

Review

FIBROCALCULOUS PANCREATOPATHY

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ABSTRACT

In this study, we have discussed the etiopathogenesis of fibrocalculous pancreatic diabetes. The role of the classical type TP Tropical Pancreatitis (TP) patients as well as non-calcific variants have been described and comparisons made between their clinical features, nutritional status and diet. We have also made comparisons of the diet and nutrition of our calcific and non-calcific patients with that of normal controls from the same geographical regions. The role of malnutrition, immunological factors, infection, antioxidant deficiency, micronutrient deficiency, Cassava (tuber), familial and genetic factors in the aetiopathogenesis of tropical pancreatitis has been analysed.

KEY WORDS : Protein deficient diabetes, Tropical pancreatitis, Alcoholic pancreatitis, Malnutrition, Infection, Cassava, Genetic factors.

A disease characterised by recurrent abdominal pain, pancreatic calculi and diabetes mellitus has been reported from several poorer countries of the tropics. Malnutrition is a usual association of this disease although there are exceptions. The term that is used to denote this disease is descriptive of the pathology in the pancreas; viz; presence of fibrosis, pancreatic calculi and the relative absence of inflammation, but does not reflect the etiological factor or factors, which are largely unknown. Because of the diabetes mellitus, that usually is part of the disease, the name "fibrocalculous pancreatic diabetes (FCPD)" has also been used to describe this syndrome. Descriptive nomenclature such as "tropical pancreatitis (TP)", "tropical calcific pancreatitis (TCP)" and "nutritional pancreatitis", which have been used interchangeably and only mirror our ignorance about the exact etiology and pathogenesis of this disease. However, many facets of this very enigmatic condition have been unravelled during the past three to four decades.

EPIDEMIOLOGY AND NOMENCLATURE

In the Western world, chronic pancreatitis is caused in the majority of instances by alcoholism, which is also true of certain developed Asian countries such as Japan. Acute recurrent pancreatitis is usually secondary to gallstone disease. In fibrocalculous pancreatopathy, both these common causes of pancreatitis are absent. Moreover, the disease affects much younger subjects than does alcoholic pancreatitis. The World Health Organization (WHO), in classifying diabetes mellitus in 1985, included a third main category apart from IDDM and NIDDM, which was labelled as "malnutrition related diabetes mellitus (MRDM)" [1]. MRDM was sub-classified into (1) diabetes with pancreatic fibrosis and calculi (FCPD) and (2) protein deficient pancreatic diabetes (PDPD), a form of diabetes which is associated with severe malnutrition, ketosis-resistance, onset at young age and without evidence of pancreatic fibrosis and calcification. PDPD had also previously been described as J-type diabetes, M-type diabetes and ketosis-resistant, youth-onset diabetes. The term PDPD applied by the WHO study group was considered unsatisfactory as there was no evidence of diffuse disorder of the pancreas and as this is for all purposes, a primary form of diabetes. Hence, the term PDDM (protein deficient diabetes mellitus) adopted in 1987 was widely accepted, including at a satellite conference of the International Diabetes Federation Congress, 1988 held at Sydney [2]. However, malnutrition, as the etiological cause of this type of diabetes, was not established. At the International Workshop on Diabetes in the Tropics held at Cuttack in 1995, this issue was extensively debated by an international group of experts and it was agreed that malnutrition plays a role in determining the incidence, age of onset and metabolic abnormalities, while the severity of diabetes suggested that the basic role must be of some yet unknown genetic, toxic, infective and /or immune factor(s). It was recommended that the term

'malnutrition modulated diabetes mellitus' (MMDM) be substituted for PDDM [3]. In a recent report by an International Expert Committee sponsored by the American Diabetes Association, a new classification of diabetes mellitus has been proposed in which the class "malnutrition related diabetes mellitus" has been dropped. FCPD has found a place under "Diseases of exocrine pancreas" [4].

A series of patients with disseminated calcification of the pancreas, malnutrition and ketosis-resistant diabetes was described in 1959 by Zuidema from Indonesia [5]. Reports of a similar syndrome came in from several other tropical countries including Uganda [6], Kenya [7], Ceylon [8], Thailand [9] and Brazil [10]. A landmark paper by Geevarghese and colleagues from Kerala in south-western India in 1962 describing a study of a hundred young patients with pancreatic calcification and diabetes mellitus, focused attention on this problem [11]. Even though this syndrome of pancreatic calculi in young diabetics who were malnourished was initially thought to be peculiar to Kerala state in India, reports from some other regions in India followed, notably Tamil Nadu [12], Karnataka [13] and Andhra Pradesh [14] in South India and Orissa [15] in eastern India. However, the maximum number of cases of tropical pancreatitis (TP) cases have been reported from Kerala state. In the reports from Tamil Nadu only 25% of patients had features of overt malnutrition, although 70% were lean [16]. There are detailed reports of both FCPD patients and MMDM patients from Orissa [17]. In our studies, both the classical type TP patients as well as non-calcific variants have been described and comparisons made between their clinical features, nutritional status and diet [18]. We have also made comparisons of the diet and nutrition of our calcific and non-calcific patients with that of normal controls from the same geographical regions.

CLINICAL FEATURES

The age of the patients at presentation was 30.5 years in the calcific group and about a decade earlier (22 years) in the non-calcific group [18]. In our observation, the age of onset of the disease was about a decade later than in the patients originally described by Geevarghese. The reason for this phenomenon is not known.

There was a male preponderance in the calcific

group (2.7:1) while in the non-calcific group, the male to female ratio was one.

Abdominal pain of varying severity occurred in 80 percent of our patients. This was almost similar in the calcific and non-calcific groups. However, the duration of pain was 7.9 years in the calcific group, whereas this was 3.6 years in the non-calcific group. We found that in many patients, the pain decreased in intensity and frequency with the onset of diabetes mellitus and with longer duration of the illness.

Diabetes mellitus usually follows the abdominal pain by a few years. Seventy-six percent of the calcific patients and 81 percent of the non-calcific patients were diabetic. Diabetes followed the onset of pain after about 2 years in the calcific group, whereas, it preceded pain by more than a year in the non-calcific variety. Complication of diabetes were also common in the non-calcific group (27% in calcific versus 46% in non-calcific). Mohan's group and other workers assessed the pancreatic beta cell function in FCPD by measuring C-peptide concentrations [16]. The C-peptide levels in FCPD was lower than in patients with NIDDM and controls, but were significantly higher than in IDDM patients. Relative resistance to ketosis in FCPD may be due to residual beta cell function, low glucagon reserve, decreased fat mass and carnitine deficiency. Various hypothesis have been proposed to explain endocrine deficiency in pancreatitis and these include secondary effect of acinar damage, fibrosis around islets and vascular occlusion, same toxin acting on exocrine and endocrine tissue, nutritional deficiency and genetic factors.

The existence of an impaired glucose tolerance (IGT) phase prior to the onset of diabetes in FCPD has been demonstrated [16]. The majority of diabetics needed large doses of insulin for diabetic control, while a few, particularly in the early stages of the disease, could be controlled with oral hypoglycemic agents. Hypoglycemic attacks are common and attacks of ketosis have been observed in upto 15% of cases. Microangiopathy is very common as in other types of diabetes. Macroangiopathy has been noted in a few patients. Peripheral neuropathy was present in 69% of patients. Diabetic nephropathy is a common cause of death.

Manifest steatorrhea is unusual in TP, probably because of the low fat content of the diet (24 g/day in

our patients). However, when stool fat is estimated by Vande Kamer method after the intake of 100 g of butter/day, nearly 75 percent of the patients manifest steatorrhea [19].

Forty percent of our patients were severely malnourished on presentation [18]. Their protein intake was low (53 g/day) and carbohydrate intake high (400 g/day). Whether the malnutrition is primary and has a causal role or whether it is secondary to the diabetes mellitus and the pancreatic exocrine deficiency is not clear.

The non-calcific patients in our series presented some interesting features. They were a decade younger than the calcific group, the onset of diabetes preceded the onset of pain and diabetic complications were more in this group (27% in calcific versus 46% in non-calcific), though the duration of diabetes was less than in the calcific group (6 years in calcific versus 4.8 years in non-calcific). It might have been that some of the patients in the non-calcific group were patients with insulin-dependent diabetes mellitus (IDDM). However, the presence of abdominal pain in 80% of this group, the presence of steatorrhea in 81% and that 15% of them underwent surgery for pain, point to the fact that the majority of these patients with diabetes were having a pancreatic pathology. Moreover, a large number of these patients had abnormalities on imaging of the pancreas and a few were found to develop pancreatic lithiasis on follow up. We have also reported earlier that the tryptic activity in the duodenal aspirate was reduced below the cut off point in 90% of our TP patients. Twenty seven percent of the non-calcific patients as compared to 93% of the calcific had subnormal tryptic activity values [20]. The incidence of steatorrhea was not significantly different between the two groups. Whether the non-calcific variant of the disease is a formae frustae of FCPD or akin to MMDM is not very clear. This may also indicate that interplay of dietary imbalances/toxins may lead to different expressions of exocrine/endocrine changes in varying combinations.

PATHOLOGY OF THE PANCREAS

The pancreas appears small, fibrosed, firm and nodular and is reduced in weight [21]. Occasionally, it may be soft and indistinguishable from fat due to replacement with adipose tissue. On section, the pancreas feels gritty and firm, with a markedly dilated

irregular duct with cystic changes and strictures. Calculi may vary in size from small sand-like particles to large ones of about 3 cm diameter. They are whitish to gray in colour and not faceted. They may be seen in the main pancreatic duct and the secondary branches. It is difficult to scoop out all the stones as they are incarcerated sometimes in the duct walls. Viscid mucoid materials is seen in the ducts.

Extensive acinar atrophy is observed, which may be local, focal or diffuse. Fibrosis starts in the periductal region and dissects into the acinar tissue dividing it into pseudo-lobules giving a "cirrhotic" appearance to the pancreas. There may be periductal round cell infiltration, which is rarely impressive. Due to the paucity of inflammatory cells, some pathologists prefer the term 'pancreatopathy' to "pancreatitis" to describe these changes [22]. The ducts show dilatation, denudation of the epithelium and in places, squamous metaplasia.

The islets appear well-preserved and even hyperplastic in some cases. In the early stages of exocrine pancreatic atrophy, there is crowding of the islets. A true proliferation of the insular cells from existing cells is nesidioblastosis. Hyaline change of the islets, which is one of the commonest changes in maturity onset diabetes, is very rare in cases of pancreatogenic diabetes.

Histochemical staining for hormones using immunoperoxidase for demonstration of insulin, glucagon and somatostatin has shown strong activity for insulin in the existing islet, hypertrophic or atrophic as well as in the newly formed islets from the ductular epithelium [23]. The activity of the A-cells and D-cells was found to be within normal limits.

Nagalotimath from Karnataka has described extensively the pathological changes in the pancreas in advanced FCPD and in "arrested FCPD" [24]. Large hypertrophic nerve bundles and ganglion cells are seen in relation to hypertrophic and surviving islet cells. Perhaps, they have some role in the secretory mechanism of the islets. The blood vessels have been reported to show sclerotic changes [25].

Glycogen infiltration and fatty degeneration are the most common changes observed in the liver. Cirrhosis has also been seen in some patients.

PANCREATIC CALCULI AND PROTEIN PLUGS

Detailed studies of pancreatic calculi have been done by our group using various analytical methods and using scanning electron microscopy [26]. The chief constituent of the stones was calcium carbonate, which constituted 95 to 98 percent. Crystallographic studies using X-ray diffraction revealed that calcium carbonate was in the calcite form. Trace elements have also been analysed in the calculi.

Scanning electron microscopy showed the presence of amorphous and crystalline material embedded in between the fibrils [27]. These are similar to the findings in alcoholic pancreatitis. Protein plugs obtained from pure pancreatic juice also revealed clumps of amorphous material deposited in the meshes between fibrils, bearing resemblance to the findings described by Japanese workers in alcoholic pancreatitis [28].

MALIGNANCY

We, as well as later workers, have noted that tropical fibrocalculous pancreatitis is a pre-malignant condition as many patients, especially in our surgical series, had malignancy complicating pancreatitis [19, 29, 30]. The incidence of complicating cancer may be from 10 to 15 percent. Naturally, the figures are higher in surgical series. The occurrence of cancer in TP far exceeds the corresponding incidence in alcoholic pancreatitis. In one study comparing carcinoma complicating TP with de novo cancer of the pancreas, it was observed that in the former group, the cancers occurred equally in all parts of the gland as opposed to chiefly the head region in the latter group [31]. These workers also noted ductal changes such as squamous metaplasia, mucinous hyperplasia, ductal papillary hyperplasia and adenomatous ductal hyperplasia in parts of resected specimens not involved by the tumour.

In a case of TP on follow-up, the appearance of jaundice, sudden aggravation of pain, weight loss, common bile duct dilatation, or appearance of a mass may all suggest the complication of carcinoma. TP complicated by cancer carries a dismal prognosis.

TROPICAL PANCREATITIS (TP) AND ALCOHOLIC PANCREATITIS (AP)

Comparative studies conducted by us between tropical pancreatitis and alcoholic pancreatitis have brought out some interesting differences [32]. The

Indian patients were at least a decade younger than the French alcoholic patients. Both Indian patients and controls were smaller and thinner than their French counterparts. There was no significant difference in the dietary content of protein, fat, carbohydrates and calories of Indian TP patients and their controls. However, there was significantly lower values of protein and fat in the Indian diet in comparison with the French. The Indian patients' diet had a significantly low fat content (23.4 ± 2.8 g in TP, 122.6 ± 50.4 g in AP).

The concentrations of lipase and chymotrypsin in the pancreatic juice of Indian controls were lower than in French controls, but outputs were no different. Concentrations of calcium, a marker of nonspecific pancreatic lesions, as well as lactoferrin concentrations were higher in Indians.

In TP patients, all parameters of pancreatic secretion, with the exception of calcium and lactoferrin, which were increased, were significantly decreased when compared to French AP patients.

In spite of the absence of pancreatic insufficiency in Indian controls, the increased secretion of calcium and lactoferrin suggests they might have subclinical pancreatopathy.

It is also possible that the low fat content of the Indian diet may be a factor in the genesis of pancreatitis.

Endoscopic Retrograde Choledochopancreatography (ERCP) done in TP patients by our group showed markedly dilated ducts with cyst-like lesions and strictures, similar to changes seen in AP [33]. There were no congenital ductal anomalies observed. We have also noted that in TP, the calculi are much larger and extensive and always intraductal, whereas in AP, the calculi are smaller and parenchymal calcification is the rule. The chemical analysis and structure of the pancreatic calculi and the appearances of the intraductal protein plugs described by us in TP closely resemble the descriptions of stones and plugs in AP.

Diabetes mellitus is less common and milder in AP than in TP.

The pathological changes of TP and AP have several similarities and a few differences [21]. In early cases, histopathological distinction may be possible, but in advanced cases, this might be difficult. Fat

necrosis, parenchymal necrosis with calcification, acute and chronic inflammation and intraductal protein plugs are more common in AP. The ducto-insular changes characteristically seen in TP are rarely seen in alcoholic pancreatitis. Malignancy, though it can occur as a complication, is rare in AP.

Thus, there are many similarities and parallelisms in the pathogenesis and progression of the lesion in TP and AP, although the triggering etiological factors or events may be different [27, 34]. Overall, TP is a more rapidly progressive devastating disease than AP.

CHANGE IN NATURAL HISTORY OF TP

It has been observed by us that there has been a change in the natural history of TP over the last few years. The onset of pain and diabetes in our series was often delayed by a decade than was originally described by Geevarghese [18]. Patients presenting in the third or fourth decade are not very uncommon. Survival has definitely increased. Perhaps, with prolonged survival, superimposed carcinomas have become more common. The improved survival might be due to earlier detection and better care. Mohan has reported on the long-term survival of patients with FCPD [16].

TREATMENT

It is not proposed to deal with management of TP in detail in this article. Pain should be managed with analgesics and tranquillizers. High protease-containing non-enteric coated preparations of pancreatic enzyme supplement may help in relieving pain by a negative feedback on pancreatic secretion. Antioxidants have been tried to prevent acute exacerbations. Coeliac block may give temporary relief. Intractable pain or complications might necessitate surgery - usually drainage operations or resections. Surgical results are good in the short to medium term. Suspected malignancy is an indication for resection. Endoscopic therapy is an alternative to surgery in a selected group of patients. Enzyme supplements have been shown to reduce but not abolish steatorrhoea [35]. Diabetes is managed with diet and insulin, although in the earlier stages, some patients respond to oral hypoglycemic agents or a combination of oral hypoglycemic drugs and insulin. Better and balanced nutrition and correction of deficiencies should be ensured.

ETIOPATHOGENESIS

Malnutrition

The predominant prevalence of TP among the impoverished populations of third world countries and the clinical association of TP patients with growth retardation and nutritional deficiencies make malnutrition a prime suspect in the causation of TP. However, there are large segments of population in several of these countries who are malnourished, yet are unaffected by this disease. Over the past few years, we have also observed the disease occurring in some well-nourished subjects from the higher socioeconomic brackets. Similar observation has been reported by Mohan and colleagues from Tamil Nadu (about 25% not malnourished) [16]. Pancreatic atrophy with some fibrosis and reduced enzyme secretion and insulin output have been described in kwashiorkor, the prototype of protein-calorie malnutrition [36]. However, abdominal pain or pancreatic calculi are not a feature of kwashiorkor. In a study conducted in Ivory Coast, kwashiorkor was not associated with or followed by pancreatitis. In dietetic studies conducted by us in TP patients inquiring into their diets before after the onset of illness, there was no difference in the content of protein, fat, carbohydrate or calories in the diets between TP and matched controls. A history of childhood kwashiorkor or severe malnutrition was not forthcoming in our patients. It is also possible that nutritional deficiency might be secondary to the severe exocrine deficiency and diabetes mellitus. Thus, while one cannot dismiss the role of protein-calorie malnutrition as a major factor in the causation of the disease, it does not seem to be the main etiological factor.

In a multinational study into the etiological factors of TP, comparing the diets and nutrition in France, Ivory Coast, India and Brazil of patients with matched controls, neither childhood malnutrition nor cassava consumption were found to be possible causes of TP [37]. On the contrary, the role of a very low fat diet, eventually associated with a low protein diet and malnutrition in the mothers of the patients is suggested by this study.

Cassava (*Manihot esculenta*, Tapioca)

This is a tuber, which is a major constituent of the diet for more than 400 million of the world's poor. It is almost pure starch with only 0.4 percent proteins and devoid of essential aminoacids. The observation that

TP is prevalent in many of those countries where cassava forms a staple diet aroused interest in this tuber as a causative agent in TP [38]. It is also true that the regions in Kerala state in India, where TP is more prevalent, are also the regions where cassava is cultivated and eaten regularly. The high carbohydrate and the low protein content of cassava along with its paucity of essential amino acids such as methionine could be responsible for pancreatic atrophy. Studies by Veghelyi and Kemeny have demonstrated atrophic changes in the pancreas that result from essential amino acid deficiency [39]. Methionine deficiency has been shown to cause pancreatitis in experimental animals. Many varieties of cassava also contain cyanogenic glycosides linamarin and laurostrolin that get converted in the presence of an enzyme rhodanese from the liver. In this process of detoxification, sulphur containing aminoacids, particularly methionine, is used up. This depletes the already low methionine reserves of the body, which predominantly affects the pancreas, an organ with the highest protein turnover in the body. The cyanogens of cassava also act as tissue toxins interfering with vital tissue metabolism and cellular enzyme systems [40]. This effect may be aggravated by similar toxic materials from cigarette smoke in chronic smokers. In fact, it has been shown that cigarette smoking increases the susceptibility to pancreatic damage [40].

Despite all the above, there are a large number of TP patients who give a history of having never eaten cassava. For example, the majority of patients reported from Tamil Nadu and almost all cases from Orissa have never consumed cassava, yet suffer from TP [16,17]. One explanation for this fact may be that several other tubers and pulses, including sorghum and maize that are consumed in regions like Karnataka and Orissa where TP is widely prevalent, contain cyanogenic glycosides. This is an area that needs further investigation.

In a dietary evaluation conducted in a large group of TP patients and matched controls, there was no difference in the intake of cassava between patients and matched controls. The mean daily intake of cassava in both groups was about 300 g/day [18].

There are very few animal studies into the role of cassava in causing pancreatic damage. Feeding cyanide to rats resulted only in transient

hyperglycemia [41]. In another study of feeding cassava to rats, no definite changes of pancreatitis were noticed [42]. Changes akin to those in TP were observed in rabbits fed on a cassava diet in yet another study [43]. In an experiment conducted more recently by Mathangi et al, a rat model, receiving cassava feeds upto one year failed to exhibit diabetes mellitus or pancreatitis [44].

Autopsy studies at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India indicated that mucoid vasculopathy was associated with cardiomyopathy, especially endomyocardial fibrosis, and endocrinopathies, goiter and pancreatic atrophy with or without calculi an diabetes mellitus in Kerala [45,46]. A similar pattern of "tropical diseases" comprising endomyocardial fibrosis, coronary artery disease, goiter and pancreatic disease with calculi was described from Uganda. In fact, we had suggested in 1987 a possible relationship between endomyocardial fibrosis and TP [27].

In a series of animal experiments, Sandhymoni and colleagues produced pancreatic changes in monkeys by feeding protein-deficient tapioca or cassava starch-based and corn-starch based diets for 3 or 5 months [47]. Marked to severe lobular and acinar atrophy in animals fed low-protein diets resembled human pancreatic atrophy resulting from protein deficiency. Animals fed low-protein high-carbohydrate diets showed lesions akin to tropical chronic calculous pancreatopathy with diatetes mellitus. The pancreatic lesions comprised moderate to marked acinar cell atrophy, marked islet hyperplasia or nesidioblastosis with hypertrophy and mucoid metaplasia of the epithelium. Mucoid vasculopathy of the pancreatic artery and arterioles was observed in all animals given protein-deficient diets. It was enhanced in those given additional carbohydrate. Identical lesions were observed after using either source of carbohydrate. This excluded in the authors' assessment, the role of toxic factors such as cyanoglycosides or heavy metals from a tapioca source in initiating the lesions.

Immunological Factors

In a chronic disease like TP, primary or secondary immunological changes are expected. In studies conducted by us in TP patients, it was found that T cells were significantly reduced compared to controls,

but B cells were normal. The leucocyte adherence inhibition to pancreatic antigen was increased. There was increase in the levels of serum IgM and IgG [48]. Parietal cell antibodies were positive in 25 percent of patients while antimitochondrial, antinuclear, antithyroglobulin, antiintrinsic factor and antismooth muscle antibodies were absent. We also found antibodies to an antigen prepared from a pancreatic extract in nearly 60% of our patients. Reports from northern India have demonstrated a paucity of islet cell antibodies in FCPD, but not in MMDM (PDPD), thus attributing a role for autoimmunity in MMDM but not in FCPD [49]. From South India, Mohan and colleagues looked at islet cell antibodies (ICAb) and glutamic acid decarboxylase antibodies (GAD-Ab) in different types of diabetes and found FCPD is unlikely to be linked etiologically to autoimmunity [50].

While a secondary role cannot be ruled out for immune factors, evidence does not point to these factors in the causation of TP.

The Role of Infection

Coxsackie, measles, mumps, rubella, cytomegalovirus and mycoplasma pneumoniae have been reported to cause diabetes mellitus and pancreatic disease in experimental animals and man.

Interstitial pancreatitis has been described in the congenital rubella syndrome. In alcoholic pancreatitis complement fixing antibody levels against cytomegalovirus (80%) and adenovirus (68%) have been shown in levels significantly greater than in controls [51]. In studies in TP patients carried out by us, a significantly higher number of patients had antibodies against mumps and CMV than in controls, whereas a higher antibody positivity for M. pneumoniae was seen in controls than in TP patients [52]. There was no significant difference between controls and patients as regards antibody levels to rubella virus. Serological evidence of current viral infection was seen in 10 patients and M. pneumoniae in 3 patients (31.6%). TP patients had also a significantly high (66.7 percent) antibody prevalence against Coxsackie B [53].

Pancreatic tissue from 13 patients cultured on VERO cell lines showed positivity for ECHO virus in only one case. We injected pancreatic tissue extract and pure pancreatic juice from TP patients into suckling mice, but failed to reproduce any pancreatic lesion.

Micronutrient Deficiency

Deficiency of micronutrients has been shown to cause damage to many organs including the pancreas. Selenium deficient diet given to chicks has been demonstrated to produce intracellular changes followed by atrophy of pancreatic acinar cells and promotion of connective tissue formation [54]. The changes resembled those observed in a protein deficient diet and were reversed on supplementing selenium. Copper deficiency in experimental animals has been shown to cause selective and progressive atrophy of pancreatic acinar tissue [55]. Rats fed a zinc-deficient diet developed cellular changes in the pancreas including reduction in zymogen granules and disorganization of cells [56]. Zinc deficiency is common in kwashiorkor.

Micronutrient deficiency is common in the malnourished population of the tropics. This may contribute to pancreatic damage in the background of genetic predisposition and exposure to environmental toxins such as cyanogens.

Antioxidant Deficiency

According to Braganza, exposure to environmental toxins or chemicals might give rise to toxic metabolites including reactive oxygen species [57]. These and xenobiotics (reactive intermediary metabolites) are produced, facilitated by the cytochrome p-450 system. In the normal course, these are scavenged by the anti-oxidants such as vitamins E and C, betacarotene and selenium. A relative deficiency of antioxidants could lead to accumulation of cytotoxic free radicals that could injure the tissues.

Braganza has shown deficiency of anti-oxidants in the serum in alcoholic pancreatitis and improvement in patients' clinical condition by anti-oxidant supplementation. Anti-oxidant deficiency has been demonstrated in other population groups with chronic pancreatitis, including TP [58].

Familial and Genetic Factors

It has been our observation as well as of others that in TP there is a familial clustering. We have observed the disease in three twins, several siblings and parents and offsprings. In 155 patients of TP (calcific and non-calcific types) studied by us, 39 (28%) had history of diabetes mellitus or chronic

pancreatitis in other members of the family [19]. One first-degree relative had carcinoma pancreas. In several families with multiple members suffering from TP, we studied HLA A and B loci and the DR loci in many subjects. One significant observation was that 6 of 7 families and 8 of 12 patients had AW19/AW10 antigen [59]. However, there are no population frequencies available for this geographical region. A high prevalence of chronic pancreatitis and NIDDM was seen in first-degree relatives of TP patients [16]. However, it should be noted that NIDDM prevalence was high in the elderly in the population studied. Mohan and co-workers have found that 40% of FCPD patients were positive for the HLA-DQ Beta marker that is associated with IDDM and 40% showed a class 3 insulin gene marker associated with NIDDM [16]. Both markers were present in 20% of FCPD patients, but only in 1% of controls. The same group also looked for a possible association between FCPD and reg 1A gene (lithostatin gene) by restricted length polymorphism (RFLP) but found no such association.

The discovery of the role of cationic trypsinogen gene defects in the etiology of hereditary pancreatitis has generated renewed interest in this field [60]. There are reports of the association of cystic fibrosis transmembrane conductance regulator (CFTR) gene and the SPINK 1 gene with idiopathic pancreatitis and some cases of alcoholic pancreatitis [61, 62]. Rossi et al in a small sample of eight FCPD and four TCP patients without diabetes found SPINK 1 mutations only in the former group and suggested this as distinguishing between FCPD and TCP [63]. Two studies (which included patients of FCPD from Tamil Nadu in India and Bangladesh) report a negative association of mutations in PRSSI with the disease [64, 65]. However, in both these studies, the whole PRSSI gene has not been analysed. Another report from northern India indicates an association between CFTR mutations and TCP patients [66]. A more recent study from Hyderabad reported absence of any mutation in the PRSS 1 gene; however, half their patients showed mutations in the SPINK 1 gene. Both FCPD and TCP patients, without diabetes, equally exhibited this mutation [67]. They also suggest a common genetic basis for TCP with additional genetic/environmental factors responsible for the variability of phenotype in FCPD and TCP patients without diabetes.

Are TP and FCPD different diseases, as some of

these workers seem to suggest? Or, are they different stages of the same disease? Though one cannot be dogmatic, available data would indicate that they are stages of the same disease.

At present, TP seems to be a familial disease, but its genetic nature is yet to be proved. Genetic studies are in preliminary stages, and it is hoped that further work might reveal interesting aspects of the relation between genetic defects and tropical pancreatitis.

The etiology of TP (FCPD) remains complex and enigmatic. Much more work needs to be done in this area. It is likely to turn out that the etiology of this disease is multifactorial, with a genetic background in which the initiating and perpetuating factors might be deficiency of dietary factors abetted by dietary or environmental toxins.

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