The pancreas

Although interventional endoscopy is well established in the management of biliary disease, its role in pancreatic disease is just evolving. Several studies indicate that in severe gallstone pancreatitis, endoscopic sphincterotomy and gallstone extraction exert a favorable effect on the outcome of the disease. Dr J Geenan described therapeutic approaches to this and other pancreatic diseases. In traumatic post endoscopic retrograde cholangiopancreatography pancreatitis, nasopancreatic drainage appears to be an effective approach to management. Acute recurrent pancreatitis can result from a variety of pathologies, some of which are amenable to endoscopic therapy. For example, dysfunction of the sphincter of Oddi with delayed clearance of contrast and basal sphincteric pressures in excess of 40 mmHg can be treated with endoscopic sphincterotomy; approximately 70% of such patients improve with this treatment. Pancreas divisum, occurring in about 7% of the population, is probably another cause of acute recurrent pancreatitis. Endoscopic approaches to this problem include stenting of the minor papilla. In chronic pancreatitis the major aim is to relieve pain. The important question here is whether the pain is a function of obstruction. If so, techniques such as balloon dilatation of localized strictures of the pancreatic duct may be helpful. Pancreatic duct stones may be removed or bypassed, though there is not yet enough follow-up to determine the value of these manoeuvres. Other pancreatic pathologies which may respond to endoscopic therapies include pseudocysts, which may occasionally be managed with nasopancreatic catheter drainage.

Dr CS Pitchumoni gave an overview of tropical, nonalcoholic, calcifying pancreatitis. This disease of obscure etiology is found in a band of ±30° from the equator. The condition does not appear to be hereditary, although about 8% of cases are familial. It characteristically affects young adults, causing chronic exocrine pancreatic insufficiency and pain. A brittle type II diabetes mellitus occurs early (60% before the age of 30 years; 90% by 40). Associated clinical features include emaciation, parotid swelling, cyanosis of the lips and abdominal distension. There is a strong association with malnutrition. A field study in Kerala, India recently identified approximately 28 cases in 28,000 individuals screened. There is a suggestion that the incidence of the disease may be declining. The pathological hallmark of the condition is extensive pancreatic calcification with large duct stones (compared with those found in chronic alcoholic pancreatitis). The stones have an amorphous centre rich in chromium, iron and nickel while the shell is predominantly composed of calcium. The nidus protein is immunologically similar to that found in stones in alcoholic pancreatitis, and is possibly pancreatic stone protein. Secretin testing shows impaired bicarbonate secretion, and there is diminished output of trypsin in the Lundh test. Pancreatic juice lactoferrin levels are raised and serum immunoreactive trypsinogen concentrations reduced. The pathogenesis, though elusive, is of great interest. A genetic factor may operate, but clearly environmental causes must be sought. There has been interest in the possible role of cyanogenic glycosides of cassava, a nutritional staple of the poorer people who tend to acquire this disease, but the evidence for this is not convincing. Other plant-derived compounds might be important. Oxygen free radical-mediated injury is a possibility, but the initiating factor is as yet unidentified.

The cellular mechanisms involved early in the pathogenesis of acute pancreatitis were reviewed by Dr A Saluja. Recent investigations suggest that intracellular activation of the proteolyte cascade of zymogens is initiated through colocalization of acinar cell zymogen granules with lysosomes.
which contain acid hydrolases such as cathepsin B, which is capable of converting trypsinogen to trypsin. In three models of acute pancreatitis - the choline-deficient, ethionine-supplemented diet model in young female Swiss mice which produces a hemorrhagic pancreatitis; the cerulein hyperstimulation model, an edematous pancreatitis; and the duct obstruction model in New Zealand rabbits - there is evidence for the co-localization phenomenon. In each of these models amino acid uptake and export protein synthesis is normal, but there is an apparent blockade of enzyme secretion by the acinar cell. There is no good evidence as yet that the co-localization phenomenon occurs in human disease and, if it does, how it is linked to the major initiating factors, ie, passage of gallstones through the biliary tract or ethanol abuse, is still unknown.

Dr Klapdor addressed the issue of pancreatic carcinoma, noting that despite considerable advances in diagnostic power, the disease was still identified at a relatively late and generally incurable stage. Appropriate radiotherapy can achieve local control of the disease in a high proportion of cases. The techniques of immunotherapy hold some promise. Evidence was presented that a combination of immunotherapy using appropriate monoclonal antibodies with cytotoxic drugs or cytokines such as the interferons or tumour necrosis factor, might provide some control of the disease, though it was emphasized that these techniques are still at a very early phase of their development.

Identification of antigens peculiar to pancreatic cancer is essential to developing specific immunotherapies. Dr Parriz-Pour described studies of blood group antigens expressed on the plasmalemma and intracellular organelles of normal and neoplastic human and hamster pancreatic cells. B and H are normal constituents of pancreatic cells, H antigen being primarily associated with zymogen granules. A antigen, on the other hand, appears to be a cancer-associated antigen when expressed in pancreatic tissue. It is found by immunohistochemistry to be localized to the microvillus membrane of the cancer cell, but is also found in association with nucleus and nucleolus. During neoplastic transformation, B and H antigens appear to redistribute in the cell, appearing on the plasmalemma of malignant cells.

A pancreatitis workshop addressed various aspects of acute and chronic pancreatitis. Dr Hans Beger reviewed the classifications of acute pancreatitis - Marseilles 1963 and 1984, and Cambridge 1983 - and discussed the laboratory determinations which are most useful in discriminating between the relatively benign acute interstitial edematous pancreatitis and the severe necrotizing pancreatitis. These comprise the serum levels of C-reactive protein, lactate dehydrogenase and the antiproteases, together with computed tomography scanning with enhancement. For determining the therapeutic strategy for managing acute pancreatitis, identification of the following clinical entities was particularly useful: interstitial edematous pancreatitis, sterile and infected necrotizing pancreatitis, pancreatic abscess and pancreatic pseudocyst.

Dr S Marks gave an overview of chronic pancreatitis, drawing attention to the heterogeneity of the condition from an etiological standpoint and from consideration of clinical features, while Dr Bordalo emphasized histopathological heterogeneity with respect to patterns of fibrosis, atrophy, calcification and the prominent lipid inclusions of chronic alcoholic pancreatitis.

Other subjects discussed in this workshop included the management of pancreatic fluid collections by percutaneous drainage. The role of somatostatin in 'drying up' external pancreatic fistulas was also discussed. Is chronic pancreatitis a premalignant condition? Dr Classen described a rare entity, hereditary chronic pancreatitis, an autosomal dominant disease in which 30 to 50% of patients develop pancreatic malignancy. This, however, represents a special situation, since epidemiological studies suggest that chronic pancreatitis in general is not a premalignant condition.

Finally, Dr Prola examined the pathogenesis of alcoholic pancreatitis. The classic hypotheses were examined: the raised sphincter pressure-obstruction theory has been called into question in view of a fall in sphincter tone, demonstrated by endoscopic techniques in response to intraduodenal ethanol. Opie's common channel theory requires a particular anatomical configuration, while the duodenopancreatic reflux theory is in some doubt in view of the relatively infrequent occurrence of acute pancreatitis following endoscopic sphincterotomy. The increased protein secretion-ductal plug hypothesis has some support, but another possible mechanism, ie, lysosomal fragility, is a plausible idea. In support of this mechanism is the observation that the lipid inclusions of alcoholic pancreatitis are rich in cholesterol esters, which can be demonstrated in vitro to destabilize lysosomal membranes. It is therefore hypothesized that the alcoholic has a 'primed' pancreas with unstable lysosomes ready to liberate proteolytic enzymes, initiating intracellular zymogen activation possibly via the same cellular mechanisms that have been demonstrated in Dr Steer's laboratory in Boston. How ethanol triggers this primed pancreas, on the other hand, is still an open question.