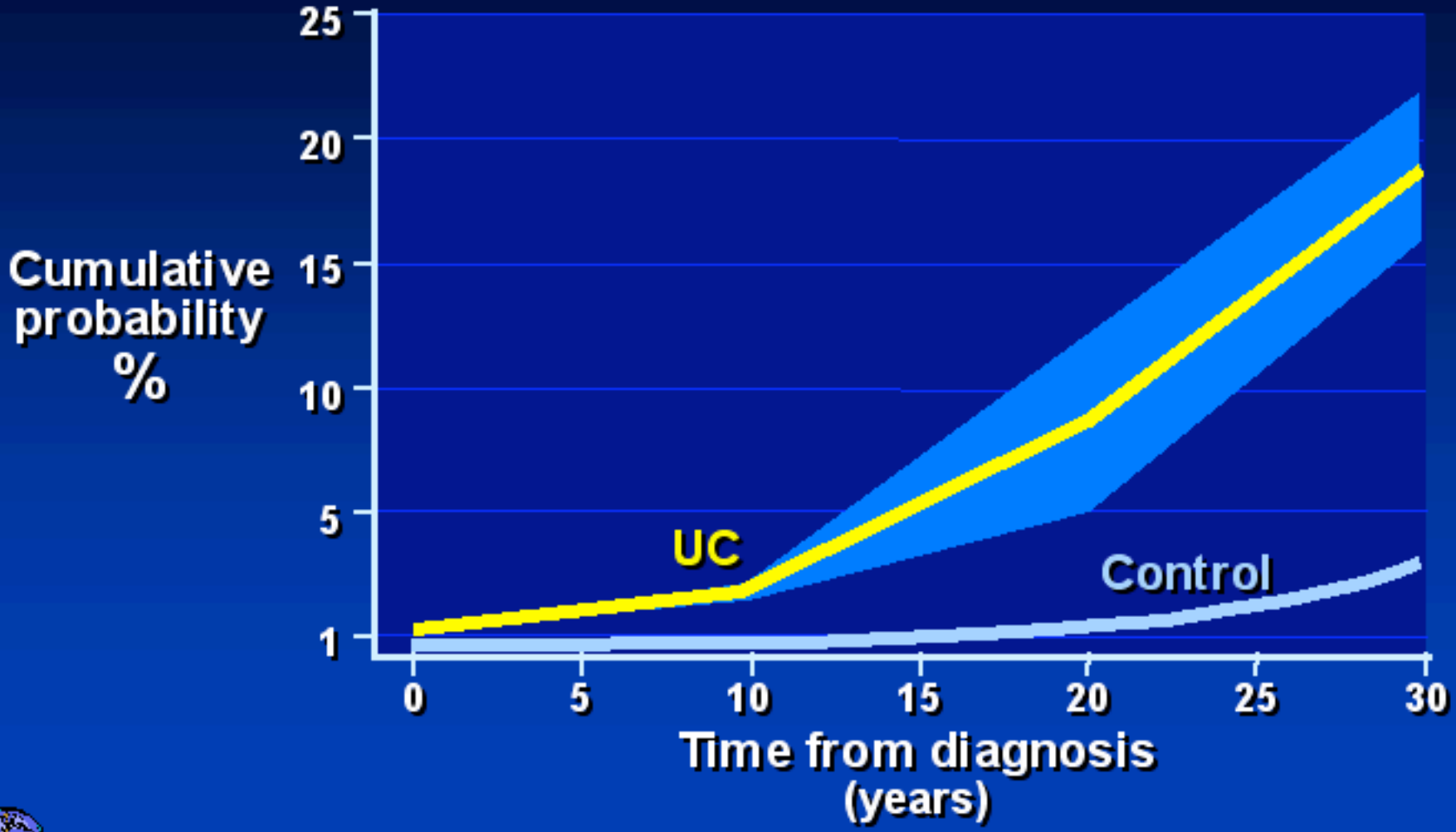
CD vs. UC



- Focal lesions
- Segmental distribution
- Asymmetrical involvement
- Fistulae
- Granulomas
- Endoscopic features
- Serology

UC - Complications

Risk of Colorectal Cancer



Gut 2001, 48:526

IBD - Colorectal Cancer

Increased risk

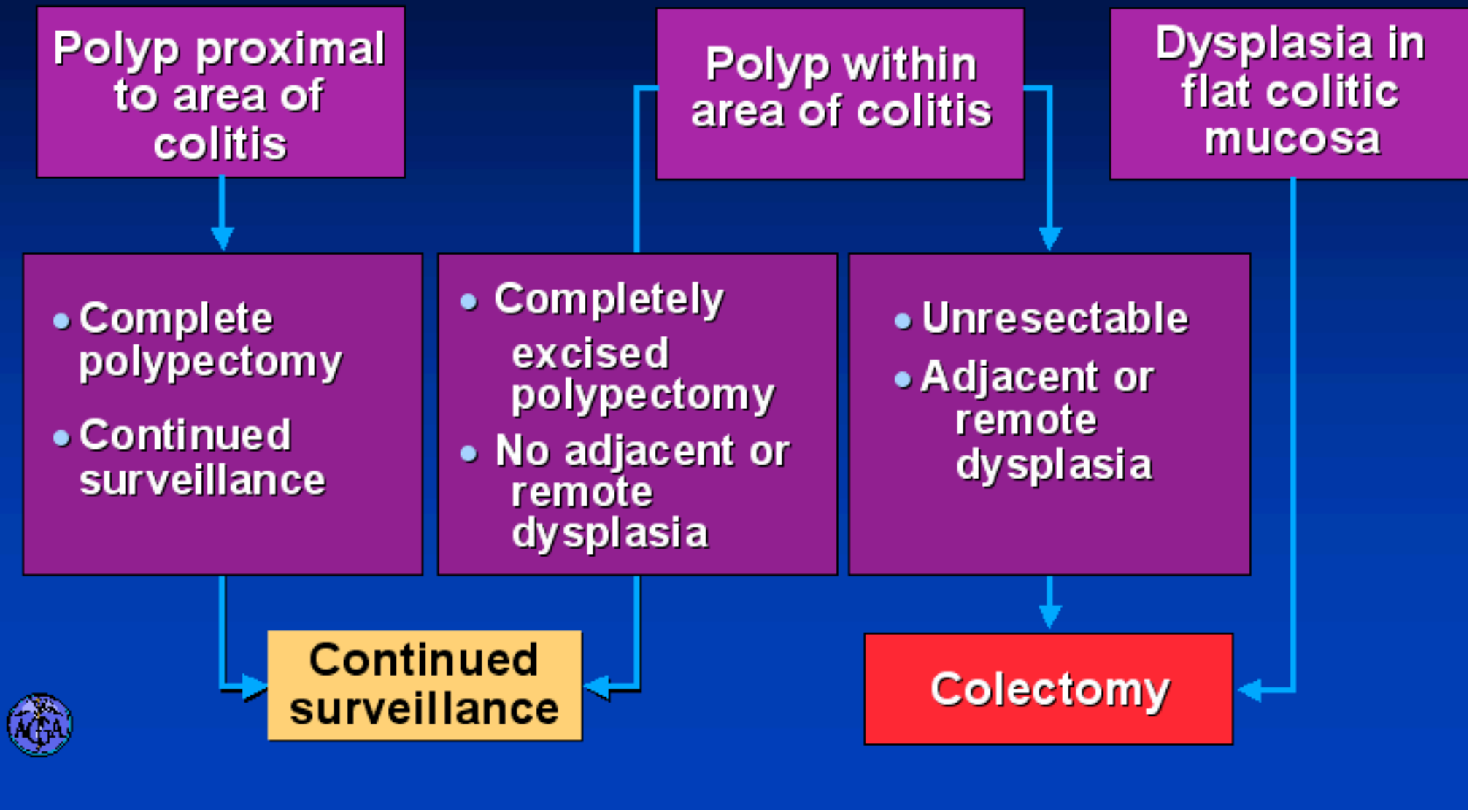
- Long duration
- Anatomical extent
- PSC
- Family history of CRC

Possible protection

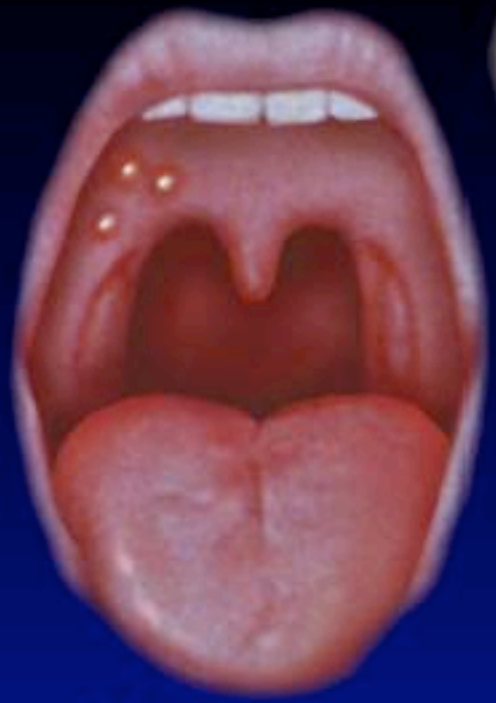
- 5-ASA
- Folate
- Tight medical control

UC - Dysplastic Lesions

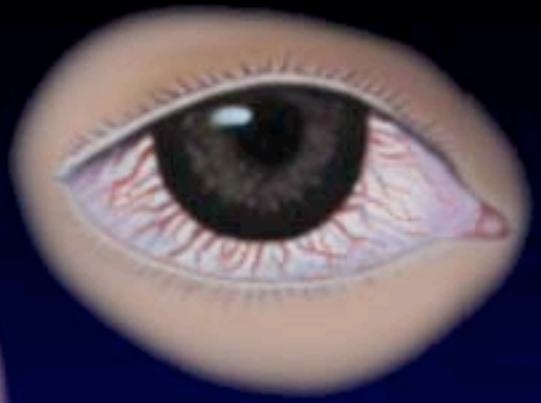
Suggested Management of Dysplasia - 2002



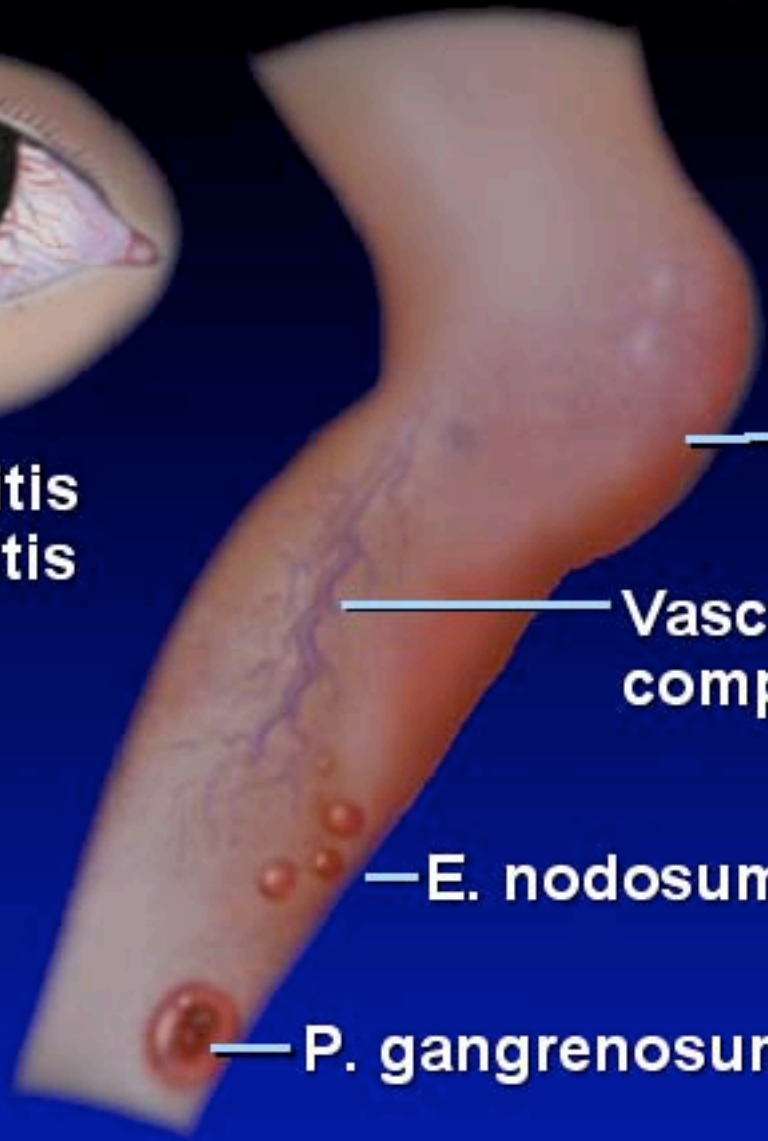
IBD - Extraintestinal Manifestations Related to Disease Activity



Aphthous stomatitis



Episcleritis and uveitis



Arthritis

Vascular complications

E. nodosum

P. gangrenosum

Osteopenia Risk Factors

Baseline

- Ethnicity
- Family History
- Lifestyle and dietary habits
- Body habitus
- Reproductive history

Disease related

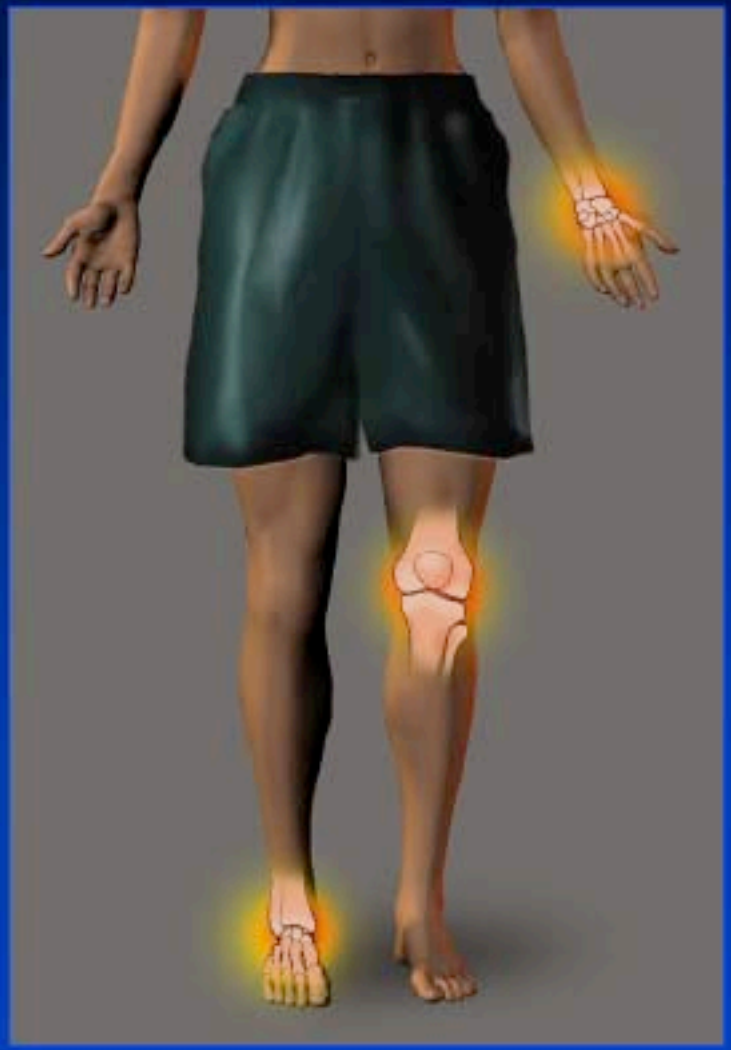
Inflammation

Cytokines
(CD > UC)

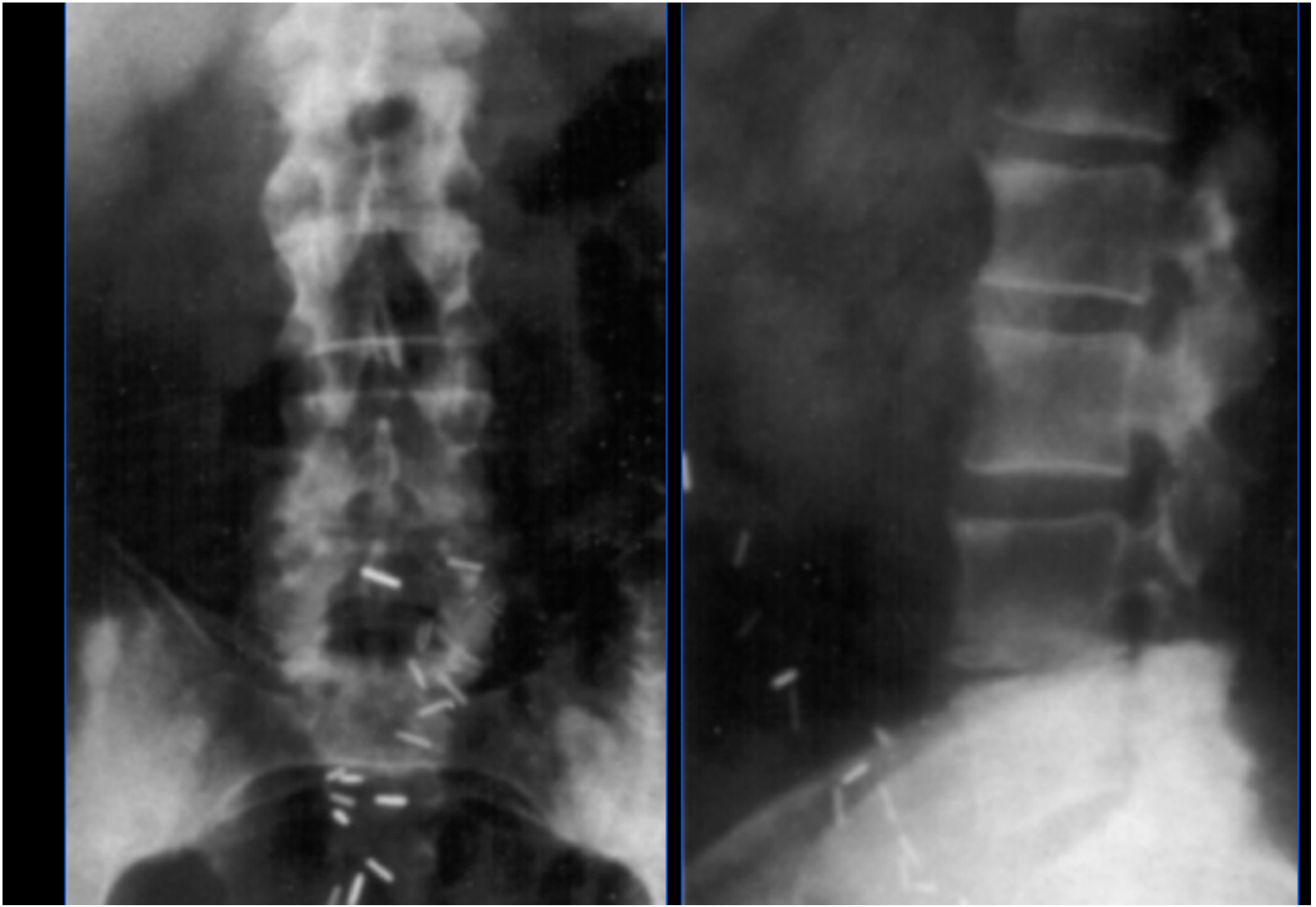
IBD medication

Corticosteroids

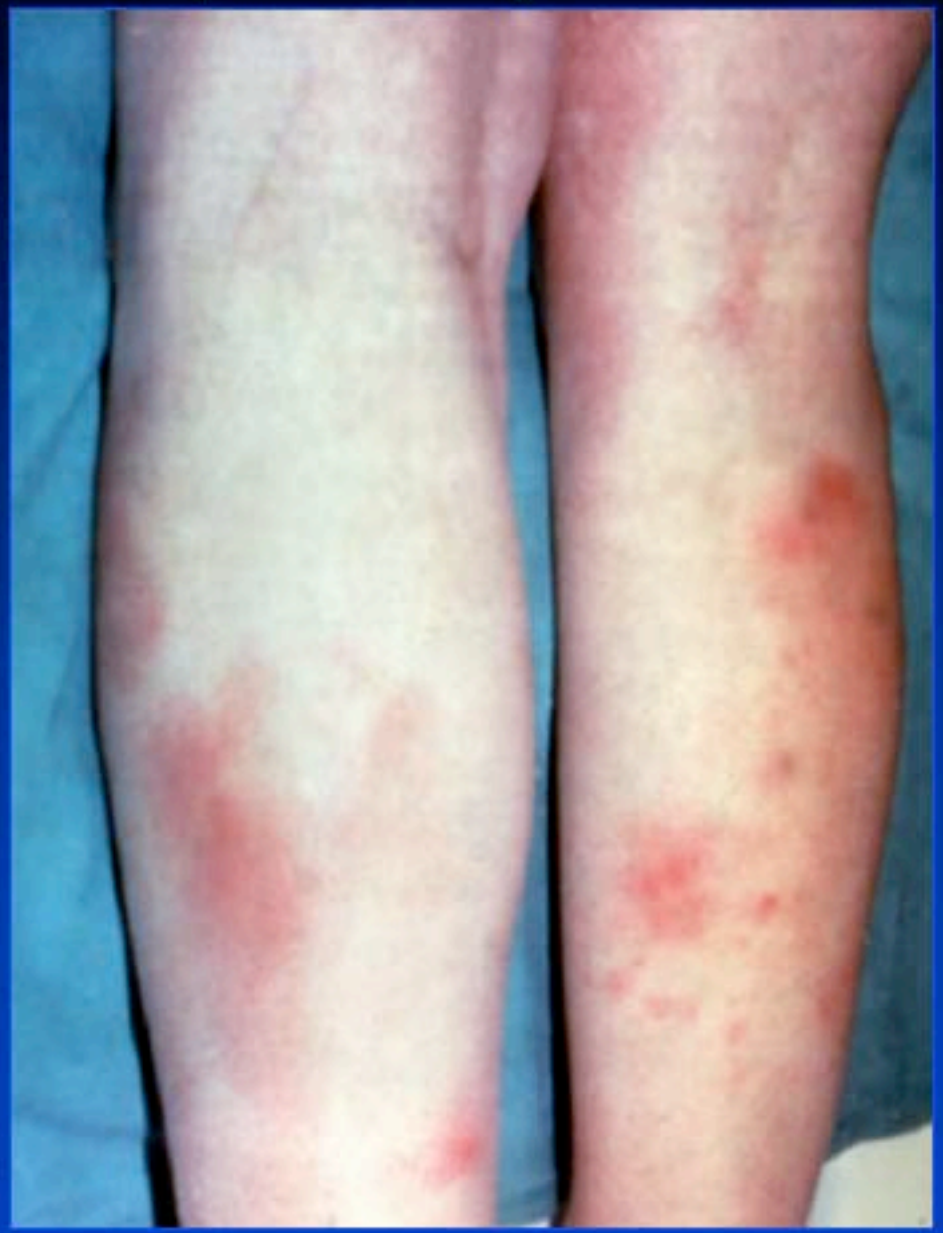
Peripheral Arthritis

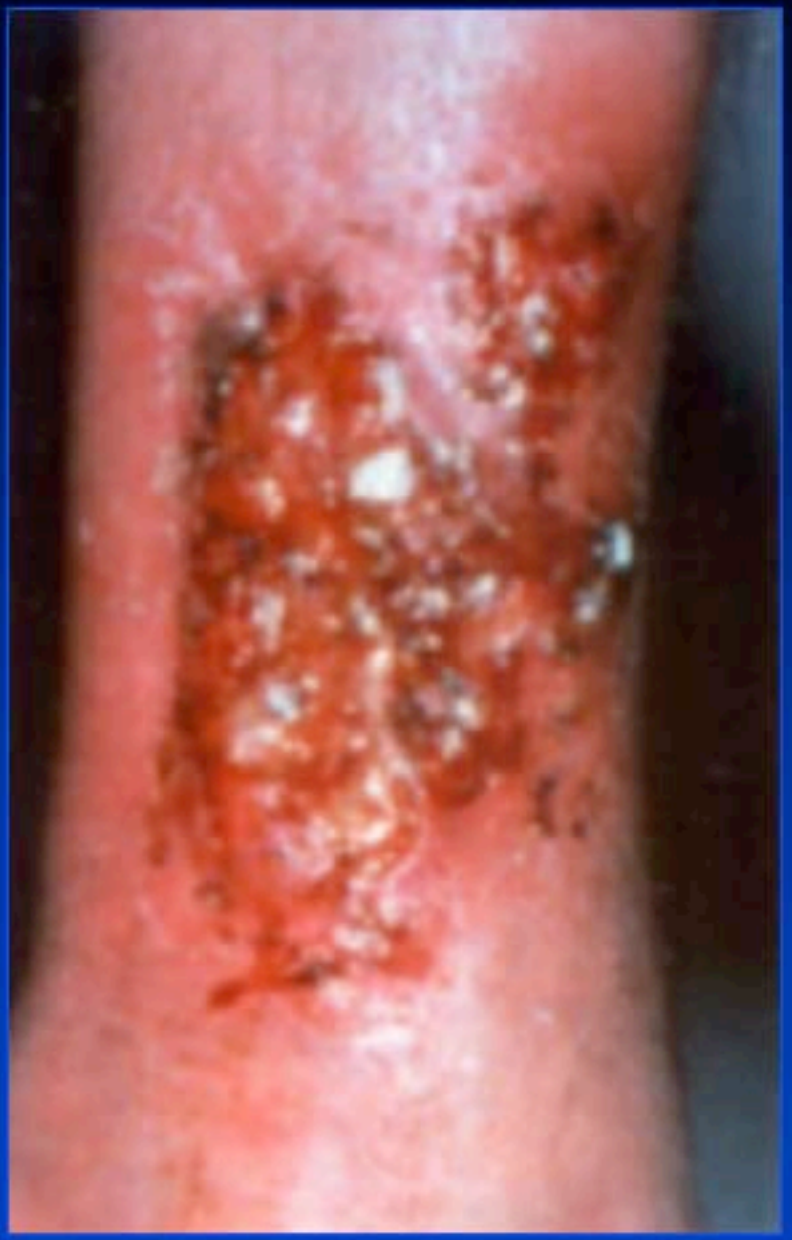


- Monoarticular
- Asymmetrical
- Large > small joint
- No synovial destruction
- No subcutaneous nodules
- Seronegative

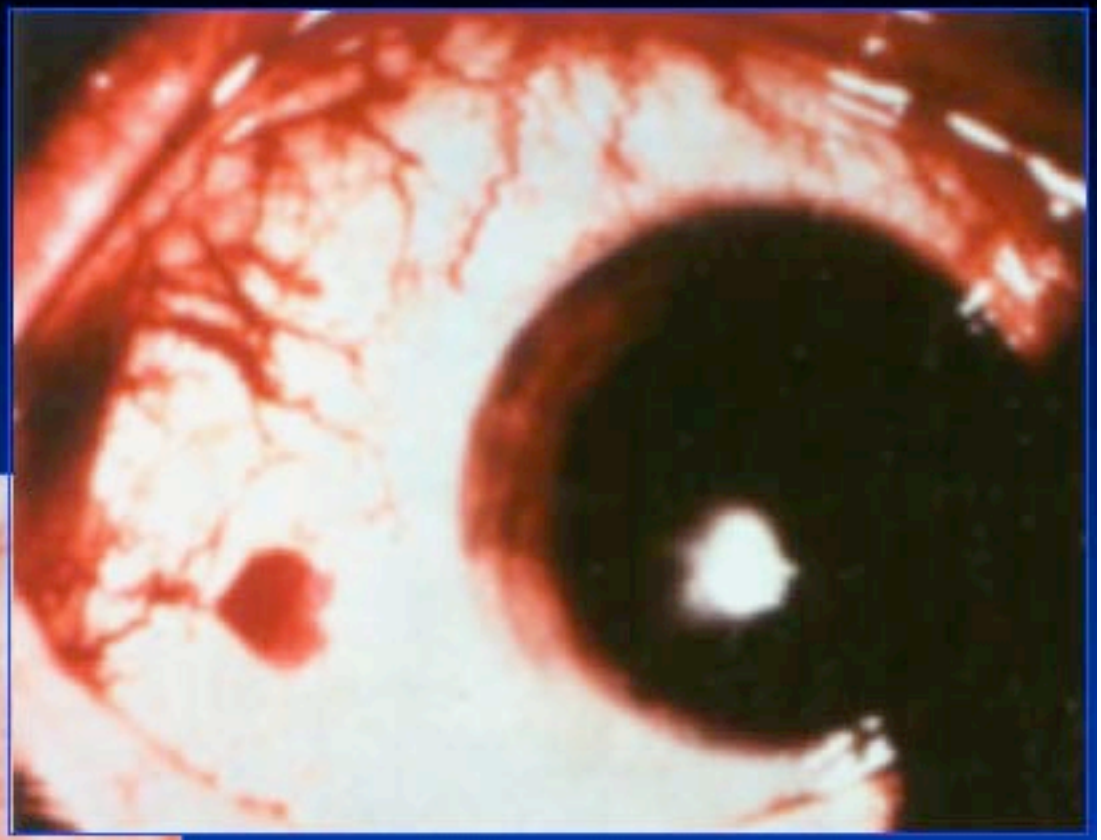


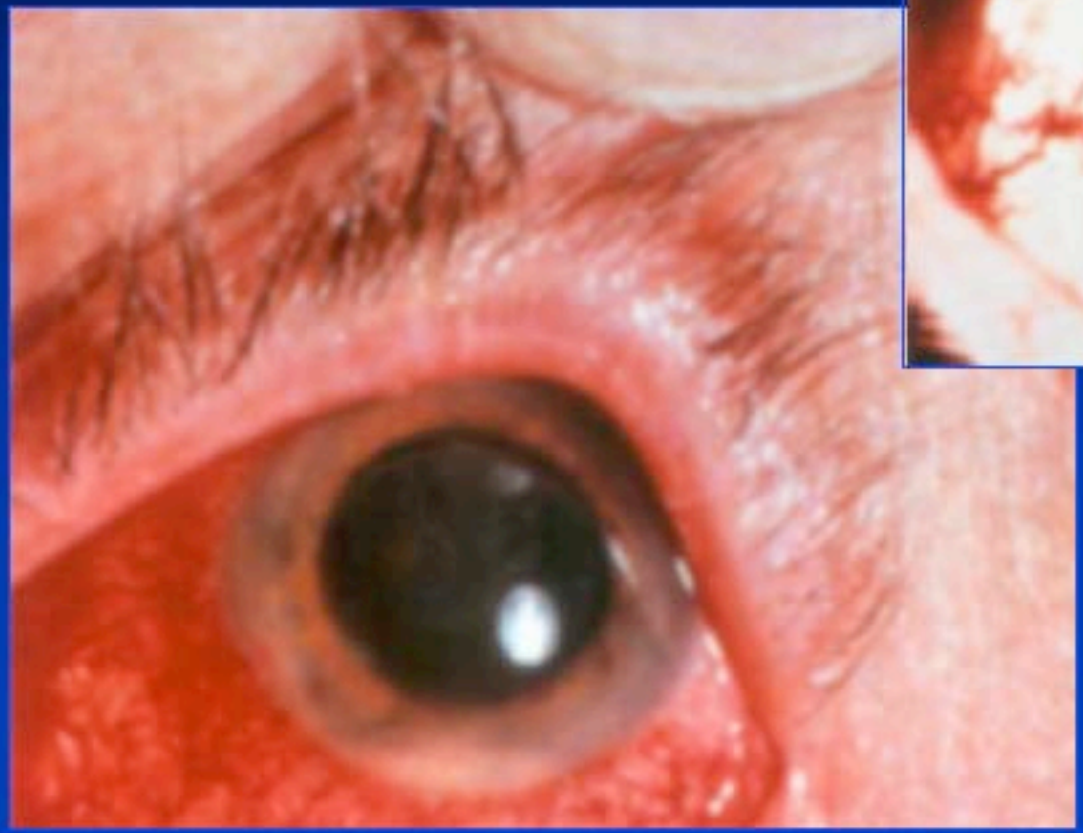
UC - IBD Systemic Complications





UC - IBD Systemic Complications



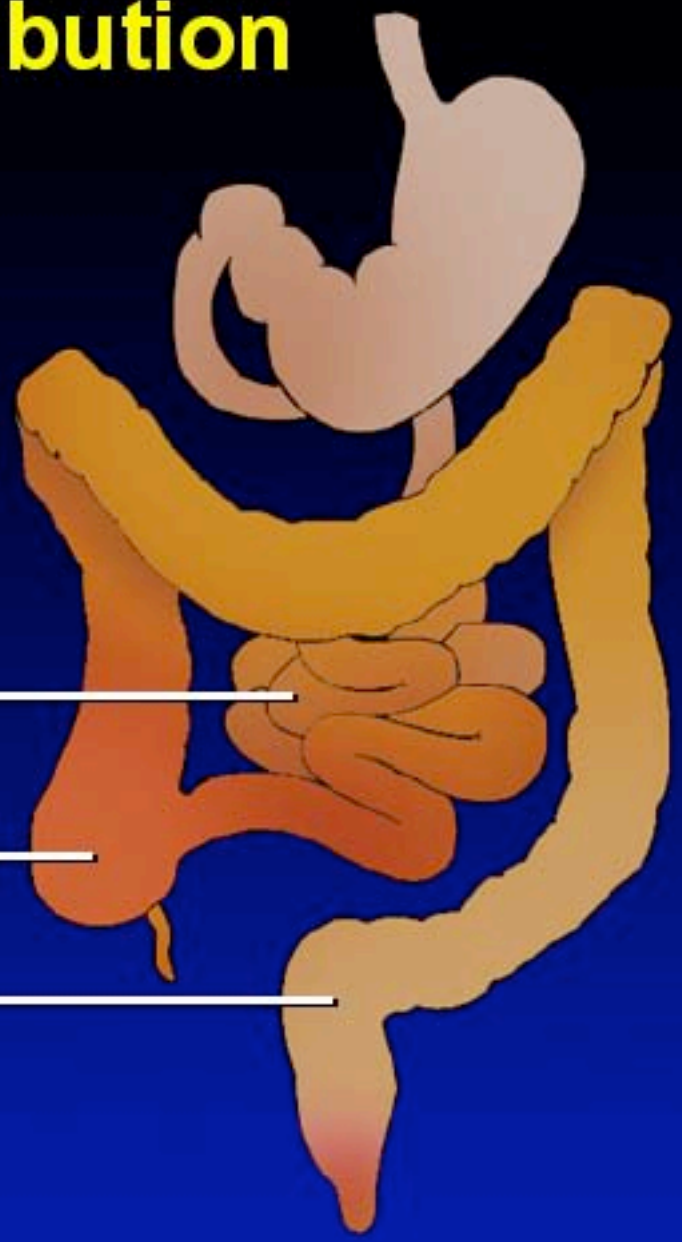


CD

Anatomic Distribution

Freq. of involvement

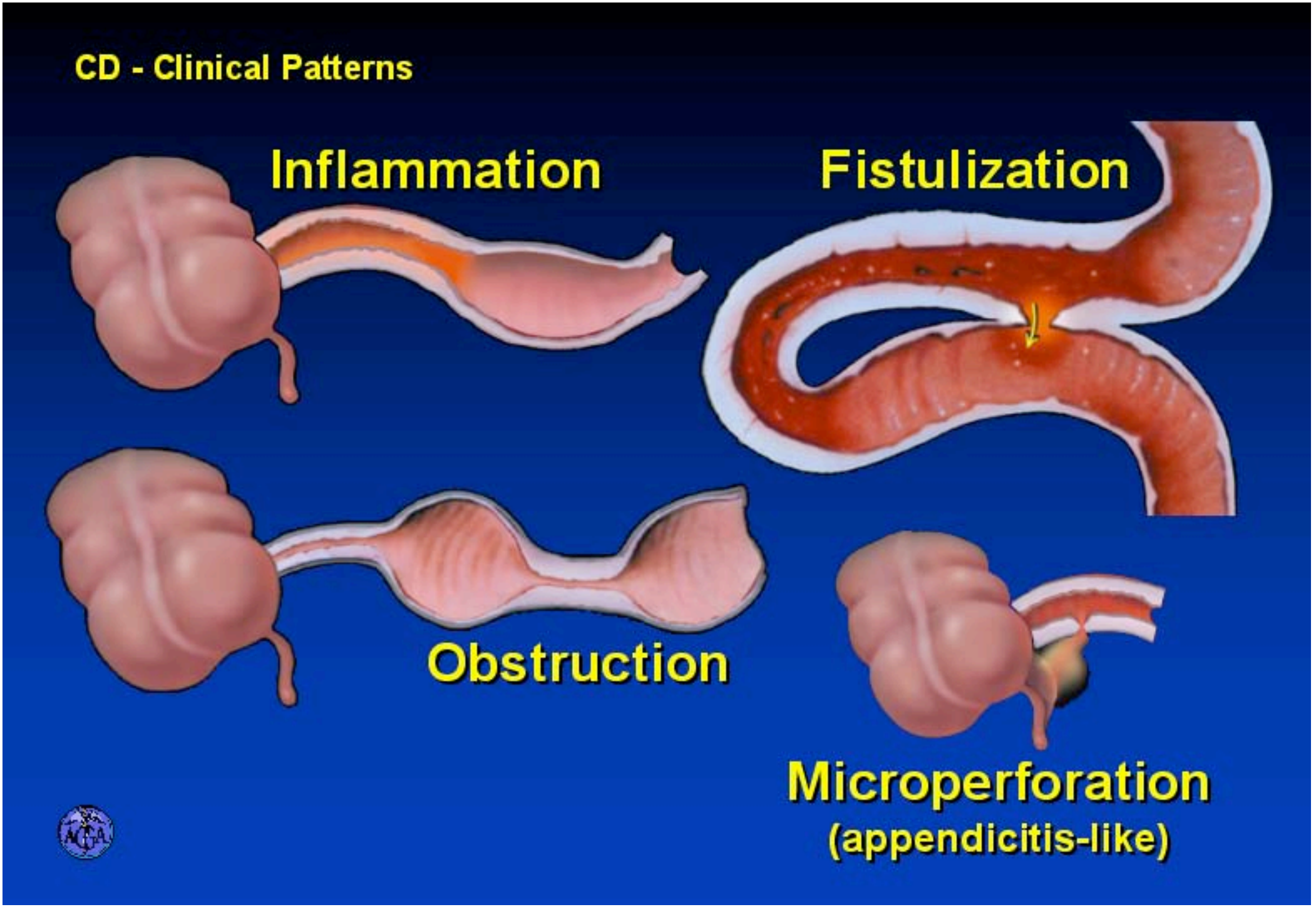
most — least



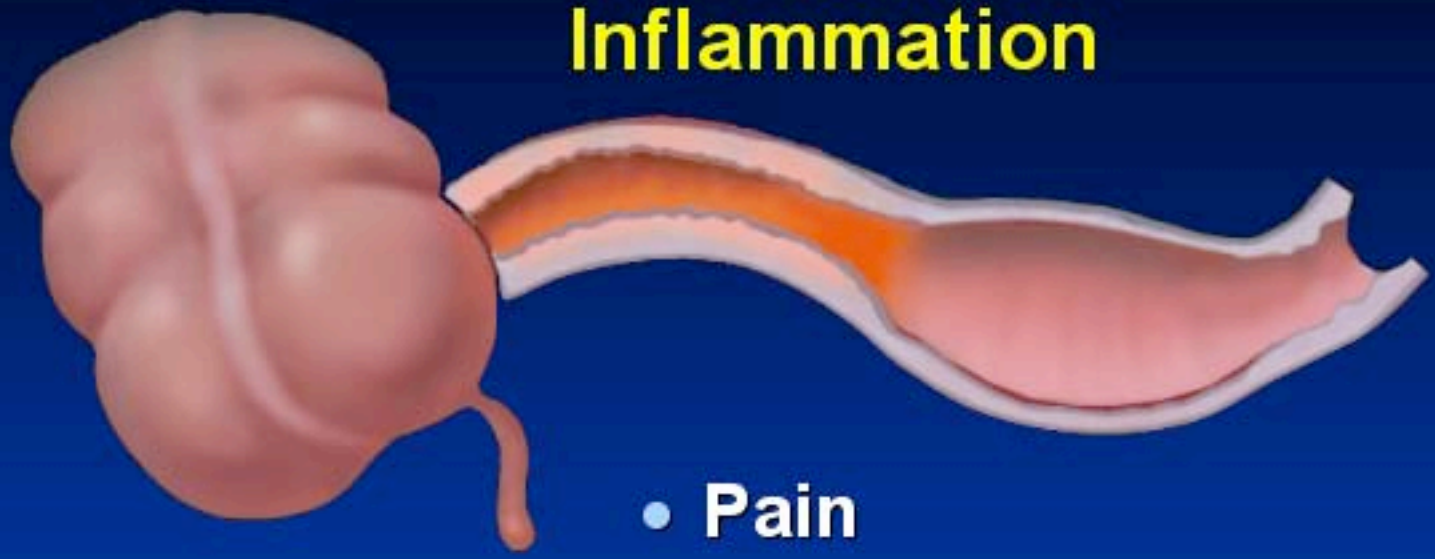
Small bowel alone 33%

Ileocolic 45%

Colon alone 20%


CD - Clinical Patterns
Inflammation
Fistulization
Obstruction
Microperforation
(appendicitis-like)

CD - Clinical Patterns

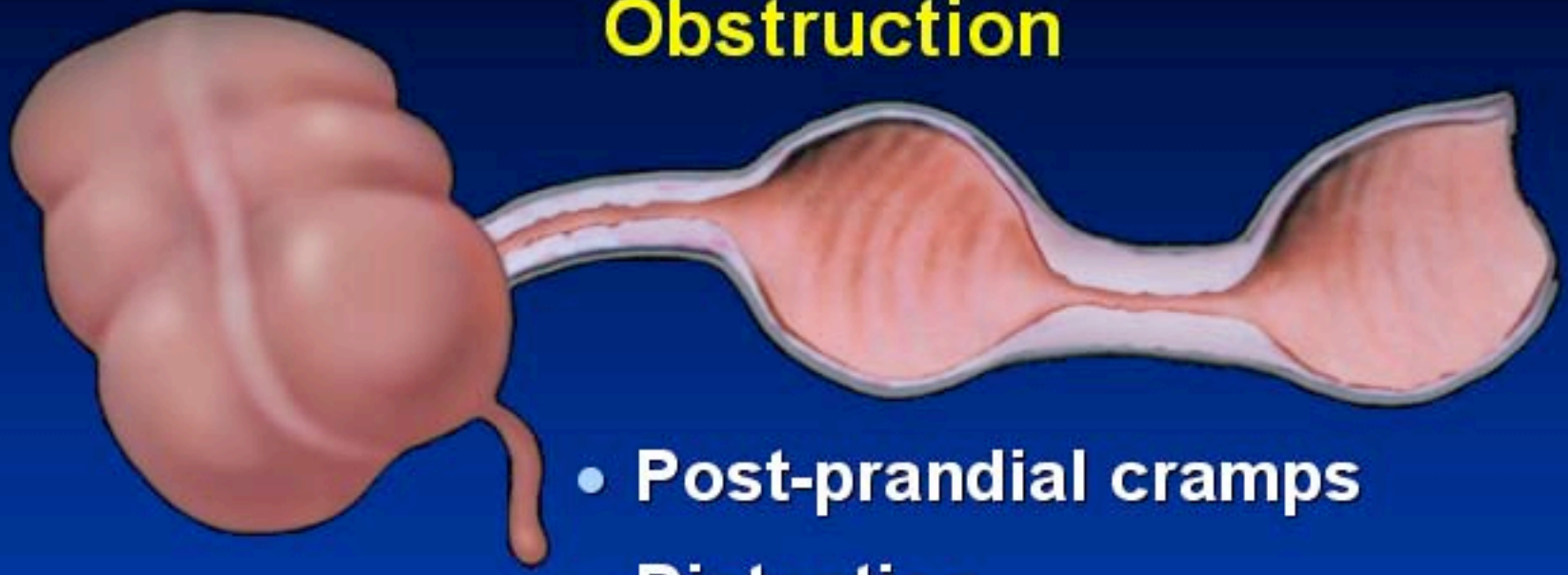


Inflammation

- Pain
- Tenderness
- Diarrhea
- Low-grade fever
- Weight loss (anorexia)

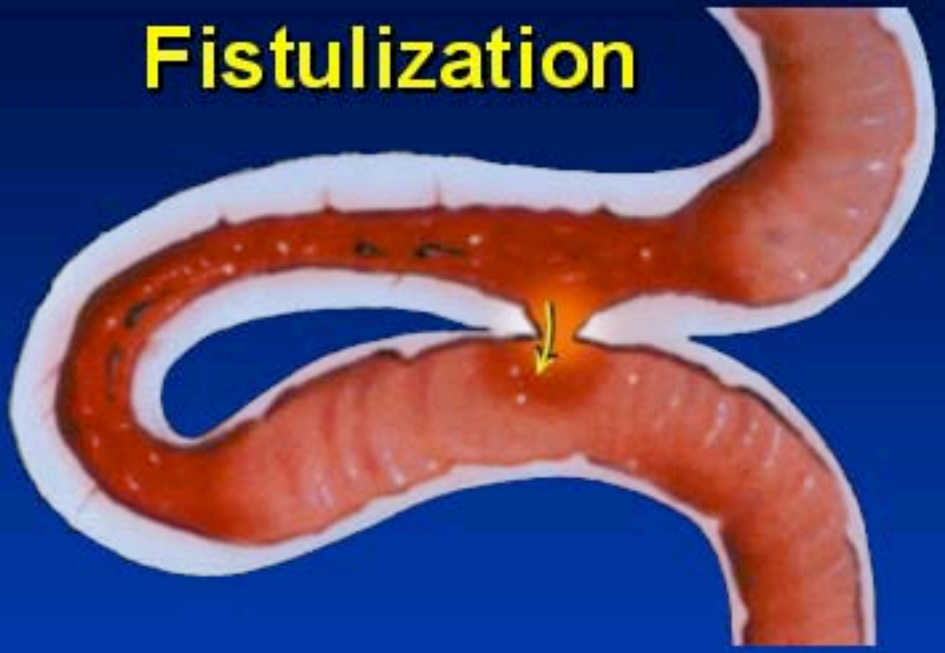
CD - Clinical Patterns

Obstruction



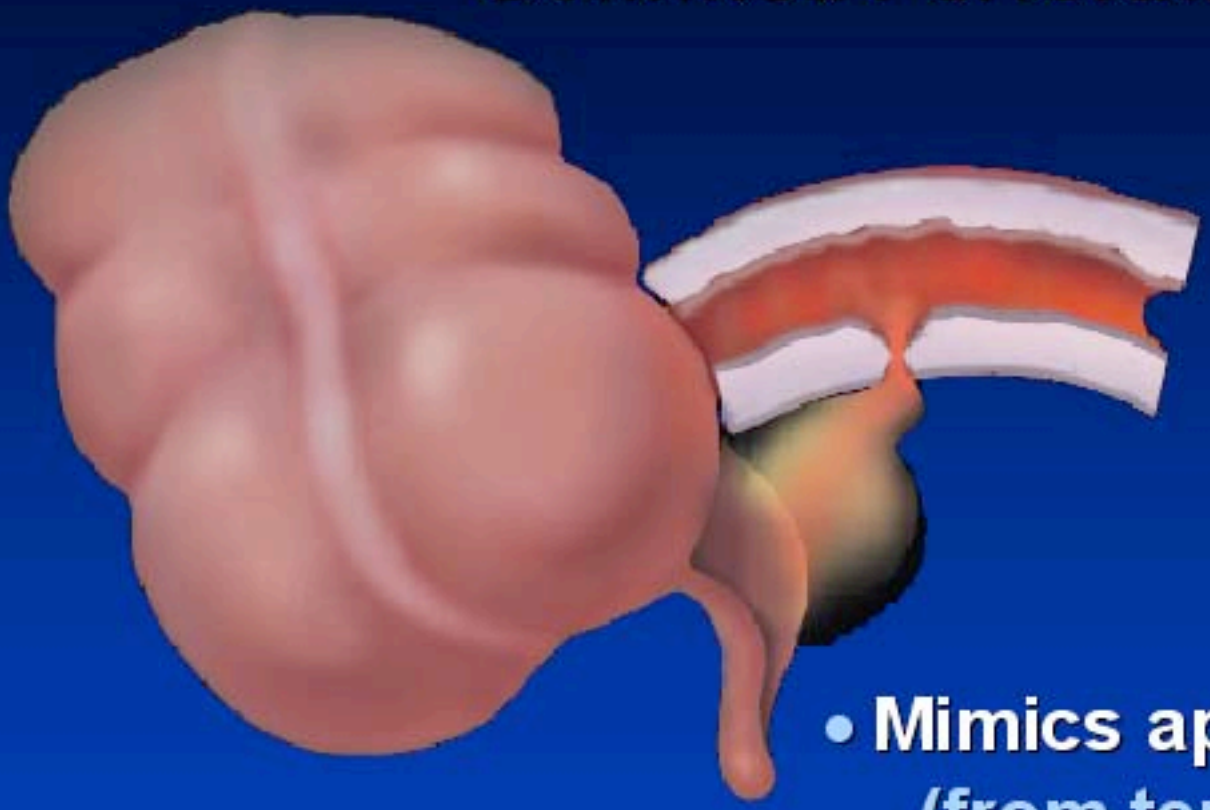
- Post-prandial cramps
- Distention
- Borborygmi
- Vomiting
- Weight loss (food avoidance)

CD - Clinical Patterns

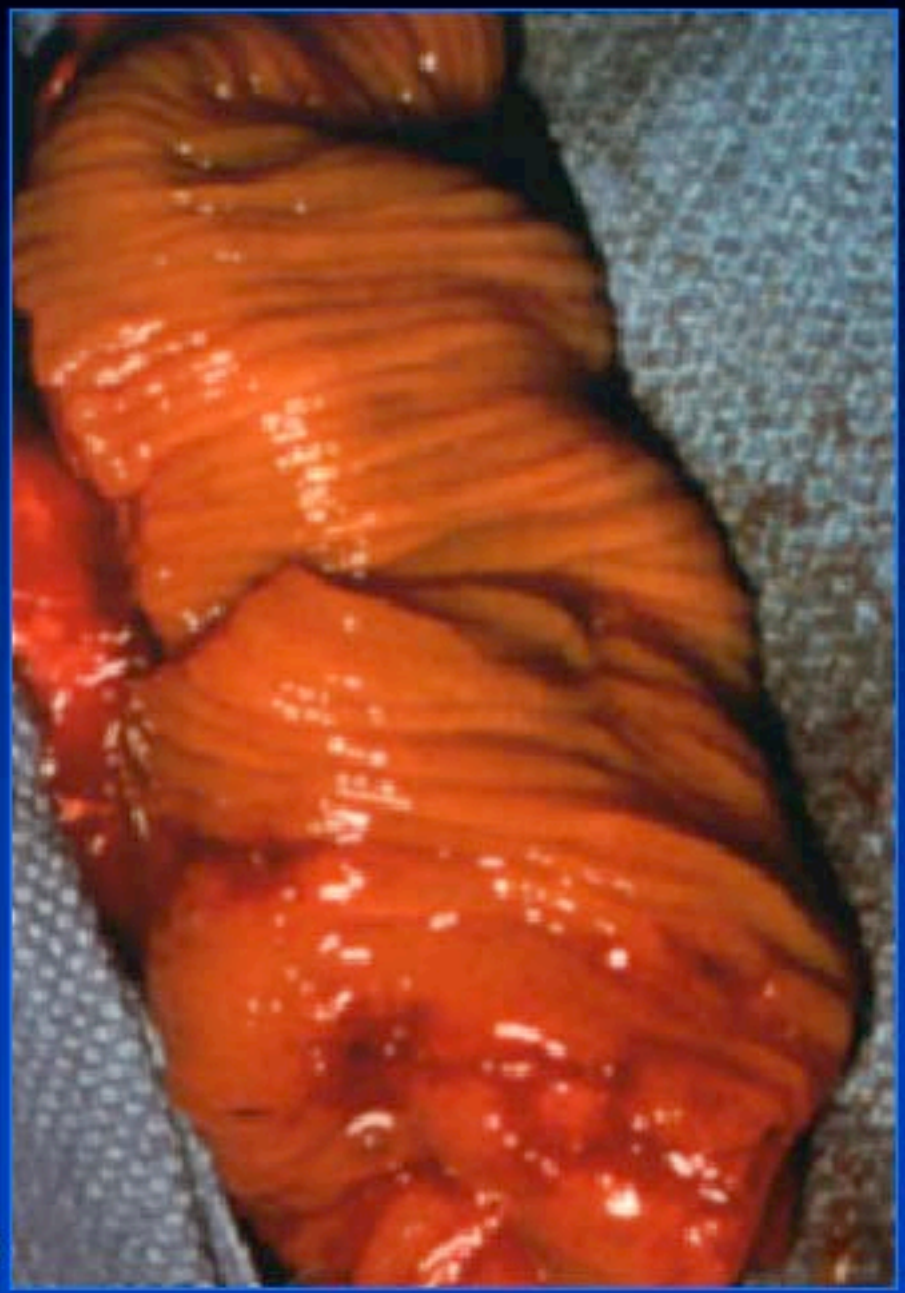


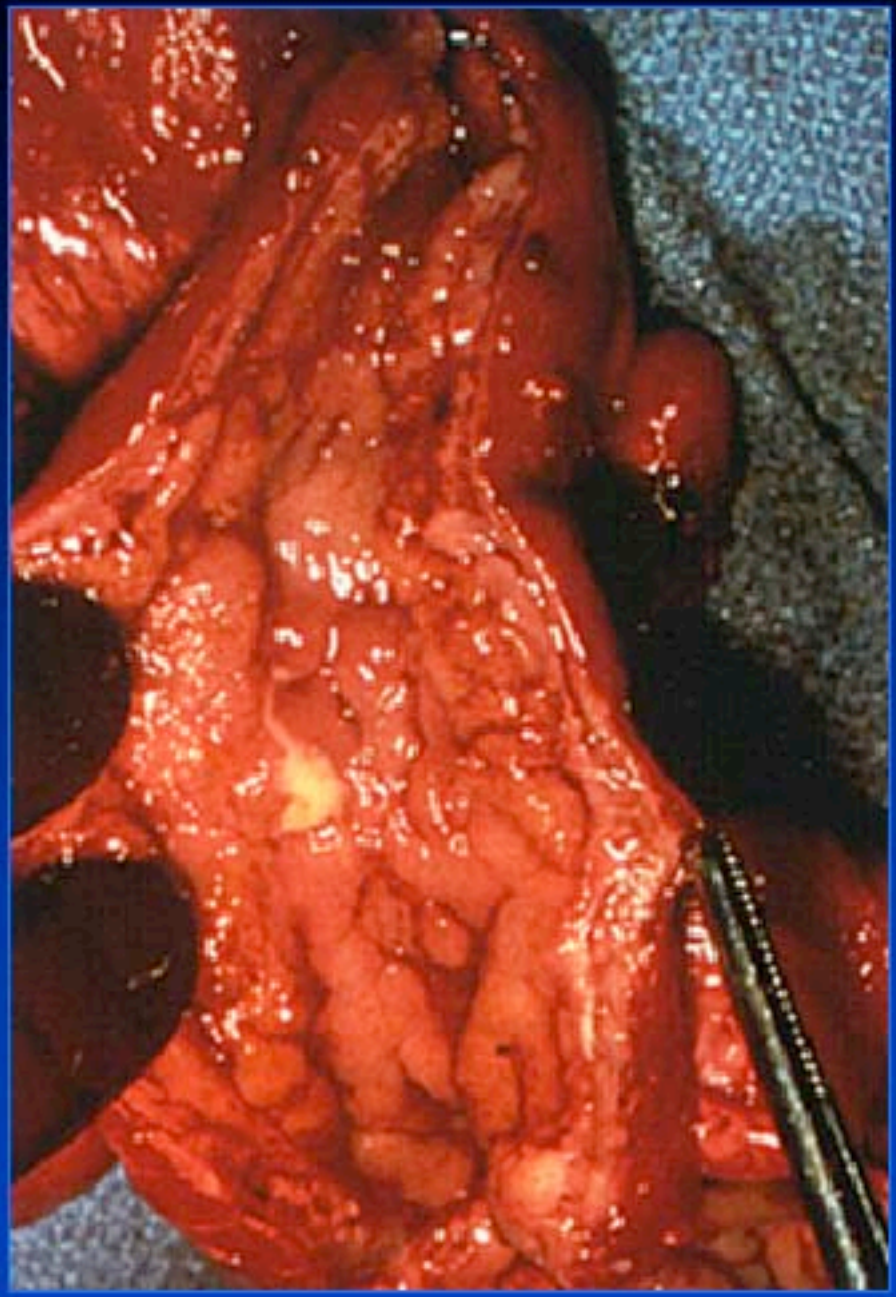
- **Enteroenteric**
  - May be asymptomatic
- **Enterovesical**
  - Recurrent UTIs, pneumaturia
- **Retroperitoneal**
  - Psoas abscess signs: back, hip, and thigh pain; limp
- **Enterocutaneous**
  - Drainage via scar
- **Perianal**
  - Pain, drainage
- **Rectovaginal**
  - Drainage: feces and/or air

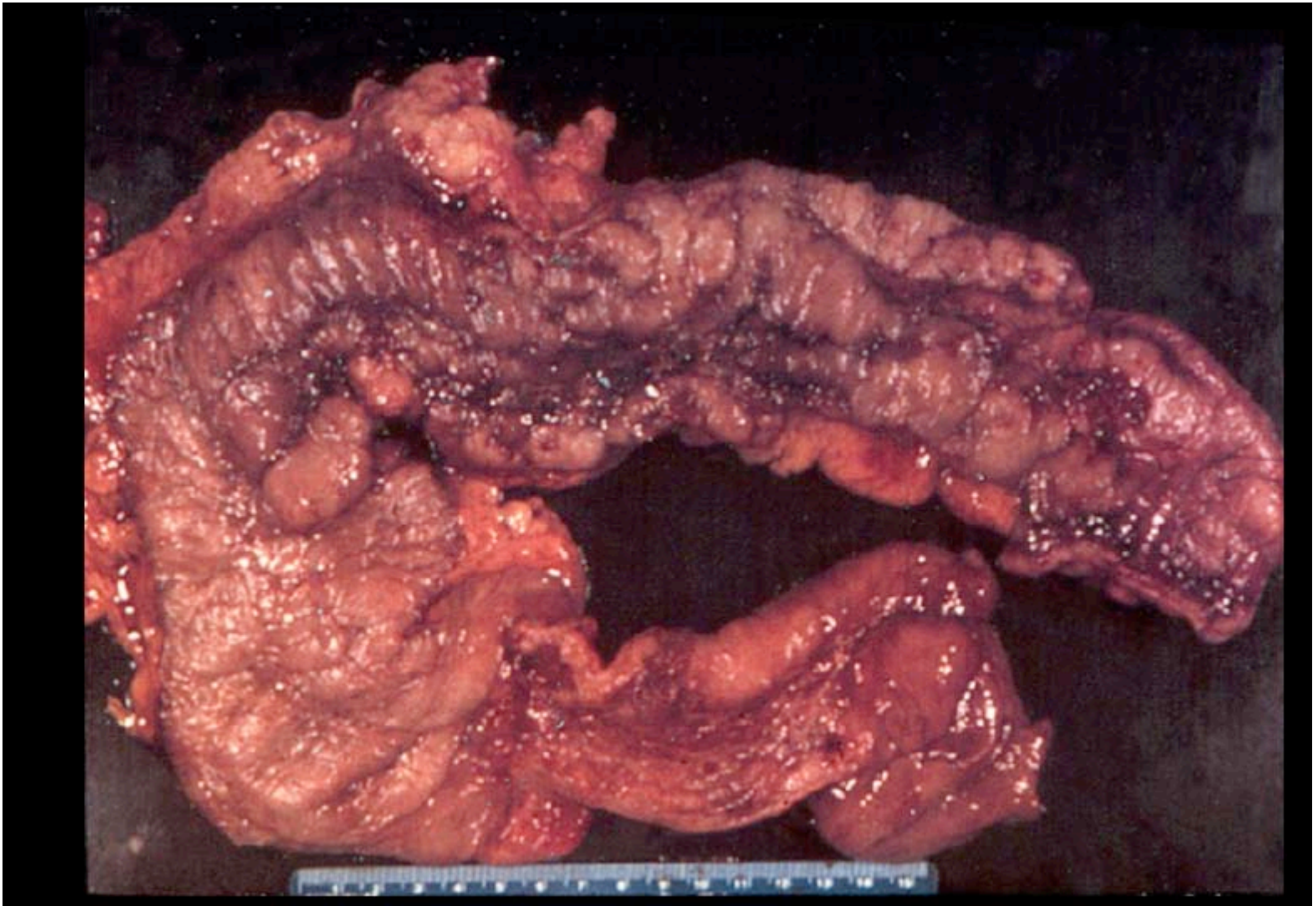
Confined Perforation

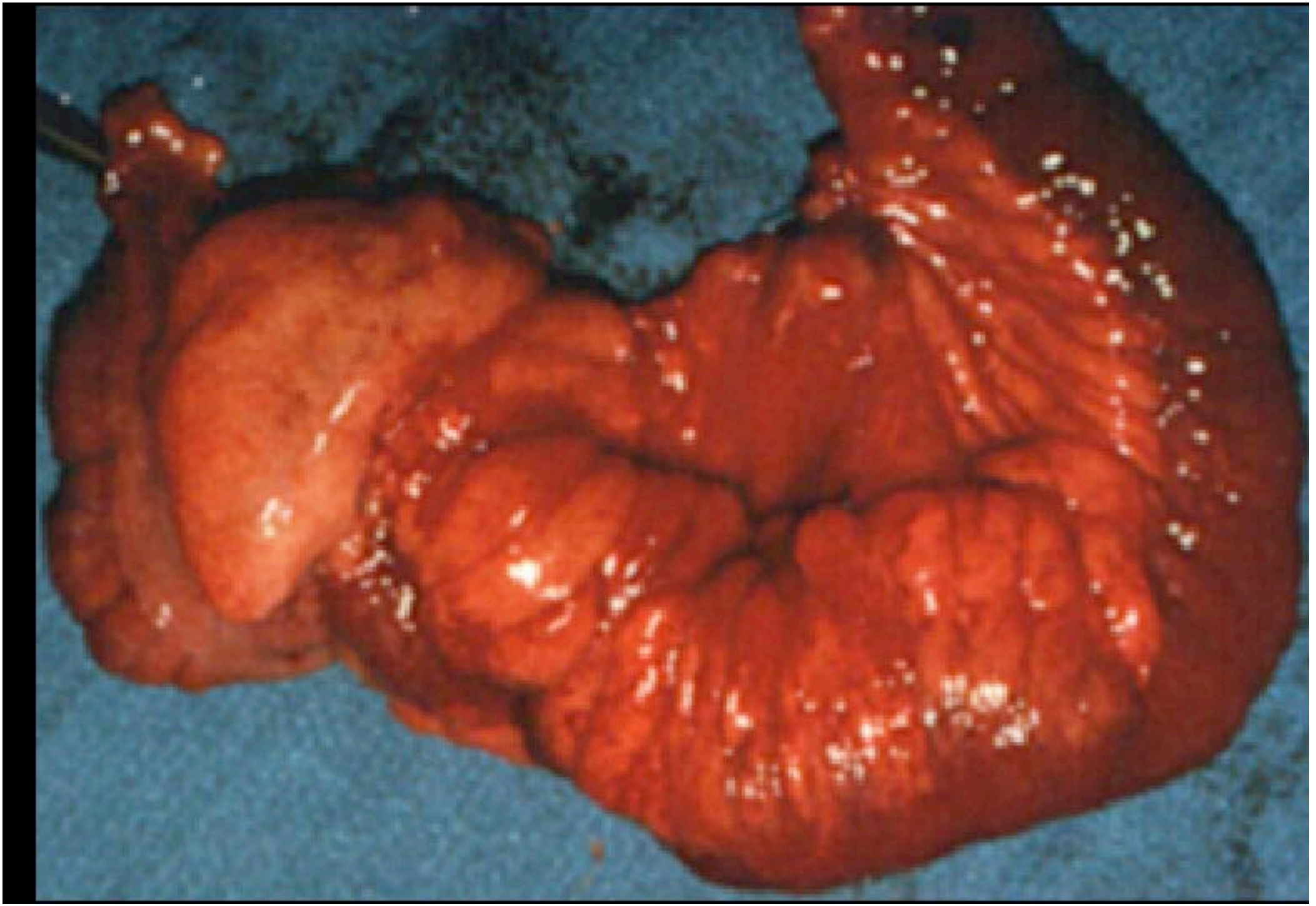


- Mimics appendicitis (from terminal ileum)
- Mimics diverticulitis (from sigmoid colon)



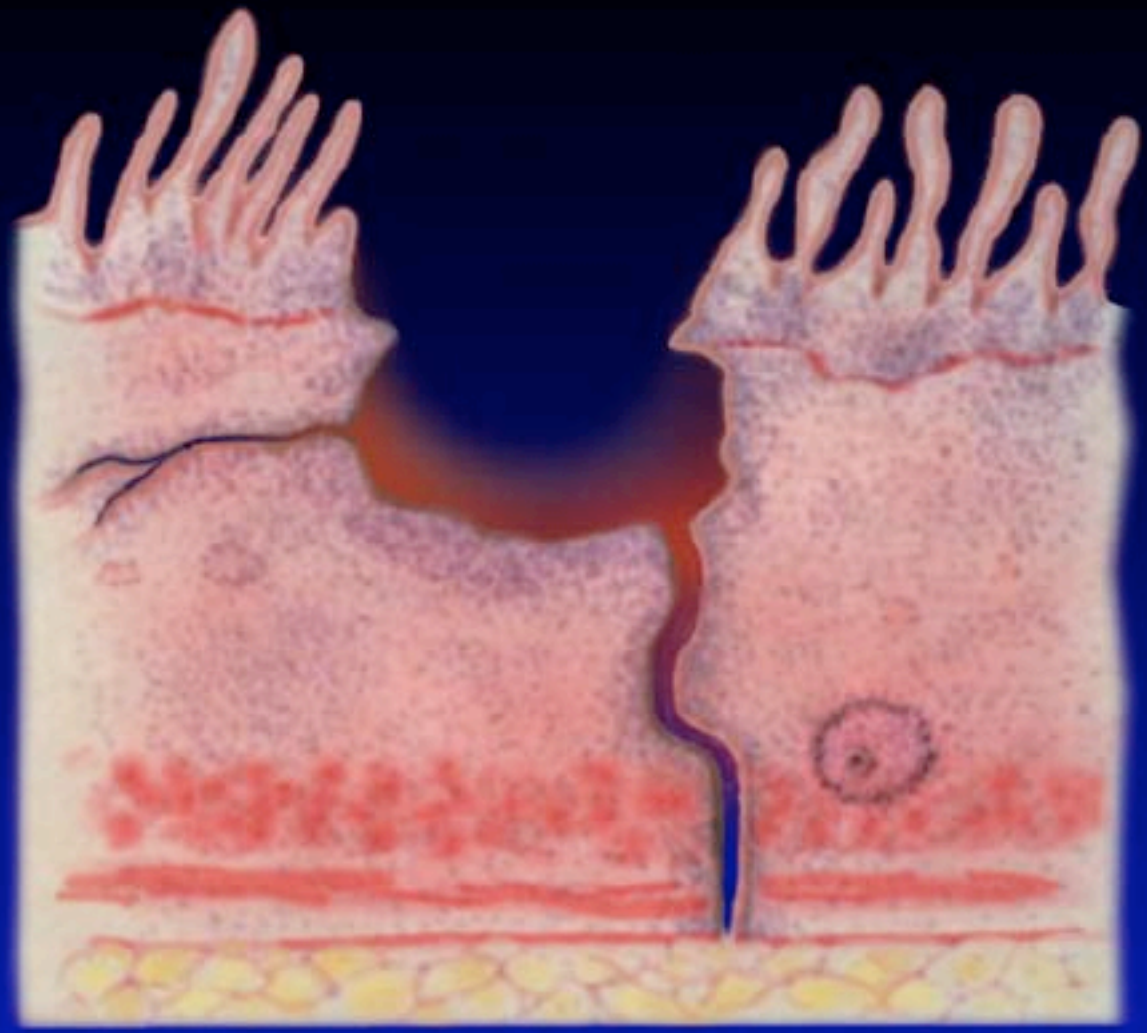


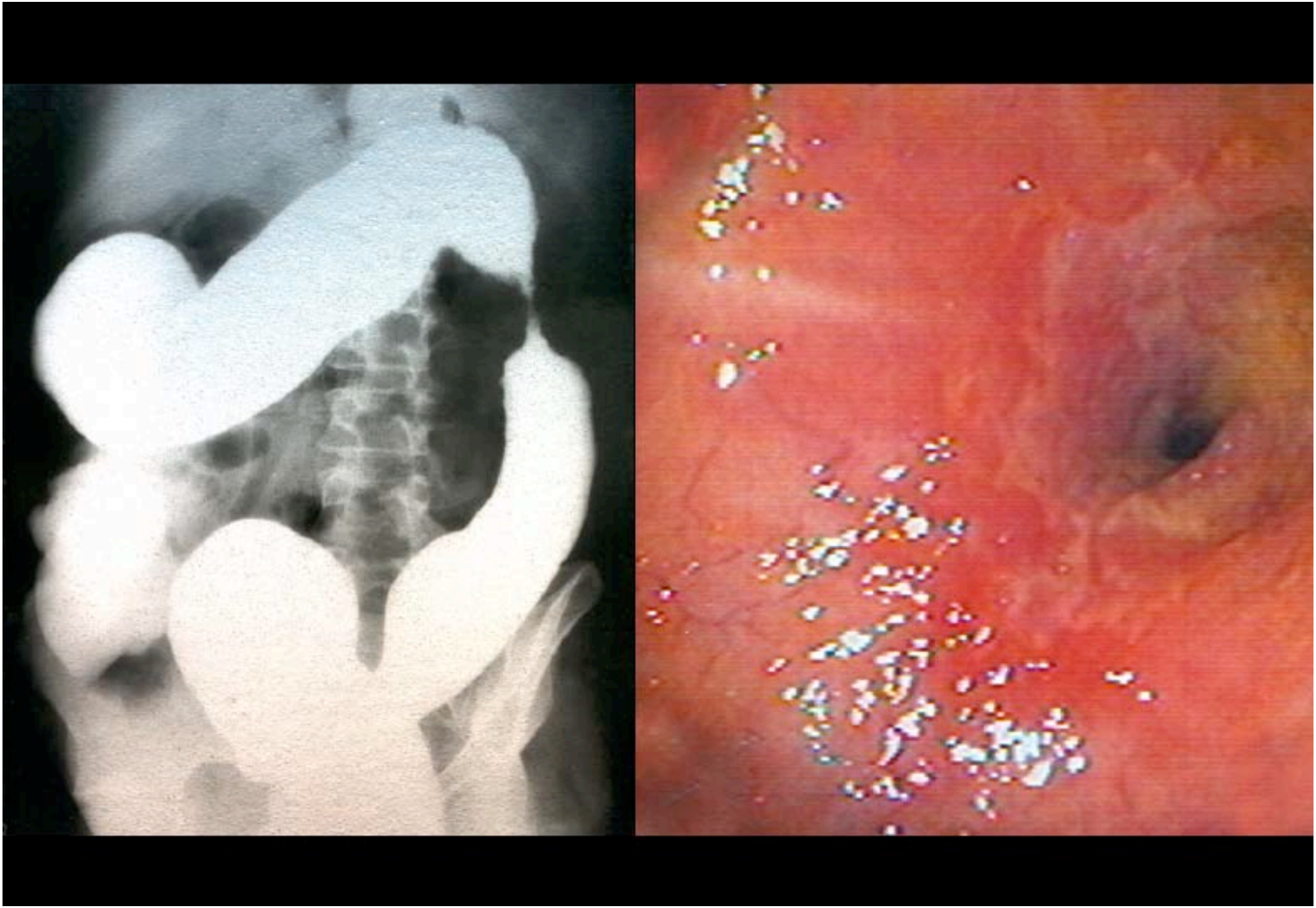


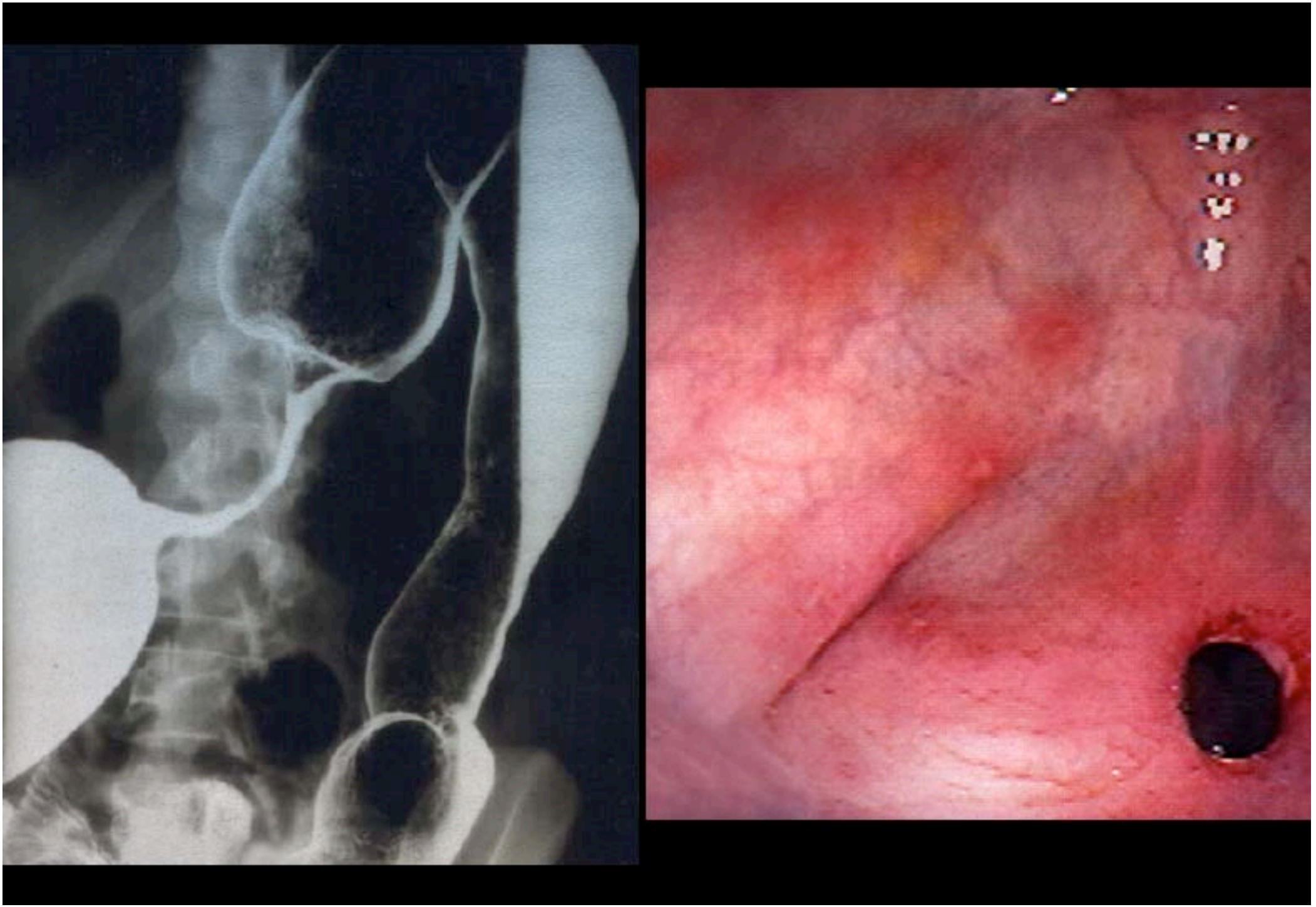


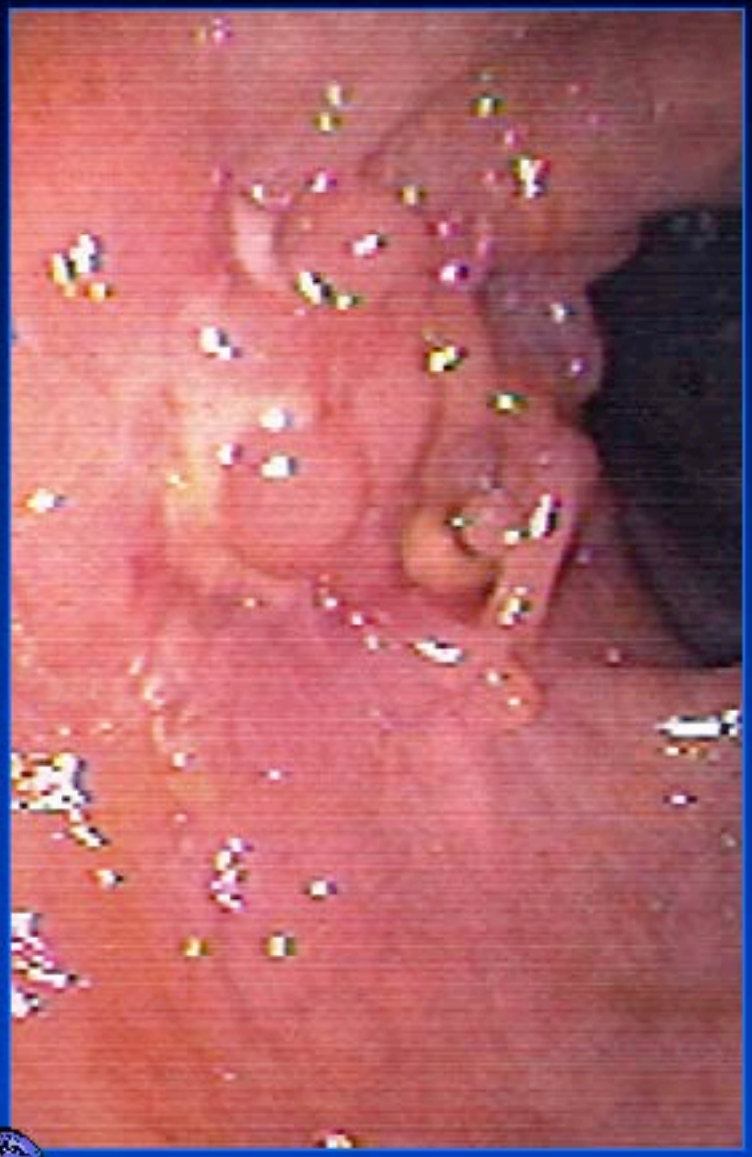
CD

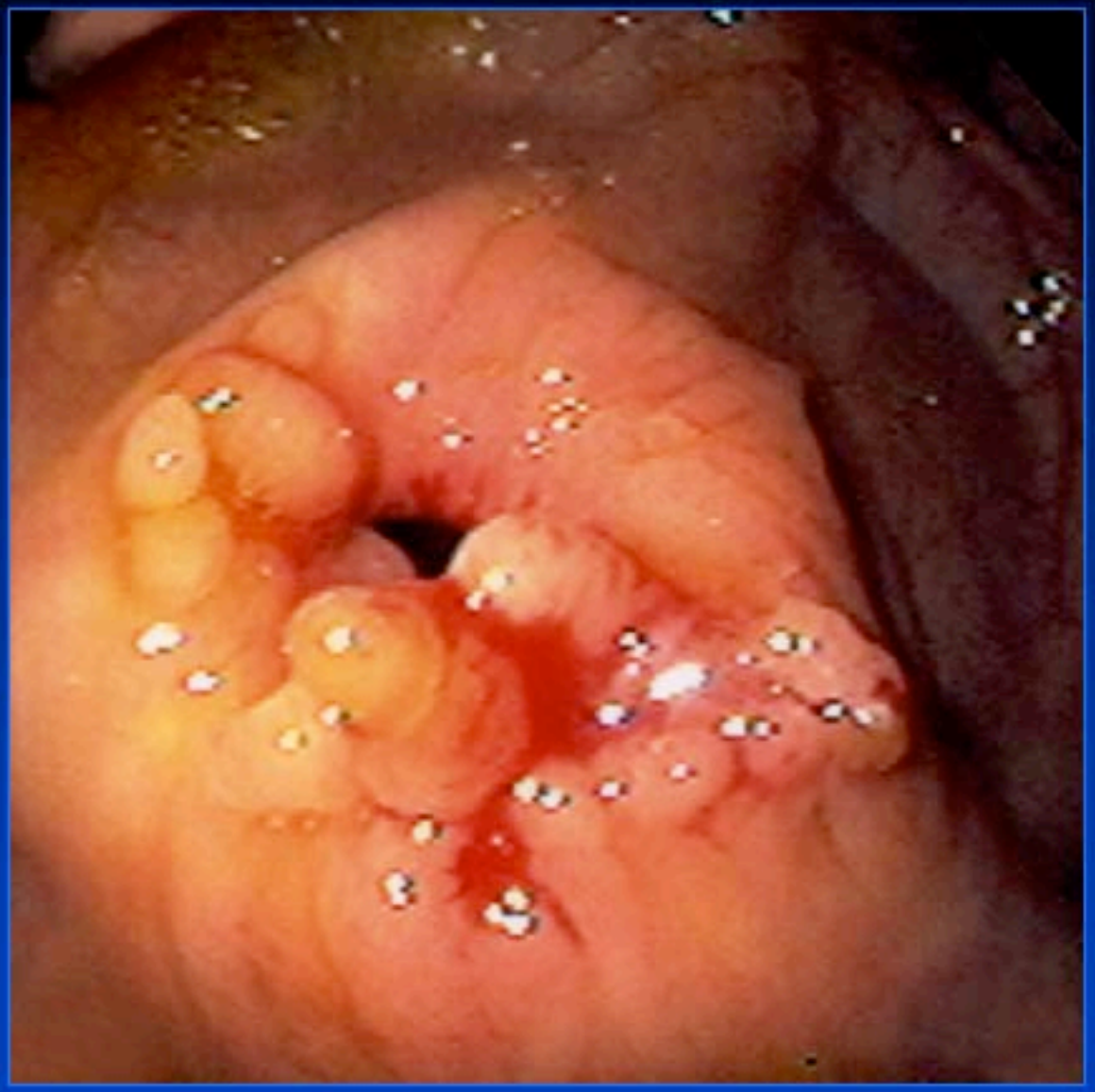
Transmural Inflammation

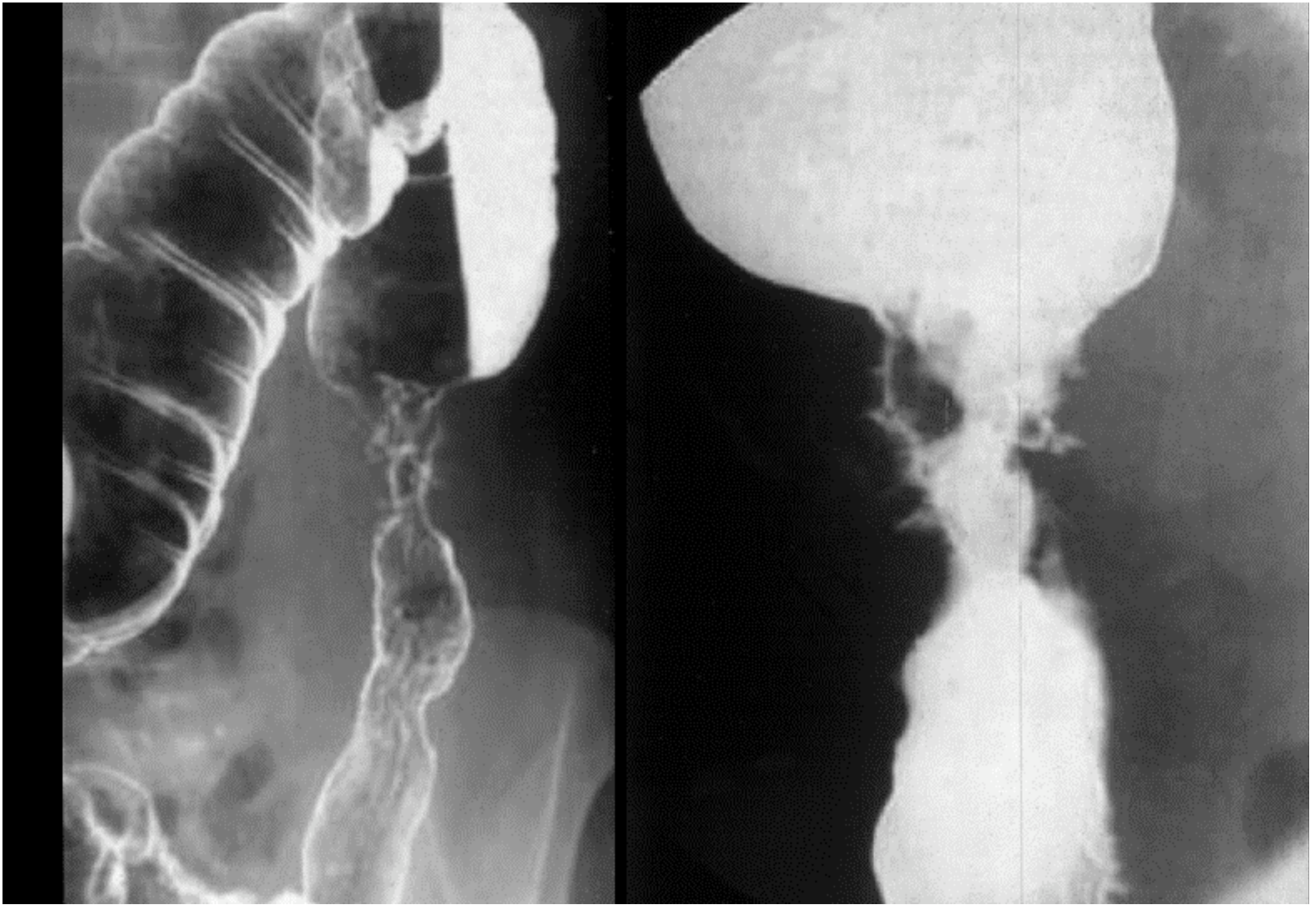




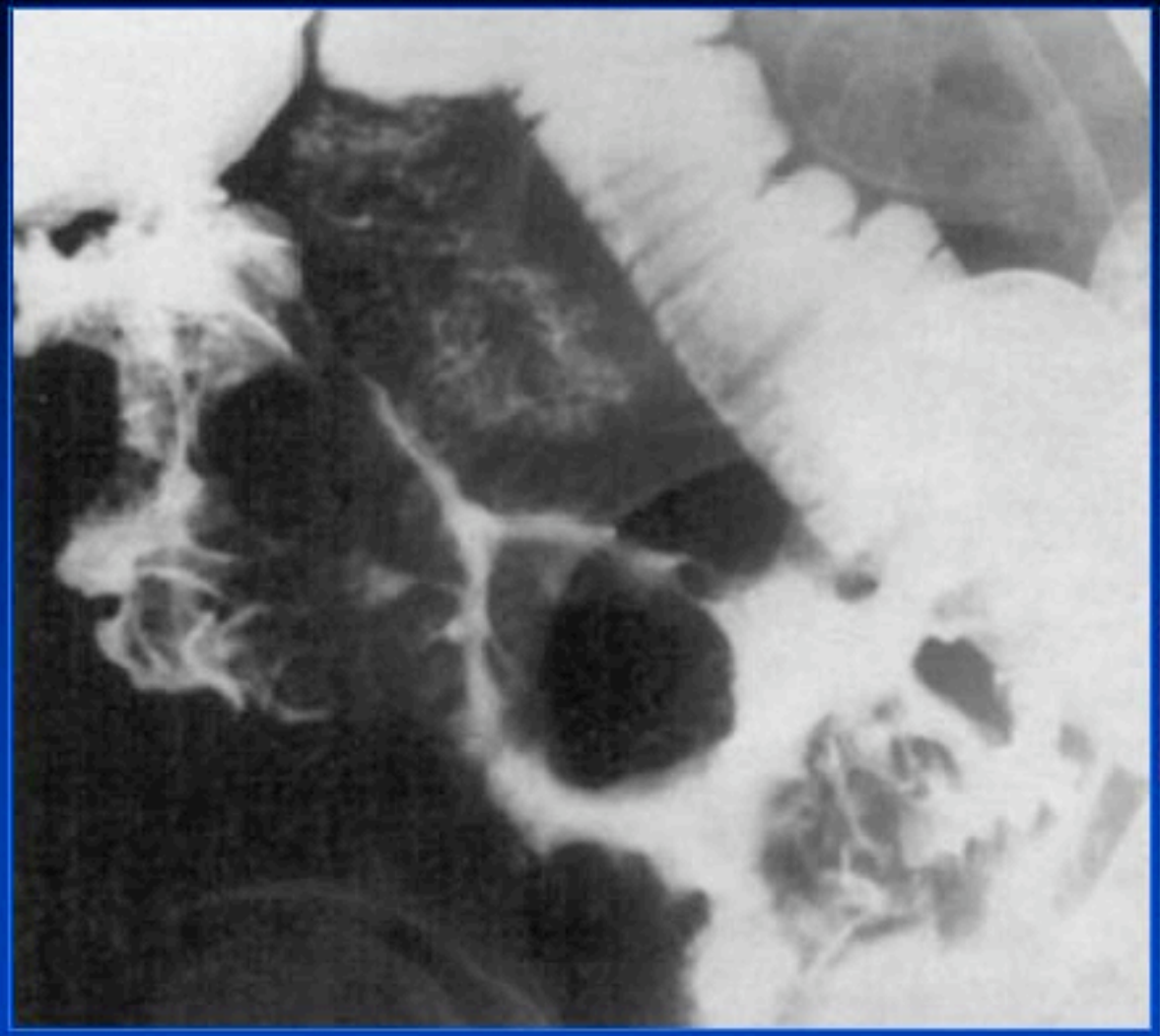


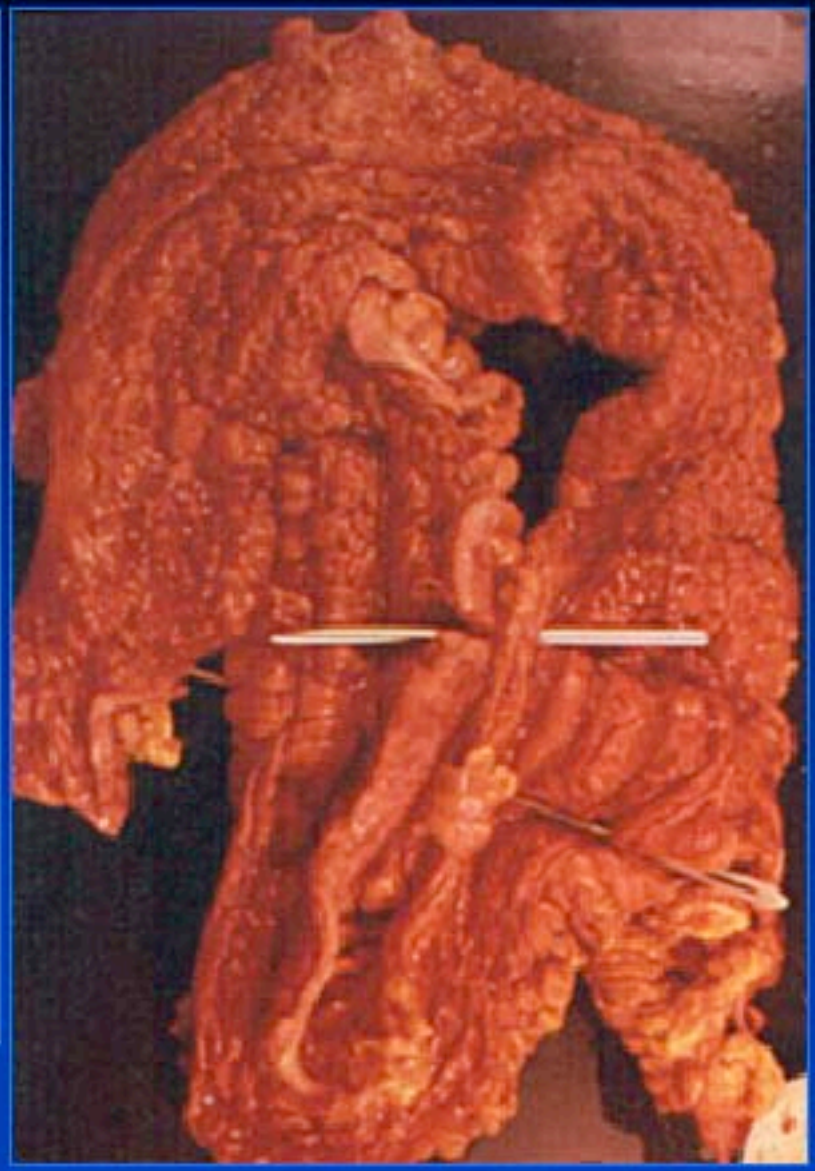


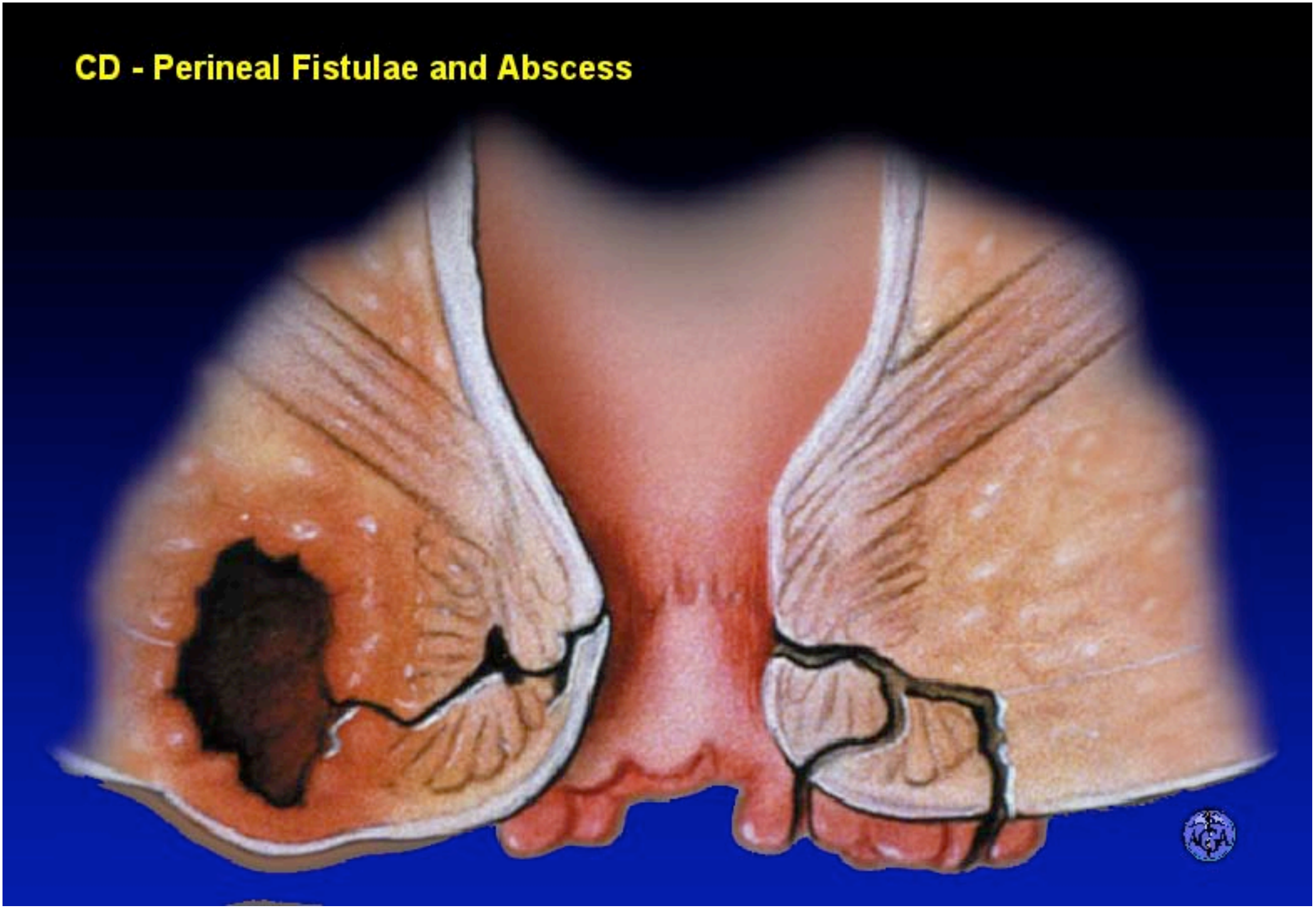




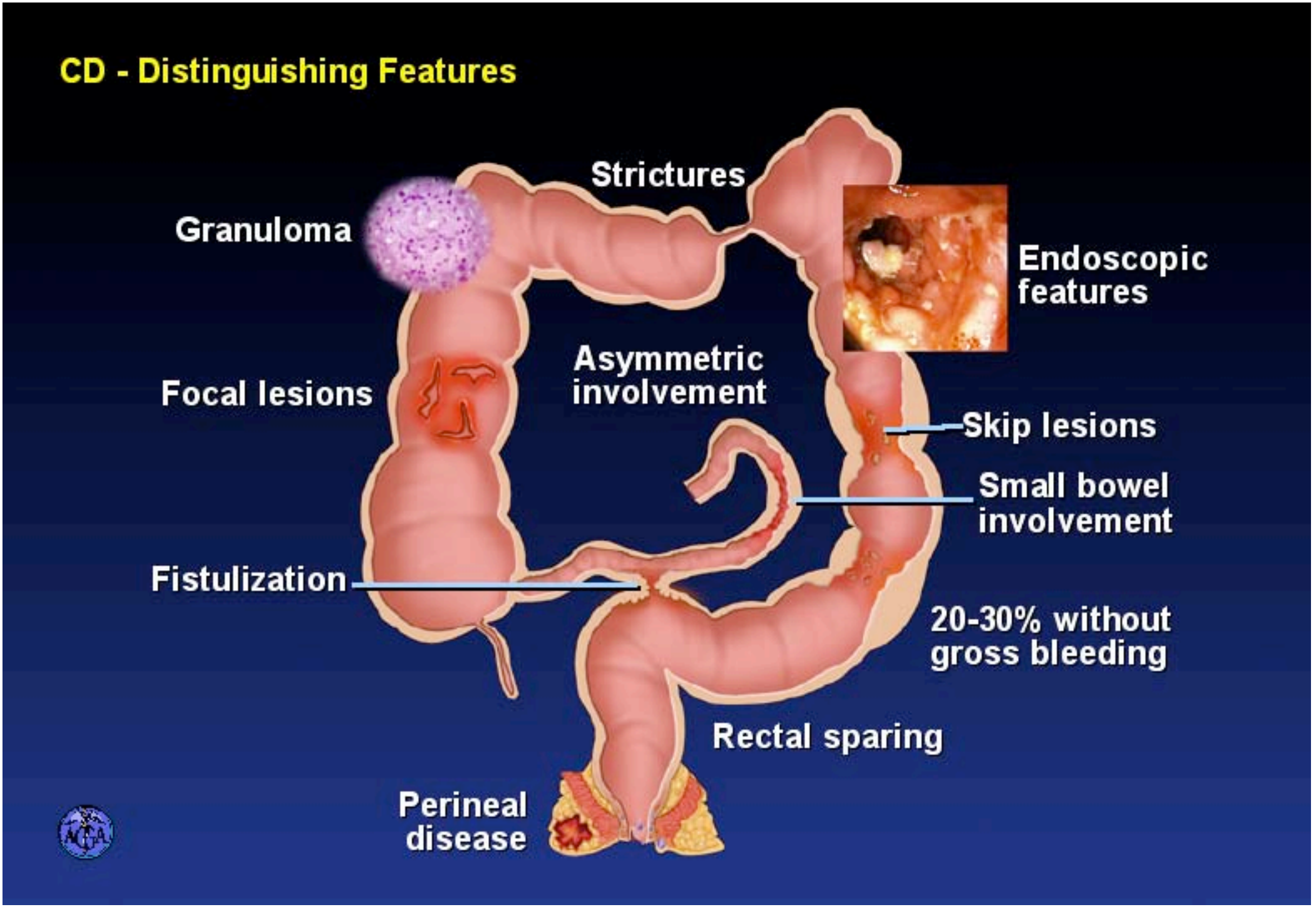
CD - Intestinal Complications

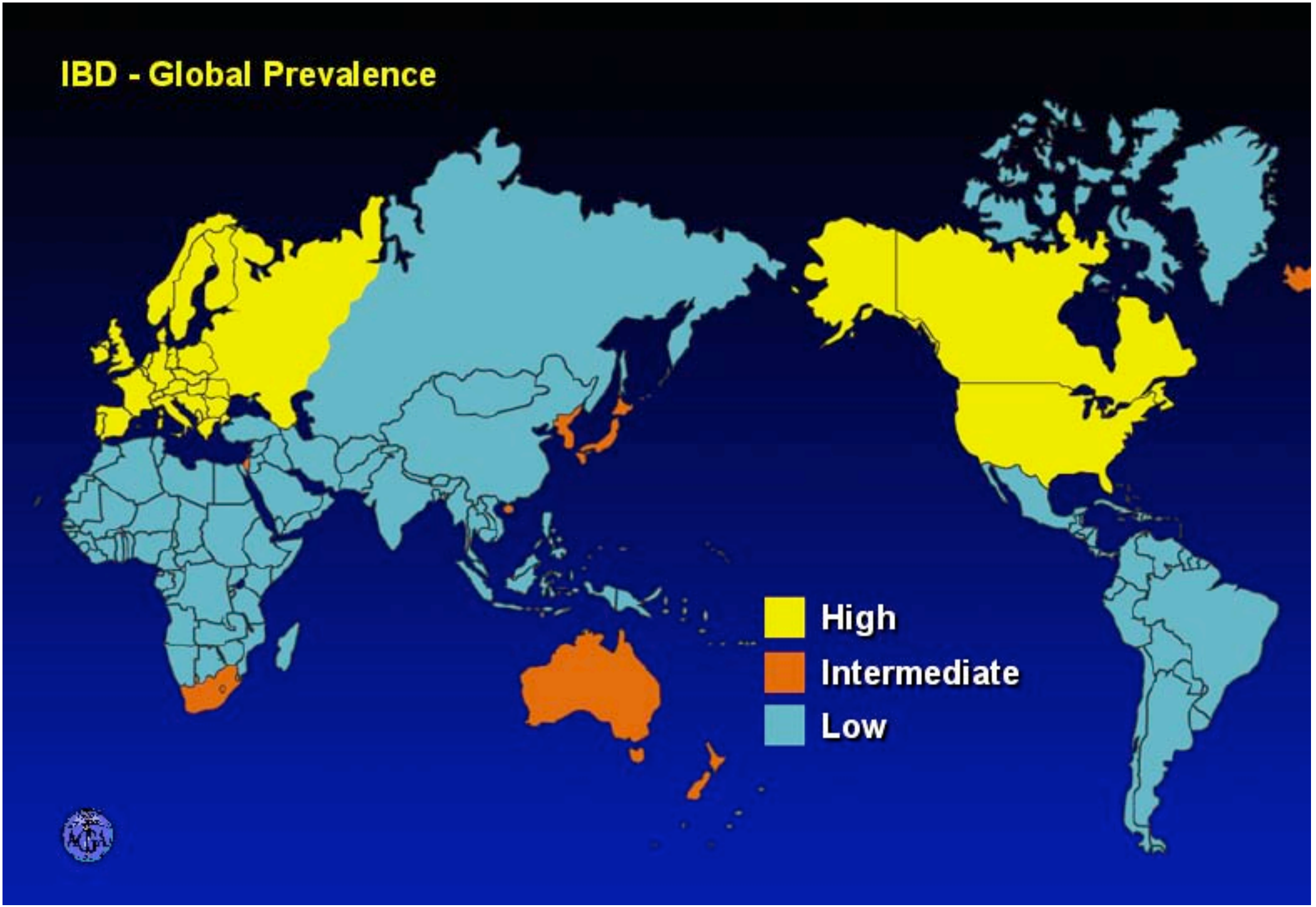




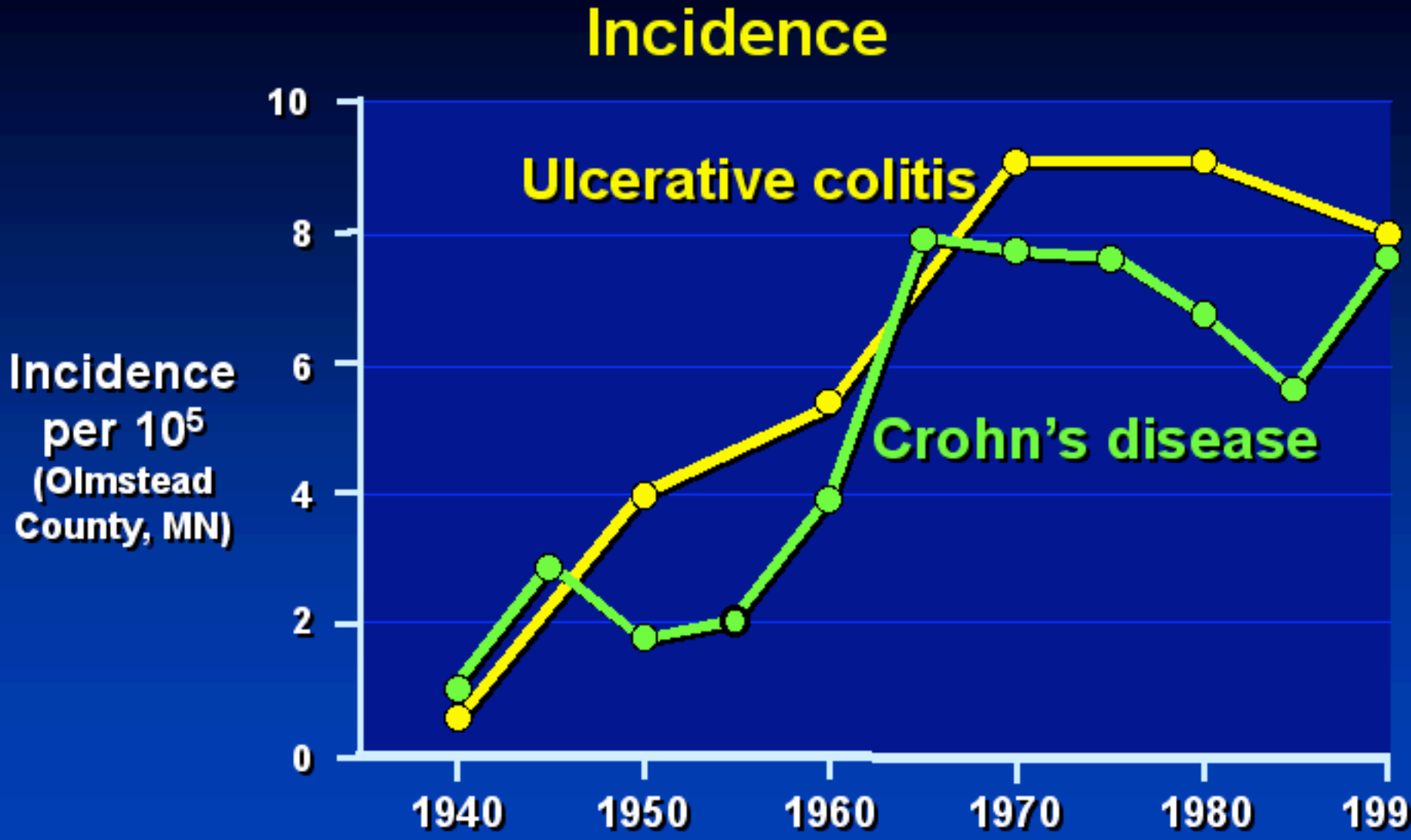

CD - Perineal Fistulae and Abscess

CD - Distinguishing Features



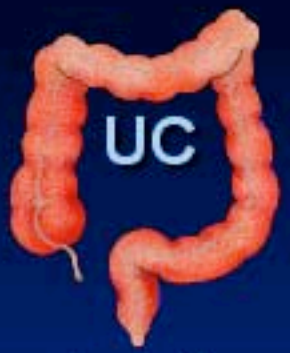

IBD - Global Prevalence
High
Intermediate
Low

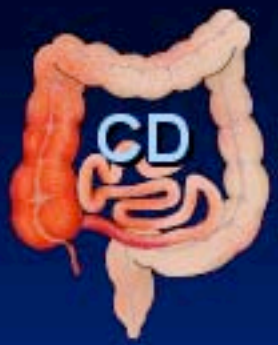
IBD



Loftus EVJ et al. Gastroenterology 1998; 114:1161
Loftus EVJ et al. Gut 2000; 46:336

IBD - Environmental Risk Factors





	UC	CD
Smoking	↓↓↓	↑↑↑
Appendectomy	↓↓	0
High sanitation level in childhood	0	↑↑
High intake refined carbohydrates	0	↑
Perinatal infection	?	↑
Breast feeding	↓?	?
Oral contraceptives	↑?	?

Etiologic Hypotheses

Persistent infection

- Mycobacteria
- *Helicobacter* sp.
- Measles-mumps
- Listeria
- Toxigenic *E. coli*

Defective mucosal integrity

- Altered mucus
- Increased permeability
- Cellular starvation
- Impaired restitution

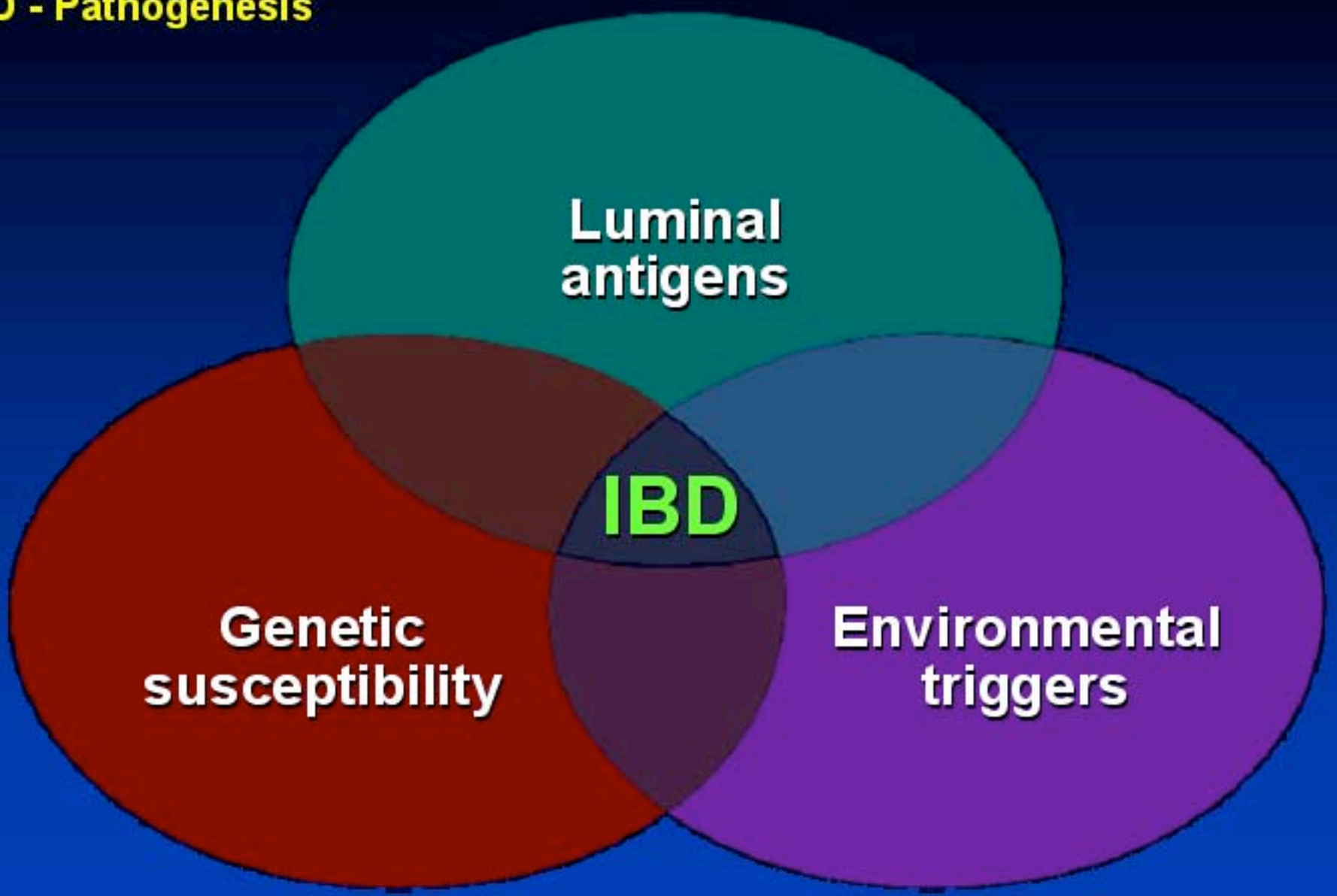
Dysbiosis

- ↓ protective bacteria
- ↑ aggressive commensals

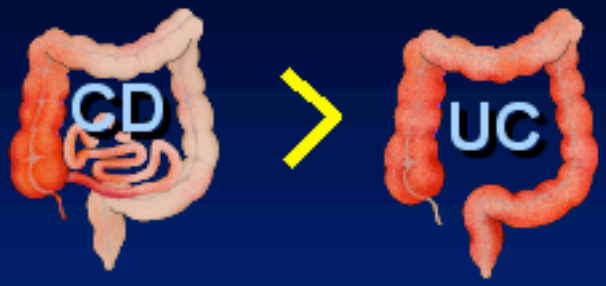
Dysregulated immune response

- Loss of tolerance
- Aggressive cellular activation
- Defective apoptosis

IBD - Pathogenesis



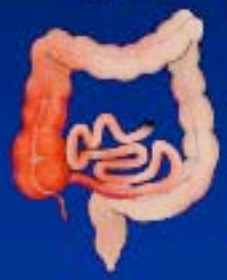
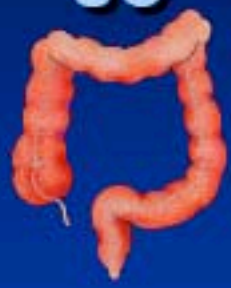
Genetic Influence



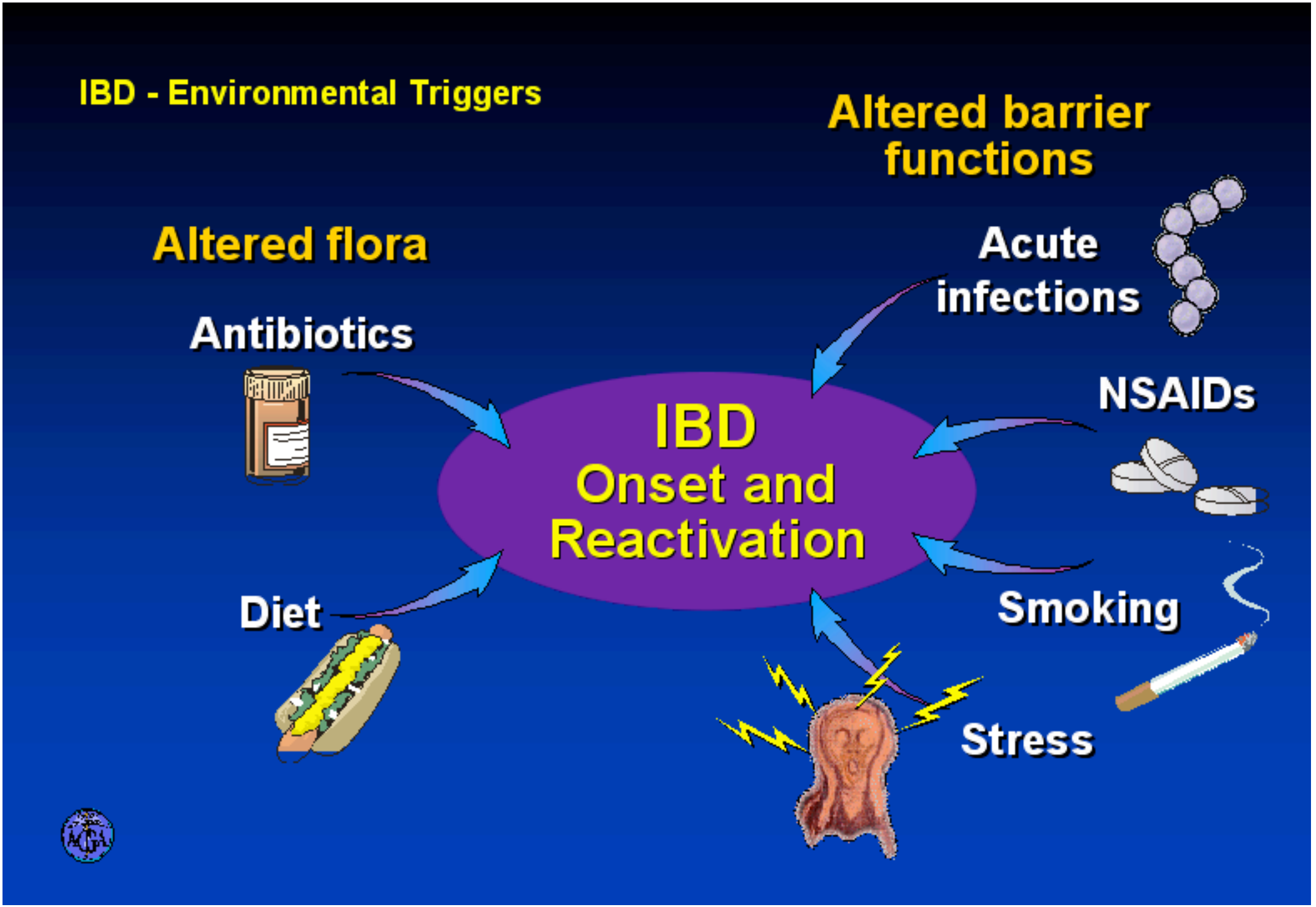
- Familial occurrence
- Clinical pattern of Crohn's disease in families
- Polygenic susceptibility
- Genome wide search: chromosomes 12>12, 6,5
- NOD-2 mutations on chromosome 16 and cytokine cluster region on chromosome 5 in Crohn's disease
- Genotype - phenotype correlations

Genetic Susceptibility

Concordance in twins:

	CD	UC
		
Monozygotic	44-50%	5-14%
Dizygotic	8%	0%

Tysk et al. Gut 1988; 29:990
Ornholm M et al. Scand J. Gastroenterology 2000; 35:1075


IBD - Environmental Triggers
Altered barrier functions
Altered flora
Acute infections
Antibiotics
NSAIDs
IBD
Onset and
Reactivation
Diet
Smoking
Stress

IBD - Pathogenesis

Role of Bacteria

No bacteria

Resident bacteria

Mice
IL-2^{KO}
IL-10^{KO}
TCRα^{KO}
CD_3E_{26}TG
SAMP1/Yit
DSS
$CD_{45}RB^{hi}$ SCID

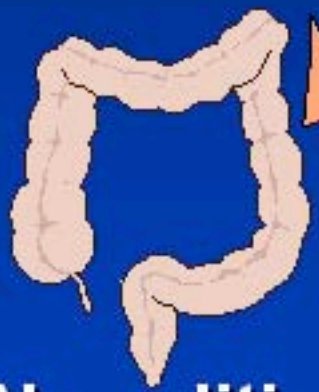
Rats
HLA-B27 TG
Indomethacin

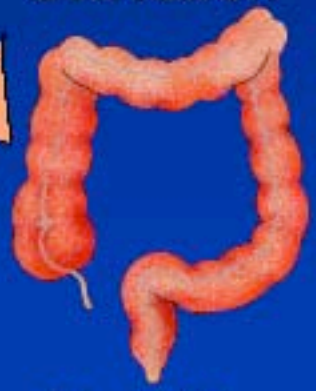
Guinea pigs
Carrageenan

Non-human primate
Cotton top tamarin

No immune activation

Macrophage and TH_1 immune activation

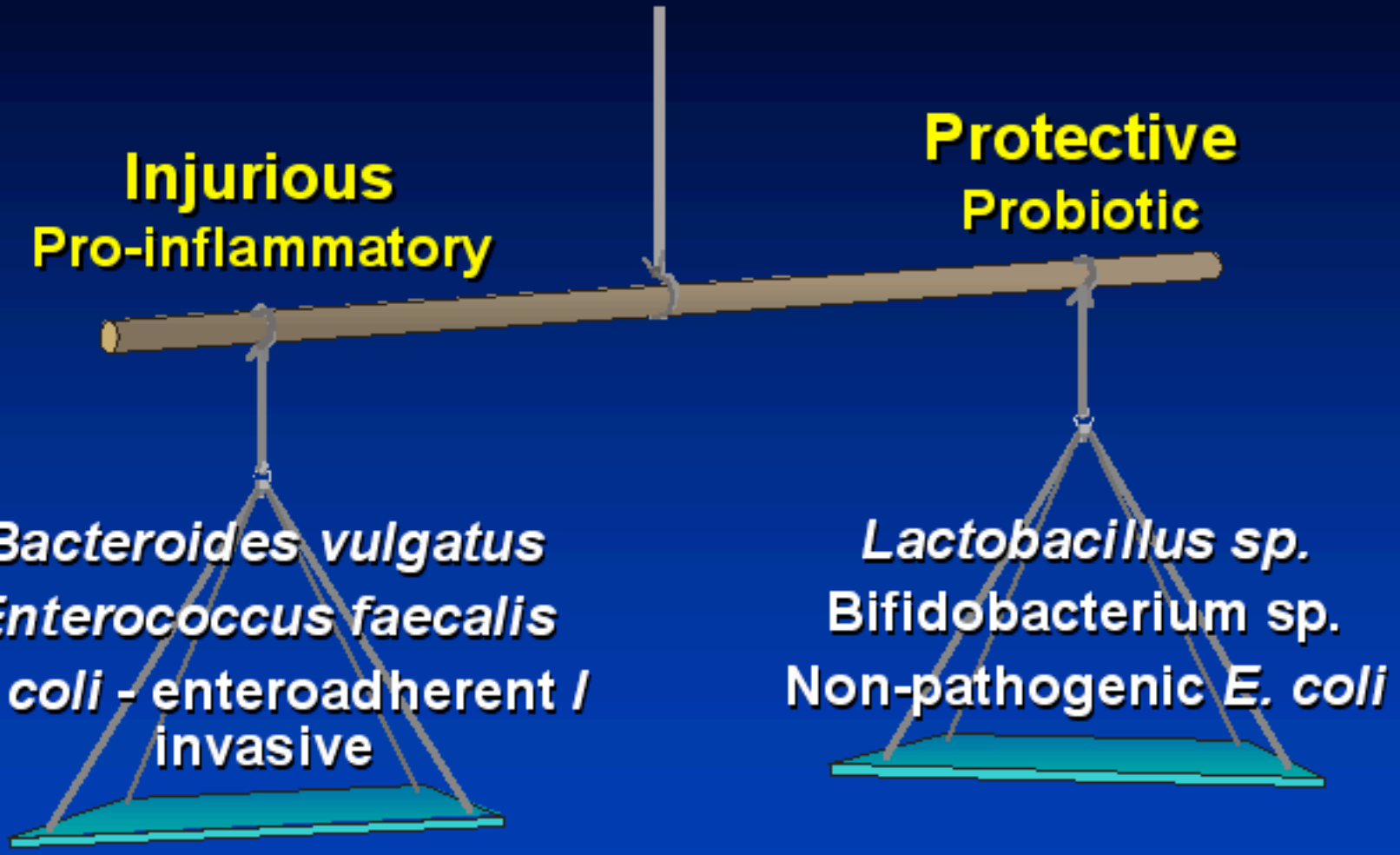




No colitis

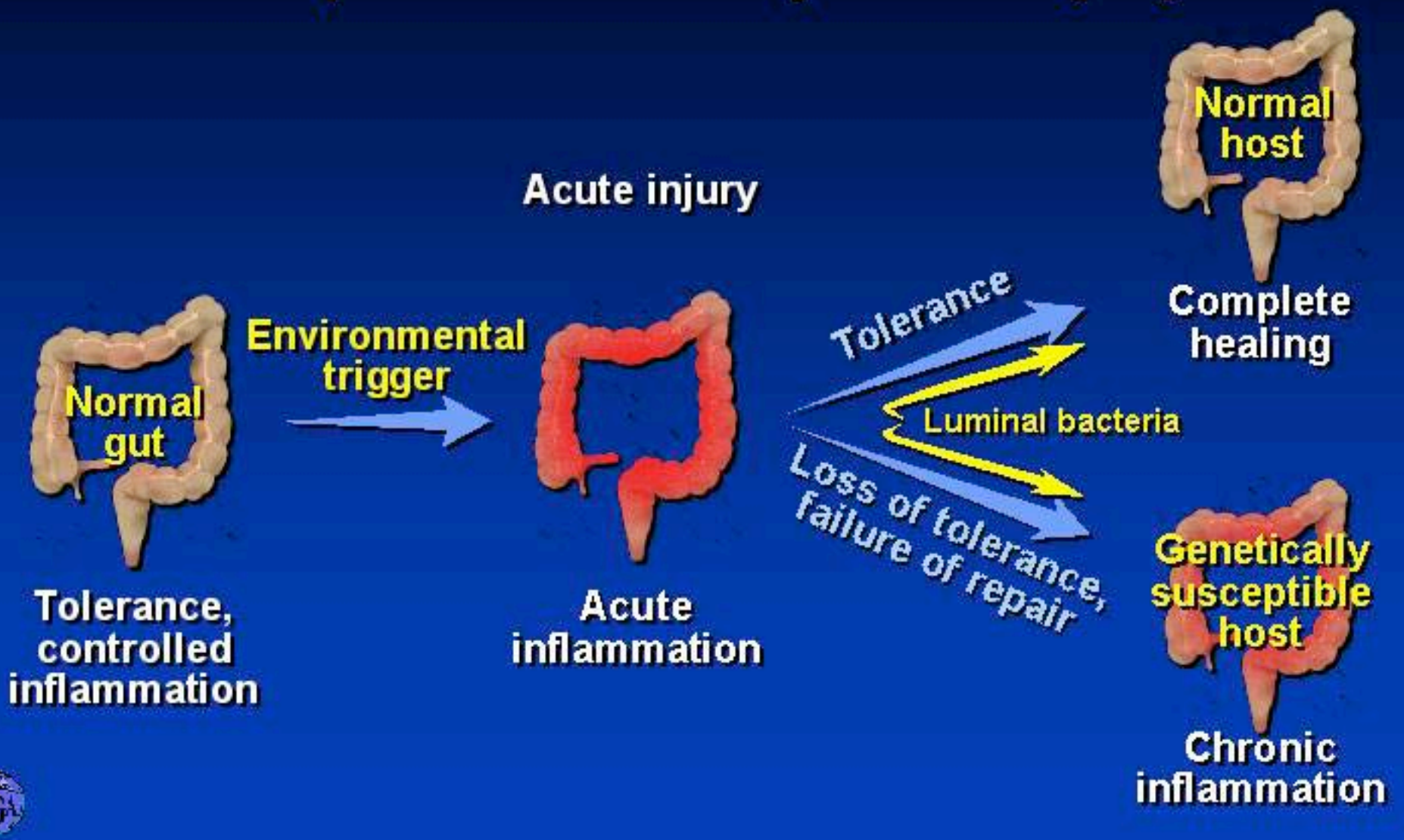
Colitis

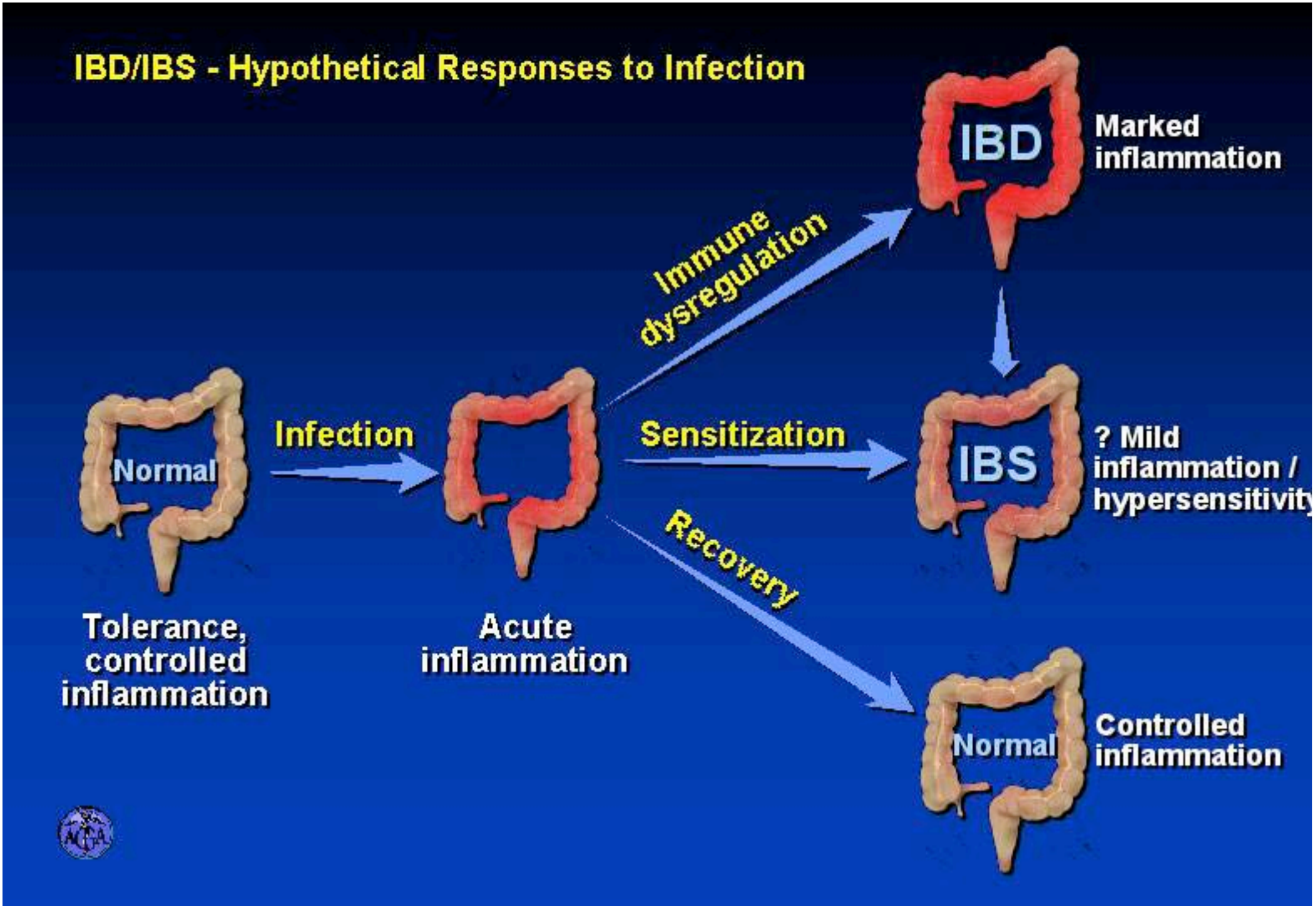
IBD - Luminal Microbial Environment



IBD- Pathogenesis

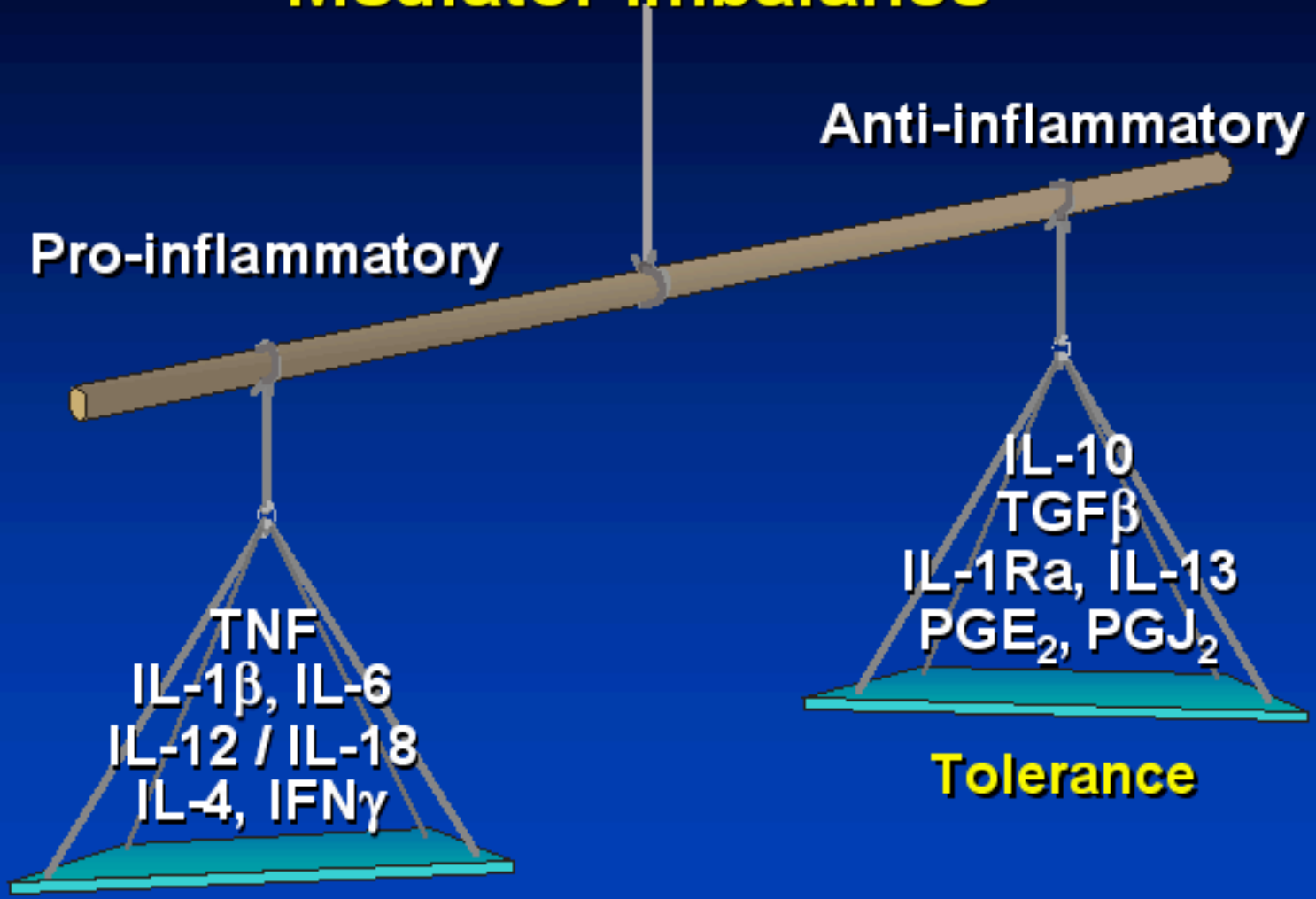
Response to Non-specific Injury

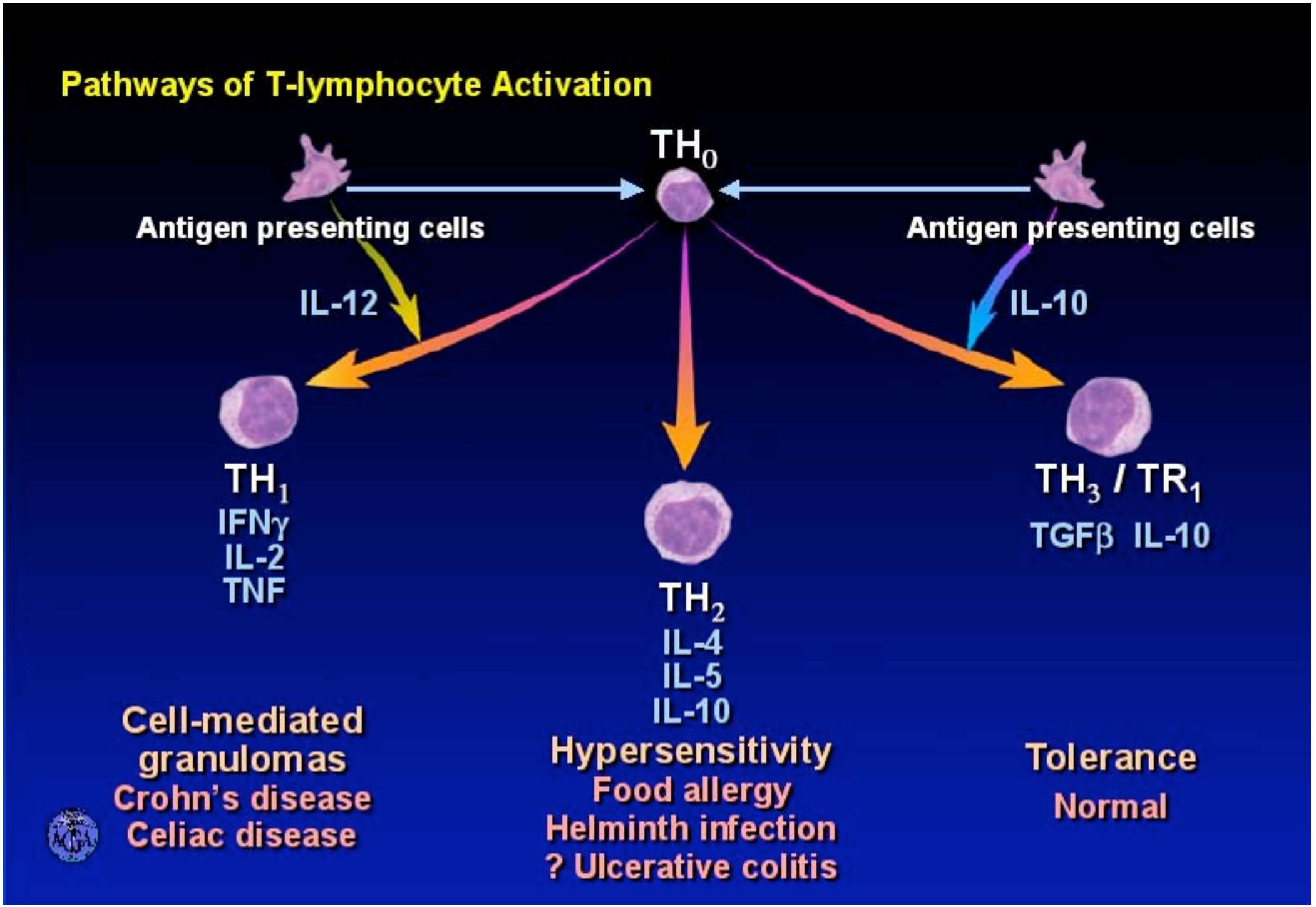



IBD/IBS - Hypothetical Responses to Infection
IBD
Marked inflammation
Immune dysregulation
Normal
Infection
Sensitization
IBS
? Mild inflammation / hypersensitivity
Recovery
Tolerance, controlled inflammation
Acute inflammation
Normal
Controlled inflammation

IBD - Pathogenesis

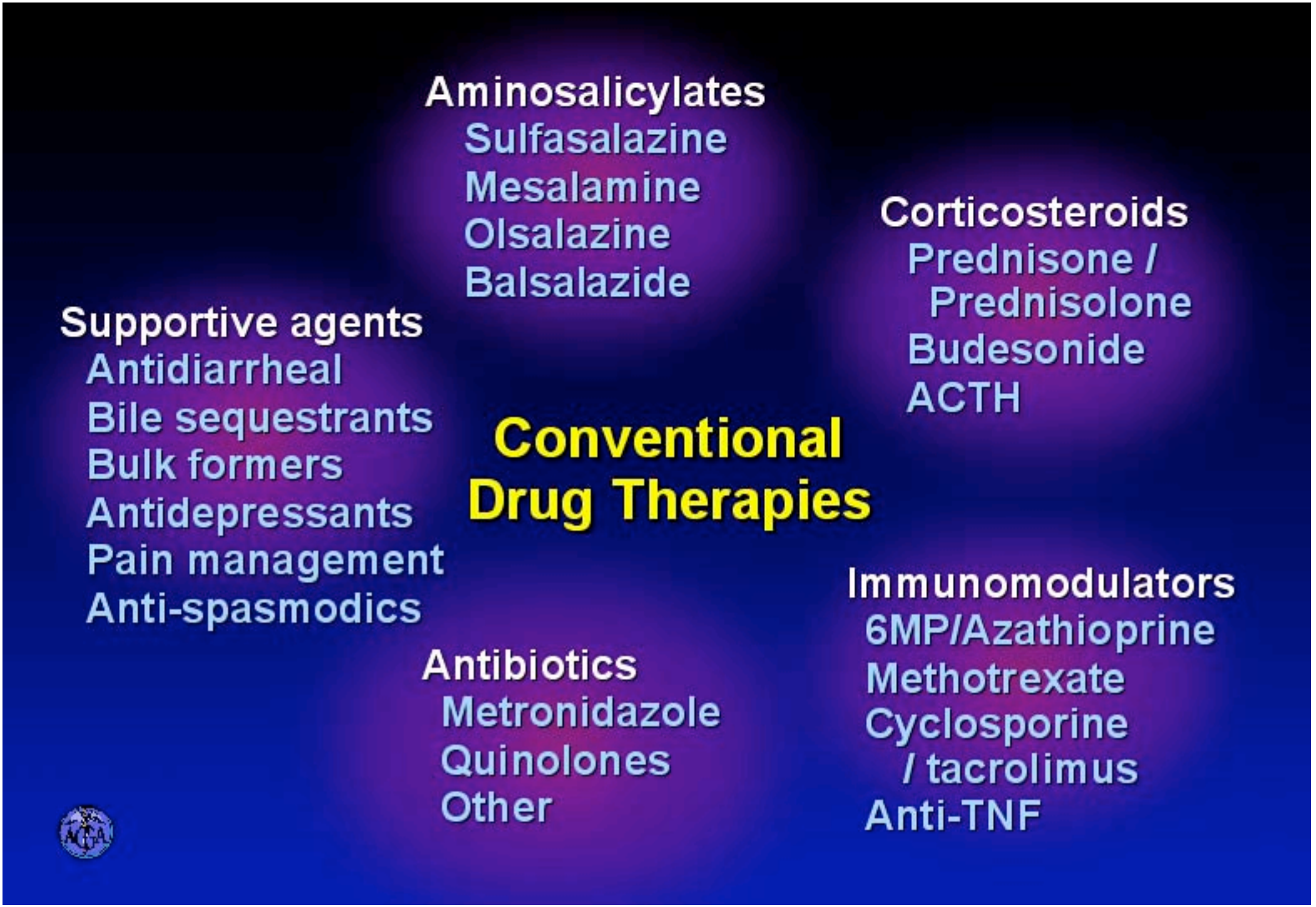
Mediator Imbalance




Pathways of T-lymphocyte Activation
TH_0
Antigen presenting cells
Antigen presenting cells
IL-12
IL-10
TH_1
IFNγ
IL-2
TNF
TH_2
IL-4
IL-5
IL-10
TH_3 / TR_1
TGFβ IL-10
Cell-mediated granulomas
Crohn's disease
Celiac disease
Hypersensitivity
Food allergy
Helminth infection
? Ulcerative colitis
Tolerance
Normal

Goals of Therapy

- Induce clinical remission
- Maintain remission
- Enhance quality of life
- Avoid long-term toxicity


Aminosalicylates
Sulfasalazine
Mesalamine
Olsalazine
Balsalazide
Corticosteroids
Prednisone / Prednisolone
Budesonide
ACTH
Supportive agents
Antidiarrheal
Bile sequestrants
Bulk formers
Antidepressants
Pain management
Anti-spasmodics
Conventional Drug Therapies
Immunomodulators
6MP/Azathioprine
Methotrexate
Cyclosporine / tacrolimus
Anti-TNF
Antibiotics
Metronidazole
Quinolones
Other

Ulcerative Colitis Therapy

Remission Induction

Aminosalicylates (oral, rectal)
Corticosteroids (IV, oral, rectal)
6MP / Azathioprine
Cyclosporine

Remission Maintenance

Aminosalicylates (oral, rectal)
6MP / Azathioprine

Crohn's Disease Therapy

Remission Induction

- Aminosalicylates
- Antibiotics
- Corticosteroids
- Immunomodulators
- Defined diets

Remission Maintenance

- Immunomodulators
- Aminosalicylates
- Antibiotics

Indices of Crohn's Disease Activity

- Crohn's Disease Activity Index
- Harvey - Bradshaw Index
- CCFA - IOIBD Index
- Present - Korelitz Response Assessment
- Crohn's disease Endoscopic Index
- Inflammatory Bowel Disease Questionnaire (IBDQ)

Crohn's Disease Activity Index

CDAI >450 - critically ill

CDAI <150 - inactive disease, remission

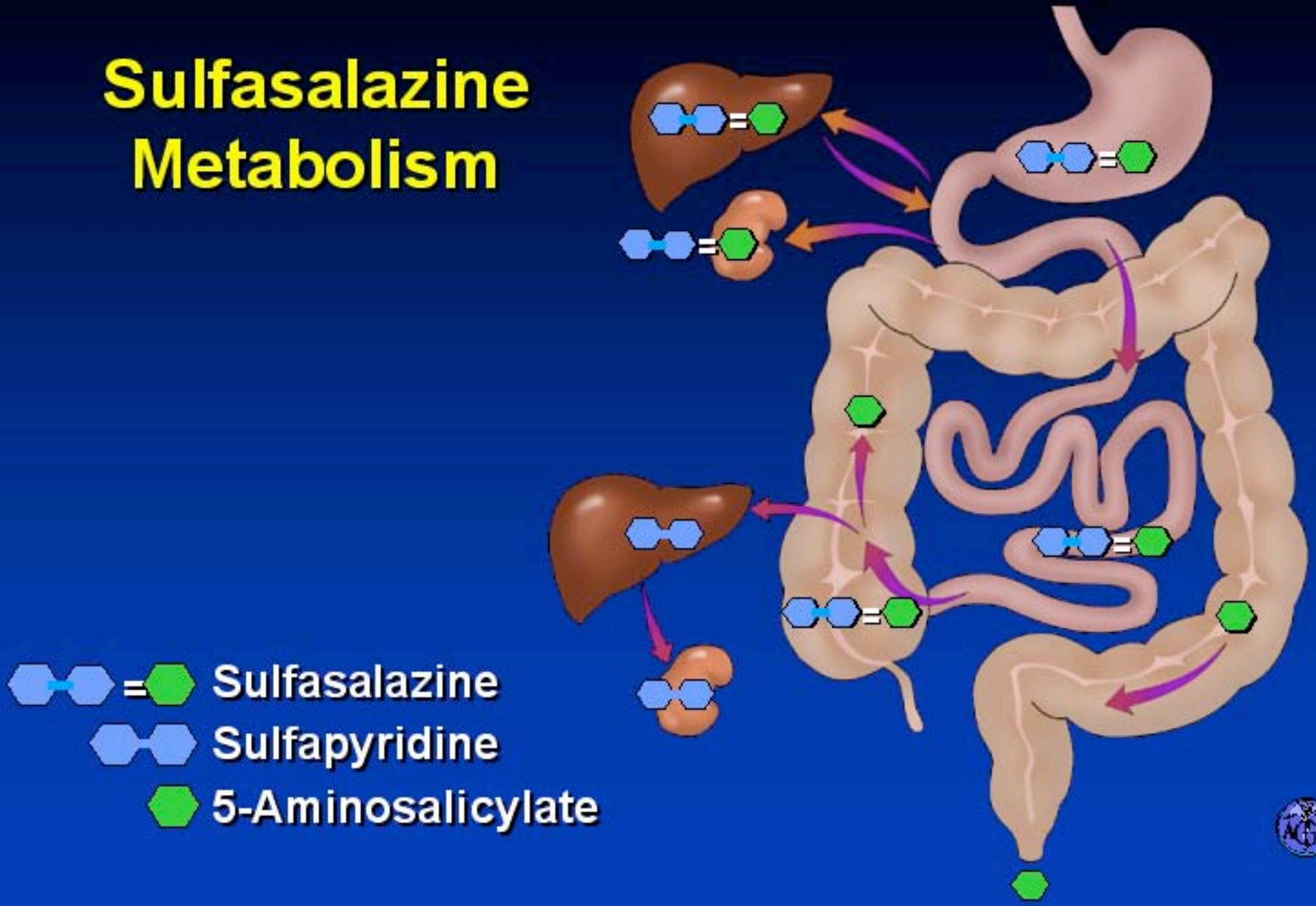
- Number of liquid or very soft stools during the previous week (*predominant component)*
- Severity of abdominal pain / cramping
- General well-being
- Extra-intestinal manifestations
- Presence of abdominal mass
- Use of antidiarrheal drug therapy
- Hematocrit
- Body weight

Sulfasalazine

Sulfapyridine
(SP)

5 - Aminosalicylic acid
(5-ASA)

Sulfasalazine Metabolism

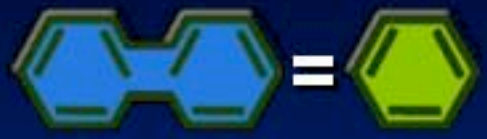


Sulfasalazine

Sulfapyridine

5-Aminosalicylate

Aminosalicylates



Sulfasalazine

Oral preparations

Mesalamine
- Acrylate coated
- Ethylcellulose encapsulated

Balsalazide — Inert vehicle

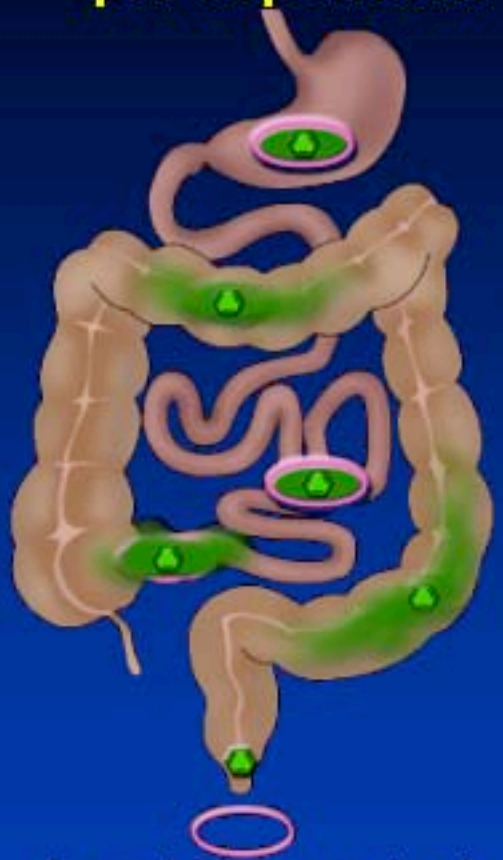
Olsalazine — 5-ASA dimer

Rectal preparations

Mesalamine

IBD - Oral Aminosalicylate Delivery

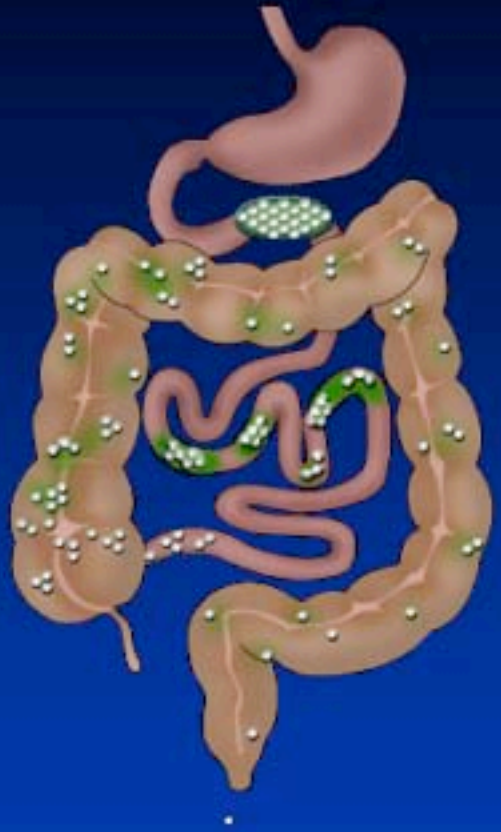
pH-dependent



Acrylate-coated mesalamine

Asacol®, Claversal®, Salofalk®, Raffersal®

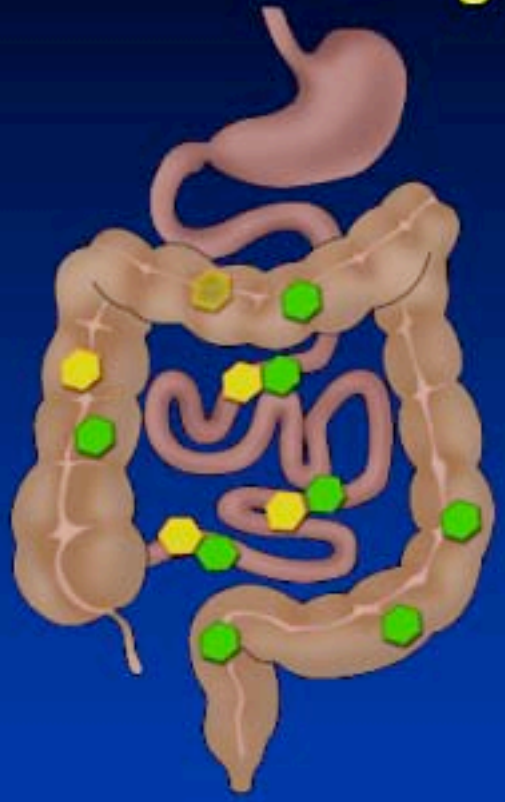
Time release



Ethylcellulose-encapsulated mesalamine

Pentasa®

Bacterial cleavage



Azobond - linked 5-ASA

Sulfasalazine - Azulfidine®

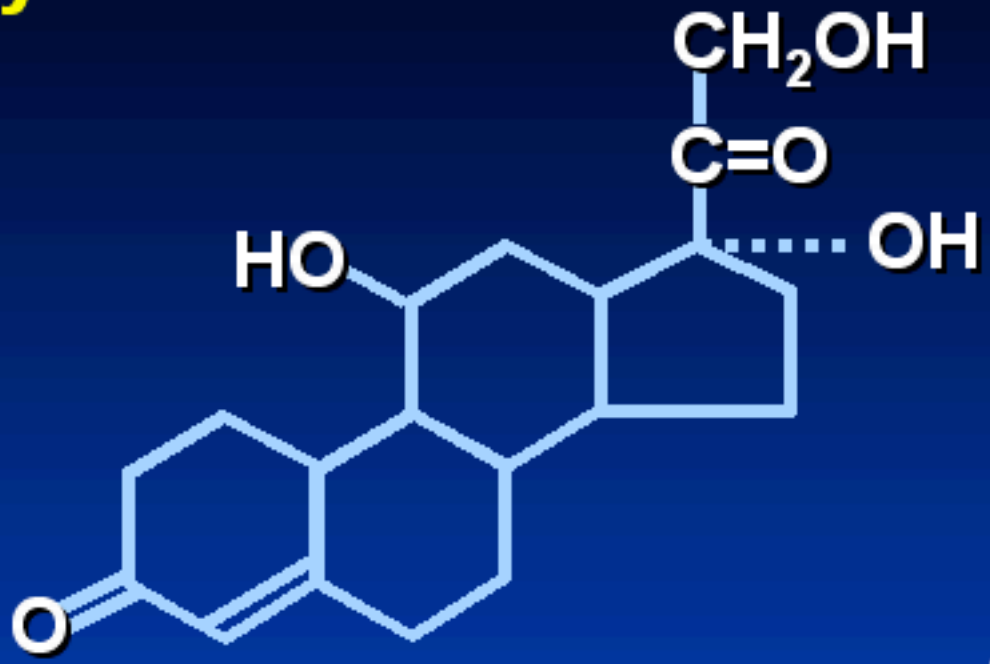
Olsalazine - Dipentum®

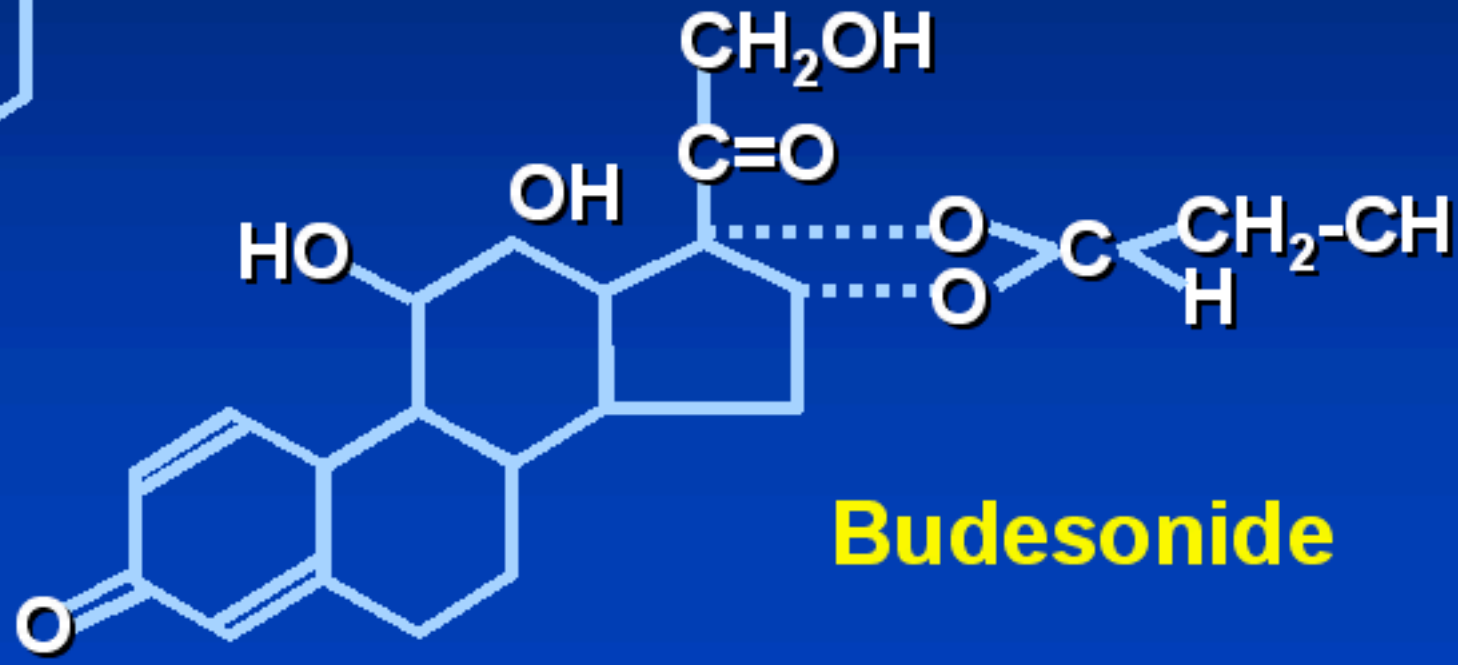
Balsalazide - Colazal®

IBD - Oral Therapy

	Sulfasalazine	5-ASA
UC (active & maintenance)	++++	++++
Crohn's disease active		
colon	++	+
ileitis	+/-	+
Crohn's disease maintenance	-	+
Adverse effects	++	+
Expense	+	++++

Hydrocortisone





Budesonide

Topical Corticosteroids

Indications

- Proctitis and left-sided colitis

Preparations

- Systemic effect (partial absorption)
  - hydrocortisone
- Less systemic effect (less absorption)
  - prednisolone - 21 - phosphate
- Less systemic effect (rapid metabolism)
  - budesonide

Systemic Corticosteroids

Oral

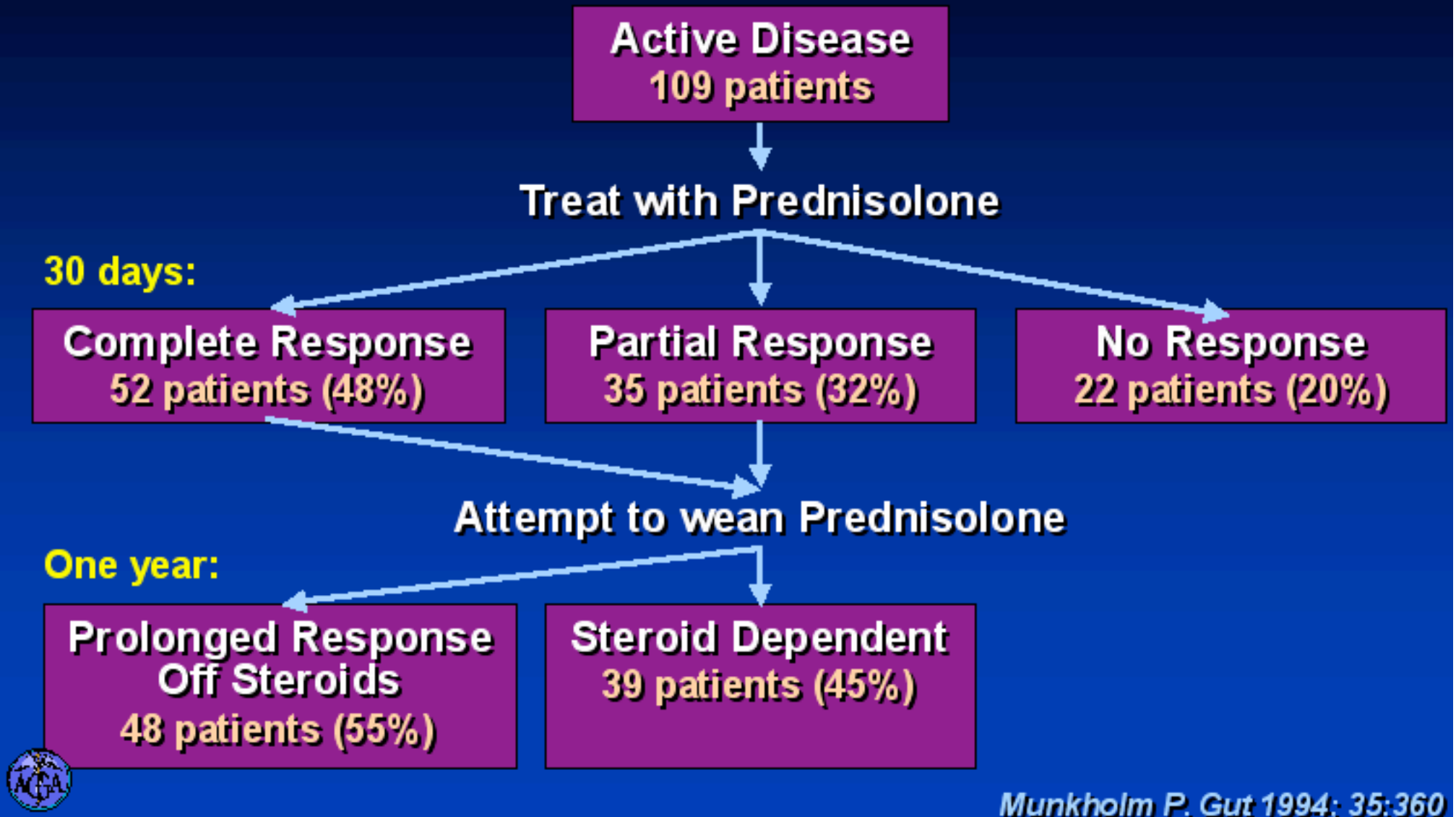
- Indications - moderate to severe ulcerative colitis or Crohn's disease
- Preparations - prednisone, prednisolone, budesonide

Parenteral

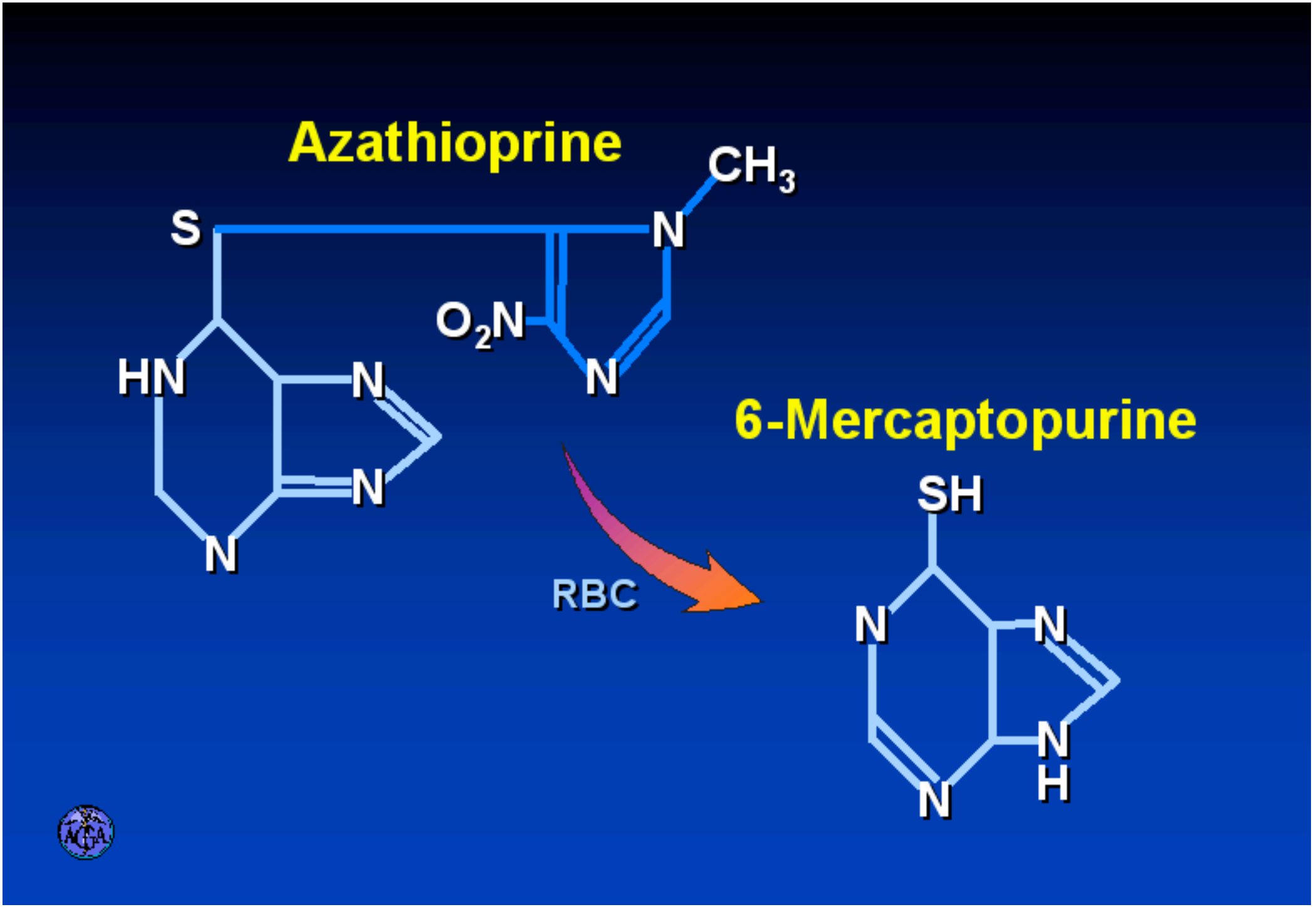
- Indications - Severe or toxic ulcerative colitis or Crohn's disease
- Preparations - hydrocortisone, methylprednisolone, corticotropin (ACTH)

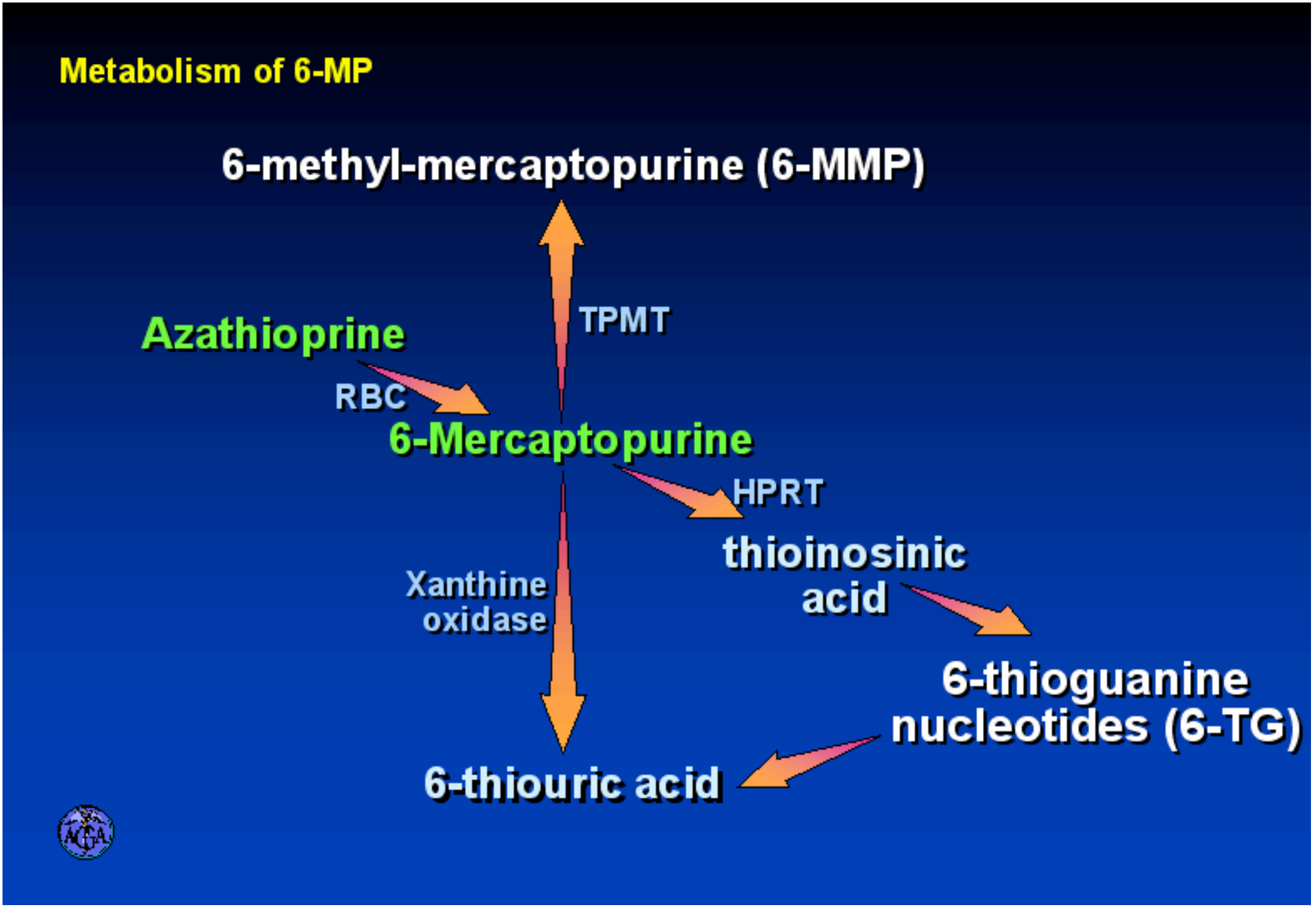
IBD - CD

Results of Corticosteroid Therapy

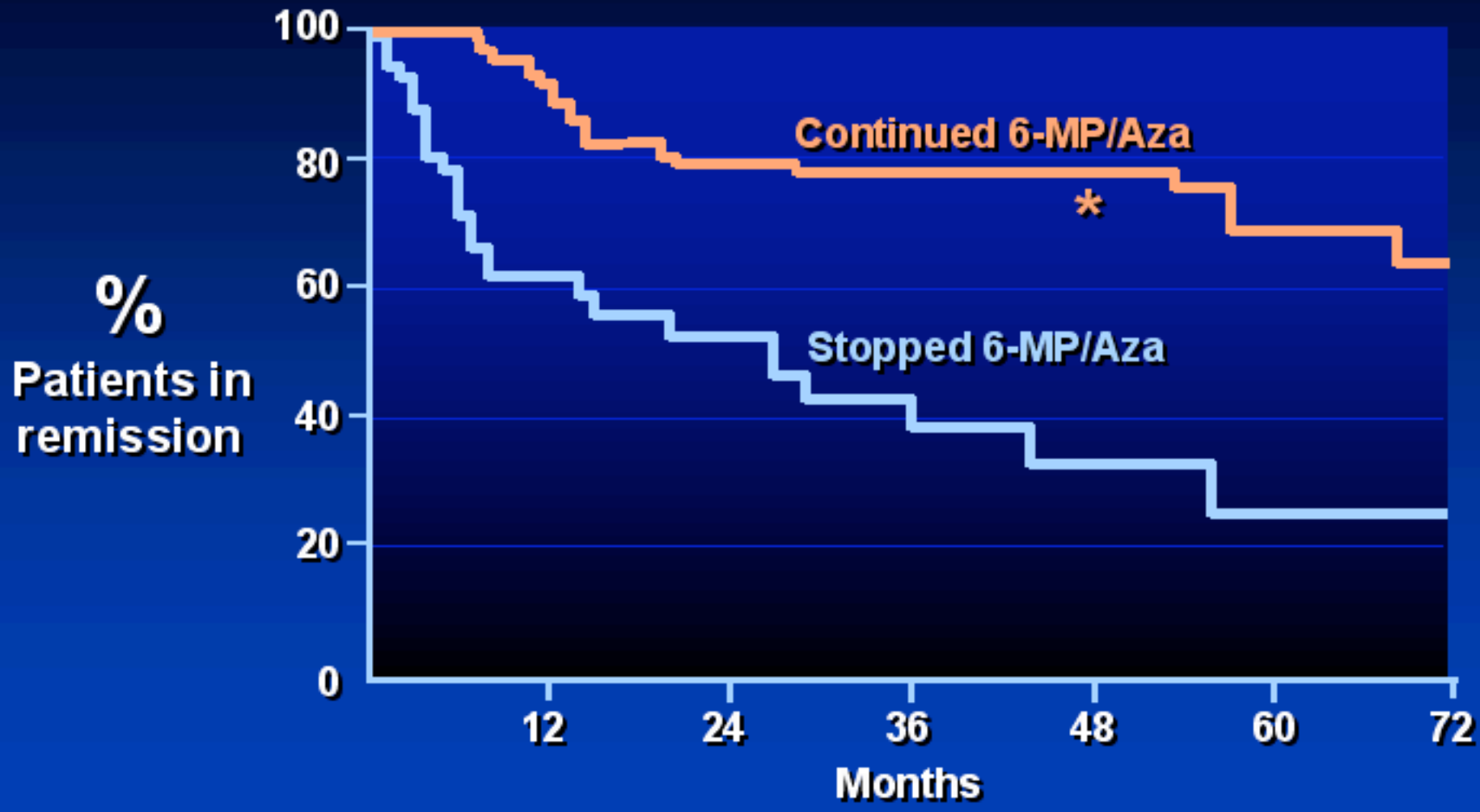


Munkholm P. Gut 1994; 35:360


Azathioprine
CH3
S
N
O2N
HN
N
N
N
RBC
6-Mercaptopurine
SH
N
N
N
H
N

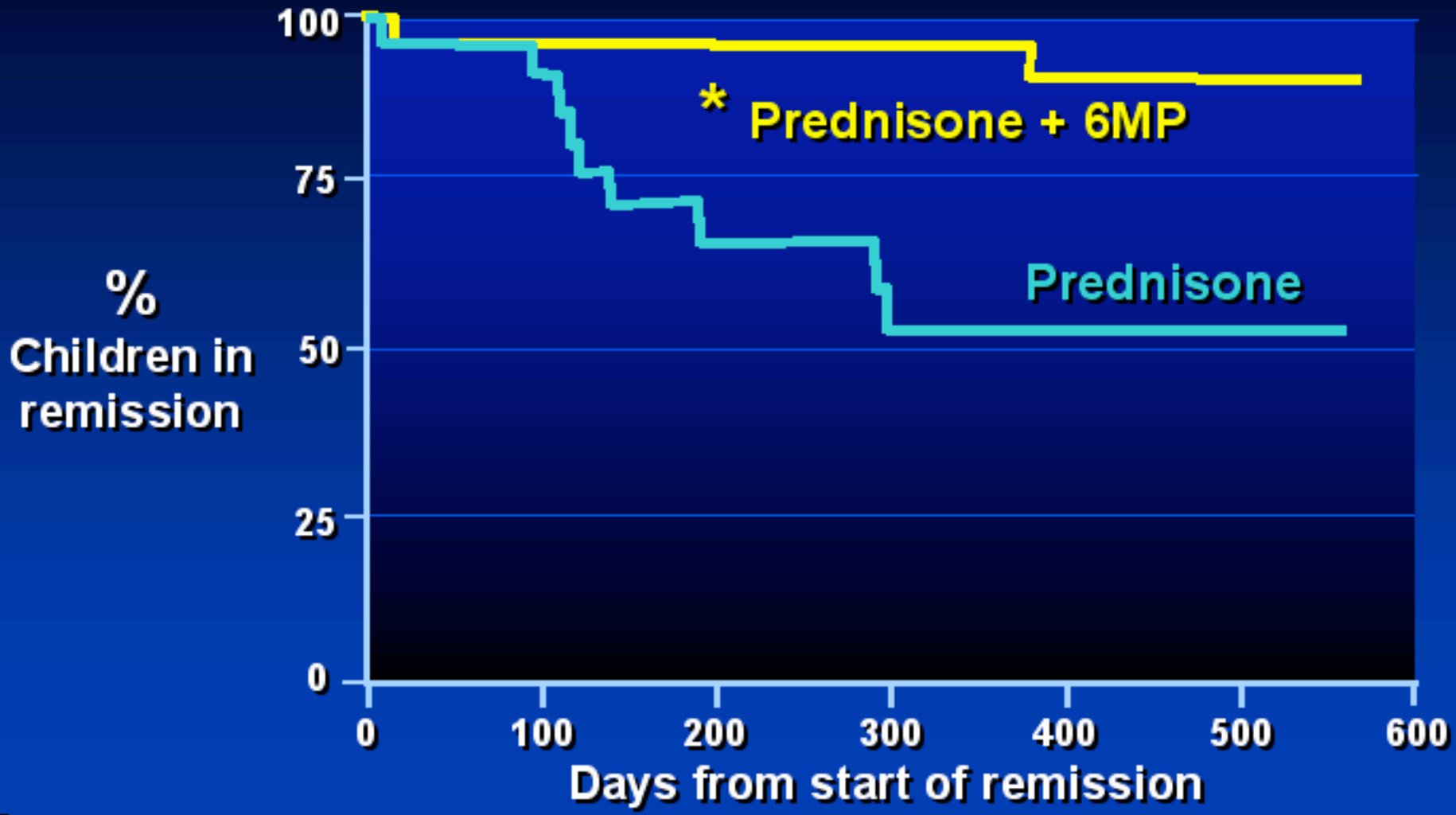

Metabolism of 6-MP
6-methyl-mercaptopurine (6-MMP)
TPMT
Azathioprine
RBC
6-Mercaptopurine
HPRT
thioinosinic acid
Xanthine oxidase
6-thioguanine nucleotides (6-TG)
6-thiouric acid

CD - Maintenance Therapy



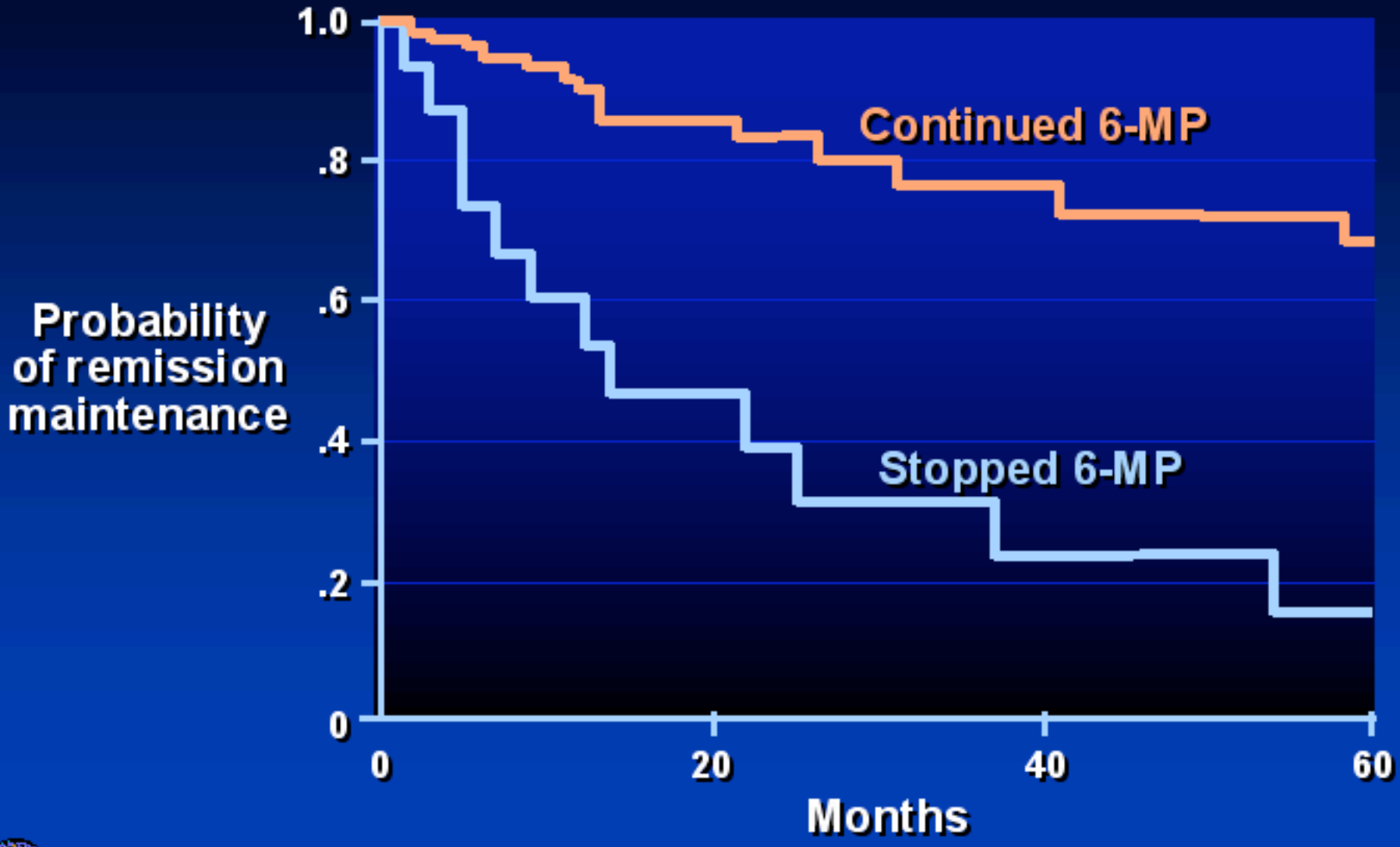
Bouhnik Y et al. Lancet 1996; 347:215

CD - Remission Maintenance



Markowitz J et al. Gastroenterology 2000; 119:895

UC - Maintenance Therapy



George J et al. Amer J Gastroenterol 1996; 91:1711

Adverse Effects of 6MP / Azathioprine

Hypersensitivity reactions

- Fever, rash
- Pancreatitis
- Hepatitis

Bone marrow suppression

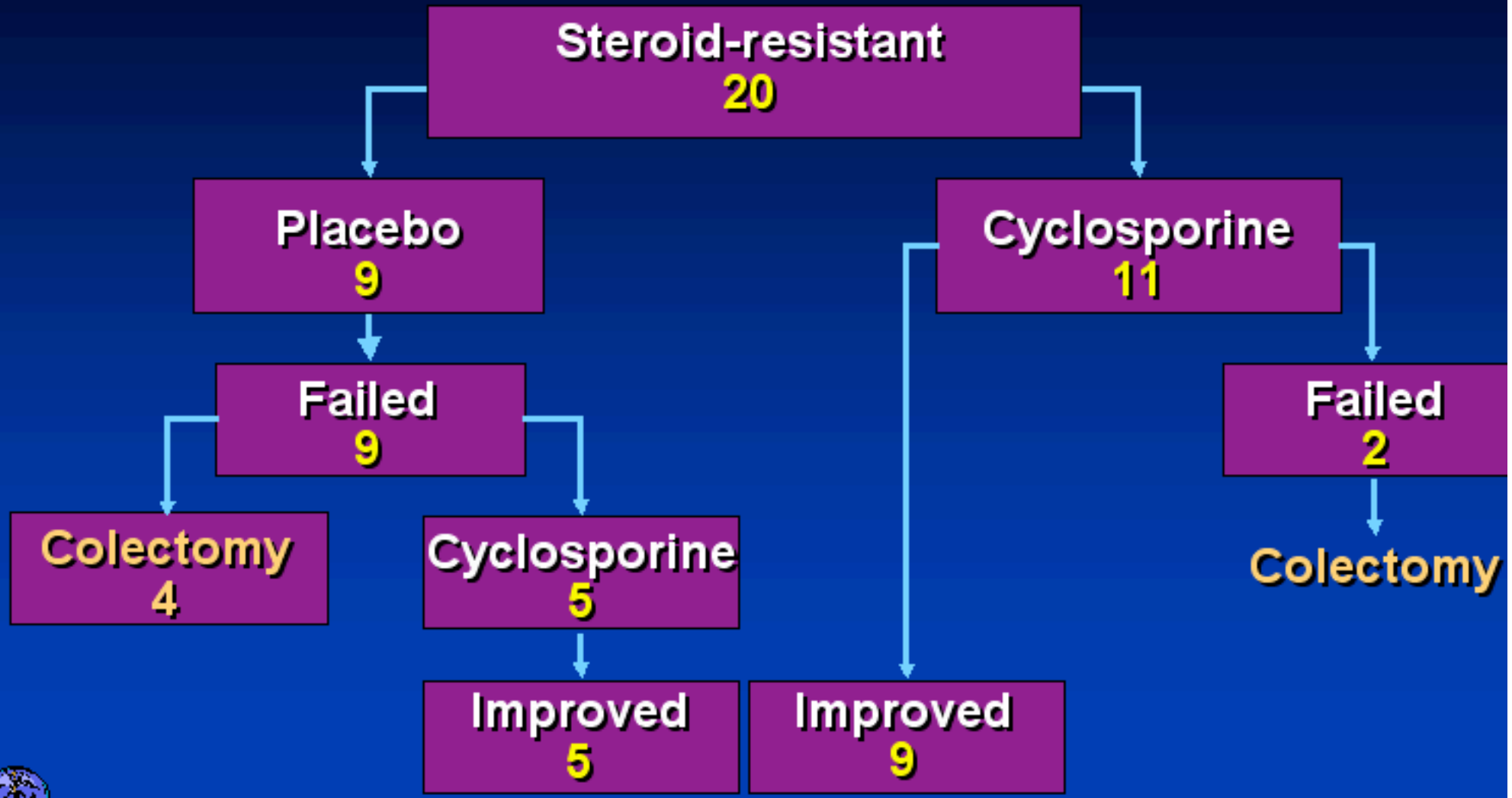
Opportunistic infections

Minimal risk of lymphoma

No steroid-like complications

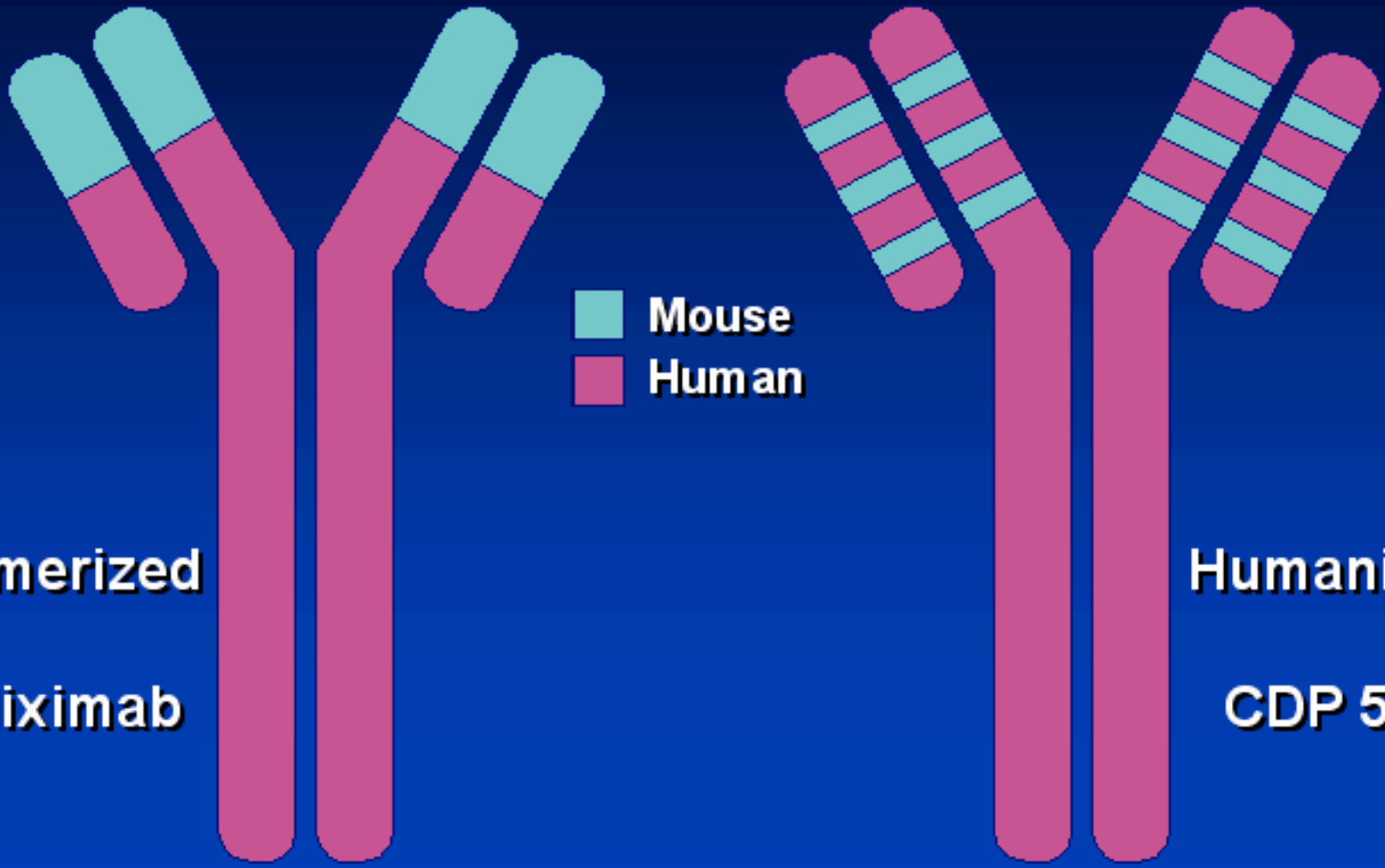
Severe UC - Therapy of Active Disease

Intravenous Cyclosporine A



Lichtiger S et al. N Engl J Med 1994; 330:1841

Antibodies to TNF



Chimerized

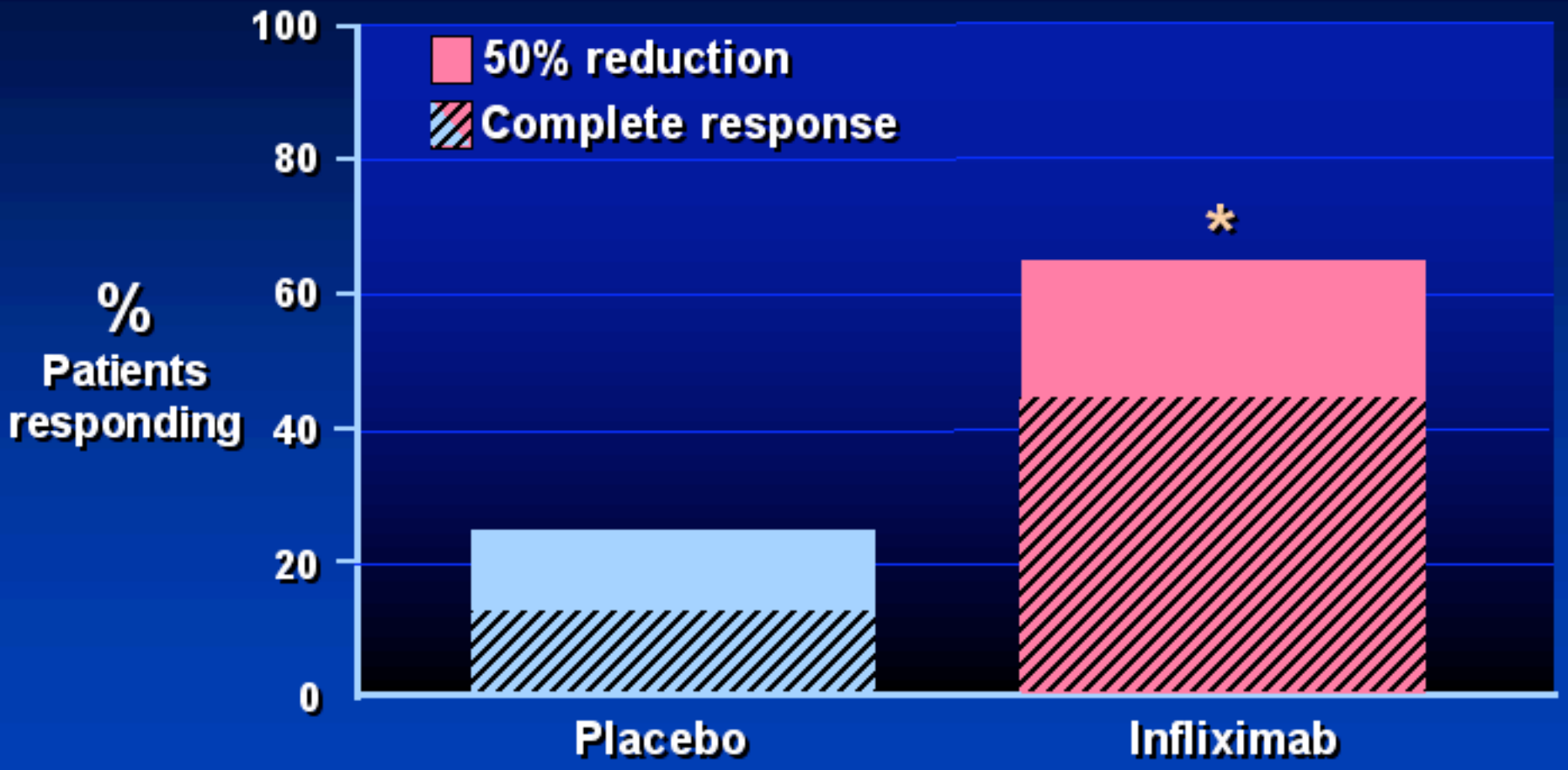
Infliximab

Humanized

CDP 571

Crohn's Disease

Treatment of Fistulae



Present DH et al. N Engl J Med 1999; 340:1398

Adverse Effects of Infliximab

- Immediate infusion reactions
  - Headache, flushing, rash, fever, abdominal pain, chest pain, wheezing, anaphylaxis
- Serum sickness-like syndrome
  - High human anti-chimeric antibody titers
- "Lupus-like" syndrome
- Infection
  - URI, peri-rectal abscess, reactivation TB
- ? Worsening of strictures
- ? Risk of cancer

Emerging Treatments for IBD - 2002

Biologics
- Anti-TNF; *e.g.*, CDP 571
- IL-10
- IL-11
- Anti IL-12
- Antisense oligonucleotide

Heparin

Probiotics

Growth hormone

Growth factors

Granulocyte colony stimulating factor

Immunomodulators
- Mycophenolate
- Thalidomide
- Tacrolimus

Therapeutic enemas
- Nicotine
- Lidocaine
- Bismuth

Complementary and alternative therapies

Tested Unconventional Therapies

- Nicotine patch
- Fish oils
- Short-chain fatty acid enemas
- Anti-tuberculous agents

Guidelines for Pregnancy

- Conceive preferably while in remission
- Males should switch sulfasalazine to another 5-ASA if no conception
- Sulfasalazine, 5-ASA agents and corticosteroids safe in pregnancy and nursing
- 6-MP and azathioprine not associated with adverse fetal outcomes
- Flexible sigmoidoscopy safe

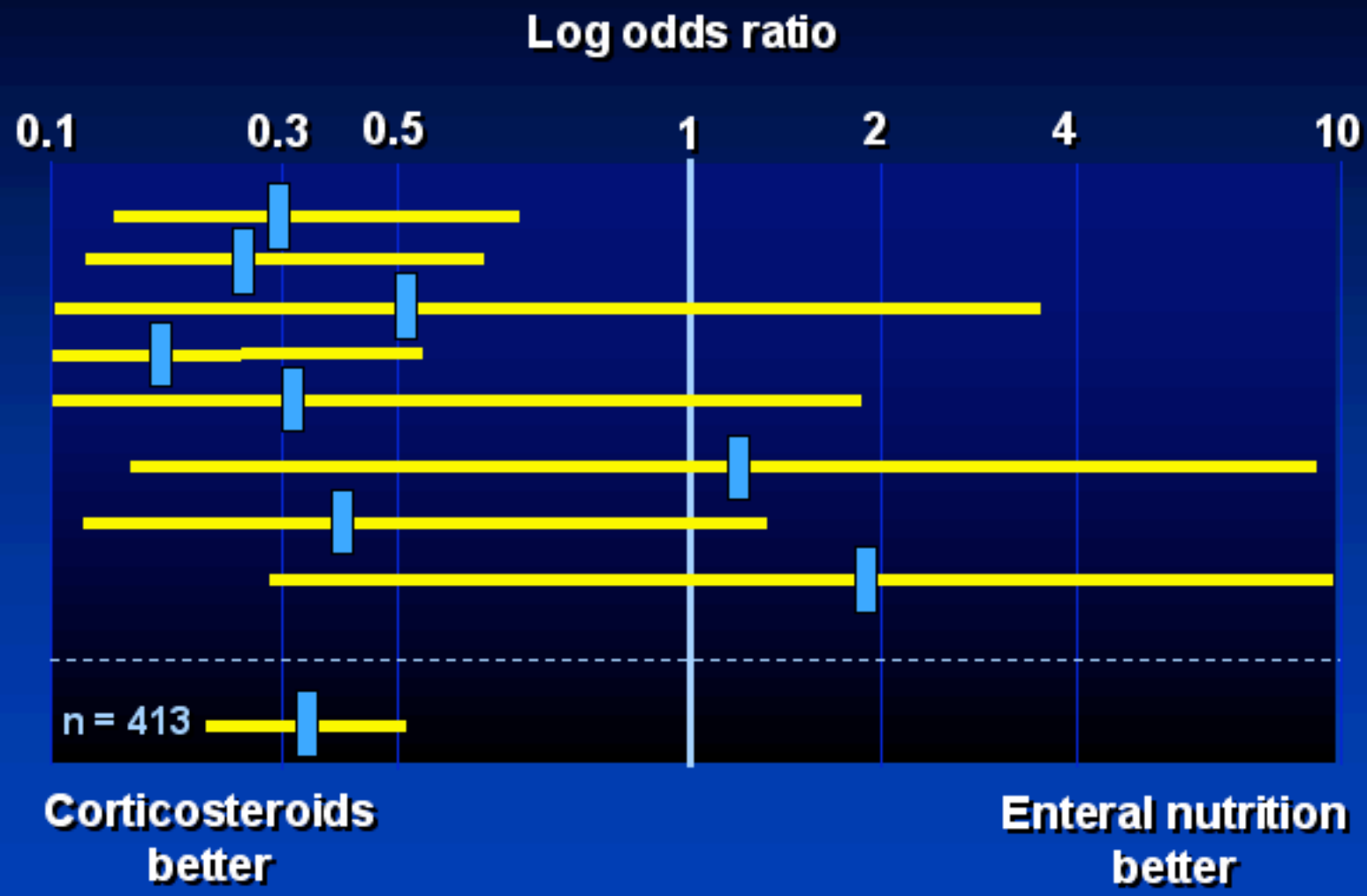
Nutritional Therapy in IBD

- Difficult to distinguish severe illness from malnutrition
- Use table foods when possible
- “Bowel rest” not proven therapy

Nutritional Therapy in IBD

- **Nutrition support as proven therapy**
  - TPN may suppress symptoms, but relapse occurs upon refeeding
  - EN is less effective than glucocorticosteroids
- **Treat with EN or TPN if**
  - 'Malnourished' and cannot maintain oral intake
  - Short bowel syndrome unable to maintain fluid / energy balance
  - Growth failure

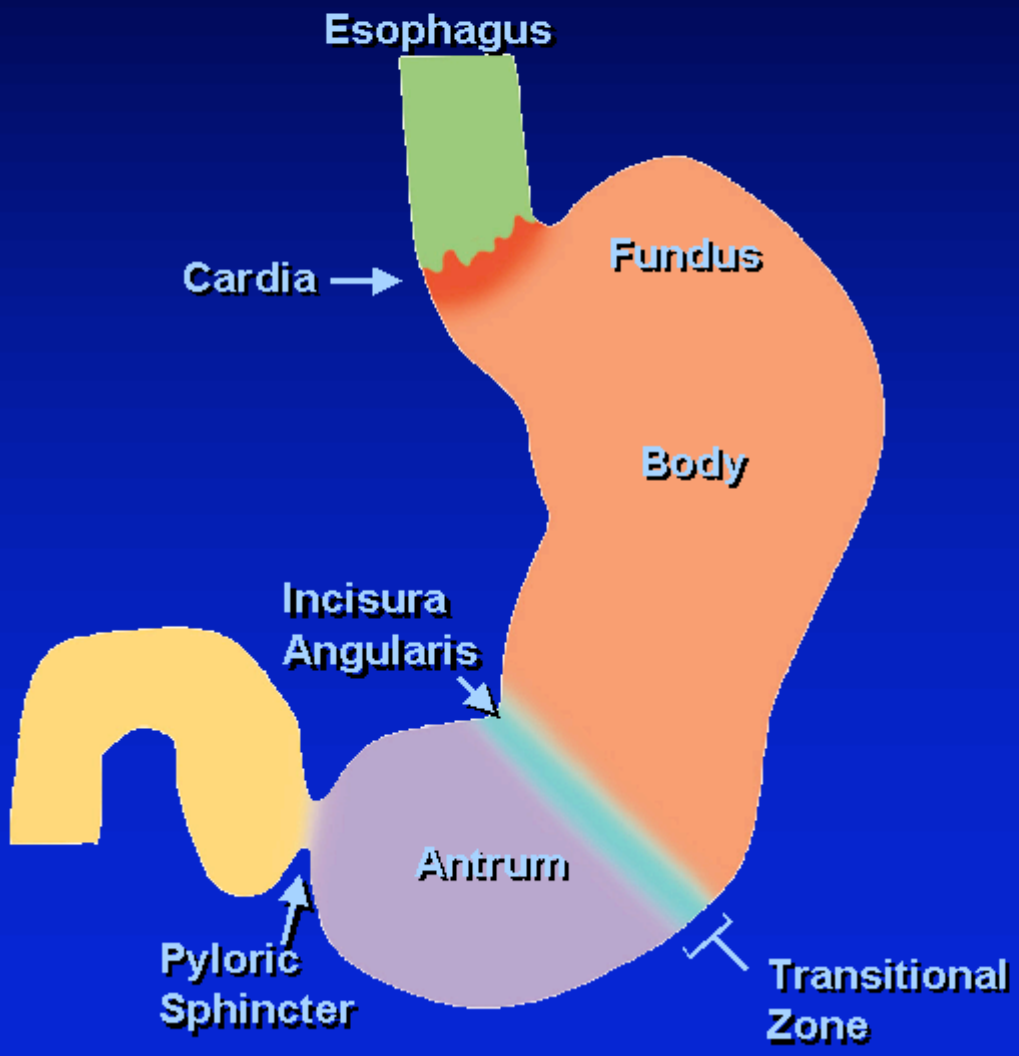
CD - Therapy of Active Disease



Griffiths AM et al. Gastroenterology 1995; 108:1056

Upper GI: Anatomy

Esophagus, Stomach, and Duodenum: Normal Anatomic Outlines and Relationships



Esophagitis (Inflammatory and Reactive Epithelial Changes of the Esophageal Mucosa) Has Many Causes

- Gastro-esophageal reflux
- Infection
  e.g., Candida, Herpes, CMV
- Pill-induced
  e.g., NSAIDs, antibiotics, quinidine, $FeSO_4$
- Radiation therapy
- Trauma
  Gastric intubation, foreign bodies
- Corrosive substance ingestion
- Allergic reaction to food or other substances

Reflux Esophagitis Is the Culmination of Gastro-esophageal Reflux-induced Increase in Epithelial Cell Turnover

Normal Epithelium

Reflux

Epithelial Reactive Changes (loss of mature cells, new cells)

More Reflux

"True" Esophagitis (infiltration of mucosa by active inflammatory cells)

Defenses Against Reflux-Induced Injury

- Competent lower esophageal sphincter
- Prompt esophageal clearing
  - Effective peristalsis
  - Normal salivary flow
  - Gravity
- Intact mucosal diffusion barrier

Symptoms and Endoscopic Findings in Reflux Esophagitis Are NOT Predictive Of Biopsy Findings

	Histopathologic Correlations	
Symptoms	Epithelial Changes	Inflammation
• Heartburn	Good	Poor
• Dysphagia	Poor	Poor
Endoscopic Findings		
• Erythema	Poor-fair	Poor
• Erosion or ulcer	Good	Good

Esophagus: G-E Reflux

Reflux-Induced Epithelial Change is a Consequence of Increased Cell Turnover

Normal

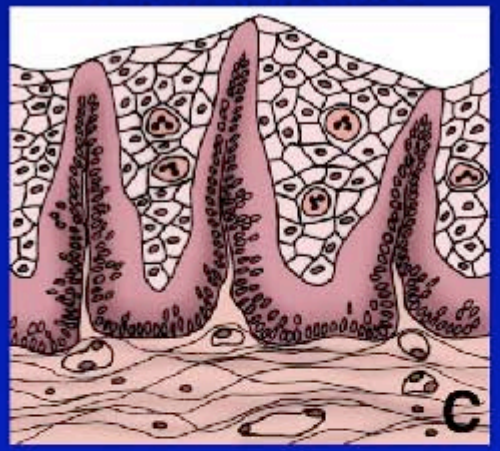
Replacement = Loss

HCl
+
Pepsin

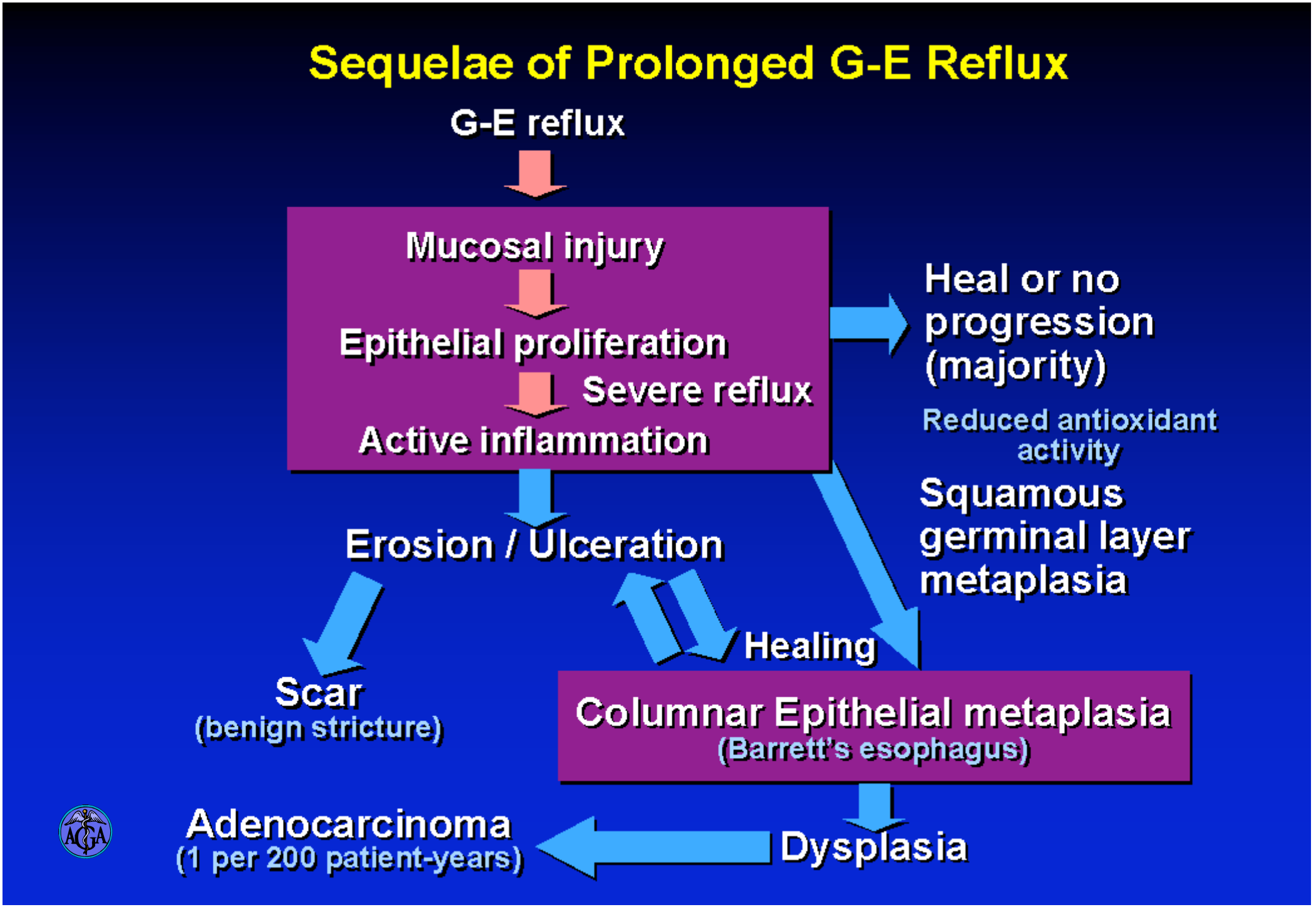
Mild Reflux Change
(compensated)

Increased Epithelial Turnover
Replacement = Loss

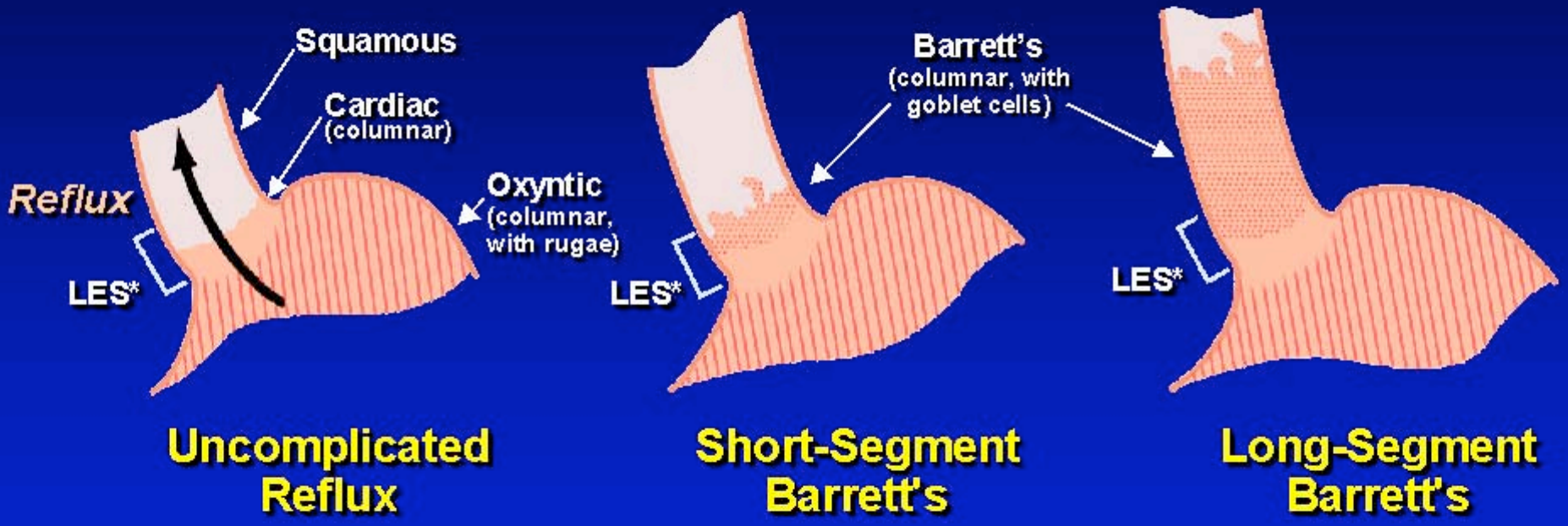
Severe Reflux Change
(decompensated)



Replacement < Loss
+ Active Inflammation
(sometimes)


Sequelae of Prolonged G-E Reflux
G-E reflux
Mucosal injury
Epithelial proliferation
Severe reflux
Active inflammation
Heal or no progression (majority)
Reduced antioxidant activity
Squamous germinal layer metaplasia
Erosion / Ulceration
Healing
Scar
(benign stricture)
Columnar Epithelial metaplasia
(Barrett's esophagus)
Adenocarcinoma
(1 per 200 patient-years)
Dysplasia

Barrett's Esophagus:
Development and Anatomic Relationships



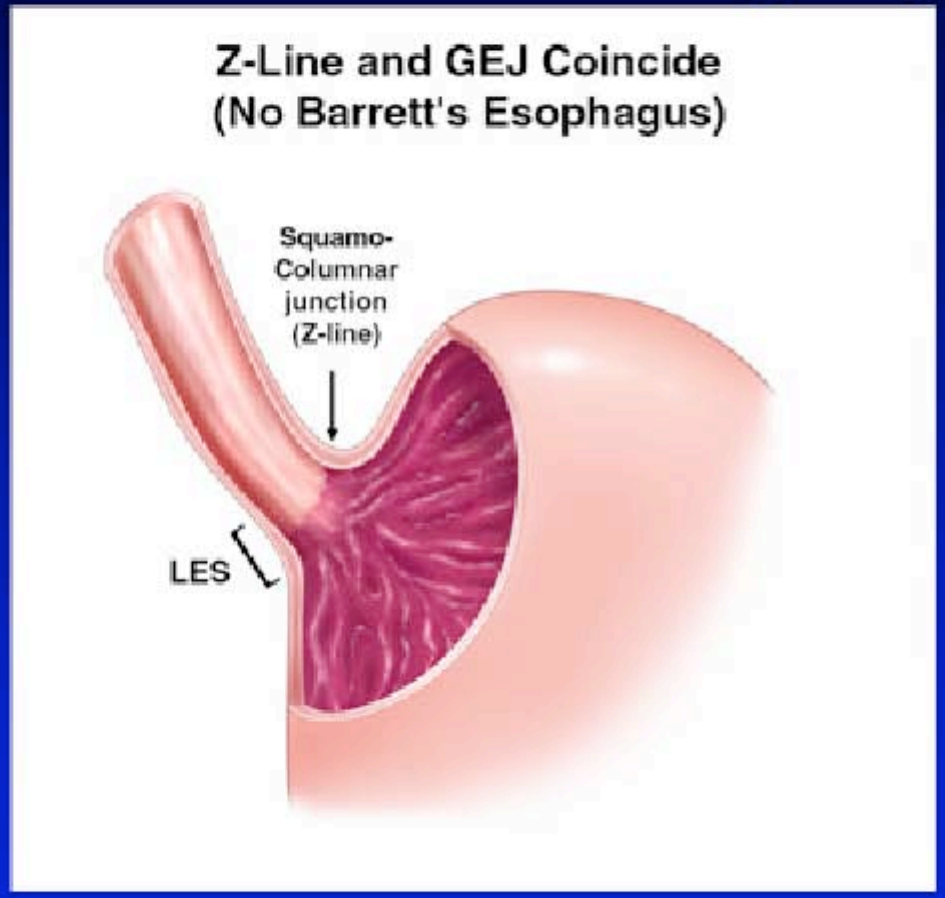
Uncomplicated Reflux

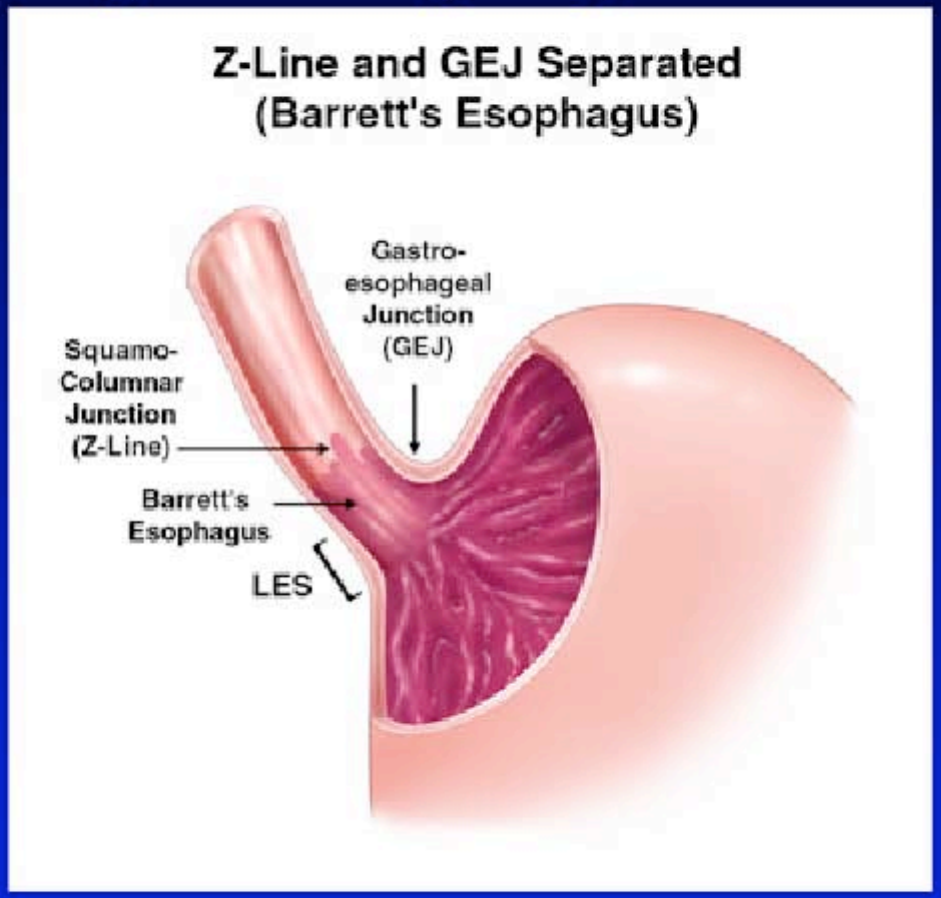
Short-Segment Barrett's

Long-Segment Barrett's

*LES = Lower Esophageal Sphincter segment

Endoscopic Landmarks in the GEJ Region: Normal vs Barrett's (Columnar-Lined) Esophagus with Location of Lower Esophageal Sphincter (LES)



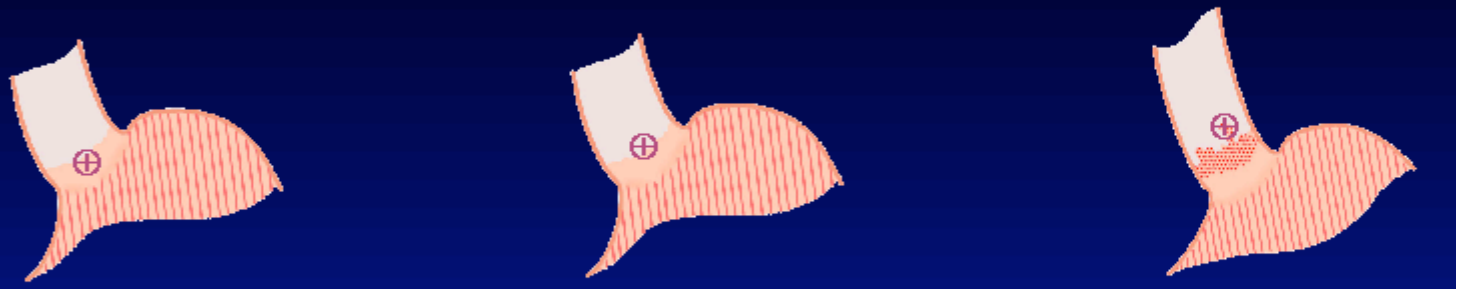


Normal

Barrett's

Adapted from: Gastroenterology 1999;117:218

Requirements for Diagnosis of BARRETT's Esophagus



	Below Z-line (SCJ)*	At Z-line No tongues	From tongues At or above Z-line
Endoscopic Biopsy site (⊕)	⊕	⊕	⊕
Histologic Findings	Columnar epithelium No goblet cells	Columnar epithelium with goblet cells	Columnar epithelium with goblet cells
	Inflammation: No / Yes		
Diagnosis	Gastric Mucosa No abnormality / Carditis	Gastric Mucosa with goblet cells	BARRETT's

Basic Needs:
- Accurate endoscopic localization of biopsy sites
- Columnar epithelium containing goblet cells

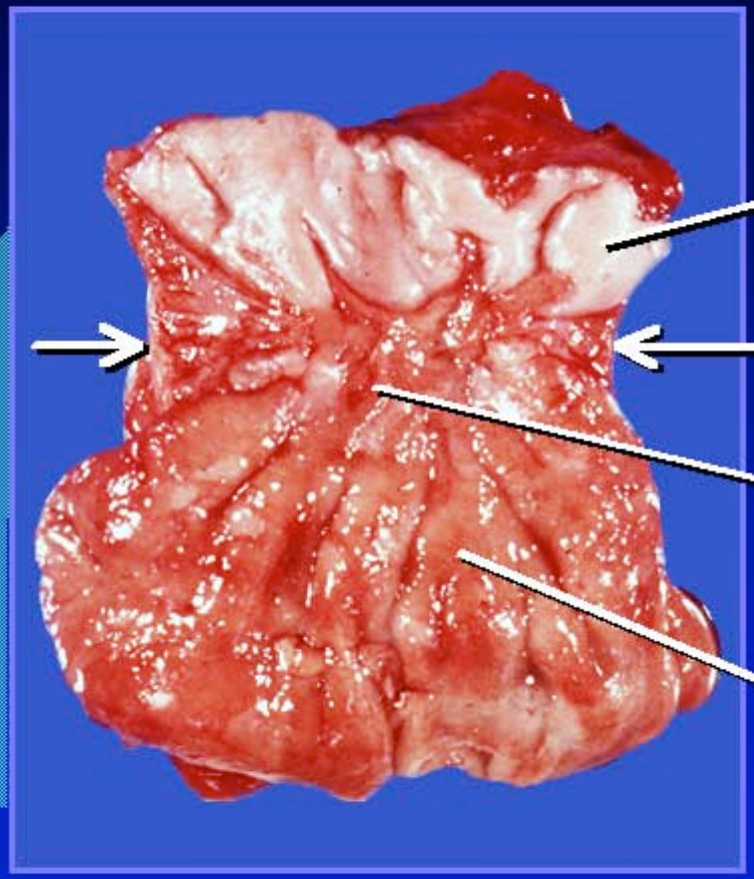
Bottom line:
- Barrett's cannot be diagnosed from Endoscopy or Histology alone

*SCJ = squamocolumnar junction

Adapted from Am J Gastroenterol 1998;93:1028 & Appelman, H. personal com.

Barrett's Esophagus: Gross Appearance

Autopsy
(original paper)



Surgical specimen

Squamous Epithelium

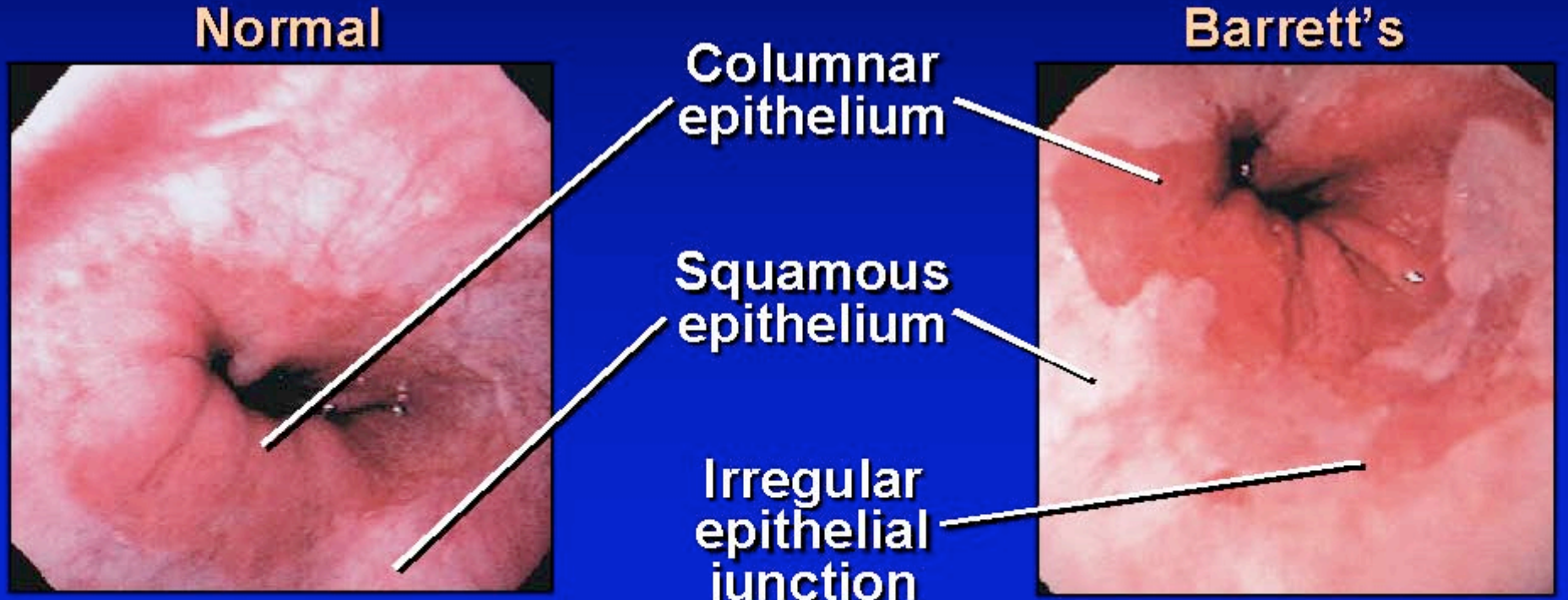
Stricture
(Between arrows)

Ulcer

Barrett's Columnar Epithelium

Barrett's Esophagus Should Be Suspected and Confirmed by Biopsy When the Squamo-columnar Junction Is Displaced or Highly Irregular

Endoscopic views of squamo-columnar junctions

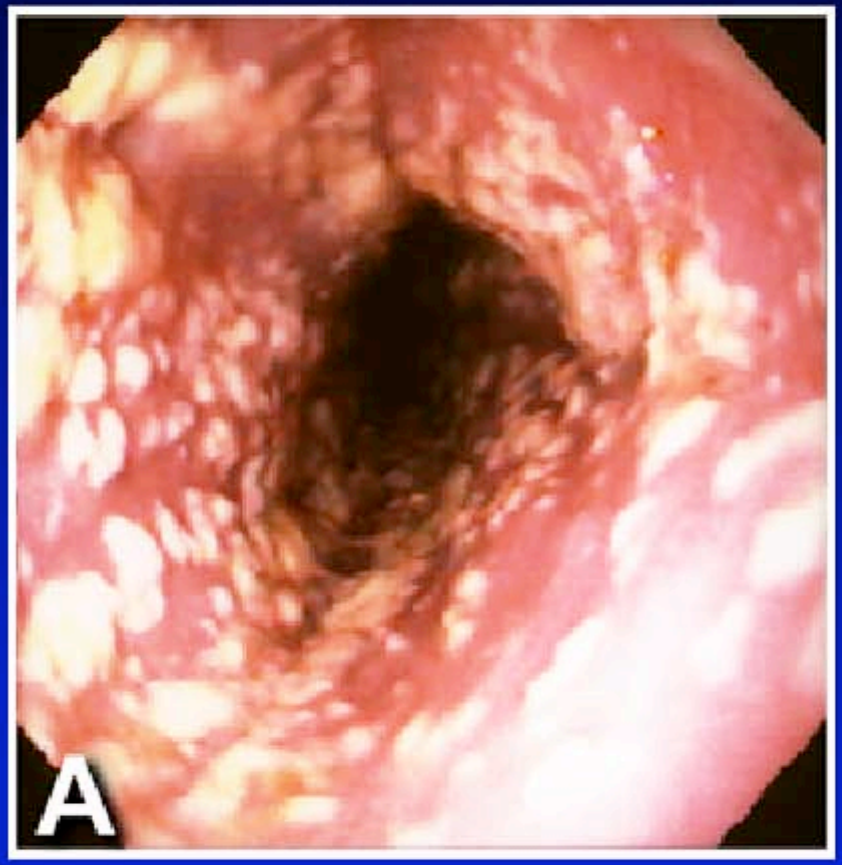


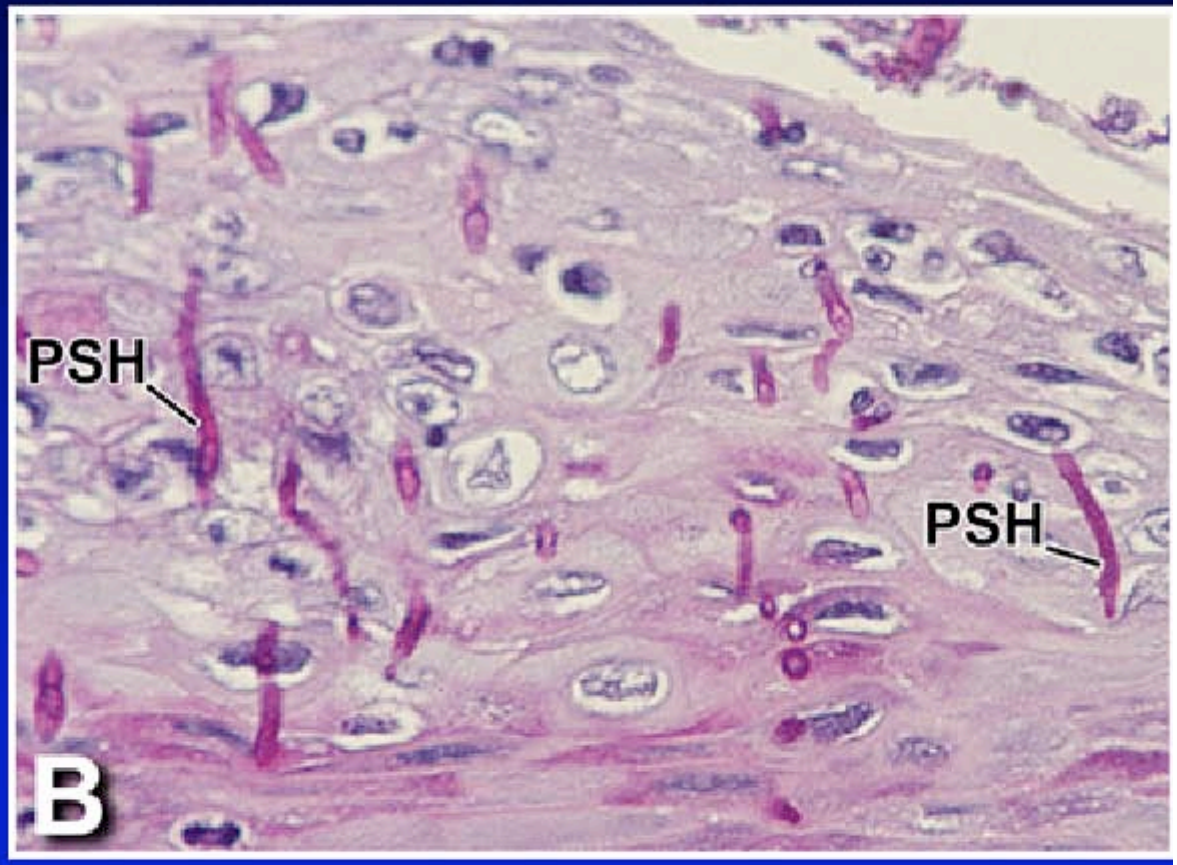
Columnar Epithelial Dysplasia In Barrett's Mucosa - Definition And Grading

- **Definition:** "Dysplasia" describes cytologic and histopathologic epithelial abnormalities that are felt to be unequivocally neoplastic.
- **Grading:**
  - Negative for dysplasia
  - Indefinite for dysplasia
  - Positive for dysplasia
    - Low grade
    - High grade
  - Dysplasia with carcinoma
    - Intramucosal
    - Extramucosal ("invasive"; "infiltrative")

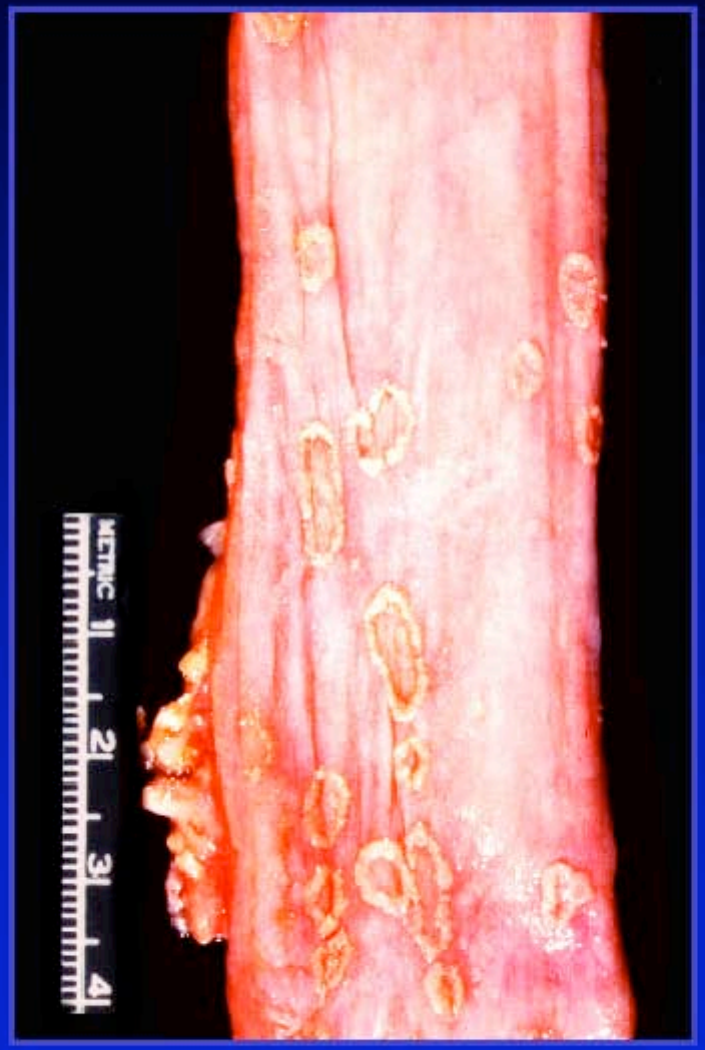
Adapted from: Hum Pathol 1988;19:166 & 2001;32:368

Candidal Esophagitis: Endoscopic and Histologic Views

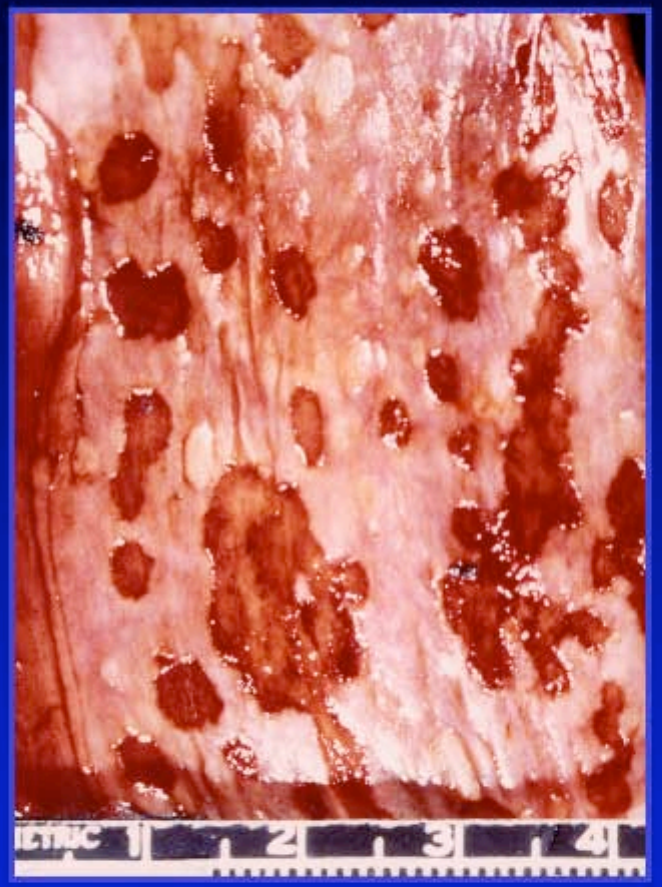




Herpes Simplex Esophagitis: Gross Appearances



Early



Late

Pill-induced Esophagitis Occurs Above Sites Where Transit Is Normally Delayed

Common Sites

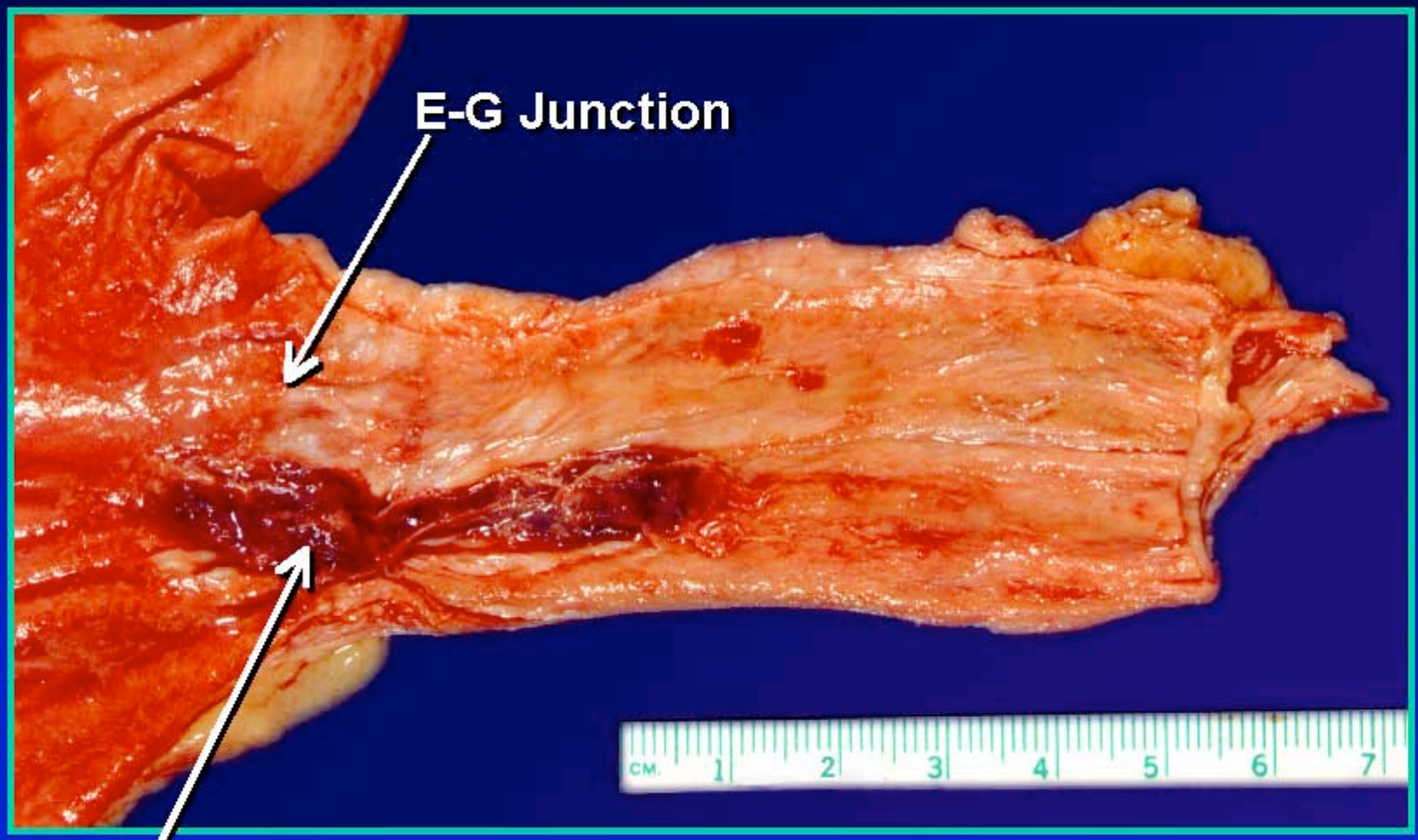
Above aortic arch

Above lower esophageal sphincter (LES)

Common Agents

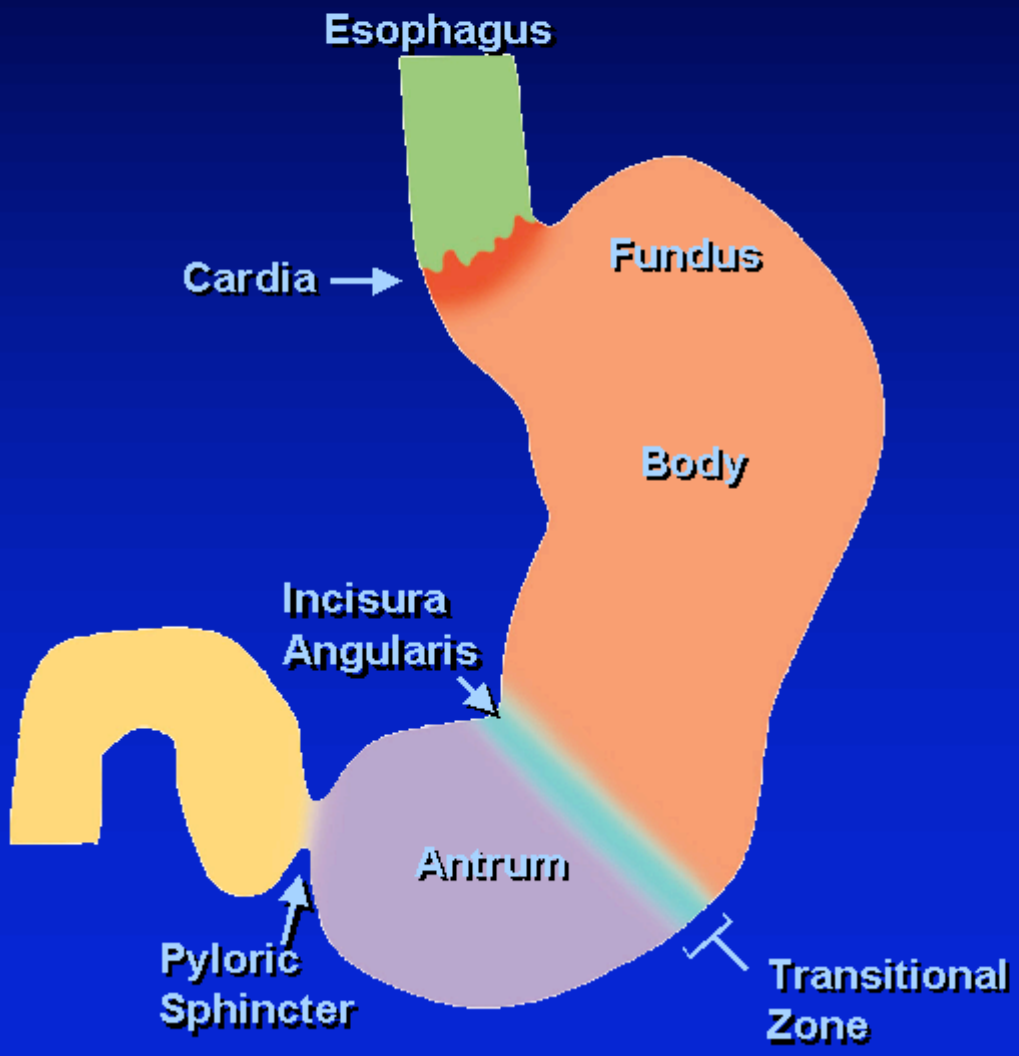
- NSAIDs
- Antibiotics
- Quinidine
- Potassium chloride
- Ferrous sulfate
- Ascorbic acid
- Alendronate

Linear Erosion and Esophagitis 2° To Mechanical Injury



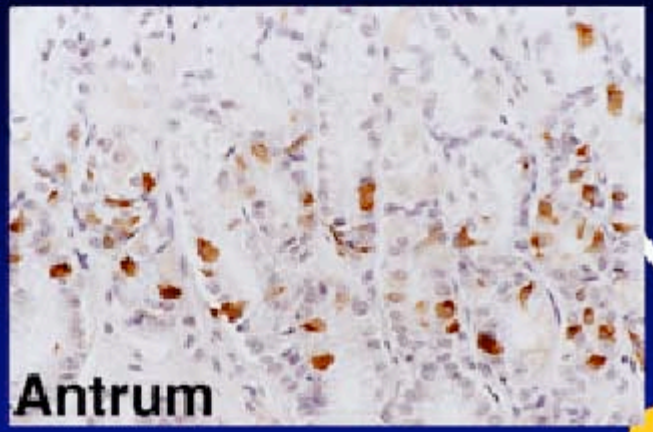
Upper GI: Anatomy

Esophagus, Stomach, and Duodenum: Normal Anatomic Outlines and Relationships

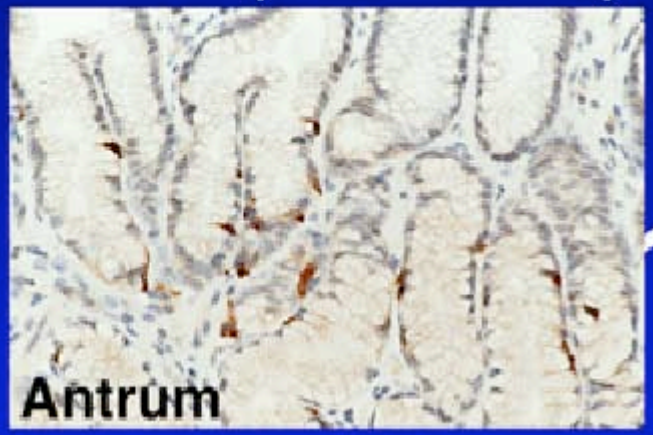


Major Endocrine Cell Types of the Stomach and Their Products – Immunostain Demonstrations

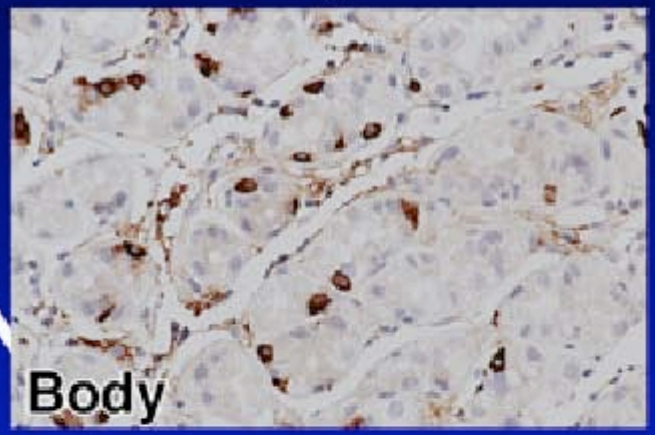
G-Cells (Gastrin)



D-Cells (Somatostatin)



ECL Cells (Histamine)



Gastropathy and Gastritis - Definitions

- GASTROPATHY - Literally, any gastric lesion
  Used as substitute for "gastritis" when inflammation absent or minimal
- GASTRITIS - Leukocyte infiltration in stomach
  - ACTIVE (=ACUTE) GASTRITIS - Neutrophil infiltration present
- CHRONIC GASTRITIS - Mononuclear leukocytes increased
- CHRONIC ACTIVE GASTRITIS - Mixed chronic and active inflammation

Classification Of Gastropathy And Gastritis

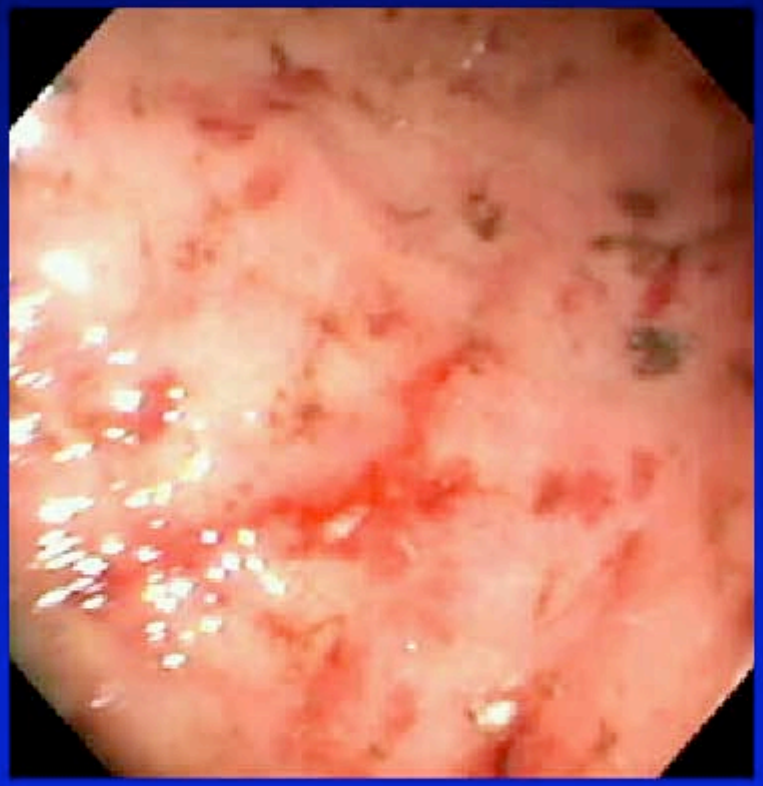
- **ACUTE GASTROPATHY AND GASTRITIS**
  - Hemorrhagic and erosive gastropathy
  - Acute *H. pylori* gastritis (rarely diagnosed)
  - Other acute infectious gastritides
- **CHRONIC GASTROPATHY AND GASTRITIS**
  - Chemical gastropathy (NSAIDs, bile, etc.)
  - *H. pylori* gastritis
  - Metaplastic Atrophic Gastritis (MAG)
    - Autoimmune (AMAG)
    - Environmental (EMAG)
  - Chronic gastritis of indeterminate type
- **UNCOMMON FORMS OF GASTRITIS**
  - (e.g. eosinophilic gastritis, Crohn's disease, lymphocytic gastritis)

Acute Gastropathy and Gastritis: Classification

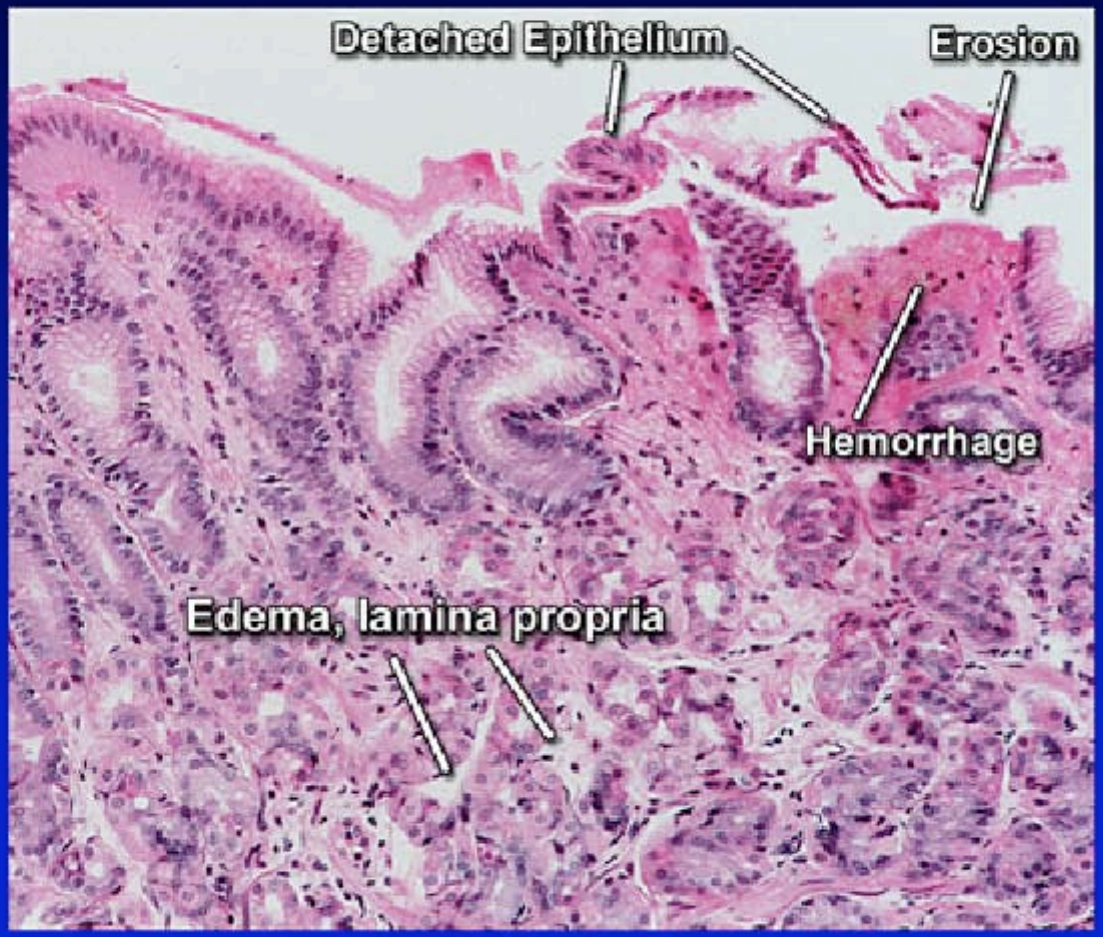
- HEMORRHAGIC / EROSIVE GASTROPATHY
  - In altered mucosal blood flow
  - Ischemia (stress, hypovolemic or cardiogenic shock, sepsis)
  - Vascular congestion (portal gastropathy)
  - In acute exposure to drugs, chemicals (e.g., NSAIDs, alcohol)

- INFECTIOUS GASTRITIS
  - Bacterial (*H. pylori*, *T. pallidum*, phlegmonous, e.g. Streptococcus)
  - Viral (CMV, Herpes)
  - Fungal (*H. capsulatum*)

Hemorrhagic and Erosive Gastropathy – Endoscopy and Histology



Endoscopy

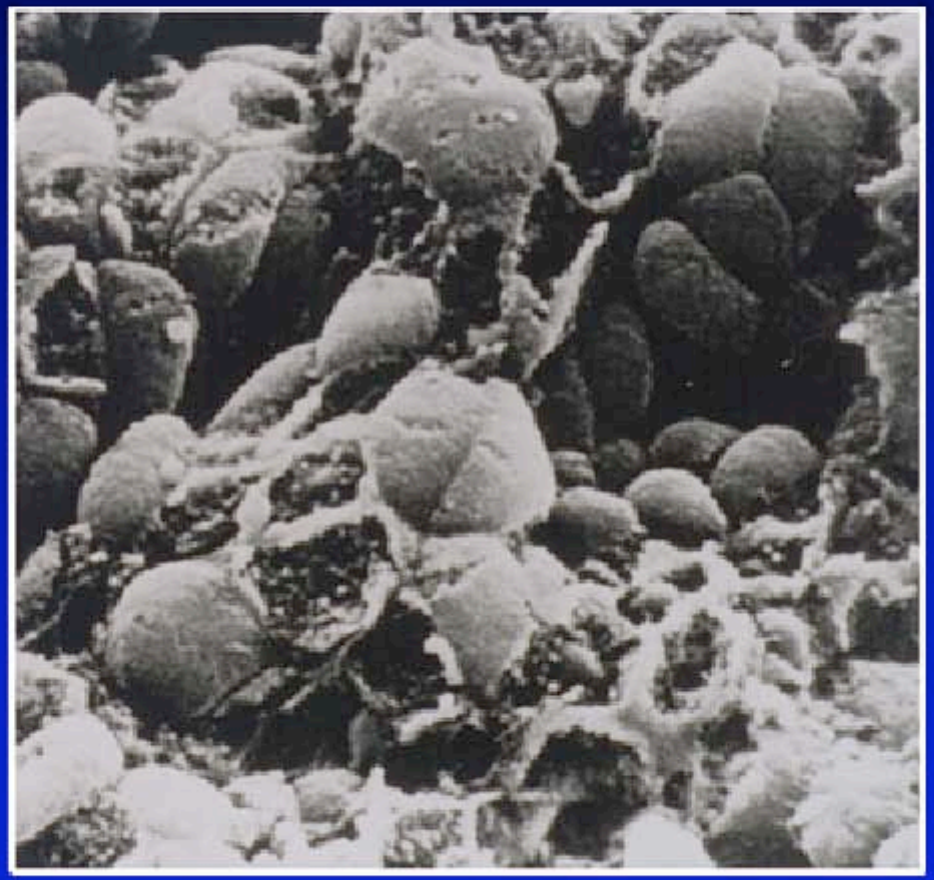


H&E Histology

Aspirin Causes Loss of Surface Mucous Cells in Human Stomach

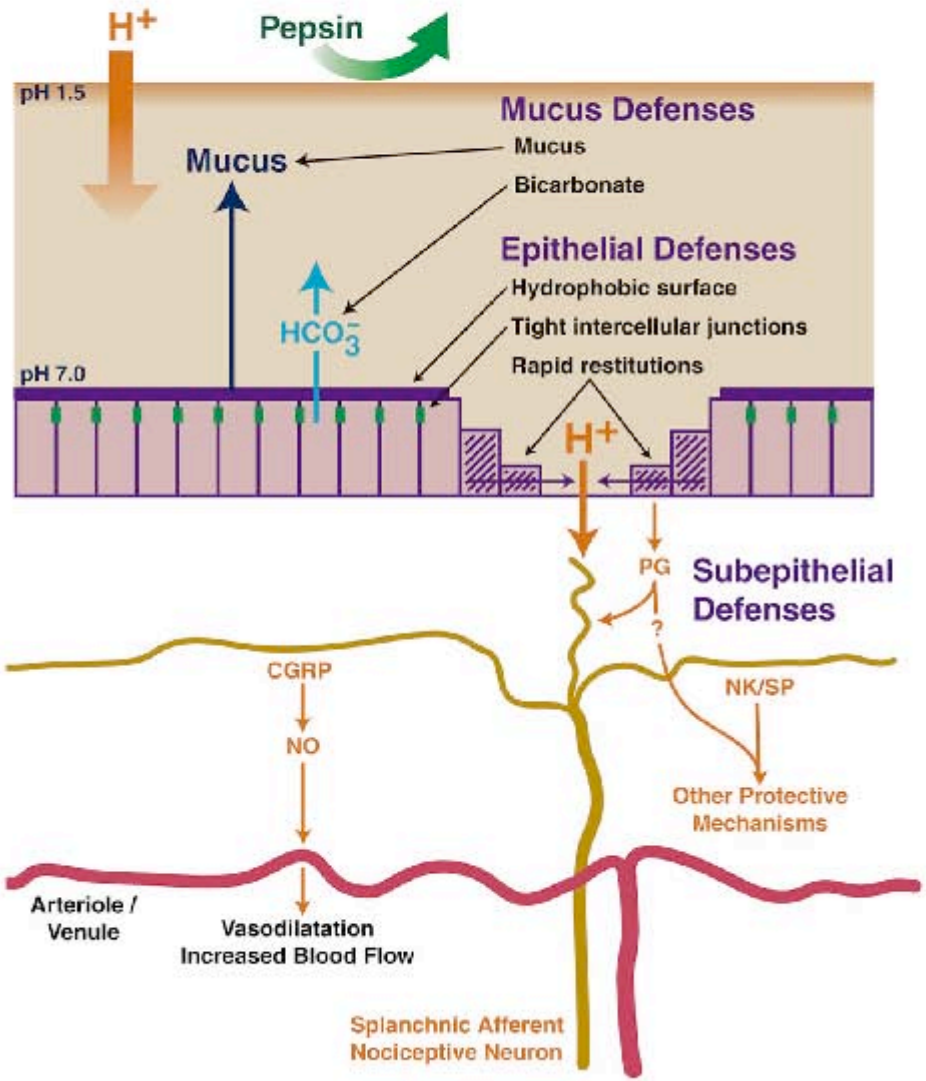
Scanning Electron Micrographs

Normal

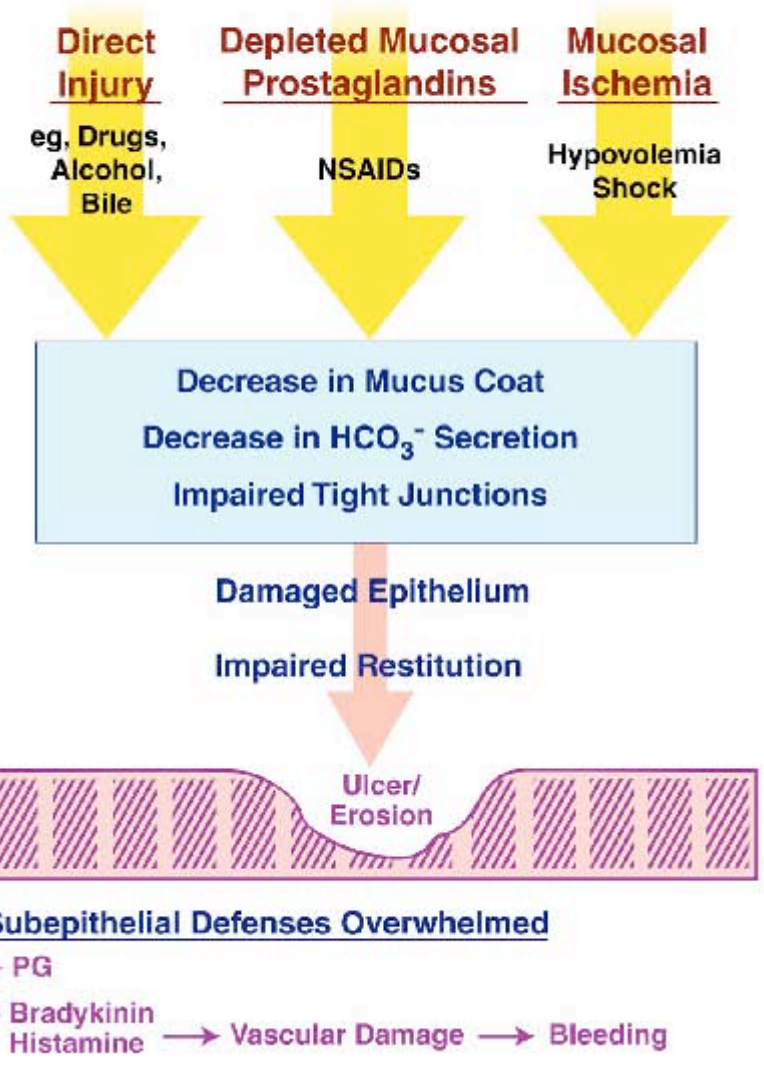


After Aspirin

The Gastric Mucosa is Protected by a Multi-layered Defense



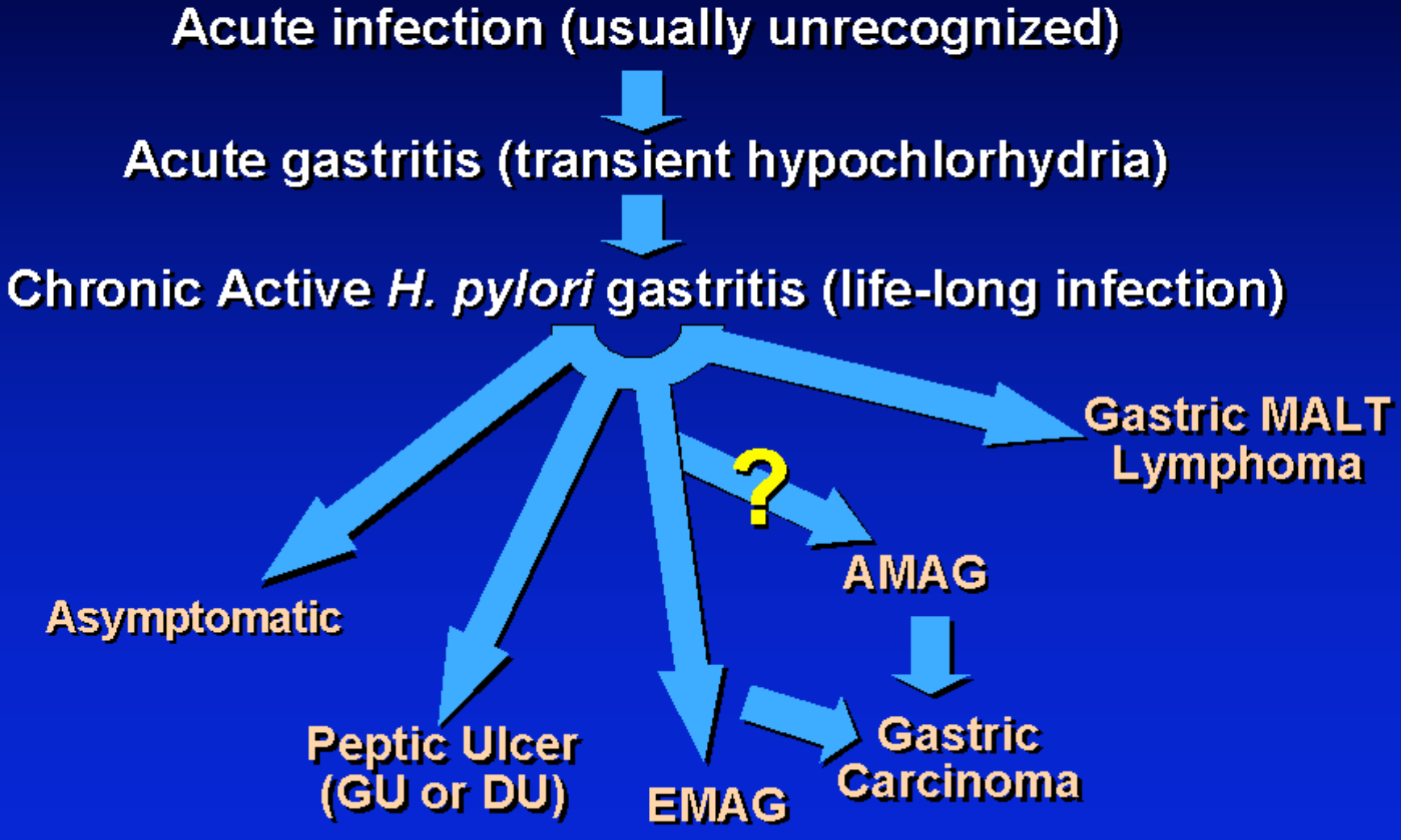
Pathogenesis of Acute Hemorrhagic and Erosive Gastropathy



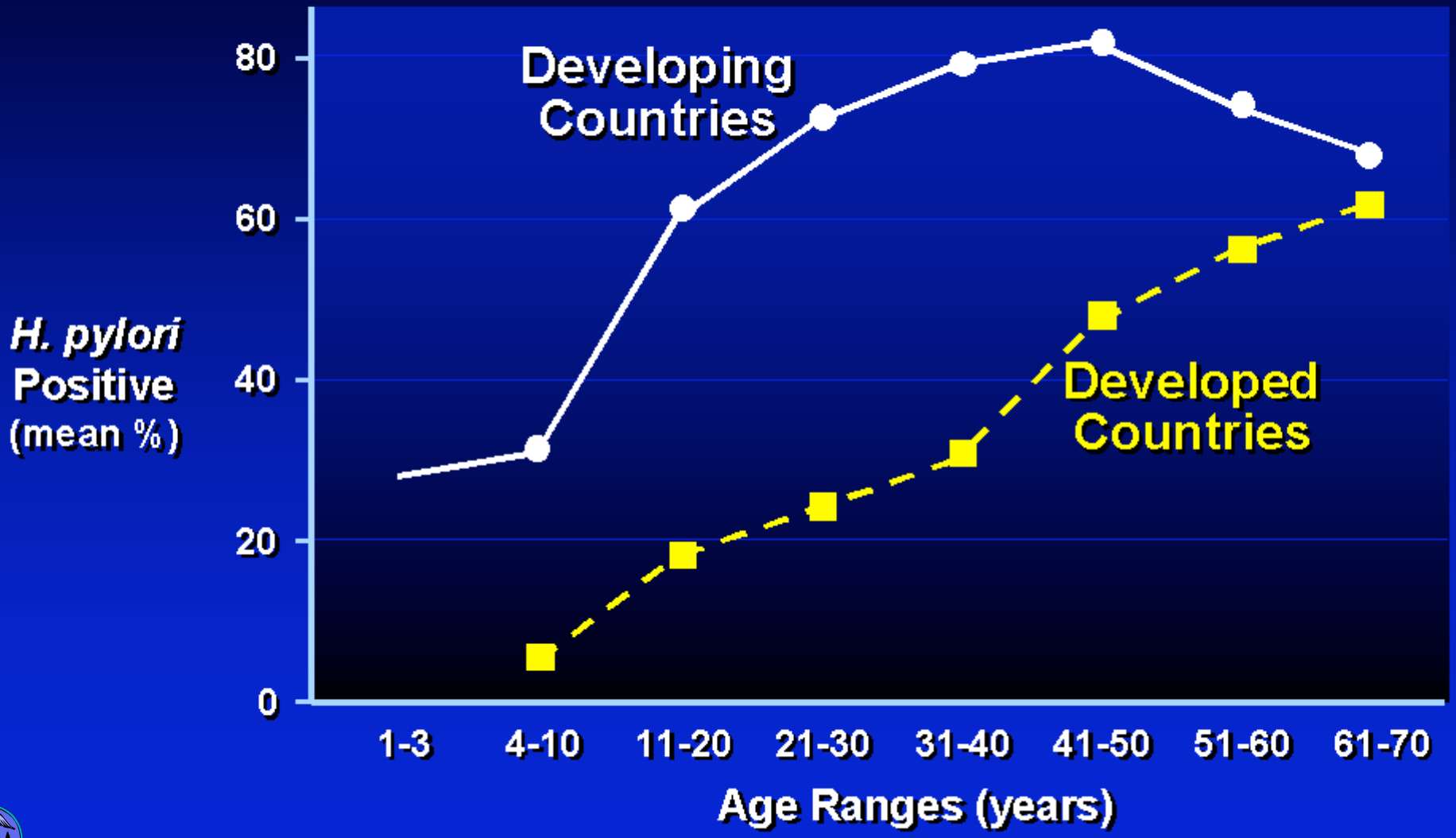
Chronic *H. pylori* Gastritis (Long-term Infection)
Major Features

- Common in adults (USA, other developed countries)
- No characteristic symptoms, & endoscopy findings
- No correlation with "Nonulcer dyspepsia"
- ORGANISMS: *Curved*, Gram neg. rods in mucus & over surface & foveolar epithelium.
- Pathology: Chronic ACTIVE inflammation, usually with lymphoid aggregates and germinal centers (=MALT).

Clinical Outcomes & Sequelae of *Helicobacter pylori* Infection

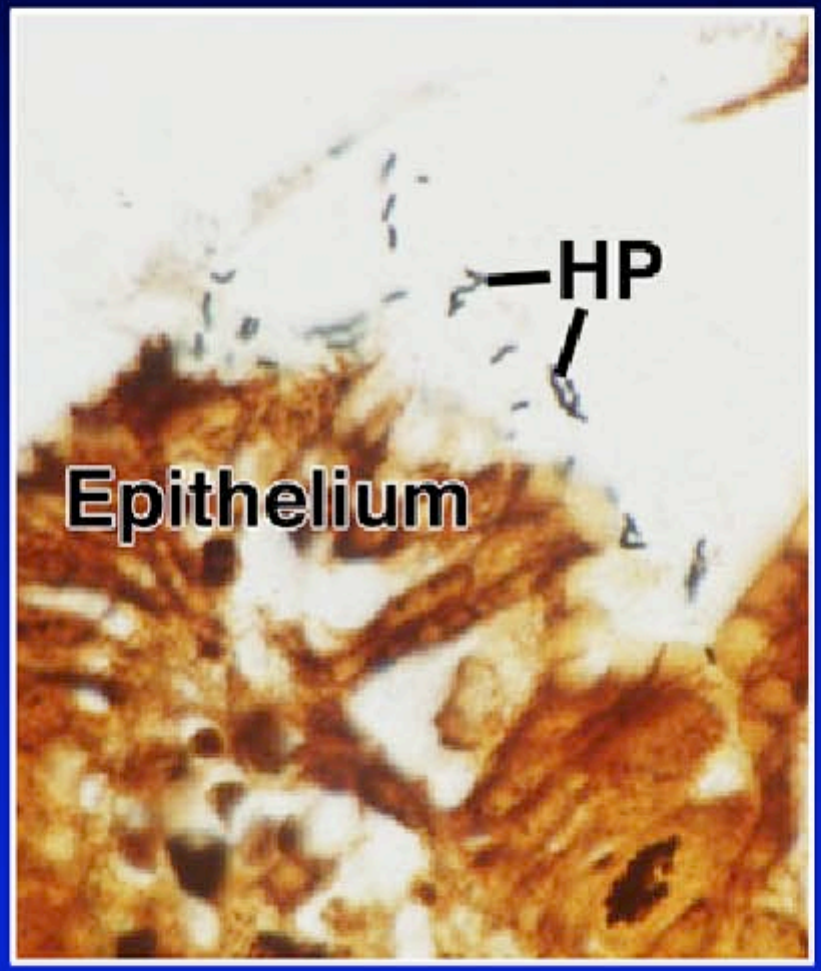


Prevalence of *Helicobacter pylori* Infection In Developing vs Developed Countries

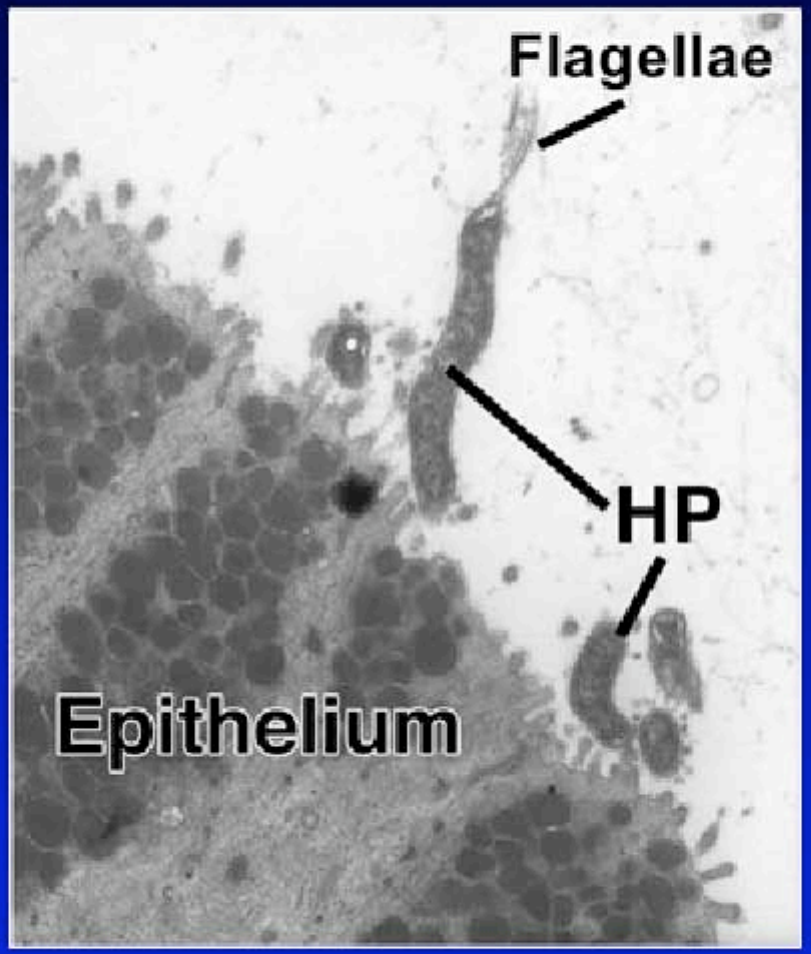


Aliment Pharmacol Ther 1995;9(Supp 2):33

Helicobacter pylori: Curved Organisms (HP) with Flagellae Over Gastric Epithelium

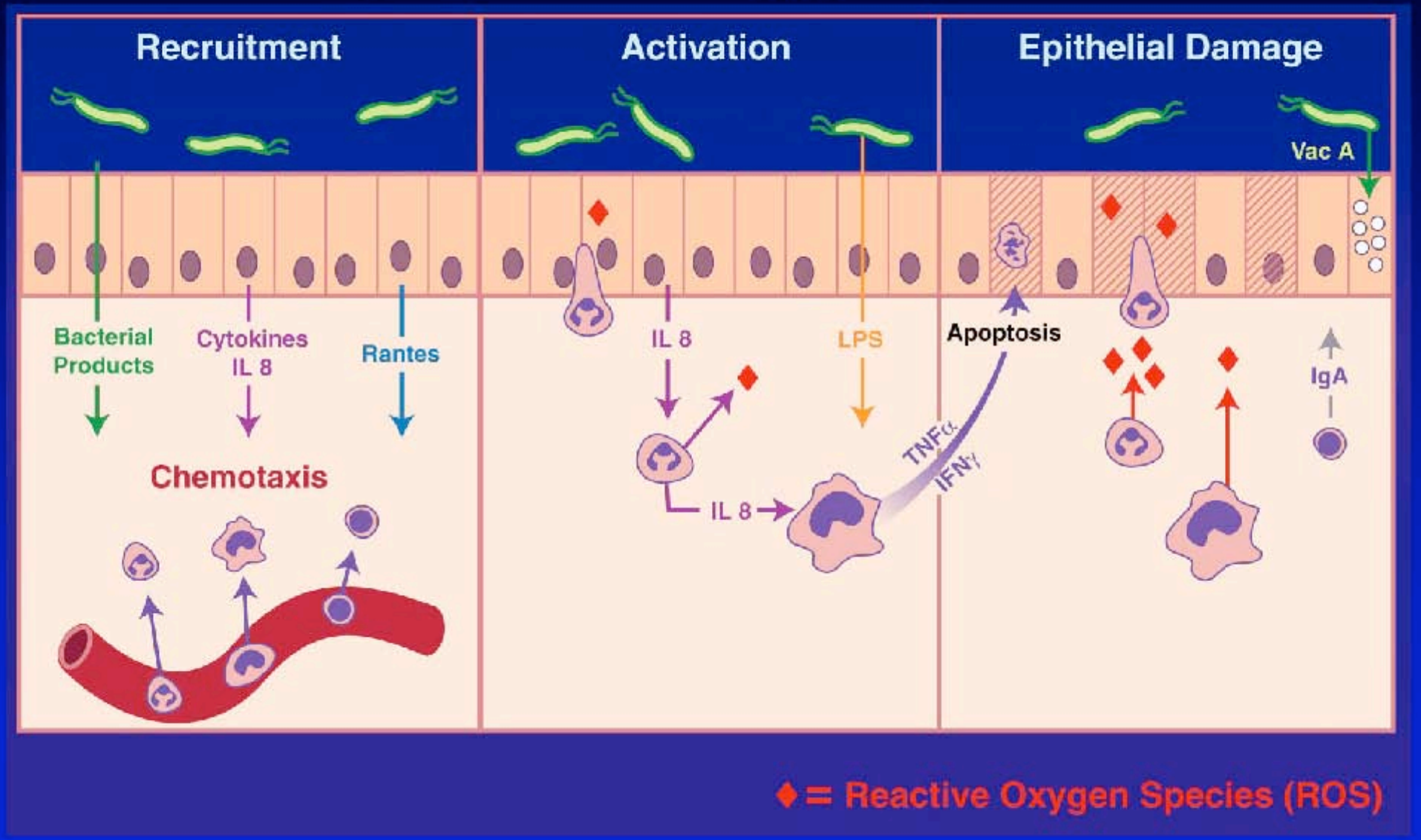


Light Microscopy



Electron Microscopy

Pathogenesis of *H. pylori* Gastritis



Chronic Chemical Gastropathy
Principal Features

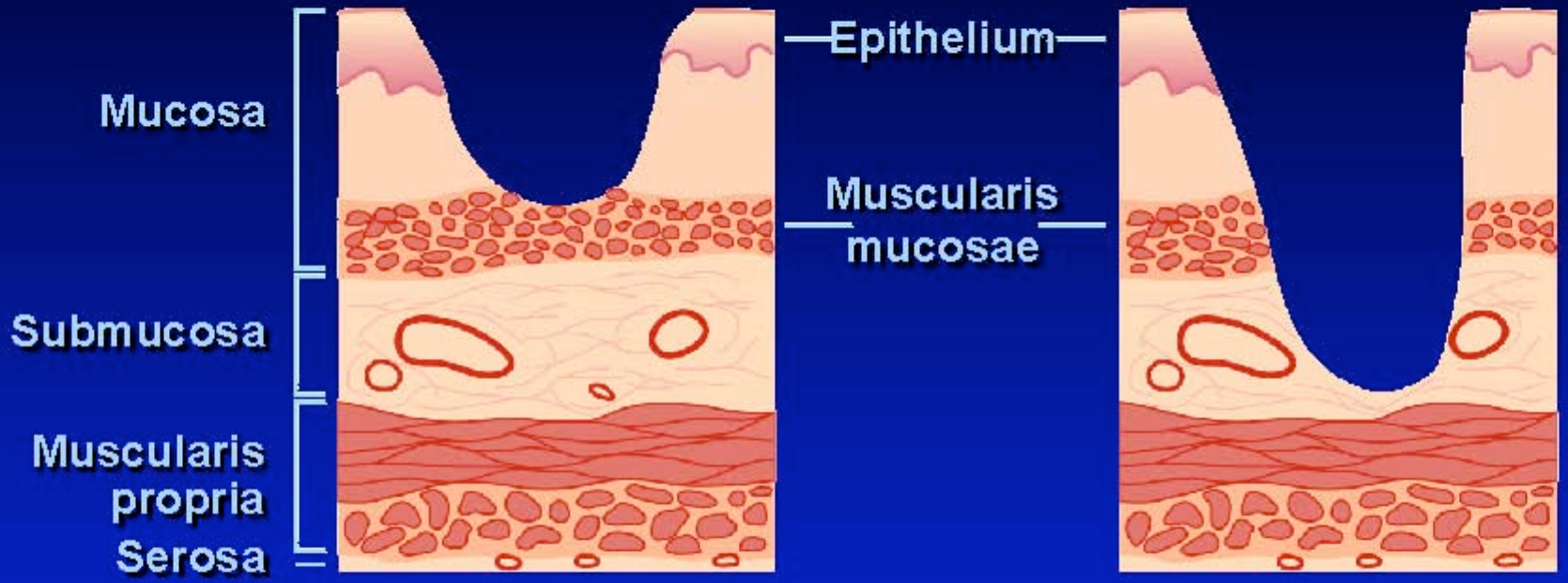
- **SYNONYMS:** Reflux gastritis; Reactive gastritis; NSAIDs gastropathy

- **CLINICAL FINDINGS & ASSOCIATIONS**
  - Presents with no symptoms or nonspecific chronic upper GI symptoms
  - Chronic NSAIDs exposure common
  - Bile reflux - Mainly with gastroenterostomy
  - Other chemical agents? - Unidentified / unconfirmed.

- **ENDOSCOPIC (GROSS) FINDINGS**
  - None characteristic or diagnostic
  - The diagnosis depends on endoscopic biopsy.

- **HISTOPATHOLOGY**
  - Paucity of inflammatory cells (Hence "gastropathy")
  - Foveolar hyperplasia
  - Smooth muscle cells increased in lamina propria
  - Vascular dilatation and congestion.

Erosion vs Ulcer - Definitions



Erosion

- Shallow break in mucosa
- Can reach muscularis mucosa, but does not penetrate it

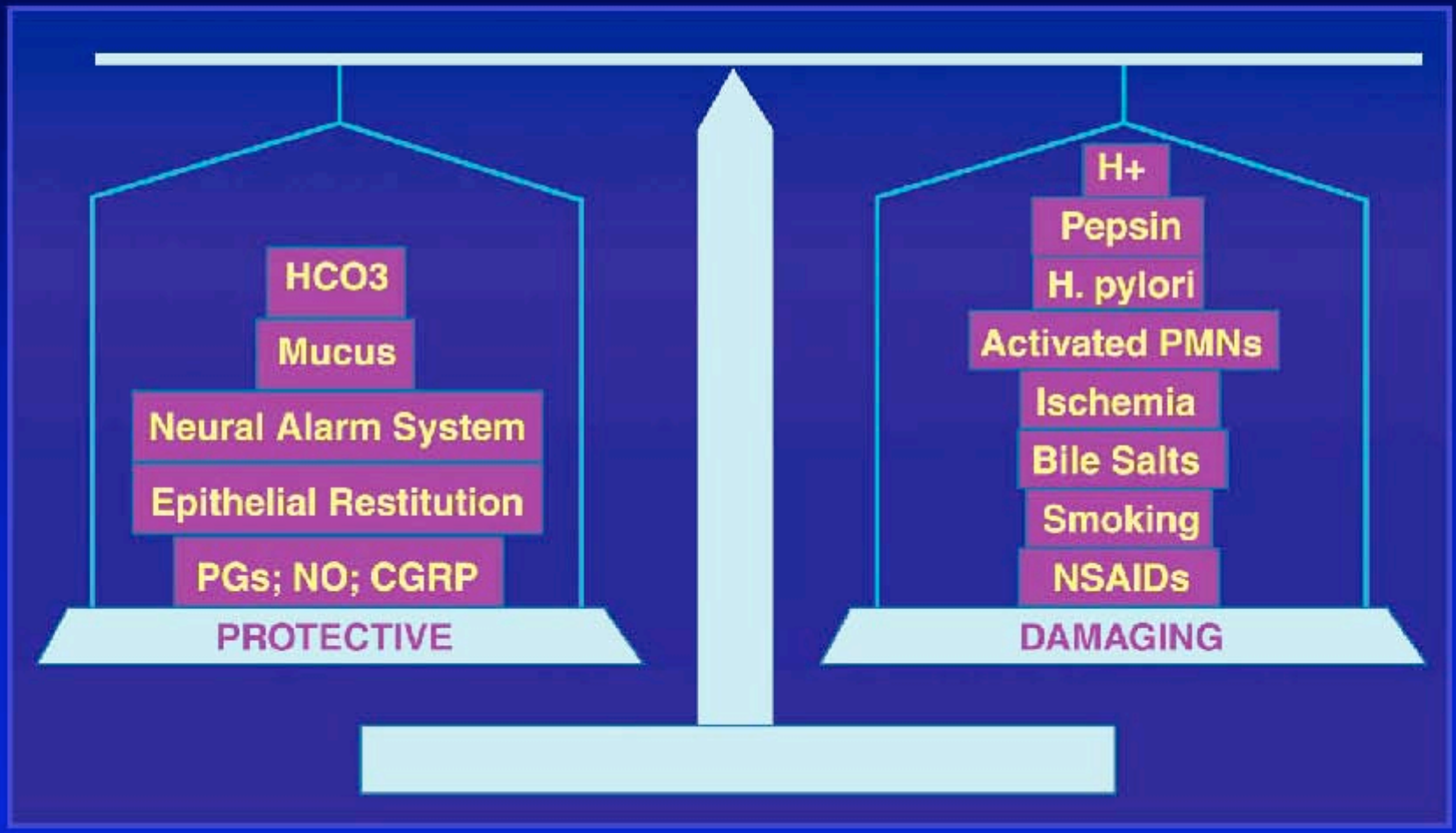
Ulcer

- Full-thickness break in mucosa
- Penetrates muscularis mucosa
- May go even deeper

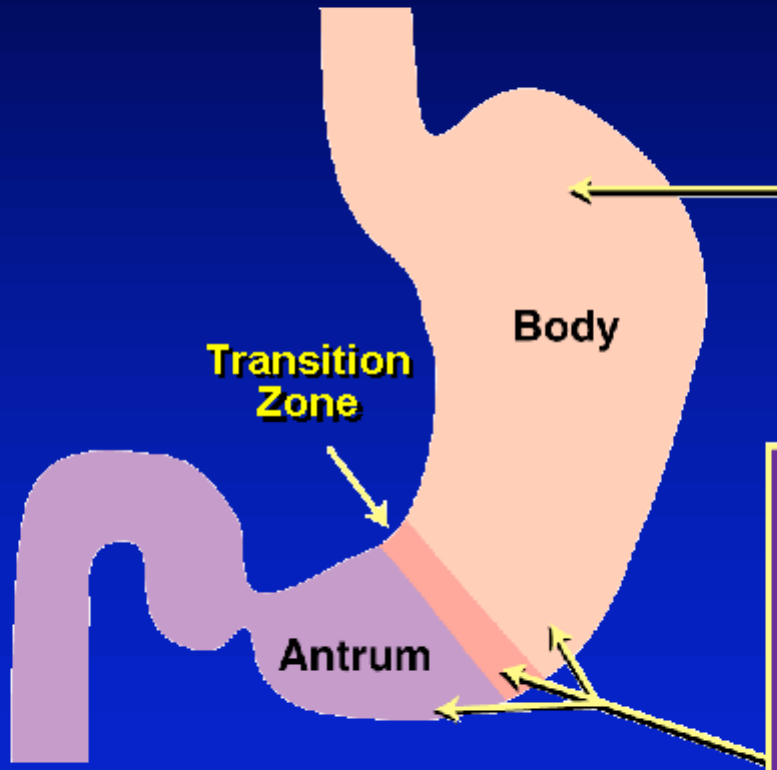
Upper GI Tract Ulcers Have Many Causes

CAUSES	ESOPHAGUS	STOMACH	DUODENUM
Acid-peptic	+	+	+
Infections			
Viral	+		
Fungal	+		
Chemical, Drugs	+	+	+
Crohn's Disease	±	±	+
Carcinoma	+	+	+ (usually pancr.)
Lymphoma	+	+	+
Idiopathic (no *H. pylori*)	±	±	±

Gastro-duodenal Mucosal Integrity is Determined by a Favorable Balance Between Protective and Damaging Factors



Multiple Factors Involved in Pathogenesis of Gastric Ulcer



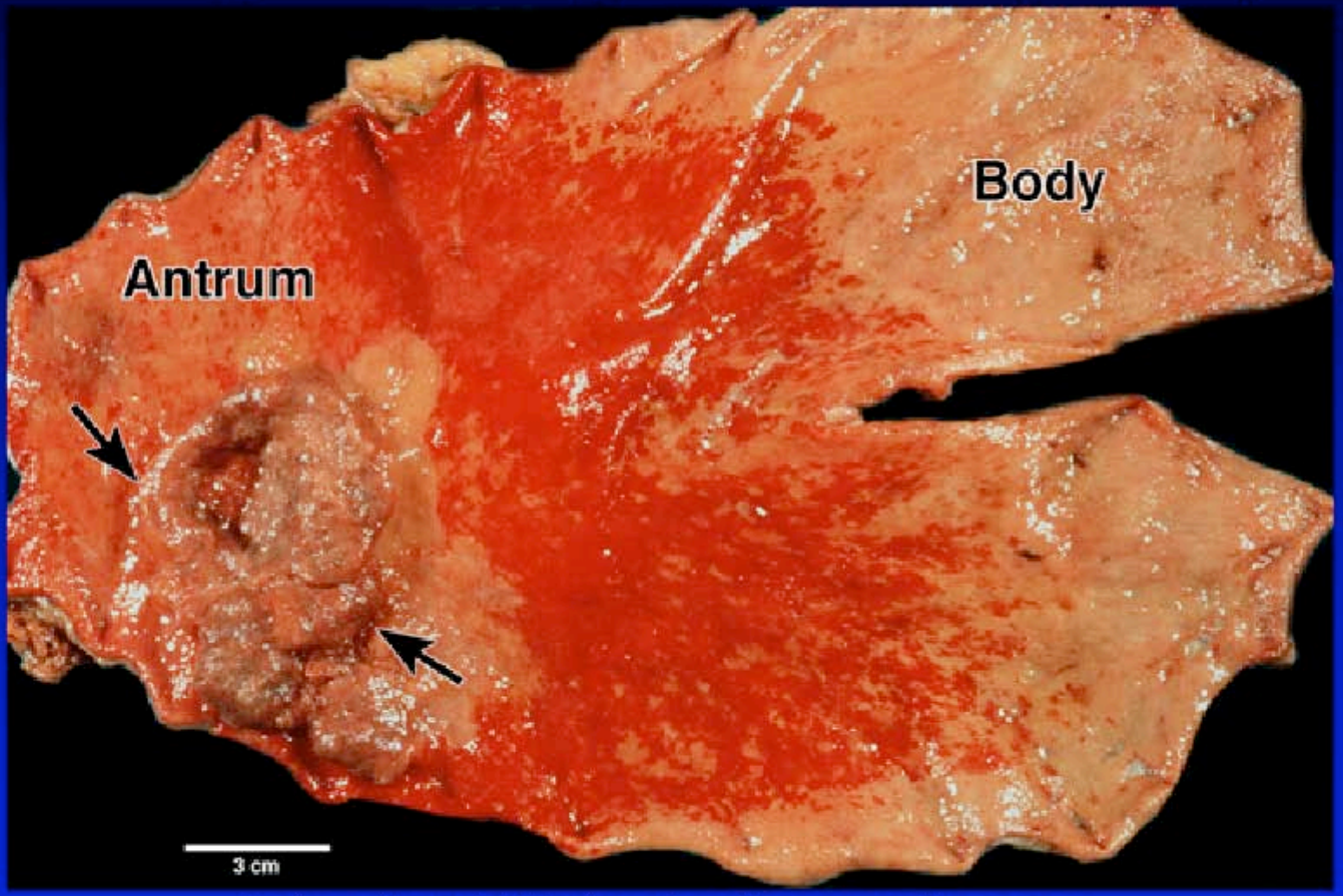
Acid Secretion

Normal or
Decreased

Compromise of Mucosal Defense

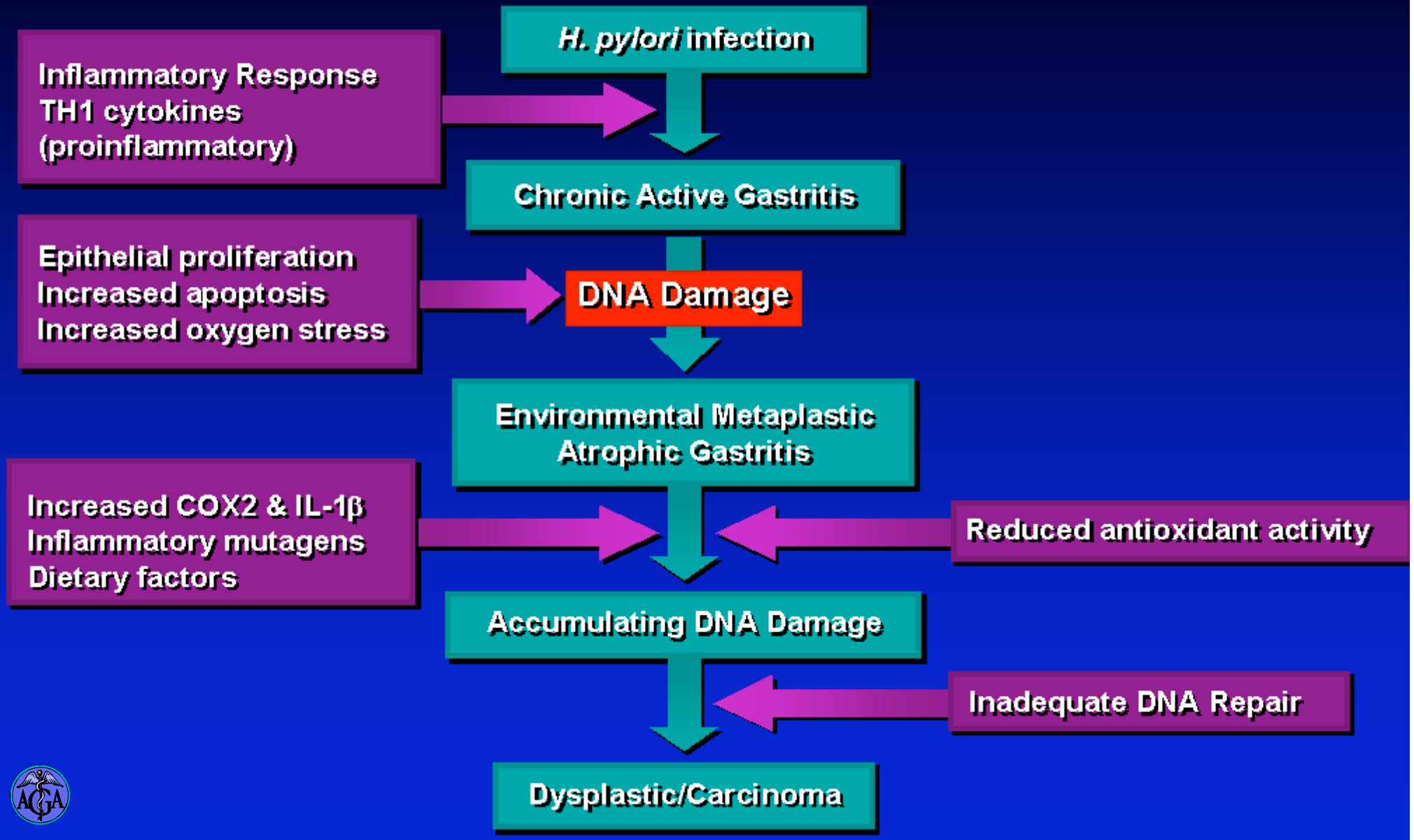
H. pylori Gastritis
Intestinal Metaplasia
Mucosal Ischemia
Chemical Damage
- NSAIDs
- Bile Reflux
- Smoking and Alcohol

Adenocarcinoma (arrows) Arising in Environmental Metaplastic Atrophic Gastritis (EMAG)

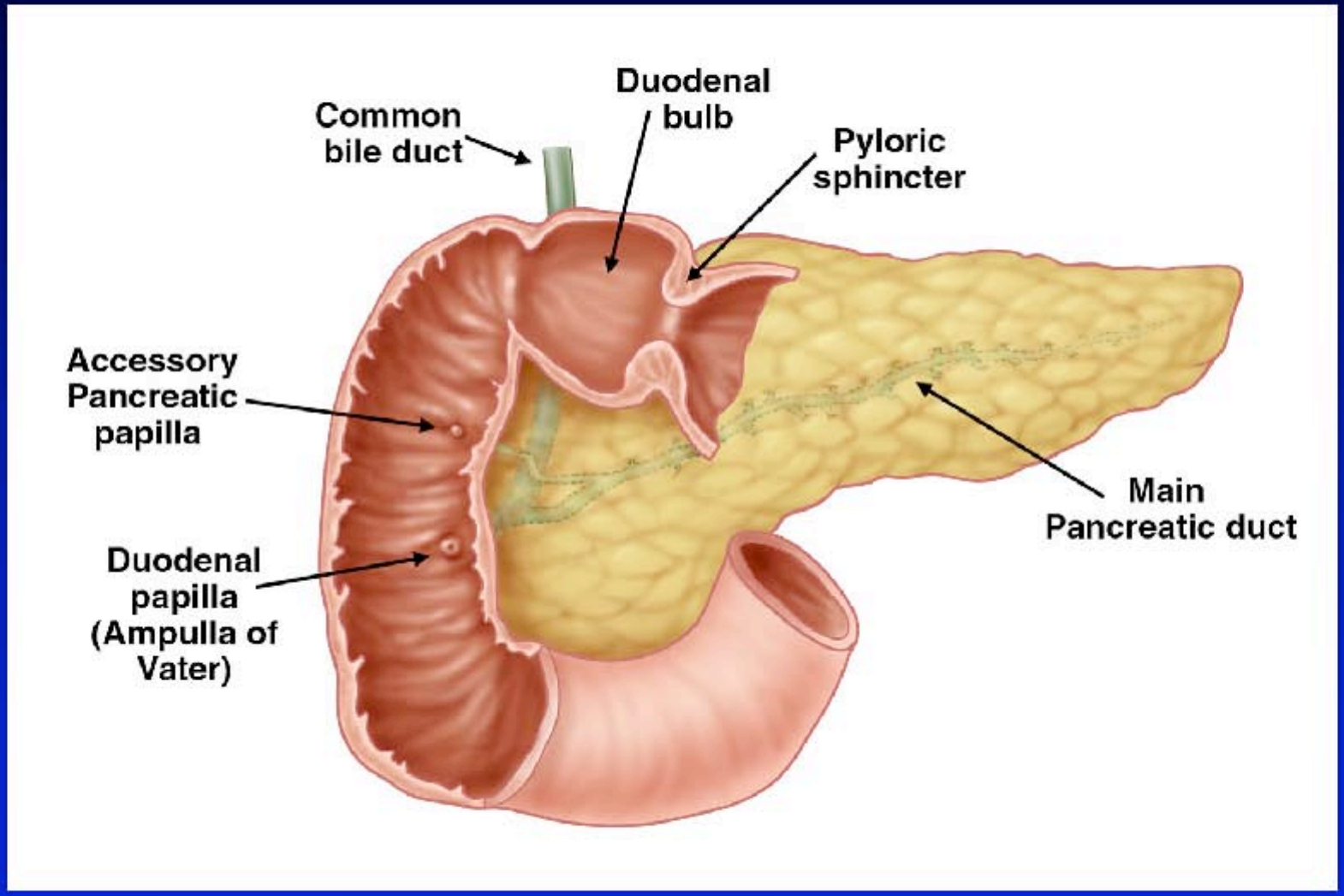


Intestinal Metaplasia = red areas

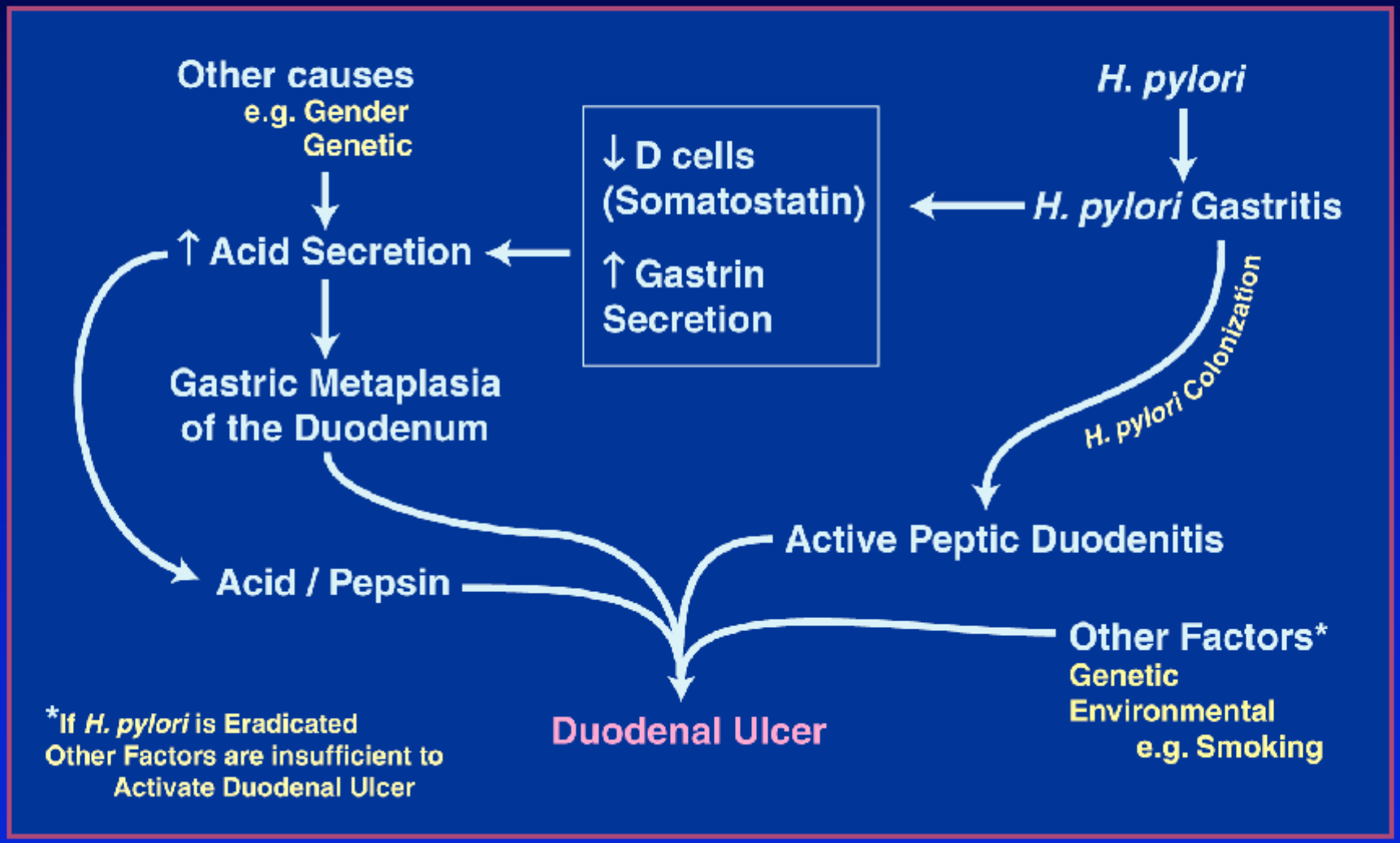
H. pylori and Gastric Cancer



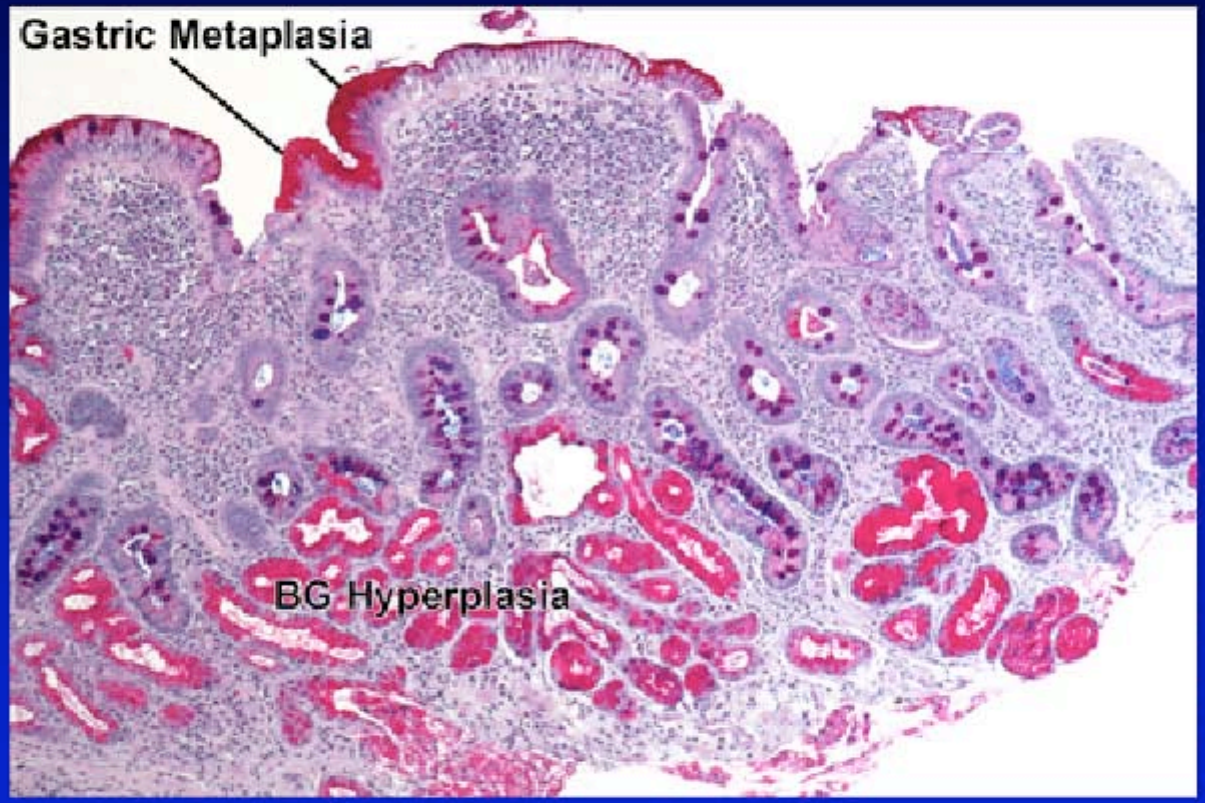
Duodenum – Normal Anatomic Relationships

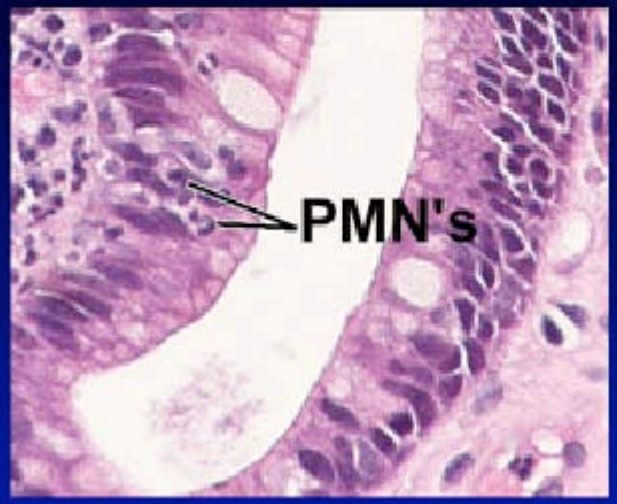


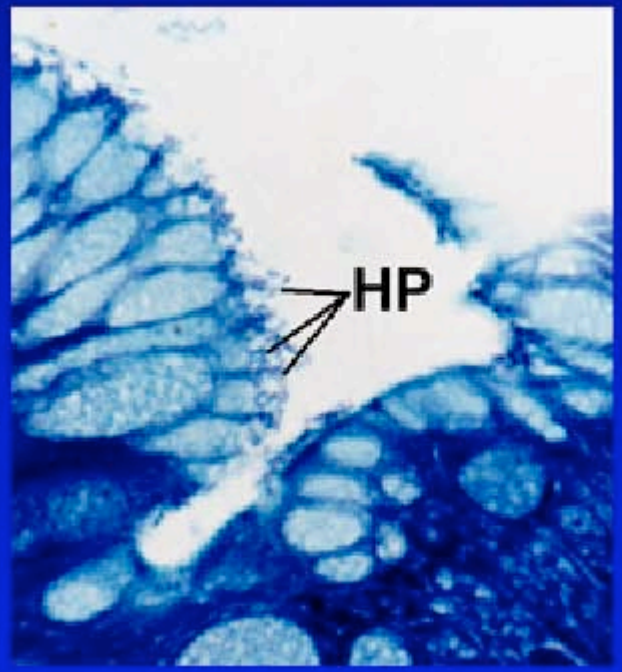
The Role of *H. pylori* in the Pathogenesis of Duodenal Ulcer



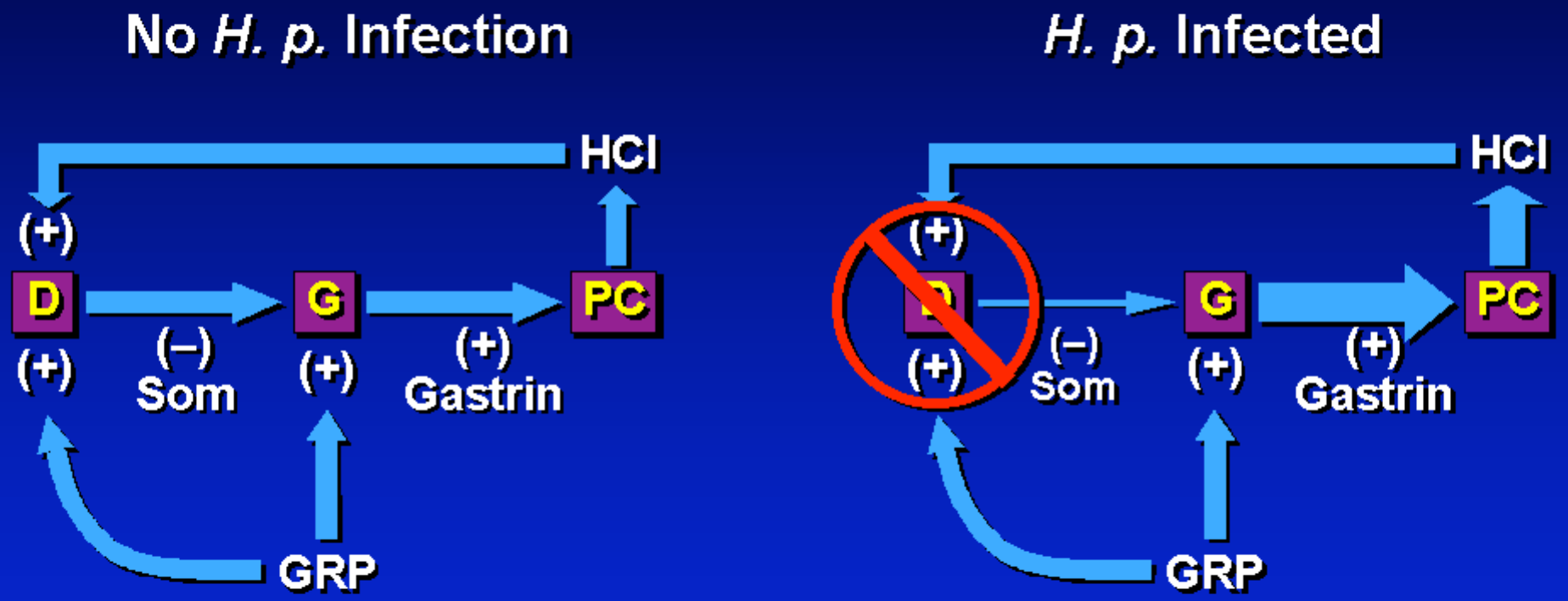
Active Peptic Duodenitis – Defining Histologic Features





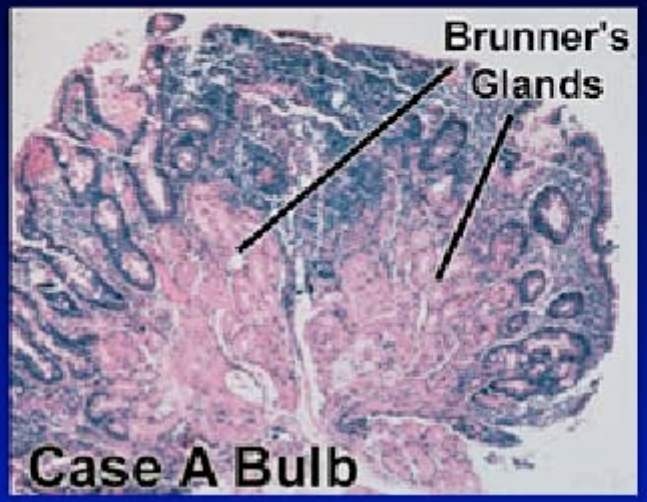


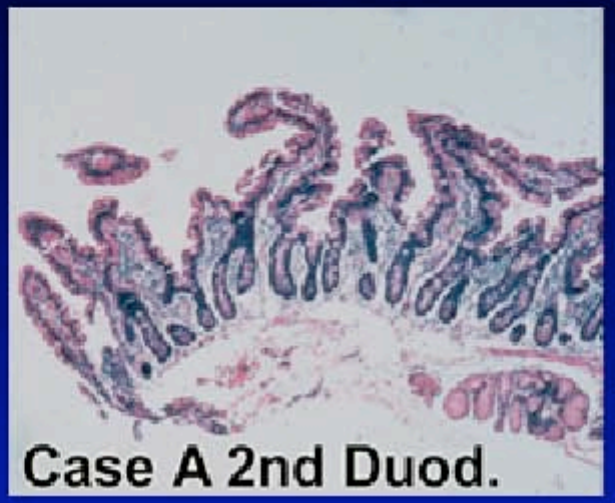
H. pylori Alters Control of Gastric Secretion by Decreasing Somatostatin Release

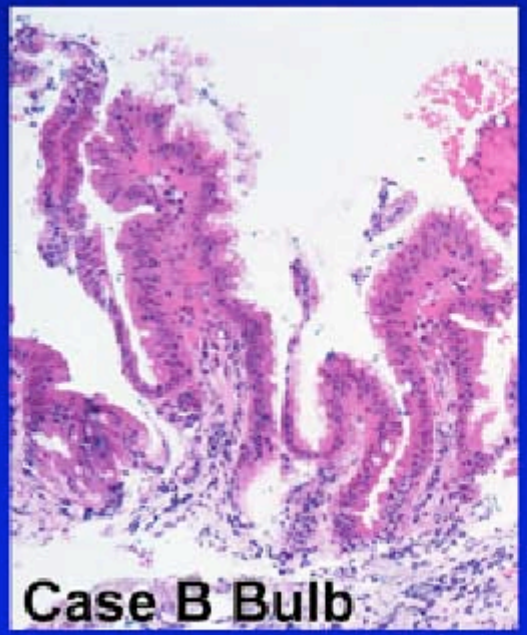


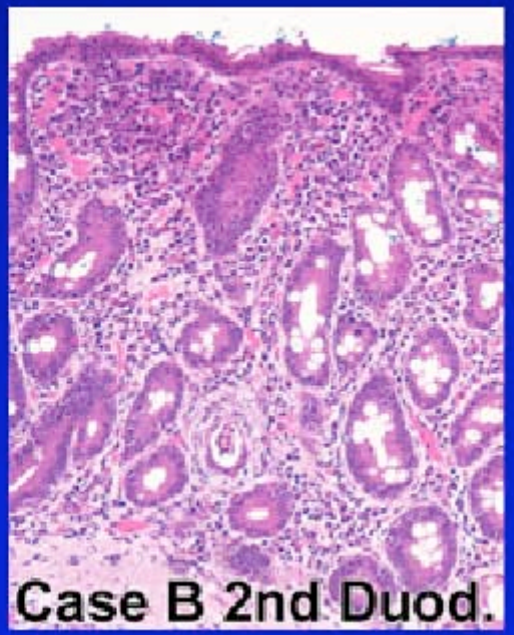
D – Somatostatin cell
G – Gastrin cell
PC – Parietal cell
GRP – Gastrin Releasing Peptide

Celiac Disease Can Be Misdiagnosed When Only The Duodenal Bulb is Biopsied









Prof. Dr. Dr. J. Stein
Medizinische Klinik I
Gastroenterologie/Hepatologie/ Ernährungsmedizin

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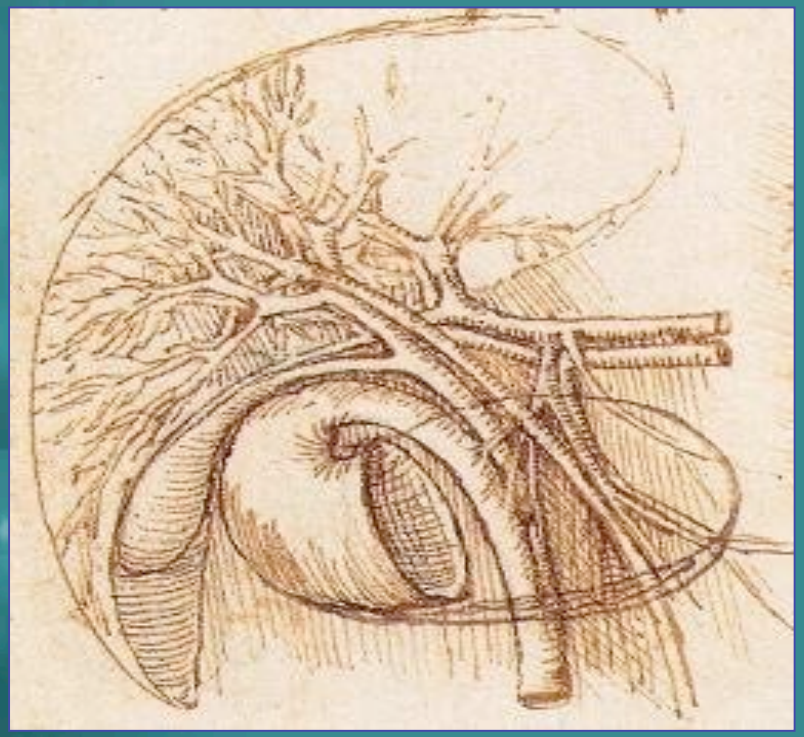
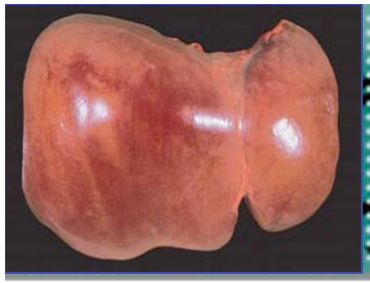
„…because the liver is a source of many diseases, And is a noble organ that serves many organs., Almost all of them: so it suffers, it is not a small suffering, but a grat and manifold one“

Theophratus Bombastus von Hohenheim, known as PARACELCUS (1493 – 1541)



Hepatology



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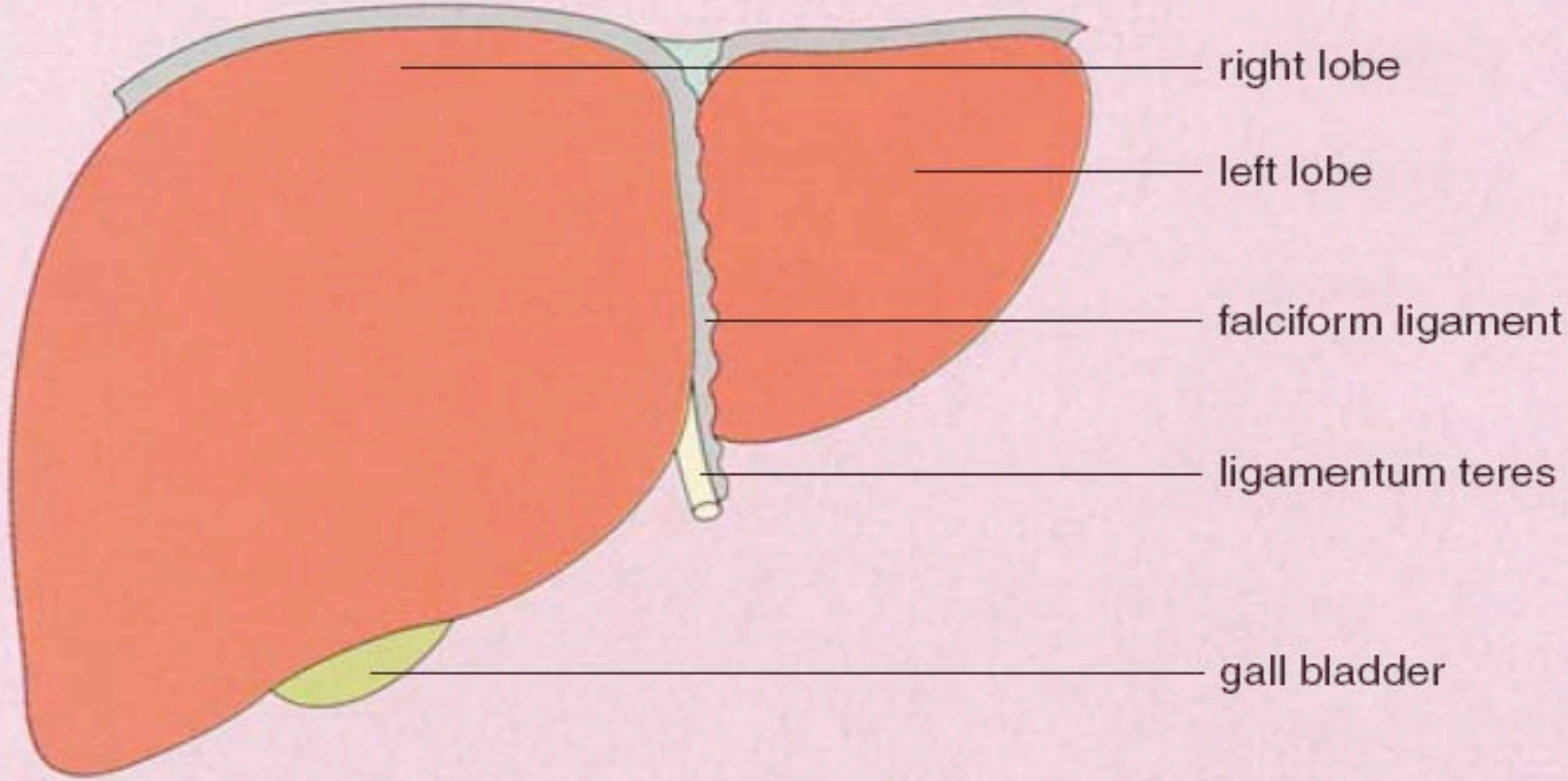
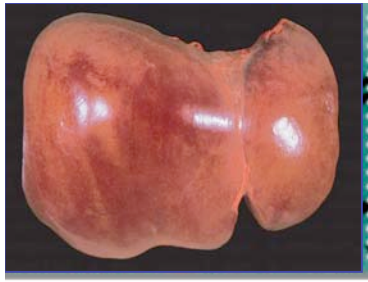
ZAFES





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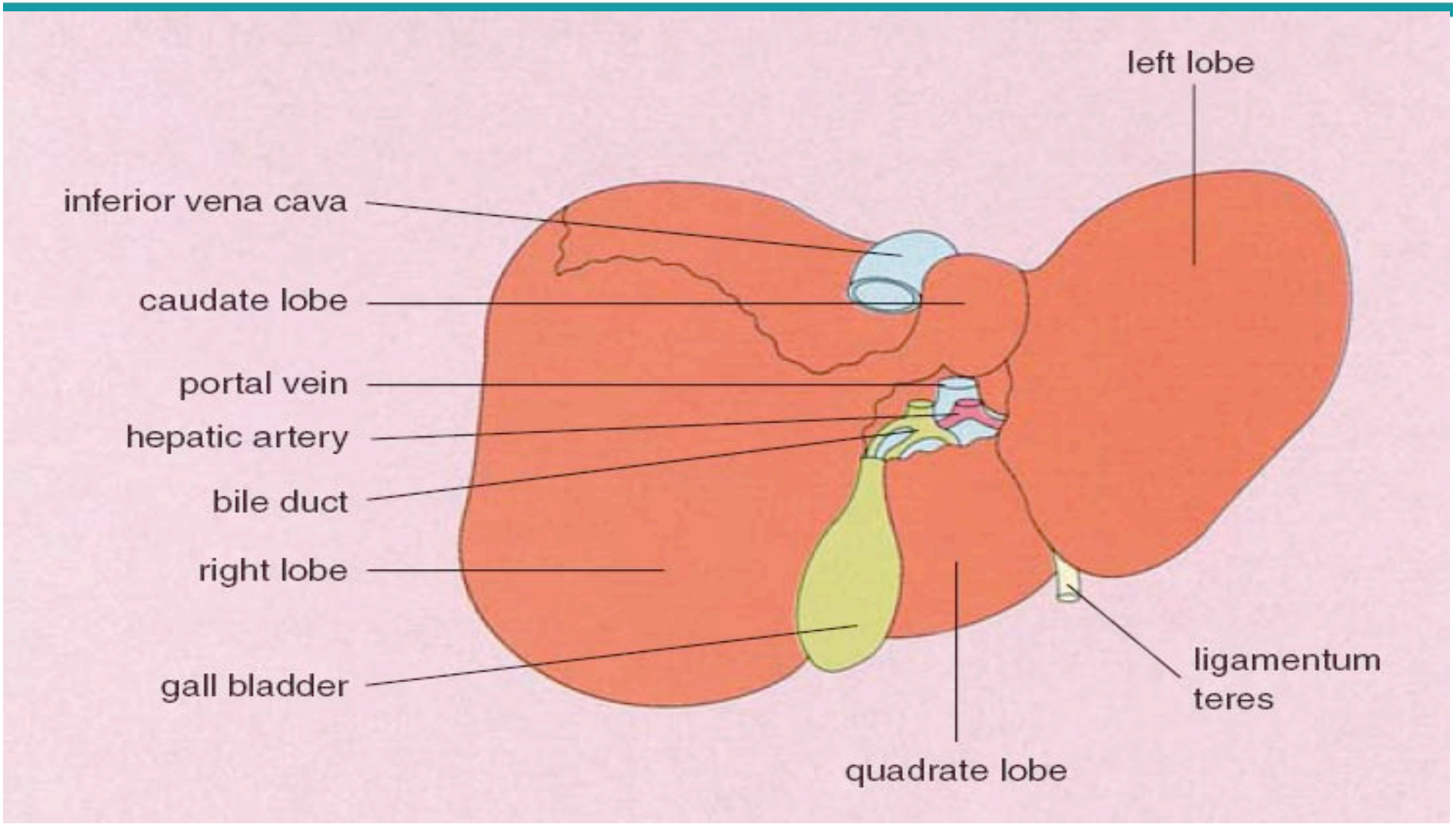

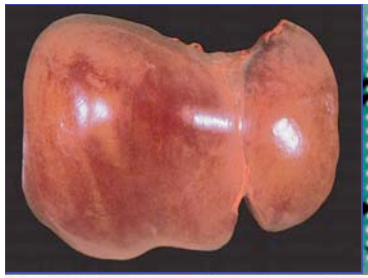

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ZAFES

portal vein

hepatic ducts

cystic artery

gall bladder

common bile duct

superior mesenteric vein

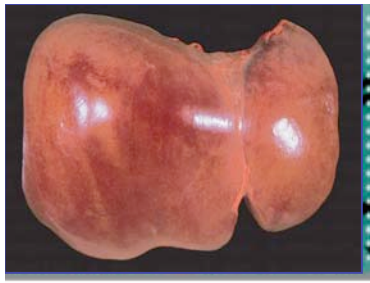
hepatic artery

celiac axis

aorta

splenic vein

gastroduodenal artery



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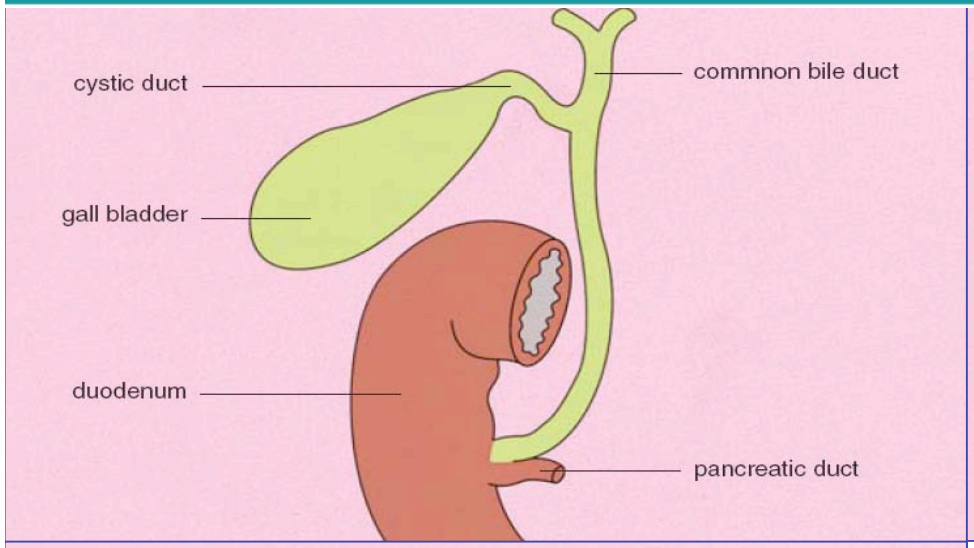

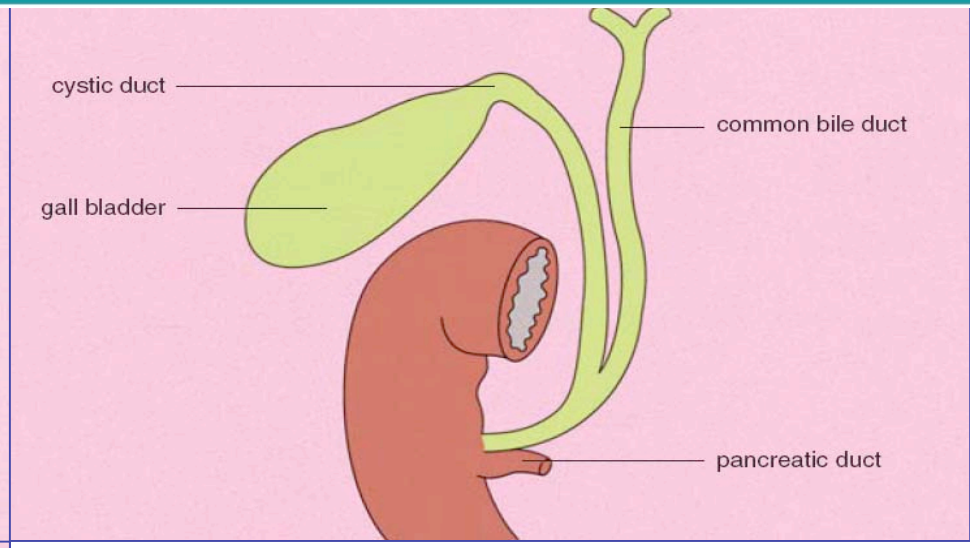

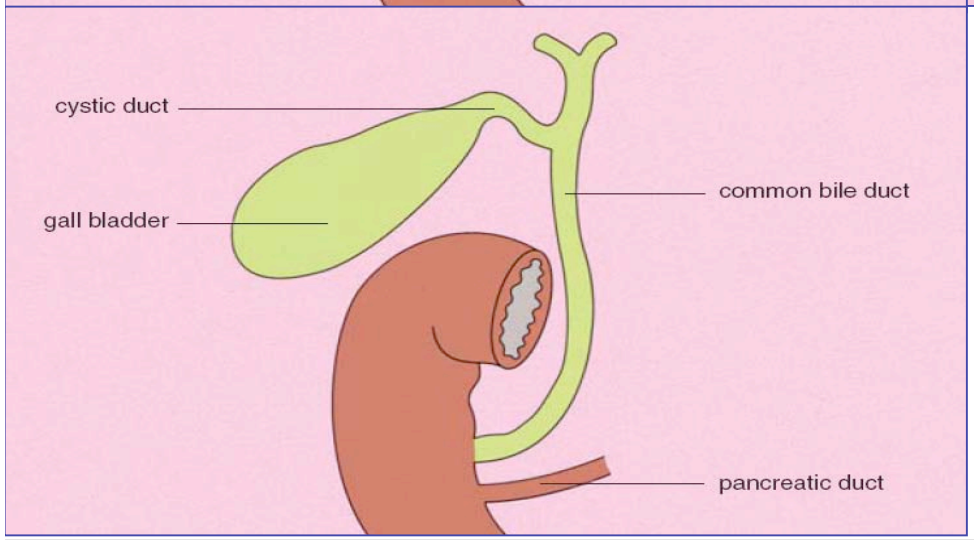

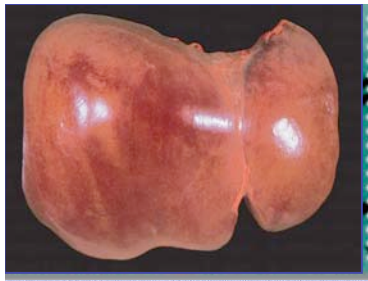

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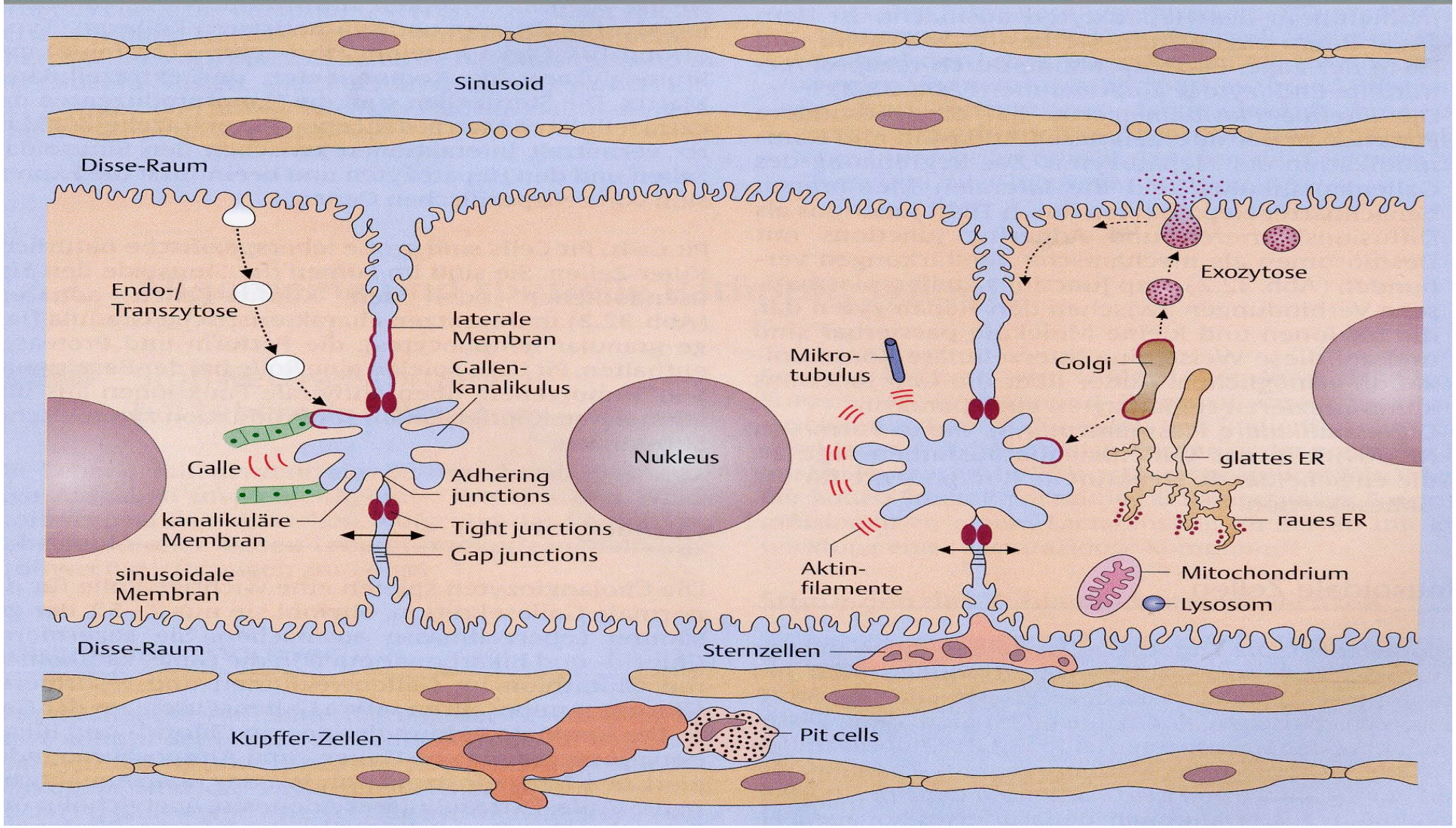
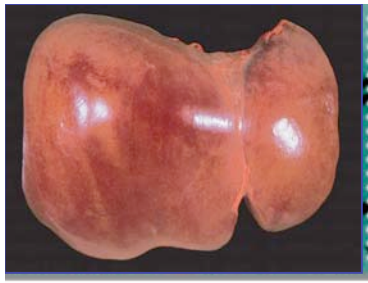


Morphology of the Liver Biochemistry and Functions of the Liver Diseases of the Liver



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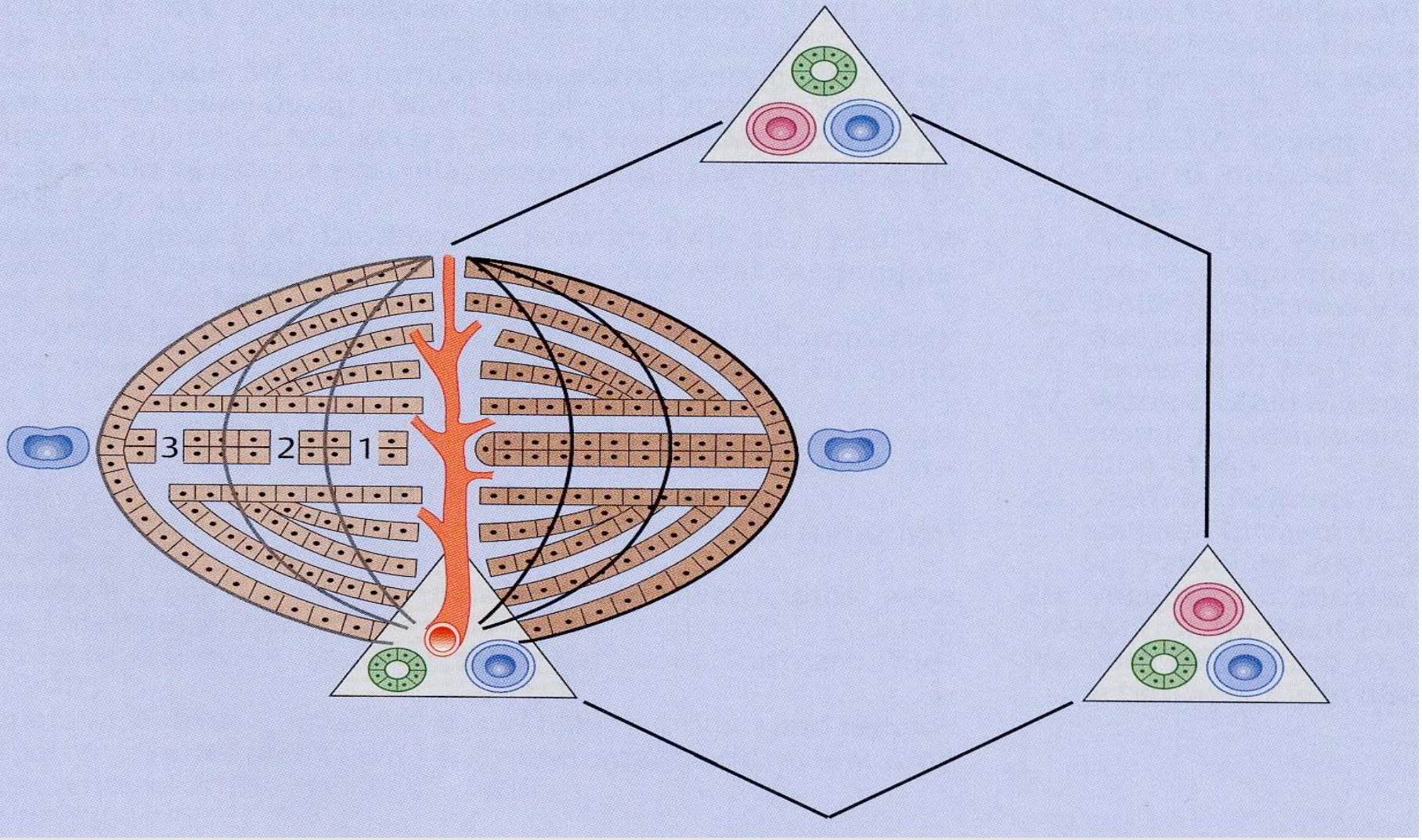
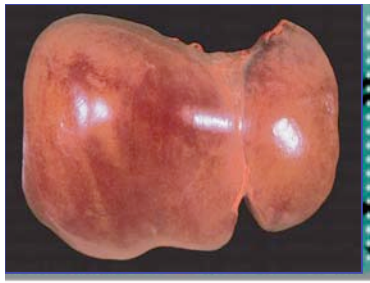


Morphology of the Liver Biochemistry and Functions of the Liver Diseases of the Liver



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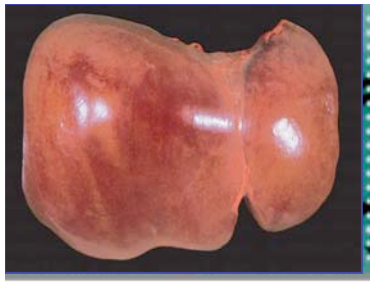
Biochemistry and functions of the liver

1. Bilirubin metabolism
2. Porphyrin metabolism
3. Bile acid metabolism
4. Amino acid and protein metabolism
5. Carbohydrate metabolism
6. Lipid and lipoprotein metabolism
7. Hormone metabolism
8. Vitamin metabolism
9. Trace elements and liverm
10. Biotransformation and detoxification
11. Alcohol metabolism
13. Acid-base balance

=> About 500 separate biochemical processes occur within one single hepatocyte



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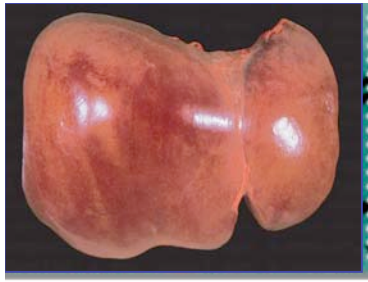
Diseases of the liver

1. Cholestatic liver disease
2. Infectious (viral, bacterial, parasitic) liver disease
3. Cholestatic liver disease
4. Drug/alcohol (ASH/NASH) liver damage
5. Metabolic disorders and storage diseases
6. Autimmune hepatitis
7. Liver cirrhosis
8. Benign and malignant liver tumours
9. Bile duct diseases (i.e. Gall stones)



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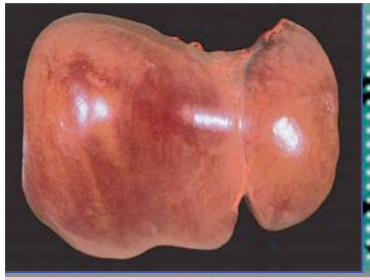
Cholestatic liver diseases



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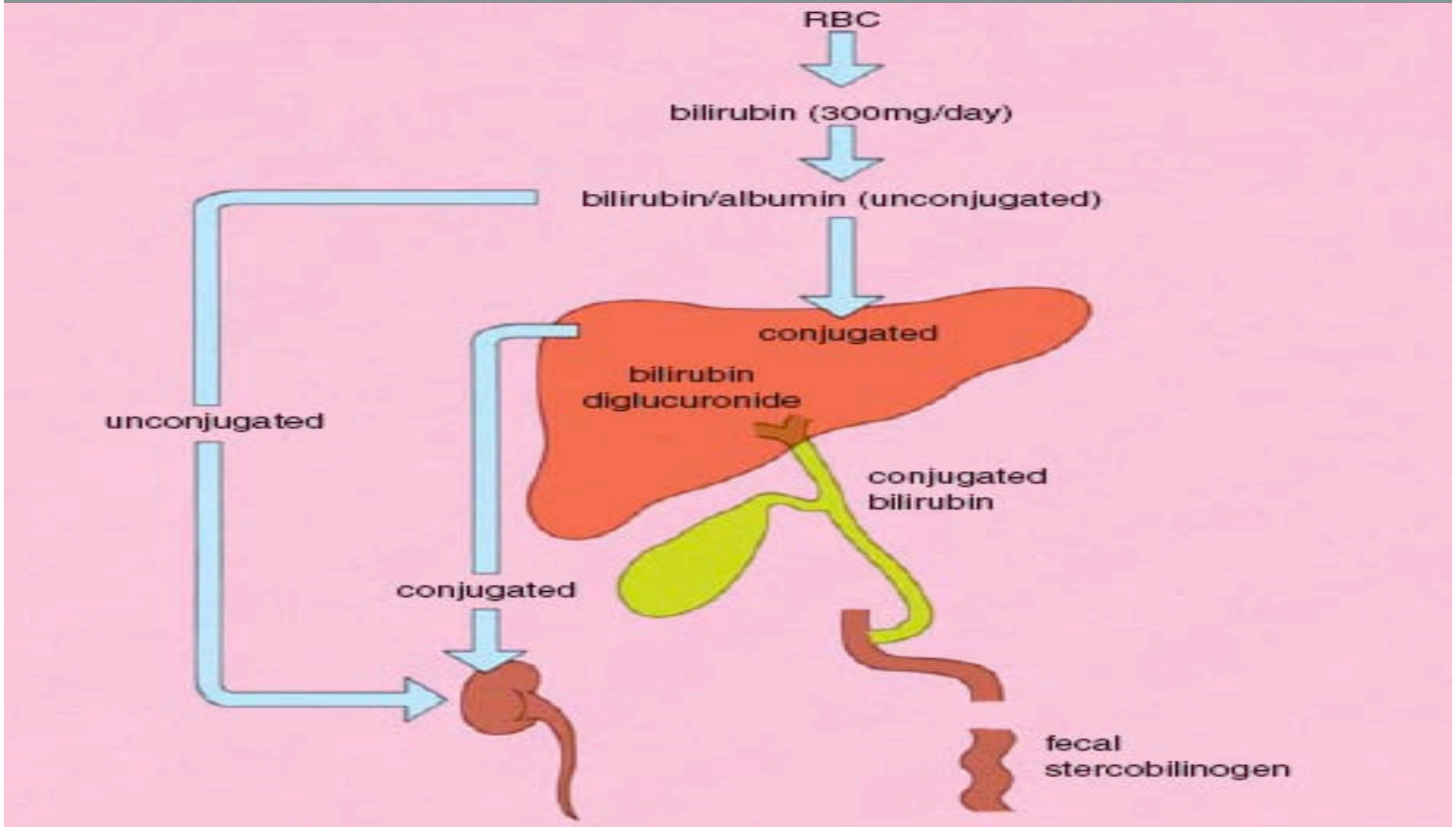
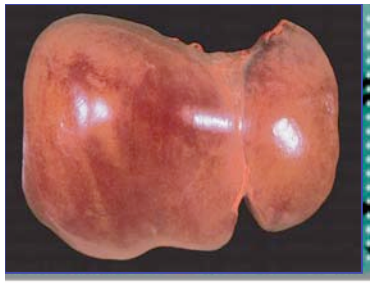
Bilirubin metabolism





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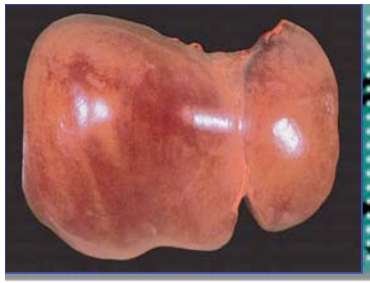
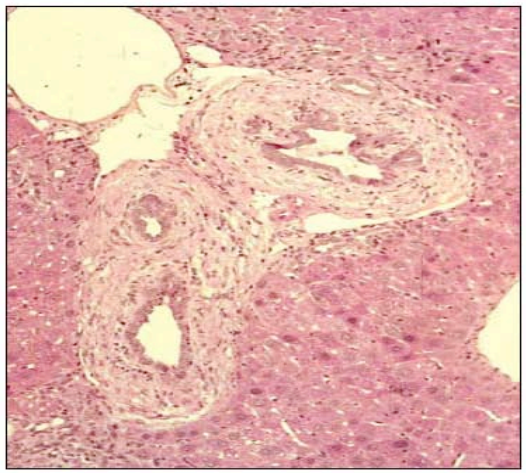
Bilirubin metabolism

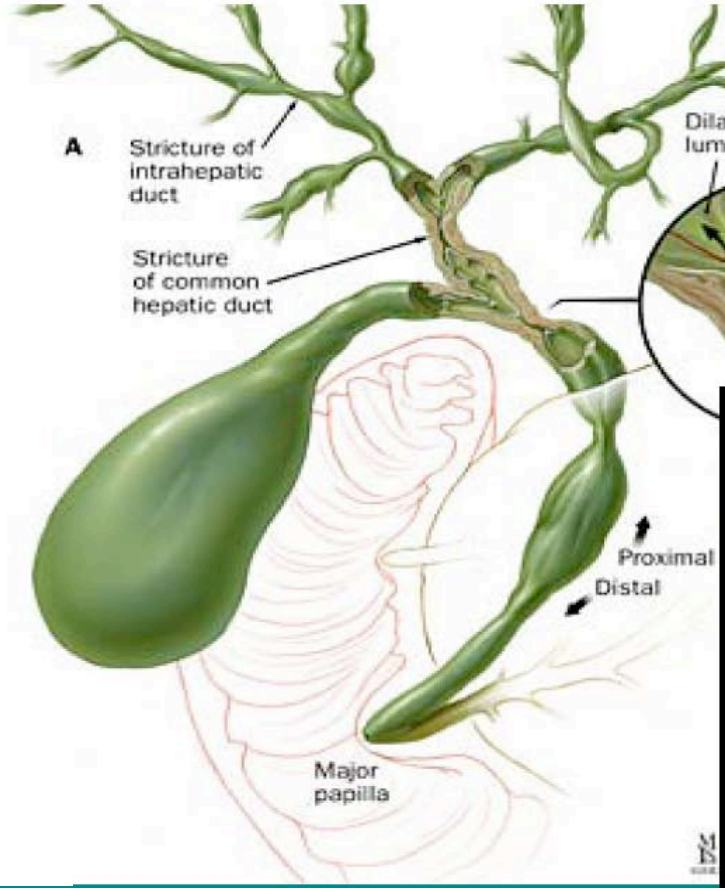
HYPERBILIRUBINEMIA		
Unconjugated		
pre-hepatic	hemolytic anemia hemoglobinopathies systemic infections	
hepatic	Gilbert's syndrome neonatal jaundice	
Conjugated		
intrahepatic	hepatitic	viral drugs alcohol
extrahepatic	cirrhosis gall stones carcinoma	pancreas bile ducts ampulla
	pancreatitis	
non-cholestatic	Dubin-Johnson syndrome	

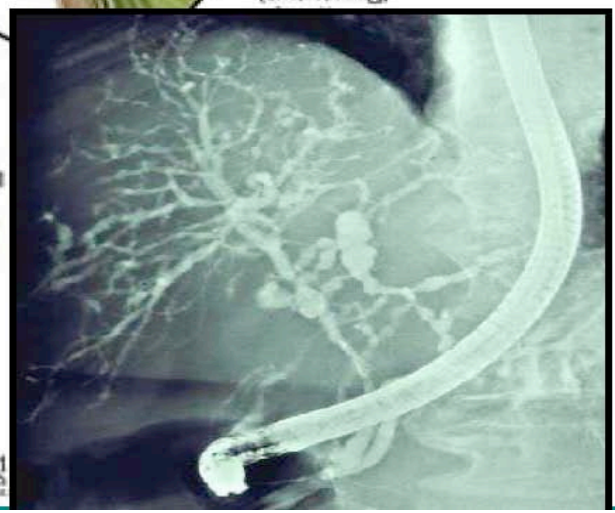


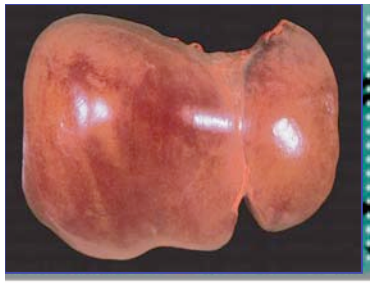
Primary sclerosing cholangitis (PSC)

Progressive, fibrous-stenosing and obliterating, segmental inflammation of the intrahepatic and/or extrahepatic bile ducts



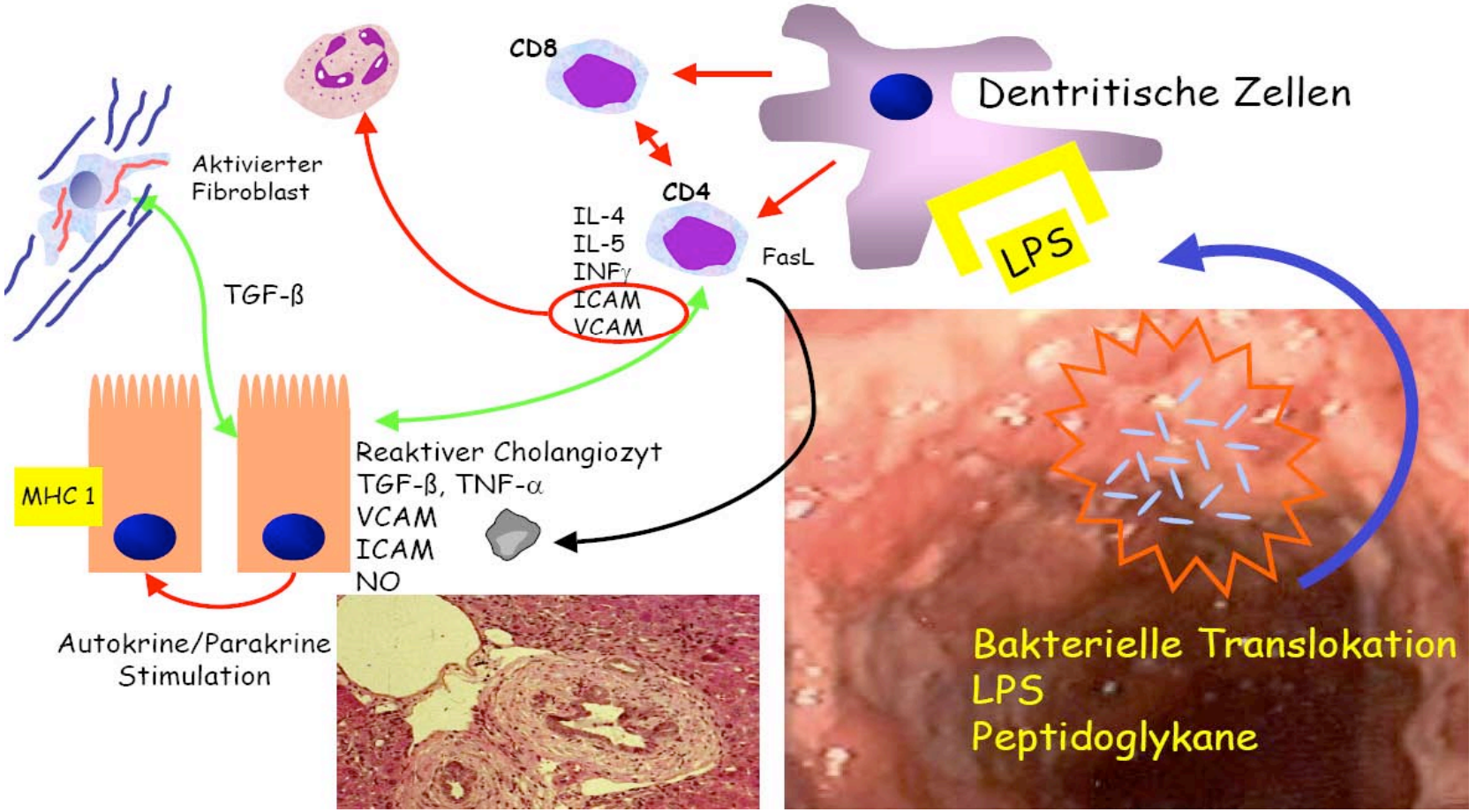


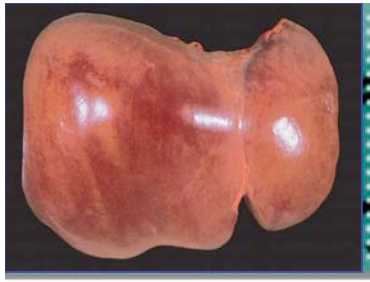




Primary sclerosing cholangitis (PSC)

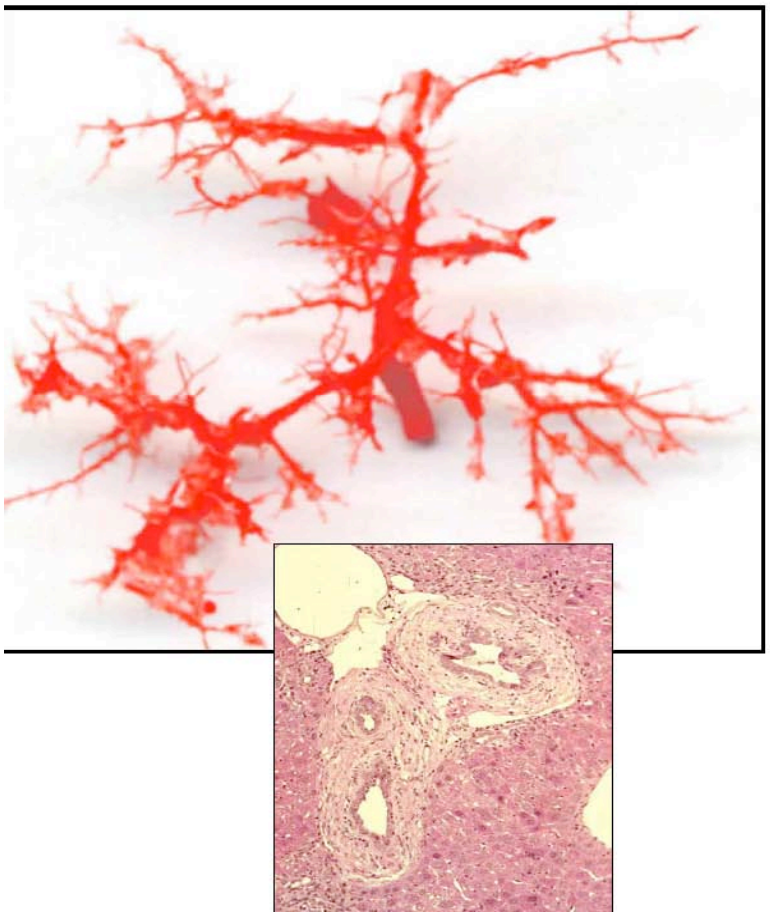
What´s the Pathogensesis of PSC ??

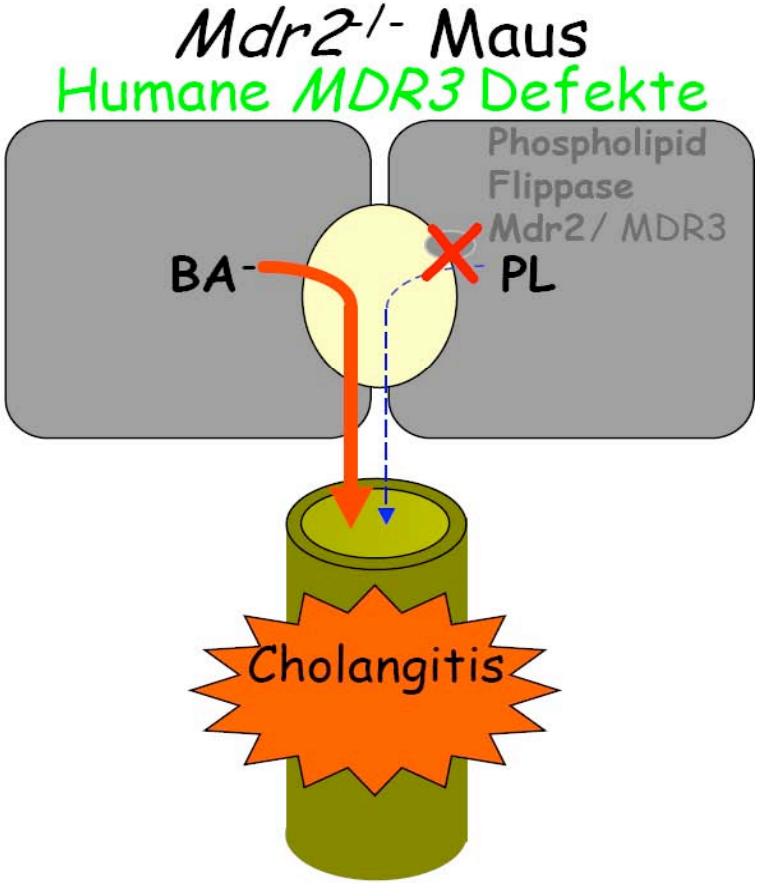


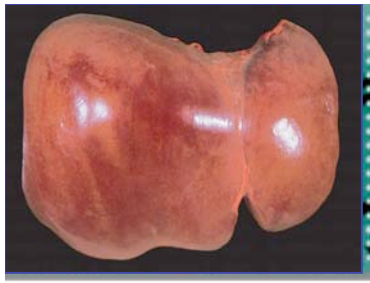


Primary sclerosing cholangitis (PSC)

Hypothesis of the toxic bile acid ??







Primary sclerosing cholangitis (PSC)

Indicative, evidential and supplementary or parameters for diagnosis

I. Suggestive factors

1. Subjective discomfort
2. Men, 20 to 45 years old
3. Non-smoker
4. Association with ulcerative colitis !!
5. Increased transaminases
6. Hepato/splenomegaly

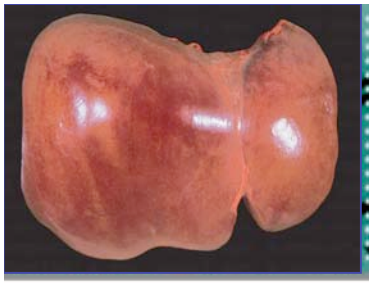
II. Definite diagnosis

1. Chronic cholestasis
2. pANCA3. Non-smoker
4. ERCP, MRCP
5. (Liver biopsy)

III. Supplementary findings

=> *Laboratory tests*

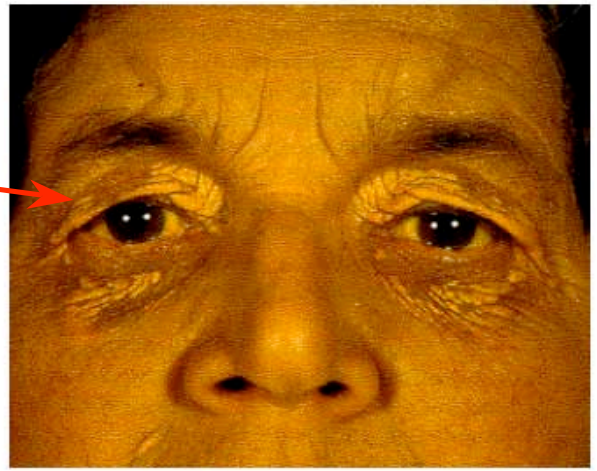
1. Bilirubin ↑
2. IgM↑
3. ANA, SMA (+)
4. Serum copper ↑
5. CRP, ESR ↑
6. Cholinesterase ↓

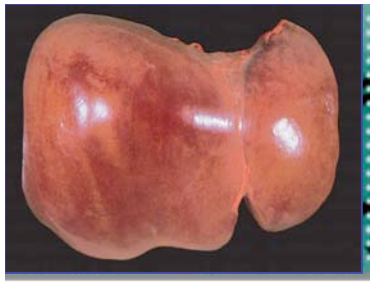


Primary biliary cholangitis (PBC)

PBC is characterized by chronic, non-suppurative, destractive cholangitis (CNDC) of the small and medium-sized bile ducts. The cause is not known ! Characteristics are:

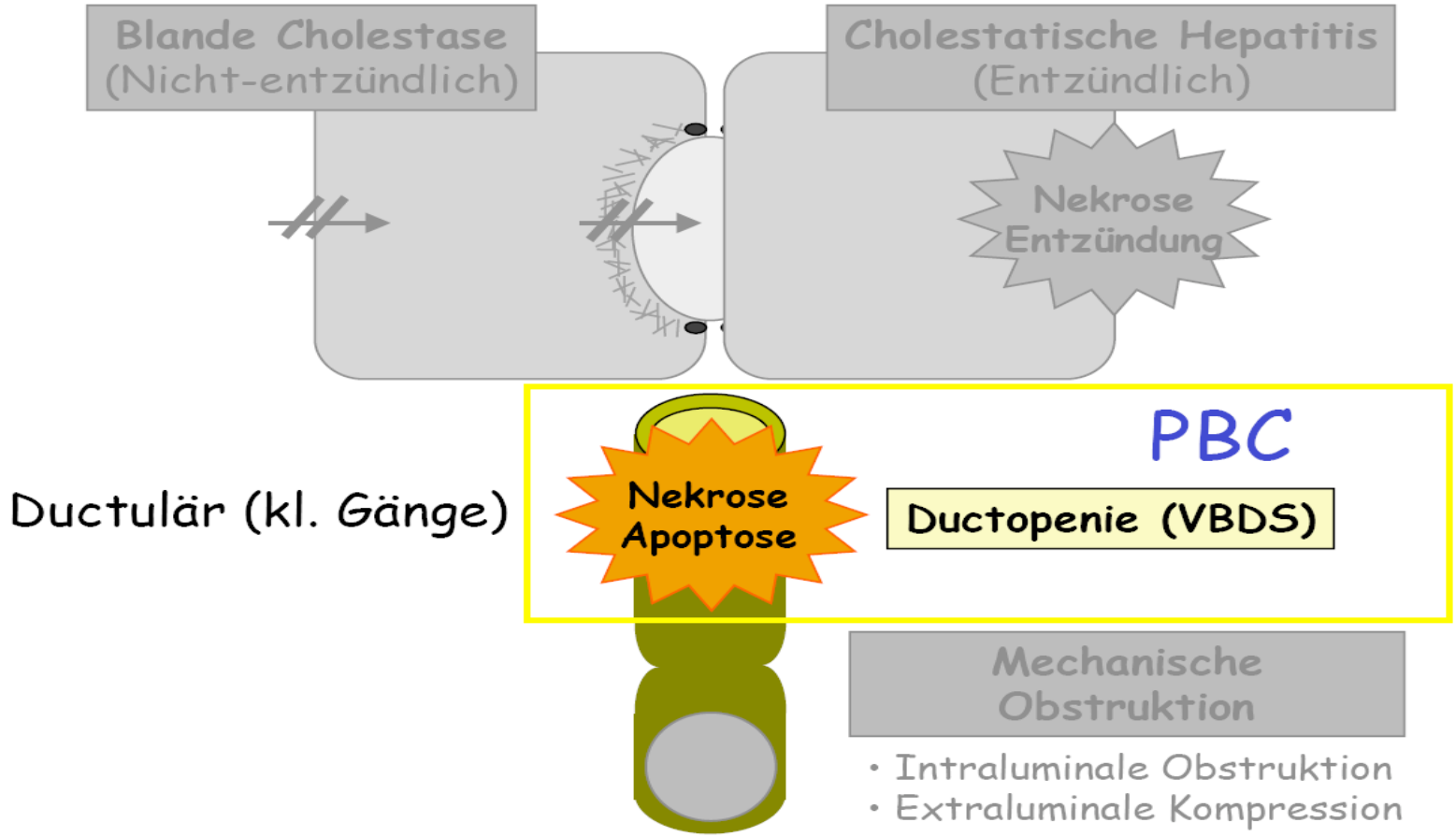
- in up to 95% AMA (anti-M2 positive)
- 90% female (40 – 45 years)
- 70 -85% Hypercholesterinemia
- 80 % extrahepatic manifestations
  e.g. Osteopathy (20 – 60 %)
- Pruritus
- Xanthomas

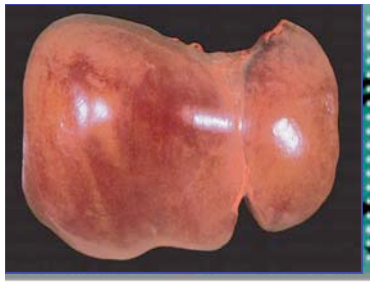




Primary biliary cholangitis (PBC)

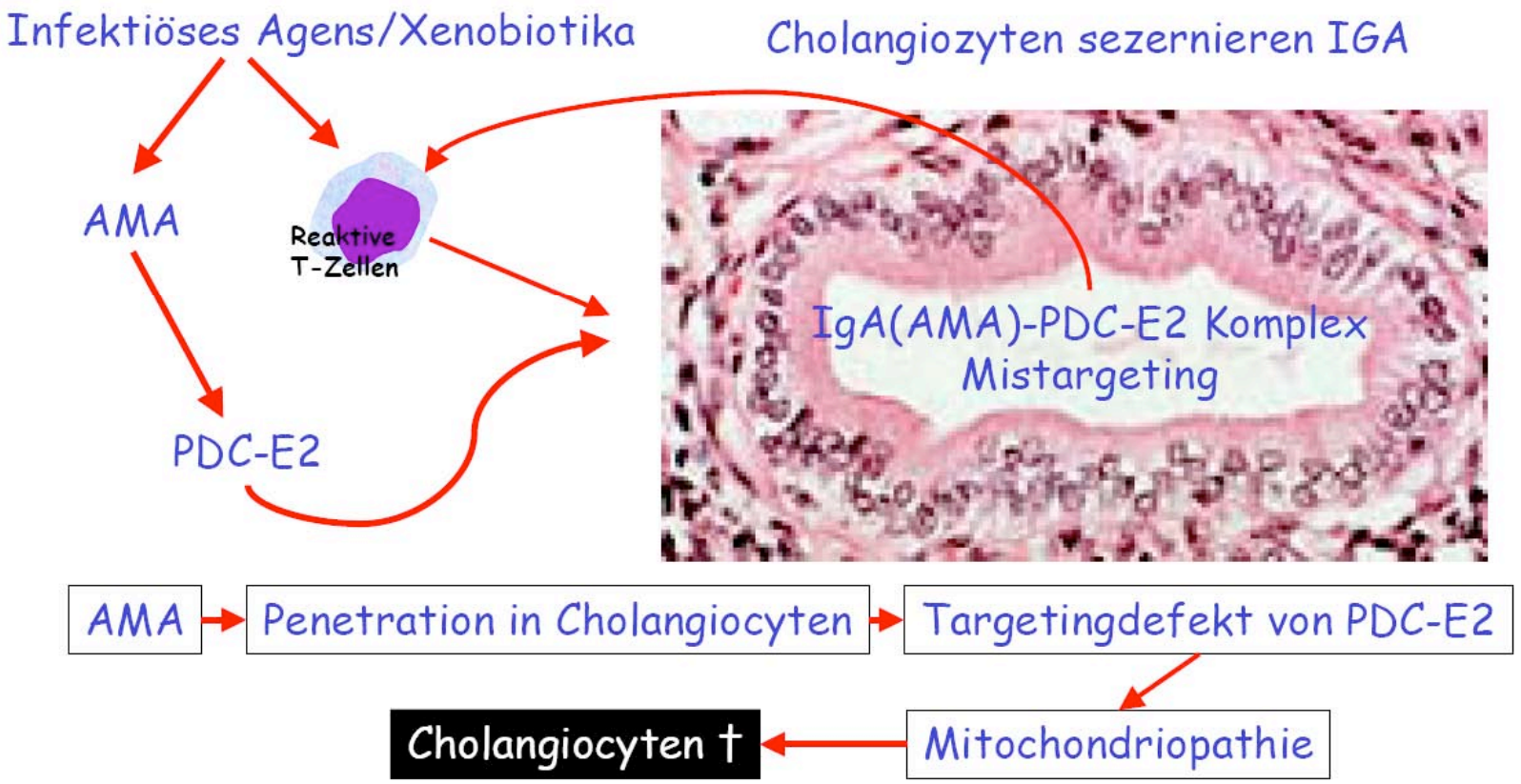
Klinisches Spektrum der Cholestase

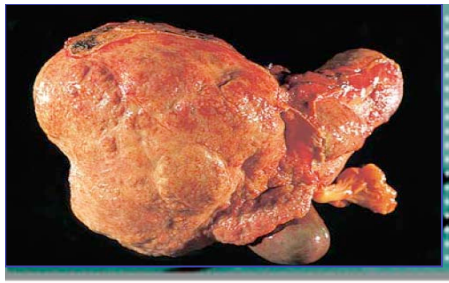




Primary biliary cholangitis (PBC)

What´s the Pathogensesis of PSC ??





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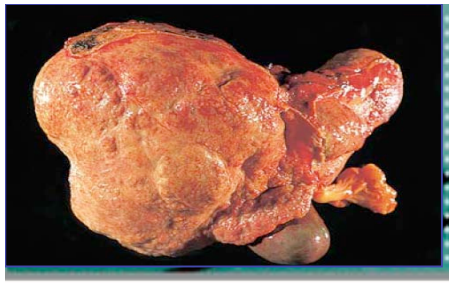
Metabolic disorders and storage diseases

1. Non-alcoholic fatty liver disease (NASH)
2. Amino acid/Carbohydrate/Lipid storage diseases
3. Porphyrias
4. Sphingolipid storage diseases
5. Wilson´s disease
5. Haemochromatosis



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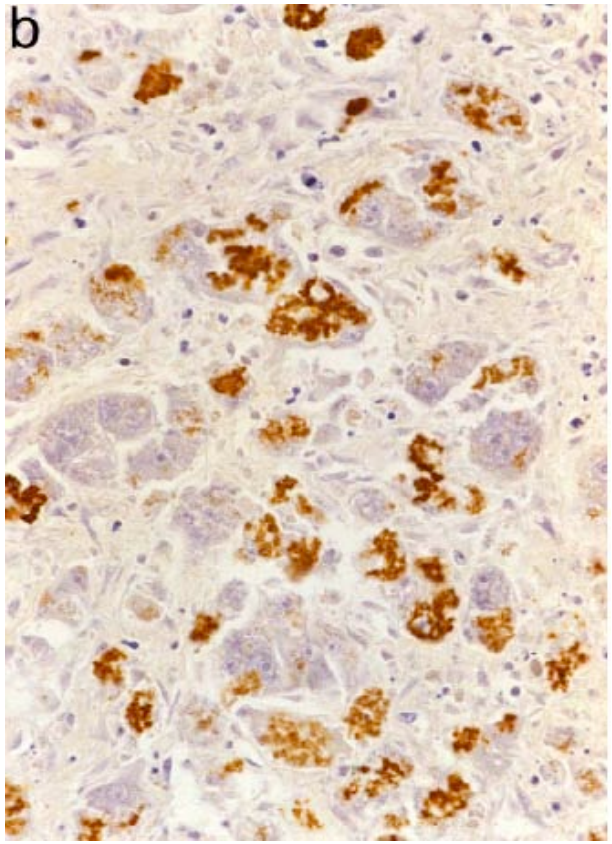
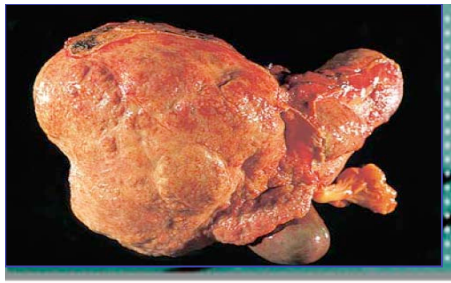
Wilson´s disease

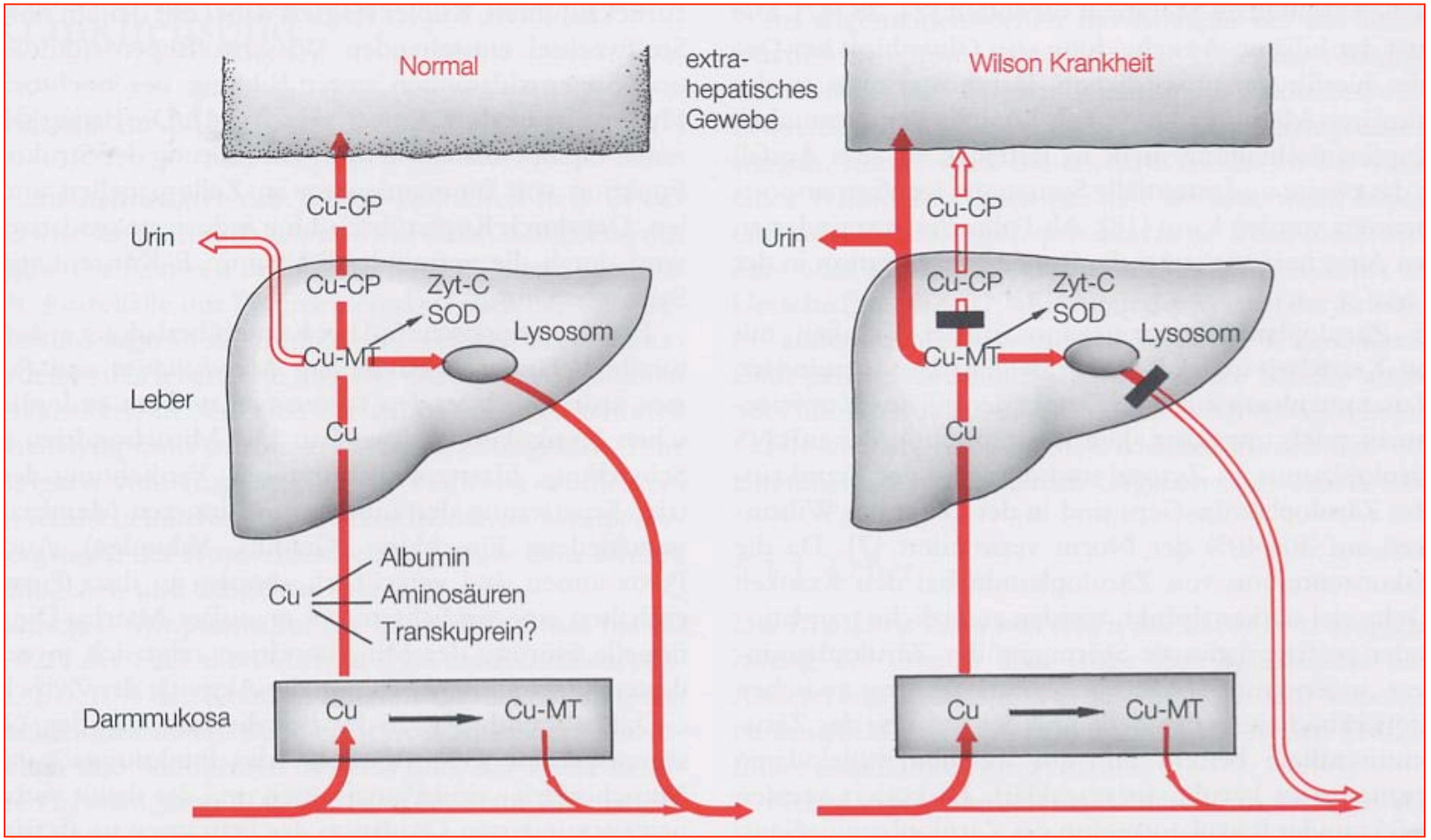
= a genetically determined, autosomal recessive **copper storage disease** with a reduced discharge of copper in the bile

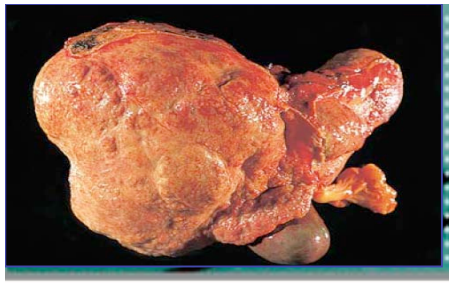




Wilson´s disease

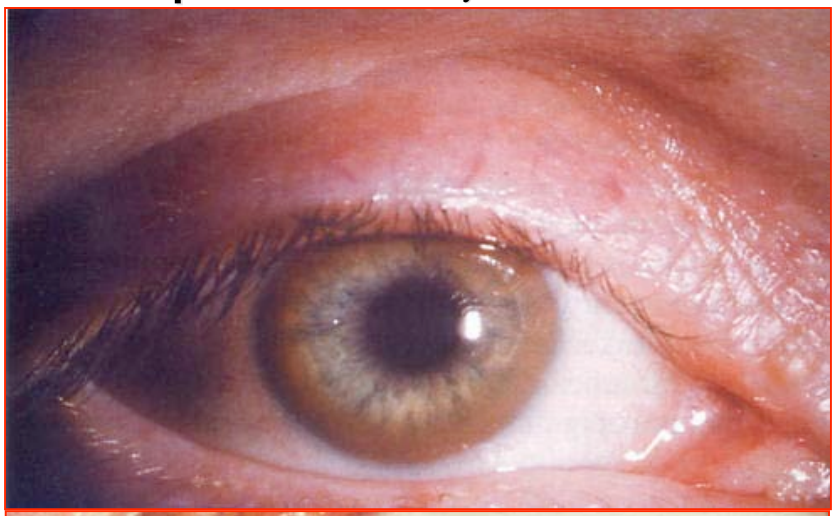
Aetiopathogenesis

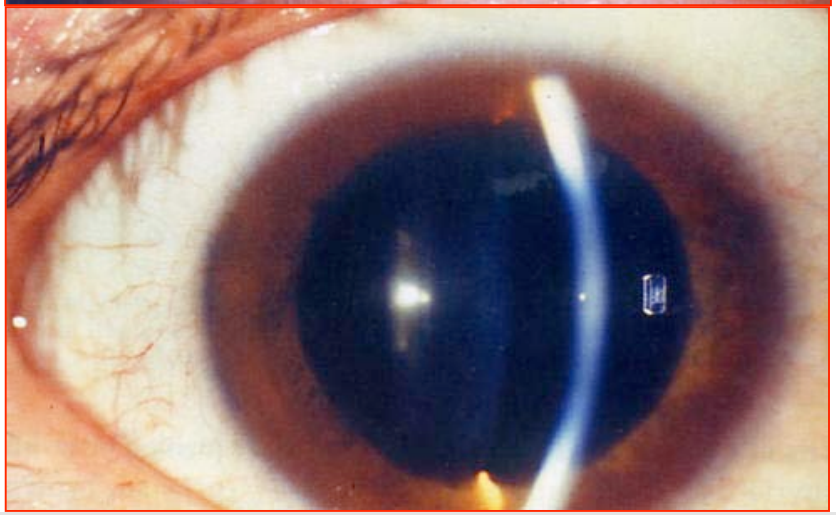




Wilson´s disease

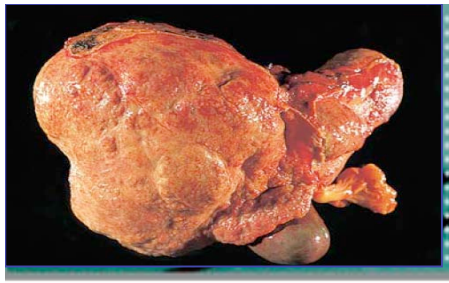
Clinical pictures => Kayser-Fleischer corneal ring





Laboratory findings

- Ceruloplasmin in the serum ↓ (< 20 mg/dl)
- Copper content of the liver ↑ (> 250 µg/g)
- Copper in the urine ↑ (> 70 µg/day)
- Free cooper in the serum ↑ (> 25 µg/dl)
- Pencillaminetest (600 mg) + (> 300 µg/day)
- Total copper in the serum ↓ (< 70 µg/dl)



Haemochromatosis (HC)

= a hereditary disease (autosomal recessive) affecting the **iron metabolism**

Heriditary (primary) haemochromatosis

HFE-related haemochromatosis

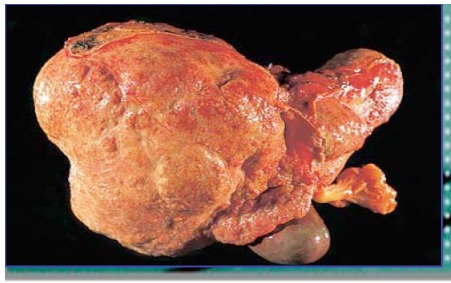
type 1 heriditary haemochromatosis

Non-*HFE-related haemochromatosis*

type 2 Juvenile haemochromatosis
type 3 Italian variant
type 4 autosomal dominant form

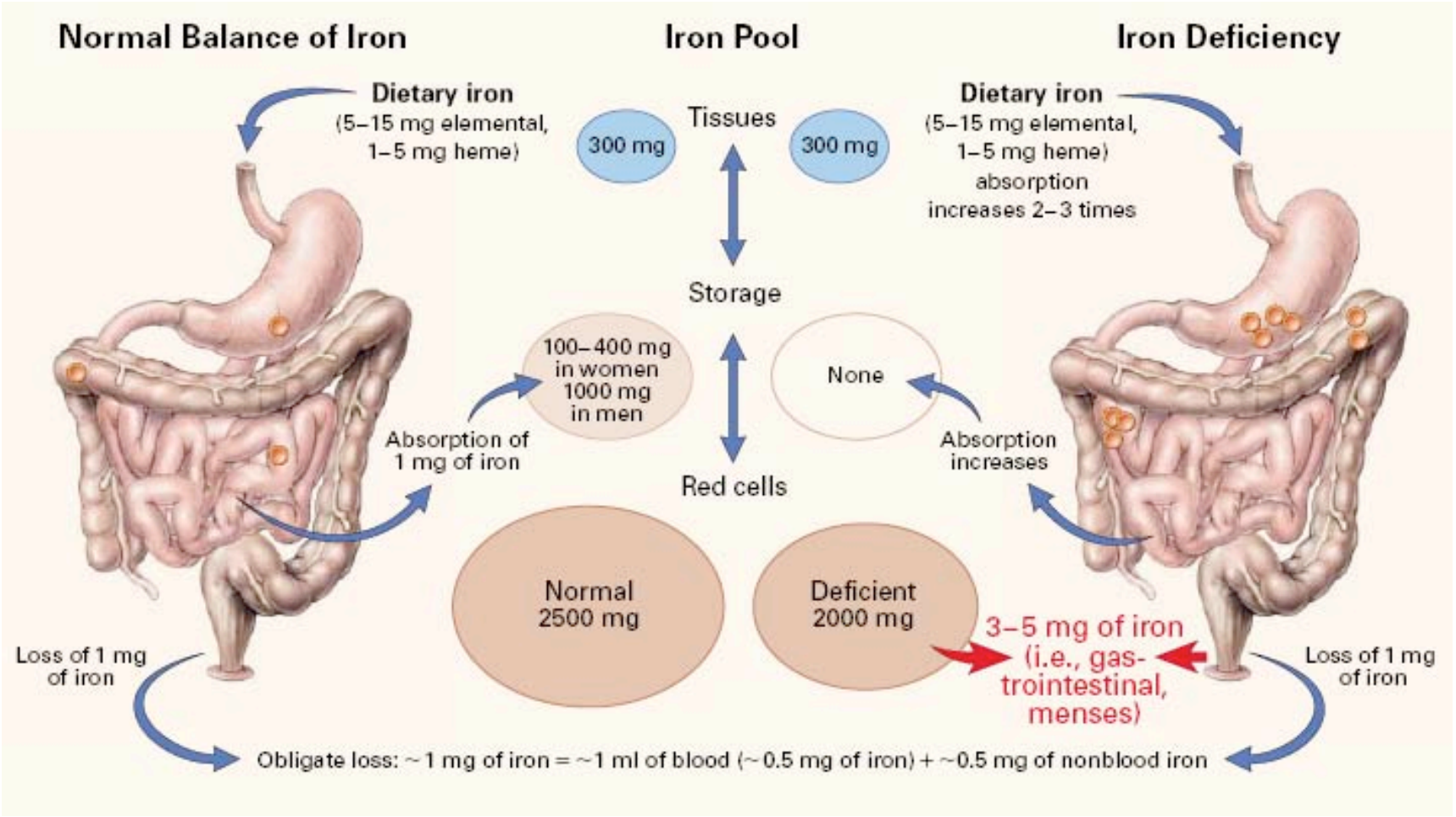
Acquired (secondary) haemochromatosis

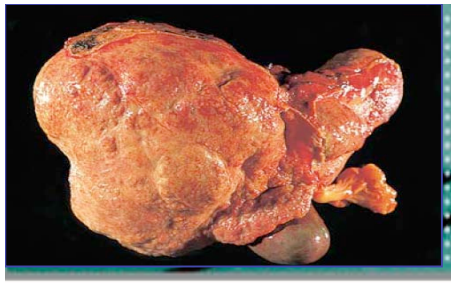
- extreme iron intake due to dietary habits
  e.g. Bantu disease or African iron overload
- extreme iron intake due to therapy (e.g. frequent blood transfusions)
- haemolytically induced (e.g. thalassaemia)
- metabolically induced (e.g. tyrosaemia..)



Haemochromatosis (HC)

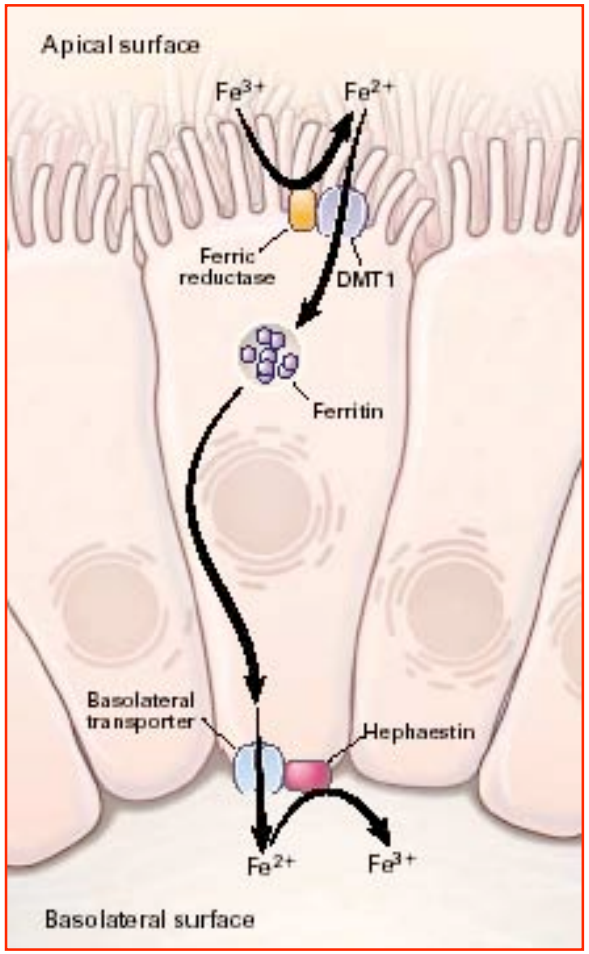
Aetiopathogenesis

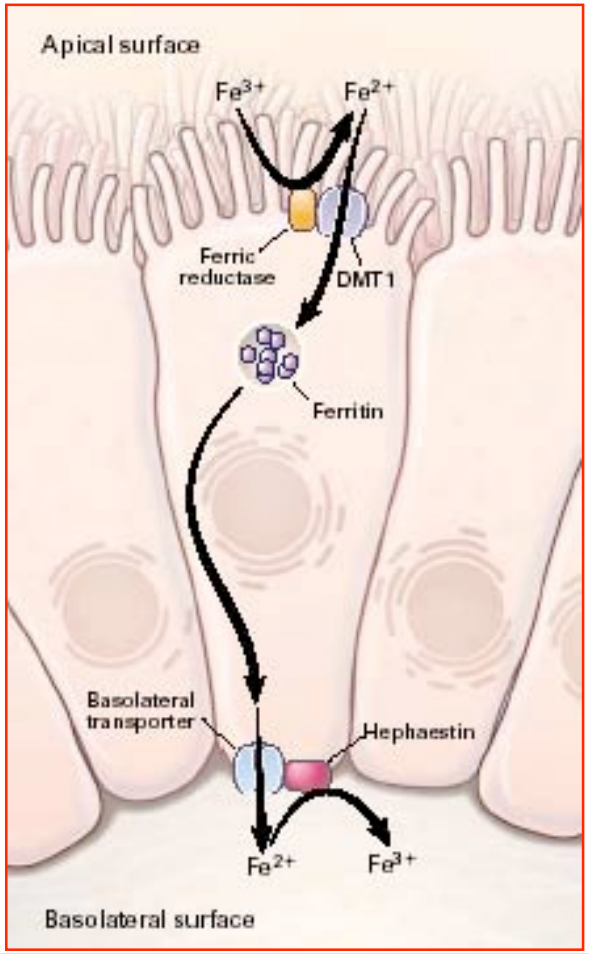


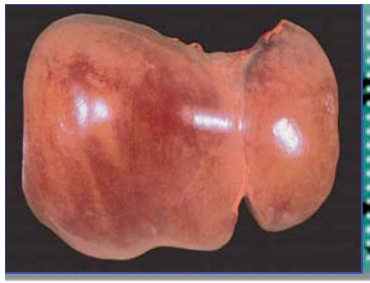


Haemochromatosis (HC)

Aetiopathogenesis

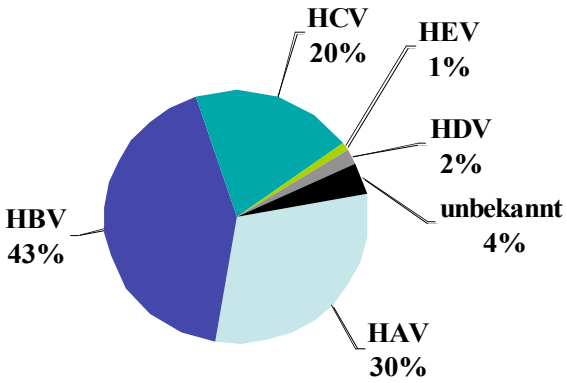




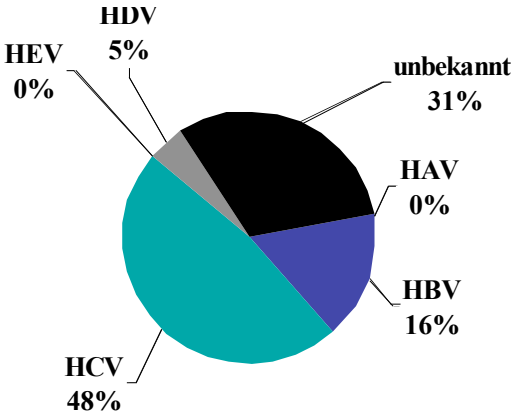


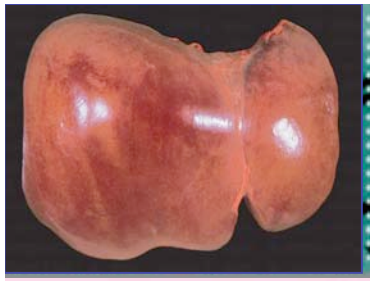
Hepatitis

Acute hepatitis



Chronic hepatitis





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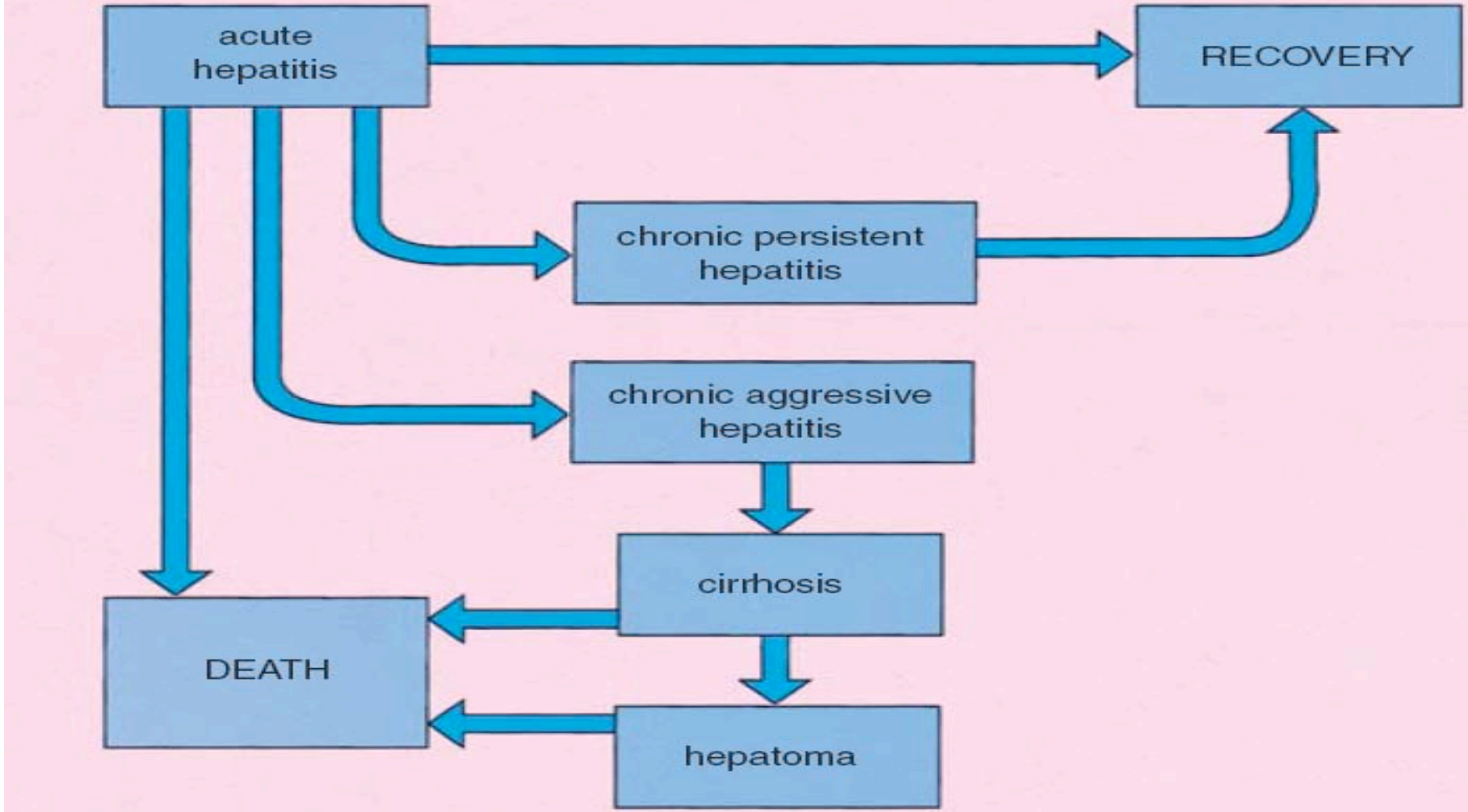

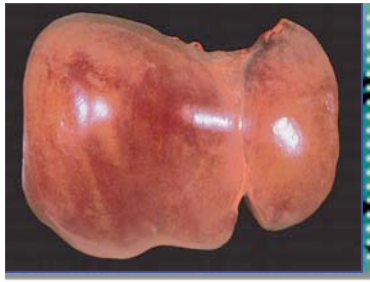

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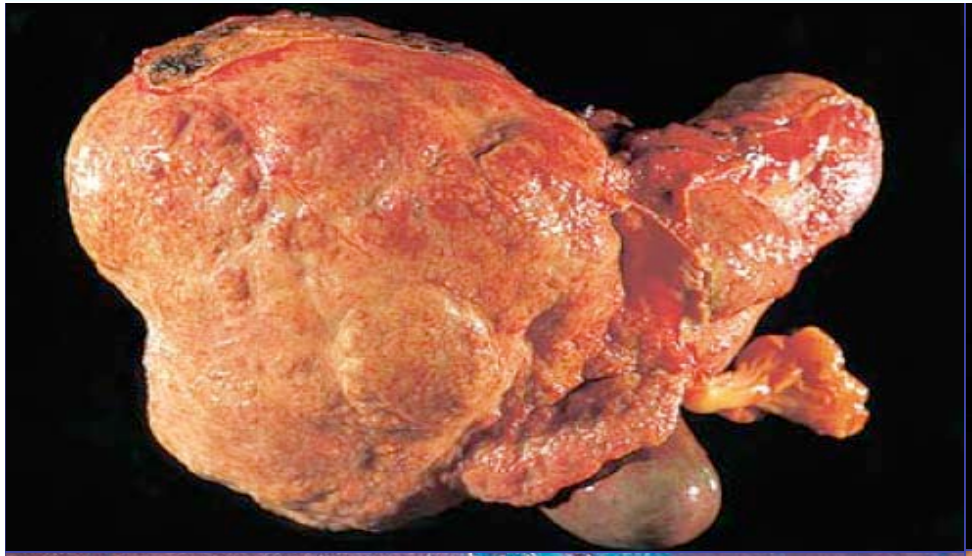
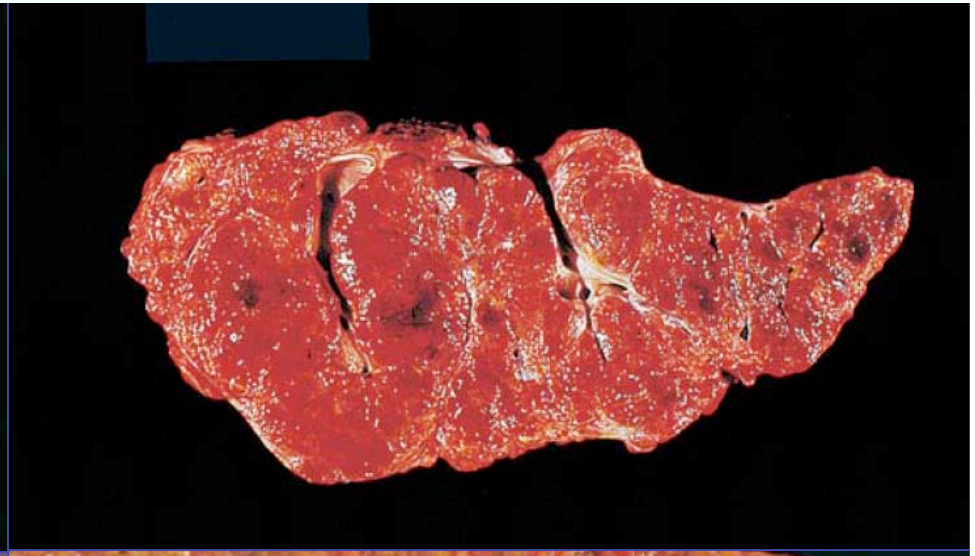
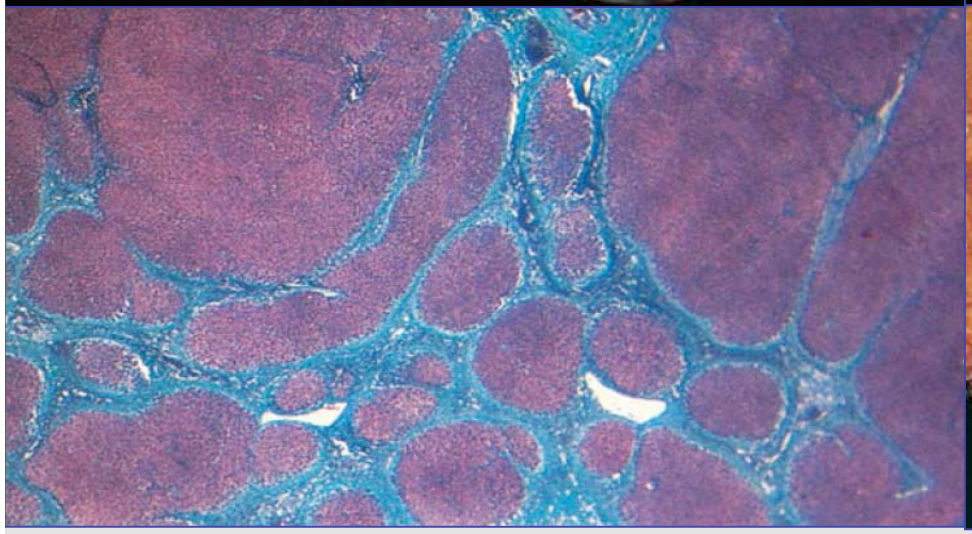
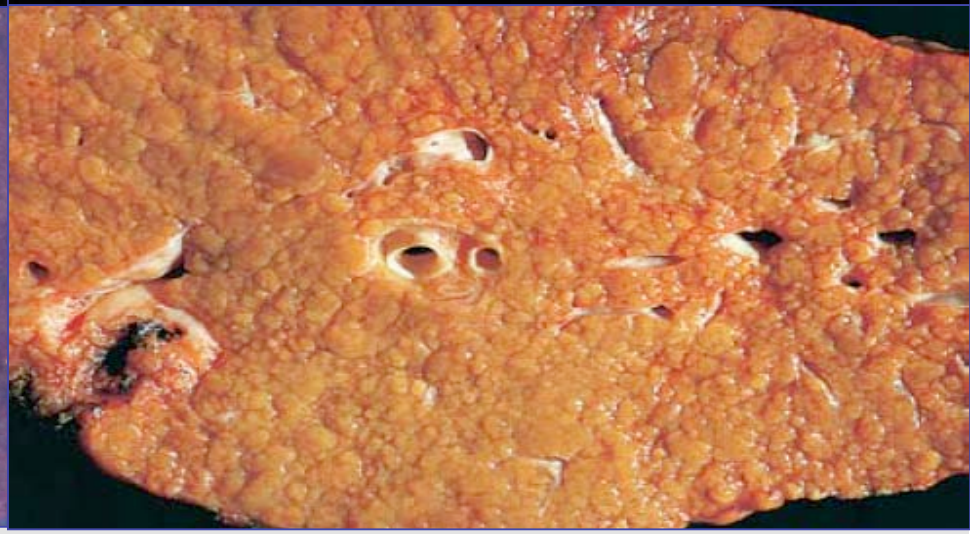
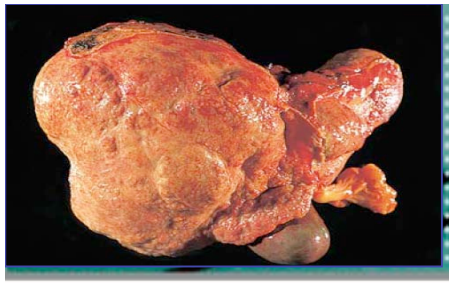
Liver Cirrhosis











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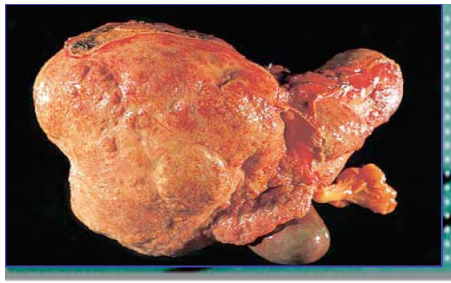
Possible causes of liver cirrhosis

1. Viral hepatitis
=> HBV > HBC

2. Metabolic disorders
=> Haemochromatosis
=> Wilson´s disease
=> NASH

3. Cholestatic diseases
=> primary biliary cirrhosis
=> primary sclerosing cirrhosis
=> NASH

4. Venous obstruction
=> veno-occlusive disease
=> Budd-Chiari syndrome
=> cardiac cirrhosis



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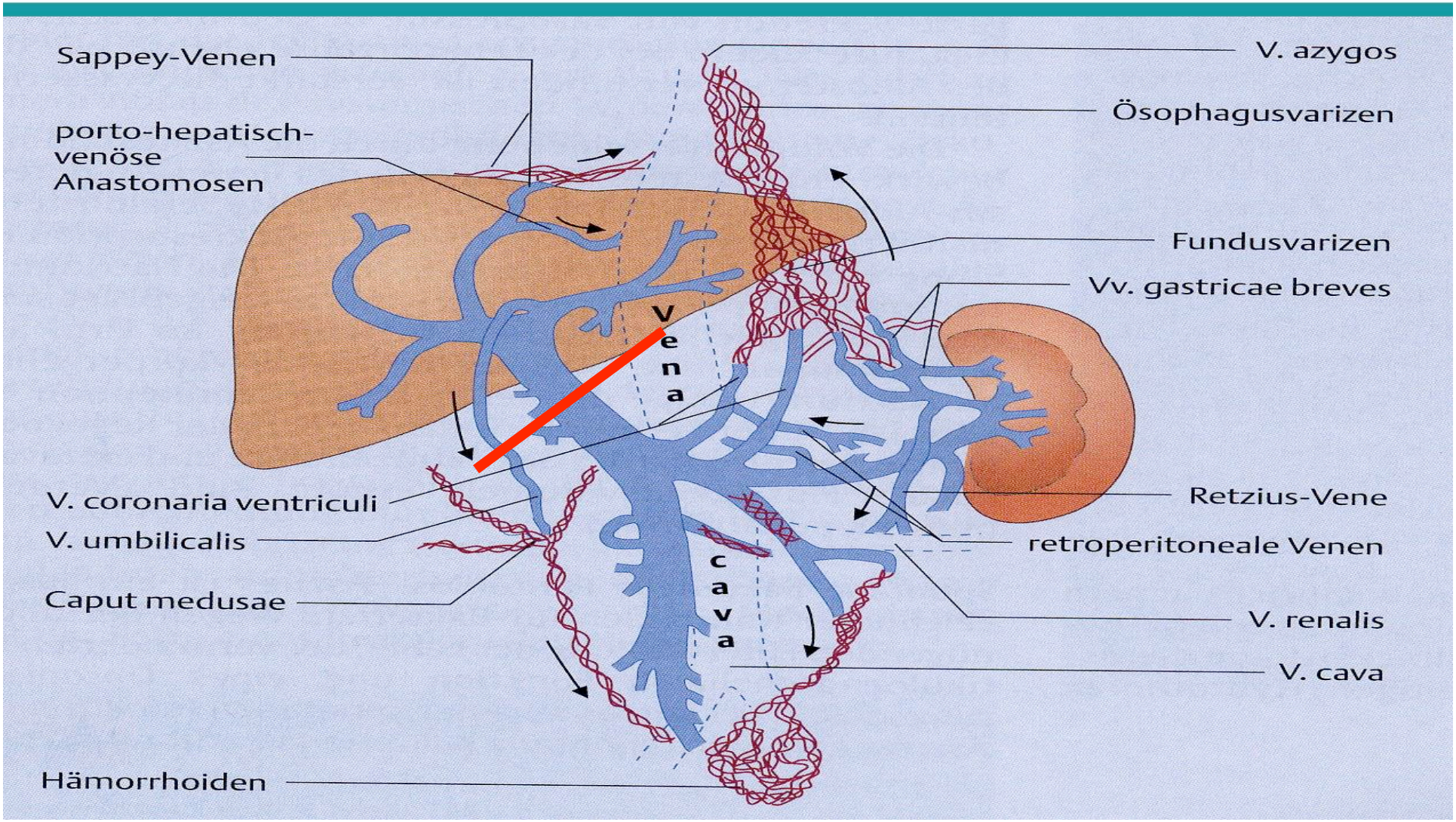
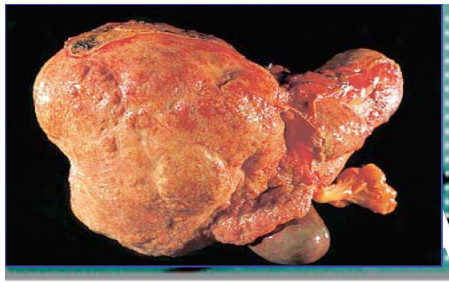
Portal hypertension





Ascites

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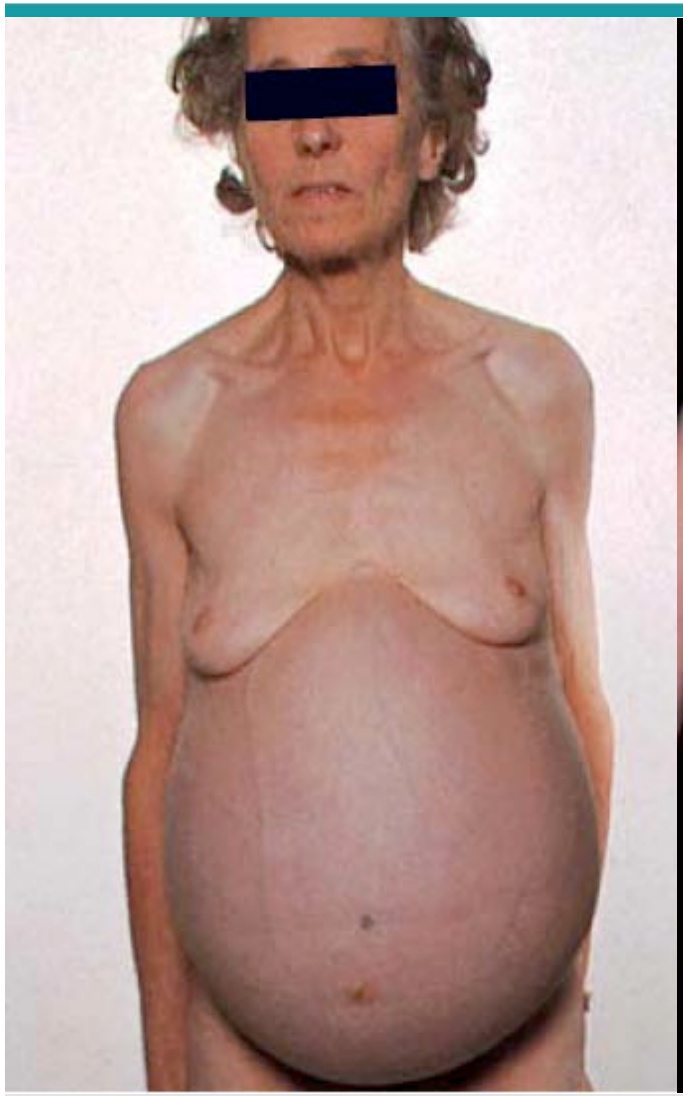
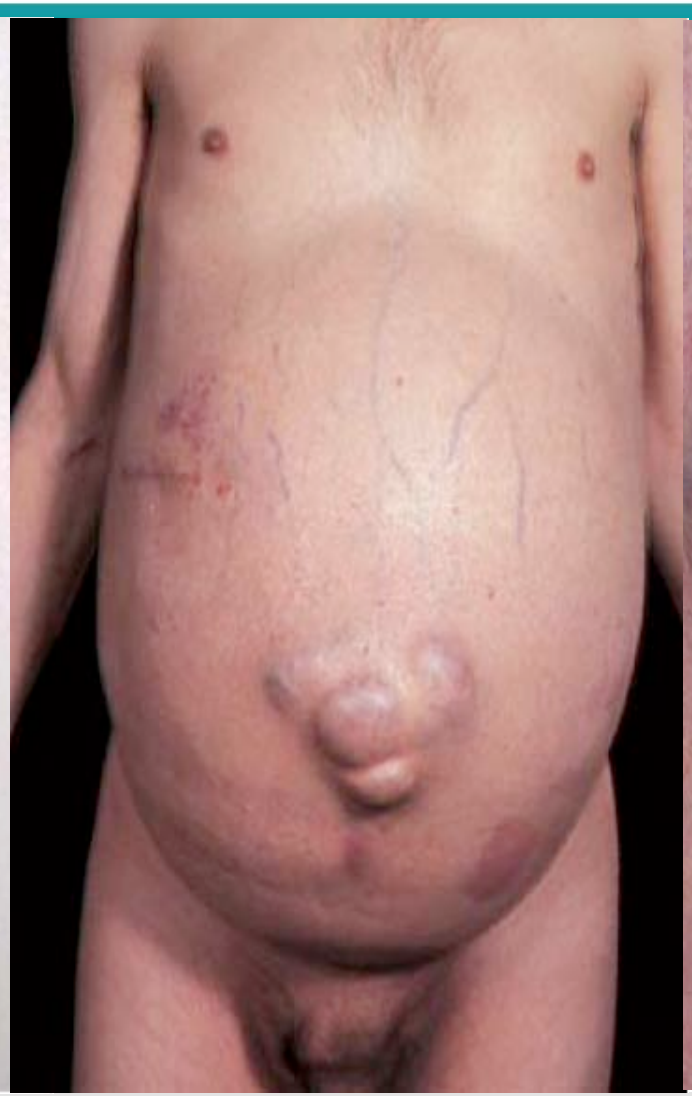
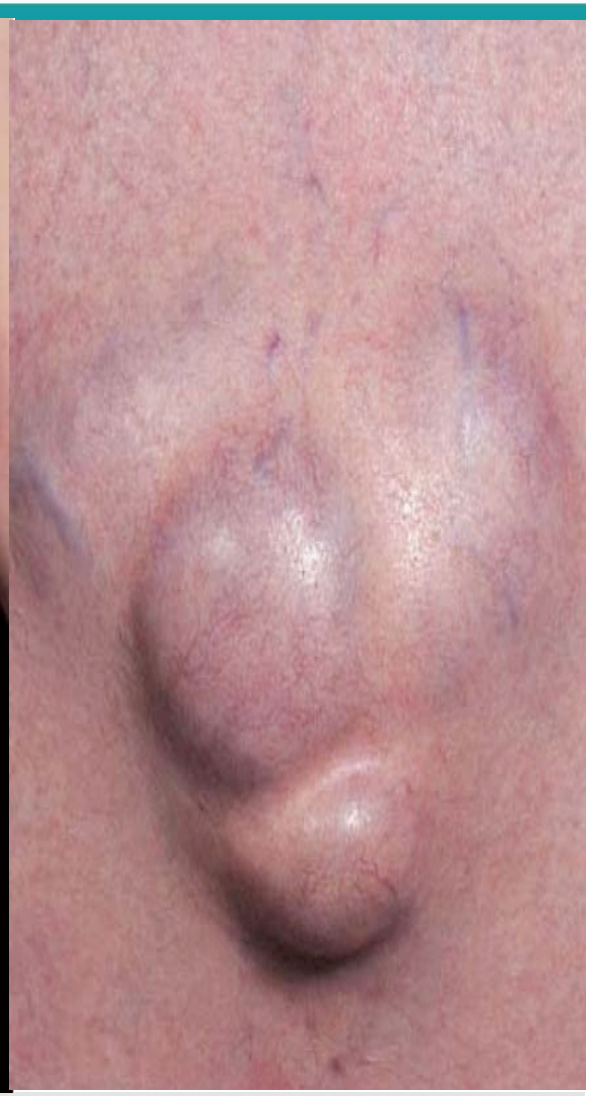
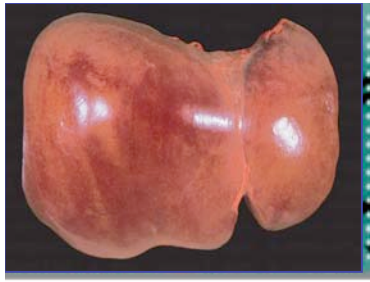
ZAFES









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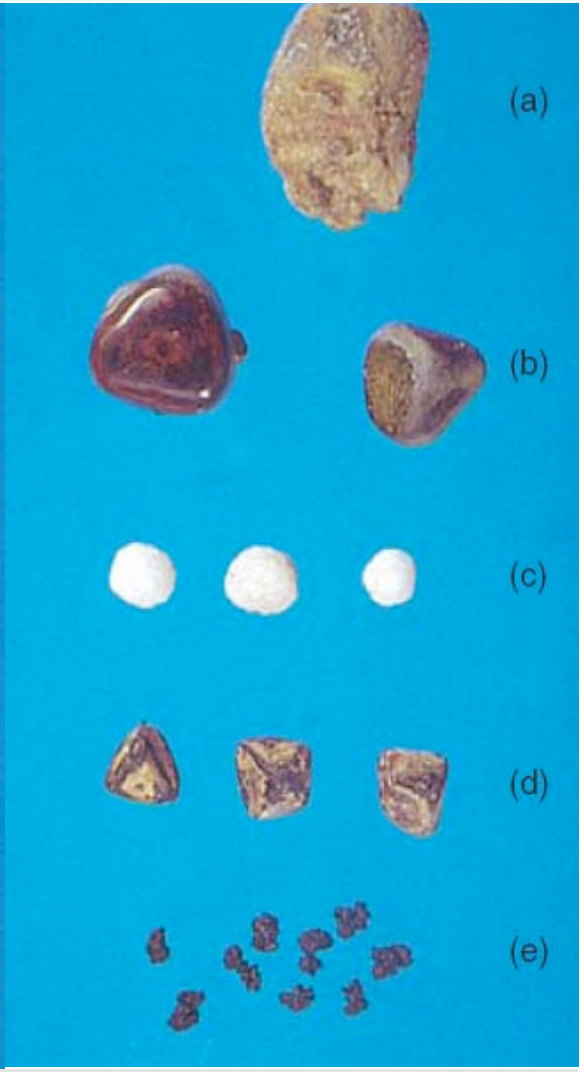
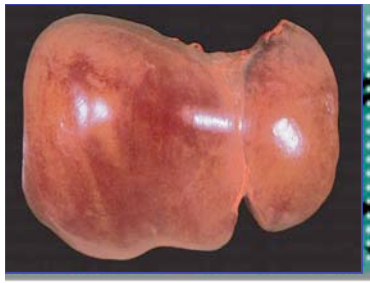
ZAFES

Gall stones





Gall stones

Epidemiology of Pigment and Mixed/Cholesterol Stones

Pigment stones

- increase with age
- female = male
- increased incidence.
  - => Hemolysis
  - => biliary infection
  - => Alcoholic infection

Mixed/Cholesterol stones

- increase with age
- female > male
- increased incidence.
  - => ileal disease
  - => cystic fibrosis
  - => hyperlipoproteinämia (typ IV)