INTRODUCTION
Chronic pancreatitis is characterized and defined by irreversible damage to the pancreas and development of histologic evidence of inflammation and fibrosis and, eventually, destruction of exocrine (acinar cell) and endocrine (islets of Langerhans) tissue.

EPIDEMIOLOGY
True prevalence of chronic pancreatitis is not known as many patients with unexplained abdominal pain may have chronic pancreatitis that eludes diagnosis. Chronic pancreatitis can be demonstrated in 0.04% to 5% of autopsies. Incidence of chronic pancreatitis in western population ranges from 8 to 10 cases per year per 100,000 population, and the overall prevalence is 27.4 cases per 100,000 population. Prevalence of chronic pancreatitis in Southern India is 114-200 cases per 100,000 population as per a recent survey conducted in different countries in the Asia-Pacific region. Prevalence in Japan was reported to be 4.2 cases per 100,000 population. A multicentre study classified 19 countries, with regard to chronic pancreatitis, into four classes presenting relative similarities. (A) Southern Europe: the pathology is dominated by chronic calcific pancreatitis (CCP). (B) Northern Europe, to which may be added Argentina and Chile, is characterized by a distinct prevalence of alcoholic pancreatitis and non-calcified chronic pancreatitis (NCCP). (C) Japan has a lipid-poor diet and a low frequency of CCP and NCCP. (D) A fourth group is mostly composed of tropical countries with mixed races. It may be divided into two subclasses: (a) India is the most characteristic country with a high frequency of CCP (at an early age); (b) Brazil and South Africa have a high frequency of CCP.

The prognosis of chronic pancreatitis is quite variable. Overall, 10-year survival is about 70%, and 20-year survival is about 45%.

ETIOLOGY
Etiologies are enumerated in Table 1.

TROPICAL PANCREATITIS
Tropical chronic pancreatitis is a juvenile form of chronic calcific non-alcoholic pancreatitis, seen almost exclusively in the developing countries of the tropical world. Non-alcoholic causes constitute more than two-thirds of causes of chronic pancreatitis in India. Tropical calcific pancreatitis (TCP) is the most common cause in many parts of India.

The first case of pancreatic calculi from India was reported by Kini in 1937 and this was followed by reports of pancreatic calculi observed at postmortem from Vellore in Southern India. However, it was after Geevarghese, one of the pioneers in the field, documented one of the largest series in the world from Kerala state in Southern India that tropical pancreatitis attracted international attention. Large series of TCP patients have also been reported by a number of workers from various stages in India. There is very little information on the prevalence of TCP in the population. Prevalence of chronic pancreatitis in Southern India is about 114-200 cases per 100,000 population. TCP constitutes about 70% of all cases of chronic pancreatitis in India. Over 90% of patients develop the illness prior to the age of 40 years with a mean age of onset of 24 years. The disease...
Risk of cancer  Very high  Higher than general population
Alcoholism  Absent by definition  Heavy alcohol abuse
Fibrosis of gland  Marked  Less severe
Ductal dilation  Usually marked  Usually mild
Pancreatic calculi  Occur >90%; aggressive course  About 50-60%
Diabetes  Occur in >90%; aggressive course  About 50% cases; slower progression
Socioeconomic status  Usually poor  All strata equally affected
Onset age  Second and third decade  Fourth and fifth decade
M:F  70:30  Almost all male

1. The ductal obstruction hypothesis focuses on the formation of ductal protein precipitates, plugs, and stones as being the most important event. Lithostathine and GP-2, a glycosyl phosphatidyl inositol (GPI)–anchored protein, may be important in the formation of pancreatic stones.

2. Toxic-metabolic hypothesis holds that alcohol, or one of its metabolites, has direct injurious effects on the pancreatic ductal or acinar cells.

3. Necrosis-fibrosis hypothesis holds that the occurrence of repeated episodes of acute pancreatitis with cellular necrosis eventually leads to the development of chronic pancreatitis as the healing process replaces necrotic tissue with fibrosis. SPINK1 is a potent protease inhibitor and is considered to be a major protective mechanism in preventing inappropriate activation of pancreatic enzyme cascade by inhibiting up to 20% of trypsin activity. An association of hereditary pancreatitis has been shown with the SPINK1 gene. The association between the SPINK1 gene and TCP has now been reported by a number of groups in India.

A recent study by Chandak GR, et al of presence of PRSS1 mutations and SPINK1 mutations in patients of hereditary and non-hereditary chronic pancreatitis in Indian patients, has come up with interesting findings. Mutations in PRSS1 gene which are found in hereditary pancreatitis in Western population, are not associated with chronic pancreatitis in India, including hereditary type. In contrast, the N34S mutation in the SPINK1 gene shows a significant correlation in these patients.

Clinical Presentation

Abdominal Pain
Abdominal pain is the most serious clinical problem in patients with chronic pancreatitis (50-90%). Pain is most commonly described as being felt in the epigastrium, often with radiation to the back. Pain is usually described as boring, deep, and penetrating and is often associated with nausea and vomiting. Pain may be relieved by sitting forward or leaning forward, by assuming the knee-chest position on one side, or by squatting and clasping the knees to the chest. Pain may increase after a meal and is often nocturnal.

Steatorrhea and Weight Loss
Steatorrhea does not occur until pancreatic lipase secretion is reduced to less than 10% of normal. It is a feature of far-advanced chronic pancreatitis when most of the acinar cells have been injured or destroyed, but may also be seen with complete blockage of the pancreatic duct. Steatorrhea is seen in about 20% of Indian patients. When the fat intake of the diet was experimentally increased to 100g/day from the average intake of 27g/day, 76% of TCP patients developed steatorrhea.

Diabetes Mellitus
Diabetes occurs in more than 90% patients of TCP and about 50% patients of alcoholic pancreatitis. In TCP, it occurs a decade or two after the first episode of abdominal pain. Diabetes in TCP is called as fibrocalculus pancreatic diabetes (FCPD).
Deficiency of insulin and glucagon in chronic pancreatitis leads to a brittle type of diabetes. Exogenous administration of insulin in these patients may therefore lead to prolonged and severe hypoglycemia.

Diagnosis
Chronic pancreatitis has been classified as either “big-duct” or “small-duct” disease. “Big-duct” disease implies substantial abnormalities of the pancreatic duct (generally, dilation visible on ultrasound, CT, or ERP), whereas “small-duct” disease implies the absence of these findings (e.g., a normal or near-normal US, CT, or ERP).

Tests of Pancreatic Function
These tests (Table 3) can be divided into those that directly measure pancreatic exocrine function by measuring the output of enzymes or bicarbonate from the pancreas and those that measure the released enzymes indirectly (through the action on a substrate or the presence in stool or serum). Secretin-pancreozymin test is the most sensitive (75-90%) and specific (80-90%) test. Lundh meal test has a sensitivity of 66-94%.

Tests of Pancreatic Structure
Tests enumerated in Table 3.

Abdominal Ultrasound
Ultrasound (US) has been widely studied as a diagnostic tool for chronic pancreatitis. Most studies suggest a sensitivity of 50% to 80%, with a specificity of 80% to 90%.

Computed Tomography
The overall sensitivity of CT for chronic pancreatitis is between 75% and 90%, with a specificity of 85% or more. CT is able to image the pancreas in all patients (Fig. 2) and hence provides an advantage over ultrasound (Table 4). CT is estimated to be 10% to 20% more sensitive than US, with a similar specificity.

Magnetic Resonance Imaging/Magnetic Resonance Cholangiopancreatography
MRCP provides an acceptable assessment of pancreatic ductal morphology in most patients. MRCP agrees with ERCP in 70% to 80% of findings, with the higher rates of agreement seen in studies using the most advanced image analysis techniques.

Endoscopic Retrograde Cholangiopancreatography (ERCP)
ERCP, specifically ERP, is generally considered the most specific and sensitive test of pancreatic structure, and many consider it the de facto gold standard (Fig. 3 and Table 5). It has the advantage that therapy may be administered (e.g., pancreatic duct stenting or stone extraction). The disadvantage is that it is the riskiest diagnostic test, with complications occurring in at least 5% of patients and a mortality rate of 0.1% to 0.5%. In most studies in patients with chronic pancreatitis, the sensitivity of ERCP is between 70% and 90%, with a specificity of 80% to 100%.

Endoscopic Ultrasonography
When EUS has been compared with ERCP, the tests agree in about 80% of cases.

TREATMENT
Treatment of chronic pancreatitis is given in Table 6.

Abdominal Pain
Therapy of abdominal pain includes following:
Decrease of Pancreatic Pressure

Pancreatic Enzymes
Two studies utilizing enzymes in nonenteric-coated (tablet) form have reported a benefit in CP.\textsuperscript{45,46} High dosages of nonenteric-coated enzymes have been used in these trials (equivalent to 30,000 units of lipase with meals and at night, which has translated to 4 to 8 pills four times daily). Since these agents are inactivated by gastric acid, the concomitant use of an agent to suppress gastric acid is required.

Endoscopic Therapy
The potential application of endoscopic therapy is limited to a subgroup of patients with amenable pancreatic ductal anatomy. These are patients with “big-duct” chronic pancreatitis with advanced structural abnormalities of the pancreatic duct.

Stent Therapy
Stent placement in the pancreatic duct is most often performed to bypass an obstructing calculus or stricture. Pain improvement is seen in about two-thirds of patients.\textsuperscript{47-51} Complications of therapy occurred in about 20%, with a mortality rate of 0.6%. In the few studies that have examined long term use, about 40% of patients had resolution of the stricture after stent removal.\textsuperscript{52}

Pancreatic Duct Stone Removal
The endoscopic removal of pancreatic duct stones can be difficult and is possible only in a subset of patients. The removal of large stones often will require lithotripsy with extracorporeal or intraductal instruments. A number of uncontrolled case series reported overall success at complete stone clearance in an average of 60% of patients.\textsuperscript{52} Clinical improvement was seen in about 75%.

Table 4: Grading of Chronic Pancreatitis by USG or CT Scan

<table>
<thead>
<tr>
<th>Grade of Chronic Pancreatitis</th>
<th>US/CT Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal pancreas</td>
</tr>
<tr>
<td>Equivocal</td>
<td>One of the following-</td>
</tr>
<tr>
<td></td>
<td>PD dilation (2-4mm) in body</td>
</tr>
<tr>
<td></td>
<td>Gland enlargement ≤ 2 times</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>One of the above + one of the following-</td>
</tr>
<tr>
<td></td>
<td>PD dilation</td>
</tr>
<tr>
<td></td>
<td>PD irregularity</td>
</tr>
<tr>
<td></td>
<td>Cavities &lt; 10mm</td>
</tr>
<tr>
<td></td>
<td>Parenchymal heterogeneity</td>
</tr>
<tr>
<td></td>
<td>Increased echo of duct wall</td>
</tr>
<tr>
<td></td>
<td>Irregular contour of head or body</td>
</tr>
<tr>
<td></td>
<td>Focal necrosis</td>
</tr>
<tr>
<td>Severe</td>
<td>Mild or moderate + one of the following-</td>
</tr>
<tr>
<td></td>
<td>PD dilatation</td>
</tr>
<tr>
<td></td>
<td>PD irregularity</td>
</tr>
<tr>
<td></td>
<td>Cavities &gt; 10 mm</td>
</tr>
<tr>
<td></td>
<td>Intraductal filling defects</td>
</tr>
<tr>
<td></td>
<td>Calculi/ calcification</td>
</tr>
<tr>
<td></td>
<td>Ductal stricture</td>
</tr>
<tr>
<td></td>
<td>Ductal irregularity/ severe dilatation</td>
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<tr>
<td></td>
<td>Contiguous organ invasion</td>
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</tbody>
</table>

Fig. 3: Endoscopic Retrograde Pancreatogram (A) Normal Pancreas, (B) Chronic Pancreatitis - revealing a dilated, tortuous main duct with stricture in midportion

Pancreatic Duct Sphincterotomy
Pancreatic duct sphincterotomy is routinely used in association with stent placement and is required for pancreatic duct stone extraction. It is used in sphincter of Oddi dysfunction, in patients with pancreas divisum and in obstructive chronic pancreatitis.

Surgical Therapy
Surgical therapy is most commonly considered for intractable abdominal pain that has failed medical therapy. Surgical options for pain can include pancreatic ductal drainage, resection of all or part of the pancreas, or both. Immediate pain relief is seen in 80% of patients.\textsuperscript{53-56} With long term follow-up, only 40% to 50% continue to experience pain relief.\textsuperscript{53-56} Various surgical interventions have been tried with fairly good results in India.\textsuperscript{57,58}

Malnutrition and Steatorrhea
It has been estimated that delivery of 30,000 units of lipase to the intestine with each meal should be sufficient to reduce steatorrhea to a clinically insignificant level. If nonenteric-coated preparations are chosen, concomitant suppression of gastric acid with an H2 receptor antagonist or proton pump inhibitor is necessary. One can replace dietary fat with medium-chain triglycerides, which do not require lipolysis (and hence lipase) for absorption. Mohan et al have reported that pancreatic enzymes supplementation help to reduce steatorrhea and also improves quality of life.\textsuperscript{60}

Diabetes Mellitus
Diabetes mellitus is an independent predictor of mortality in patients with chronic pancreatitis. Given the risk of treatment-
Table 5: Cambridge Grading of Chronic Pancreatitis by ERCP

<table>
<thead>
<tr>
<th>Grade</th>
<th>Main pancreatic duct</th>
<th>Side branches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Equivocal</td>
<td>Normal</td>
<td>&lt; 3 Abnormal</td>
</tr>
<tr>
<td>Mild</td>
<td>Normal</td>
<td>≥ 3 Abnormal</td>
</tr>
<tr>
<td>Moderate</td>
<td>Abnormal</td>
<td>&gt; 3 Abnormal</td>
</tr>
<tr>
<td>Severe</td>
<td>Abnormal with at least one of the following:</td>
<td>&gt; 3 Abnormal</td>
</tr>
<tr>
<td></td>
<td>Large cavity&gt;10 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ductal obstruction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intraductal filling defect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe dilation or filling defect</td>
<td></td>
</tr>
</tbody>
</table>

induced hypoglycemia and the difficulty of close follow-up in patients who continue to abuse alcohol, therapy is usually directed at controlling urinary losses of glucose rather than tight control of blood sugar.

Complications

Pancreatic Pseudocyst

Pseudocysts occur in about 25% of patients with chronic pancreatitis. The diagnosis of pseudocyst is made by imaging studies, including US, CT, MRI, or even EUS. ERCP is usually not required for diagnostic purposes, although around 70% of pseudocysts communicate with the pancreatic duct. Overall, complications of pseudocysts occur in 5% to 41% of cases.\(^{61-66}\) Symptomatic, complicated, or enlarging pseudocysts require therapy that can be percutaneous, endoscopic, or surgical. Surgical therapy has a long-term success rate of 90% and an operative mortality of less than 3%.\(^{61-66}\) Percutaneous tube (catheter) drainage of pseudocysts has an initial success rate of 85% or greater, with recurrence rates of less than 10%. Endoscopic therapy of pseudocysts is possible if the fluid collection can be accessed through the papilla or through the wall of the stomach or duodenum. Success rates of 70% to 90% are reported in small numbers of highly selected patients, with complications reported in 10% to 20%.

Bleeding

Gastrointestinal bleeding in the setting of chronic pancreatitis may develop from a variety of causes. Some are not specific for chronic pancreatitis, such as a Mallory-Weiss tear, esophagitis, peptic ulcer disease, or varices from concomitant alcoholic cirrhosis. Others occur as a direct result of the pancreatic process, most notably bleeding from a pancreatic pseudocyst, a pseudoaneurysm, or portal or splenic vein thrombosis.

Pseudoaneurysms

Pseudoaneurysmal bleeding may complicate 5% to 10% of all cases of chronic pancreatitis with pseudocysts. The finding of high-density material within a pseudocyst on noncontrast images of CT scan is highly suggestive of a pseudoaneurysm. Once a pseudoaneurysm has been identified, it should be treated whether or not it has caused bleeding.

Common Bile Duct Obstruction

Table 6: Treatment of Chronic Pancreatitis

1. Apply specific treatment for complications:
   - Pseudocyst
   - Common bile duct obstruction
   - Duodenal obstruction
   - Gastroparesis
2. Give analgesics, with or without adjunctive agents (e.g. antidepressants)\(^{61-66}\)
3. Stop alcohol
4. Decrease intrapancreatic pressure
   - Suppress pancreatic secretion (nonenteric coated pancreatic enzymes with gastric acid suppression, octreotide)
   - Relieve ductal obstruction (endoscopic stent or removal of ductal stone, surgical duct decompression)
5. Modify neural transmission
   - Celiac plexus block
   - Thoracoscopic splanchnicectomy
6. Remove pancreatic parenchyma
   - Pancreatic head resection (Beger, Frey, or Whipple resection)
   - Total or subtotal pancreatectomy

Symptomatic common bile duct obstruction occurs in about 10% of patients. ERCP characteristically demonstrates a long, tapered stenosis of the distal bile duct. Therapy usually requires surgical biliary bypass, either with a choledochojejunosotomy or choledochojjunostomy or endoscopic therapy\(^67\)

Duodenal Obstruction

Approximately 5% of patients with chronic pancreatitis experience symptomatic duodenal stenosis. Surgical therapy is required for those who fail conservative management. The simplest and safest approach is a gastrojejunostomy.

Pancreatic Fistula

External

External pancreatic fistulas occur most commonly as a consequence of surgical or percutaneous therapy for chronic pancreatitis or pseudocyst. Octreotide, and placement of an endoscopic stent across the site of ductal disruption is effective at closing these fistulas rapidly. In those who fail endoscopic therapy surgical treatment can include pancreatic resection (if the fistula is in the tail) or a fistulojejunostomy.\(^{68}\)

Internal

Internal fistulas occur mainly in the setting of chronic pancreatitis after rupture of a pseudocyst. The fluid may track to the peritoneal cavity (pancreatic ascites) or into the pleural space (pancreatic pleural effusion). Endoscopic treatment is effective if the leak is in the body or head of the pancreas,\(^69\) otherwise, resection and/or surgical drainage of the pseudocyst is required.

Cancer

Chronic pancreatitis is a risk factor for pancreatic adenocarcinoma. The lifetime risk for pancreatic cancer in patients with chronic pancreatitis is about 4%.\(^70\) The risk of pancreatic cancer is highest in hereditary pancreatitis, particularly in those patients who smoke. The risk of pancreatic cancer is increased 53-fold in patients with hereditary pancreatitis compared with the general population, and the cumulative lifetime risk may approach 40%.
REFERENCES