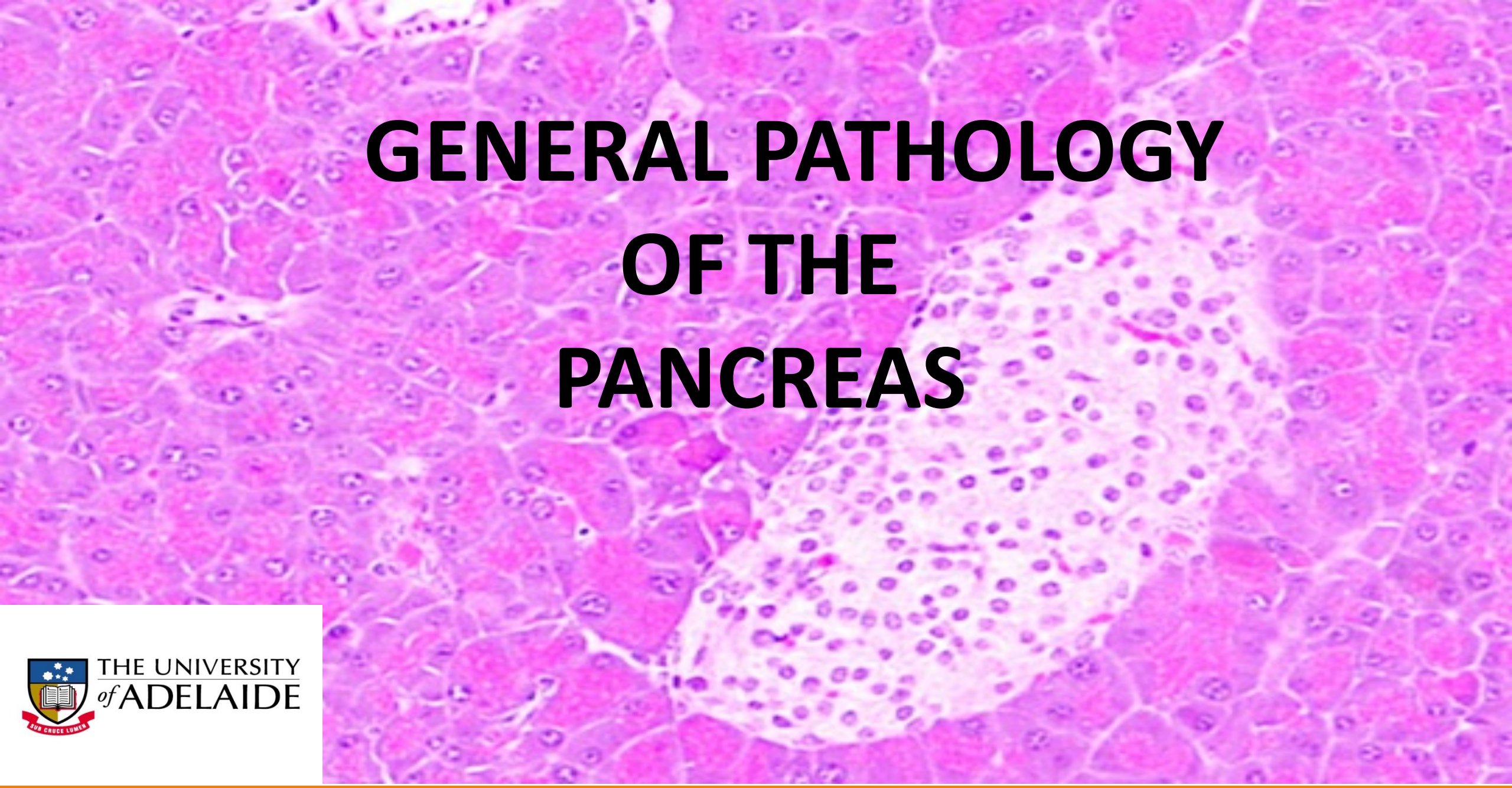
GENERAL PATHOLOGY OF THE PANCREAS



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Pancreatic function

Functional and structural changes in the normal pancreas are not self-initiated, but occur in response to systemic metabolic activity

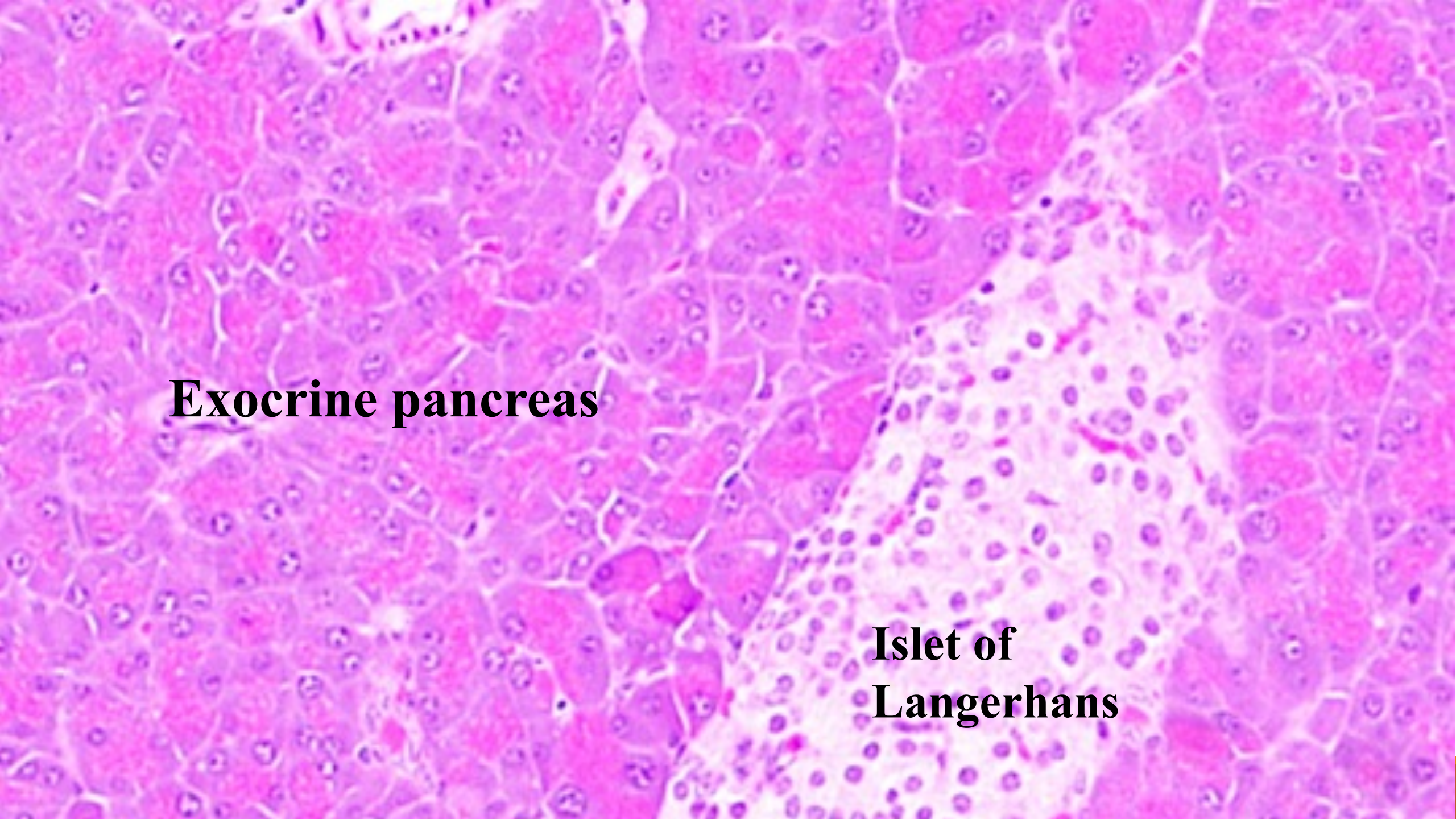
Pancreatic function is largely controlled by entero-endocrine hormones derived from the gastrointestinal mucosa, but also from the endocrine pancreas

Important interdependence between endocrine and exocrine elements and hormones produced by the islets are important for regulation of exocrine functions

Pancreatic function

Endocrine tissue comprises 1-2% of the pancreatic mass and is organised into islets

Insulin and pancreatic polypeptide are trophic for acinar tissue, while somatostatin and glucagon are inhibitory, facilitated by an insulo-acinar circulatory system, with afferent vessels flowing through the islets before supplying exocrine tissue


Exocrine pancreas
Islet of
Langerhans

Exocrine pancreas

Pancreas is mainly comprised of acinar tissue

Acinus is drained by an intercalated duct, while then becomes intra- and interlobular ducts

Innervation of the pancreas is important for regulating exocrine secretion – parasympathetic autonomic stimulation via the vagus promotes pancreatic secretion, abetted by the enteric nervous system

Exocrine functions

Major function of exocrine pancreas is the synthesis and secretion of digestive enzymes

Acinar cells secrete trypsin, chymotrypsin, collagenase, phospholipase, elastase, and carboxypeptidases as inactive pro-enzymes, and amylase and lipase as fully active enzymes

Entry of gastric acid and fatty acids into the duodenum causes secretin release which, in turn, stimulates secretion of water and bicarbonate (contributes to neutralisation of gastric acid) by the pancreatic duct epithelium

Exocrine functions

Undigested lipid and amino acids in the duodenum cause the release of cholecystokinin by mucosal epithelial cells and release of digestive enzymes from the pancreas

Exocrine secretions also inhibit bacterial proliferation, have a trophic effect on the intestinal mucosa, and have a role in zinc homeostasis

Exocrine pancreas produces intrinsic factor, which is essential for vitamin B12 absorption in the ileum

Exocrine pancreas

Exocrine pancreas is a labile tissue, which synthesises more protein on a weight-for-weight basis than any other tissue and correspondingly consumes a large amount of substrate

Response to changes in nutrient intake is rapid, with acinar hypertrophy and hyperplasia

Acinar, ductal and islet cells are capable of regeneration and restoration of the exocrine pancreas following injury occurs rapidly

Exocrine pancreas

Stem cells are not believed to play an important role in regeneration, but this is still somewhat controversial

Stellate cells (similar to those in the liver) are major mediators of fibrogenesis

Autolysis occurs rapidly because of post-mortem release of digestive enzymes

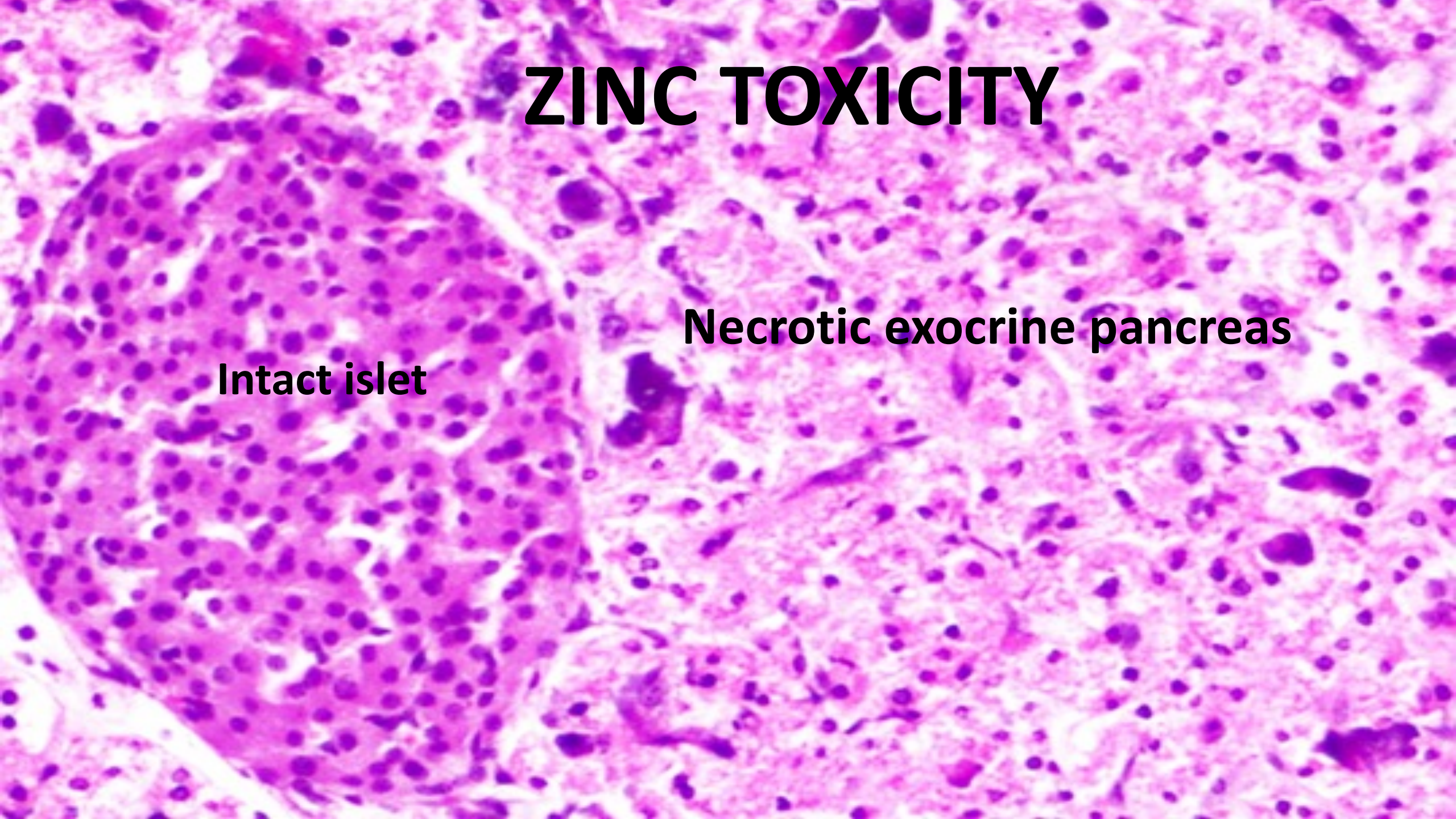
Injury to exocrine pancreas

Necrosis of individual or groups of acinar cells occurs in febrile states, viral and bacterial infections, intoxications (e.g. by anticholinesterases), and hypovolaemic or septic shock

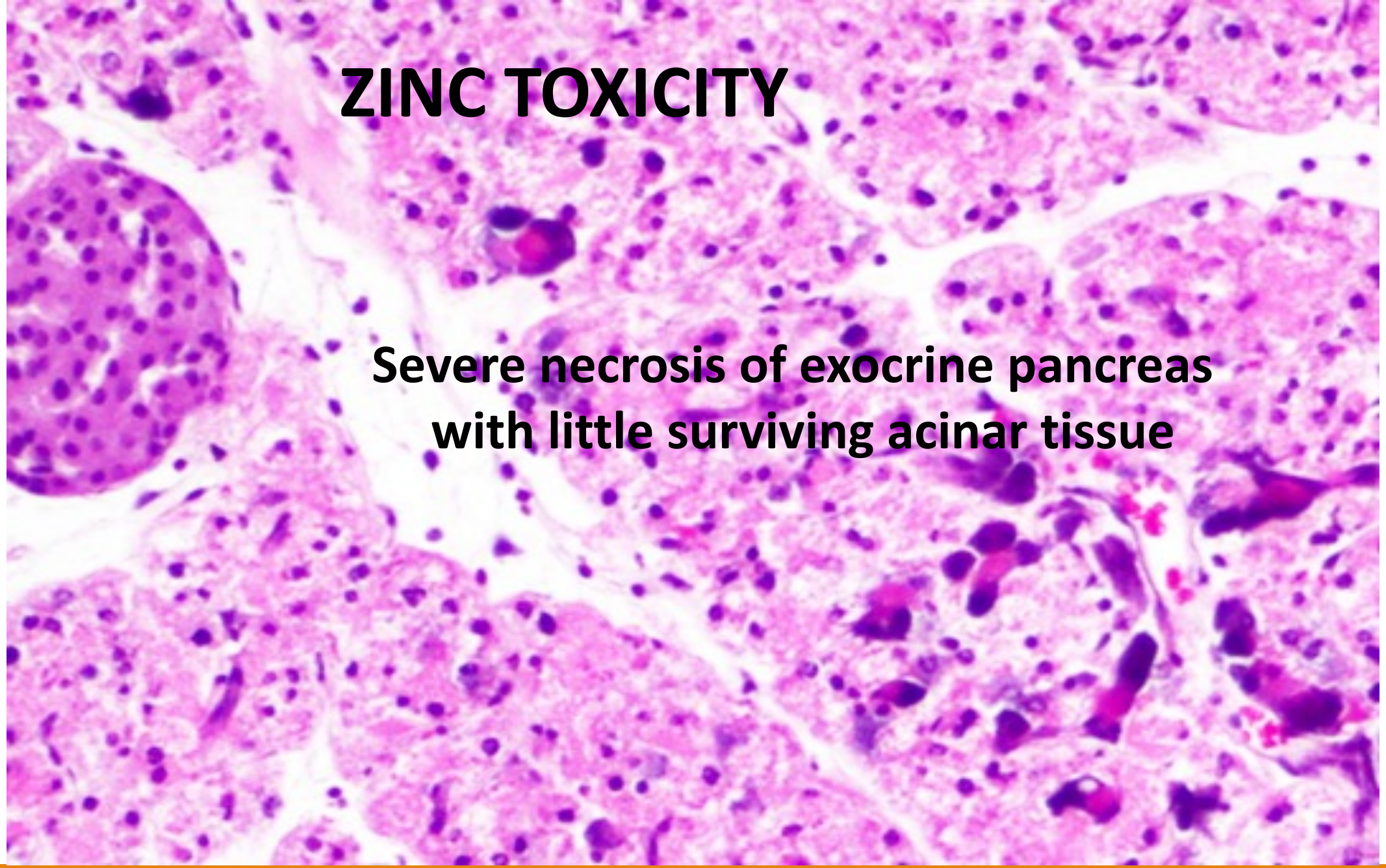
Zinc toxicity causes marked pancreatic exocrine damage as the pancreas is the major route of Zn excretion with degeneration/necrosis of acinar elements, followed by atrophy and fibrosis

Many chemicals, including ethanol, produce abundant free radicals and, since the exocrine pancreas normally generates a large free radical load, any additional burden may overwhelm anti-oxidant pathways. P450 activity by acinar cells can also exacerbate damage by toxin biotransformation

ZINC TOXICITY



ZINC TOXICITY



Severe necrosis of exocrine pancreas with little surviving acinar tissue

Pancreatic necrosis versus pancreatitis

The predominance of pancreatic necrosis over inflammation favours the use of the term acute pancreatic necrosis over acute pancreatitis

Acute pancreatic necrosis

Acute or chronic, intermittent or relapsing syndrome, the latter often subclinical

May result in exocrine pancreatic insufficiency and diabetes mellitus

Earliest lesions are in the peri-pancreatic adipose tissue with necrosis and saponification of adipocytes, followed by necrosis of adjacent acinar tissue with autodigestion by activated pancreatic enzymes, especially amylase, and leucocytic infiltration

Inciting causes are hypoperfusion, abdominal trauma, and some drugs

Acute pancreatic necrosis

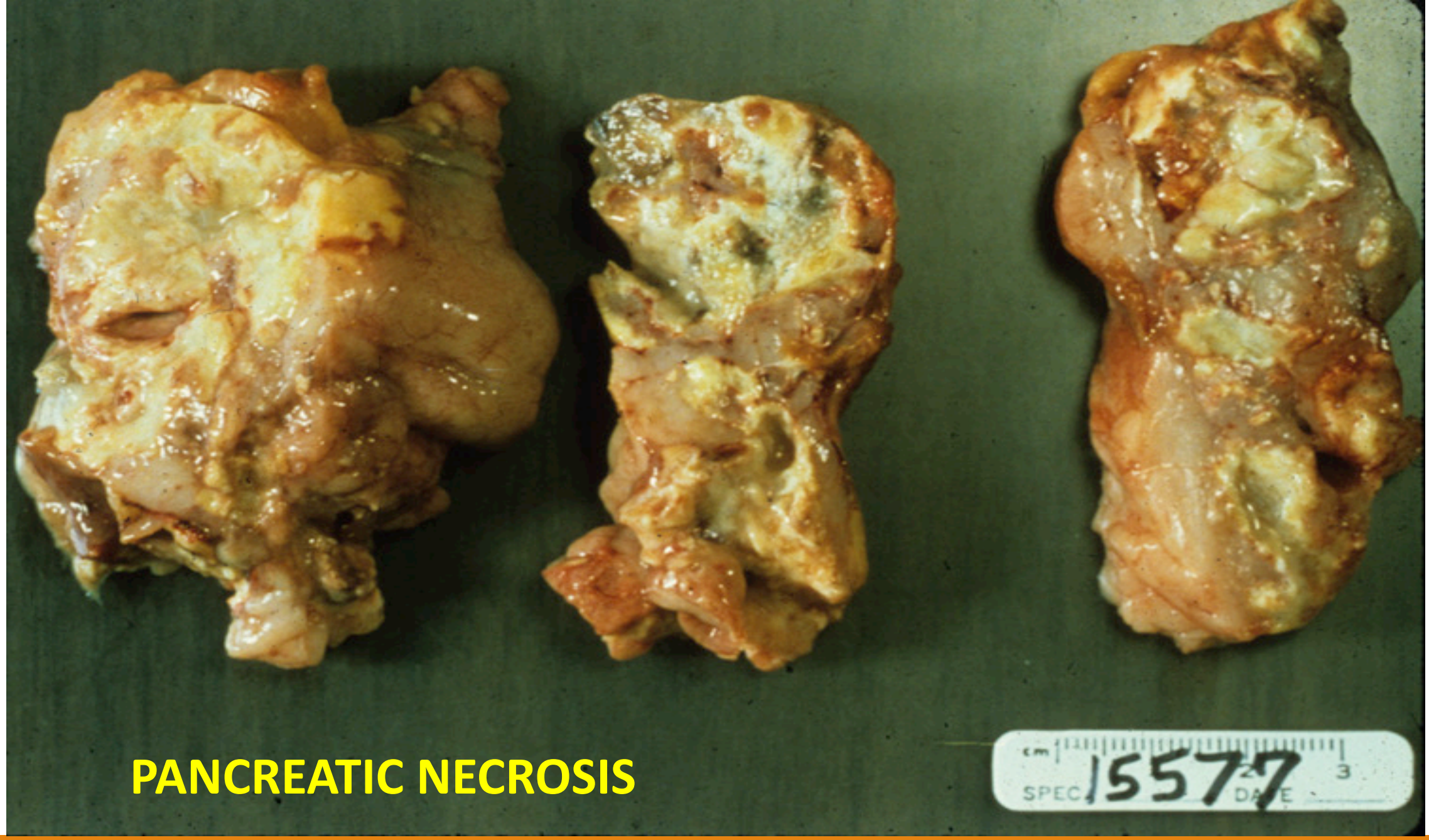
Normally the exocrine pancreas possesses robust defences against autodigestion by pancreatic enzymes, but these can be overwhelmed with pancreatic necrosis

Intense inflammation induces by pancreatic necrosis may produce devastating systemic consequences (including disseminated intravascular coagulation or DIC associated with widespread endothelial damage) and multiple organ dysfunction

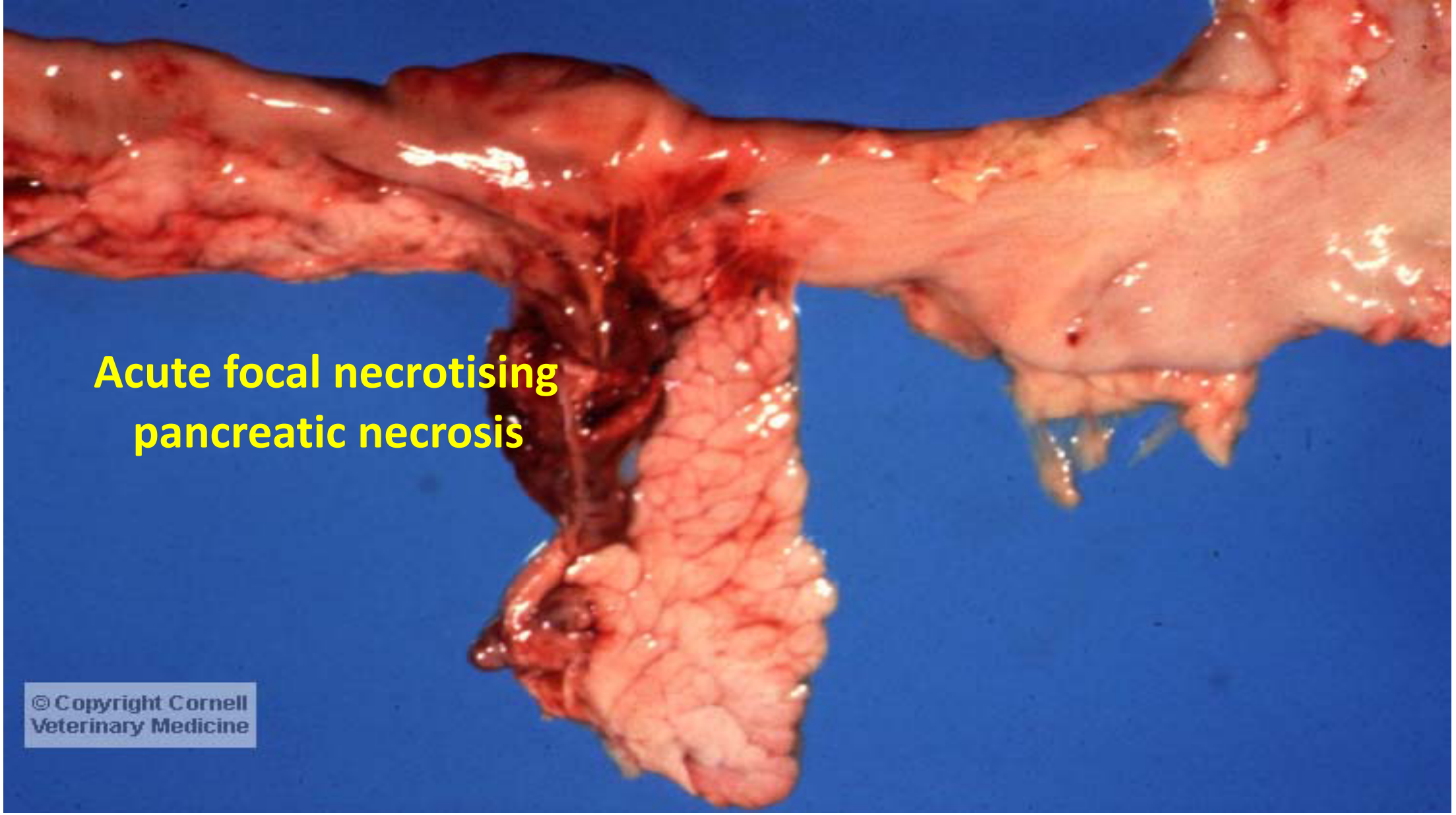
Acute pancreatic necrosis

Doubtful whether complete restitution of pancreatic tissue ever occurs after necrosis, but rather typically smoulders continuously, and often asymptomatically (although clinical signs of exocrine and endocrine insufficiency can develop), until almost complete pancreatic destruction occurs

Histologically, there is necrosis of peri-pancreatic and pancreatic parenchymal tissue, reactive inflammation, and thrombosis. Necrotic fat saponifies and may undergo dystrophic mineralisation



PANCREATIC NECROSIS


Acute focal necrotising
pancreatic necrosis
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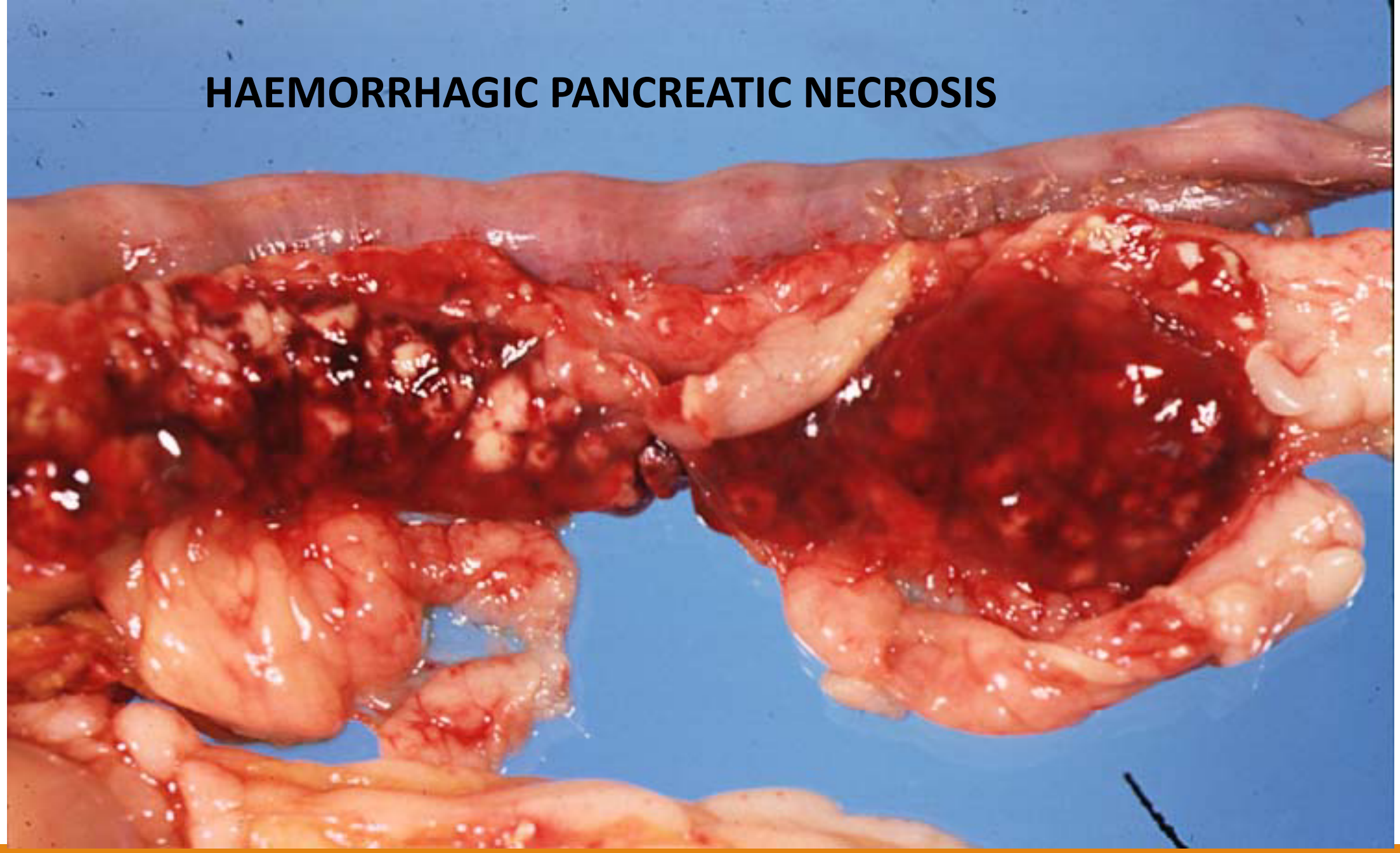
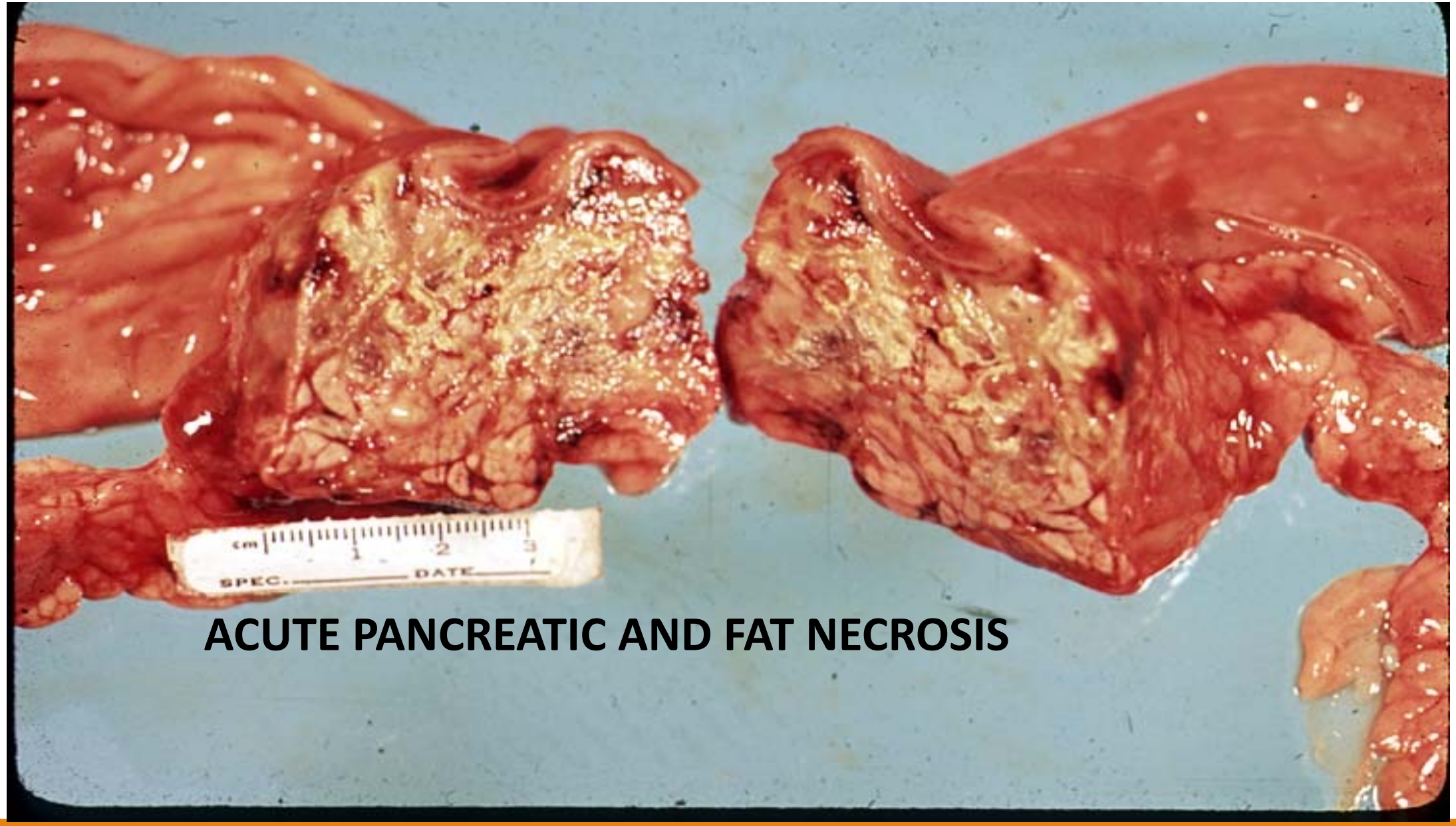
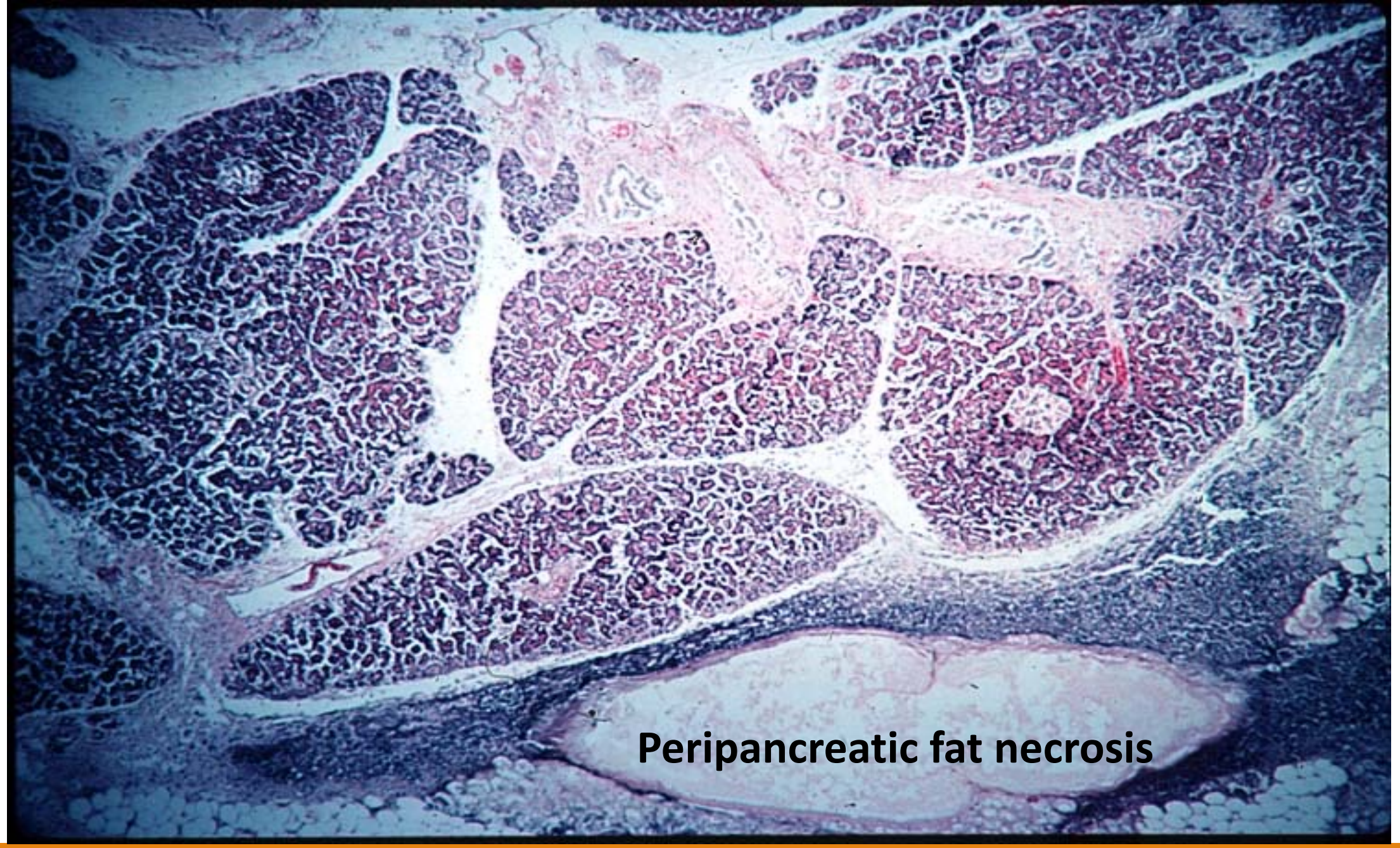
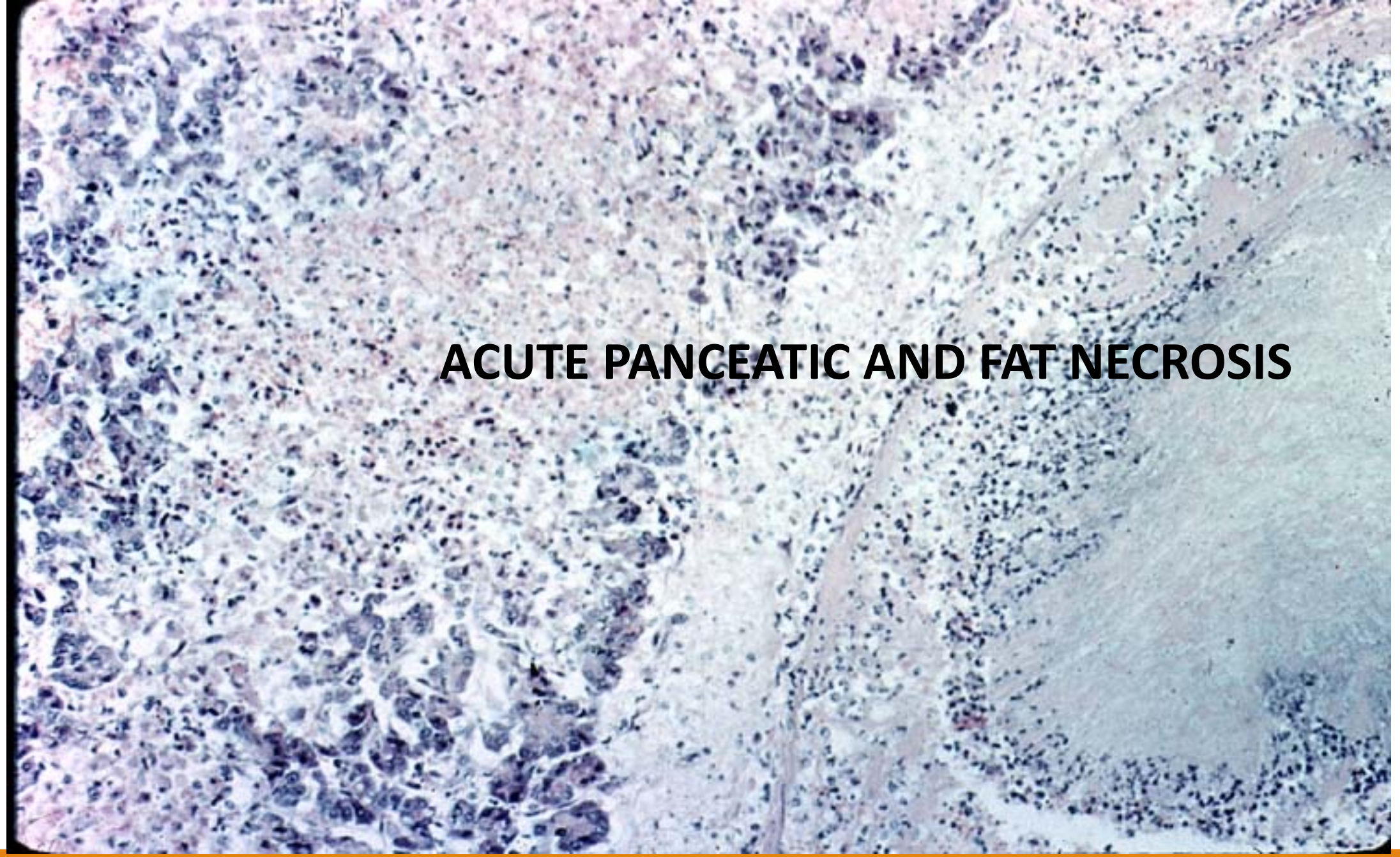
HAEMORRHAGIC PANCREATIC NECROSIS

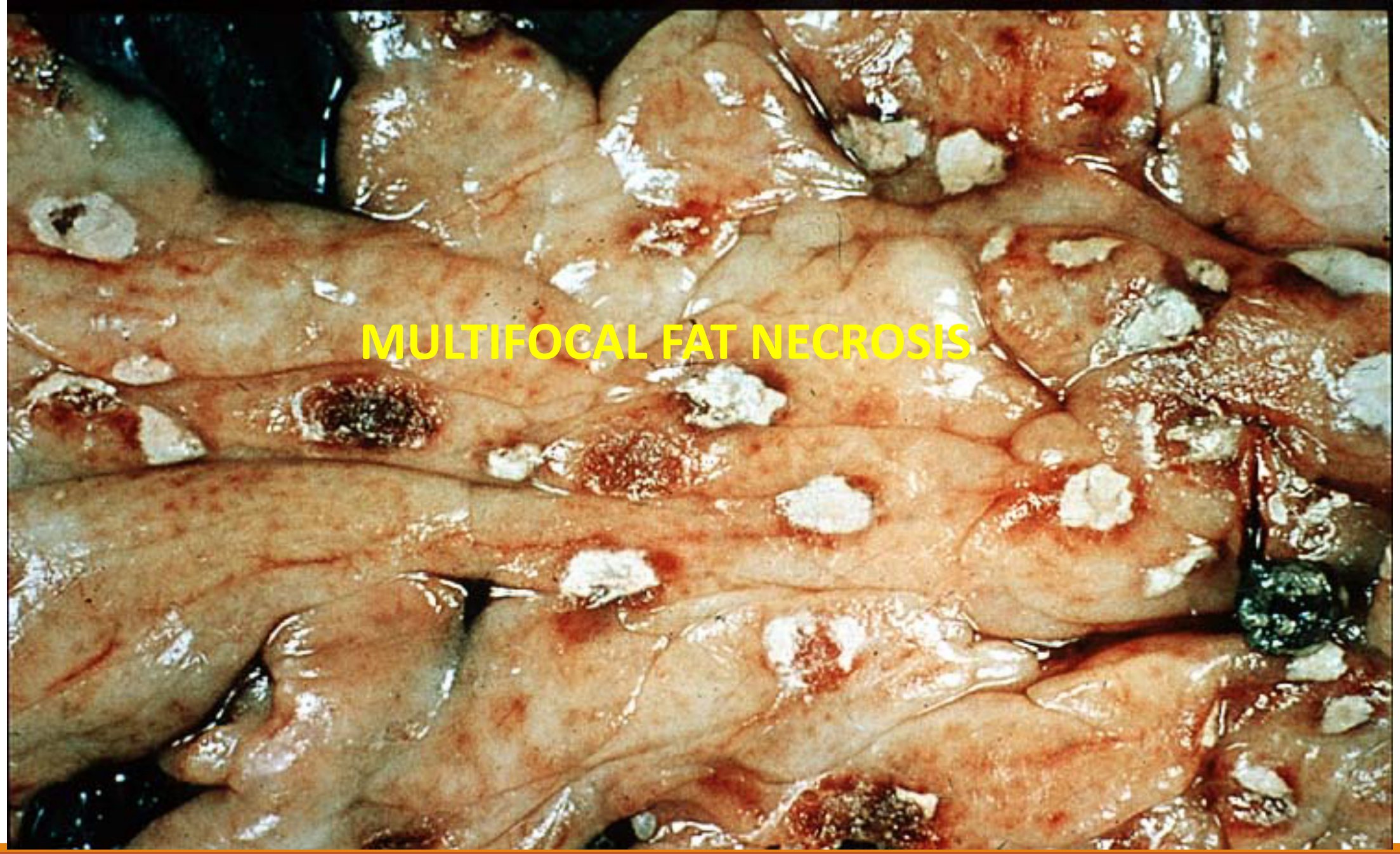




ACUTE PANCREATIC AND FAT NECROSIS


Peripancreatic fat necrosis


ACUTE PANCEATIC AND FAT NECROSIS

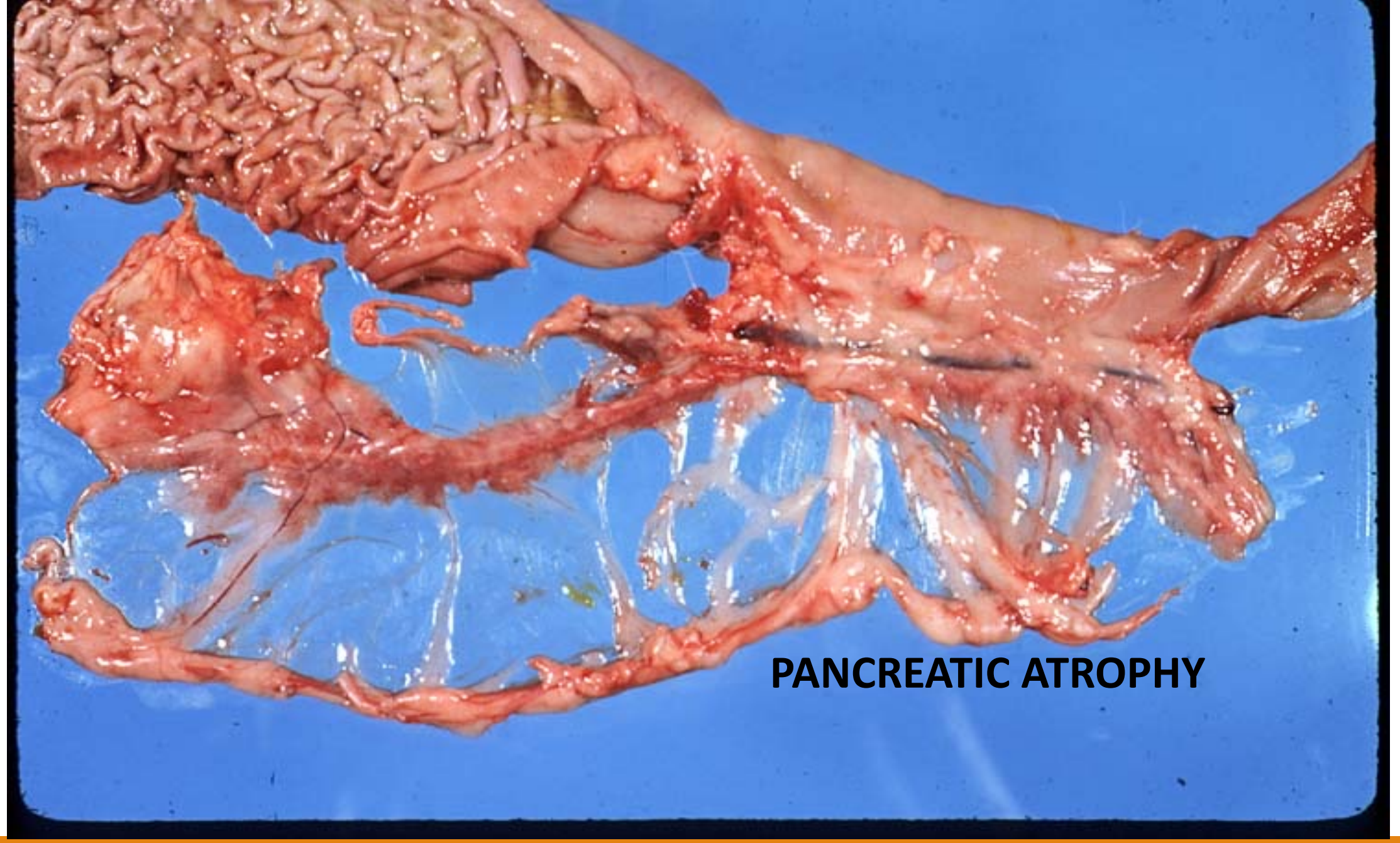

MULTIFOCAL FAT NECROSIS

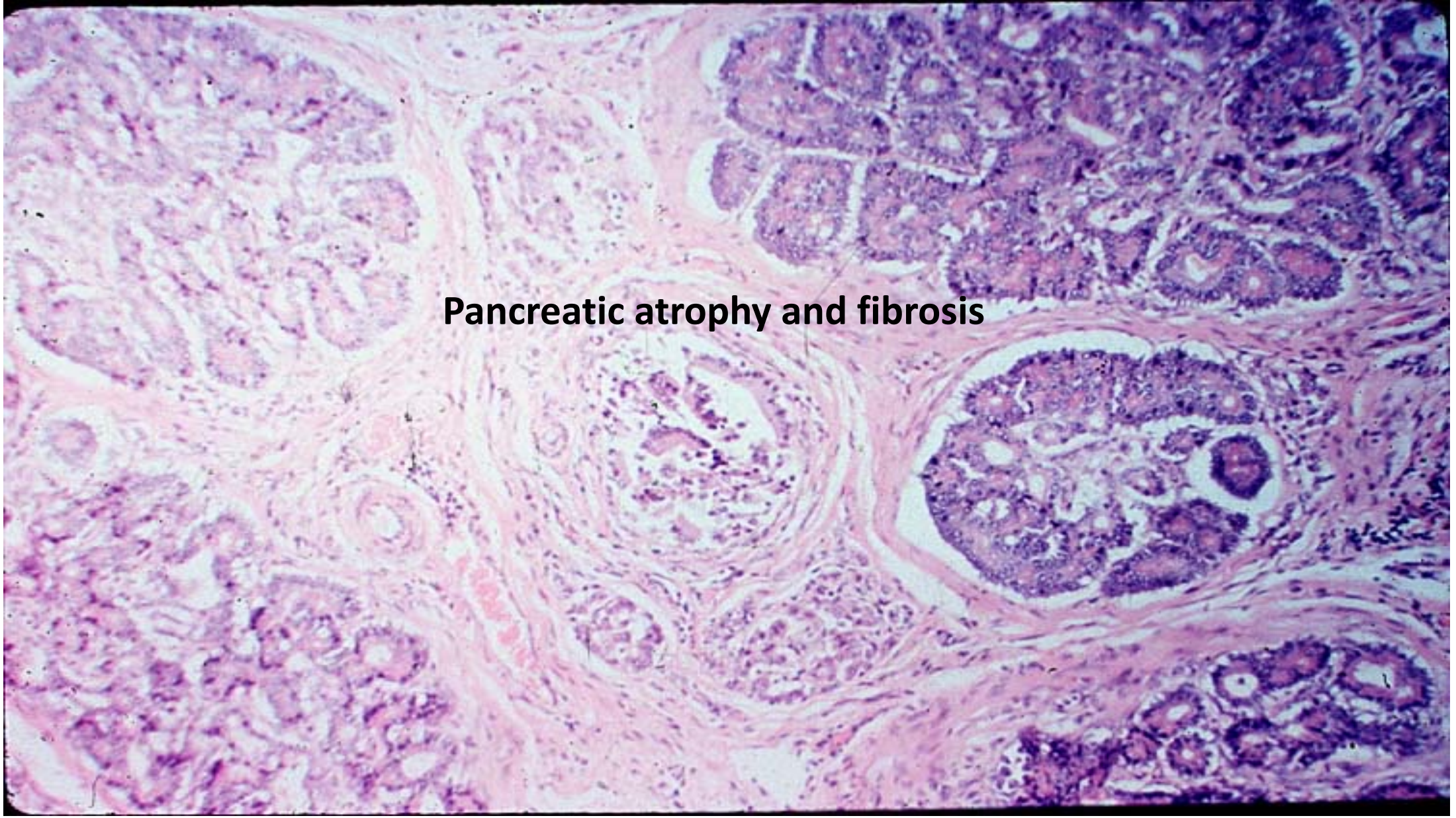
PANCREATIC FAT NECROSIS

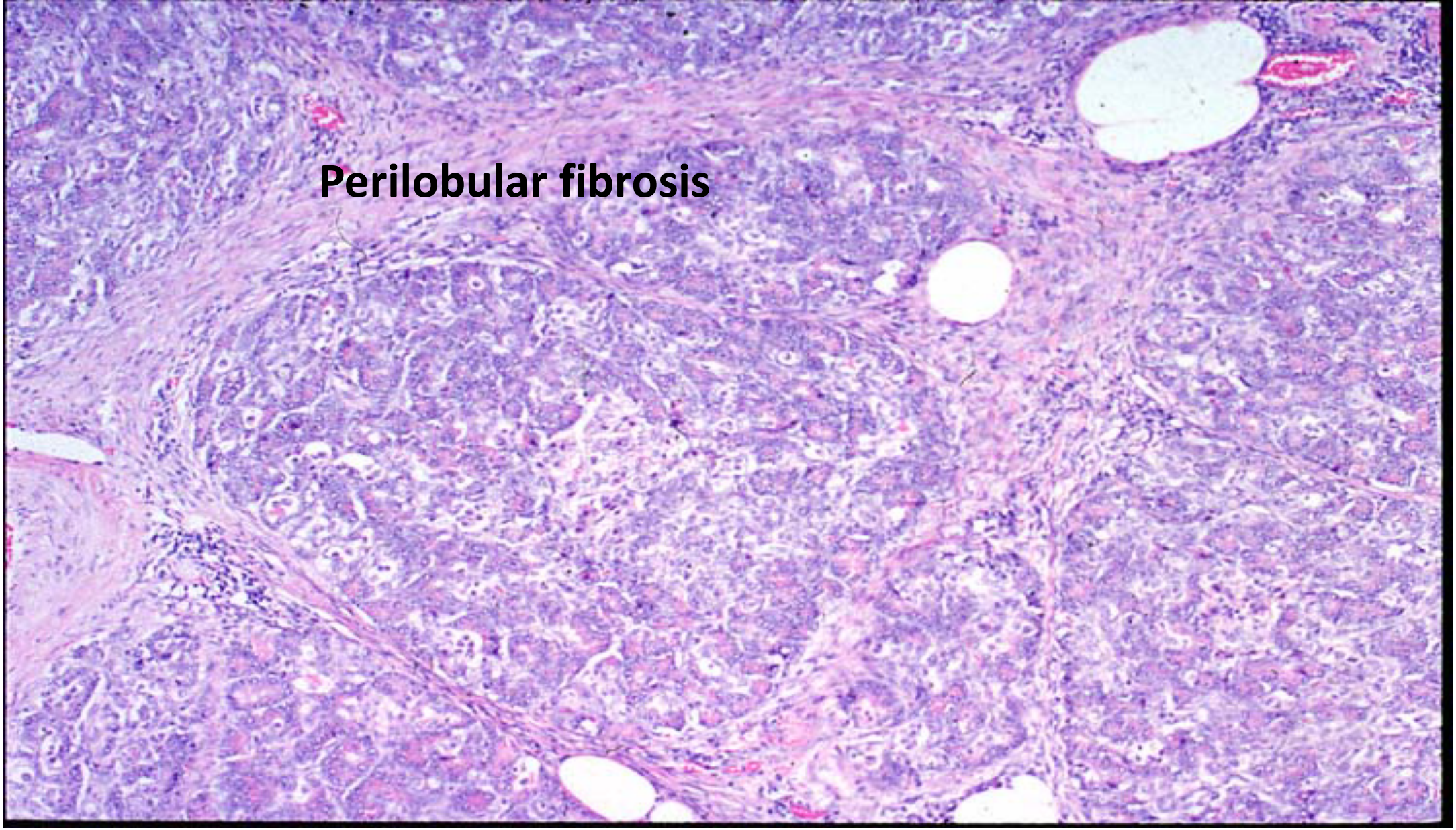
Pancreatic atrophy

Can be secondary to other pancreatic disorders, but also common with nutrient deprivation (with protracted anorexia, the pancreas may be reduced to <10% of its normal mass)

Susceptible to atrophy because: (1) pancreatic protein turnover is high and therefore subject to catabolic loss of acinar cell proteins to compensate for a nutritional protein shortfall and (2) loss of neurogenic and endocrine stimulation due to damage to the gastrointestinal mucosa


PANCREATIC ATROPHY


Pancreatic atrophy and fibrosis


Perilobular fibrosis

Exocrine pancreatic insufficiency

Although the normal pancreas possesses substantial functional reserve, numerous pancreatic pathologies can lead to reduced secretion of pancreatic enzymes, resulting in maldigestion and malabsorption of nutrients

Can be slow or rapid, but clinical disease only occurs when ~90% of the secretory capacity is lost

Clinical signs are pale, soft, voluminous and malodorous faeces and chronic weight loss, despite a normal to voracious appetite

Small intestine bacterial overgrowth commonly ensues

Clinical chemistry

Amylase and lipase produced by acinar cells may leak into plasma during pancreatic cellular injury, resulting in increased serum activity

Late in the course of pancreatic disease, decreased serum enzyme activity may occur from depletion of stored enzymes or disturbed enzyme synthesis

Trypsinogen and trypsin are increased in serum in some species with pancreatic disease and are pancreas-specific in dogs and cats

ENDOCRINE PANCREAS

Islet is a discrete glomerular organ perfused by capillary blood flow and produces specific hormones

Pancreatic circulation initially flows through the islets before supplying acinar tissue, facilitating acinar trophic factor (especially insulin) exposure from the islets

Endocrine pancreas

5 main cell types in islets:

β-cells produce insulin and amylin (islet amyloid polypeptide) – 60-70% of islet cell population

α-cells produce glucagon

γ-cells produce somatostatin

PP (pancreatic polypeptide) cells produce pancreatic polypeptide and adrenomedullin

ε-cells produce ghrelin

Endocrine hormones

Insulin is the main regulator of serum glucose and is released in response to hyperglycaemia

Stimulates glucose uptake and glycogenesis by hepatocytes, skeletal myocytes, fibroblasts and adipocytes

Also has potent anabolic effects, promoting DNA, RNA, triglyceride, and protein synthesis and suppressing proteolysis

Promotes cellular growth and differentiation

Endocrine hormones

The hypoglycaemic effects of insulin are countered by glucagon, which promotes hepatocellular glycogenolysis and gluconeogenesis in response to low blood sugar, as well as stimulating lipolysis

Glucagon release is suppressed by amylin, which is co-secreted with insulin

By contrast, somatostatin inhibits release of glucagon, insulin and pancreatic polypeptide

Ghrelin is secreted by PD/1 cells in the gastric fundus as well as islets and its main role is suppression of insulin secretion (also an important appetite stimulant)

Pancreatic polypeptide antagonises the effects of cholecystokinin

Diabetes mellitus

A metabolic syndrome characterised by sustained hyperglycaemia, weight loss, polyphagia, and polyuria.

Hyperglycaemia is the result of:

1. Failure to synthesise or release adequate insulin

2. Reduced sensitivity of tissue to insulin, particularly liver, striated muscle and adipose tissue

Diabetes mellitus

Typically preceded by a period of impaired glucose tolerance, in which a return to euglycaemia after glucose administration is slowed or incomplete

Classified as type 1, type 2, and type S

Type 1

Characterised by hyperglycaemia and an insulin deficiency caused by primary immune-mediated loss of β-cell mass or (rarely) idiopathic – termed insulin-dependent diabetes mellitus (IDDM)

β-cell destruction is effected mainly be CD8+ T cells, the initial immune response against β-cells perhaps triggered by a viral infection

Diabetes mellitus

Type 1

Genetic polymorphisms, especially those involved in T cell activation and antigen recognition, play an important role in the development of many cases

Type 2

A complex, multifactorial disease, but primarily characterised by failure of glycaemic control in the face of excess energy load, influenced by predisposing genetic and environmental factors, including obesity, inactivity, and micronutrient imbalances such as vitamin D deficiency

The pathophysiology of type 2 reflects both inadequate insulin secretion + increased resistance to insulinic effects in peripheral tissues (which suppress insulin uptake, especially by skeletal muscle)

Diabetes mellitus

Type 2

β-cells attempt to compensate by increasing insulin secretion, but they eventually become refractory to hyperglycaemic stimuli

Hyperglycaemia also causes direct β-cell glucotoxicity

Type S

Includes cases in which insulin action is antagonised by hormones and drugs, as well as secondary β-cell destruction by inflammation, necrosis or neoplasia

Lesions in diabetes mellitus

Lesions are widespread and reflect the ubiquity of glucose dependence in the body

Muscle wastage occurs because of the catabolism of proteins for glucogenic substrates + lipolysis and fatty acid mobilisation from adipose tissue

Hepatic lipidosis and fatty change in renal proximal convoluted tubule epithelium

Intracellular glycogen accumulation in many organs, especially in rapidly developing cases

Lesions in diabetes mellitus

Cataracts develop due to osmotic stress in the lens caused by accumulation of the glucose metabolite, sorbitol

Osmotic diuresis and dehydration develop since the renal threshold for glucose resorption is exceeded + electrolyte disturbances, especially hypokalaemia

Lesions of diabetes mellitus

With chronic hyperglycaemia,

Diabetic neuropathy

Diabetic nephropathy : characterised by glomerulosclerosis, mesangial proliferation, and hyaline thickening of vascular basement membranes

Diabetic retinopathy: due to deleterious vascular changes (pericyte depletion, capillary endothelial loss, microaneurysms, neovascularisation)

Ketoacidosis: insulin lack suppresses the use of ketones by peripheral tissues + stimulates lipolysis and ketogenesis in the liver, resulting in accumulation of ketones in the circulation, exacerbating dehydration and causing marked acidosis and hypokalaemia