Chronic pancreatitis is a progressive fibroinflammatory disease that exists in large-duct (often with intraductal calculi) or small-duct form. In many patients this disease results from a complex mix of environmental (eg, alcohol, cigarettes, and occupational chemicals) and genetic factors (eg, mutation in a trypsin-controlling gene or the cystic fibrosis transmembrane conductance regulator); a few patients have hereditary or autoimmune disease. Pain in the form of recurrent attacks of pancreatitis (representing paralysis of apical exocytosis in acinar cells) or constant and disabling pain is usually the main symptom. Management of the pain is mainly empirical, involving potent analgesics, duct drainage by endoscopic or surgical means, and partial or total pancreatectomy. However, steroids rapidly reduce symptoms in patients with autoimmune pancreatitis, and micronutrient therapy to correct electrophilic stress is emerging as a promising treatment in the other patients. Steatorrhoea, diabetes, local complications, and psychosocial issues associated with the disease are additional therapeutic challenges.

Introduction

Chronic pancreatitis is a progressive inflammatory disorder in which pancreatic secretory parenchyma is destroyed and replaced by fibrous tissue, eventually leading to malnutrition and diabetes. Two forms are recognised—a large-duct calcifying type and a small-duct variant. The disease is uncommon in Europe and the USA; its prevalence in France is 26 per 100 000 people. This prevalence is not dissimilar to the middle of three figures of 114–200 per 100 000 in south India.

The main symptom of chronic pancreatitis is usually pain, which occurs as attacks that mimic acute pancreatitis or as constant and disabling pain. Despite decades of research, treatment of chronic pancreatitis remains mostly empirical, and thus patients are repeatedly admitted to hospital and have interventional procedures, which strains medical resources. This absence of progress in treatment is a sign of uncertainty about how the identified causative factors lead to the disease. Therefore, in this Seminar we focus on the pathophysiology and pathology of chronic pancreatitis before describing clinical management.

Definition

Traditionally, chronic pancreatitis has been classed as fundamentally different from acute pancreatitis—the latter is usually characterised by restoration of normal pancreatic histology after full clinical recovery. However, acute, recurrent acute, and chronic pancreatitis are now regarded as a disease continuum. There are several reasons for this change: recurrent acute pancreatitis can develop into chronic pancreatitis; there is an overlap in causative factors, both genetic and environmental; experimental protocols can be modified to induce each condition; and the pancreatitis attack is stereotyped—patients have severe abdominal pain and increased blood amylase, lipase, and trypsinogen.

Pathophysiology and pathology

Experimental studies since the 1950s have shown that an attack of pancreatitis begins as pancreastasis, prevention of apical exocytosis in the pancreatic acinar cell (figure 1). The acinar cell quickly releases newly synthesised enzyme via the basolateral membrane into lymphatics, by way of the interstitium, and directly into the bloodstream. Some zymogen granules also release their stored enzyme basolaterally. These events result in inflammation. Findings from prospective clinical studies concur with this pancreastasis–pancreatitis sequence.

Experimental work has pinpointed a burst of reactive oxygen species (ROS) as the trigger of so-called pancreastasis and as the potentiator of inflammation by activating signalling cascades that convert the damaged acinar cell into a factory for chemokines and cytokines. ROS serve several physiological roles, including in signal transduction, but an excess of ROS compared with antioxidant capacity (electrophilic stress) is potentially very damaging. The exocytosis blockade seems to be caused by disruption of the methionine trans-sulphuration pathway that produces essential methyl and thiol (principally glutathione) moieties. This problem also occurs in clinical acute or acute-on-chronic pancreatitis.

In patients who develop large-duct chronic pancreatitis, studies in the quiescent phase of the disease show that the composition of pancreatic fluid changes in a manner...
that, for uncertain reasons, facilitates protein deposits—the precursors to calcium carbonate stones.1 (1) There is an early increase in secretion of enzyme and calcium, but a decrease in the serine protease inhibitor Kazal type 1 (SPINK 1), bicarbonate, and citrate.1 (2) Concentrations of free radical oxidation products are raised in the pancreatic fluid,26 which suggests ongoing electrophilic stress, and in an apparent attempt to compensate, concentrations of the natural antioxidants27 lactoferrin and mucin are increased.1,2,28 (3) Concentrations are altered of two secretory stress proteins29 (increased concentration of pancreatitis associated protein [PAP]/regIII, which is activated by electrophilic stress; and variable concentration of pancreatic stone protein [PSP]/reg, formerly called lithostatin;1 figure 1) that tend to form fibrous lattices upon partial digestion by trypsin. (4) There is an increase of GP-2, which is a secreted component of zymogen granule membranes (analogous to the renal cast protein).30 (5) Concentrations of lysosomal enzymes are increased in ductal fluid, and traces of trypsin appear.31 Moreover, the methionine metabolic pathway remains fractured.32–34

On histology, the defining triad of stable disease (irrespective of main causes or location)10 is acinar loss, mononuclear cell infiltration, and fibrosis. The early lesions are distributed in patches; thus, normal findings on needle biopsy are unreliable. An unusual form of so-called groove (paraduodenal) pancreatitis has been identified.11 Each inflammatory attack can cause foci of fat necrosis that seem to lead to both pseudocysts and fibrosis.11 Nerves show breaching of the perineurium adjacent to inflammatory foci, while the expression of nociceptive chemicals in nerve endings is increased.36 Immunocytochemistry gives valuable insights into the development of chronic pancreatitis. Acinar cells, which are hyperplastic at disease outset,1 show strong expression of cytochrome P450 (CYP) monooxygenases,37–39 as do proliferated islets of Langerhans,37–39 and hepatocytes (figure 2).37,38 After birth, CYP enzymes are mainly located in the liver. CYP metabolises environmental lipophilic chemicals (xenobiotics). In the first phase, the enzyme uses ROS to hydroxylate the substrate, which then usually undergoes second-phase conjugation reactions, often with glutathione and catalysed by glutathione transferases. So-called enzyme induction might be accompanied by expansion of the endoplasmic reticulum so that, at least initially, the cell secretes more of its normal products. However, this defence reaction backfires if first-phase processing (eg, by CYP2E1, CYP1A, and CYP3A4 isoforms) produces a reactive xenobiotic metabolite. Cell injury depends on whether or not there is enough by way of defences to ROS and reactive xenobiotic species: antioxidant enzymes (including the selenium-dependent glutathione peroxidase), glutathione transferases, glutathione, and ascorbic acid (the bioactive form of vitamin C, which can substitute for glutathione).32,40 Immunochemistry shows that these defence mechanisms are insufficient to meet the increased oxidant load in acinar cells,32,40 which therefore
show signs of electrophilic stress, such as excess lipo-fuscin and cytoplasmic microvesiculation.41

Fibrosis is a sign that interstitial stellate cells are activated in chronic pancreatitis; these cells play a central part in disease progression by regulating the synthesis and degradation of extracellular matrix proteins.42,43 Findings from histochemistry suggest a causal influence of two factors—an increase in lipid peroxidation products caused by an excess of ROS in adjacent acini,44 and the release of mast cell degranulation products,45 transforming growth factor β1 in particular.46 The two factors are linked in that ROS and their oxidation products are natural activators of mast cells.47 Activation of stellate cells is increased by cytokines from infiltrating leucocytes and the injured acinar cell.43 The end stage of chronic pancreatitis is identified by loss of all secretory tissue, disappearance of inflammatory cells, and intense fibrosis. This progression resembles that from chronic active hepatitis to liver cirrhosis.2,12,47

The table summarises the histological features of ordinary chronic pancreatitis compared with features of three variants in which the lesions are diffuse. The pancreatic lesion in cystic fibrosis is a diffuse form of chronic pancreatitis wherein inflammatory stigmata disappear by birth,48 except in patients with mild mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR), who might have recurrent attacks.49 Uniform lesions also occur upstream of an obstructed duct1,11 and in autoimmune pancreatitis.50,51 The latter can involve the whole or part of the gland and has two subtypes. Characteristics of the more common type-1 autoimmune pancreatitis are a dense lymphoplasmacytic infiltrate with predominantly IgG4+ cells, periductal swirling sclerosis, and oblitative venulitis. In the type-2, duct-destructive form, hordes
of neutrophils infiltrate the wall of the duct, accompanied by lymphocytes and plasma cells.51

**Causes**

Panel 1 lists causative factors of chronic pancreatitis. In adults, excluding those with cystic fibrosis, 90–95% of patients are regarded as having alcoholic or idiopathic disease. Infective causes are rare.52 The connection between chronic pancreatitis and drugs (eg, valproate) is mostly anecdotal. Studies from Italy,53 China, and Japan54 report an association with gallstones in about 30% of patients.

**Alcoholic**

Alcohol has long been regarded as the leading cause of chronic pancreatitis in Europe, the USA, Brazil, Mexico, and South Africa, and is now regarded as the main cause of the disease also in Australia and South Korea.7 However, excess alcohol was the predominant factor in only 34% of cases of chronic pancreatitis in a recent multicentre study from Italy53 and in 44% of cases in an audit from the USA,55 with another study reporting that African-Americans are at particular risk.56 Whether these new data reflect differences in the definition of alcoholic disease55 or a genuine change in the cause of chronic pancreatitis is not clear.57

Experimental studies have shown that, although the pancreas processes ethanol efficiently (via a non-oxidative route that produces fatty acid ethyl esters, and by oxidation via the acetaldehyde pathway), its metabolites injure acinar cells and activate stellate cells in vitro.42,58 However, prolonged ethanol feeding does not induce chronic pancreatitis.58,59 Hence, the finding of a latent interval of 15 years or more in patients who consumed 150 g or more of ethanol per day—as most recently noted in India60—is unsurprising. Moreover, less than 10% of people who drink alcohol in excess develop the disease.61 Collectively, these findings suggest that other factors interact to amplify ethanol toxicity in vivo.

In animal models, small doses of ethanol induce CYP2E1, thus increasing the toxicity from other chemicals to which the animal is simultaneously exposed.62,63 These results might rationalise the old observation that there is no threshold for the pancreatic toxicity of ethanol,1 but recent data suggest there is a threshold at 60 g per day.63 Moreover, CYP2E1 is the main pathway that metabolises ethanol upon chronic excessive ingestion,10 but this pathway releases ROS.64

**Idiopathic**

60–70% of cases of chronic pancreatitis in India and China are labelled as idiopathic, as are around half the cases in Japan.7 Tropical pancreatitis is a form of idiopathic pancreatitis that affects young people and has a propensity to diabetes and large calculi.65 This disease is mainly reported in developing countries of Asia, Africa, and Central America, where severe malnutrition and cyanogenic glycosides in *cassava* (manioc) were implicated. The classic description of tropical pancreatitis was from Kerala, south India;66 however, hospital admission statistics revealed a decline in the disease by six times between 1962 and 1987,66 without a change in *cassava* consumption. Instead, the decline coincided with the introduction of electricity in this province, which removed the dependence on traditional lighting (see below). At present, tropical pancreatitis accounts for just 3·8% of cases of chronic pancreatitis in India.60

**Other toxic causes**

Cigarette smoke has emerged as a strong independent risk factor for chronic pancreatitis;10,67 the link was verified.
Idiopathic chronic pancreatitis is associated with a mutation in the CFTR gene.\(^{43,52,53}\) Patients can have one abnormal recessive allele, but possession of two confers a 40 times increased risk of developing idiopathic chronic pancreatitis, which rises to 500 times in patients who also have a SPINK1 mutation.\(^{41}\) Some patients with apparent idiopathic chronic pancreatitis who have CFTR mutations have an atypical form of cystic fibrosis.\(^{46}\) Three overlooked aspects of CFTR function have been reviewed recently.\(^{22}\) CFTR is present in the luminal pole of acinar cells where it might facilitate membrane recycling and exocytosis, like it does elsewhere. CFTR transports bicarbonate and glutathione—which facilitate the solubility of mucins in secretions—across the luminal membrane of ductal cells adjacent to the centroacinar space. CFTR is inactivated by electrophilic stress but is protected by thiols and ascorbic acid. Moreover, CFTR is mislocalised to the cytoplasm of ductal cells in patients with chronic pancreatitis; this misplacement is corrected in autoimmune disease by steroids, which also reduce inflammation, restore bicarbonate and enzyme secretion, and regenerate acinar cells.\(^{46}\) Mutations in CFTR and SPINK1 have also been described in patients with hypertriglyceridaemia or hyperparathyroidism who develop pancreatitis.\(^{32}\) At present, molecular deficits that contribute to chronic pancreatitis have been identified in less than 10% of alcoholic chronic pancreatitis and around 50% of cases overall.\(^{19}\)

Pathogenesis
There is no agreement as to how these diverse causative factors lead to chronic pancreatitis. There are many hypotheses about the pathogenesis of the disease,\(^{14}\) which fall into five main categories.

Ductal theory
One hypothesis suggests that ducts are the primary target of the disease: theories centre on the primacy of calcifying protein deposits (protein plug hypothesis), stagnation of pancreatic juice, reflux of noxious bile and duodenal juice (facilitated by passage of gallstones), and primary autoimmune attack.

Acinar theory
Another hypothesis suggests that acini are the primary target: alcohol is thought to injure acinar cells directly (toxic metabolite hypothesis) or by increasing the cell’s sensitivity to cholecystokinin (CCK) or via CYP2E1, while also activating stellate cells, especially in the presence of endotoxin.\(^{50,58}\) Another suggestion is that the disease is caused by cyanide toxicity of the pancreas.

Two-hits theory
Two so-called hits are additionally suggested as causing the disease: variations include a duct-to-acinar sequence, vice versa, or double acinar hits. The last of these is the
most popular theory and incorporates the idea that recurrent necrosis leads to periductal fibrosis. The first attack of pancreatitis is taken to represent autodigestion caused by unregulated trypsin activity in the acinar cell. If this attack is severe enough to recruit macrophages (sentinel acute pancreatitis event hypothesis), subsequent damage to the gland (by alcohol or electrophilic stress) leads to fibrosis via macrophage-primed stellate cells.

Electrophilic stress theory
The electrophilic stress theory is the pancreatic equivalent of paracetamol or carbon tetrachloride hepatotoxicity, which results from insufficient protection by glutathione against electrophilic attack (via CYP) on key macromolecules—not least, enzymes in the methionine trans-sulphuration pathway towards glutathione. However, in chronic pancreatitis electrophilic stress from toxic metabolites—and, thereby, recurrent pancreatitis—develops over many years as a result of repetitive exposures to multiple xenobiotics. Previous dietary insufficiency of micronutrients, especially methionine and ascorbic acid, facilitates the problem. The diversion of free radical oxidation products into the interstitium causes mast cells to degranulate, leading to inflammation, activation of nociceptive axon reflexes, and fibrosis. The realisation that compromised availability of methyl and thiol (glutathione) moieties underlies chronic pancreatitis has allowed an extension of the electrophilic stress concept to chronic pancreatitis that is associated with gene mutations. Thus, the daily exposure of acinar cells to traces of trypsin in people with PRSS1 or SPINK1 mutations is expected to strain glutathione reserves. Of particular note, those with a CFTR mutation would be left vulnerable not only to pancreatitis but also to intraductal calcifying protein plugs (large duct disease) when the residual CFTR protein is immobilised by electrophilic stress.

Multiple-cause theory
The final hypothesis states that different causative factors lead to damage via different pathways: this concept incorporates the other theories while noting that pancreatic ischaemia can aggravate the disease.

Clinical features
Alcoholic chronic pancreatitis presents in the fourth or fifth decade of life and mainly affects men. Idiopathic disease has early-onset (second decade) and late-onset (sixth decade) forms, which have equal gender distribution. Hereditary disease manifests at around 10 years and tropical pancreatitis at between 20 and 30 years, whereas the more common type-1 form of autoimmune disease affects men in the sixth decade.

Presenting features of chronic pancreatitis usually fall into one of four groups: apparent acute or recurrent acute pancreatitis (the true diagnosis of chronic pancreatitis is suspected when attacks recur after cholecystectomy); constant pain; symptoms and signs of local complications of the disease (eg, pseudocyst, obstruction of adjacent organs, or vascular thrombosis); or complaints that suggest exocrine or endocrine pancreatic failure, or both, by which stage pancreatic calculi are often present. These features form the basis for the most recent classification system (figure 3). In alcoholic disease, the interval from first attack to steatorrhoea (signifying >95% loss of acini) is around 13 years, which is substantially shorter than in early-onset idiopathic disease or hereditary pancreatitis (≥26 years). Pancreatic calculi appear earliest in tropical pancreatitis, and earlier in alcoholic than idiopathic disease. Diabetes might precede, begin at the same time as, or start after steatorrhoea.

Pain is the over-riding symptom in all but 10–15% of cases of chronic pancreatitis; these cases are usually elderly patients with idiopathic disease, or patients with autoimmune pancreatitis who might present with steatorrhoea, diabetes, or jaundice. The pain is wearying and occurs in episodes that last about 1 week, or is constant. It starts in the epigastrium and moves through to the dorsal spine or localises to the left hypochondrium, radiating to the left infrascapular region. The pain is sometimes associated with nausea and vomiting and can be partially eased by sitting up and leaning forward or by application of local heat or other counterirritants to the dorsal spine or epigastrium. The pain can be so severe that patients fear food and lose weight. Most but not all studies have reported that pain diminishes markedly once the disease burns out (which suggests that viable acini are a prerequisite for pancreatic pain). However, by then patients often have become addicted to narcotic analgesics, which could cause them to lose their jobs, homes, or families.

Panel 2 lists factors that might contribute to pain in patients with chronic pancreatitis: mast cell degranulation products and hydrogen sulphide are plausible mediators of the pancreatic component. The intensity of the pain contrasts with the absence of specific signs in

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**Clinical criteria**
- Pancreatic failure
- Complications
  - Pseudocyst
  - Pancreatic fistula
  - Pancreatic ascites
  - Reri, eg, colonic stricture
- Attacks of apparent acute pancreatitis
- Pain

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**Cause**
- Early
- Intermediate
- End stage
  - 1 endocrine
  - 2 exocrine
  - 3 both

Figure 3: Proposal for a clinically based classification system for chronic pancreatitis
For example, a patient may be described as having chronic pancreatitis (idiopathic), stage B, bile duct.
uncomplicated disease. Erythema ab igne is a useful pointer for diagnosis of chronic pancreatitis in these patients, as is meteorism in patients whose pain has led to dependence on narcotic analgesics (figure 4). An epigastric swelling suggests a pseudocyst, inflammatory mass, or cancer. Patients with multisystem involvement usually have the autoimmune form of chronic pancreatitis.

Ordinary chronic pancreatitis has a high mortality rate—nearly 50% within 20–25 years of disease onset, as a result of complications of an attack, coexisting disease, or the effects of alcoholism. Patients with chronic pancreatitis have an increased risk of pancreatic cancer, which accounts for 3% of deaths. Although the risk of pancreatic cancer is especially high in patients with hereditary pancreatitis, they do not have a higher mortality risk than the general population. Autoimmune pancreatitis also does not affect long-term survival.

**Diagnosis**

Routine laboratory tests might reveal incipient diabetes, type-1 hyperlipidaemia, or hypercalcaemia in patients with suspected chronic pancreatitis. If type-1 autoimmune disease is a possibility, serology will show raised concentrations of γ-globulin, IgG (IgG4 predominantly), and various antibodies, including anti-lactoferrin, anti-carbonic anhydrase, rheumatoid factor, and anti-nuclear antibody. An abnormal liver function profile suggests alcoholic liver disease, non-alcoholic steatohepatitis, sclerosing cholangitis, metastases from superimposed pancreatic cancer, gallstones, or, most commonly, constriction of the intrapancreatic bile duct, which occurs early in autoimmune pancreatitis, but is late otherwise.

Confirmation of the diagnosis of (non-calcific) chronic pancreatitis is by histology of a wedge biopsy or resected specimen of pancreas. However, this is impractical. A reduction in bicarbonate with or without enzyme content of duodenal aspirates after intubation and hormonal stimulation (by secretin with or without CCK or its analogue caerulein), and abnormalities in the pancreatic duct system on endoscopic retrograde cholangio pancreatography (ERCP) are the most efficient alternative diagnostic techniques—with the former substantially better at detecting small-duct disease than the latter. However, the secretory test is available in only a few centres worldwide (and whether or not an
endoscopic secretory test is as good is unclear.5 Moreover, ERCP for diagnosis has largely been abandoned in favour of magnetic resonance cholangiopancreatography (MRCP) because ERCP can precipitate pancreatitis in up to 4% of patients.9

There is no non-invasive test that can substitute for the hormonal test for chronic pancreatitis.5 By contrast, sophisticated imaging methods have rapidly developed, such that the traditional ultrasound scan to visualise the pancreas itself is virtually obsolete (but see figure 5). The repertoire of imaging techniques is impressive: multidetector CT (MDCT; figure 5); MRI;9 MRCP (figure 6), which provides excellent images of the main pancreatic duct10 but not always of the side-branch changes as shown by ERCP; secretin-enhanced MRCP, which also shows duodenal filling by pancreatobiliary secretions11 and is more accurate than standard MRCP in identifying small-duct disease;12 endoscopic ultrasound (EUS);13,14 which identifies both parenchymal and ductal alterations (figure 6; now classified as the Rosemont criteria),15 but which is observer-dependent and tends to overdiagnose the disease;17 diffusion-weighted MRI;13 PET.16 The last two imaging techniques have not been properly assessed in chronic pancreatitis, whereas the role of EUS continues to advance.

No investigation algorithm is suitable worldwide, because much depends on available resources and expertise, but a battery of tests should not be used for diagnosis of suspected chronic pancreatitis because this will generate many false positive outcomes and cause distress to the patient.2 Figure 7 presents a sequential scheme for diagnosis of the disease, on the basis of whether or not the secretin test is available. This scheme recognises that an abdominal radiograph will show pancreatic calculi (nearly 100% specificity; figure 4) in at least 30% of patients overall and in most patients with tropical pancreatitis. This stepwise approach is unnecessary in a patient who presents with fatty stools after a long history of pancreatitis attacks or pain. In this event, any of the following tests is probably sufficient for diagnosis: acid steatocrit (high value) on a spot stool sample (which obviates the need for the traditional 3-day faecal fat test);10 faecal elastase (low);10 recovery in expired sample (which obviates the need for the traditional 3-day diagnosis: acid steatocrit (high value) on a spot stool event, any of the following tests is probably sufficient for after a long history of pancreatitis attacks or pain. In this stepwise approach is unnecessary in a patient who presents with fatty stools overall and in most patients with tropical pancreatitis. This stepwise approach is unnecessary in a patient who presents with fatty stools after a long history of pancreatitis attacks or pain. In this event, any of the following tests is probably sufficient for diagnosis: acid steatocrit (high value) on a spot stool sample (which obviates the need for the traditional 3-day faecal fat test);10 faecal elastase (low);10 recovery in expired sample (which obviates the need for the traditional 3-day diagnosis: acid steatocrit (high value) on a spot stool event, any of the following tests is probably sufficient for after a long history of pancreatitis attacks or pain. In this event, any of the following tests is probably sufficient for diagnosis: acid steatocrit (high value) on a spot stool sample (which obviates the need for the traditional 3-day faecal fat test);10 faecal elastase (low);10 recovery in expired sample (which obviates the need for the traditional 3-day diagnosis: acid steatocrit (high value) on a spot stool event, any of the following tests is probably sufficient for after a long history of pancreatitis attacks or pain. In this event, any of the following tests is probably sufficient for diagnosis: acid steatocrit (high value) on a spot stool sample (which obviates the need for the traditional 3-day faecal fat test);10 faecal elastase (low);10 recovery in expired sample (which obviates the need for the traditional 3-day diagnosis: acid steatocrit (high value) on a spot stool event, any of the following tests is probably sufficient for after a long history of pancreatitis attacks or pain. In this event, any of the following tests is probably sufficient for diagnosis: acid steatocrit (high value) on a spot stool sample (which obviates the need for the traditional 3-day faecal fat test);10 faecal elastase (low);10 recovery in expired sample (which obviates the need for the traditional 3-day diagnosis: acid steatocrit (high value) on a spot stool event, any of the following tests is probably sufficient for after a long history of pancreatitis attacks or pain. In this event, any of the following tests is probably sufficient for diagnosis: acid steatocrit (high value) on a spot stool sample (which obviates the need for the traditional 3-day faecal fat test);10 faecal elastase (low);10
A recent review gives valuable guidance. PRSS1 mutation testing for diagnostic purposes is acceptable in symptomatic young individuals or in those with a family history of pancreatitis, but counselling and clinical follow-up are needed if the result is positive. There is no indication for SPINK1 mutation testing. At present there is no rationale for CFTR mutation testing in the setting of pancreatitis alone. Instead, a sweat test should be done if atypical cystic fibrosis is suspected, and patients should be referred to a specialist clinic when sweat chloride concentration is borderline (40–59 mmol/L) or abnormal (>60 mmol/L). However, the vulnerability of CFTR to electrophilic stress potentially explains both false positive sweat tests and abnormal nasal potential difference studies in a variety of conditions (eg, severe malnutrition).

**Treatment**

**Treatment goals**

The goals of treatment for chronic pancreatitis are to relieve acute or chronic pain, calm the disease process to prevent recurrent attacks, correct metabolic consequences such as diabetes or malnutrition, manage complications when they arise, and address psychosocial problems. Endoscopic treatment, surgery, or both, are only needed when optimum medical treatment fails to relieve pain (figure 8) and to deal with specific complications (figure 3).

A detailed discussion of complications is beyond the scope of this Seminar.

When providing treatment to control the pain associated with chronic pancreatitis, the patient’s fears and misconceptions about the disease should be addressed sympathetically. Time should be spent discussing the disease with the patient at the first clinic visit, with particular attention paid to circumstances surrounding the first attack. Patients should be advised to avoid alcohol and cigarettes, although there is no evidence that abstinence from alcohol slows the disease and the effect of alcohol on pain is debated. A dietary assessment should be done (see later). Where warranted, the help of a psychologist or pain therapy specialist should be sought, and the primary-care practitioner must also be briefed on treatment strategy. Continuity of care is important to gain the patient’s trust and to minimise the risk of addiction to narcotics.

**Analgesics**

Regular analgesics are superfluous in patients with sporadic attacks but are needed in those with background pain. Use of analgesics should broadly follow WHO guidelines for cancer pain. Briefly, analgesic treatment begins with paracetamol or a non-steroidal anti-inflammatory drug, or both, followed by a mild opioid such as tramadol, perhaps coupled with a neuroleptic antidepressant. Narcotic analgesics should be avoided if possible. A simple pain diary with a 10 cm visual analogue scale is useful, as is a baseline quality-of-life assessment. Analgesia devices to deliver morphine that are controlled by the patient should not be used, even in an attack. Such drugs can worsen pain by inducing mast cell degranulation and (possibly thereby) cause gastroparesis and constipation (figure 4).

**Steroids and enzyme therapy**

Treatment with steroids is associated with rapid relief of symptoms in autoimmune pancreatitis. The starting dose is 30–40 mg per day of prednisolone, which is tapered over 3 months while monitoring serum IgG concentrations and imaging findings. Long-term maintenance with 5·0–7·5 mg per day of prednisolone is recommended to prevent relapses. Recurrences, which typically occur in type-1 disease, favour the development of pancreatic calculi.

In patients with small-duct disease, pancreatic acinar cells are suggested to be under constant stimulation by CCK because subnormal delivery of pancreatic proteases into the duodenum allows improved survival of a CCK-releasing peptide from the duodenal mucosa. Hence, the following potential treatments have been successfully tested: oral pancreatic enzymes (non-enteric coated, two trials), subcutaneous octreotide (one trial), and oral dosing with the CCK-A receptor antagonist loxiglumide (one trial). However, this issue is contentious, and the explanation that these measures “allow the pancreas to rest” is at odds with the finding that the exocytosis apparatus is already paralysed in an attack (figure 1) and...
hindered thereafter. Other explanations might be that such treatments act by blunting an effect of CCK on pain pathways in the CNS or by ameliorating electrophilic stress (see later).

Micronutrient therapy

Micronutrient therapy is designed to supply methyl and thiol moieties that are essential for the exocytosis apparatus (figure 1) while protecting it against electrophilic attack, as by CYP-derived ROS or reactive xenobiotics species (figure 2). Findings from six clinical trials have reported that micronutrient therapy controls pain and curbs attacks in patients with chronic pancreatitis. Of these trials, three were descriptive and three were placebo-controlled. However, the different ways of expressing outcome precludes a meta-analysis. The study with the highest power (80%) to detect a difference between treatment and placebo was from Delhi, after 6 months' treatment (which included pancreatic enzymes in all patients) there was a greater reduction in the number of painful days per month and in the use of analgesic tablets in the treatment group than in the placebo group; substantially more patients became pain free, and biochemical markers of electrophilic stress were lowered by active treatment.

Studies from Manchester, UK, suggested that the micronutrient therapy formulation should include methionine and vitamin C, with the need for selenium assessed by measuring blood concentrations. Vitamin E and β carotene were included in the first trial because there was no commercial preparation that did not include them, and three of the other five trials also used this protocol. Improvement, as judged by the number of attacks, admission episodes, pain diaries, pain intensity, or permutations and combinations of these factors, occurred by 10–12 weeks. In the UK, the micronutrient therapy preparation Antox (Pharma Nord, Morpeth, UK) is a convenient means of dosing because it contains all the desired items. A starting regimen of two tablets of Antox three times per day provides daily doses of 2-88 g methionine (but up to 4 g might initially be needed in some patients). 720 mg vitamin C, 300 µg organic selenium, and 210 mg vitamin E (which is unnecessary until steatorrhoea develops). This treatment has no significant side-effects now that β carotene has been withdrawn because of cosmetic problems; one patient (of >300) developed schizophrenia when on 4 g of methionine daily but, of note, this patient had a strong family history of psychiatric disease. Patients should also be given dietary advice on antioxidant-rich foods to aid the long-term management of the disease. It should be stressed that culinary practices — eg, frying vegetables at high temperature (as in south India) — could compromise the bioavailability of antioxidants, notably of ascorbic acid. Blood monitoring is essential to ensure that plasma and erythrocyte glutathione levels have increased and that concentrations of the prescribed micronutrients are not excessive, because this would compromise the physiological roles of ROS. Very recent reports indicate the need to keep track of blood homocysteine, and concentrations of vitamins (B6, B12, folic acid) that serve as cofactors of enzymes that govern homocysteine removal — either by facilitating its transmethylation back to methionine, or by ensuring its passage along the transsulphuration pathway towards glutathione. Of particular interest, elevated homocysteine has been recorded in people at Soweto (South Africa) who drank more than 100 g alcohol per day for many years — a group that is traditionally regarded as being at high risk of chronic pancreatitis.

Figure 8. Algorithm for the management of painful chronic pancreatitis

Note that the solid mass in autoimmune pancreatitis is often in the head of pancreas and suggests cancer, but that ducts are usually constricted. *Procedures include thoracic splanchnicectomy, coeliac plexus block, and neurostimulation.
because of non-compliance (eg, in patients who misuse alcohol) or a large cyst or pseudocyst; otherwise, symptom control was achieved by choline supplements to boost methyl supply. Moreover, micronutrient therapy has no effect on painful conditions that might be misdiagnosed as chronic pancreatitis (unpublished); once validated, this finding could form the basis for a therapeutic trial when the diagnosis remains equivocal after full testing (figure 7). Finally, there is increasing evidence to support the idea that a daily micronutrient supplement might abort the development of chronic pancreatitis in groups or even populations at risk of the disease.

Micronutrient treatment is better at controlling pain and improving quality of life than conventional treatment. Moreover, long-term micronutrient treatment might curb disease progression. Excluding typical autoimmune pancreatitis, which can be treated with steroids, micronutrient treatment has been effective irrespective of cause (including mutations in PRSS1, CFTR, and SPINK1), disease duration, or duct anatomy (large-duct calcifying or small-duct disease), and also when there is an inflammatory calcified mass. By contrast, the antioxidants allopurinol and curcumin have been ineffective for treatment of chronic pancreatitis in clinical trials. Two multicentre trials of Antox are in progress (Current Controlled Trials numbers ISRCTN21047731 and ISRCTN44912429).

Treatment of steatorrhoea and diabetes

The treatment of pancreatic steatorrhoea usually begins with 30000 IU of lipase per meal in an acid-resistant enzyme preparation. In patients who do not respond to this treatment, a low-fat diet (50–75 g per day), dose increase, gastric proton-pump inhibitor, or a combination thereof should be recommended. A check on fat-soluble vitamin status is advisable. The main aim in the treatment of diabetes in patients with chronic pancreatitis is to prevent hypoglycaemia caused by deficiency of glucagon; simple insulin regimens are preferable.

Endoscopic treatment

Of the many potential indications for endoscopic treatment of chronic pancreatitis, two are undisputed. First, EUS can be used to facilitate transmural drainage of pseudocysts that are not connected to the pancreatic duct system, and endoscopically placed transpapillary stents in the duct are useful when they do or when a duct leak leads to pancreatic ascites or pleural effusion. Second, endoscopic stenting of the bile duct is a useful temporary measure in patients with a distal duct stricture.

Limited comparative data suggest that surgery is more effective and has a more durable effect in controlling pain than endoscopic dilatation or stenting of the pancreatic duct. Findings from a randomised clinical trial showed that extracorporeal shock-wave lithotripsy with or without endoscopic clearance of stone fragments was equally effective at reducing pain over the subsequent 2 years in patients with intraductal calculi; however, lithotripsy can occasionally precipitate acute pancreatitis. Thoroscopic splanchnicectomy can provide good initial pain relief, but pain recurs by 15 months in more than 50% of patients.

Surgery

Historically, around 50% of patients with chronic pancreatitis referred to surgical clinics require an operation compared with around 25% on long-term follow-up in a specialist medical clinic. Micronutrient treatment seems to substantially reduce the need for surgery. The objectives of surgery are to decompress obstructed ducts (to relieve pain) and at the same time to preserve pancreatic tissue as well as adjacent organs (to preserve function), while recognising that the head of the pancreas constitutes the so-called pacemaker of chronic pancreatitis. The simplest operation—lateral pancreaticojejunostomy—provides immediate pain relief in many patients but pain tends to recur with the passage of time. Distal pancreatectomy, like pancreaticojjunostomy, does not address the problem of disease in the head of the pancreas, which can continue to deteriorate. Moreover, distal pancreatectomy can result in removal of the functionally most active part of the gland. Pancreatodudenumectomy gives good pain relief, but is a major operation. It is indicated in groove pancreatitis if there is duodenal obstruction or when neoplasia cannot be ruled out preoperatively.

Duodenum-preserving head resection combined, when appropriate, with lateral pancreaticojejunostomy has been a major advance: only 8–7% of patients continued to have pancreatic pain at a median of 5–7 years follow-up, whereas 93% of patients had pancreatic pain preoperatively. The operation was simplified by carving out an inverted cone from the pancreatic head, allowing the cavity and the distal duct to drain into a jejunal loop, thus removing the complex mass of obstructed ducts and inflammatory tissue that frequently lies within the head of the gland. A further simplification made this operation suitable for patients in whom there was little in the way of duct dilatation: a so-called ice-cream scoop is taken out of the pancreatic head to leave a thin rim of pancreas laterally and posteriorly. Pain improved in 55% of patients after 41 months of follow-up.

A precise assessment of the merits of the different operations for painful chronic pancreatitis has been confounded by an absence of agreement about indications for surgery, details of the surgical techniques, and methods used to measure outcomes. However, there is no doubt that the safety of conservative operations (eg, lateral pancreaticojejunostomy combined with limited excision of the head of the gland) has improved: operative mortality, about 5% with traditional resection of the head of pancreas, has fallen to 0–3% and morbidity has been halved. There seems to be little if any advantage to be gained from total pancreatectomy with islet transplant.
Conclusions
Chronic pancreatitis remains a challenging disease. Resective surgery continues to be the definitive treatment for persistent pain, but is not ideal in a chronic inflammatory process. Micronutrient treatment might offer a viable alternative.

Contributors
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Conflicts of interest
We declare that we have no conflicts of interest.

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Seminar


