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Chronic diseases of the pancreas and spleen

Guidelines for students and interns

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DISEASES OF THE PANCREAS AND SPLEEN
CHRONIC PANCREATITIS

Chronic pancreatitis is defined as a progressive inflammatory disease of the pancreas, characterized by irreversible morphologic changes and gradual fibrotic replacement of the gland. Loss of exocrine and endocrine function results from fibrosis and parenchymal damage. The primary symptoms of chronic pancreatitis are abdominal pain and maldigestion, which may be physically and socially debilitating. Because of diagnostic and therapeutic challenges, an interdisciplinary management strategy is required.

ANATOMY AND PHYSIOLOGY

The pancreas is a soft, elongated gland situated at the back of the upper abdominal cavity behind the stomach .

It is divided into the head (through which the common bile duct runs as it enters the duodenum) and the body (which extends across the spine and the tail), which is close to the left kidney and to the spleen. Because the pancreas lies at the back of the abdominal cavity, diseases of the pancreas may be difficult to diagnose.

The pancreas has two main functions:

1. It produces a series of enzymes which help in the digestion of food. Enzymes produced in the pancreas are important in the digestion of proteins, carbohydrates and, particularly, fats:

- Acinar cells secrete isozymes: amylases, lipases, and proteases.
- **Major stimulants**: cholecystokinin, acetylcholine, secretin, VIP.
- Synthesized in the endoplasmic reticulum of the acinar cells and are packaged in the zymogen granules.
- Released from the acinar cells into the lumen of the acinus and then transported into the duodenal lumen, where the enzymes are activated.

Physiology – Exocrine Pancreas:

- 500 to 800 ml pancreatic fluid secreted per day.
- Alkaline pH results from secreted bicarbonate which serves to neutralize gastric acid and regulate the pH of the intestine.
- Enzymes digest carbohydrates, proteins, and fats.

Enzymes of Pancreas:

- Amylase:
  - only digestive enzyme secreted by the pancreas in an active form;
  - functions optimally at a pH of 7;
  - hydrolyzes starch and glycogen to glucose, maltose, maltotriose, and dextrins.
- Lipase:
  - function optimally at a pH of 7 to 9;
  - emulsify and hydrolyze fat in the presence of bile salts.
- Proteases:
  - essential for protein digestion;

- secreted as proenzymes and require activation for proteolytic activity;
- duodenal enzyme, enterokinase, converts trypsinogen to trypsin;
- Trypsin, in turn, activates chymotrypsin, elastase, carboxypeptidase, and phospholipase

- Within the pancreas, enzyme activation is prevented by an antiproteolytic enzyme secreted by the acinar cells

Bicarbonate is also produced in large amounts to neutralise the acid produced by the stomach:

- Centroacinar cells and ductular epithelium secrete 20 mmol of bicarbonate per liter in the basal state.
- Fluid (pH from 7.6 to 9.0) acts as a vehicle to carry inactive proteolytic enzymes to the duodenal lumen.
- Sodium and potassium concentrations are constant and equal those of plasma.
- Chloride secretion varies inversely with bicarbonate secretion.
- Bicarbonate is formed from carbonic acid by the enzyme carbonic anhydrase.
- **Major stimulants**: secretin, cholecystokinin, gastrin, acetylcholine.
- **Major inhibitors**: atropine, somatostatin, pancreatic polypeptide and glucagon.
- Secretin – released from the duodenal mucosa in response to a duodenal luminal pH<3.

Digestion

Food is partly broken down by the acid and churning action of the stomach. After 1–2 hours food is slowly released into the duodenum through a valve called the pylorus. Here, and as it moves along the rest of the small bowel, the food is broken down into tiny particles. Nutrients are absorbed by the small intestine and used for energy and maintaining strong muscles and bones. Unwanted material passes into the large bowel (colon) and after 24 hours or so is excreted as stool via the rectum and anus.

Digestion of food which consists of carbohydrates (e.g. glucose), proteins (e.g. meat) and fat (e.g. butter) is not possible without the pancreas. Groups of glands in the pancreas (called acini) make 30 or so different **enzymes** each of which is responsible for breaking down clumps of different types of food into small particles for absorption. These enzymes are collected from the small glands in the pancreas into small ducts and finally into the main pancreatic duct to be released into the duodenum. The enzymes when they are first made in the acini are not active (otherwise they would digest the pancreas as well!). When they pass into the duodenum however, they are made active by the juice of the duodenum. The main enzymes are called amylase for digesting carbohydrates, trypsin for digesting proteins and lipase for digesting fats.

Digestion is also assisted by enzymes made and released by the salivary glands (amylase), tongue (lipase), stomach (pepsin and lipase) and small intestine (peptidases).

Fat needs to be dispersed before the pancreatic enzymes can properly break it down. This dispersion of fats is made by bile acids which are present in bile produced by the liver and stored in the gall bladder. Bile acids act in exactly the same way as detergents which are used to wash up greasy dishes. Therefore, both bile acids and pancreatic enzymes are needed for fat digestion. This is why the main pancreatic duct and the main bile duct join up together so that pancreatic juice and bile can be emptied together. If there are not enough pancreatic enzymes, fat is not digested and the stools (bowel motions) become pale and greasy. These greasy stools may become difficult to flush away from the toilet and may give off a strong offensive smell. Doctors call this **steatorrhoea**, which is a way of saying fatty stool.

For the same reason if the main bile duct becomes blocked, then the bile cannot get into the duodenum, fat cannot be properly digested and the stools are again pale in colour. Because the bile made by the liver cannot go into the bowel it goes into the blood and out through the kidneys into the urine. This results in the eyes and skin becoming yellow and is known as yellow jaundice. As the bile is in the urine this now becomes dark in colour. Because the flow of bile is blocked (or obstructed), doctors call this condition obstructive jaundice. As the bile duct goes through the head of the pancreas yellow jaundice can be caused by disease of the pancreas (such as pancreatitis or cancer).

2. It produces a series of hormones which are important in maintaining a normal level of sugar in the blood. The best known of these hormones is insulin. Insulin deficiency of this hormone results in the development of diabetes. Another hormone (glucagon) helps to raise blood sugar, and several other hormones control intestinal function.

Histology-Endocrine Pancreas:

- Accounts for only 2% of the pancreatic mass.
- Nests of cells – islets of Langerhans.
- Four major cell types:
  - Alpha (α) cells secrete glucagon.
  - Beta (β) cells secrete insulin.
  - Delta (D) cells secrete somatostatin.
  - F–cells secrete pancreatic polypeptide.

Insulin:

- Synthesized in the β–cells of the islets of Langerhans.
- 80% of the islet cell mass must be surgically removed before diabetes becomes clinically apparent.
- Proinsulin, is transported from the endoplasmic reticulum to the Golgi complex where it is packaged into granules and cleaved into insulin and a residual connecting peptide, or C peptide.
- **Major stimulants**: glucose, amino acids, glucagon, GIP, CCK, sulfonylurea compounds, β-sympathetic fibers.
- **Major inhibitors**: somatostatin, amylin, pancreastatin, α-sympathetic fibers.

Glucagon:

- Secreted by the α–cells of the islet.
- Glucagon elevates blood glucose levels through the stimulation of glycogenolysis and gluconeogenesis.
- **Major stimulants**: aminoacids, cholinergic fibers, β-sympathetic fibers.
- **Major inhibitors**: Glucose, insulin, somatostatin, α-sympathetic fibe.

Somatostatin:

- Secreted by the D–cells of the islet.
- Inhibits the release of growth hormone.
- Inhibits the release of almost all peptide hormones.
- Inhibits gastric, pancreatic, and biliary secretion.
- Used to treat both endocrine and exocrine disorders.

A HISTORICAL AND CRITICAL APPRAISAL OF CHRONIC PANCREATITIS

Although the Greeks were thought to be the first to recognize the pancreas as a distinct organ, rabbis in the earlier Babylonian Talmud refer to a structure designated by them as the "finger of the liver". While Galen provided a modest description of the organ, neither he, Hippocrates, Erasistratus nor Herophilus were able to identify a relationship to disease. These ancient anatomists regarded the pancreas as unusual, given that it had no cartilage or bone present, and Rufus of Ephesus (c. 100 AD) named the organ pancreas (Greek pan: **all** and kreas: **flesh or meat**). Andreas Vesalius referred to the pancreas in the fifth book of his opus as a "glandulous organ or kannelly body of substance growing in the neather pannicle of the caule (omentum)" and presumed the pancreas to exert a protective effect on the stomach by serving as a cushion (Schutzorgan) upon which it rested.

Even though the main duct of the human pancreas was described in 1642, it was utterly misunderstood since contemporary views considered that "chime" from the duodenum ascended into the pancreas to provoke secretion of a "sharp juice not unlike to the gall" Sylvius and his brilliant pupil, Regnier de Graaf of Delft, ingeniously developed a method for the direct investigation of the nature of pancreatic juice utilizing canine pancreatic fistula through which he inserted feather quills into the pancreatic duct orifice to obtain succus pancreaticus. They believed that pancreatic juice effervesced with bile, and that this combination of acids and alkalis was a critical component of digestion. They also postulated that pancreatic juice exhibited a dual function by both "attenuating the mucous lining of the gut as well as initiating segregation of the useful food elements." The use of the acid secreting complex gastric pyloric ceca from fish complicated this work and it was not until the end of the 17th century that Johann Bohn successfully demonstrated that the pancreatic juice was not acid.

By 1682, Brunner noted that his pancreatectomized dogs survived for up to a year despite polyuria, polydypsia, and bulimia, but failed to identify the presence of sugar in the urine. The clinical correlation of pancreatic disease and diabetes was only recognized in 1788 when Thomas Cawley broadly alluded to such a disease entity. The subject of the duct and the structure of the gland led

Sommering (1755–1830) to first employ the vernacular term Bauchspeicheldruse (abdominal salivary gland) in the medical and scientific literature and as a result, the pancreas was until the late 19th century considered to be an abdominal salivary gland. During the 18th century, Albrecht von Haller (1708–1777) noted the close relationship of the pancreatic duct to the bile duct and proposed that pancreatic juice and bile interacted in the process of digestion. Further contributions included Santorini's identification of the accessory duct (1742) while a detailed description of the embryology of the pancreas was provided by Meckel (1806). Trypsin was identified by Willy Kuhne (1837–1900) and in 1815, Alexander Marcet (1770–1822) identified lipase. Between 1849 and 1856 Claude Bernard (1813–1878) of Paris unified the concepts of pancreatic digestion by demonstrating that gastric digestion "is only a preparation act" and that pancreatic juice emulsified fatty foods, splitting them into glycerin and fatty acids. In addition, he demonstrated the power of the pancreas to convert starch into sugar and its solvent action upon the "proteides that have not been cleaved in the stomach." Further work by Eberle in 1843 demonstrated that pancreatic juice emulsified fat, and a year later Valentin demonstrated its activity on starch. Differences in the exocrine and endocrine pancreas were elucidated by Paul Langhans (1869) while in 1882, Kuhne and Lea noted the complex capillary network which embraced the collection of islets. The regulation of pancreatic secretion led I.P. Pavlov (1849–1936) and his pupils to use novel pancreatic fistula preparations to demonstrate the role of the vagus nerve in the neural regulation of pancreatic secretion. Thereafter Dolinski noted that acid introduced into the duodenum stimulated pancreatic secretion and interpreted this as indicative of a local neural reflex, while Chepovalnikov demonstrated that pancreatic juice acquired and exerted a powerful solvent action on proteids only after contact with either the duodenal membrane or extracts thereof. This led to the discovery of enterokinase. It was left to Bayliss and Starling to introduce the concept of hormonal regulation of the organ.

Pancreatitis

Since the anatomic location of the organ was not well known and its physiological functions ill defined, pathological conditions of the pancreas were difficult to delineate. Descriptions of pancreatic abnormalities from antiquity refer mostly to "scirrhous" disease, without any specific identification of pathology. In Germany Friedreich and Claasen were prominent in establishing the role of alcohol in pancreatitis and defined its clinical and pathological sequel in the 1880s. Subsequently, Reginald Fitz of Boston, who had studied with Claasen, defined the signs and symptoms of pancreatitis and categorized the disease in terms of its gangrenous, hemorrhagic and suppurative forms. His reflections on the nature and causes of the disease were published in the Boston Medical and Surgical Journal of 1889, and have remained little changed in the centuries since their initial proposal. Eugene Opie in 1901 further elucidated the pathogenesis of pancreatitis and proposed a *"*common channel*"* hypothesis whereby acute pancreatitis was the aftermath of the flow of infected bile into the pancreatic duct

from the common bile duct. He proposed that this clinical circumstance occurred when a gallstone became impacted in the ampulla of Vater and caused obstruction. Further credence for this theory was provided by E. Archibald (1919) who experimentally demonstrated that spasm of the sphincter of Oddi increased biliary pressure and culminated in the development of acute pancreatitis. Although alcohol and gallstones remain among the common denominators of the etiology of acute pancreatitis to this day, Rich and Duff in 1936 proposed that a combination of pathological vascular changes and local pancreatic enzyme damage were implicated in the pathogenesis. The diagnosis of acute pancreatitis, which had initially been purely clinical, was subsequently supported by the work of R. Elman of St. Louis who in 1929 described the quantitative determination of blood amylase using a viscometer. Subsequent investigations have proposed that the cytokine cascade of acute pancreatitis may be a consequence of disorganized intracellular trafficking or activation of acinar zymogen granules. Unfortunately the etiology of both acute and especially chronic pancreatitis remains shrouded in dogma and conjecture.

Early observations on chronic pancreatitis

The identification of the etiology of chronic pancreatitis has frustrated physicians since the very earliest observations of the entity. Initially the pathological examination of the pancreas was the most defining focus in the diagnosis with clinical assessment of the patient as the only available diagnostic tool for the physician. As early as 1788, Cawley became the first to suggest a link between lifestyle and pancreatic disease. His patient, "a 34 year old man accustomed to free living and strong corporeal exertions in the pursuit of country living," was noted to have extensive pancreatic disease at autopsy.

One of the earliest reports of pancreatitis was by Edwin Klebs who reported a case of hemorrhagic pancreatitis in 1870. This was followed by many scattered reports throughout the medical literature without much focus toward a diagnosis before the patients demise. At the turn of the 19th century Mayo Robson presumed the etiology to be due to bacterial infection; however, the distinction between acute, sub-acute and chronic pancreatitis was still controversial. Other physicians, including Reginald Fitz, felt that the underlying insult was the hemorrhage of the pancreas which resulted in necrosis of the gland as evidenced at autopsy. This assessment resulted in some prejudicial views, since cases described by pathologists represented advanced and fatal forms of pancreatitis. Thus many early attempts at classification resulted in contradictions as physicians and pathologists differed on the nature of the process and in addition lacked scientific data to address the question of etiology.

In 1946 Comfort provided a significant analysis of the clinical entity of chronic pancreatitis and in so doing produced the seminal manuscript on the subject that has for 50 years remained the critical commentary on the disease. Although there had been references to the relationship between alcohol and chronic pancreatitis, there were no clinical studies and proof remained anecdotal until Comfort described in detail the connection between alcohol abuse and chronic pancreatitis. His study added considerable credibility to the much earlier description of the "drunkard's pancreas" by Friedrich in the 19th century.

The criteria utilized by Comfort to characterize the diagnosis included recurrent attacks of abdominal pain, disturbances of acinar function and alterations in endocrine function. During the last fifty years, despite the fact that much has been learned from studies of alcoholic pancreatitis the definitive mechanisms are for the most part obscure. The relative increase in the diagnosis of pancreatitis probably reflects a wide variety of factors including increased awareness, greater diagnostic skill and more sophisticated technology as well as an increase in alcohol consumption. Considerable debate has centered around the question of whether pancreatic lithogenesis is a diagnostic criterion of chronic pancreatitis or whether it merely represents a correlatible epiphe-nomenon. Prior to the twentieth century, pancreatic stones were thought of as exceedingly rare. Calcium carbonate was known to be the main chemical in the composition and, as might therefore be predicted, diagnosis of the condition increased substantially as the new technique of roentgenography facilitated visualization. The similar increase in surgical recognition further dispelled the notion of rarity. While exhaustive analysis confirmed the composition of the calculi the mechanism of the initiation of the pancreatic precipitates eluded identification. A wide variety of agents including lactoferrin, alcohol, and the pancreatic stone protein lithostatine have been associated with pancreatic calculi. The question however of whether the calculi are caused by an increase in calcium production, precipitation of proteins or a yet to be defined mechanism remains as yet unclear. Indeed the correlation between the mere presence of pancreatic calculi and the diagnosis of chronic pancreatitis itself remains debated. Thus in the condition of "senile pancreatitis", described by Amman, the presence of idiopathic asymptomatic pancreatic calculi in the elderly suggests that chronicity and calculi may not necessarily occur pari passu.

There is however little disagreement that pancreatic stones may obstruct the ducts and play a part in the development of pancreatic pain. This observation has resulted in efforts to remove stones by either medical dissolution (including HCL) or mechanical intervention. Thus lithotripsy, endoscopic sphincterotomy with or without stent placement and a wide variety of ductal and pancreatic surgical techniques have been proposed to eliminate calculous disease of the pancreas.

In 1959, Zuideman labeled dietary factors as an additional etiologic agent and proposed that the entity known as "tropical pancreatitis" in underdeveloped countries was associated with the standard low protein, fat-deficient diet prevalent in such areas. Subsequent reports have suggested that the Cassava root (manioc) might be the agent implicated in tropical pancreatitis, but rigorous confirmation of this theory is still required. Despite considerable attention to the identification of the basis of chronic pancreatitis approximately 30% of patients diagnosed with the disease still are regarded as idiopathic with no known evidence of any associated disease or inciting event.

In the absence of minimal evidence for etiology the identification of a mechanistic explanation of the disease process has been similarly frustrating. Various theories have been propounded to explain the pathology, including the necrosis-fibrosis concept of Kloppel, the obstruction theory of Sarles, the toxic

metabolic hypothesis of Bordalo and the oxidative stress hypothesis of Braganza. No rigorous data in support of any of these hypotheses exists though each in its own right has attractive elements.

As a result of the absence of a defined etiology and the lack of a mechanism of disease, clinical attention to chronic pancreatitis has for the most part focused on establishing a diagnosis and thereafter management of the sequelae, including pain, ductal obstruction and the exocrine and endocrine deficits based upon acinar and islet cell destruction.

ETIOLOGY AND PATHOGENESIS

At least 70% of adult cases are caused by chronic alcohol use, and most patients have consumed more than 150 g/day of alcohol over six to twelve years.

The pancreatic injury induced by ethanol exposure is likely to be multifactorial. Proposed mechanisms include: a) ductal hypertension induced by increased viscosity of secretions in combination with obstruction secondary to sphincter of Oddi dysfunction, stimulation of secretion, and increased duct permeability, b) decreased pancreatic blood flow, c) inflammation and oxidant stress, d) direct acinar cell toxicity, e) changes in protein synthesis, f) an enhanced inflammatory response, and g) stimulation of pancreatic fibrosis. A growing body of evidence suggests that alcohol can cause acute injury even in the absence of underlying chronic disease. Future studies should define the factors that result in patients developing either acute bouts of disease or chronic pancreatitis. Since only a fraction of patients that abuse alcohol develop pancreatic disease, elucidation of the determinants that increase an individual's susceptibility to alcohol is an important topic for study.

Gallstone-associated pancreatitis is predominantly acute or relapsing-acute in nature, and some cases of chronic pancreatitis are of undetermined or idiopathic origin. A few are inherited or secondary to Sphincter of Oddi dysfunction.

Other less frequent causes include chronic steroid and or anti-inflammatory use. In up to one quarter of cases, no cause can be found. Autoimmune pancreatitis is increasingly recognised and may be associated with raised IgG4 levels, other autoimmune features and bile duct involvement. Autoimmune chronic pancreatitis (AIP) is a rare condition, but may account for a substantial proportion of patients with "idiopathic" chronic pancreatitis. The entity known as "non-alcoholic duct-destructive chronic pancreatitis" may actually represent AIP. AIP may occur in isolation or in association with other autoimmune diseases, such as Sjögren's syndrome, PSC, and inflammatory bowel disease. Clinical features include minimal pain, hypergammaglobulinemia, autoantibodies (ANA, anti-lactoferrin, anti-carbonic anhydrase I and II, anti-smooth muscle, others), diffuse enlargement of the pancreas on imaging, typical lack of calcifications and cysts, and improvement with steroids. Histopathological findings include fibrotic changes with infiltration of lymphocytes and plasmacytes, often concentrated around the pancreatic duct.

Pancreatic duct obstruction (~10%) is increasingly recognised and may be associated with stones, stricture, tumor, pseudocyst, pancreas divisum etc.

Cystic fibrosis is the most common cause of chronic pancreatitis in children. In other parts of the world, severe protein-energy malnutrition is a common cause. Hereditary Pancreatitis, which is defined as recurrent pancreatitis attacks, can progress to chronic pancreatitis. This form of pancreatitis should be suspected in younger patients and those with relatives who also suffer from pancreatic disease. Both hereditary and chronic pancreatitis are major risk factors for developing pancreatic cancer. Yet the hereditary form increases the risk for cancer significantly, making a proper diagnosis essential.

New discoveries of genetic, immune-mediated, and environmental risk factors for chronic pancreatitis have caused this category to dwindle in recent years. However, 10–30% of patients with chronic pancreatitis possess no clear risk factors for the disease. Idiopathic chronic pancreatitis has been classified as early and late onset, given its bimodal age presentation and differences in presentation. Early-onset idiopathic chronic pancreatitis typically presents in the first two decades of life with severe abdominal pain. Structural changes, exocrine insufficiency, and calcifications occur much later in the course. Late-onset idiopathic chronic pancreatitis occurs in the fourth or fifth decade with minimal pain, often with pancreatic insufficiency at the time of diagnosis. Exocrine and endocrine dysfunction and pancreatic calcifications are much more likely to occur in late-onset idiopathic chronic pancreatitis. Possible mechanisms for both early and late onset idiopathic chronic pancreatitis include occult alcohol use and undiagnosed genetic defects. The serine protease inhibitor Kazal type 1 (SPINK-1) mutation has been noted in many patients previously characterized as having early idiopathic chronic pancreatitis. SPINK-1 is the gene that encodes pancreatic secretory trypsin inhibitor, a protein that plays a primary role in counteracting the effects of activated trypsin. Mutations causing loss of function of this protein increase the risk of development of acute and chronic pancreatitis. It is likely that underlying CFTR mutations exist in many of patients with idiopathic chronic pancreatitis as well.

In recent years, there have been great discoveries in genetic mechanisms for several inherited causes of chronic pancreatitis (HP, cystic fibrosis gene, SPINK-1, *etc.*). These discoveries have provided important insights into the genetics of pancreatic disease, as well as understanding of pathogenesis of acute and chronic pancreatitis. The details of these important genetic discoveries are discussed in a recent, excellent review.

Other causes include:

- high levels of calcium in the blood;
- abnormalities in anatomy which are usually present at birth;
- high blood fats (hypertriglyceridaemia);
- in rare cases, some drugs can cause pancreatitis;
- tropical;
- trauma;
- idiopathic (~10%).

The recently generated TIGAR-O etiological classification of chronic pancreatitis incorporates new insights into genetic, environmental, immunological and pathobiological risk factors associated with chronic pancreatitis.The TIGAR-O etiological classification consists of 6 groups:

1. Toxic-metabolic
- Alcoholic.
- Tobacco smoking.
- Hypercalcaemia.
- Hyperlipidaemia.
- Chronic renal failure.
- Medicines-phenacetin abuse.
- Toxins-organotin compounds, for example, di-N-butyltin dichloride (DBTC).

2. Idiopathic
- Early onset.
- Late onset.
- Tropical.

3. Genetic
- Hereditary pancreatitis-cationic trypsinogen.
- Cystic fibrosis transmembrane conductance regulator (CFTR) mutations.
- Serine protease inhibitor, Kazal type 1 (SPINK1) mutations.

4. Autoimmune
- Isolated auto-immune chronic pancreatitis.
- Syndromic autoimmune chronic pancreatitis associated with Sjogren's syndrome, inflammatory bowel disease, primary biliary cirrhosis.

5. Recurrent and severe acute pancreatitis.
- Post-necrotic (severe acute pancreatitis).
- Recurrent acute pancreatitis.
- Vascular diseases/ischaemia.
- Post-irradiation.

6. Obstructive
- Pancreas divisum.
- Sphincter of Oddi disorders (controversial).
- Duct obstruction (e.g., tumour).
- Peri-ampullary duodenal wall cysts.
- Post-traumatic pancreatic duct scars.

PATHOLOGY

Chronic inflammation of pancreas:
- Mononuclear cell infiltrate.
- Fibrosis/calcification/irreversible anatomic changes.
- Characteristic duct changes.
- With or without calcification.
- Affects exocrine and/or endocrine organ (including α–cells).

Chronic pancreatitis is defined by the presence of chronic inflammation, destruction of acinar and ductal cells, intra- and perilobular fibrosis and finally by the irreversible scarring of parenchyma.

SYMPTOMS OF CHRONIC PANCREATITIS

The symptoms are very variable.

Pain occurs in most patients at some stage of the disease. This may vary in intensity from mild to severe. It may last for hours or sometimes days at a time and may require strong painkillers to control it.

It often radiates through to the back and can sometimes be relieved by crouching forward. It is commonly brought on by food consumption and so patients may be afraid to eat. It is also commonly severe through the night.

The pain varies in nature, being gnawing, stabbing, aching or burning, but it tends to be constant and not to come and go in waves. It may sometimes burn itself out but can remain an ongoing problem.

The mechanism of the pain is unclear. It seems to be related to pancreatic activity since it is frequently caused by food, especially fatty or rich foods.

Some patients will have obstruction to the small ducts in the pancreas by small stones, and this is thought to cause back pressure and destruction of the pancreas. There is no relationship between the severity of the pain and the severity of the pancreatic inflammation.

The pain is often difficult to diagnose and can be mistaken for pain caused by virtually any other condition arising from the abdomen or lower chest.

It can be difficult to distinguish pain caused by pancreatitis from pain caused by a peptic ulcer, irritable bowel syndrome, angina pectoris, gallstones.

Given that pain is the result of increased activity in a specific neural network linking the brain to the pancreas caused by inflammation and injury, an important question is the physiological role of this network activation. Pain during visceral inflammation could be thought of as a disabling and unfortunate consequence of disease. This would mean that visceral afferents carry the signal from the inflamed pancreas to the brain, where pain is perceived, but that does not lead to any kind of meaningful behavioral or neurogenic response. This is most unlikely. At the very minimum, perception of pain will lead to behavioral changes, which may be quite nonspecific for any given illness, but would likely be aimed at minimizing injury. For example, aff licted by pancreatitis pain, the patient will rest more and stop eating, all of which will tend to minimize the risk of further health compromise.

Second, an attractive alternative based on evidence across species is that pain has a profoundly adaptive significance as a promoter of salutogenic bodily responses (although one can say that pain-induced behavioral changes can be viewed as a type of salutogenic mechanism, in this paper we define salutogenic mechanism as the specific modulation of the immune system induced by brain activity changes), some of which may be quite disease or organ specific. The

activation of pain-processing brain structures in response to nociceptive inputs from the viscera may activate a two-way pathway and trigger brain-mediated healing-promoting responses. Activation of such salutogenic mechanisms may necessarily be mediated by pain-processing brain structures or be independent of them. In the first instance, pain might be an indicator of the activation of salutogenic bodily responses. In the other instance, pain and salutogenic responses may be both independent, brain-mediated mechanisms for a summary of the relationship between pain and salutogenic brain mechanisms). If pain in chronic pancreatitis is a salutogenic mechanism, reducing it by techniques of brain modulation might worsen the pancreatic inflammation.

A recent pathophysiological concept interprets the generation of pain as an interplay between the nerve- and immune system. Immunohistochemical analysis shows a high density of enlarged nerve fibres in chronic pancreatitis tissue. R. Keith et al. (1985) could show that the pain level in patients with chronic pancreatitis correlated more with the degree of eosinophil infiltration of these enlarged nerves rather than with the degree of duct dilatation. Electrone microscope analysis of these nerves reveals damaged perineurium and infiltration of leucocytes which may explain how pancreatic enzymes and mediators of inflammation enter neural structures and alter their structure and functioning. Immunhistochemical analysis of chronic pancreatitis tissue revealed an altered pattern of intrinsic and extrinsic innervation with overexpression of different neurotransmitters such as “Substance P” und “Calcitonin Gene Related Peptide” (CGRP) in enlarged intrapancreatic nerves. Since both cytokines are important pain transmitters, these findings provide evidence that alterations of pancreatic nerves themselves are involved in the pathogenesis of the disease and lead to the concept of neuroimmune interaction as a basic mechanism in the pathogenesis of chronic pancreatitis and chronic pain syndrome.

This interesting hypothesis is confirmed by the fact, that the presence of growth-associated-protein-43 (GAP-43), an established marker of neuronal plasticity, correlates with individual pain scores in patients with chronic pancreatitis.

Diabetes is also a common symptom which affects over half of all patients with long-standing chronic pancreatitis.

Long-standing chronic inflammation results in scarring of the pancreas which destroys the specialised areas of the pancreas which produce insulin.

Deficiency of insulin results in diabetes. Diabetes causes thirst, frequent urination and weight loss. It may be possible in the early stages of chronic pancreatitis to treat the diabetes with tablets, but in the late stage of chronic pancreatitis, insulin injections are usually needed.

Diarrhoea occurs in just under half of patients. Normally, all the fat in food is broken down by enzymes from the pancreas and small intestine, and the fat is then absorbed in the small bowel. With a reduced level of digestive enzymes the fat is not absorbed. When the fat reaches the large intestine, it is partially broken down by the bacteria in the colon. This produces substances

which irritate the colon and result in diarrhoea. The undigested fat also traps water in the faeces, resulting in pale, bulky, greasy stools which are difficult to flush away. They may make the water in the toilet look oily, smell offensive and may be associated with bad wind.

Weight loss occurs in virtually all patients with chronic pancreatitis. It is due to failure to absorb calories from food, and diabetes may also contribute to this. In addition, patients may be afraid to eat because eating brings on the pain. Depression is also common in chronic pancreatitis and this can also reduce appetite and lead to weight loss.

Jaundice (when patients develop yellow eyes and skin) occurs in about a third of patients with chronic pancreatitis. It is usually due to damage to the common bile duct which drains bile from the liver to the duodenum.

The common bile duct normally passes though the head of the pancreas. In long-standing chronic pancreatitis, the scarring in the head of the pancreas narrows the common bile duct.

Some degree of narrowing may occur in up to half the patients with chronic pancreatitis but when the narrowing is severe, it prevents the bile draining from the liver into the duodenum. It then spills back into the blood and the patient's eyes and skin become yellow. In addition, the stools become paler (since bile makes the stools brown) and the urine becomes dark (because it contains more bile than normal).

Vomiting after meals is a less common symptom but can occur as a result of severe pain. It may also be due to duodenal ulceration, which is often connected with chronic pancreatitis. In rare cases, the duodenum may be narrowed as a result of scarring secondary to chronic pancreatitis.

Vitamin and mineral deficiency. Prolonged passage of stools containing fat can result in low levels of calcium and magnesium in the blood. In addition, some vitamins may not be absorbed properly. This includes vitamins D and A.

COMPLICATIONS

Chronic pseudocysts are benign cysts formed of pancreatic fluid and surrounded by a fibrous wall.

The pathogenesis of pseudocysts in chronic pancreatitis is believed to be ductal obstruction, leading to upstream dilation and cyst formation. Endoscopic retrograde cholangiopancreatography may show communication of the cyst with the main pancreatic duct. The typical clinical presentation of a pseudocyst is worsening abdominal pain in the setting of known chronic pancreatitis, with or without mild elevation in the serum amylase and lipase levels. Biliary obstruction and gastric outlet obstruction may occur because of compression of the bile duct and duodenum from severe fibrosis, enlarging pseudocysts, or pancreatic cancer. Pancreatic adenocarcinoma contributes substantially to mortality, developing in 4% of patients with long-standing chronic pancreatitis. The diagnosis may be difficult but should be suspected in the setting of

worsening abdominal pain, weight loss, or functional decline. Imaging tests often produce uncertainty in differentiating cancer from inflammatory masses, and brushings are frequently nondiagnostic. A definitive diagnosis might not be made until the time of surgical resection.

Pancreatic fistulas, ascites, and pleural effusions arise from a communication of pancreatic pseudocysts with adjacent cavities or from disruption of the pancreatic ducts. The diagnoses of pancreatic ascites and pleural effusions are based on the finding of elevated fluid amylase content. Endoscopic stent placement across the pancreatic duct disruption may ameliorate these complications. Splenic vein thrombosis is common and usually asymptomatic; however, recurrent bleeding from secondary gastric varices develops in some patients.

DIAGNOSIS

Chronic pancreatitis often causes no symptoms and may be discovered by accident during the course of investigation of symptoms not related to pancreatitis. For example, calcification in the pancreas may be seen on an X-ray of the abdomen performed for other reasons.

Ultrasound examination of the abdomen

This type of examination is identical to that performed in pregnant women to assess the growth of the baby. It uses a transponder to generate high-frequency sound waves that bounce back from the deep tissues and are detected by the transponder (transmitter and responder). It is a very safe technique and is widely used. It is performed by smearing some jelly over the upper abdomen and then moving the transponder across the skin of the upper abdomen.

However, because the pancreas lies at the back of the abdominal cavity and, therefore, a long way from the transponder, images of the pancreas may be difficult to obtain. Sometimes the problem is obesity, sometimes the pancreas is obscured by air within the intestines.

Even if the result of the ultrasound examination is normal, this does not rule out the possibility of chronic pancreatitis.

Abdominal CT scanning

A CT scan is a very sophisticated X-ray in which the patient lies on a table which is moved through an X-ray tube. The information thus obtained is then analysed by a powerful computer which then produces ‘slices’ though the abdomen. This technique is more reliable in imaging the pancreas than abdominal ultrasound.

However, a normal CT scan does not exclude a diagnosis of chronic pancreatitis.

Abdominal MRI scanning

MRI scanning is a newer technique of examining abdominal organs. It does not involve X-rays.

The patient is passed though a large and powerful magnet which energises molecules in the tissues. Radio pulses are then generated to create a signal that analysed by powerful computers. It is harmless, does not involve X-rays, but is very noisy.

MRI–Cholangiopancreatography is currently under evaluation with regard to the accuracy of diagnosis of pancreatic disease.

Endoscopic retrograde cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) is a procedure whereby X-ray contrast material is injected into the bile duct and pancreatic duct to allow X-ray pictures to be taken of these ducts.

Under sedation, an endoscope is passed into the duodenum, a small cannula (a very small tube) is inserted into the pancreatic duct and X-ray contrast is injected. X-rays are then taken.

This is currently regarded as the 'gold standard' for the diagnosis of chronic pancreatitis. At present, it is the only method by which minor changes (minimal change pancreatitis) can be reliably demonstrated.

Abnormalities which range from minor changes in side branches of the pancreatic duct to major changes in the main pancreatic duct can be identified by this method. It is sometimes possible to remove stones from the pancreatic duct.

However, ERCP is not routinely used as the first line of investigation in suspected pancreatitis because it requires a high degree of endoscopic expertise. There is also a very real risk of inducing a further attack of pancreatitis in the patient as a result of the irritant effect of the X-ray contrast within the duodenum.

Analysis of pancreatic juice

This was widely used before the advent of CT scanning and ERCP. The idea is that analysis of the pancreatic juice within the duodenum would identify pancreatic failure. However, the function of the pancreas has to be severely impaired for the test to be abnormal. In the UK this test is rarely performed outside of research centres.

Endoscopic ultrasound scan (EUS)

This is a special ultrasound investigation in which the ultrasound transponder is mounted on an endoscope. This technique is not widely available and is not as sensitive as ERCP at detecting minor degrees of chronic pancreatitis.

Abdominal X-ray

This may sometimes show calcification of the pancreas in chronic pancreatitis. This tends to occur late in the natural history of the disease and therefore, usually after the diagnosis has already been made. If the diagnosis has not already been made, then further tests are unnecessary.

FUNCTION TESTING

1. **Fecal elastase** – "gold standart". An indirect pancreatic function test; reduced in severe disease to less than 200 micrograms/g. All indirect pancreatic function tests have relatively high sensitivity and specificity in severe chronic pancreatitis with malabsorption. All are inaccurate for diagnosing mild-to-moderate pancreatic insufficiency.

Faecal elastase has an unacceptably low sensitivity for diagnosing exocrine pancreatic insufficiency, ranging from 64% for severe disease to 40% for mild-to-moderate disease. Similarly, reduced fecal elastase has only 58% specificity for exocrine pancreatic insufficiency in patients with type 1 diabetes mellitus.

2. **Fecal fat test.** This test is performed by administering 100 g fat per day and measuring the faecal fat excretion over 72 hours. Increased faecal fat over 7 g/day is a late-stage manifestation of chronic pancreatitis.

- Distinguish between pancreatic dysfunction and intestinal malabsorption.
- In Pancreatic disease when lipase secretion is reduced by 90% – 24-hour fecal fat content is elevated to more than 20 g.
- Intestinal dysfunction – steatorrhea with low levels of fecal fat.
- Use-efficacy of pancreatic enzyme replacement.

3. **Steatocrit.** A rapid gravimetric method to measure stool fat. When performed on samples from a 72-hour stool collection, steatocrit is as sensitive and specific as a 72-hour quantitative stool fat, and may be as accurate if performed on a 24-hour stool collection or random stool samples

4. **Direct pancreatic function tests.** Most sensitive and specific test for diagnosing mild-to-moderate pancreatic insufficiency or chronic pancreatitis, but only available in a few centres. Pancreatic juice is collected with a gastroduodenal tube during exogenous hormone stimulation with cholecystokinin (CCK) and/or secretin. Helps differentiate pancreatic from non-pancreatic types of malabsorption.

5. **Genetic screening**. A consensus conference stated that only cationic trypsinogen or serine protease I (PRSS1) mutation testing (for hereditary pancreatitis) had definite clinical benefit and that testing for all other mutations, for example, the cystic fibrosis transmembrane conductance regulator (CFTR) or serine protease inhibitor, Kazal type 1 (SPINK1), should be relegated to research protocols.

6. **Biopsy.** Rarely, biopsy is required, particularly for distinguishing between auto-immune pancreatitis and pancreatic cancer. Changes produced by chronic pancreatitis depend on disease severity and include an increase in connective tissue, inflammatory and fibrotic changes, loss of acini and plugs of precipitated protein in the ductal tissue. Ruling out malignancy is a major diagnostic problem, especially in patients with an enlarged pancreatic head. Exclusion of malignancy frequently requires surgical resection to ensure a reliable histopathological examination. In 10% of patients, the diagnosis of pancreatic cancer is only established by histological proof at the time of operation.

7. **Serum ANA antibodies + IgG4 levels.** Positive testing for serum ANA antibodies and IgG4 levels suggests autoimmune pancreatitis. These tests are an alternative to biopsy, but should only be used by specialists.

8. **Therapeutic trial of corticosteroids**. A positive response suggests autoimmune pancreatitis. This test is an alternative to biopsy, but requires follow up and should only be used by a specialist.

DIFFERENTIAL DIAGNOSIS

- Pancreatic cancer.
- Acute pancreatitis.
- Biliary colic.

- Peptic ulcer disease.
- Mesenteric ischaemia.
- Aneurysm, abdominal aorta.
- Intestinal obstruction.
- Irritable bowel syndrome.
- Gastroparesis.
- Somatisation disorders.
- Radiculopathy.
- Post-herpetic neuralgia.
- Abdominal wall pain.
- Nephrolithiasis.

TREATMENT

Three components are essential to the optimal management of chronic pancreatitis: 1) control of pain; 2) improvement of maldigestion; and 3) management of complications.

Control of Abdominal Pain

The management of chronic pancreatic pain is challenging. The American Gastroenterological Association (AGA) has published an evidence-based technical review on the management of pain in chronic pancreatitis. In this review, the available medical, endoscopic, and surgical techniques for pain control are critically evaluated in the context of existing literature. The following discussion reflects these guidelines.

Maldigestion

Pancreatic enzymes are used for the treatment of maldigestion in chronic pancreatitis. Exogenous pancreatic enzymes are safe, well tolerated, and produce few side effects. There are a multitude of available pancreatic enzyme preparations; they differ based on enzyme content, the use of microspheres versus microtablets, and the presence of a coating for delayed release. Lipase is the most important determinant of the effectiveness of individual preparations. A minimum of 30,000 U lipase per meal allows adequate intraluminal digestion of fat and protein in most patients. The dose may need to be titrated to as much as 60,000 to 80,000 U lipase per meal, because not all the lipase may reach the proximal small intestine in active form. Enzymes may be taken entirely at the onset of each meal; however, dosing is more physiologic if one half the amount is taken at the onset of the meal and the other half is taken approximately 15 minutes into the meal.

Because the enzyme “microspheres” contained in most coated preparations are typically released too distally in the small bowel, uncoated preparations are optimal for the management of maldigestion. Alternatively, patients may break open coated capsules and sprinkle the microspheres over food to ensure proper delivery to the proximal bowel. Because uncoated preparations are more easily denatured by gastric acid, acid suppression with a proton pump inhibitor (e.g.,

omeprazole, 20 mg once daily) or histamine-receptor antagonist (e.g., famotidine, 20 mg twice daily) is required.

Response to enzyme therapy may be monitored through an assessment of symptoms or, more objectively, through 72-hour stool fat quantification. A poor response to pancreatic enzymes may suggest noncompliance, loss of enzyme potency, improper timing of enzymes in relation to meals, or coexisting mucosal disease. A daily proton pump inhibitor may be added for those refractory to therapy because gastric acid may denature exogenous enzymes.

Management of Complications

Large or symptomatic pseudocysts may be drained endoscopically through transmural or transpapillary approaches. Large pseudocysts may also be definitively drained surgically through cyst gastro-stomy. Biliary and gastric outlet obstructions are best managed through surgical decompression. Complications of pancreatic duct disruption or fistulas (pancreatic ascites or pleural effusions) are managed by prolonged pancreatic rest (parenteral nutrition) and endoscopic placement of pancreatic duct stents.

Cleveland Clinic Approach

Because of the significant challenges inherent in the management of this disease, we have developed a multidisciplinary approach similar to the AGA algorithm. Patients first undergo a diagnostic and staging evaluation. Most patients undergo CT and/or MRCP to evaluate the pancreatic ducts and parenchyma. Secretin-stimulated direct PFT, ERCP, and EUS are used as second-line tests to diagnose early CP in patients in whom initial imaging is negative.

Once the diagnosis of CP has been established, patients with severe pancreatic pain refractory to initial conservative management are referred for a differential nerve blockade to clarify the origin of their pain syndrome. Patients with nonvisceral pain are referred for psychotherapy and chemical dependency treatment. Patients with visceral pain are first given a trial of conservative medical management. If pain persists, patients with large duct disease or pseudocysts are referred for surgical management or endoscopic therapy. Patients with small duct disease are referred for anesthesia pain management for a visceral pain block. Minimal change disease that fails to respond to nerve blocks may be considered for resection or experimental drug trials. Patients who fail to improve with these medical and surgical therapies may benefit from thorascopic splanchnicectomy.

Surgical management

There are a number of different surgical interventions available in the treatment of chronic pancreatitis.

Major goals of surgery are to:

- Eliminate or reduce intractable pain.
- Address associated complications, for example, biliary obstruction, duodenal obstruction, and pseudocyst compression.

- Exclude pancreatic carcinoma.
- Conserve functional tissue.

Predictors of surgical success are:

- Segmental fibrosis (distal or proximal).
- Diffuse ductal dilation (length >10 cm and diameter > 5 to 7 mm).
- Associated or adjacent organ complication, for example, biliary obstruction, duodenal obstruction, and pseudocyst compression.

SURGICAL PROCEDURES OF CHRONIC PANREATITIS

The ideal procedure for treating pain in chronic pancreatitis should be the one which is simple, easy to perform, associated with a low morbidity/mortality rate and at the same time providing adequate drainage and not for augmenting its endo/exocrine insufficiency. Surgeries for chronic pancreatitis can be broadly classified as:

A. Drainage procedures:

1. Partial: draining the duct partially e.g. Duval, Puestow.

2. Complete: consists of draining the main duct completely e.g. Partington's, Bapat's.

B. Resectional procedure: resecting a part of pancreas with adjoining organs: e.g. Whipples, Child's.

C. Extended drainage procedure: adding a pancreatic sphincterotomy to the drainage procedure e.g. Rumpf's.

D. Resection with extended drainage: a combination e.g. Beger's, Frey's.

The rationale for various procedures are:

- Drainage procedures were developed on the basis that pain in chronic pancreatitis is due to ductal hypertension and proper drainage would decompress it.
- On the other hand, theory of perineural inflammation as the cause of pain led to development of resectional procedures.

A. Drainage Procedures

It has been more than 3/4th of a century since these procedures were proposed. Duval and Zollinger first applied this principle. These procedures provide pain relief in upto 60–80% of cases.

I. Partial Drainage Procedures

1. ***Duval procedure*** (1954)**:** developed on the basis of presumption that a single stricture of duct of Wirsung near the ampulla was responsible for the obstructive pathology and terminal drainage would treat the condition. It consists of a distal pancreatectomy with splenectomy and retrograde drainage of the main duct into a defunctioned jejunal loop.

2. ***Peustow-Gilesby procedure*** (1958): these authors demonstrated that multiple strictures (chain - of - lake appearance) were the pathology involved in chronic pancreatitis. They recommended a longitudinal opening of pancreatic duct from site of transection of the pancreatic duct after resection of pancreatic tail and splenectomy, to a point just to the right of mesenteric vessels and

invagination of the open duct with pancreas into a Roux-en-Y loop of jejunum. This achieved wider drainage of the ductal system.

3. ***Leger's procedure*** (1974): developed for distal stricture and consists of upto 40% distal pancreatectomy with splenectomy and opening of pancreatic duct into a loop of jejunum by a retrograde, lateral pancreatico-jejunostomy.

II. Complete Drainage Procedures

1. ***Partington-Rochelle procedure*** (1960): suggested a refinement in Peustow's procedure. A dilated mainpancreatic duct (minimum 8 mm) is a prerequisite for a good duct to mucosa anastomosis, however people have even reported a mucosa to capsule anastomosis when the duct size is 5 mm. It consists of a side to side, long, lateral pancreaticojejunostomy without resection of pancreatic tail or spleen.

B. Resectional Procedures

These procedures were resorted to when lesser procedures failed especially when malignancy could not be ruled out.

1. ***Whipples procedure*** (1935): described by Allen O. Whipple first in 1946, but published later for malignant lesions of head of pancreas, now used for benign, inflammatory mass in head of pancreas with a non dilated pancreatic duct. It consists of a pancreaticoduodenectomy with reconstruction by a pancreatico – jejunostomy/gastrostomy+gastrojejunostomy+choledochojejunostomy. This is a complex, challenging technical exercise with higher mortality rates as compared to a drainage procedure however with good results. This procedure involves excising normal organs much against the principles of surgery for a benign disorder and has led to more conservative approaches.

2. ***Traverso-Longmire procedure*** (1978): it is a pylorus preserving pancreatico-duodenectomy. To overcome the problems of postgastrectomy syndrome associated with classical Whipples, pylorus is preserved. Originally used for carcinoma of head of pancreas, now also used for the head related sequelae of chronic pancreatitis.

3. ***Subtotal Pancreatic resection***: consists of resection less than 80% of pancreas. Spleen may be conserved. It is indicated when disease is confined to body and tail e.g. pseudocyst, failed pancreaticojejunostomy, non dilated duct, pseudoaneurysm and when it is not possible to rule out a malignant lesion in body and tail.

4. ***Child's Resection*** (1965): it is a 95% distal pancreatectomy. First described by Barret and Bowers18 in 1957, Child popularized it. The spleen, the tail, the body and the uncinate process of pancreas are completely removed. A small cuff of head is preserved along the lesser curvature of the duodenum, no more than 5% of the entire gland. This cuff protects the vascularity and common bile duct during surgery. Not frequently done and indicated when entire pancreas is uniformly and severely diseased and if previous or lesser procedures have failed. Following this procedure the incidence of insulin dependent diabetes mellitus rises upto 74% in non diabetics.

5. ***Total Pancreatectomy:*** rarely indicated primarily as less radical procedure suffice. Indicated secondarily after a pancreatico-duodenectomy or distal subtotal resection has failed to provide pain relief. Duodenum preserving total pancreatectomy is also reported to be effective. Since patients require insulin and also there are significant alteration in digestive and absorptive function, 95%. Distal pancreatectomy is preferred which preserves normal GI and biliary continuity.

C. Extended Drainage Procedures

1. ***Rumpf's extended drainage*** (1983): it is a combination of Partingtons with a transduodenal pancreaticoplasty. It is indicated when there is a prepapillary obstruction to the drainage of pancreatic duct due to stones or stricture. With the advent of endoscopy, the second half of theprocedure has become unpopular.

D. Resection with extended drainage

As incidence of inflammatory mass in head of pancreas is about 30% of which only 10% are malignant, 21 resection with extended drainage provide cure in upto 94-95% of cases (Izbicki J.R. et al., 1995).

1. ***Hans Beger's***: it is a duodenum preserving resection of pancreatic head. Two major steps are involved viz sub total resection of pancreatic head conserving the duodenum and restitution of the exocrine pancreatic secretory flow.

The technique of "duodenum preserving pancreatic head resection"

Long before sophisticated imaging techniques were available, Hans Beger identified the pancreatic head as the pacemaker of chronic pancreatitis. In 1972, he was the first to describe a novel surgical technique which allowed the isolated resection of the pancreatic head without further organ loss. If performed in specialized centers, the duodenum preserving pancreatic head resection can be performed with a very low morbidity and mortality. The advantage of preservation of the duodenal passage is a nearly physiological regulation of enteral function and blood glucose level. In addition, preservation of islet rich parts of the pancreatic parenchyma in the tail of the pancreas results in a low incidence of postoperative diabetes mellitus compared to other resective procedures. The effectiveness of this surgical technique on long-term pain release is high (>80% after a median follow-up of 5 years). Endocrine function is mostly impaired and a high rate of professional rehabilitation can be achieved (~ 70%). In all relevant aspects, duodenum preserving pancreatic head resection is comparable or even superior to more radical resective procedures.

2. ***The Berne modification.*** The Berne modification spares the dissection of the pancreatic body from the portal vein. In this case, a single cavum results after the resection of the pancreatic head, wich can be anastomosed side-to-side with a Roux-en-Y jejunal loop.

If stenosis of the intrapancreatic part of the common bile duct cannot be resolved by decompression and resection of the surrounding pancreatic tissue, or if the intrapancreatic portion of the common bile duct is opened accidentally

during pancreatic head resection, the wall of the opened bile duct is fixed with single stitches to the surrounding tissue like an opened door and is included in the same anastomosis. In this case the gallbladder has to be removed to prevent from ascending cholangitis.

3. ***Frey's procedure.*** In 1985 Frey and Smith introduced a modification of duodenum preserving pancreatic head resection which combines a longitudinal pancreatico-jejunostomy with a local resection of the pancreatic head. This technique combines the principle of duodenum preserving pancreatic head resection with drainage of the ductus wirsungianus. Compared to the original Beger procedure, this variant is simpler to perform as it spares the dissection of the pancreas from the portal vein and the division of the pancreatic body.

4. ***Izbicki's "V" Shaped Ventral Pancreatic Excision*** (1998): indicated for sclerosing ductal pancreatitis (small duct disease) with maximum diameter of Wirsung duct less than 3 mm. In this procedure, a long "V" shaped excision of ventral aspect of pancreas is done with a lateral pancreaticojejunostomy by a mucosa to capsule anastomosis. This procedure drains the main as well as second and third order ducts.

SURGICAL COMPLICATIONS OF CHRONIC PANREATITIS

Duodenal obstruction. Obstruction of the duodenum is also quite common. This happens because the pancreatitis in the head of the pancreas can press on the duodenum and cause it to be come partly blocked. This causes a feeling of sickness (nausea) and vomiting after food. This will obviously contribute to weight loss. If this is persistent you will usually need major surgery such as a **Beger's operation**. If this is not possible then the narrowing (or stricture) is "bypassed" connecting the small bowel to the stomach. This operation is called a **gastro-jejunostomy** or **gastric-bypass**.

Pancreatic ductal decompression. This option can be considered in patients with intractable pain and main pancreatic duct dilation (>5 to 7 mm) to provide pain relief. It is not a first-line therapy and should be considered only after failure of other measures. Malignant stricture or obstruction should be considered as causes if the length of main duct narrowing is >10 mm. Surgical decompression has better long-term results than endoscopic techniques, possibly because surgery addresses other hypothesized etiologies of pain by denervating pancreatic sensory nerves and reducing pancreatic tissue pressure, an endpoint that may predict the magnitude of pain resolution. In contrast to a common misconception, pain relief is immediate with surgery but delayed with endoscopic decompression. However, the choice of surgical versus endoscopic therapeutic options may be influenced by patient comorbidities and considerations that long-term pain can also recur in surgical groups.

Pancreatic pseudocyst decompression. Decompression of pseudocysts is indicated for persistent pain, cyst enlargement, or complications of the pseudocyst. In the setting of chronic pancreatitis, pseudocysts are more likely to

be longstanding and complicated. Unlike pseudocysts associated with acute pancreatitis, those associated with chronic pancreatitis have a lower risk for serious complications. Drainage can be done surgically, endoscopically, or percutaneously. Endoscopic drainage is successful in 8% to 89%, and recurrence rates range from 4% to 18% after 2 years. Surgical drainage fails in around 7% to 10% of patients. Until randomized controlled trials are performed, the choice of drainage method will depend on local expertise. All pseudocyst drainage procedures have complication rates ranging from 8% to 34% due to infection, bleeding, perforation, and leak/fistula.

Summary

Surgery for pancreatic pseudocysts:

- Pancreatic resection.
- Internal drainage.
- Endoscopic or percutaneous drainage.

Biliary decompression. No randomized controlled trials have assessed biliary decompression (surgical or endoscopic) for patients with biliary obstruction secondary to chronic pancreatitis. However, biliary decompression should be considered if 2-fold elevation in alkaline phosphatase persists for longer than 1 month, and after excluding other causes of cholestasis (e.g., parenchymal disease, abscess). Surgical options include Roux-en-Y choledochojejunostomy or choledochoduodenostomy. Surgery is usually definitive and long-lasting, but has a morbidity rate of around 30%.

Endoscopic therapy involves biliary sphincterotomy with placement of multiple simultaneous plastic stents rather than single stents. It is reserved for patients with severe jaundice and cholangitis, in the presence of a large inflammatory mass in the head of the pancreas, or if severe comorbidity is present. Endoscopic approaches require repeated therapy sessions and place patients at higher risk for stent-related complications, particularly cholangitis, so are not suitable for all patients. A major endoscopic complication is recurrent obstruction.

Splenic vein thrombosis. A thrombus simply means blood clot. In severe chronic pancreatitis the splenic vein may become blocked because of a clot. This is because the pancreatitis irritates the splenic vein to cause the clot and the blockage of the splenic vein usually becomes permanent. The patient is now at risk of venous bleeding (bleeding from the system of veins). The treatment of venous bleeding is described below.

Hepatic portal vein thrombosis. This is another serious complication of chronic pancreatitis. The pancreatitis irritates the hepatic portal vein to cause a clot and permanent blockage of the hepatic portal vein. This can then cause venous bleeding (bleeding from the system of veins) or a build of fluid in the abdomen (ascites). The treatment of venous bleeding and ascites is described below.

It may be possible to clear the clot (also called a thrombectomy) in the hepatic portal vein using a procedure performed in the X-ray department. You will be placed on an X-ray table, the skin cleansed with antiseptic and covered

with sterile gowns. Usually using local anaesthetic (but sometimes requiring a general anaesthetic) a wire is pushed through the skin and into one of the branches of the hepatic portal vein within the liver. The guide wire is then advanced towards and through the blood clot. A special miniature wire basket is then used to try and retrieve the blood clot. The full name of this procedure is percutaneous transhepatic portal venous thrombectomy or just percutaneous thrombectomy.

If this is not successful then it may be possible to insert a tube through the clot to keep the vein open using the same guide wire. This is known as percutaneous transhepatic portal venous stenting or just percutaneous venous stenting. If stenting is successful then your doctors may decide to give you long term aspirin (which prevents the platelets that cause a clot from sticking together) or warfarin (which keeps the blood thin).

There is a special way of checking if there is blood flow through the hepatic portal vein using ultrasonic waves (similar to that used by submarines). This test is called duplex scanning and is performed in the X-ray department. This is similar to a normal ultrasound examination.

Venous bleeding. If there is permanent splenic vein thrombosis and/or hepatic portal vein thrombosis then the blood pressure will build up in the tiny vessels that normally drain into these big veins. The tiny veins now become much larger and are called venous collaterals. These slowly increase in size over some months or years and become windy or tortuous. These are then referred to as varices (similar to varicose veins in the legs, but now inside the abdomen). The varices may appear in the stomach and in the lower gullet. There is a small but real danger that bleeding may occur from rupture of one of these varices. For this reason it is important that you maintain close contact with your consultant in out-patients. From time to time the consultant will organise for you to have an endoscopy of the gullet and stomach to see if the varices have enlarged. If the varices are large then they can injected using the endoscope – this is called endoscopic sclerotherapy.

If bleeding does occur you will need to come to hospital as an emergency – usually there is vomiting of blood. In this situation you will have a blood transfusion and a balloon placed in the stomach and gullet to press on the varices to stop them bleeding. You will also be given injections or a continuous infusion of special drugs that will reduce the pressure in the varices. This will then be followed by endoscopic sclerotherapy. These measures are usually successful.

Very occasionally the bleeding will keep recurring and in this case surgery is required. The operation will involve removal of the spleen and disconnection of the varices from the stomach. This operation is called gastric devascularisation and splenectomy. In exceptional cases this procedure will also prove not to be successful in which case you will require removal of the whole stomach (total gastrectomy) and connection of the gullet to the small bowel (jejunum). It is common practice to recreate a small ‘stomach’ from the small bowel called a pouch. This is therefore called a Roux-en-Y esophago-pouch-jejunostomy.

Arterial bleeding. This can sometimes happen during the natural course of severe chronic pancreatitis because the pancreatitis causes an irritation and erosion of the outer wall of an artery near the pancreas. Sometimes this may cause a pulsating sac to be created next to the artery. This is called a pseudo-aneurysm (pronounced 'Sue-doe an-new-rism'). This is very likely to bleed with serious consequences. In either case it is important to block off the small gap in the artery responsible.

You will be taken to the X-ray department, placed on an X-ray table, the skin cleansed with antiseptic and covered with sterile gowns. Under local anaesthetic a tube will be inserted into the artery in either the left or right groin (called an arterial catheter).

'Dye' (or contrast) is then injected into the catheter to see where it goes using an X-ray television screen. The catheter can be guided to the exact place where the damaged artery is (this is called selective arteriography or angiography). The small hole in the damaged vessel will then be blocked by injecting special metal coils and glues into the catheter (this is called embolisation). The whole procedure is called selective arterial embolisation and is highly successful. Only rarely is it necessary to try to stop the bleeding with open surgery and is only performed if the selective arteriography has not identified the source of bleeding or if the selective arterial embolisation has failed.

External and Internal Pancreatic Fistula. The term "fistula" is an old medical term meaning an abnormal connection between one surface and another. When there is a connection between the pancreatic duct and some other surface in the body this is called an internal fistula. An example is when pancreatic fluid leaks into the abdomen to cause pancreatic ascites (see below). If the pancreatic fluid leaks into the chest cavity this is sometimes called a pleural fistula. This fluid as such is not harmful as the enzymes in the pancreatic juice are not activated (see above).

When there is connection between the pancreatic duct and the skin this is known as an external pancreatic fistula. As the enzymes reach the skin they now become activated by skin bacteria (see above). This causes the skin to become raw and can be very sore. A special bag needs to be placed on the skin to keep the fluid away from the skin, although this is often not entirely successful.

Many pancreatic fistulas dry up with no special measures except by using external drainage tube inserted in the X-ray department. Only in exceptional circumstances is it necessary to encourage closure of the fistula by pancreatic stenting or the use of octreotide injections to reduce pancreatic secretions. In even more exceptional circumstances surgery is needed to control the fistula such as using a small bowel channel to drain the fistula internally. This operation is called a Roux-en-Y fistulo-jejunostomy

Ascites. (Pronounced 'ass-eye-teas'). This refers to the build up of straw coloured fluid in the abdomen. This sometimes follows hepatic portal vein thrombosis. Because of the pressure in the venous collaterals not all of the fluid

that should be returned to the liver can be. This fluid therefore accumulates in the abdomen. Normally this condition will slowly improve but sometimes you will need treatment with a special water tablet (called spironolactone) and tablets or injections (often using a drug called octreotide) to reduce the pressure in the varices and venous collaterals. In addition you may need to be admitted to hospital to drain the fluid by inserting a tube into the abdomen (usually in the X-ray department) under local anaesthetic. This type of drainage is called an ascitic tap. If the ascites is still a problem you may need surgery to drain the fluid from the abdomen into one of the veins in your neck or leg. The fluid then becomes part of the normal blood circulating around the body.

Another rare cause of ascites is specifically called pancreatic ascites. This is because the fluid instead of being straw coloured is white and contains a large amount of pancreatic juice. The pancreatic fluid escapes from the main pancreatic duct because of direct damage to the duct by the pancreatitis or indirectly by a small hole in a pancreatic pseudocyst. This is therefore called an internal pancreatic fistula (see above). Dealing with pancreatic ascites can be very complicated depending on all of the other things that may be causing it such as a pseudocyst. Thus the treatment may be simple, needing only an ascitic tap, it may be necessary to use pancreatic stenting or octreotide injections to reduce pancreatic secretions or a Roux-en-Y pseudocyst-jejunostomy if there is also a pseudocyst (see above). It may be necessary to combine one or more of these operations with a Beger's operation if there is also considerable long standing pain (see below).

Severe pain. Once it is necessary to be taking strong pain killers on a regular basis, then surgery will be required. If a patient is already receiving regular pethidine or morphine, attendance at a drug addiction unit may also be necessary following surgery. A pain team will always be involved to help obtain the best kind of pain relief.

If you drink alcohol then you must stop – as good pain control is not possible if you continue to do so.

The chances of achieving a good result following surgery for pain are at least 80% in the first instance. There is, however, no guarantee of success and some patients may develop a recurrence of pain sometime after surgery. This may necessitate further surgery. For these reasons, it is essential that the patient and relatives and friends remain committed to addressing all the social problems as well as the medical problems involved. Patience and optimism are required by all.

The underlying disease process will largely dictate the choice of operation. Some operations can be relatively simple – for example removal of a single pancreatic stone, enlarging a narrowing of the pancreatic duct or performing an internal drainage operation for a dilated pancreatic duct. In principle, however, a resection of part of the pancreas (partial pancreatectomy) will be required if there has been severe pain.

Operations have become more 'conservative' in recent years. This means that only the affected pancreas tissue is removed and that other nearby organs such as the duodenum, stomach and spleen are left untouched.

This is so-called "designer-pancreatic surgery".

This type of surgery is particularly demanding and requires a specialist pancreatic surgeon to undertake the procedure. Although it is nearly always intended to preserve the spleen, this may prove excessively difficult at operation when it becomes necessary for reasons of immediate safety to the patient to remove the spleen (splenectomy).

In addition to relieving pain, the principal aims of designer-pancreatic surgery are to improve drainage of the pancreas, reduce the risk of developing sugar diabetes (diabetes mellitus), and maintain important normal anatomy.

Pleural nerve block

This involves injection a local anaesthetic along one or more of the nerves that run along the underside of each rib. The idea is that the local anaesthetic then runs back towards the spinal cord in the spinal canal. The local anaesthetic then paralyses the pain nerves that go between the brain (where the pain is felt) and the pancreas. The results are variable and only last for a few days or weeks but usually for several months. This procedure *is recommended* for patients who are not fit for surgery (especially older patients) but who need some extra pain relief.

Celiac plexus nerve block

The nerves from the pancreas collect just behind the pancreas in a thick bundle called the celiac plexus (coeliac is pronounced 'see-lee-ack'). These nerves can be injected using a long needle and local anaesthetic in the X-ray department or using a needle with the endoscope during EUS (see above). If a local anaesthetic is used this may improve the pain, usually for a few weeks. It is also possible to block the nerves permanently using special chemicals (called sclerosants) such as concentrated alcohol. Unfortunately the pain relief only lasts for a few weeks or months and causes severe damage to surrounding tissues. This includes the pancreas itself, major veins and major arteries. If surgery on the pancreas is then needed it will be extra dangerous and may not be possible. For these reasons permanent celiac plexus block is not recommended.

Bilateral Thoracoscopic Sympathectomy (BITS)

The BITS procedure involves cutting the pain nerves from the pancreas as they travel through the chest towards the spinal cord in the spinal canal. The operation is done using fine instruments and telescopes using general anaesthetic and is surprisingly simple and safe to perform. This is so called 'keyhole' surgery. The operation lasts only 30 minutes and may be performed as an outpatient. The operation is most successful in patients with rather moderate pain but the pain returns in most patients after about 12 months. In some cases in which surgery has failed to control pain even though all the pancreas has been removed it may be helpful to undergo this operation.

Endoscopic shock wave lithotripsy

This is offered to patients with pancreatic duct calcifications when other measures fail to provide pain relief. The effect of the procedure on pain relief is unknown due to a lack of appropriate controlled studies. The perceived effectiveness of individual therapies may be attributable to the placebo effect, which is as high as 40% for treatment of pancreatic pain. The presence or absence of stones does not predict pain relief or persistence of pain.

Summary

- Alcohol remains the most common cause of chronic pancreatitis; however, genetic, autoimmune, and environmental factors may also contribute.
- Abdominal radiography and computed tomography scanning allow for the detection of advanced chronic pancreatitis.
- Endoscopic retrograde pancreatography, endoscopic ultrasound, and direct pancreatic function tests allow for the detection of early, or minimal change, chronic pancreatitis.
- Management strategies for chronic pancreatic pain include analgesics, pancreatic enzyme supplementation, celiac plexus blockade, endoscopic or surgical duct decompression therapy, surgical resection, and thorascopic splanchnicectomy.

SPLEEN DESEASE

The spleen is an organ found in virtually all vertebrate animals with important roles in regard to red blood cells and the immune system. In humans, it is located in the left upper quadrant of the abdomen. It removes old red blood cells and holds a reserve of blood in case of hemorrhagic shock while also recycling iron. It synthesizes antibodies in its white pulp and removes antibody-coated bacteria along with antibody-coated blood cells by way of blood and lymph node circulation. The spleen is purple and gray. Recently, it has been found to contain in its reserve half of the body's monocytes within the red pulp. These monocytes, upon moving to injured tissue (such as the heart), turn into dendritic cells and macrophages while promoting tissue healing. It is one of the centers of activity of the reticuloendothelial system and can be considered analogous to a large lymph node, as its absence leads to a predisposition toward certain infections.

Anatomy

The spleen, in healthy adult humans, is approximately 11 centimetres (4.3 in) in length. It usually weighs 150 grams (5.3 oz) and lies beneath the 9th to the 12th thoracic ribs.

- Like the thymus, the spleen possesses only efferent lymphatic vessels.
- The spleen is part of the lymphatic system.
- The germinal centers are supplied by arterioles called penicilliary radicles.

The spleen is unique in respect to its development within the gut. While most of the gut viscera are endodermally derived (with the exception of the neural-crest derived suprarenal gland), the spleen is derived from mesenchymal tissue. Specifically, the spleen forms within, and from, the dorsal mesentery. However, it still shares the same blood supply – the celiac trunk – as the foregut organs.

Function

- The function of the human spleen is to filter abnormal RBCs, stores platelets, produce tuftsin and properdin (opsins) produces antibodies (IgM) and is site of phagocytosis .
- During fetal development the spleen produces red blood cells.
- By the fifth month of gestation the spleen no longer has hematopoietic function but retains the capacity throughout life.
- Red cells that pass through the spleen undergo a "cleaning" or repair (*Table 1*).

Table 1 –Function of the spleen

Area	Function	Composition
Red pulp	Mechanical filtration of red blood cells. Reserve of monocytes	• "sinuses" (or "sinusoids") which are filled with blood; • "splenic cords" of reticular fibers; • "marginal zone" bordering on white pulp.
White pulp	Active immune response through humoral and cell-mediated pathways	Composed of nodules, called Malpighian corpuscles. These are composed of: • "lymphoid follicles" (or "follicles"), rich in B-lymphocytes; • "periarteriolar lymphoid sheaths" (PALS), rich in T-lymphocytes.

Other functions of the spleen are less prominent, especially in the healthy adult:

- Production of opsonins, properdin, and tuftsin.
- Creation of red blood cells. While the bone marrow is the primary site of hematopoiesis in the adult, the spleen has important hematopoietic functions up until the fifth month of gestation. After birth, erythropoietic functions cease, except in some hematologic disorders. As a major lymphoid organ and a central player in the reticuloendothelial system, the spleen retains the ability to produce lymphocytes and, as such, remains an hematopoietic organ.
- Storage of red blood cells and other formed elements. In horses roughly 30% of the red blood cells are stored there. The red blood cells can be released when needed. In humans, it does not act as a reservoir of blood cells. It can also store platelets in case of an emergency.
- Storage of half the body's monocytes so that upon injury they can migrate to the injured tissue and transform into dendritic cells and macrophages and so assist wound healing.

SPLENIC TRAUMA

Clinical features depend on:

- degree of hypovolaemia;
- presence of associated injuries.

- Clinical features range from left upper quadrant pain to shock and peritonitis.
- 30 to 60% of patients have other assocaited intraperitoneal injuries.

Diagnosis

- If cardiovascularly unstable requires resuscitation and early surgery.
- If cardiovascularly stable consider either ultrasound or CT scan.

Splenic trauma grading

- Grade 1 – minor subcapsular tear or haematoma.
- Grade 2 – parenchymal injury not extending to the hilum.
- Grade 3 – major parenchymal injury involving vessels.

Management of splenic injury

- Overall 20–40% of patients are suitable for conservative management.
- Children can often be managed conservatively as they have increased proportion of low grade injuries.
- Multiple injuries should be monitored in high dependency unit.
- Require cardiovascular and haematological monitoring.

Splenic trauma (management)

If successful patients should remain on:

- Bed rest for 72 hours.
- Limited physical activity for 6 weeks.
- No contact sports for 6 months.
- Surgery needed if clinically hypovolaemic of they have a falling haematocrit.
- Failed conservative management often results in surgical management
- Surgical management can involve either splenectomy or splenic repair.

SPLENOMEGALY

Enlargement of the spleen is known as splenomegaly. It may be caused by sickle cell anemia, sarcoidosis, malaria, bacterial endocarditis, leukemia, pernicious anaemia, Gaucher's disease, leishmaniasis, Hodgkin's disease, Banti's disease, hereditary spherocytosis, cysts, glandular fever (mononucleosis or 'Mono' caused by the Epstein-Barr Virus), and tumours. Primary tumours of the spleen include hemangiomas and hemangiosarcomas. Marked splenomegaly may result in the spleen occupying a large portion of the left side of the abdomen.

The spleen is the largest collection of lymphoid tissue in the body. It is normally palpable in preterm infants, in 30% of normal, full-term neonates, and in 5% to 10% of infants and toddlers. A spleen easily palpable below the costal margin in any child over the age of 3–4 years should be considered abnormal until proven otherwise.

Splenomegaly can result from antigenic stimulation (e.g., infection), obstruction of blood flow (e.g., portal vein obstruction), underlying functional abnormality (e.g., hemolytic anemia), or infiltration (e.g., leukemia or storage disease, such as Gauche's disease). The most common cause of acute splenomegaly in children is viral infection, which is transient and usually moderate. Basic work-up for acute splenomegaly includes a complete blood count with differential, platelet count, and reticulocyte and atypical lymphocyte counts to exclude

hemolytic anemia and leukemia. Assessment of IgM antibodies to viral capsid antigen (a rising titer) is indicated to confirm Epstein-Barr virus or cytomegalovirus. Other infections should be excluded if these tests are negative.

Splenomegaly may lead to hypersplenism (pancytopenia as cells become trapped in an overactive spleen and are destroyed). So anaemia, infection, or haemorrhage may result.

HYPERSPLENISM

Hypersplenism is a type of disorder which causes the spleen to rapidly and prematurely destroy blood cells.

Causes & symptoms

Hypersplenism may be caused by a variety of disorders. Sometimes, it is brought on by a problem within the spleen itself and is referred to as **primary hypersplenism. Secondary hypersplenism** results from another disease such as chronic malaria, rheumatoid arthritis, tuberculosis, or polycythemia vera, a blood disorder.

Symptoms of hypersplenism include easy bruising, easy contracting of bacterial diseases, fever, weakness, heart palpitations, and ulcerations of the mouth, legs and feet. Individuals may also bleed unexpectedly and heavily from the nose or other mucous membranes, and from the gastrointestinal or urinary tracts. Most patients will develop an enlarged spleen, anemia, leukopenia, or abnormally low white blood cell counts, or thrombocytopenia, a deficiency of circulating platelets in the blood. Other symptoms may be presents that reflect the underlying disease that has caused hypersplenism.

An enlarged spleen is one of the symptoms of Malaria, Cirrhosis of the liver, leukaemia, lymphoma, Hodgkin's disease, polycythaemia, etc. Spleen enlarges when called on to remove massive numbers of red blood cells, defective cells, or bacteria from circulation. Splenomegaly occurs in about 10% of systemic lupus erythematosus patients. Sometimes, it is caused by recent viral infection, such as mononucleosis.

Summary

- Refers to a variety of ill effects resulting from increased splenic function that may be improved by splenectomy.
- The criteria for diagnosis included:
  - Anemia, leukopenia, thrombocytopenia or a combination of the three.
  - Compensatory bone marrow hyperplasia.
  - Splenomegaly.
- Hypersplenism can be categorized as primary or secondary.

Banti's syndrome

Banti's syndrome (also known as Banti's disease) is a chronic congestive enlargement of the spleen resulting in premature destruction of the red blood cells by the spleen. However, the term Banti's syndrome is a term that was used in the past (but isn't any longer) to describe patients with splenomegaly, hypersplenism and portal hypertension without cirrhosis and without occlusion of the portal venous system. It is named for Guido Banti (1882).

Pathogenesis

The basic pathology is some kind of obstructive pathology in the portal, hepatic or splenic vein that causes obstruction of venous blood flow from the spleen towards the heart. The cause of such obstruction may be abnormalities present at birth (congenital) of certain veins, blood clots, or various underlying disorders causing inflammation and obstruction of veins (vascular obstruction) of the liver.

Clinical presentation

Enlargement of spleen, ascites, jaundice, and the result of destruction of various blood cells by spleen – anemia, leukopenia, thrombocytopenia, gastrointestinal tract bleeding – may constitute the presenting symptoms.

Gaucher's disease

Gaucher's disease is a genetic disease in which a fatty substance (lipid) accumulates in cells and certain organs. Gaucher's disease is the most common of the lysosomal storage diseases. It is caused by a hereditary deficiency of the enzyme glucocerebrosidase (also known as acid β-glucosidase). The enzyme acts on a fatty substance glucocerebroside (also known as glucosylceramide). When the enzyme is defective, the substance accumulates, particularly in cells of the mononuclear cell lineage. Fatty material can collect in the spleen, liver, kidneys, lungs, brain and bone marrow.

Symptoms may include enlarged spleen and liver, liver malfunction, skeletal disorders and bone lesions that may be painful, severe neurologic complications, swelling of lymph nodes and (occasionally) adjacent joints, distended abdomen, a brownish tint to the skin, anemia, low blood platelets and yellow fatty deposits on the white of the eye (sclera). Persons affected most seriously may also be more susceptible to infection. Some forms of Gaucher's disease may be treated with enzyme replacement therapy.

The disease is caused by a recessive mutation in a gene located on chromosome 1 and affects both males and females. About 1 in 100 people in the United States are carriers of the most common type of Gaucher disease, while the carrier rate among Ashkenazi Jews is 8.9% while the birth incidence is 1 in 450.

The disease is named after the French doctor Philippe Gaucher, who originally described it in 1882.

Classification

Gaucher's disease has three common clinical subtypes.

- Type I (or non-neuropathic type) is the most common form of the disease, occurring in approximately 1 in 50,000 live births. It occurs most often among persons of Ashkenazi Jewish heritage. Symptoms may begin early in life or in adulthood and include enlarged liver and grossly enlarged spleen (together hepatosplenomegaly); the spleen can rupture and cause additional complications. Skeletal weakness and bone disease may be extensive. Spleen enlargement and bone marrow replacement cause anemia, thrombocytopenia and leukopenia. The brain is not affected pathologically, but there may be lung and, rarely, kidney

impairment. Patients in this group usually bruise easily (due to low levels of platelets) and experience fatigue due to low numbers of red blood cells. Depending on disease onset and severity, type 1 patients may live well into adulthood. Many patients have a mild form of the disease or may not show any symptoms.

- Type II (or acute infantile neuropathic Gaucher's disease) typically begins within 6 months of birth and has an incidence rate of approximately 1 in 100,000 live births. Symptoms include an enlarged liver and spleen, extensive and progressive brain damage, eye movement disorders, spasticity, seizures, limb rigidity, and a poor ability to suck and swallow. Affected children usually die by age 2.
- Type III (the chronic neuropathic form) can begin at any time in childhood or even in adulthood, and occurs in approximately 1 in 100,000 live births. It is characterized by slowly progressive but milder neurologic symptoms compared to the acute or type 2 version. Major symptoms include an enlarged spleen and/or liver, seizures, poor coordination, skeletal irregularities, eye movement disorders, blood disorders including anemia and respiratory problems. Patients often live into their early teen years and adulthood.

These subtypes have come under some criticism for not taking account of the full spectrum of observable symptoms (the phenotypes). There are also compound heterozygous variations which considerably increase the complexity of predicting disease course.

Signs and symptoms

- Painless hepatomegaly and splenomegaly; the size of the spleen can be 1500-3000 ml, as opposed to the normal size of 50–200 ml.
- Hypersplenism: the rapid and premature destruction of blood cells, leading to anemia, neutropenia and thrombocytopenia (with an increased risk of infection and bleeding).
- Cirrhosis of the liver is rare.
- Neurological symptoms occur only in some types of Gaucher's (see below):
  - Type II: serious convulsions, hypertonia, mental retardation, apnea.
  - Type III: muscle twitches known as myoclonus, convulsions, dementia, ocular muscle apraxia.
- Osteoporosis: 75% develop visible bony abnormalities due to the accumulated glucosylceramide. A deformity of the distal femur in the shape of an Erlenmeyer flask is commonly described (aseptic necrosis of the femur joint).
- Yellowish-brown skin pigmentation.

Pathophysiology

The disease is caused by a defect in the housekeeping gene *lysosomal gluco-cerebrosidase* (also known as beta-glucosidase, EC 3.2.1.45, PDB 1OGS) on the first chromosome (1q21). The enzyme is a 55.6 KD, 497 amino acids long protein that catalyses the breakdown of glucocerebroside, a cell membrane constituent of red and white blood cells. The macrophages that clear

these cells are unable to eliminate the waste product, which accumulates in fibrils, and turn into *Gaucher cells*, which appear on light microscopy to resemble crumpled-up paper.

In the brain (type II and III), glucocerebroside accumulates due to the turnover of complex lipids during brain development and the formation of the myelin sheath of nerves.

Different mutations in the beta-glucosidase determine the remaining activity of the enzyme, and, to a large extent, the phenotype.

Heterozygotes for particular acid beta-glucosidase mutations carry about a fivefold risk of developing Parkinson's disease, making this the most common known genetic risk-factor for Parkinson's. A study of 1525 Gaucher patients in the United States suggested that while cancer risk is not elevated, particular malignancies (non-Hodgkin lymphoma, melanoma and pancreatic cancer) occurred at a 2–3 times higher rate.

Genetics

The three types of Gaucher's disease are inherited in an autosomal recessive fashion. Both parents must be carriers in order for a child to be affected. If both parents are carriers, there is a one in four, or 25%, chance with each pregnancy for an affected child. Genetic counseling and genetic testing is recommended for families who may be carriers of mutations.

Each type has been linked to particular mutations. In all, there are about 80 known mutations, grouped into three main types:

- Type I (N370S homozygote), the most common, also called the "non-neuropathic" type occurs mainly in Ashkenazi Jews, at 100 times the occurrence in the general populace. The median age at diagnosis is 28 years of age, and life expectancy is mildly decreased. There are no neurological symptoms.
- Type II (1 or 2 alleles L444P) is characterized by neurological problems in small children. The enzyme is hardly released into the lysosomes. Prognosis is dismal: most die before reaching the third birthday.
- Type III (also 1–2 copies of L444P, possibly delayed by protective polymorphisms) occurs in Swedish patients from the Norrbotten region. This group develops the disease somewhat later, but most die before their 30th birthday.

Diagnosis

A definitive diagnosis is made with genetic testing. As there are numerous different mutations, sequencing of the beta-glucosidase gene is sometimes necessary to confirm the diagnosis. Prenatal diagnosis is available, and is useful when there is a known genetic risk factor.

A diagnosis can also be implied by biochemical abnormalities such as high alkaline phosphatase, angiotensin-converting enzyme (ACE) and immunoglobulin levels, or by cell analysis showing "crinkled paper" cytoplasm and glycolipid-laden macrophages.

Some lysosomal enzymes are elevated, including tartrate-resistant acid phosphatase, hexosaminidase, and a human chitinase, chitotriosidase. This

latter enzyme has proved to be very useful for monitoring Gaucher's disease activity in response to treatment, and may reflect the severity of the disease

Treatment

For type 1 and most type 3 patients, enzyme replacement treatment with intravenous recombinant glucocerebrosidase (imiglucerase) can dramatically decrease liver and spleen size, reduce skeletal abnormalities, and reverse other manifestations. This treatment costs approximately $200,000 annually for a single patient and should be continued for life. The rarity of the disease means that dose-finding studies have been difficult to conduct, so there remains controversy over the optimal dose and dosing frequency. Due to the low incidence, this has become an orphan drug in many countries, meaning that a government recognizes and accommodates the financial constraints that limit research into drugs that address a small population.Velaglucerase alfa was approved by the Food and Drug Administration (FDA) as an alternative treatment on February 26, 2010.

Successful bone marrow transplantation cures the non-neurological manifestations of the disease, because it introduces a monocyte population with active beta-glucosidase. However, this procedure carries significant risk and is rarely performed in Gaucher patients. Surgery to remove the spleen (splenectomy) may be required on rare occasions if the patient is anemic or when the enlarged organ affects the patients comfort. Blood transfusion may benefit some anemic patients. Other patients may require joint replacement surgery to improve mobility and quality of life. Other treatment options include antibiotics for infections, antiepileptics for seizures, bisphosphonates for bone lesions, and liver transplants. Substrate reduction therapy may prove to be effective in stopping Type 2, as it can cross through the blood barrier into the brain. There is currently no effective treatment for the severe brain damage that may occur in patients with types 2 and 3 Gaucher disease. Gene therapy may be a future step.

HYPOSPLENISM

- Is a potentially lethal syndrome characterized by diminished splenic function.
- The patient peripheral blood smears appear as if they are asplenic.
- Hyposplenism can occur in the presence of abnormal sized or enlarged spleen.
- The danger of hyposplenism is the risk of developing potentially lethal sepsis.
- Sickle cell anemia is the most common disease associated with hyposplenism.
- The most common surgical disease associated with hyposplenism is chronic UC.

ASPLENIA

Asplenia is the absence of normal spleen function. It predisposes to some septicaemia infections. Therefore, vaccination and antibiotic measures are essential in such cases. There are multiple causes:

- Some people congenitally completely lack a spleen, although this is rare.
- Sickle-cell disease can cause a functional asplenia (or autosplenectomy) by causing infarctions of the spleen during repeated sickle-cell crises.

- It may be removed surgically (known as a splenectomy), but this is rarely performed, as it carries a high risk of infection and other adverse effects. Indications include following abdominal injuries with rupture and hemorrhage of the spleen, or in the treatment of certain blood diseases (Idiopathic thrombocytopenic purpura, hereditary spherocytosis, etc.), certain forms of lymphoma or for the removal of splenic tumours or cysts.

ANEMIA

- Hemolytic anemia results from an increase in the rate of red blood cell destruction.
- Many hemolytic anemias have a hereditary basis:
  - congenital hemolytic anemias have defects in the cell membrane, cell structure or problems with hemoglobin structure or synthesis (G-6-PD);
  - acquired hemolytic anemias have factors attached to the outside cell structure.

Sickle Cell Anemia

Symptoms:

- Severe abdominal pain.
- Signs of peritoneal irritation.

Chronic features:

- Retarded growth and development, bone and joint problems, cardiovascular, pulmonary, hepatobiliary, genitourinary, and neurologic manifestations, hematuria, priapism and ulcerations over the distal portions of the legs.
- The incidence of pigmented gallstones increases with age.

Diagnosis

- Characteristic sickle cells on blood smear.
- Hemoglobin electrophoresis.

Treatment

- Palliative-directed towards minimizing complications of the disease.
- Many patients die during childhood from infections, renal failure and heart failure.

Sickle Cell Crisis

- Splenic involvement.
  - Is unknown or unclear.
  - During a crisis the spleen sequesters a large volume of blood – to the point of hypovolemia.
    - ✓ Hypovolemic shock and death may occur within hours.
    - ✓ So treat them as shock pts with ABCs and they may need splenoctomy after they become stable. (?)

Thalassemia

- These hereditary hemolytic anemia's result from a defect in hemoglobin synthesis.
- Beta thalassemia is the most common type.

- Hemoglobin electrophoresis in thalassemia major reveals a absence of hemoglobin A and an increase in hemoglobin F.
- Treatment includes transfusions, iron chelation and splenectomy.

Autoimmune Hemolytic Anemia

- Is an acquired hemolytic anemia resulting from antibodies that are produced by the body against its own red cells.
- Patients have hemolysis with anemia, reticulocytosis, shortened erythrocyte lifespan, fluctuating jaundice and splenomegaly.
- The distinguishing feature is a positive direct Coombs test-this identifies antibodies on the red cell surface.
  - The type of antibody attached to the red cell determines the mechanism of hemolysis.
- Drugs can be associated or related to this anemia.
  - Penicillin, cephalothin, streptomycin, methyldopa, quinidine, aspirin, phenacetin and several sulfonamides.
- Pallor and splenomegaly are the main physical findings.
- Treatment is directed towards the hemolytic anemia and any underlying disease.
  - Blood transfusion, steroids and splenectomy are often used.

Idiopathic (autoimmune) Thrombocytopenic Purpura (ITP)

Thrompocytopenia results from immune destruction of platelets. The features of ITP is shown in the *Table 2*.

Table 2 – Idiopathic Thrombocytopenic Purpura

Features	Acute ITP	Chronic ITP
Peak age	2–6 years	20–40 years
Sex predilection	None	F > M (3:1)
Hx of recent infection	Common (Often viral)	Rare
Onset of bleed	Abrupt	Insidious
Platelet count	$<20\times10^9$/L	$30–80\times10^9$/L
Duration	Usually weeks	Months to years
Spontanous remission	80% or more	Uncommon

Chronic (adult – type) ITP

- Most common cause of isolated thrombocytopenia
  - diagnosis of exclusion;
- Idiopathic but may occur with autoimmune disorders e.g: SLE, thyroid disease, chronic lymphocytic leukemia, HIV or the same drugs that cause autoimmune hemolytic anaemia.

Pathophysiology

- IgG autoantibody.
- Spleen :
  - site of antibody production & platelet destruction.
- Usually not palpable (enlarged in 10%).

Clinical presentation

- Insidious onset.
- May be seen after mild viral illness or after immunization.
- Mucosal or skin bleeding.
- Petechia and easy bruising.
- Hematuria.
- Melena.
- Epistaxis.
- Female with menorrhea.

Laboratory results

- Peripheral blood film: ↓ platelet, large platelets.
- Bone marrow: plentiful megakaryocytes critical test to rule out other causes of thrombocytopenia.
- Anti-platelet antibodies present in most .
- ↑ bleeding time.
- PT & PTT normal.

Management

- Conservative if mild:
  - steroids;
  - splenoectomy if steroids fail has 60 % cure rate.
- IV gamma globulin if steroids and splenoectomy fail or rapid response is required.
- Others: prednisolone, platelets, plasma exchange, danazol

Prognosis

- Fluctuating course.
- Overall relatively benign, mortality 1–2%.
- Major concern is cerebral hemorrhage at platelets count $<5\times10^9$/L.

CYSTS AND TUMORS OF THE SPLEEN

- The differential diagnosis of splenomegaly should include splenic masses and primary tumors (these conditions are rare however they must be considered).
- Cystic lesions comprise parasitic and nonparasitic cysts:
  - parasitic cysts are due almost exclusively to echinococcal disease (rare disease);
  - nonparasitic cysts are classified as primary (true) which have an epithelial lining or pseudocysts (more common).
- Symptoms of splenic cysts are vague and are caused primarily by mass effect (compression of adjacent viscera).

Diagnosis

- Ultrasound.
- CN scan.
- Laparoscopy.

Selected and treatment

- Selected nonparasitic cyst may be managed by aspiration.
- Splenectomy should be performed for all large cyst and those with an uncertain diagnosis.
- Malignant and benign primary tumors of the spleen are rare.
- Most primary malignant tumors are angiosarcomas.

SPLENIC INFARCTION

In medicine, splenic infarction is a condition in which oxygen supply to the spleen is interrupted, leading to partial or complete infarction (tissue death due to oxygen shortage) in the organ.

Splenic infarction occurs when the splenic artery or one of its branches are occluded, for example by a blood clot. Although it can occur asymptomatically, the typical symptom is severe pain in the left upper quadrant of the abdomen, sometimes radiating to the left shoulder. Fever and chills develop in some cases. It has to be differentiated from other causes of acute abdomen.

An abdominal CT scan is the most commonly used modality to confirm the diagnosis, although abdominal ultrasound can also contribute.

There is no specific treatment, except treating the underlying disorder and providing adequate pain relief. Splenectomy is only required if complications ensue; surgical removal predisposes to overwhelming post-splenectomy infections.

Complications include a ruptured spleen, hemorrhage, splenic abscess (for example, if the underlying cause is endocarditis) or pseudocyst formation. Splenectomy may be warranted for persistent pseudocysts due to the high risk of subsequent rupture.

Causes

Several factors may increase the tendency for clot formation, such as specific infections (such as infectious mononucleosis, cytomegalovirus infection, malaria or babesiosis), inherited clotting disorders (thrombophilia, such as Factor V Leiden, antiphospholipid syndrome), malignancy (such as pancreatic cancer) or metastasis, or a combination of these factors.

In some conditions, blood clots form in one part of the circulatory system and then dislodge and travel to another part of the body, which could include the spleen. These emboligenic disorders include atrial fibrillation, patent foramen ovale, endocarditis or cholesterol embolism.

Splenic infarction is also more common in hematological disorders with associated splenomegaly, such as the myeloproliferative disorders. Other causes of splenomegaly (for example, Gaucher disease or hemoglobinopathies) can also predispose to infarction. Splenic infarction can also result from a sickle cell crisis in patients with sickle cell anemia. Both splenomegaly and a tendency towards clot formation feature in this condition. In sickle cell disease, repeated splenic infarctions lead to a non-function spleen (autosplenectomy).

Any factor that directly compromises the splenic artery can cause infarction. Examples include abdominal traumas, aortic dissection, torsion of

the splenic artery (for example, in wandering spleen) or external compression on the artery by a tumor. It can also be a complication of vascular procedures.

Splenic infarction can be due to vasculitis or diffuse intravascular coagulation. Various other conditions have been associated with splenic infarction in case reporters, for example Wegener's granulomatosis or treatment with drugs that predispose to vasospasm or thrombosis, like vasoconstrictors used to treat esophageal varices, sumatriptan or bevacizumab.

Therapeutic splenic infarction

Splenic infarction can be induced for the treatment of such conditions as portal hypertension or splenic injury. It can also be used prior to splenectomy for the prevention of blood loss.

SPLENIC ABSCESS

Abscesses of the spleen have been reported periodically since the time of Hippocrates. He postulated that 1 of 3 courses was followed by a patient with a splenic abscess: 1) the patient might die; 2) the abscess might heal; or 3) the abscess might become chronic and the patient may live with the disease.

Splenic abscess is a rare entity, with a reported frequency of 0.05–0.7%. Its reported mortality rate is still high, up to 47%, and can potentially reach 100% among patients who do not receive antibiotic treatment. Appropriate management can decrease the mortality to less than 10%.The timely and widespread use of imaging methods (eg, computed tomography scanning, ultrasonography) facilitates early diagnosis and guides treatment, thus improving the prognosis.

Frequency

Published autopsy statistics suggest that splenic abscess is rare (0.05–0.7%); the incidence may depend on the study population. For example, the incidence of splenic abscesses in Denmark was 0.056% per 1000 somatic hospital discharges per year or 0.0049% per year of all hospital deaths.

The literature suggests a wide variability of causative pathogens, demography, and clinical material.

Etiology

Splenic abscesses have diverse etiologies. The most common is hematogenous spread originating from an infective focus elsewhere in the body. Infective endocarditis, a condition associated with systemic embolization in 22–50% of cases, has a 10–20% incidence of associated splenic abscess. Other infective sources include typhoid, paratyphoid, malaria, urinary tract infection, pneumonias, osteomyelitis, otitis, mastoiditis, and pelvic infections. Pancreatic, other retroperitoneal, and subphrenic abscesses, as well as diverticulitis, may contiguously involve the spleen. Splenic trauma is another well-recognized etiologic factor. Splenic infarction resulting from systemic disorders (see the image below), such as hemoglobinopathies (especially sickle cell disease), leukemia, polycythemia, or vasculitis, can become infected and evolve into splenic abscesses.

Alcoholics, diabetics, and patients who are immunosuppressed are among the most susceptible to splenic abscesses.

Pathophysiology

Splenic abscesses occur in a variety of clinical scenarios, as shown in the images below. Published studies suggest that preexisting splenic tissue injury and bacteremia are required to form a basis for an abscess.

Published scenarios are grouped below:

Hematogenous embolization to a previously normal spleen – typical examples include patients with septic endocarditis who have abused IV drugs and patients undergoing chemotherapy who develop fungemia, resulting in a splenic abscess. Typically, patients in this category either are immunosuppressed or have an overwhelming bacteremia. This group of patients is expected to expand and include analogous groups from the domains of transplantation and HIV/AIDS.

Hematogenous spread in the presence of previously altered splenic architecture – this group includes patients with single splenic infarcts (from trauma) or multiple splenic infarcts (from sickle cell disease or vasculitis). Bacteremia from an intercurrent infection (eg, pneumonia, cholecystitis, central line sepsis) can colonize a splenic avascular area and form an abscess, as depicted in the image below.

Contiguous spread – this includes direct involvement from a pancreatic abscess, gastric or colonic perforations, or subphrenic abscesses.

Microbiology

- Aerobes (in most published cases).
- Gram-positive cocci – *Streptococcus*, *Staphylococcus*, *Enterococcus* (predominant in most reports).
- Gram-negative bacilli – *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus*, *Pseudomonas* species, *Salmonella* species (occasionally predominant).
- Anaerobes – *Peptostreptococcus, Bacteroides, Fusobacterium, Clostridium, Propionibacterium acnes*.
- Polymicrobial (up to 50% of cases).
- Fungal – *Candida.*
- Unusual flora – *Burkholderia pseudomallei* (occasionally reported in melioidosis), actinomycotic and mycobacterial abscesses, most typically seen in immunosuppressed patients.

Presentation

The history and physical examination are not sufficiently reliable to make the diagnosis of splenic abscess. However, information derived from the history and physical examination can suggest this diagnosis. Therefore, the clinician must maintain a high index of suspicion, particularly in the above-listed higher risk clinical scenarios and patient groups.

History

The signs and symptoms of splenic abscess have been well described but are not very specific. Therefore, splenic abscess remains a substantial diagnostic challenge. The classical triad of fever, left upper quadrant pain, and splenomegaly is seen in only about one third of patients.

The symptoms of splenic abscess can be variable and depend on the location, size, and progression of the process. They can also be acute, subacute, or chronic. Deep-seated, small abscesses can be painless and accompanied by septic symptoms.

Fever (>90%) can be moderate, continuous, intermittent, or even absent.

• Abdominal pain (>60%) typically occurs suddenly, with a punctum maximum in the left hypochondrium (>39%). Remember that pain usually signifies perisplenitis.

• Involvement of the diaphragmatic pleura can cause shoulder pain. The associated eponym is the Kehr sign, although there is no clear demonstration that Kehr either described it or suffered from it.

• Pleuritic chest pain around the left lung base (>15%) is aggravated by coughing or forced expiration.

• General malaise and other constitutional and dyspeptic symptoms can be included, all of which can also be seen in a variety of other septic conditions.

Physical examination:

• Abdominal tenderness (>50%) may or may not be accompanied by muscle guarding in the left upper quadrant. There may be edema of the soft tissues overlying the spleen. Costovertebral tenderness may also be noted.

• Splenomegaly (<50%) is less frequently observed, probably because of early diagnosis resulting from the widespread use of imaging methods.

• Chest findings are nonspecific and reportedly include dullness at the left lung base (>30%), left basilar rales (>21%), or elevation of the left hemidiaphragm (>15%).

TROPICAL SPLENOMEGALY SYNDROME

Several reports were published over the last century describing patients from tropical areas with massive splenomegaly. After excluding known causes of splenomegaly, tropical splenomegaly syndrome was defined as a separate entity. This condition was later defined as hyperreactive malarial syndrome (HMS) using clear diagnostic criteria.

Pathophysiology

HMS is prevalent in native residents of regions where malaria is endemic and visitors to those regions. Patients with HMS have high levels of antibody for *Plasmodium falciparum*, *Plasmodium vivax*, or *Plasmodium ovale*.

Genetic factors, pregnancy, and malnutrition may play a role in the etiology of HMS. Relative protection against HMS is observed in patients with sickle cell trait, as it is with malaria. In experimental models, animals developed a similar syndrome after malarial infection.

Although the exact mechanism is uncertain, evidence suggests that exposure to malaria elicits exaggerated stimulation of polyclonal B lymphocytes, leading to excessive and partially uncontrolled production of immunoglobulin M (IgM) as the initiating event. IgM is polyclonal and is not specific for any particular malarial species.

Defective immunoregulatory control of B lymphocytes by suppressor or cytotoxic T lymphocytes causes the increase in B lymphocytes, although the mechanism by which malarial parasitemia drives these changes is unclear. T-cell infiltration of the hepatic and splenic sinusoids accompanies this process. Serum cryoglobulin and autoantibody levels increase, as does the presence of high molecular weight immune complexes. The result is anemia, deposition of large immune complexes in Kupffer cells in the liver and spleen, reticuloendothelial cell hyperplasia, and hepatosplenomegaly.

Antimalarial treatment is effective in decreasing the size of the spleen, but premature discontinuation of treatment may lead to relapse. Effective malarial chemoprophylaxis and eradication measures have been associated with a decrease in the incidence of HMS.

International

HMS is restricted to native residents of and visitors to the malaria belt which roughly encompasses equatorial regions of South America, Africa, the Middle East, South Asia, and Southeast Asia.

HMS has been reported in the following countries: Algiers, Congo, Madagascar, Ivory Coast, Sudan, New Guinea, Nigeria, India, Philippines, Brazil, China, Uganda, Yemen, Bangladesh, Ethiopia, Hong Kong, Ghana, Somalia, Zambia, Chile.

Accurate assessment of the incidence of HMS is difficult because many conditions that cause splenomegaly are prevalent in areas where malaria is endemic. These conditions include hemoglobinopathies, lymphoreticular disorders, schistosomiasis, hepatic cirrhosis, leishmaniasis, typhoid, and tuberculosis.

The incidence of massive splenomegaly is estimated to be 1–2% in rural Nigeria, and HMS accounts for 11–45% of massive splenomegaly cases in Africa. The incidence of HMS is highest among the people of the Upper Watut Valley in Papua New Guinea, where the rate is estimated to be 80%.

Mortality/Morbidity

The natural history of HMS is not well documented. HMS is associated with a high mortality rate in untreated individuals; overwhelming infections are the leading cause of death. A 5-year mortality rate of 50% was reported in Uganda and New Guinea, with a mortality of 85% in hospitalized patients.[6] However, other series found a much lower mortality rate.

HMS is not a premalignant condition, although an overlap with chronic lymphocytic leukemia has been noted. Whether HMS can undergo clonal evolution to splenic lymphoma with villous lymphocytes (SLVL) is unclear; these entities appear to evolve independently in response to chronic antigen stimulation.

HMS has also been documented in patients with HIV infection and splenomegaly following the exclusion of other disease entities, such as Epstein-Barr virus, cytomegalovirus, or lymphoproliferative disorders.

Race

Certain racial and immunologic factors may be important in the pathogenesis of HMS, although results of phenotypic studies of human lymphocyte antigens have not been conclusive.

The incidence of splenic enlargement at autopsy was greater in individuals who migrated from malaria-free Rwanda to malaria-endemic Uganda, than in local residents. Rwandan immigrants have also shown evidence of familial clustering, and many Rwandans with HMS were born and raised in the Baganda groups in Uganda. In Ghana, patients with HMS were more likely to have family members with splenomegaly.

HMS has been reported in whites who resided in or moved to areas where malaria was endemic. It has also been described among visitors who received inadequate prophylaxis against malaria.

Sex

Overall, HMS is more common in female individuals, especially lactating mothers, than in male individuals, with a female-to-male ratio of 2:1. Only one study in Eastern Sudan showed men to have a higher incidence.

Age

HMS is most common in young and middle-aged adults, although the process probably commences during childhood. HMS is rare in children younger than 8 years but was reported in a 3-year-old patient. These observations support the theory that chronic antigenic stimulation is an important factor in the development of HMS.

History

- The most common presenting symptoms of hyperreactive malarial syndrome (HMS), or tropical splenomegaly syndrome, are chronic abdominal swelling (64%) and pain (52%).
- Abdominal swelling may wax and wane.
- Almost all patients (97%) report weight loss.
- Many patients do not have any symptoms and are capable of normal daily activity.
- Rarely, patients have intermittent fever. Persistent, severe fevers should raise the possibility of an alternative diagnosis.
- Some patients present with acute abdominal pain.
- Patients physiologically adapt well to the chronic evolution of anemia and are symptomatic only when anemia is severe.
- Weakness and loss of energy may reflect the degree of anemia.
- Nonspecific symptoms include cough, dyspnea, epistaxis, and headache.
- Pressure on the abdominal contents may lead to hernias and leg swelling.
- A history of chronic splenic enlargement differentiates HMS from simple malarial splenomegaly.

- Bleeding complications are uncommon because thrombocytopenia is usually not severe.
- Susceptibility to infections, especially skin and respiratory infections, is slightly increased.
- Pregnant women are susceptible to episodes of massive Coombs-negative hemolysis, which are usually preceded by febrile episodes; the basis for hemolysis remains uncertain.

Physical

- The hallmark of HMS is splenomegaly, which is usually moderate to massive.
- Most spleens are not tender (63%).
- The spleen has a smooth surface (99%), soft consistency (91%), and sharp border (93%). The enlarged spleen may be seen to protrude against the abdominal wall.
- A splenic bruit may be audible.
- Despite the size of the spleen, splenic rupture is rare.
- Hepatomegaly is common; in a study of 69 Nigerian patients, 93% had accompanying hepatomegaly.[3]
- Pallor is common.
- Patients are usually afebrile at presentation.
- In general, tachycardia is absent. If tachycardia is present, it indicates a concurrent complication.
- Dilatation of the veins, cardiomegaly, low blood pressure, and flow murmurs reflect hypervolemia.
- Lymphadenopathy is absent, but bilateral parotid swelling has been described.
- The patient may be malnourished and jaundiced.
- Ascites is uncommon.

Causes

The most important predisposing factor for HMS is residence in or visitation to an area where malaria is endemic.

Other risk factors include malnutrition and an as-yet-undefined genetic predisposition.

Навчальне видання

Модуль 2
Хірургічна гастроентерологія

Тема 12
Хронічні захворювання підшлункової залози та селезінки

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Module 2
Surgical Gastroenterology

TOPIC 12
CHRONIC DISEASES OF THE PANCREAS AND SPLEEN

Guidelines for students and interns