G.I. Oncology

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Slide Author:

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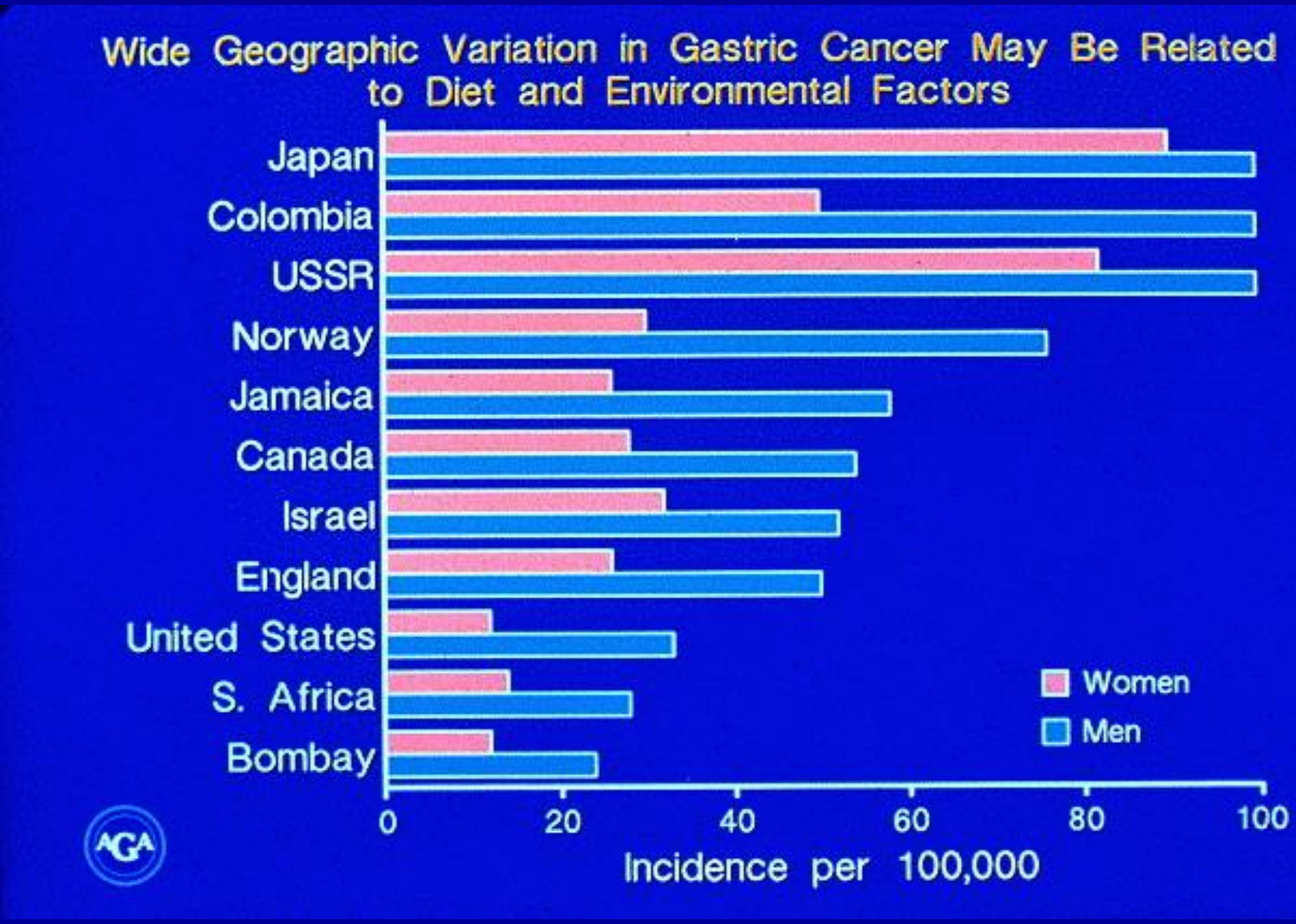
I have no disclosures to make

I am employed by the Cruators of the University of Missouri

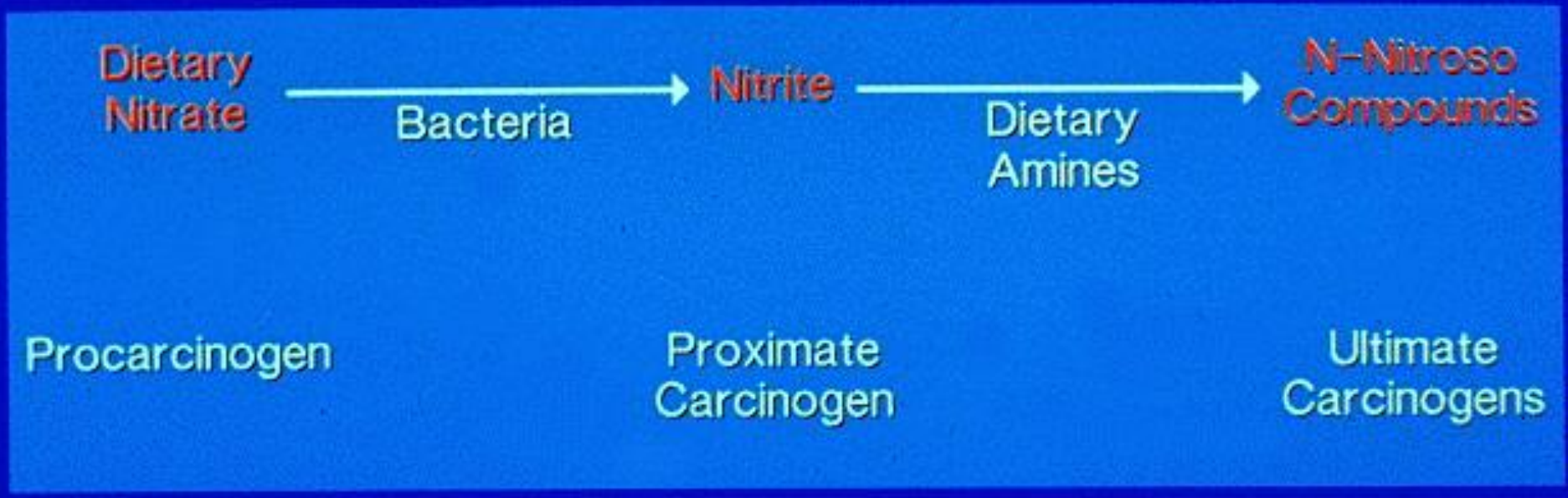
Gastric Tumors Arise from Many Cell Types But Adenocarcinoma is Most Common

- Carcinoma
  - Adenocarcinoma (>90%)
  - Adenocanthoma
  - Squamous cell
  - Carcinoid

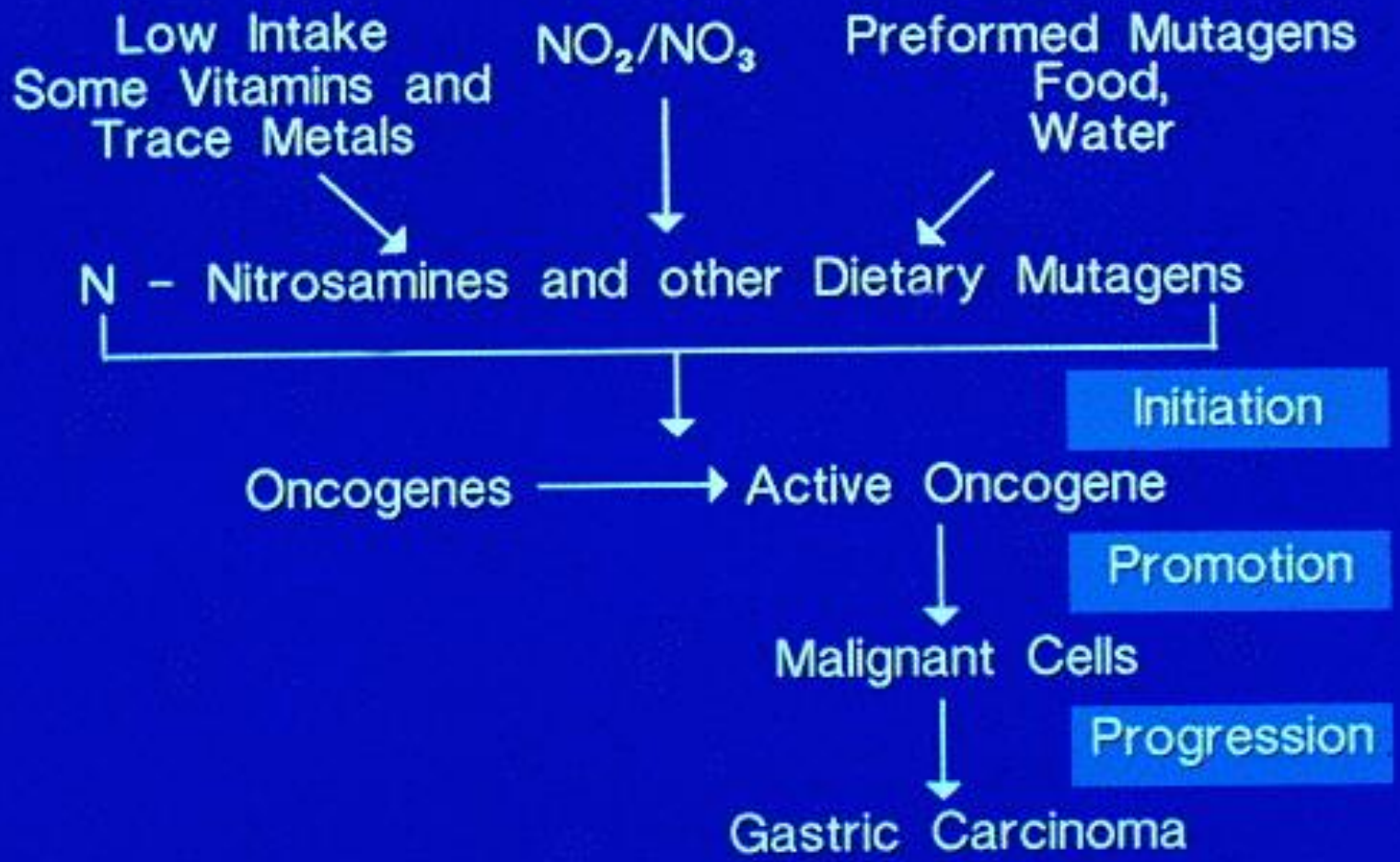
- Leiomyosarcoma
- Lymphoma (8%)
- Other sarcomas


Wide Geographic Variation in Gastric Cancer May Be Related to Diet and Environmental Factors
Japan
Colombia
USSR
Norway
Jamaica
Canada
Israel
England
United States
S. Africa
Bombay
Women
Men
0
20
40
60
80
100
Incidence per 100,000
AGA

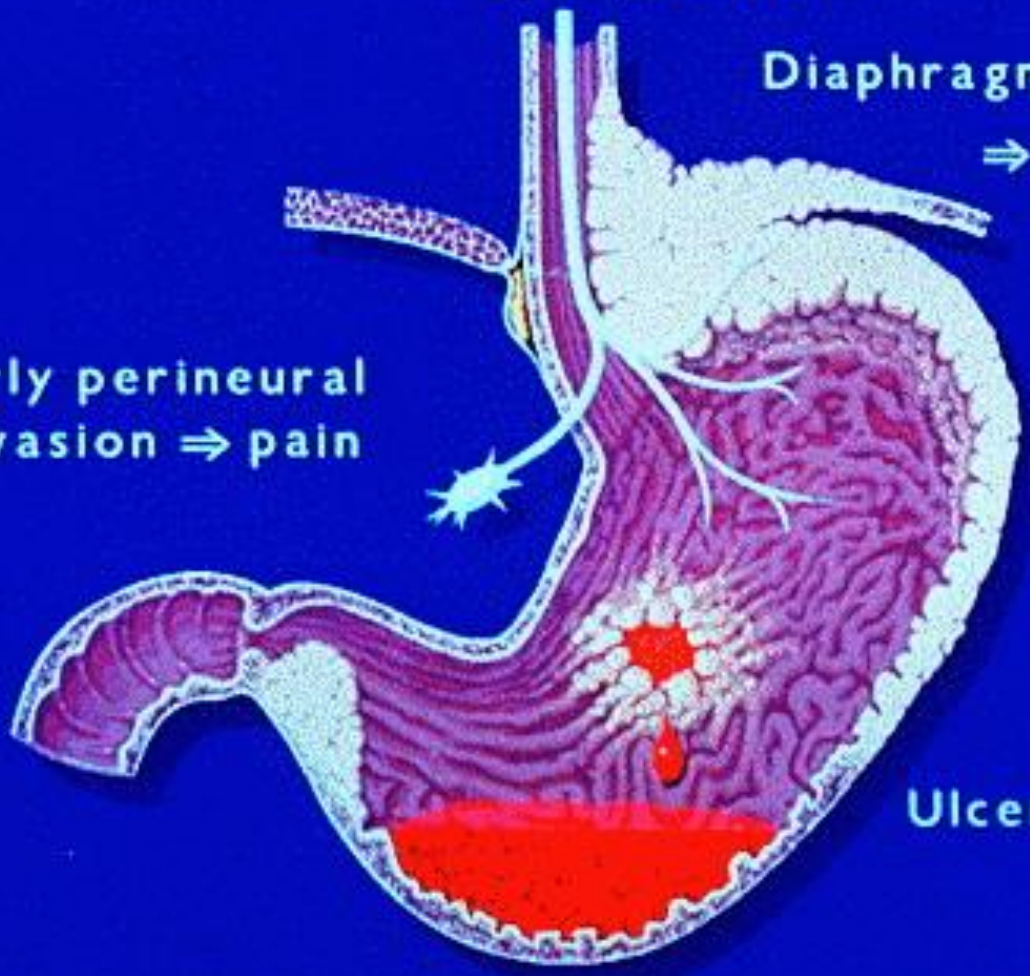
Nitrites Formed from Dietary Nitrates React to Form Ultimate Carcinogens



Gastric Cancer May Arise from Interaction of Chemical Mutagens and Cellular Oncogenes



Gastric Cancer May Cause a Variety of Symptoms



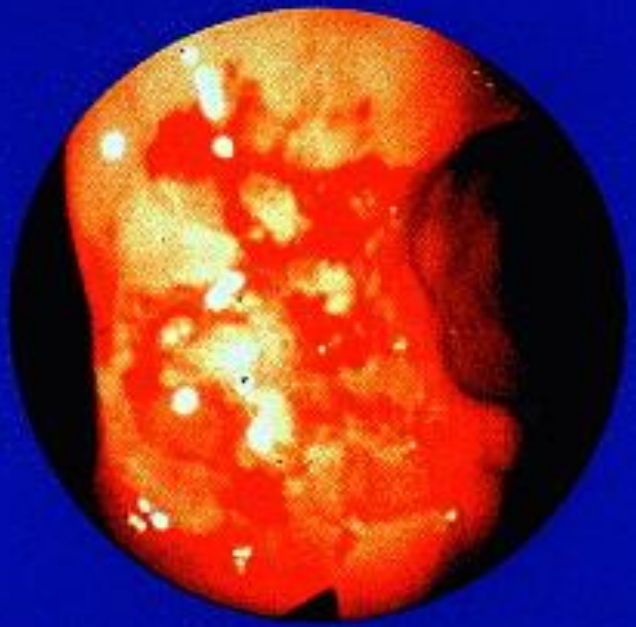
Diaphragmatic invasion
⇒ Hiccoughs

Early perineural invasion ⇒ pain

Infiltration →
↓ Compliance ⇒
Early satiety
Weight loss

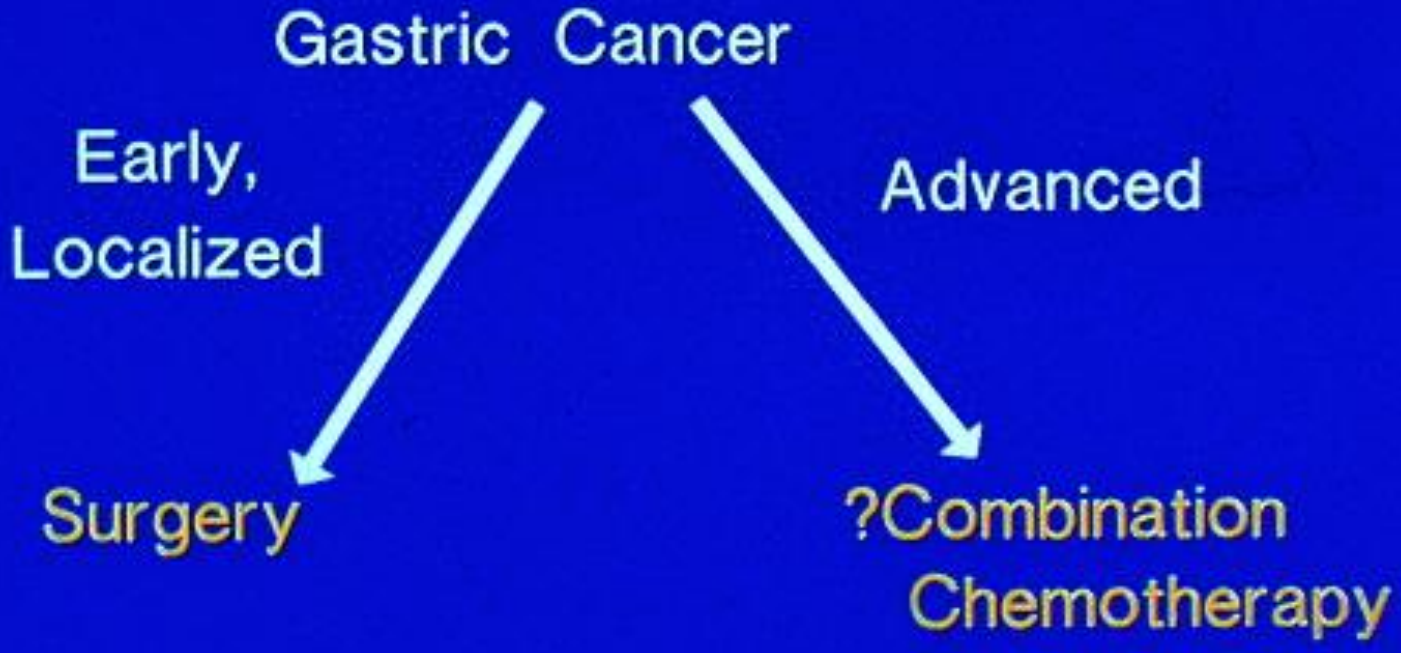
Ulceration ⇒ bleeding

Gastric Cancers May Be Detected by X-Ray or Endoscopy



Histologic confirmation is required for diagnosis.

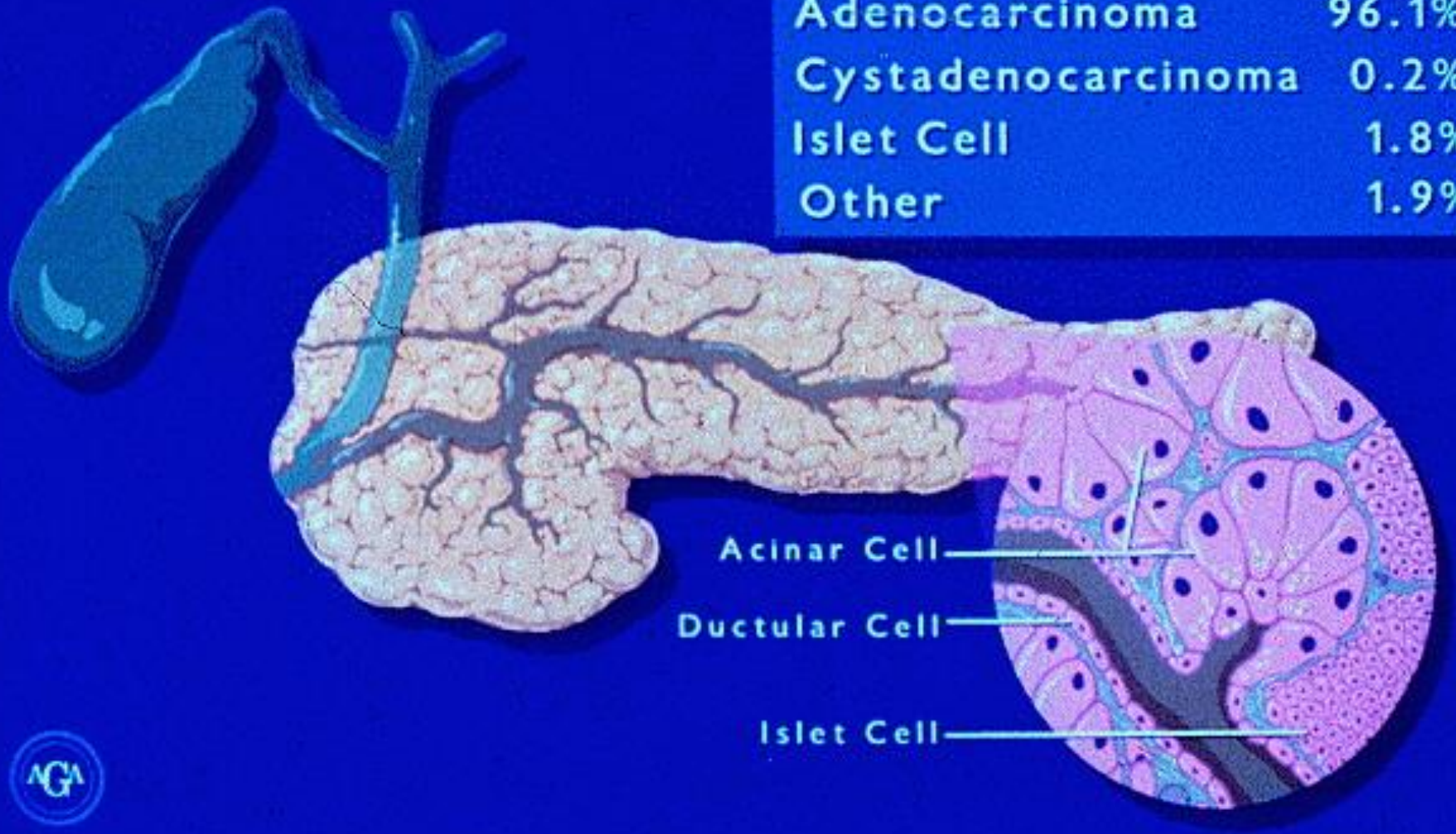
Extent of Gastric Carcinoma at Diagnosis Determines Approach to Treatment



But: Overall 5 Year Survival ~10%

Pancreatic Tumors Arise from Many Cellular Elements but Ductal Adenocarcinoma is Most Common

Adenocarcinoma	96.1%
Cystadenocarcinoma	0.2%
Islet Cell	1.8%
Other	1.9%

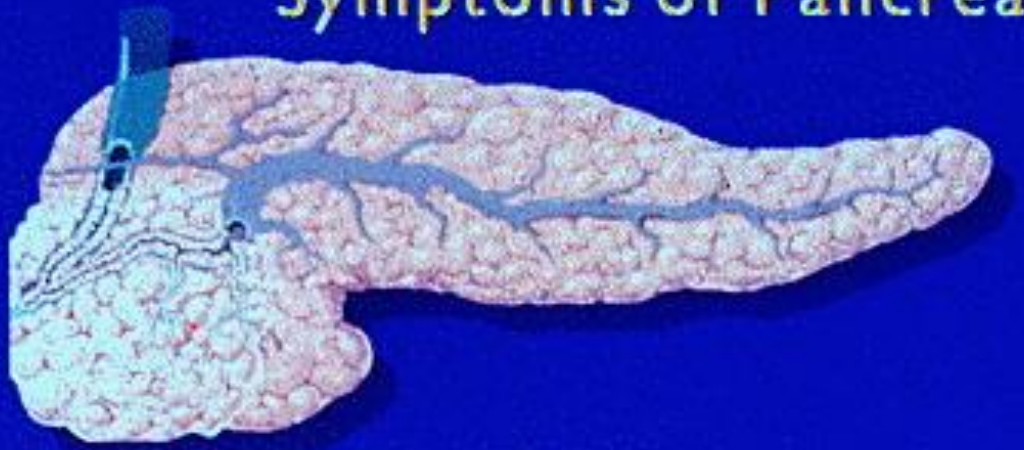


Epidemiologic Associations with Pancreatic Cancer Are Not Strong

Male > Female
Black > White
Urban > Rural

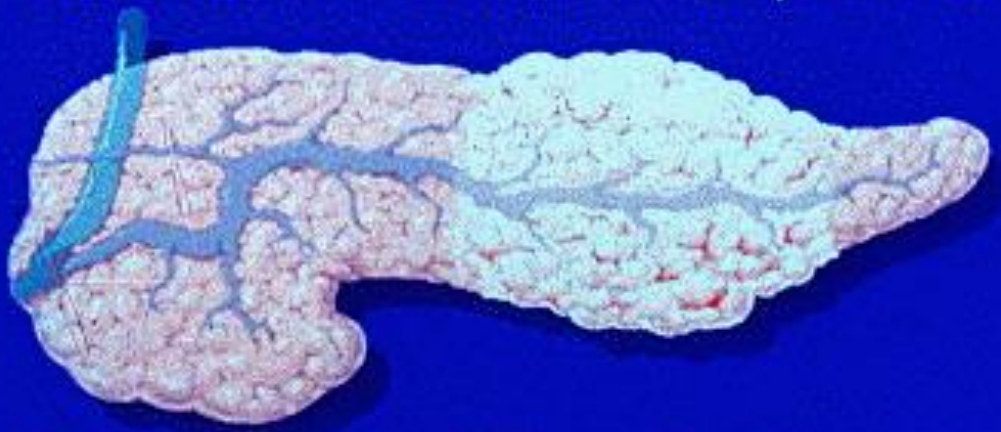
? Tobacco
? Alcohol
? Diet
? Chronic Pancreatitis
? Diabetes

Symptoms of Pancreatic Cancer



→ Jaundice

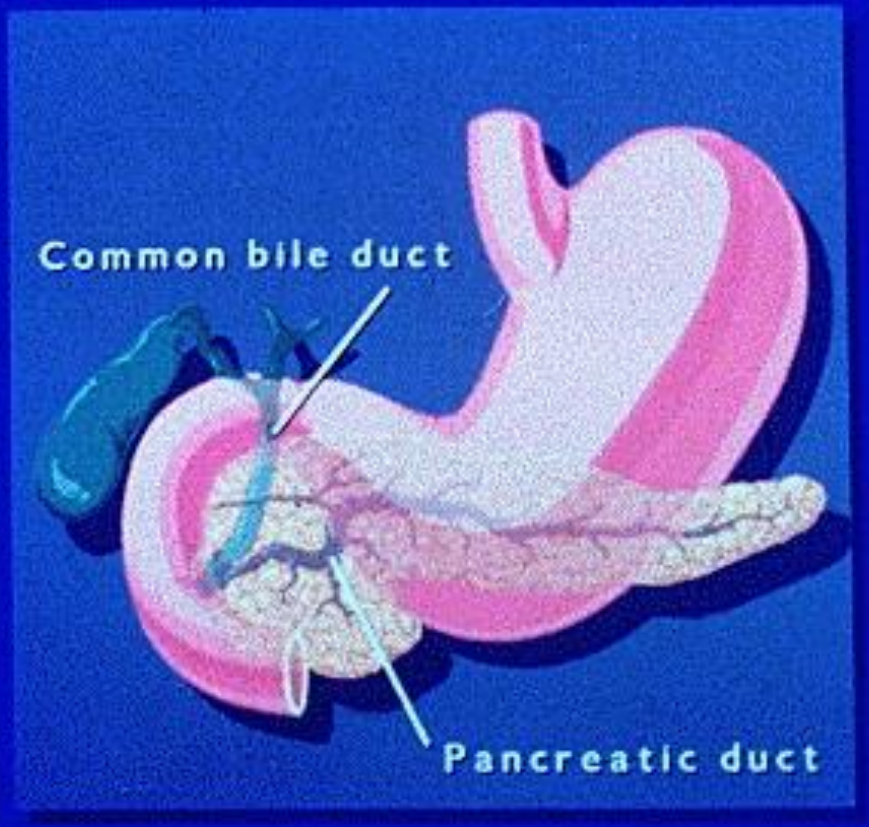
Tumors in the head of the pancreas produce symptoms by obstruction of the bile or pancreatic duct.

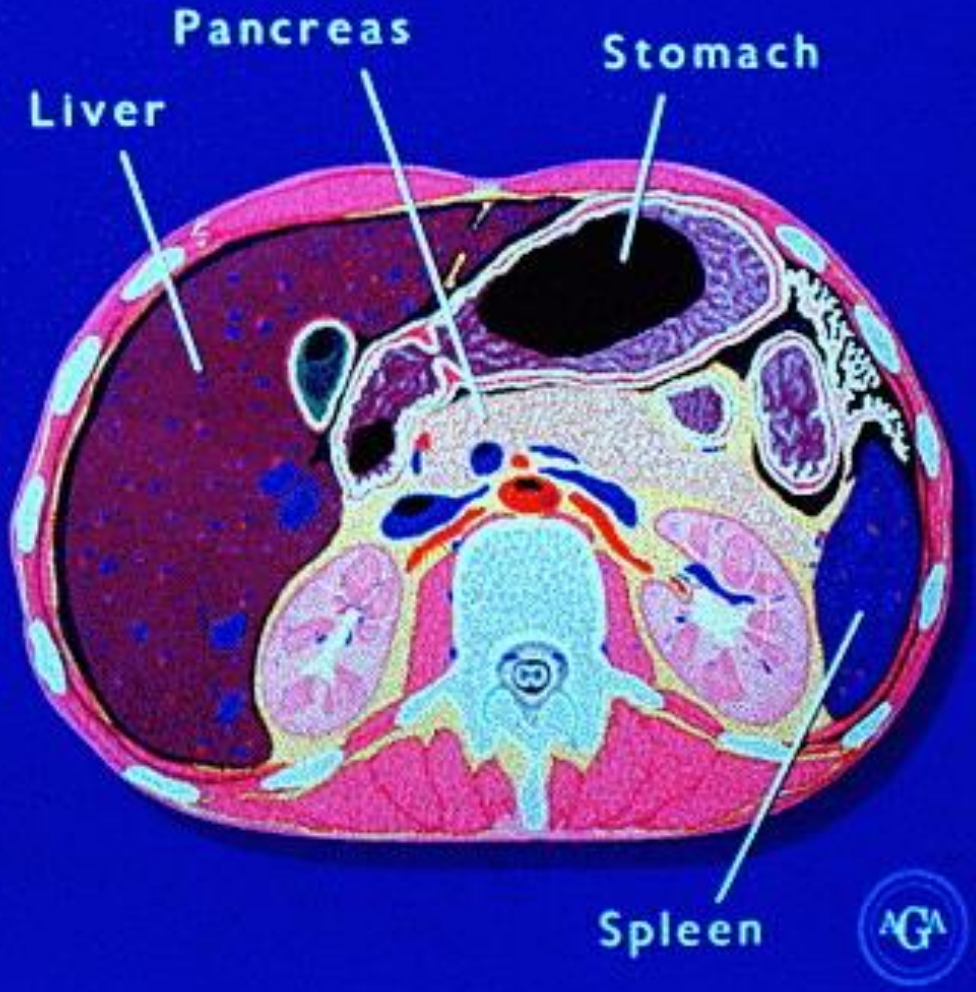


→ Pain
Weight loss

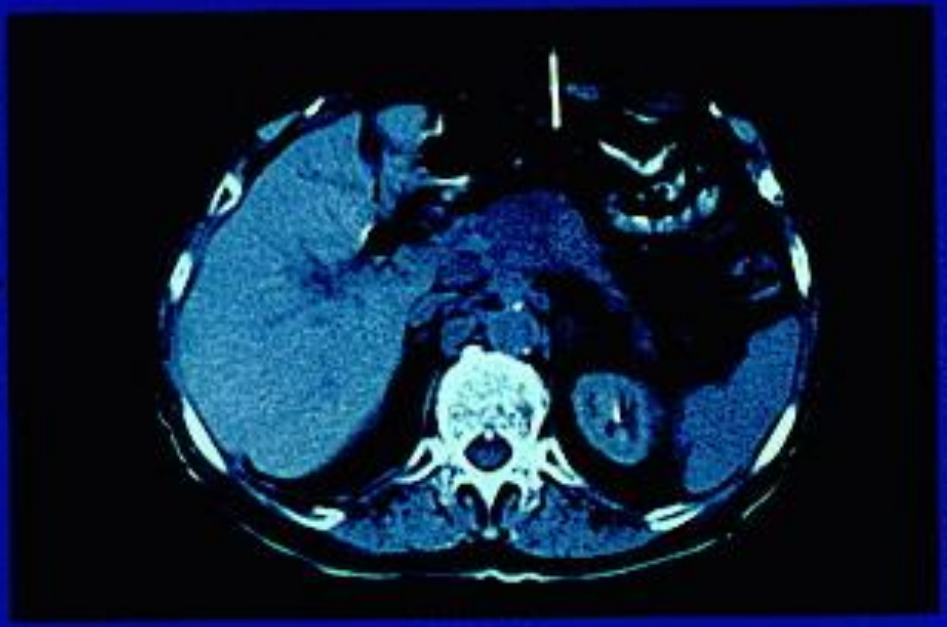
Tumors in the body and tail produce symptoms by local or distant spread.

The Anatomic Location of the Pancreas makes Diagnosis Difficult and Facilitates Early Dissemination

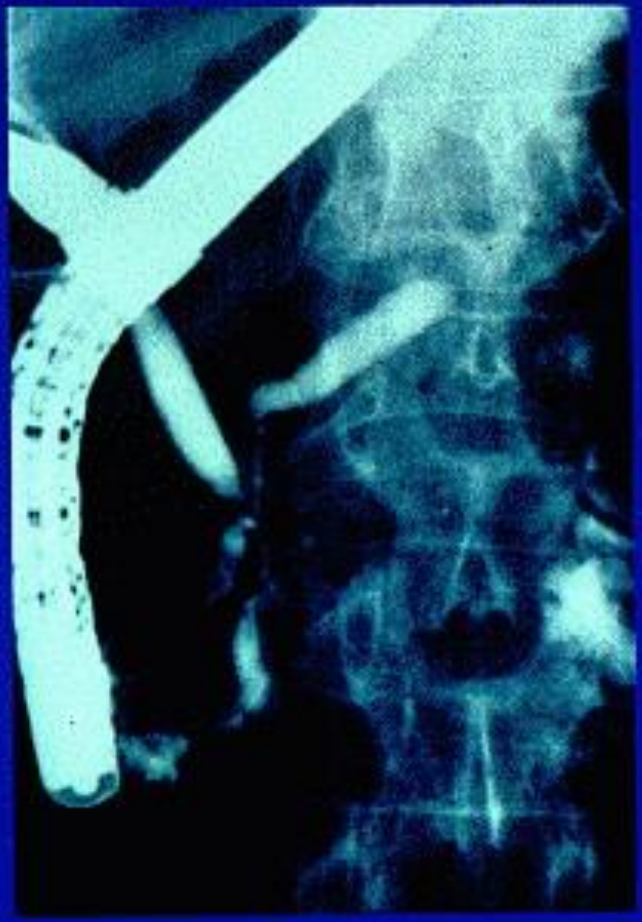




Pancreatic Carcinoma May Be Detected Through a Variety of Diagnostic Modalities

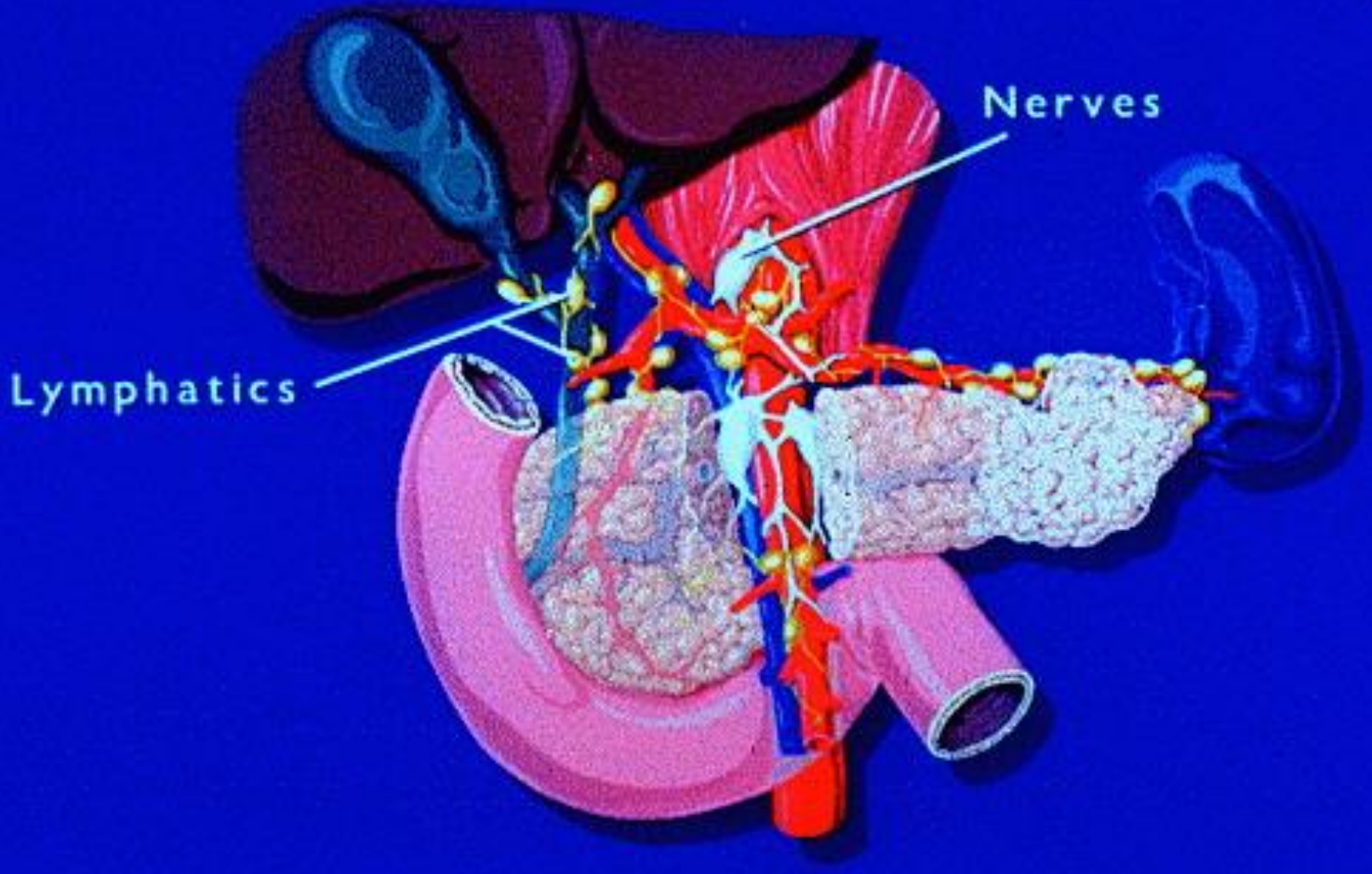


CT

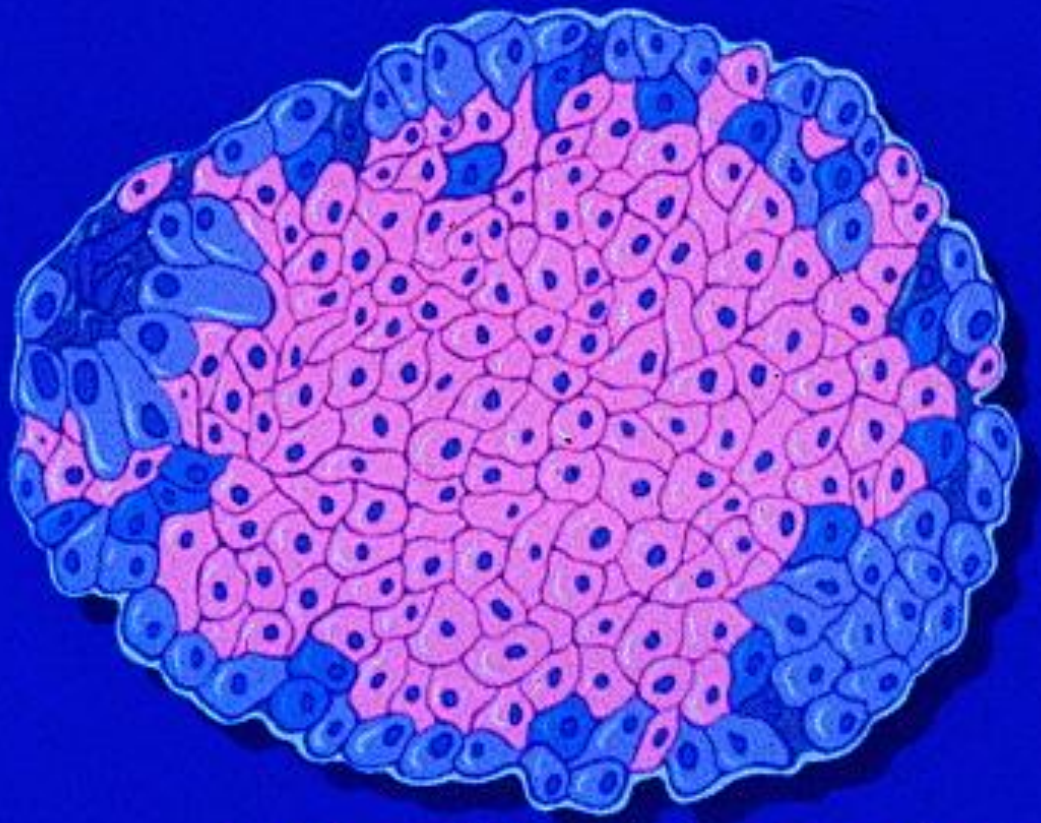


ERCP

Pancreatic Cancer May Spread Through Lymphatic, Hematogenous and Perineural Pathways, but Direct Extension is Most Important



Pancreatic Islet Cell Tumors May Arise From Any Endocrine Producing Cell



- A cells (glucagon)
- D cells (somatostatin)
- B cells (insulin)
- Other (? product)

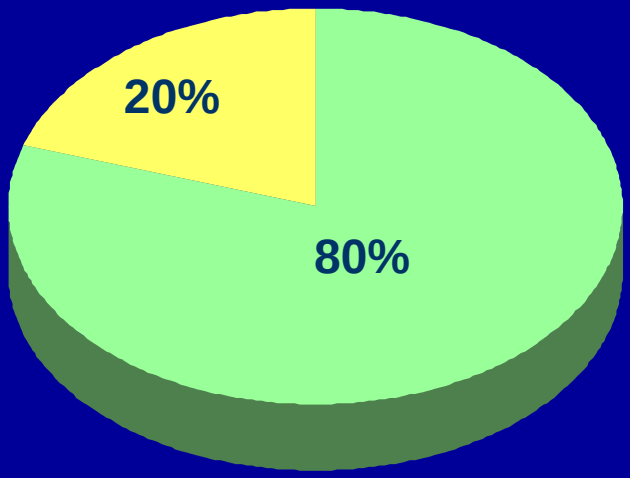
Islet cell tumors are often associated with overproduction of peptide hormones.

Islet Cell Tumors Grow Slowly: Clinical Manifestations Are Often Dominated by Effects of Hormonal Excess

Tumor	Cell Type	Product	Clinical Features
Glucagonoma	α	Glucagon	Diabetes, Rash
Insulinoma	β	Insulin	Hypoglycemia
Somatostatinoma	D	Somatostatin	Diarrhea, Diabetes
Gastrinoma	G	Gastrin	Peptic Ulcer
Vipoma	?	VIP	Watery Diarrhea, Alkalosis
Non-functioning Islet Cell Tumor	?	?	Mass Effects

Hereditary Colorectal Cancers

Cancers with potential inheritable component



Sporadic cancers

- Familial adenomatous polyposis (FAP)
  - APC gene
- Hereditary non-polyposis colorectal cancer (HNPCC)
  - MMR genes: hMSH2, hMLH1, hMSH6, hPMS1, hPMS2

Cruz-Correa M, et al. *Gastroenterol Clin N Am*. 2002;31:537.

Features of FAP

- Caused by germline mutations of the *APC* gene
- Hundreds to thousands of adenomatous polyps
- Near 100% risk of CRC without colectomy
- Mean age at diagnosis of colon cancer is 39 years

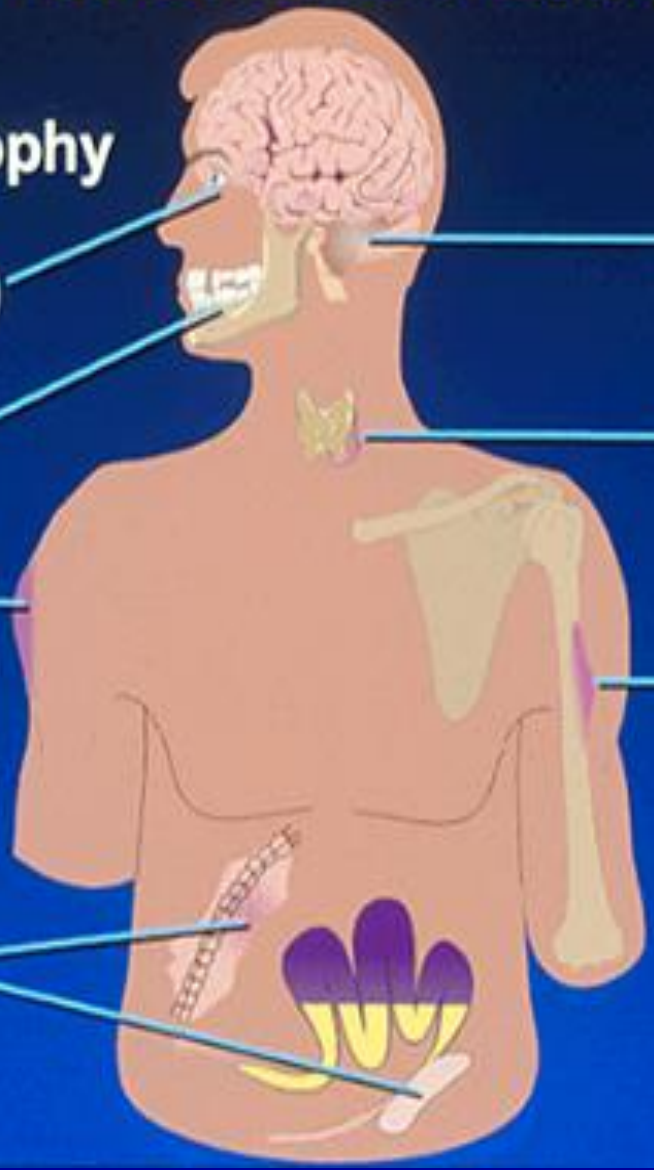
Image courtesy of John R. Minarcik, MD.
Cruz-Correa M, et al. *Gastroenterol Clin N Am.* 2002;31:537.

Familial Adenomatous Polyposis

Gastrointestinal Lesions

Familial Adenomatous Polyposis

Extraintestinal Features



Congenital hypertrophy of retinal pigment epithelium (CHRPE)

Abnormal dentition

Epidermal cysts

Desmoid tumors

Brain tumors

Thyroid tumors

Osteomas

Features of HNPCC

- Caused by a mutation in any 1 of 5 mismatch repair (MMR) genes
- 70%-80% lifetime risk of developing CRC
- Average age at diagnosis of colon cancer is 44 years
- Multiple colon cancers and proximal (right colonic) cancers are more common, compared with cancer in the general population
- Other cancers might occur: eg, genitourinary (endometrial, ovarian, ureter, renal pelvis), gastric, small bowel and pancreatic cancers

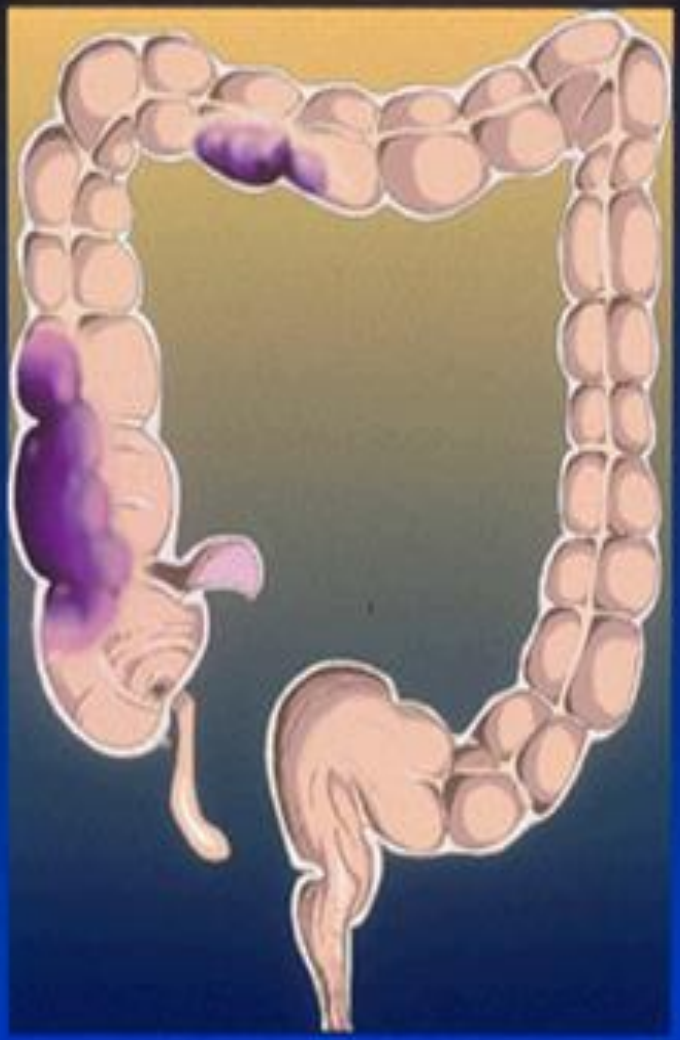
Cruz-Correa M, et al. *Gastroenterol Clin N Am*. 2002;31:537.

Hereditary Nonpolyposis Colorectal Cancer

Early age at onset

Multiple primary cancers

Right colon predominance



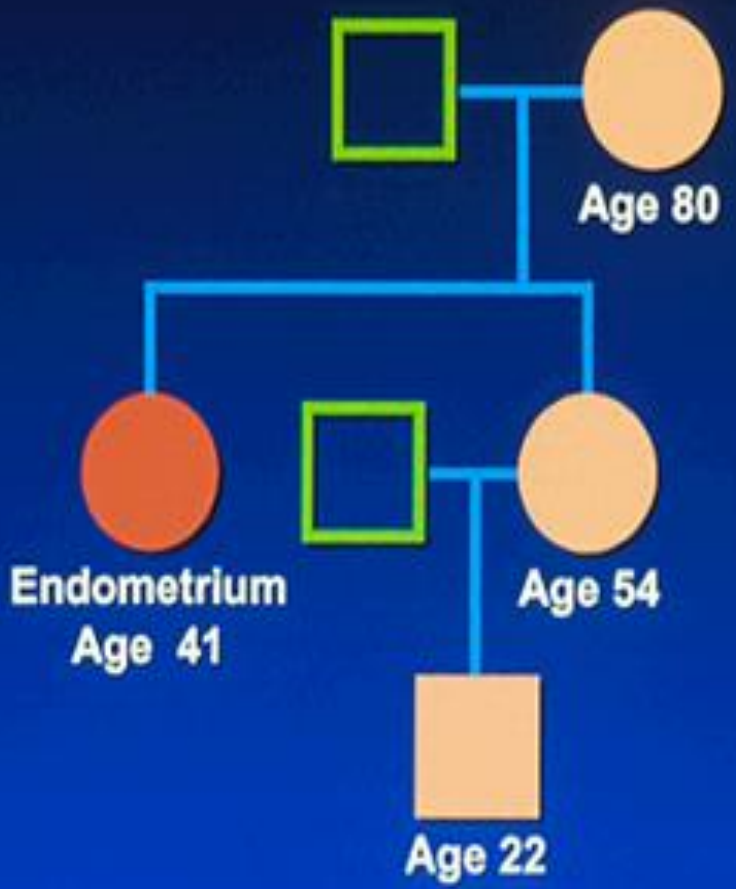
Few or no adenomas

Autosomal dominance

Endometrial cancer

Hereditary Nonpolyposis Colorectal Cancer

Amsterdam Criteria



- Three or more CRC
- Two or more generations
- One case a 1^0 relative of the other two
- One affected age by 50
- FAP excluded

Extracolonic Features of FAP and HNPCC

Extracolonic Cancers in FAP

- Duodenal (5%-11%)
- Pancreatic (2%)
- Thyroid (2%)
- Brain (medulloblastoma) < 1%
- Hepatoblastoma (0.7% of children < 5 years old)

Extracolonic Cancers in HNPCC

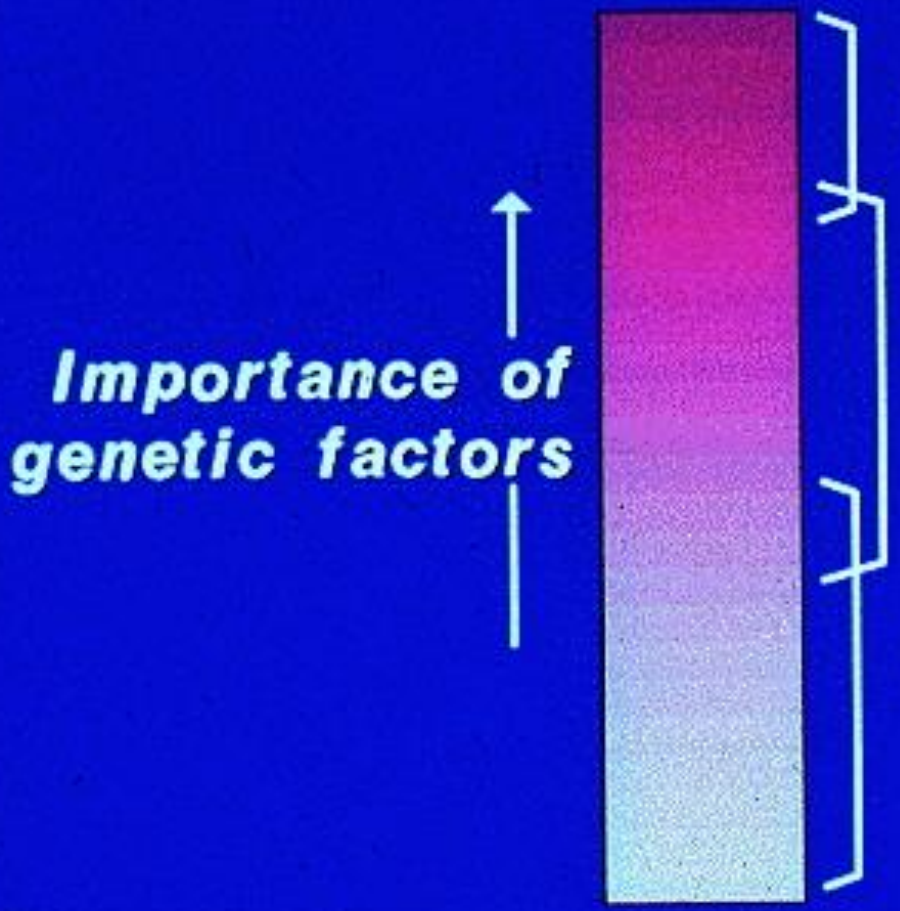
- Stomach (12-19%)
- Ovarian (9%)
- Ureter and renal pelvis (4-10%)
- Biliary tract (2-18%)
- Brain (glioblastoma) (4%)
- Small bowel (1-4%)
- Endometrial (39-60%)

Other lesions

- Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
- Nasopharyngeal angiofibroma
- Osteomas
- Radiopaque jaw lesions
- Supernumerary teeth
- Lipomas, fibromas, epidermoid cysts
- Desmoid tumors
- Gastric adenomas/fundic gland polyps
- Duodenal, jejunal, ileal adenomas
- Café au lait spots
- Sebaceous gland adenomas, carcinomas
- Keratoacanthomas

Adapted from Cruz-Correa M, et al. *Gastroenterol Clin N Am*. 2002;31:537.

The Relative Contribution of Genetic Factors to Colon Cancer is Variable

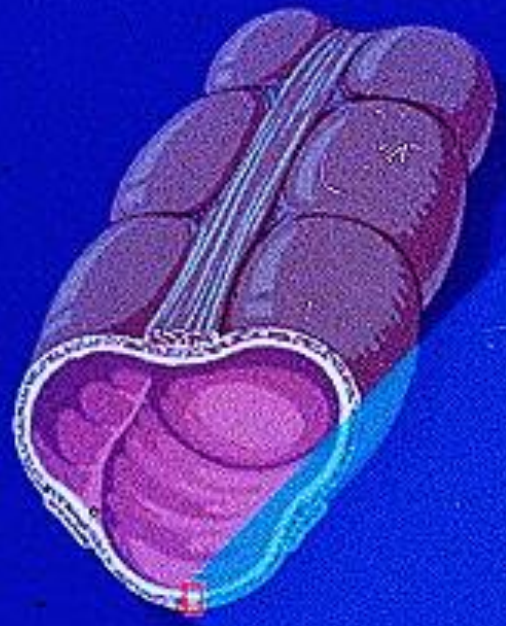


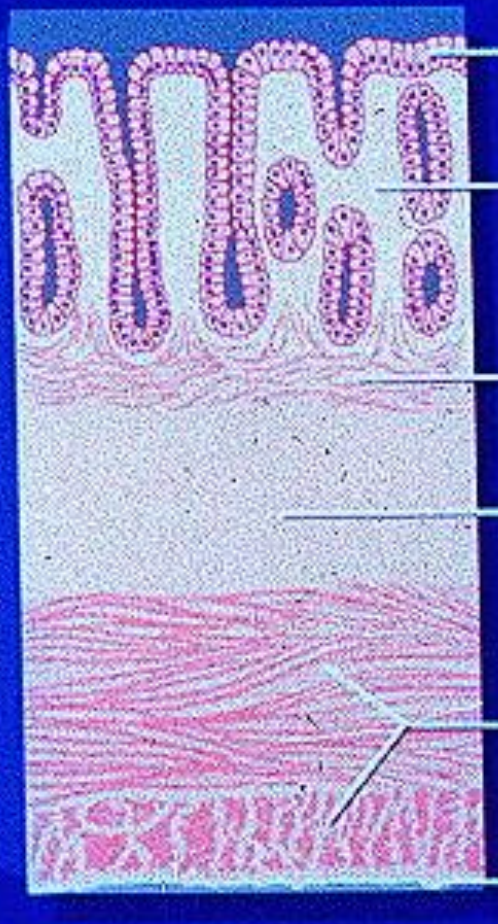
Familial polyposis

High prevalence kindreds
organ specific
organ non-specific

"Sporadic"

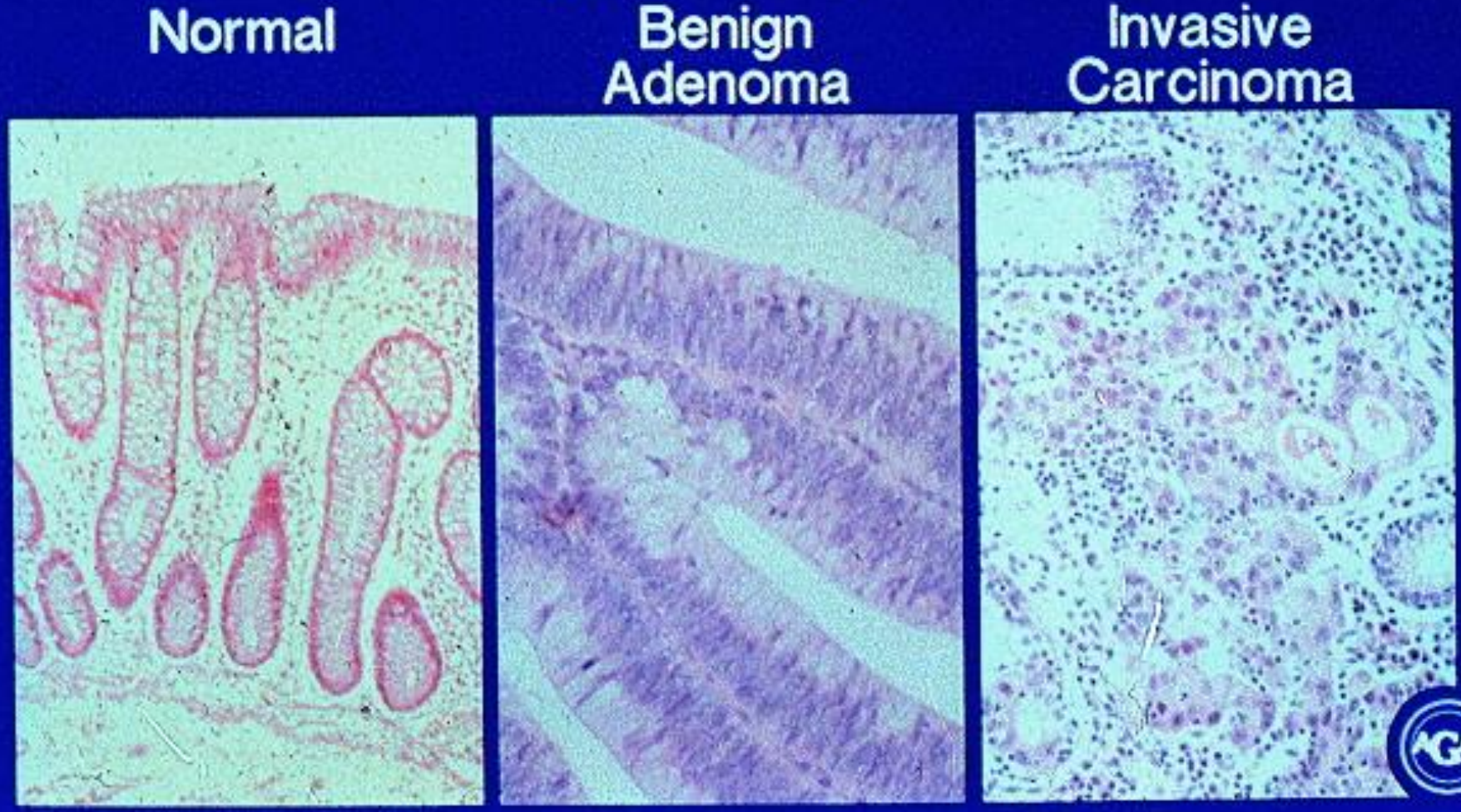
Almost All Colonic Malignancies Arise from Mucosal Epithelial Cells





- Adenocarcinoma >98%
- Sarcoma <1%
- Other 1%

Colonic Mucosa Shows Progressive Architectural Alterations in Transition to Benign and Malignant Neoplasia



Risk Factors for CRC Development

- Age
- Prior personal history of colorectal adenoma or colorectal carcinoma
- Family history of CRC
- Inflammatory bowel disease
- Potential environmental factors
  - High fat and low fiber consumption
  - Beer and ale consumption (especially in rectal cancer)
  - Low dietary selenium
  - Environmental carcinogens and mutagens (from colonic bacteria and charbroiled meats)

Bresalier RS. Chapter 115. In *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 7th ed. 2002:2215.

Diagnostic Modalities for Colorectal Cancer

Test	Advantages	Disadvantages
Digital Rectal Exam	Specific, sensitive	Low compliance, rectum only
Fecal Occult Blood	Simple, inexpensive	Low compliance, specificity and sensitivity limited
Flexible Sigmoidoscopy with Biopsy	Specific, sensitive tissue obtained	Left side only
Air Contrast Barium Enema	Specific, sensitive	Expensive, expertise needed, rectum not well examined
Colonoscopy with Biopsy	Sensitive, specific therapeutic, tissue obtained	Expensive, expertise needed, complications

Colorectal Cancer

Predisposing Conditions

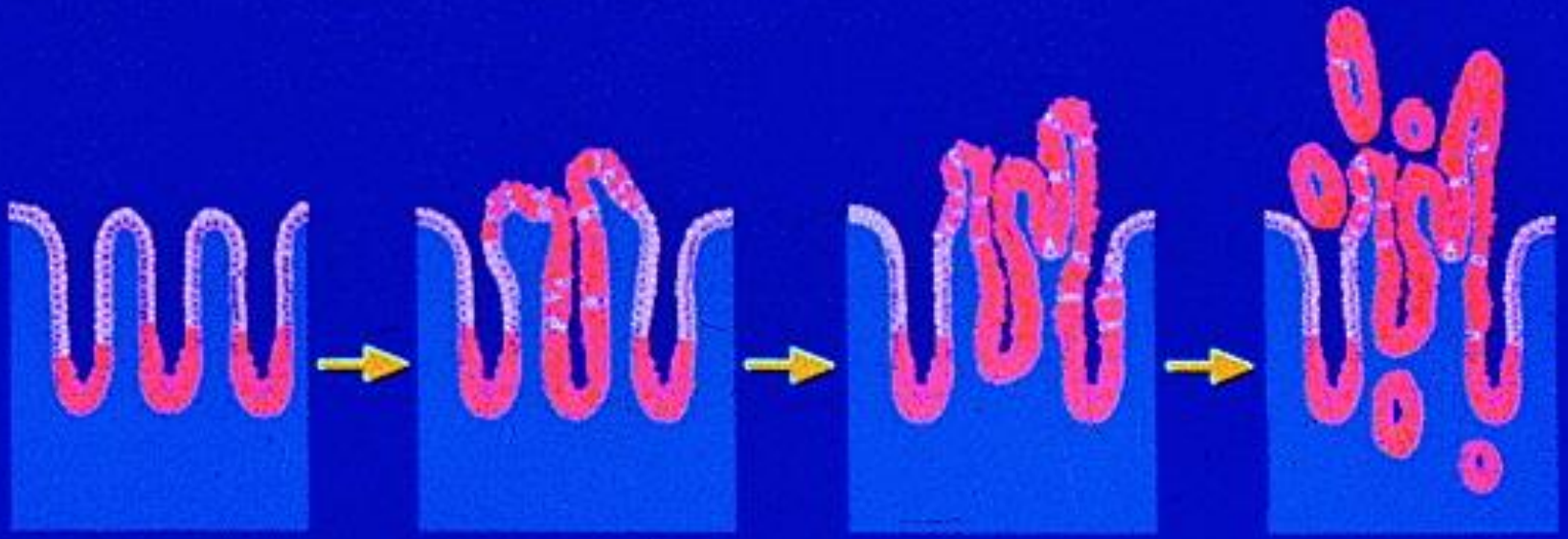
Inflammatory bowel disease

Hereditary nonpolyposis colorectal cancer

Familial adenomatous polyposis

The Adenoma-Carcinoma Hypothesis

Expansion of the Proliferative Compartment Leads to Polyp Formation and Possibly Cancer

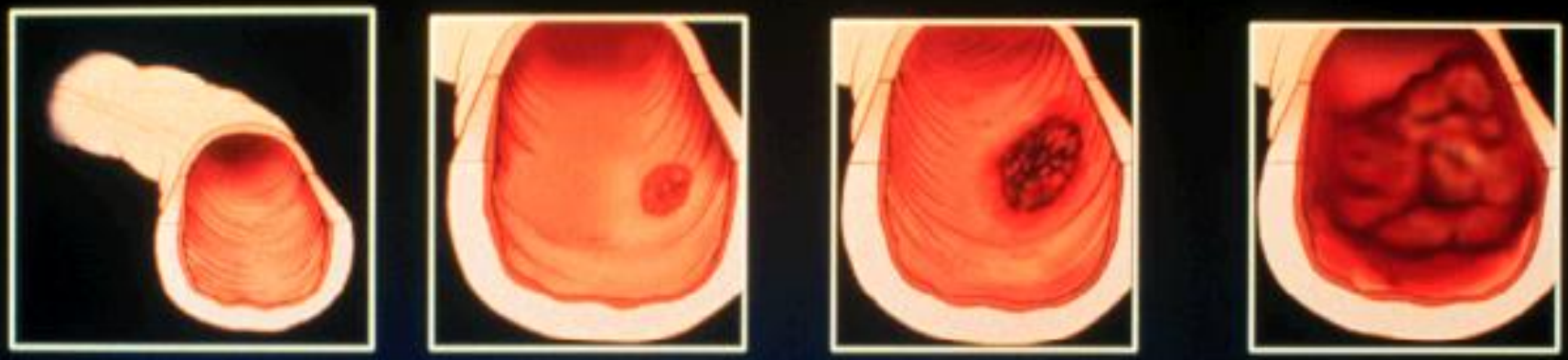


Proliferative zone

But: only 15% polyp → cancer

Colorectal Cancer

Adenoma - Carcinoma Sequence

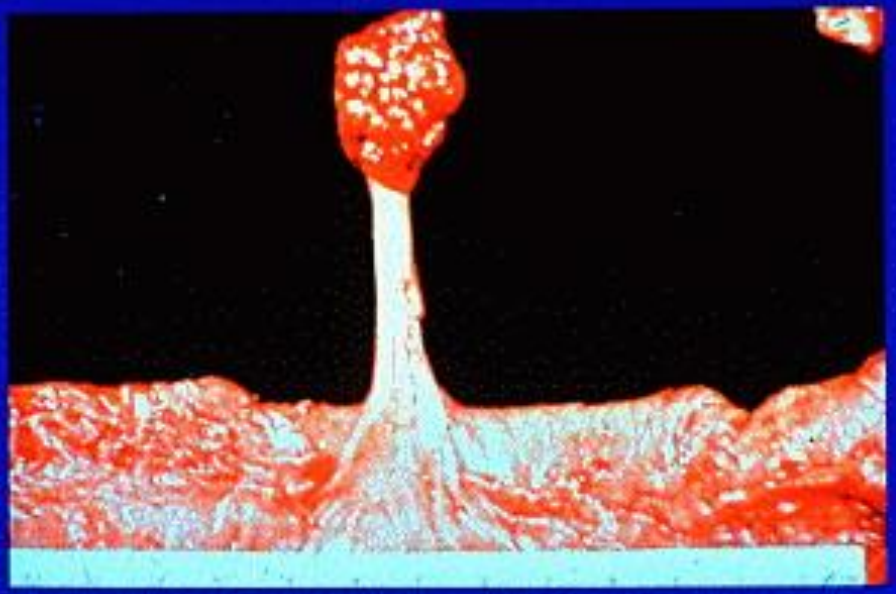


Normal mucosa → Adenoma → Severe dysplasia → Cancer

- Hyperproliferation
- DNA hypomethylation
- Oncogene mutations
- Allelic deletions
- Aneuploidy

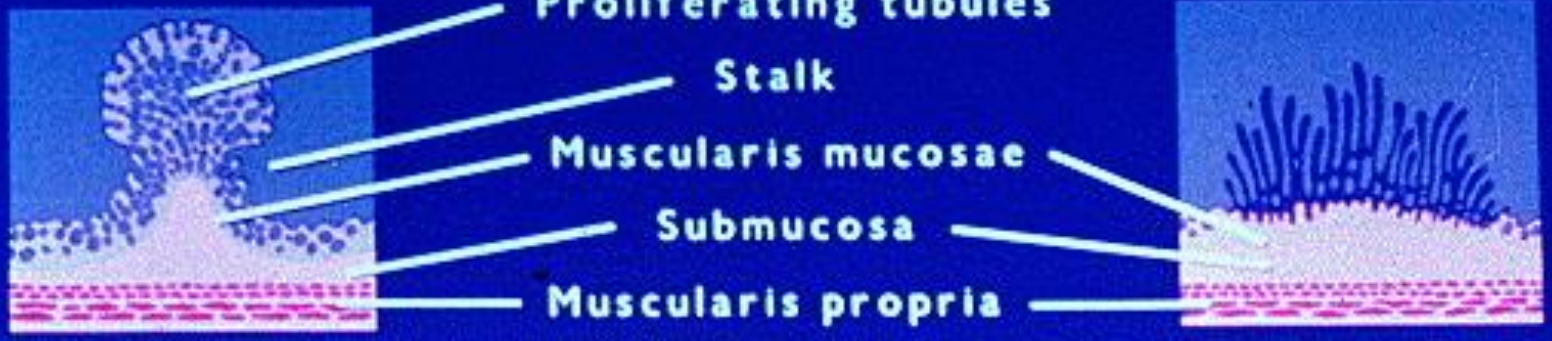
A Polyp is a Visible Protruding Mass Covered with Mucosa

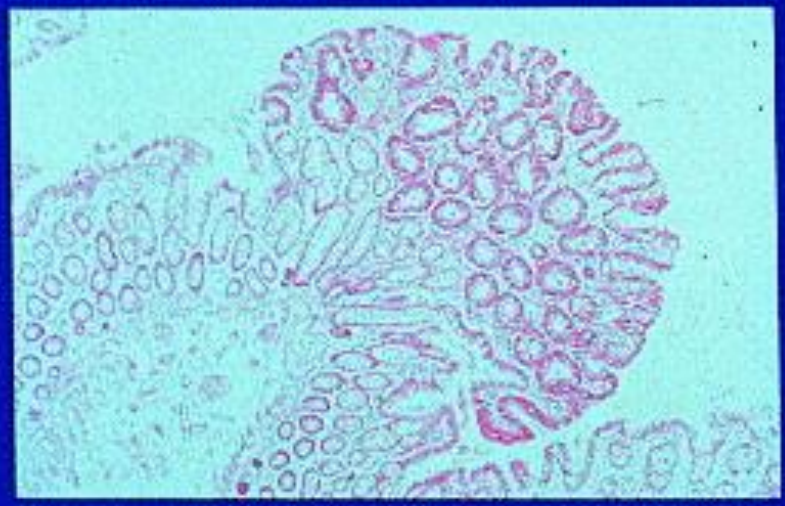
Pedunculated Adenoma



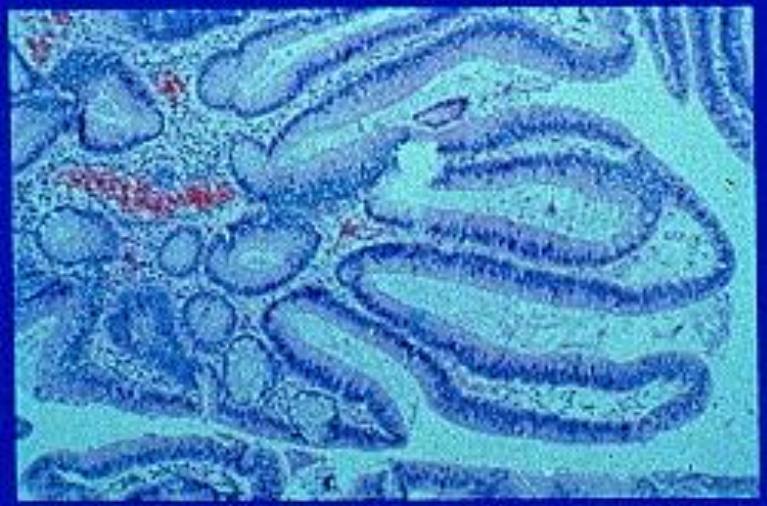
Villous Adenoma

Neoplastic (Adenomatous) Polyps are Subclassified by Histology and Morphology





Tubular Adenoma



Villous Adenoma

Polyps of the Colon and Rectum are Classified Histologically and Differ in Malignant Potential

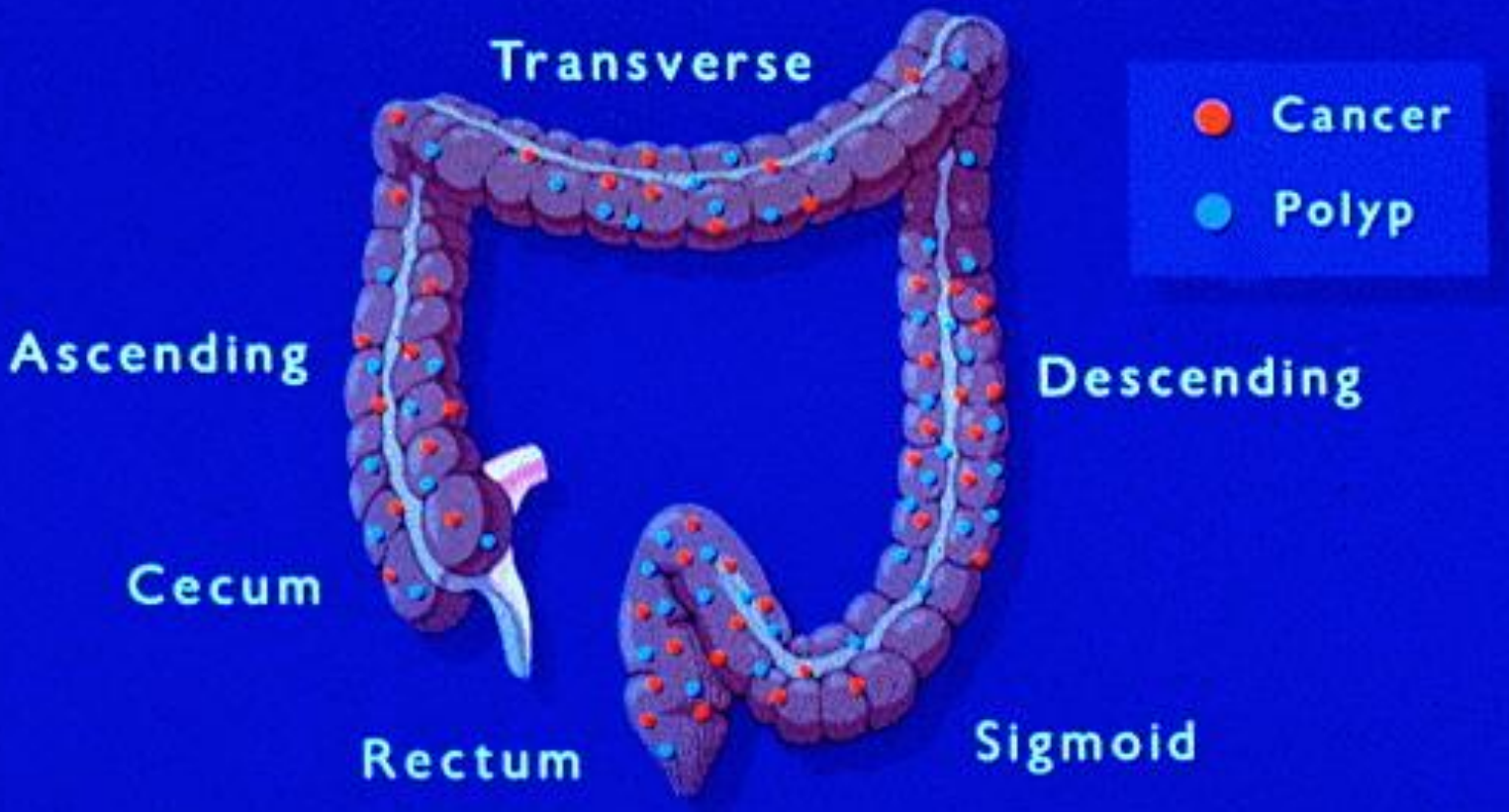
Type	Malignant Potential	Single or Isolated Polyp	Polyposis Syndrome
Neoplastic	+++	Tubular Adenoma Tubulo-Villous Adenoma Villous Adenoma	Familial Adenomatous Polyposis Gardner's Polyposis
Hamartomatous	–*	Juvenile Polyp	Juvenile Polyposis Peutz-Jeghers Syndrome
Inflammatory	–	Benign Lymphoid Polyp Pseudopolyp	Inflammatory Polyposis
Miscellaneous	–*	Hyperplastic Lipoma, Neurofibroma, etc.	Familial Hyperplastic Polyposis Neurofibromatosis

* Except where adenomatous component also present

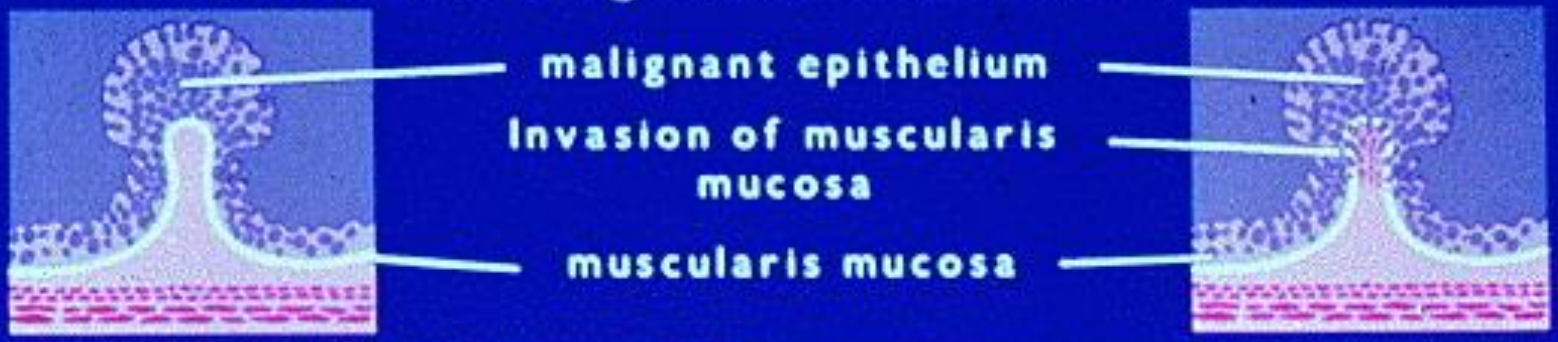
AGA

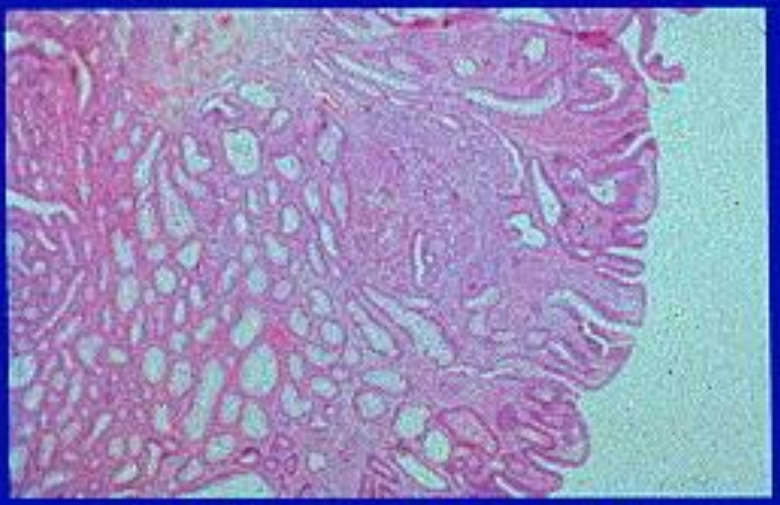
Colorectal Cancer and Polyps have a Similar Anatomical Distribution

Both are More Common in the Left Side of the Colon

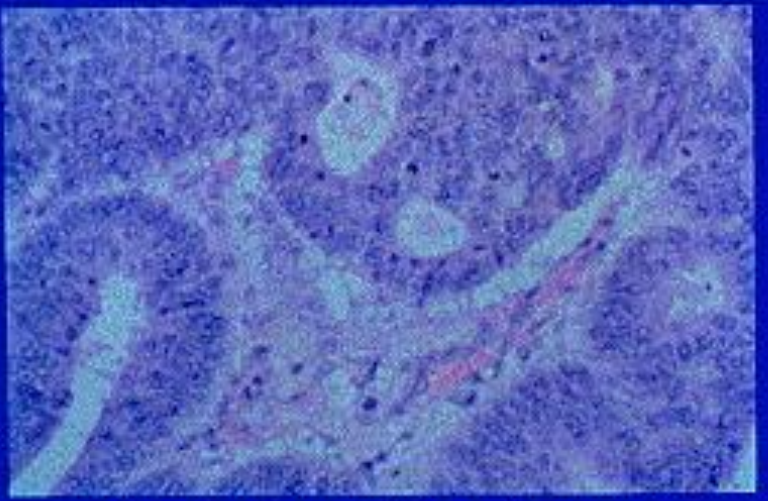


Development of Malignancy in Polyps is Characterized by Cellular Atypia and/or Invasion Through the Muscularis Mucosa





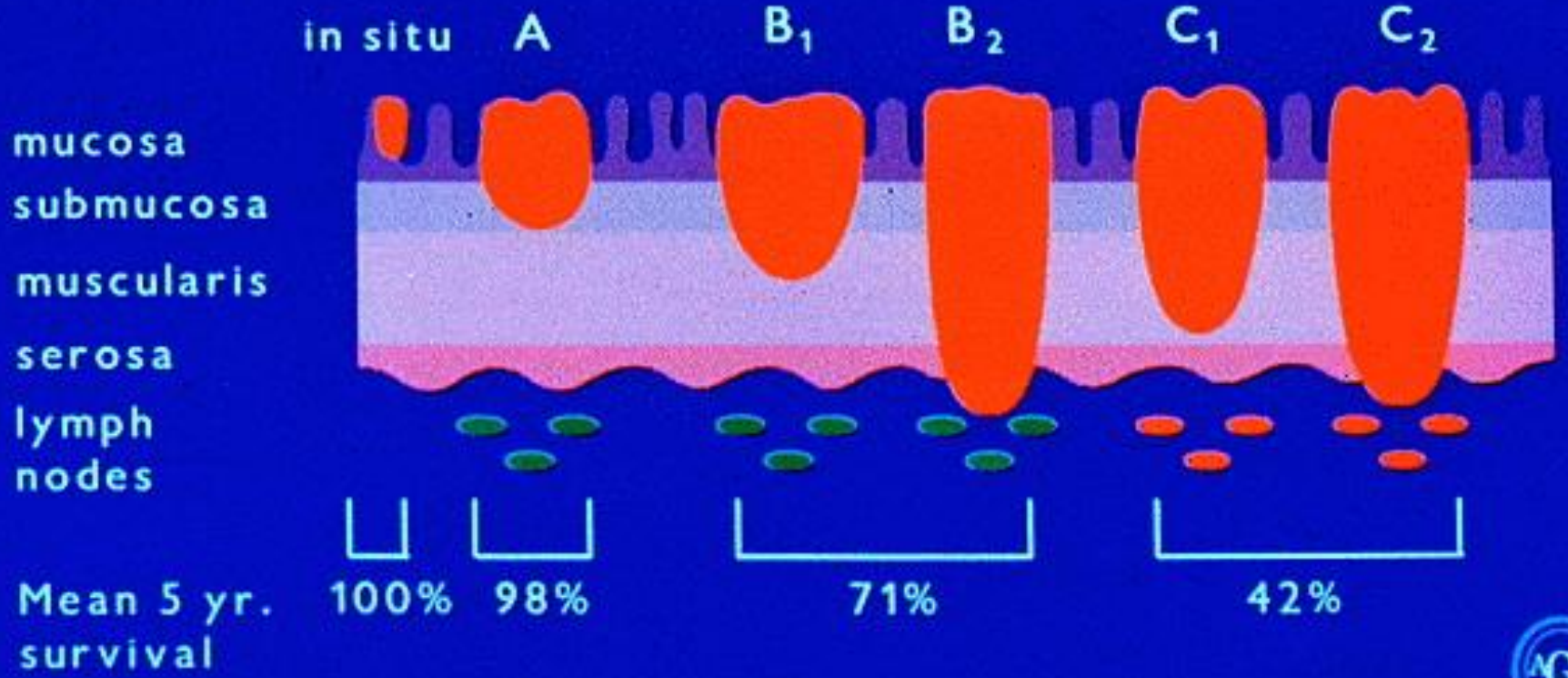
In situ Carcinoma

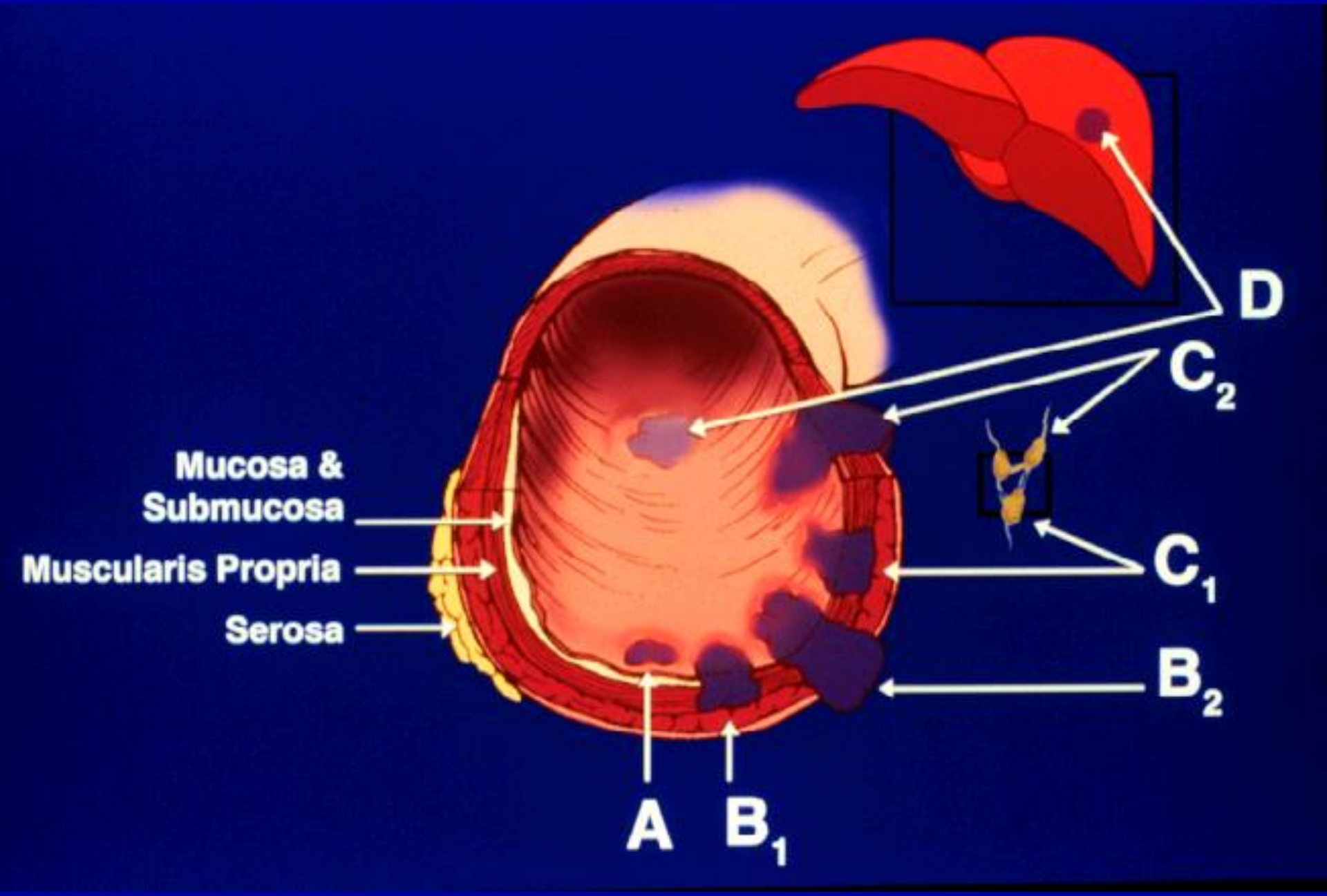


Invasive Carcinoma

Prognosis of Colon Cancer Worsens as Extent of Invasion Increases

Modified Dukes' Classification

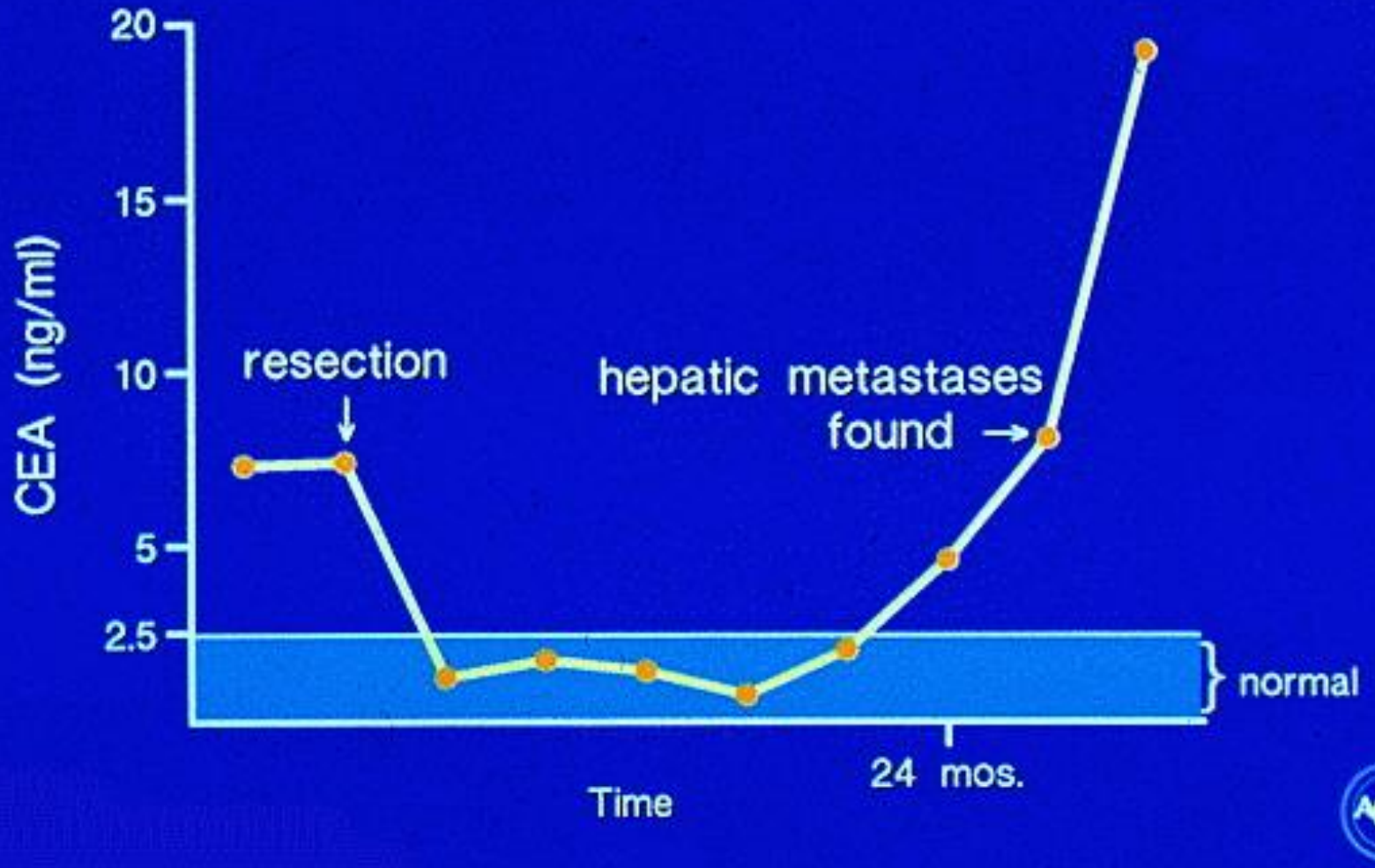



Mucosa &
Submucosa
Muscularis Propria
Serosa
D
C2
C1
B2
A
B1

Colorectal Cancer Staging

	TNM			Modified Dukes
Stage	Tumor	Node	Metastasis	
0	T_{is} (In situ)	N_0	M_0	-
I	T_1 (Submucosa)			A
	T_2 (Muscularis propria)			B_1
II	T_3 (Serosa)			B_2
	T_4 (Adjacent organs)			? B/C/D
III	$T_{1,2}$	N_{1-3}		C_1
	$T_{3,4}$	N_{1-3}		C_2
IV	T_{1-4}	N_{0-3}	M_1	D

CEA, A Serologic Marker, May be Used to Monitor Patients for Recurrence of Colorectal Cancer



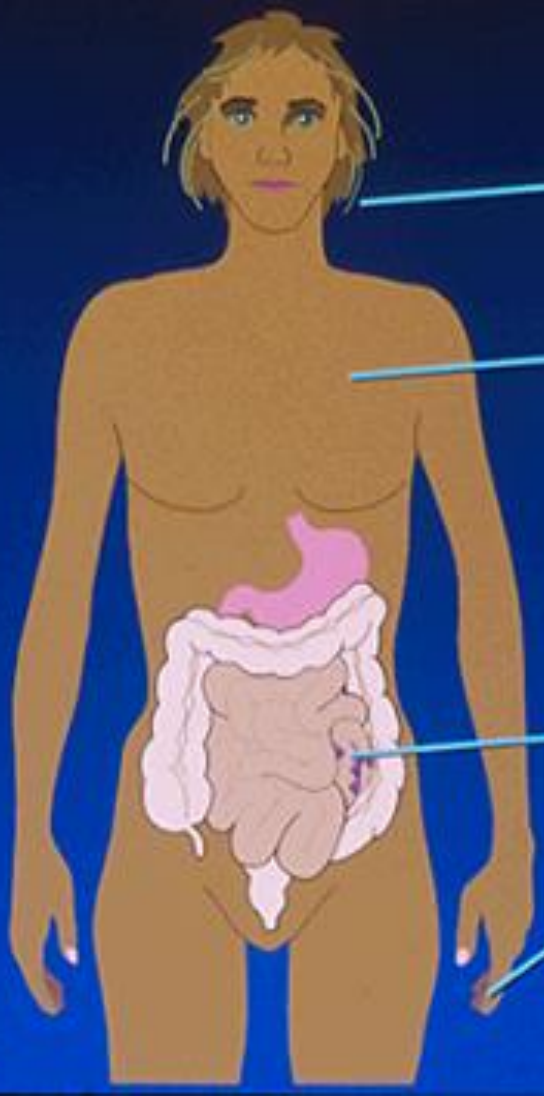
Cronkhite-Canada Syndrome

Symptoms

Weight loss

Abdominal pain

Diarrhea



Findings

Alopecia

Hyperpigmentation

Protein losing enteropathy - malabsorption

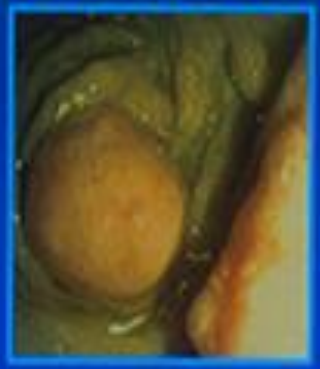
Juvenile polyps

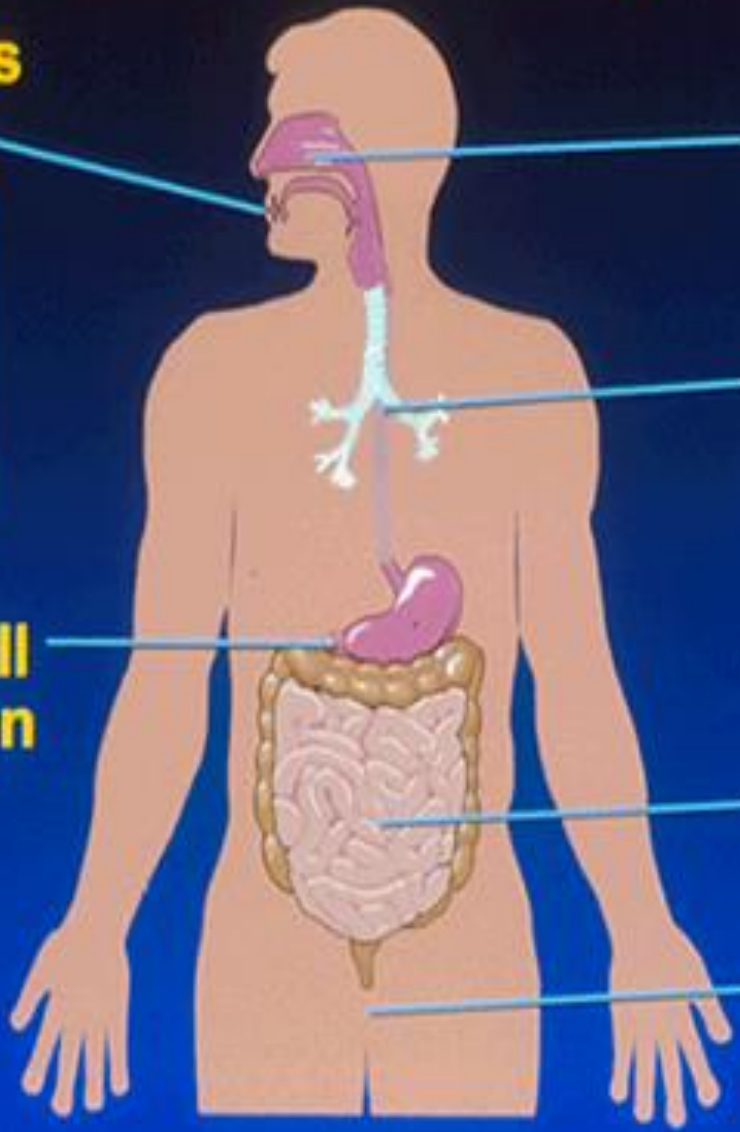
Nail atrophy and dystrophy

Peutz-Jeghers Syndrome

Mucocutaneous pigmentation

Hamartomas stomach, small intestine, colon





Nasal polyps

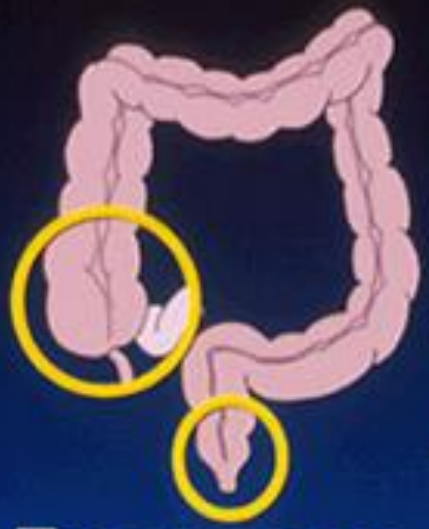
Bronchial polyps

Genetic linkage to Ch19

Carcinoma

Reproductive tract tumors

Carcinoids

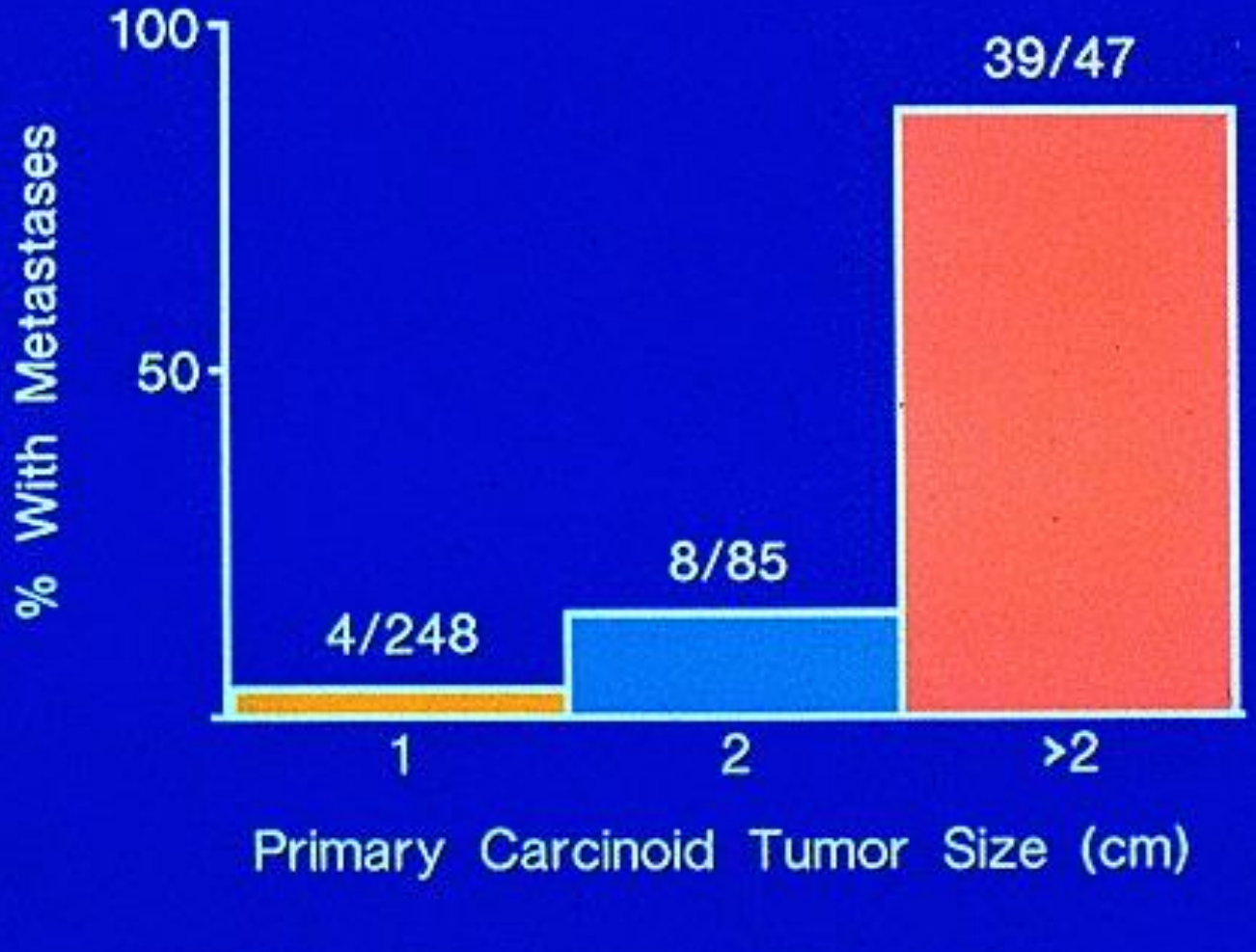


	Appendix	Rectum	Ileum
Frequency	50%	20%	30%
Syndrome	rare	rare	common
Metastasis	rare	rare	80%

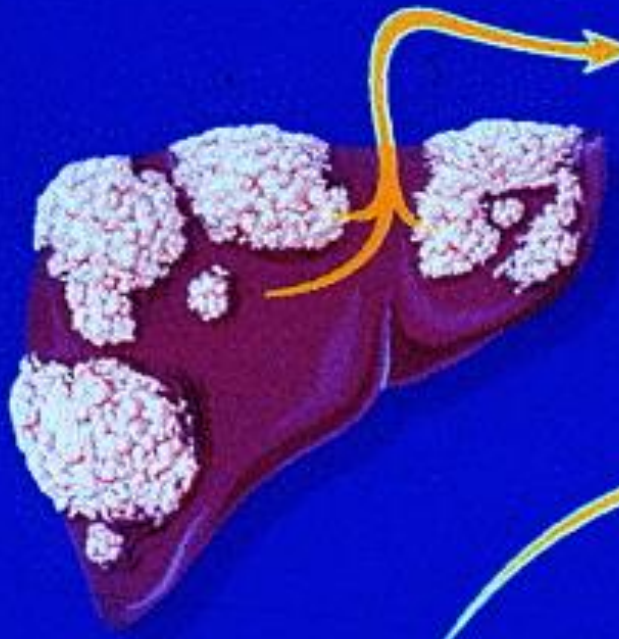
Carcinoid Tumors Arising From Foregut, Midgut and Hindgut Differ in Their Histologic and Secretory Features

	Foregut	Midgut	Hindgut
Granule Properties			
Staining			
Argyrophilic	+	+	–
Argentaffin	–	+	–
Bioamine	5-Hydroxy-tryptophan	Serotonin	None
Flush	Atypical	Typical	None
Carcinoid Syndrome	Atypical	Typical	None

Metastatic Spread Correlates with Size of Primary Carcinoid Tumor



Carcinoid Flush Depends on the Production of Bradykinin



Inactive kallikrein

Activation
Epinephrine
Ethanol
Spontaneous

Active kallikrein

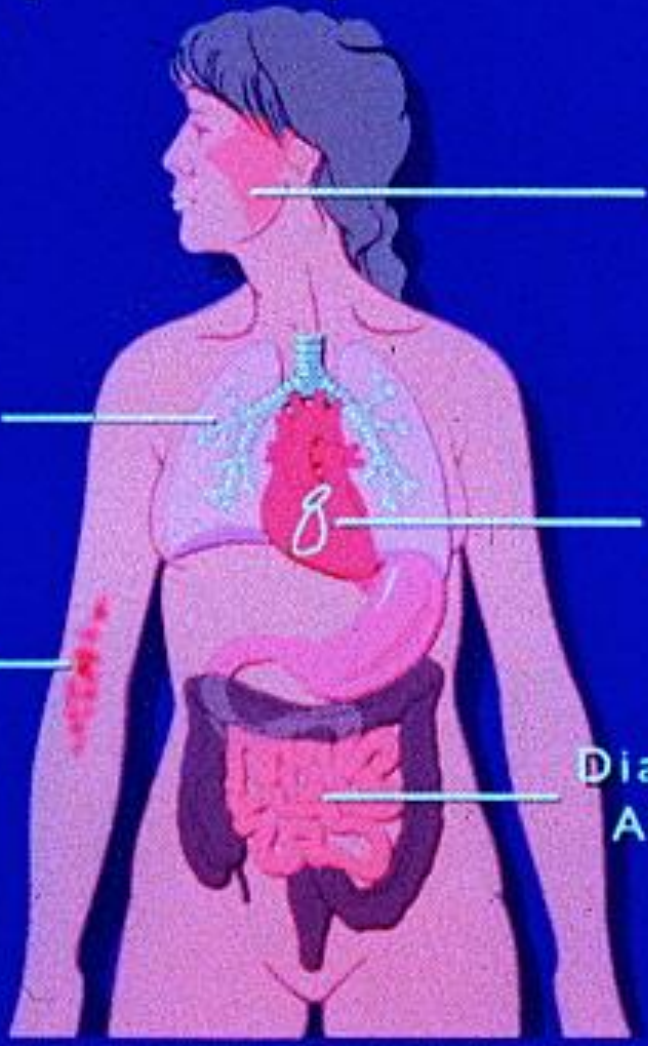
Kininogen
(in plasma)

Lysyl bradykinin

Bradykinin

Vasodilation

Carcinoid Syndrome is Characterized by a Variety of Symptoms and Signs



Paroxysmal Flush (95%)

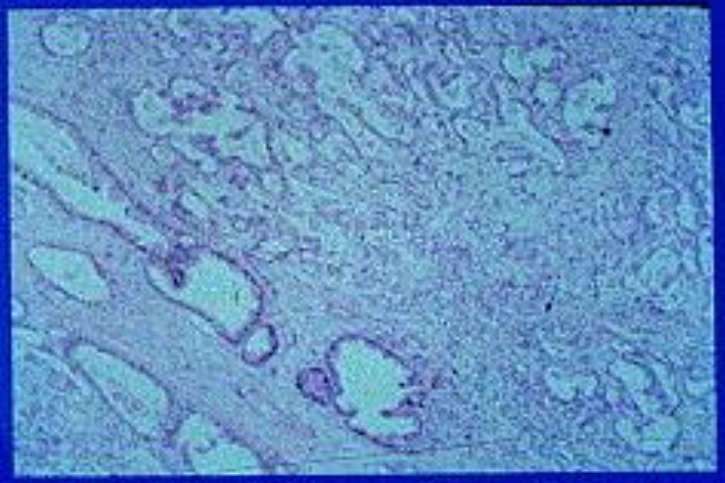
Wheezing (20%)

Valvular heart disease (60%)

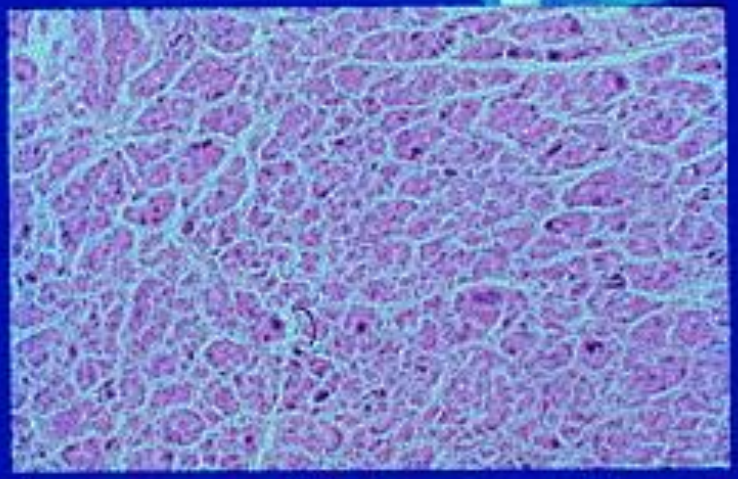
Dermatitis (5%)

Diarrhea/malabsorption
Abdominal pain (75%)

Tumors of the Liver May Arise from Hepatocytes (most common) or the Biliary Epithelium

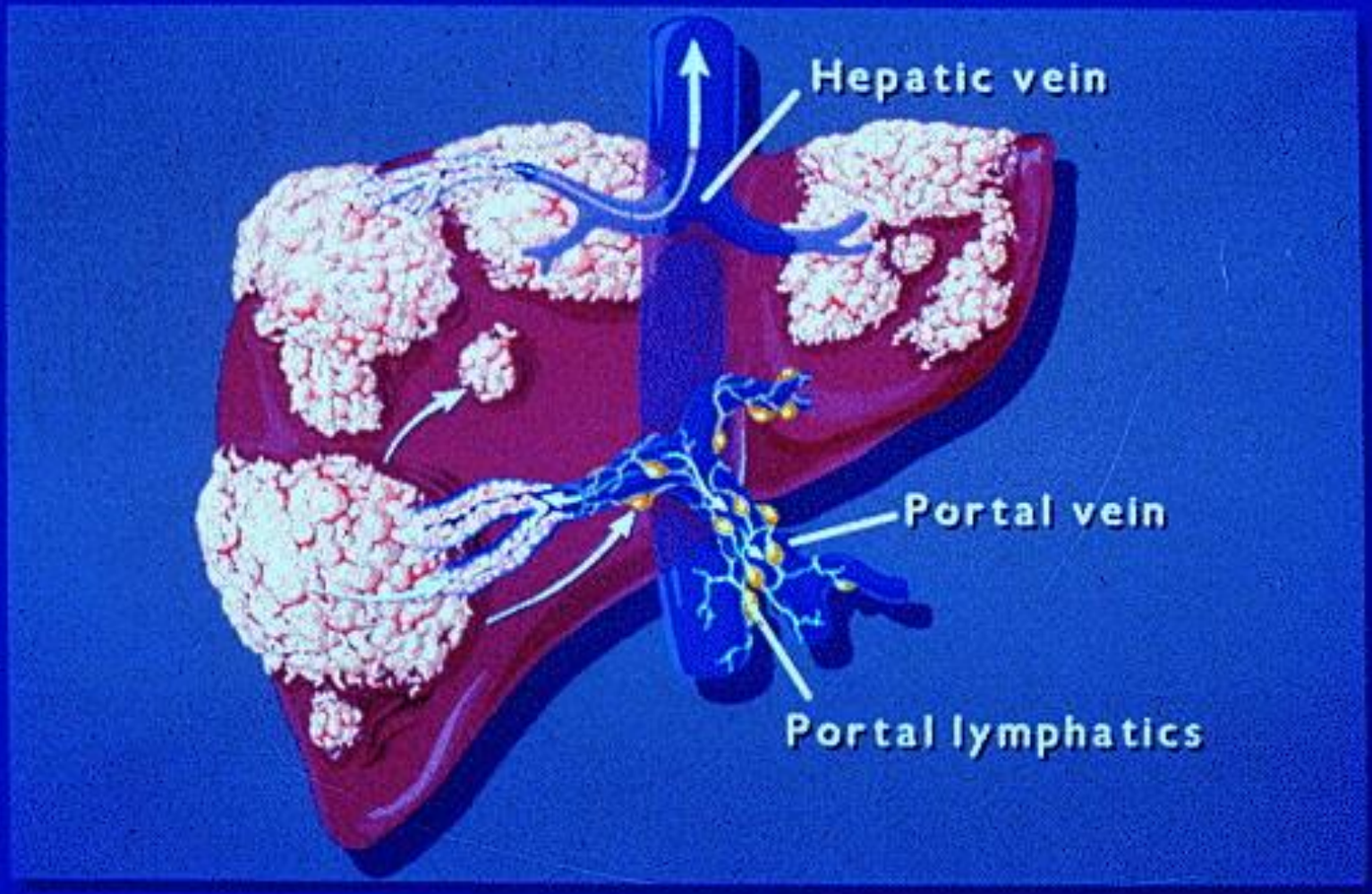


Cholangiocarcinoma



Hepatocellular carcinoma

Hepatocellular Carcinoma Spreads Through a Variety of Routes



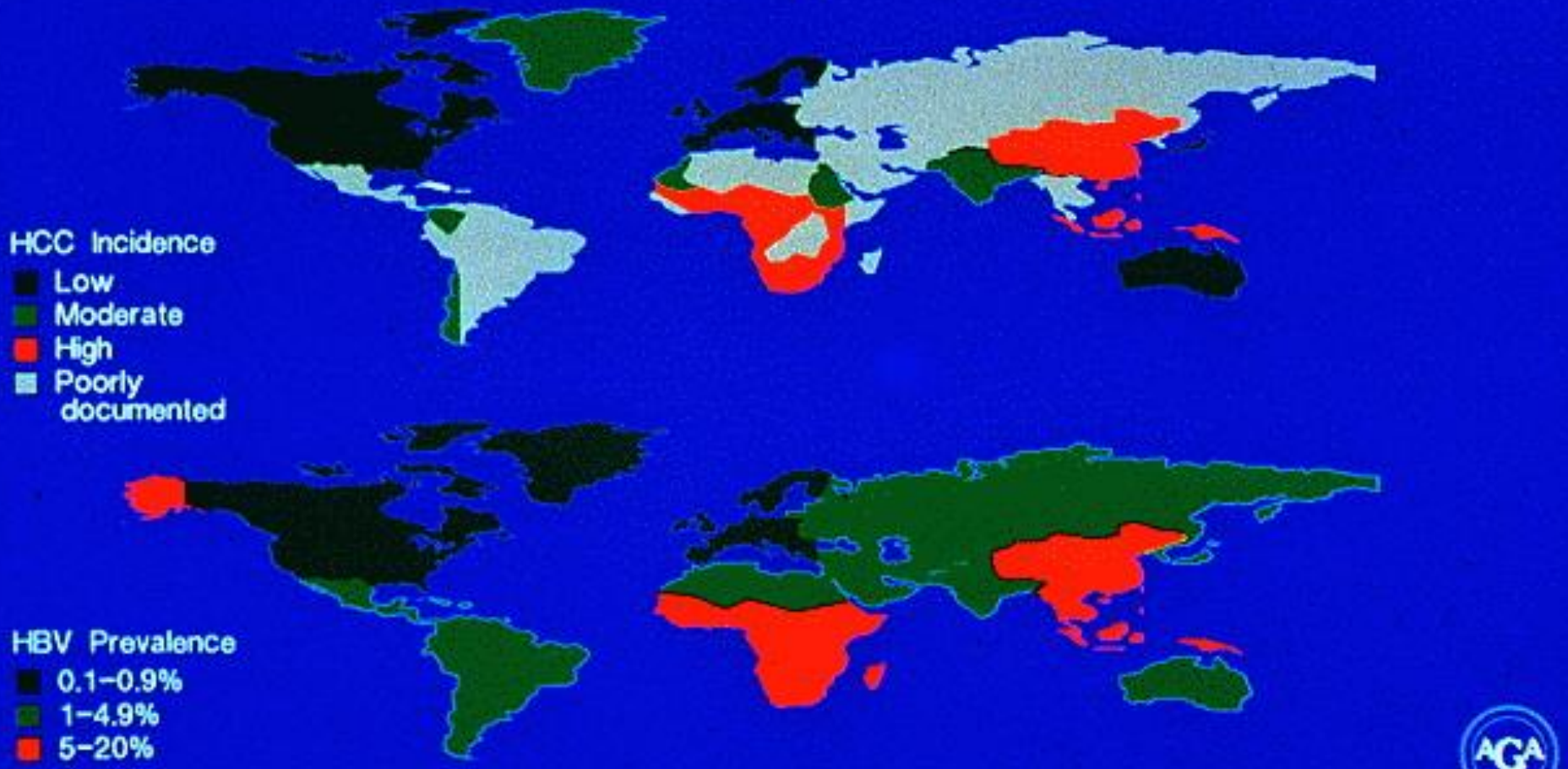
Hepatocellular Carcinoma (HCC) Usually Arises in a Cirrhotic Liver

Risk Factors for HCC:

- Alcoholic Cirrhosis
- Post-viral Cirrhosis
- Hemachromatosis
- Cryptogenic Cirrhosis
- α1 Antitrypsin Deficiency
- Schistosomiasis
- Other

→ ? ↑ Regeneration → ↑ Risk

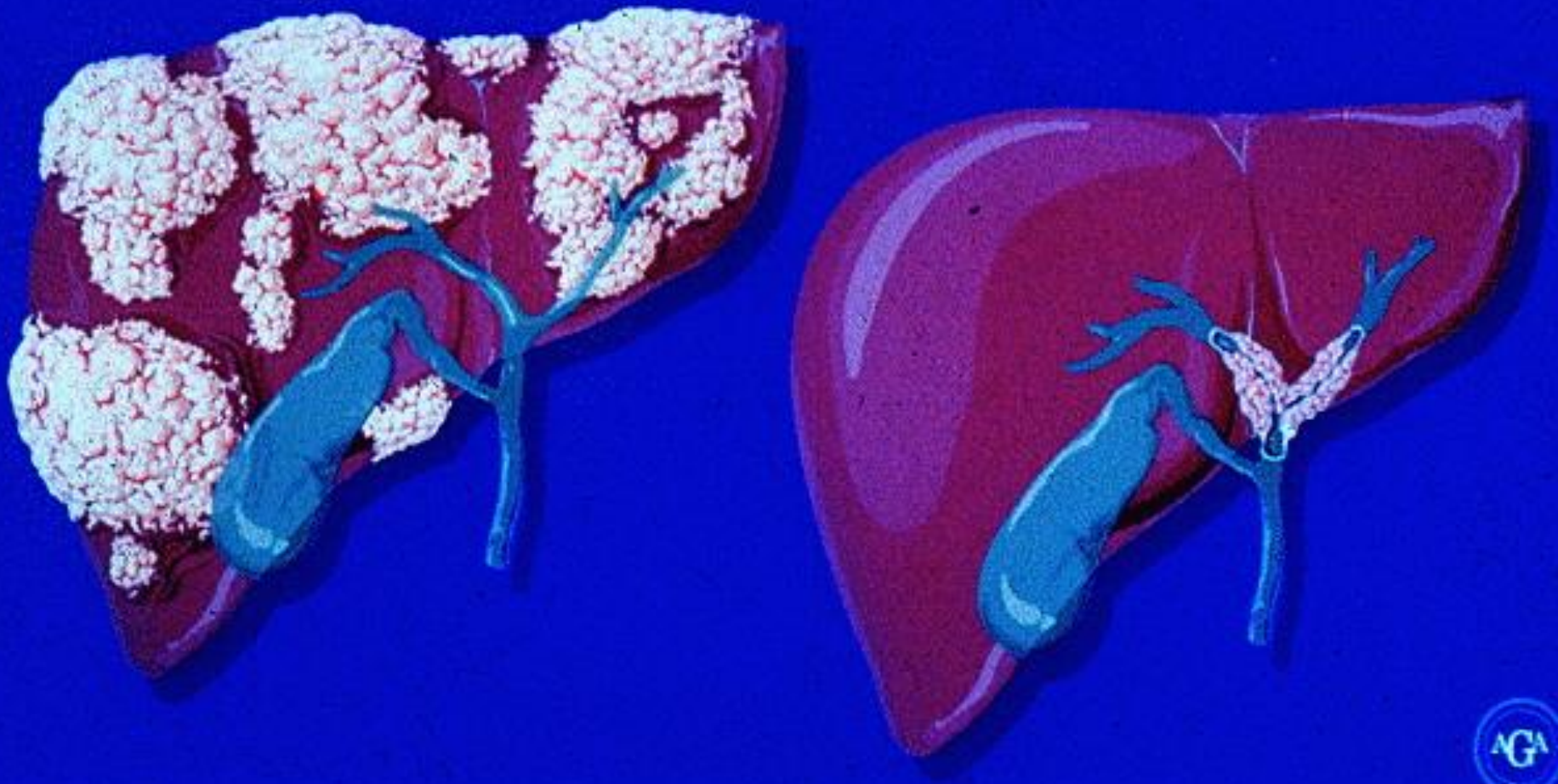
Incidence of Hepatocellular Carcinoma Varies Widely But is Correlated with the Prevalence of Infection with Hepatitis B Virus



Various Liver Tumors Have Been Associated with Exposure to Many Compounds

	HCC	Sarcoma	Cholangio-carcinoma
Aflatoxin	+		
Plant Alkaloids	+		
Sex Steroids		+	
Thorotrast	+	+	+
Methotrexate	+		
Arsenic	+		
PVP	+		
$CuSO_4$		+	
Vinyl Chloride		+	

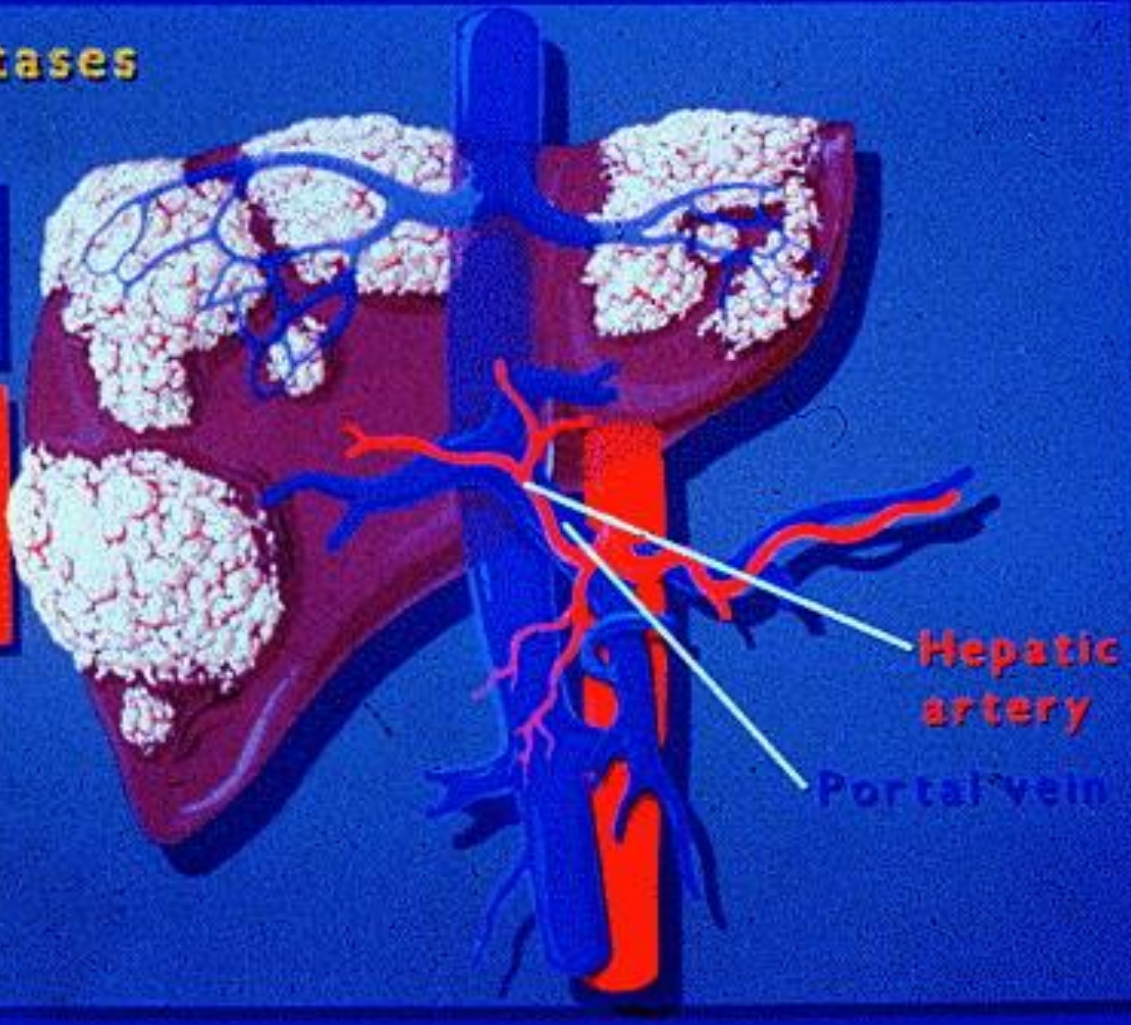
Metastatic Cancer May Cause Jaundice by Massive Replacement of Liver Tissue or Obstruction of Bile Ducts



The Liver is a Frequent Site of Metastatic Cancer Spread by Vascular Routes

Hepatic metastases come from:

Colon	20%
Pancreas	20%
Stomach	14%
Breast	12%
Lung	8%
Unknown primary	8%



Anal Cancer

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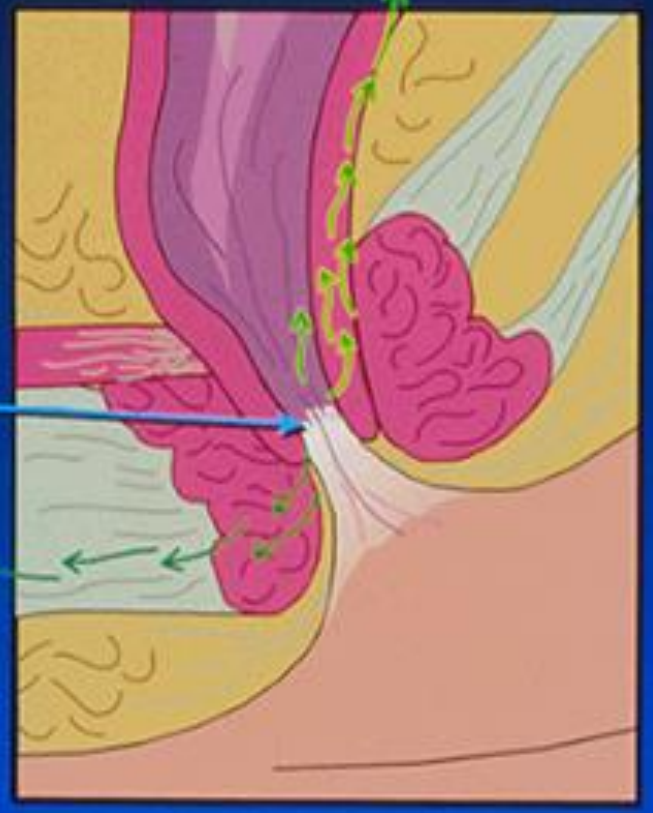
- Epidermoid predominates
- Papilloma virus
- Poor hygiene



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