The exocrine Pancreas (P)

The exocrine P composed of:

(I) Acinar cells	(II) Ductules & ducts
that produce enzymes, mostly as an inert proenzymes forms (e.g. trypsinogen); {amylase & lipase are exceptions & are secreted in an active form} & store proenzymes in membrane-bound zymogen granules.	that transport & convey enzymes to the duodenum. The proenzymes remain largely inactive until they reach the duodenum; there, enteropeptidase (a brushborder enzyme) cleaves trypsinogen into active trypsin.
→ When acinar cells are stimulated to secrete, the zymogen granules fuse with the apical plasma membrane & release their contents into the central acinar lumen.	→ Activated trypsin then functions to catalyze the cleavage of the other proenzymes.

**Surgical rule:→ Don't mess around with the pancreas.

CONGENITAL ANOMALIES

●Agenesis: totally absent P, very rare.

●Pancreatic divisum:

***is the most common clinically significant congenital P anomaly { incidence of 3%-10%}.**

***It occurs when the fetal duct systems of the P primordia fail to fuse.**

*As a result, the main P duct (Wirsung) is very short & drains only a small portion of the head of the P,

*while the bulk of the P drains through the minor sphincter.

***This predisposes such individuals to chronic pancreatitis.**

●Annular Pancreas:

***uncommon variant** of P fusion

*the outcome is a ring of pancreatic tissue that completely encircles the duodenum >>> cause duodenal obstruction.

●Congenital cysts:

**result from abnormal duct development.

**Cysts

*range from mm to 5 cm in ∅,

*lack a cell lining or lined by duct cuboidal epithelium

* enclosed in a thin fibrous capsule.

**In polycystic disease, the kidney, liver, & P can all contain cysts.

:/ Rule:

unilocular P cysts	multilocular P cysts
tend to be benign	are more often neoplastic & possibly malignant.

●Ectopic Pancreas:

**Abnormally situated, or ectopic, P tissue occurs in 2% of the population

**favored sites are the stomach & duodenum, followed by the jejunum, Meckel diverticulum, & ileum.

**Typically small (mms to cms in ∅) & are located in the submucosa; they are composed of normal P acini with occasional islets.

**Although incidental & asymptomatic, ectopic P can cause:

► pain from localized inflammation,

or rarely

► mucosal bleeding,

even more rarely an

►intussusception (Personal 2 cases),

► 2% of islet cell T arises in ectopic P tissue.

Pancreatitis = inflammation of the pancreas

• By definition, in acute pancreatitis the P can return to normal if the underlying cause of inflammation is removed.

•In contrast, chronic pancreatitis is defined by the presence of irreversible destruction of exocrine P parenchyma.

Acute Pancreatitis (Ac P)

• Ac P is an acute autodigestion of the P substance by inappropriately activated P enzymes.

•It ranges from

1-mild, self-limited disease

2- to a life-threatening

• Ac P is a group of reversible lesions characterized by inflammation; ranging from:

1- focal edema & fat necrosis

2- to widespread parenchymal necrosis with severe hemorrhage.

• Ac P is relatively common, with an annual incidence in industrialized world of 100 to 200 cases/million people.

Etiologic Factors in Ac P:

• 80% of cases are attributable to either :			10% to 20%
(I)**Biliary tract disease**	(2) Alcoholism; excessive alcohol intake as a cause of Ac P varies		are idiopathic with no identifiable cause
(GS are implicated in 35% to 60% of cases, & about 5% of patients with GS develop Ac P)	from 65% of cases in the US	5% or less in the UK	

Other causes of Ac P are:

Causes	Example
Trauma, both blunt force & Iatrogenic injury	(Perioperative or Endoscopic procedures with dye injection).
● Non-gallstone obstruction of pancreatic ducts	1-periampullary tumors 2- P divisum, 3- biliary "sludge," 4- Ascaris lumbricoides,
●Medications	thiazide furosemide, procainamide, pentamidine azathioprine,estrogens, methyldopa, sulfonamides,,
● Infections:	1-Mumps 2- Coxsackie virus 3- Mycoplasma pneumoniae,
● Metabolic disorders:	1- hypertriglyceridemia, 2- hyperparathyroidism 3- other hypercalcemic states,
● Vascular	Shock, Ischemia due to thrombosis, embolism, vasculitis (eg Polyarteritis nodosa).
● Genetic	**Hereditary pancreatitis** **** is an autosomal dominant** disease with an 80% penetrance **characterized by recurrent attacks of severe pancreatitis usually beginning in childhood. **It is caused by mutations in the PRSS1 gene that affect a site on the trypsinogen molecule that is essential for the cleavage (inactivation) of trypsin by trypsin itself. **When this site is mutated >>> trypsinogen & trypsin become resistant to inactivation >>> leading to ongoing activation of other digestive proenzymes, & eventually the development of pancreatitis.

►Basic pathological changes are

(1) edema,

(2) proteolytic destruction of pancreatic parenchyma,

(3) fat necrosis by lipases

(4) an acute inflammatory reaction,

(5) BV destruction with hemorrhage.

▲ In mild Ac P	►In more severe Ac P = acute necrotizing pancreatitis:
there are (I) **interstitial edema** (2) enzymatic destruction of peripancreatic fat cells >> the released fatty acids combine with calcium to form insoluble salts that precipitate in situ. **>>focal areas of fat necrosis in the pancreatic substance**	(a) Necrosis of P tissue affects acinar, ductal as well as the islets of Langerhans; (b) vascular damage causes hemorrhage into P parenchyma.
# Grossly, **the P shows 1-red-black hemorrhages interspersed with 2- foci of yellow-white, chalky fat necrosis (F 17-1B). **Fat necrosis can also occur in extra-pancreatic fat, including: 1- the omentum (F1-13 & 5.44), 2- bowel mesentery 3- even outside the abdominal cavity e.g., in subcutaneous fat, 4- peritoneum contains a serous, slightly turbid, brown fluid with globules of fat (derived from enzymatically digested adipose tissue).	Grossly, ▼The severest form, Acute Hemorrhagic pancreatitis (F5.43) shows **extensive diffuse hemorrhage **P tissue necrosis.

Pathogenesis

- The histologic changes seen in Ac P strongly suggest autodigestion of the P substance by inappropriately activated P enzymes.

- Zymogen forms of P enzymes must be enzymatically cleaved to be activated by trypsin; therefore activation of trypsin is a critical triggering event in Ac P.

- If trypsin is inappropriately generated from its proenzyme trypsinogen :

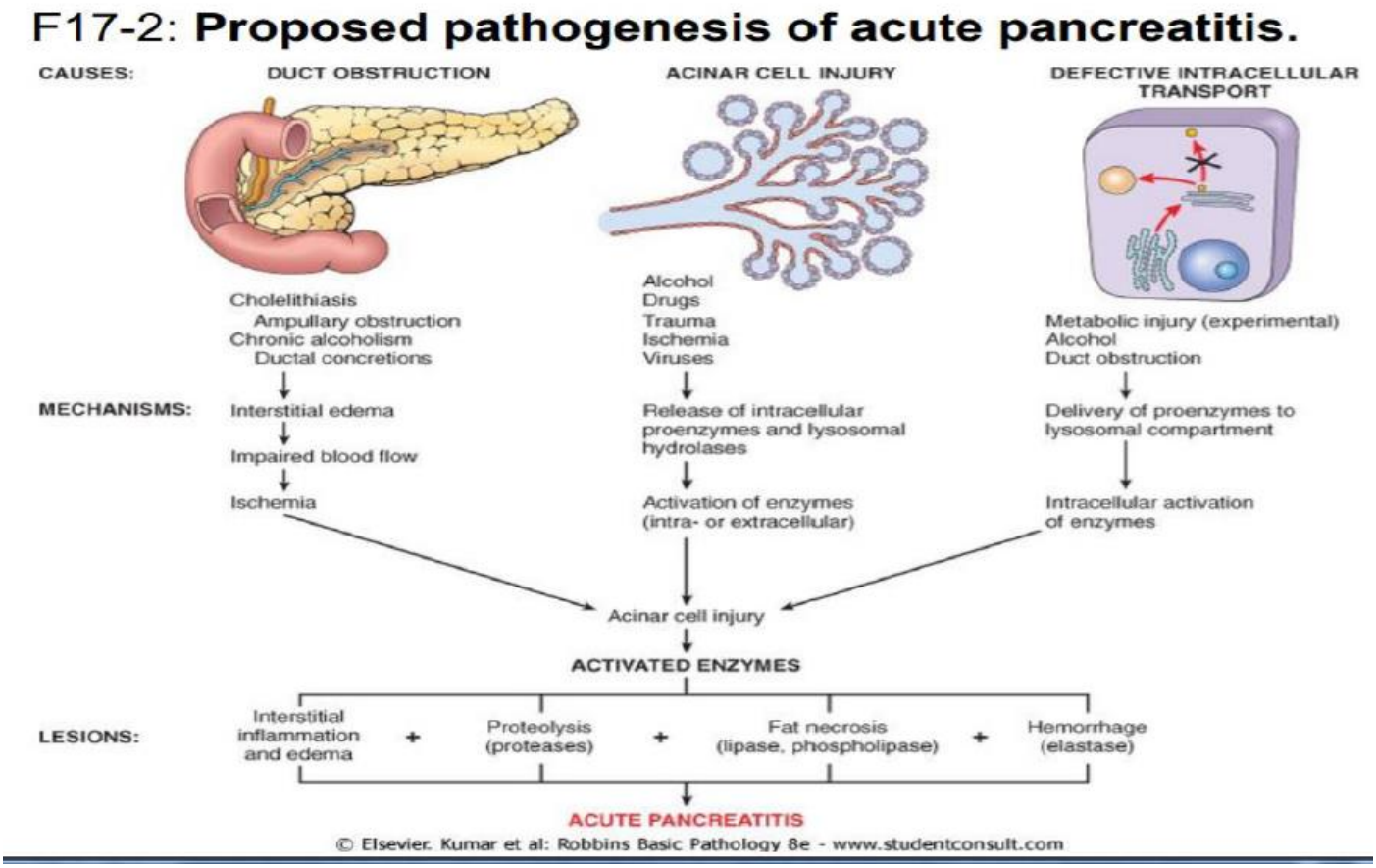
1- it can activate elastases & phospholipases that can cause autodigestion.

2- Trypsin also converts prekallikrein to its activated form Kallikrein, activating the kinin system &, by activation of Hageman factor {factor XII} also sets in motion the clotting & complement systems.

☼ Three possible pathways can incite the initial enzyme activation that may lead to Ac P :

(1)Pancreatic duct obstruction:

→Impaction of a GS or biliary sludge, or extrinsic compression of the ductal system by a mass blocks ductal flow >>> ↑ intraductal pressure
>>> allows accumulation of an enzyme-rich interstitial fluid.
→ Since lipase is secreted in an active form, this can cause local fat necrosis, with the result that
→ injured tissues, periacinar myofibroblasts, & WBCs release pro-inflammatory cytokines
that promote local inflammation & interstitial edema.
Edema further compromises local blood flow, causing vascular insufficiency & ischemic injury to acinar cells



(2) Primary acinar cell injury.

can incite Ac P caused by ischemia, viruses (eg mumps), drugs, & direct trauma to P.

(3) Defective intracellular transport of proenzymes within acinar cells:

*In normal acinar cells

1) digestive enzymes intended for **zymogen** granules (& eventually extracellular release)

2**)** **hydrolytic enzymes** destined for lysosomes

>>> are transported in discrete (separate) pathways after synthesis in the ER.

*However, at least in some animal models of metabolic injury,

pancreatic proenzymes & lysosomal hydrolases become packaged together.

>>>> This results in proenzyme activation

>>>> lysosomal rupture (action of phospholipases)

>>>> local release of activated enzymes.

☻How alcohol causes Ac P? is unknown, although:

(1) abnormal proenzyme trafficking has been implicated.

It leads to

(2) contraction of the sphincter of Oddi

(3) direct toxic effects on acinar cells,

(4) Alcohol ingestion causes ↑ secretion of protein-rich P fluid, leading to deposition of inspissated protein plugs & obstruction of small P ducts.

Clinically,

** Abdominal pain

*is cardinal symptom

* vary from mild to sudden severe constant pain

* often referred to the upper back,

*with rigid abdomen.

Diagnosis of Ac P depends on

1) markedly elevated

serum amylase during the first 24 hours,

followed (within 72-96 hours) by rising serum lipase levels.

2) Hypocalcemia can result from precipitation of calcium in the extensive areas of fat necrosis.

3) The enlarged inflamed pancreas can be visualized by CT or MRI

4) the exclusion of other causes of acute abdominal pain

- acute appendicitis ,
- perforated PU ulcer,
- intestinal obstruction & bowel infarction
- acute cholecystitis,
- ruptured ectopic pregnancy

**Severe Ac P manifestations are due to systemic release of digestive enzymes & explosive activation of the inflammatory response.

Patients may show

1) increase vascular permeability,

2) DIVC

3) ARDS (due to alveolar capillary injury)

4) diffuse fat necrosis.

5) Shock can rapidly follows as a result :

a) of loss of blood volume & electrolyte disturbances

b) & in 40% - 60% of Ac P the necrotic debris becomes infected, usually by gram negative bacteria from the GIT & may cause endotoxemia.

Management of Ac P is by supportive therapy.

Most Ac P patients eventually

recover; 5% (or more) die from shock.

If the patient survive, a common sequelae is:

- P Pseudocyst (PP) forms by:

(1) walling off areas of hemorrhagic fat necrosis, &

(2) drainage of P secretions (from damaged pancreatic ducts) into cyst over months or years cause massive cyst enlargement (2 to 30 cm in ∅).

- PP account for 75% of all pancreatic cysts

- PP are solitary; attached to the surface of the pancreas & involve peripancreatic tissues such as the lesser omental sac or the retroperitoneum between the stomach & transverse colon or liver .

• PP contains necrotic debris encased by fibrous granulation tissue lacking an epithelial lining (pseudo).

• Many PP spontaneously resolve,

some can become secondarily infected

& larger PP can compress or even perforate into adjacent structures

Chronic Pancreatitis (Ch P)

• Is longstanding inflammation & fibrosis of the pancreas, with destruction of the exocrine part; later, the endocrine part is also lost.

•Prevalence: 0.04% to 5% of populations.

• Although Ch P can result from recurrent attacks of acute pancreatitis the chief distinction between acute & Ch P is the irreversible impairment of pancreatic function in Ch P.

Causes :

***

The most common cause of Ch P	•Less common causes of Ch P include
• is long-term alcohol abuse, middle aged men constitute the bulk of the group.	• Long-standing pancreatic duct obstruction (pseudocysts, calculi, neoplasms, or pancreas divisum), • Tropical pancreatitis, attributed to malnutrition, is a poorly characterized disorder seen in Africa and Asia, • Hereditary pancreatitis due to PRSS1 mutations, or mutations in the SPINK1 gene encoding trypsin inhibitor. • Ch P associated with CFTR gene mutations (cystic fibrosis) in which there is decrease bicarbonate secretion, thereby promoting protein plugging. .

*** 40% of Ch P cases have no predisposing factors

►Grossly, in Ch P, :

*the pancreas is hard

*sometimes with extremely dilated ducts & visible calcified concretions.

◙ H,

1) Acinar cell loss (reduced number & size) is a constant feature (leading to pancreatic insufficiency & malabsorption),

2) with a chronic inflammatory cell infiltration around remaining lobules & ducts

3) severe parenchymal fibrosis

4) variable dilation of the pancreatic ducts

5) with atrophic; hyperplastic, or squamous metaplasia of ductal epithelium

6) ductal concretions .

**Initially, there is sparing of the islets of Langerhans

**later, they become embedded in the fibrotic tissue & may fuse & appear enlarged; & eventually they disappear → DM

Pathogenesis:

Several hypotheses are proposed;

● Ductal obstruction by concretions.

Many of the inciting agents in Ch P (e.g., alcohol) ↑ the protein concentration of pancreatic secretions, & forming ductal plugs.

● Toxic-metabolic. Toxins, including alcohol, can exert a direct toxic effect on acinar cells, leading to lipid accumulation, acinar cell loss, & eventually parenchymal fibrosis.

● Oxidative stress. Alcohol-induced oxidative stress may

(A) generate FR in acinar cells, leading to membrane lipid oxidation & subsequent chemokine expression that recruits mononuclear inflammatory cells,

(B) promotes abnormal proenzyme trafficking with resulting acinar cell necrosis, inflammation, & fibrosis.

● Necrosis-fibrosis.

Acute pancreatitis can cause local perilobular fibrosis, duct distortion, & altered pancreatic secretions.

Over time & with multiple episodes, this can lead to loss of pancreatic parenchyma & fibrosis.

Clinically,

***Ch P can present in several different ways:

1) Repeated attacks of jaundice {with ↑ in serum levels of alkaline phosphatase}

2) vague indigestion,

3) persistent or recurrent, severe abdominal & back pain.

The attacks can be precipitated by overeating (⇑ demand on pancreatic secretions), alcohol abuse, or opiates or other drugs that ↑ the muscle tone of the sphincter of Oddi.

*** Entirely silent until one or both of the following develop:

(A) Pancreatic insufficiency resulting in malabsorption with hypoalbuminemic edema & weight loss,

(B) DM (islets loss).

- Pancreatic pseudocysts develop in 10% of Ch P.
- Individuals with hereditary pancreatitis have a 40% lifetime risk of developing pancreatic cancer !.

Diagnosis

- Diagnosis of Ch P requires a high degree of suspicion.
- A very helpful finding is visualization of calcifications within the pancreas by CT or U/S.

EXOCRINE PANCREATIC TUMORS (T)

Cystic Neoplasms

→ Pancreatic Pseudocyst account for 75% of all pancreatic cysts.

→ 5% to 15% of all pancreatic cysts are neoplastic; these constitute less than 5% of all pancreatic T.

→Some, like:

• Serous cystadenoma	• Mucinous cystic T	Intraductal Papillary Mucinous T
• T are entirely benign, & surgical resection is curative in the vast majority of patients.	• Both can be *benign, because it lacks significant cytologic or architectural atypia; *borderline malignant, showing significant cytologic & architectural atypia but no tissue invasion. *or malignant, which are invasive	
• T typically presents in the 7th decade of life with abdominal pain; M/F ratio is 2: 1. • T composed of glycogen-rich cuboidal cells lining cysts containing clear, straw-colored fluid . • T account for about a 25% of all pancreatic cystic tumors;	• Always arise in women, in the body or tail of the pancreas, •The cystic spaces are filled with thick, tenacious mucin, & the cysts are lined by a columnar mucinous epithelium with an associated densely cellular stroma . • P/A painless, slow-growing masses.	• IPMNs arise more frequently in men than in women & • more frequently involve the head of the pancreas. • IPMNs arise in the main pancreatic ducts & lack the cellular stroma seen in mucinous cystic T • IPMNs also produce cysts containing mucin; BUT In contrast to mucinous cystic neoplasms,

Pancreatic Carcinoma (P Ca)

**P Ca is the 4 leading cause of cancer death in the US, preceded only by lung, colon, & breast cancers.

** 30,000 Americans are diagnosed with P Ca annually & all will die of it; the 5-year survival rate is dismal <5% (as in GB carcinoma!)

Pathogenesis of P Ca .

** There is a progressive accumulation of genetic changes in pancreatic epithelium as it proceeds

from non-neoplastic

>> to noninvasive lesions in small ducts & ductules

>> to invasive ca

**Antecedent lesions are "pancreatic intraepithelial neoplasias" (PanINs) (Fig. 17- 8).

**Evidence in favor of their precursor relationship to frank ca:

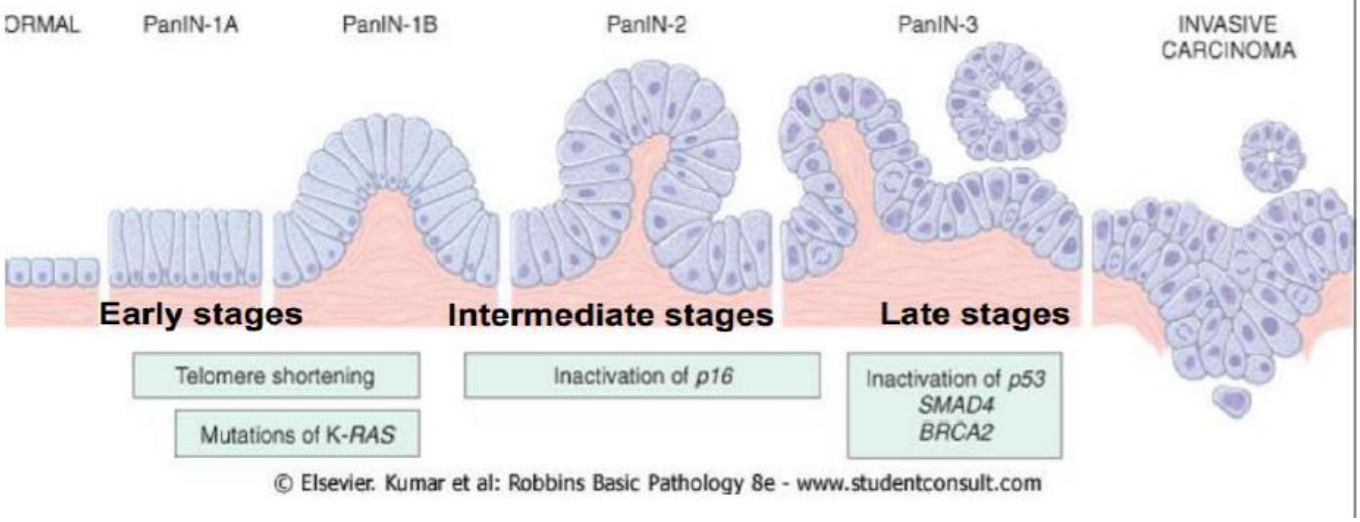
(1) They are often found adjacent to infiltrating P Ca &

(2) Share a number of the same genetic mutations,

(3) PanINs epithelial cells show dramatic telomere shortening, potentially predisposing them to accumulating additional chromosomal abnormalities.

**Commonest molecular alterations in pancreatic carcinogenesis:

F17-8: **Model for the development of pancreatic cancer.**



1) K-RAS gene is the most frequently altered oncogene, it is activated by point mutation in up to 90% of P Ca cases.

2) p16 (CDKN2A) T suppressor gene is inactivated in 95%,

3) p 53 T suppressor gene inactivation occurs in 60%, &

4) SMAD4 T suppressor gene is inactivated in 55%

**What causes these molecular changes? is unknown.

Risk factors :

** P Ca is a disease of elderly, 80% of patients are 60 to 80y,

** P Ca is more common in blacks than in whites.

** Smoking, strongest environmental influence doubles the risk.

**Chronic pancreatitis & DM are both associated with an increase risk of P Ca.

BUT it is difficult to sort out whether chronic pancreatitis is the cause of P Ca or an effect of it ?

since small P Ca can block the pancreatic duct & thereby produce chronic pancreatitis.

Similarly, DM can occur as a consequence of P Ca.

** Familial clustering of P Ca has been reported.

In particular, familial pancreatitis (related to mutations in the PRSS1 trypsinogen gene; see above) incurs an X 50- to 80-fold increase risk of P Ca.

Morphology.

60%	15%	5%	20%,
of P Ca arise in the pancreatic head	in the body	in the tail;	in the P Ca involves the entire organ

● P Ca is hard, stellate, gray-white, poorly defined T.

● **P Ca vast majority are ductal adenoca**, forming glands & secreting mucin.

● Even early invasive P Ca is highly & extensively invasive T

● P Ca elicits an intense desmoplastic fibrotic response.

● **In 50% of cases of P Ca of the head, there is obstruction of the distal CBD as it courses through the head of the pancreas, resulting in obstructive jaundice**;

In contrast,

● P Ca of the body & tail do not impinge on the biliary tract & hence remain silent.

Spread:

● P Ca invade & **infiltrate directly** the retroperitoneal space, entrapping nerves, & occasionally invading the transverse colon, spleen, adrenals, spine, & stomach.

● Commonly, peripancreatic, gastric, mesenteric, omental, & portahepatic **LNs are involved**, as well as the liver.

● Distant metastases occur, mainly to lungs & bones.

◙ H, P Ca is usually a moderately to poorly differentiated adenoca forming abortive tubules or cell clusters & with deeply infiltrative growth pattern , dense stromal fibrosis & **a tendency for lymphatic & perineural invasion.**

P Ca less common variants include:

** Acinar cell ca	** Adenosquamous ca	**Undifferentiated ca
showing prominent acinar cell differentiation with zymogen granules & exocrine enzyme production	with focal squamous differentiation in addition to glandular differentiation	with osteoclast-like giant cells

Clinical Features of P Ca

**P Ca typically remains silent until it infiltrates or spreads.

** Pain is usually the first, but unfortunately, very late symptom,

** Obstructive jaundice occurs in 50% of pancreatic head Ca.

**S & S of advanced P Ca include weight loss, anorexia, malaise & weakness.

** Migratory thrombophlebitis (Trousseau syndrome) occurs in about 10% of patients

is due to the elaboration of platelet-aggregating factors & procoagulants from P ca.

**<20% of P Ca are resectable at the time of diagnosis.

**Serum levels of many enzymes & antigens (e.g., CEA & CA19-9 Ag) are elevated, but are neither specific nor sensitive to be used as screening tests.

**CT & endoscopic U/S are helpful

1- in the diagnosis

2- in performing percutaneous needle biopsy,

but are not useful as screening tests.