Diabetes/Metabolism Reviews
Diabetes Metab. Rev. **14**, 153–170 (1998)

Fibrocalculous Pancreatic Diabetes

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Summary. Fibrocalculous pancreatic diabetes (FCPD) is a unique form of diabetes secondary to chronic pancreatitis seen in developing countries of the world associated with either overt protein–calorie malnutrition or, more likely, with deficiency of certain micronutrients. FCPD affects young individuals and runs an aggressive course to reach the endpoints of diabetes, pancreatic calculi and exocrine pancreatic dysfunction (steatorrhoea) in the majority of cases. There are characteristic features of FCPD radiologically, ultrasonographically, on endoscopic retrograde cholangiopancreatography and on histopathology which distinguish it from chronic pancreatitis of other aetiologies seen in temperate zones, e.g. alcoholic chronic pancreatitis. Although a secondary form of diabetes, specific diabetes-related complications like retinopathy and nephropathy do occur in FCPD. There appears to be a high risk of developing pancreatic carcinoma. Although the aetiology of FCPD is still unclear, the role of micronutrient (antioxidant) deficiency is emerging as a possible aetiological or predisposing factor. The contribution of genetic factors and environmental toxins, e.g. cyanogenic glycosides or other nutritional/toxic factors, merit further study. Studies on FCPD, a good model of a secondary form of diabetes, could lead to improved understanding of other primary forms of diabetes as well. If the underlying aetiological factors are identified, it may also be possible to prevent this type of diabetes. © 1998 John Wiley & Sons, Ltd.

1. INTRODUCTION

Fibrocalculous pancreatic diabetes (FCPD) is a unique form of diabetes secondary to non-alcoholic, chronic, calcific pancreatitis seen in tropical, developing countries of the world. Several terms have been proposed for this syndrome, including tropical calcific pancreatitis, tropical chronic pancreatitis, tropical pancreatic diabetes, nutritional pancreatitis and endemic pancreatic syndrome. For sake of uniformity and international agreement, it is advisable to adopt the term fibrocalculous pancreatic diabetes proposed by the WHO Study Group Report on Diabetes when this entity was introduced as a subtype of malnutrition-related diabetes mellitus (MRDM).[1] In the recent Expert Committee on Classification of Diabetes,[2] the entity known as "malnutrition-related diabetes mellitus" was deleted and FCPD is now classified as a "disease of exocrine pancreas" under

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Key Words: fibrocalculous pancreatic diabetes; tropical chronic pancreatitis; pancreatic lithiasis; cassava
Received: 14 November 1997; accepted (revised): 17 April 1998

CCC 0742–4221/98/020153–18$17.50

the category of "Other types of diabetes". The commonly used suffix "tropical" may not be appropriate as the disorder has been recently reported from temperate zones in migrants from tropical countries.[3] We propose that the term "fibrocalculous pancreatitis" (FCP) be used when one refers to this unique form of chronic pancreatitis restricted to developing countries of the world and the term fibrocalculous pancreatic diabetes when one refers to the diabetes secondary to FCP. The differences between FCP and alcoholic (temperate zone) chronic pancreatitis (ACP) reported earlier[4,5] are summarized in Table I.

2. DISTRIBUTION AND PREVALENCE OF FCPD

Zuidema[6] from Indonesia was the first to describe diabetes associated with pancreatic calculi and severe malnutrition. Reports from several tropical parts of the world including Uganda,[7] Nigeria,[8,9] other parts of Africa,[10] Brazil[11,12] and several countries in Asia including Thailand,[13] Bangladesh[14] and Sri Lanka[15] indicated the widespread occurrence of this syndrome. However, the highest prevalence of FCPD in the world appears to be in southern India, where 1700 cases have been documented by Geevarghese alone.[16,17] Large series have also been reported by other workers from Kerala[18–21] and also from Tamil Nadu,[22,23] Orissa,[24,25] Karnataka,[26] Maharashtra,[27,28] Delhi,[29] Tripura,[30] and several other places such as Calcutta and Lucknow. However, the disease is much more frequent in southern than in northwestern states of India.

There are few notable population-based studies on the prevalence of FCP. Balaji *et al.*[31] made a systematic survey of 6079 families in Quilon district, Kerala. A population of 28,507 was studied by clinical history, ultrasonography and *para*-aminobenzoic acid (PABA) tests. Twenty-eight cases (1 : 1000) had chronic calcific pancreatitis. In another door-to-door survey in the Munacil Taluk district of Kerala, radiographic screening of 4000 persons aged 16–60 years revealed calcific pancreatitis in eight (2 : 1000).[32] These figures are probably much higher than the prevalence of chronic pancreatitis among Europeans although due to methodological differences accurate comparisons are not possible.

At the M.V. Diabetes Specialities Centre (MVDSC) at Chennai (Madras), a large referral centre for diabetes, about 50 patients with FCPD are registered annually, which constitutes about 1% of all diabetic patients and 4% of "young" diabetic patients (defined as onset below 30 years of age).[33] During the 1980s at the S.C.B. Medical College Hospital at Cuttack, in Orissa, FCPD constituted 2.5% of all diabetic patients[34] while at Trivandrum in Kerala it comprised 7% of all diabetic patients.[35] Recently, there appears to have been a decline in the number of patients seen at most centres. More population studies are needed on the prevalence/incidence of FCPD in different parts

Table I. Differences between fibrocalculous pancreatitis and alcoholic chronic pancreatitis

	Fibrocalculous pancreatitis	Alcoholic chronic pancreatitis
Sex ratio M : F (%)	70 : 30	Almost all male
Age at onset	2 and 3 decades	4 and 5 decades
Socio-economic status	Usually poor, may occur in others as well	All strata of society equally affected
Course of disease	More aggressive and accelerated	Slower rate of progression
Diabetes	Occur in >90%	About 50% of cases
Pancreatic calculi	Occurs in >90%	About 50–60% of cases
Appearance of pancreatic calculi	Large and dense with discrete margins	Usually small and speckled; ill-defined margins
Location of calculi	Always in large ducts	Usually in small ducts
Ductal dilation	Usually marked	Usually mild
Fibrosis of gland	Marked	Less severe
Alcoholism	Usually absent	Heavy alcohol abuse
Prevalence of pancreatic cancer	High	Low

of the world. Global occurrence of FCPD is indicated in Annexure 7 of the "WHO study group on diabetes mellitus".[1]

3. CLINICAL FEATURES

The classical description is of a patient who is quite poor and presents with extreme degrees of emaciation and protein–energy malnutrition, bilateral parotid enlargement, distension of the abdomen and, occasionally, a cyanotic hue of the lips. Recent reports from Chennai, Pune, Orissa and Kerala suggest a change in the clinical features of FCPD patients because of improved nutritional status. At MVDSC[36,37] overt malnutrition was observed only in 25% of patients, although 70% were lean. In Orissa, the majority of FCPD patients were poor and many were malnourished.[25,34] However, a sizeable number of patients from the middle and even a few from the upper class of society have been documented at all the major centres. While leanness continues to be a general feature, FCPD may be occasionally seen in obese individuals.[38] In the majority of patients the diagnosis of diabetes is made between the ages of 20 and 40, but onset in childhood,[39] in infancy[40] and at older age groups[41] are not uncommon.

The cardinal triad of FCPD is abdominal pain, pancreatic calculi and diabetes.

In the natural history of FCPD, quite often the first manifested symptom is abdominal pain. After periods varying from a few months to several years, pancreatic calculi may be diagnosed by routine abdominal radiography. At this time the patient may still have normal glucose tolerance. After some months to years, investigations may reveal glucose intolerance (or diabetes) and exocrine pancreatic dysfunction (Figure 1).

The existence of a stage of impaired glucose tolerance (IGT) preceding the onset of clinical diabetes in FCPD has been shown by recent studies.[42,43]

A. Painful Abdomen

History of abdominal pain is given only in 10–20% of patients, while on direct questioning

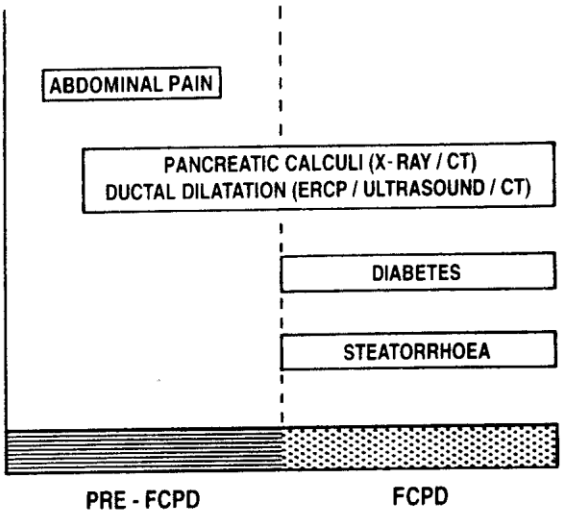

Figure 1. Natural history of FCPD showing Pre-FCPD and FCPD stages. Reproduced with permission from *International Journal of Diabetes*, 10: 24–26, 1990 (see ref. 33).

up to 70–80% of patients may recall a childhood history of pain. The pain is usually very severe, epigastric in location, may radiate to the back and is relieved by stooping forward or lying in a prone position. It is characterized by periods of remission and exacerbation and usually, but not necessarily, abates by the time diabetes or steatorrhoea sets in. Those with intense pain may become addicted to powerful narcotic analgesic drugs.

B. Steatorrhoea

Overt steatorrhoea is seen in less than a third of patients. However, in the rest, it can be demonstrated by exocrine pancreatic function tests. Absence of overt steatorrhoea may be attributed to low fat content of diet. When the fat content of diet is experimentally increased, steatorrhoea becomes evident in 90% of the patients.[18,44]

C. Nature of Diabetes

Diabetes is usually severe and commonly occurs a decade or two after the first episode of abdominal pain. Onset of symptoms is usually gradual. In the lean and the undernourished

polyuria and polydipsia are the major complaints. In the course of time loss of weight, asthenia, weakness, indigestion and muscle cramps compel them to seek medical help. In the better nourished patients symptoms may be insidious. Diagnosis is made during investigations for abdominal pain and unless there is a high index of suspicion the diagnosis is often delayed.

Unlike patients with Type 1 diabetes, FCPD patients rarely develop ketoacidosis on withdrawal of insulin although insulin is usually needed for control of hyperglycaemia. This may be due to several factors. Some studies[45–48] have shown that the pancreatic β-cell function, as measured by C-peptide estimation, is partly preserved in patients with FCPD. This residual β-cell reserve may be sufficient to protect against ketoacidosis. Other explanations for the resistance to ketosis include a low glucagon reserve and decreased adipose tissue mass.[43,49,50] Figure 2 summarizes the factors which may be involved in the ketosis resistance seen in FCPD patients.

Contrary to earlier reports, we found that the insulin requirement is not very high and the mean daily insulin dose in our patients is 40 ± 12 units, especially if sulphonylureas are also used.[36,37] The latter are often combined with insulin as they help to reduce the cost of treatment, as insulin is expensive and most patients are poor. Thus insulin resistance is not a common feature of FCPD. On the contrary, many patients may be sensitive to insulin and hypoglycaemia may occur frequently. There is a wide spectrum with respect to the clinical severity of FCPD[32,36,51,52] (Figure 3). While most patients require insulin injections, about 10–20% may respond to oral hyperglycaemic agents, at least for the first 5–10 years. While the majority of the insulin-requiring patients are ketosis resistant, a few (~10%) may indeed be prone to ketosis. The response to therapy appears to correlate with pancreatic β-cell function, as assessed by serum C-peptide levels.[36]

4. RADIOLOGICAL FEATURES

Presence of pancreatic calculi is the hallmark of FCPD. The calculi are usually multiple, large, rounded, dense, discrete and almost always confined to larger ducts. They may occasionally be seen as a solitary stone located at the right of the first or second lumbar vertebra, but more often the whole length of the pancreatic duct is studded with calculi (Figure 4).

Ultrasonography[43,53–57] helps to confirm the location of calculi within the pancreatic duct and provides additional information regarding the size and shape of the pancreas and the degree of ductal dilatation. Figure 5 shows the ultrasound appearance of the pancreas in a patient with FCPD.

5. COMPUTERIZED TOMOGRAPHY (CT SCAN)

CT scan also helps to pick up microcalculi which are missed on a plain abdominal X-

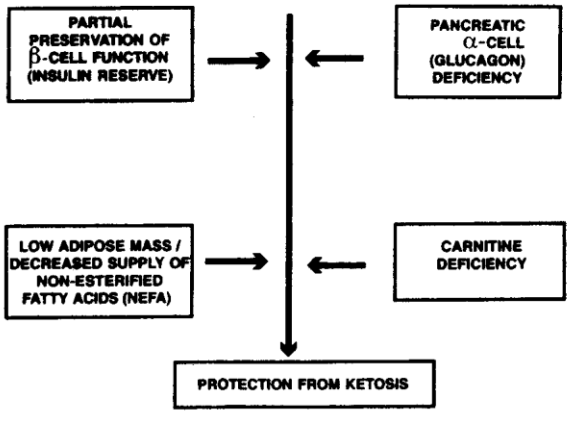

Figure 2. Summary of possible factors involved in ketosis resistance in FCPD patients.

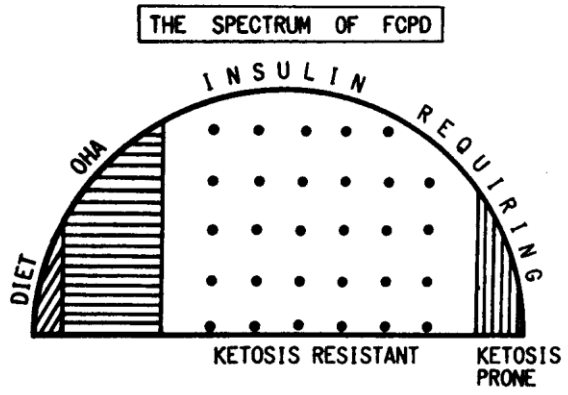

Figure 3. Clinical spectrum of FCPD. Reproduced with permission from the *International Textbook of Diabetes Mellitus* published by John Wiley & Sons, Ltd. (see ref. 52).

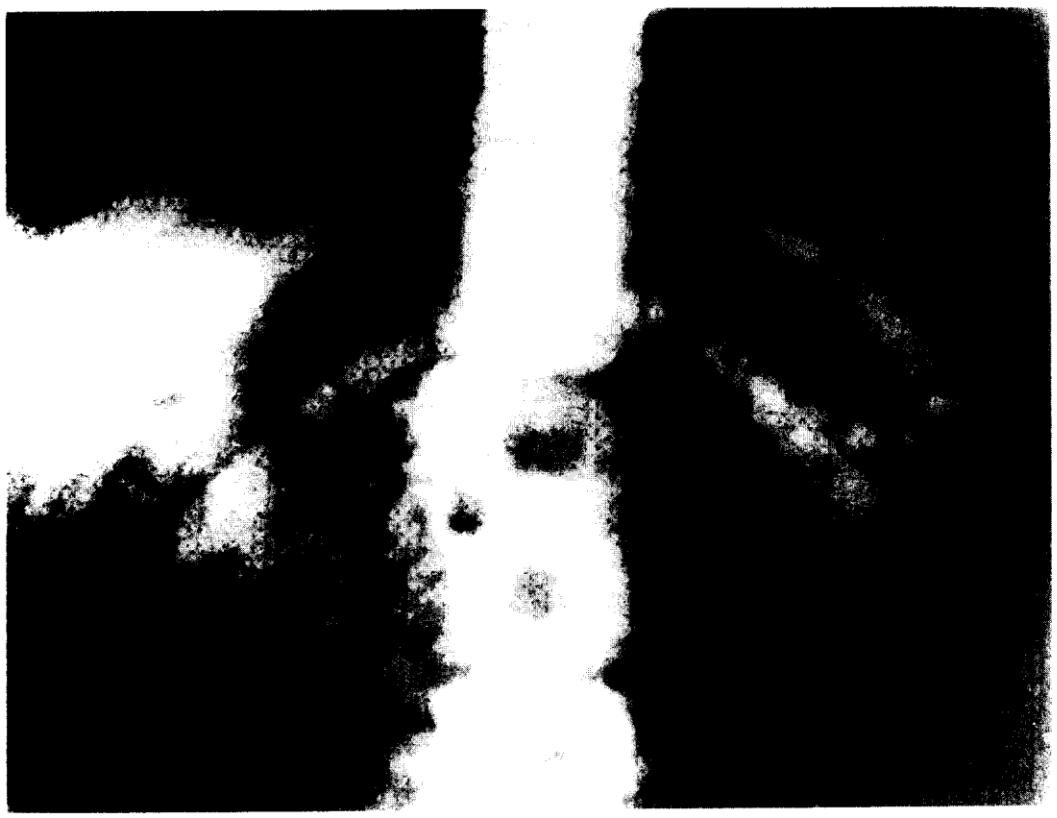

Figure 4. Pancreatic calculi. Note large, dense, rounded calculi which are characteristic of FCPD. Reproduced with permission from the *International Textbook of Diabetes Mellitus* published by John Wiley & Sons, Ltd. (see ref. 52).

ray. Mass lesions (e.g. carcinoma) are also well delineated on CT scan.

Endoscopic retrograde pancreatography (ERP) is rarely required to diagnose FCPD. However, it is useful to diagnose "non-calcific FCPD", where the ductal abnormalities help to diagnose this condition.[59,60] ERP is more useful as a preoperative procedure as knowledge of the duct morphology could help to decide the type of surgery. Finally ERP is often used as a therapeutic procedure to remove stones near the head of the pancreas following a sphincterotomy.

6. PATHOLOGY OF THE PANCREAS

There are several excellent descriptions of the pathological changes in the pancreas in FCPD.[26,61–64] Nagalotimath has observed two distinct pathological types.[26,61] In one type, the changes are extensive and appear to be progressive. In the second type, only portions of the pancreas are affected, there is patchy fibrosis, the duct is only mildly dilated and one or two small stones may be found in the ducts. This type is referred to as "abortive FCPD" or "arrested FCPD".

Macroscopically, in most cases the pancreas is shrunken in size and the shape is distorted. The capsule is opaque and the lobular pattern is not evident (Figure 6). There may be adhesions to the surrounding organs. On palpation, the pancreas appears to be a bladder-like structure with stones inside. Whole organ X-ray reveals dilated ducts and ductules with a number of stones in them.

Secretions present in the ducts may be radio opaque. It is easy to probe the duct through the ampula of Vater as there are usually no kinks or narrow strictures. On cutting open the gland, one finds markedly dilated ducts and tributaries (Figure 7).

The lumen contains stones and mucoid secretion which is usually sticky and tenacious,

Figure 5. Ultrasound appearance of FCPD. Reproduced with permission from the *International Textbook of Diabetes Mellitus* published by John Wiley & Sons, Ltd. (see ref. 52).

and the pH may be acidic or neutral. When allowed to dry, the secretions form sand-like particles. The luminal surface of the ducts is smooth and shiny. Sometimes the stones found in the main duct show extensions into the tributaries and they usually take on the shape of the duct. The stones may be smooth or spiky and may show holes and tunnels in them. Some stones are hard in consistency while others can be crushed like an egg shell. The stones may vary in size from small sand-like particles to huge stones several centimetres in diameter. They are mainly composed of calcium carbonate (90–95%) in the form of calcite. The ductal walls are quite thin and can usually be lifted from the parenchyma, which is markedly reduced. At places the residual pancreatic parenchyma can be seen to be closely dissected by strands of fibrous tissue.

7. HISTOPATHOLOGY

The features noted on gross pathology are confirmed by microscopic examination (Figures 8 and 9). The capsule is thickened. There is evidence of intra- and interlobular fibrosis. Inflammatory changes characterized by the presence of lymphocytes and plasma cells are noticeable particularly in the early stages of the disease. Some investigators[62,63] have not found any inflammatory cells in their slides and hence object to the term "pancreatitis", preferring to call it a "pancreatopathy". It is generally agreed that the basic changes in the parenchyma are degenerative and atrophic rather than inflammatory. Hypertrophied nerve bundles and ganglion calls may be seen within the fibrous tissue. The blood vessels are thickened and may show changes suggestive of endarteritis.

Figure 6. Specimen of intact pancreas in an FCPD patient. Note shrunken size, loss of lobular pattern and adhesions. Reproduced with permission from *Secondary Diabetes: the Spectrum of Diabetic Syndromes* published by Raven Press (see ref. 61).

The exocrine tissue appears quite sparse and the acini are reduced in number. The intercalated ducts also appear to be dilated and the ductules, smaller ducts and ducts appear to occur in clusters. The lining epithelium of the smaller ductules show metaplastic cells of the mucous secreting type. Larger ducts show squamous cell metaplasia.

The islets of Langerhans are seen to be dispersed and occasionally they are seen in clusters of 10–30. Overall, the islets appear to be normal and the proportion of different cells is undisturbed. Immunocytochemistry shows that the insulin content of the cells is normal. There is no evidence of active inflammation to suggest insulitis. Unlike Type 2 diabetes there is no evidence of hyaline changes of amyloidosis in the islets.[64] In some cases where the ducts and ductules are intact, there is evidence of nesidioblastosis.

8. SEQUENCE OF PATHOLOGICAL CHANGES

Based on findings in biopsy and autopsy material it is postulated that the initial lesion occurs in the epithelial cells of the intercalated and acinar cells.[61,64] Necrotic changes in ductal epithelium results in a decrease in secretion of water, alkaline radicals and possibly lithostatin. Formation of protein plugs and fibrillary material occurs in the low-volume acidic fluid leading to precipitation of calcium salts. Thus the ductal contents become turbid and thick, containing mud- or putty-like material. Consequent stagnation in the flow promotes formation of calculi and increased intraductal pressure.

Pathological changes in the acinar cells are initially characterized by loss of zymogen granules and bipolar staining properties. Subjected

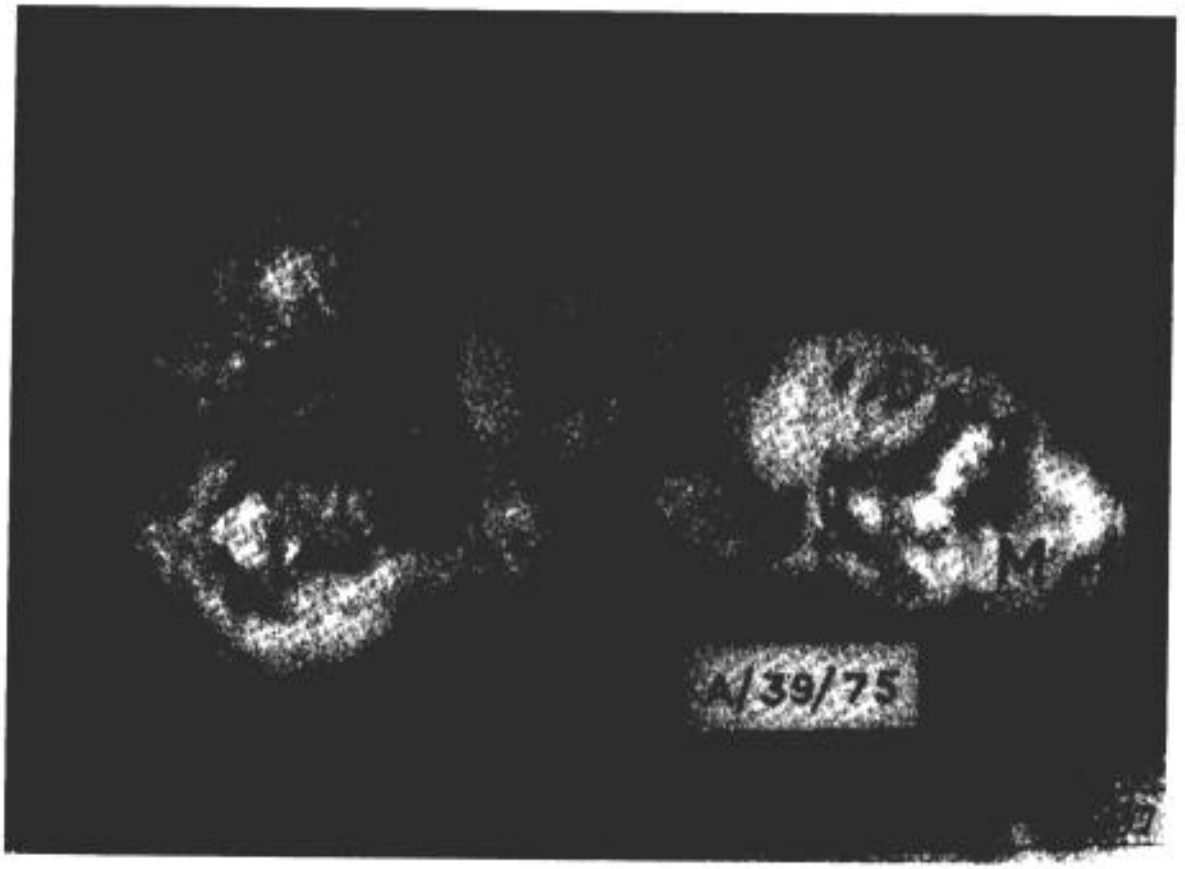

Figure 7. Specimen of cut-open pancreas in an FCPD patient. Note markedly dilated duct, mucinous material and stones. Reproduced with permission from *Secondary Diabetes: the Spectrum of Diabetic Syndromes* published by Raven Press (see ref. 64).

to back-pressure from the ductular contents, the alveoli undergo atrophy. Leakage of fluid from the ducts into the interstices may lead to inflammatory reactions in the early stages of the disease. Proliferation of fibrous tissue finally occurs to replace the atrophic acini.

The ductal epithelium undergoes metaplasia due to irritation by calculi or gravel in the lumen. Weakness of the walls, raised intraductal pressure and adjacent fibrosis result in wide dilatation of the ducts, formation of pouches at some places and narrowing at others.

The fibrous tissue around the islets possibly hinders the transport of the insulin into the circulation. This, combined with a reduction of islet cell mass in later stages, results in deficiency of insulin, leading to IGT and finally to diabetes.

The mechanism of abdominal pain remains unclear but it may be caused by the distended ducts. The inflammatory changes could be an additional factor for the pain, as also the incarceration of nerve fibres within the fibrous tissue.

The loss of exocrine tissue leads to a reduction in enzymes and in digestive capacity. This results in malabsorption (steatorrhoea) and impaired nutrition.

9. EXOCRINE PANCREATIC FUNCTION

Exocrine pancreatic function has been studied by many authors using a variety of tests. Punnose *et al.* have reported on the usefulness of the Lundh meal test.[65] Using a cut-off point of 21 u/ml, 93% of the calcific FCP cases, compared with 27% of the non-calcific variety, had low tryptic activity. Secretion–pancreozymin tests[66] reveal gross reduction in volume, bicarbonate, trypsin and lipase content of the pancreatic secretion. Further, the lactoferrin level of the pancreatic juice was considerably higher in FCP patients and indeed even in South

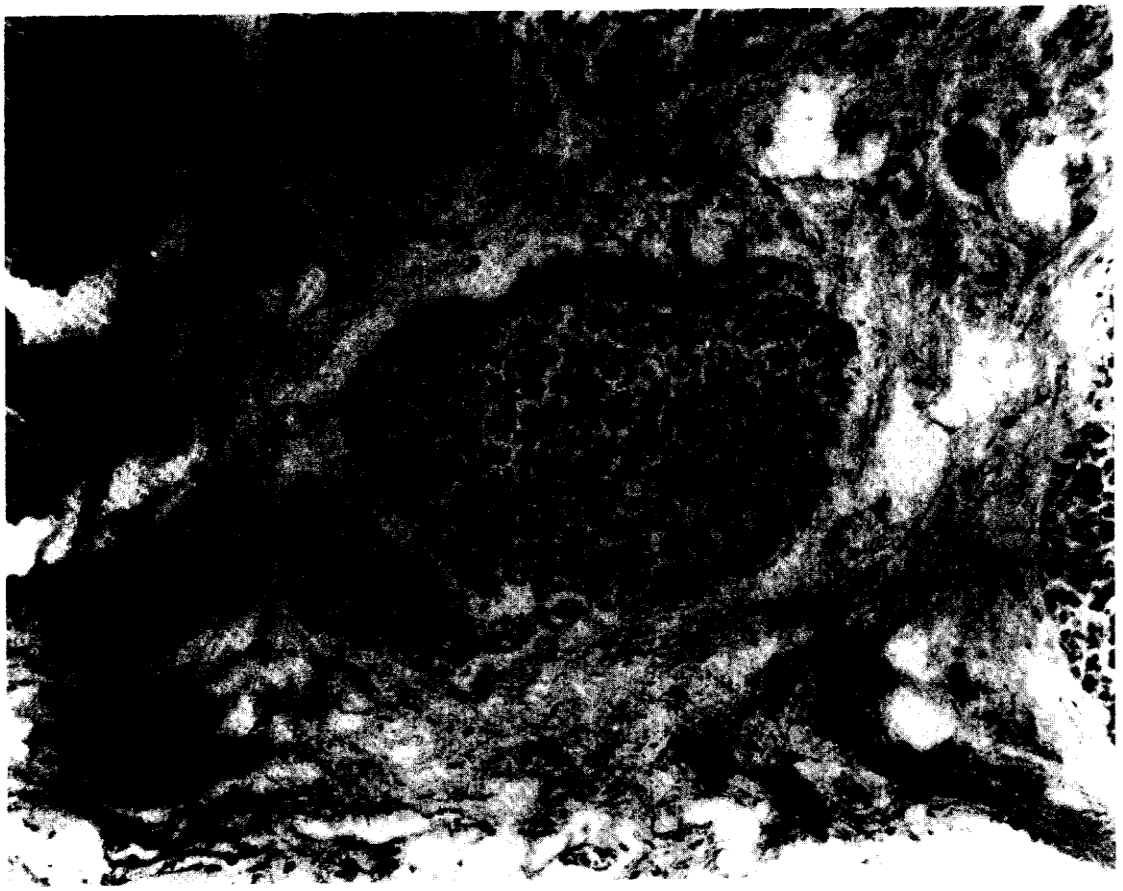

Figure 8. Microscopic picture of FCPD. Pancreas. The lobules are split into smaller fragments by the introlobular fibrous tissue. Inter- and intralobular fibrosis have merged together. Haematoxylin and eosin. Reproduced with permission from *Secondary Diabetes: the Spectrum of Diabetic Syndromes* published by Raven Press (see ref. 61).

Indian control subjects, compared to their European counterparts.

Serum immunoreactive trypsin measurements show a spectrum of exocrine pancreatic involvement.[67,68] In early cases the levels are reduced only in a few subjects, while in some others it may be elevated, possibly due to acute pancreatitis. In advanced cases, trypsin levels are markedly reduced.

Faecal chymotrypsin (FCT) measurements[68,69] and pancreatic isoamylase[67,68–70] have also been used to assess exocrine pancreatic function. In our experience, the FCT test is a simple and inexpensive method for estimating exocrine pancreatic function with a high specificity, although the sensitivity is not satisfactory particularly in picking up early stages of the disease.[69] The modified PABA-PAS test described recently has a very high degree of sensitivity and specificity for diagnosis of FCPD.[71]

10. HETEROGENEITY (VARIABILITY) OF FCP

All the above studies highlight the fact that FCP is a highly variable (heterogeneous) condition, in contrast to the earlier descriptions of the disease made three decades ago.[16]

Table II summarizes the heterogeneity with respect to the clinical, biochemical, ERP and histopathological features of FCP.

11. CRITERIA FOR FCPD

Despite excellent clinical descriptions of the disease, until recently no criteria had been established for the diagnosis of FCPD. Mohan *et al.*[33,52,72] were the first to propose a set of criteria for the diagnosis of FCPD, based on an

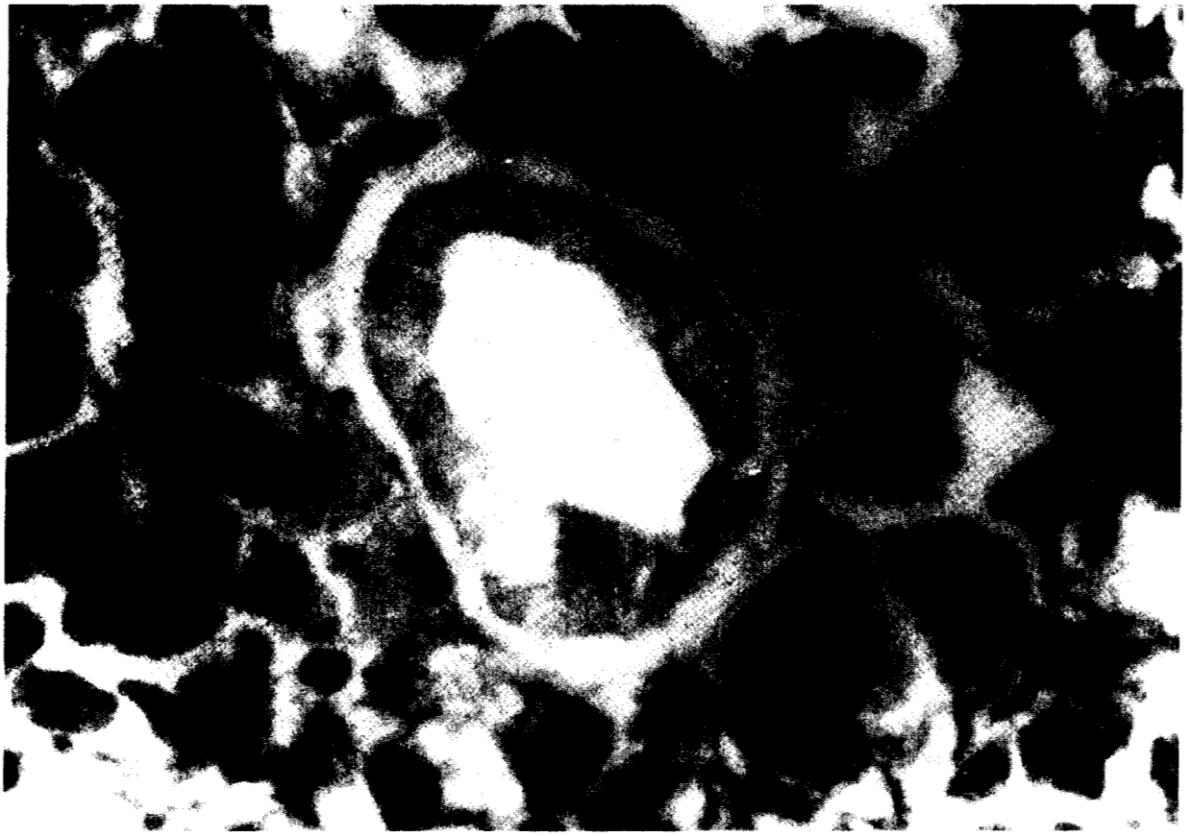

Figure 9. Pancreas. Degenerative changes in the epithelium lining the intercalated ducts. Haematoxylin and eosin. Reproduced with permission from *Secondary Diabetes: the Spectrum of Diabetic Syndromes* published by Raven Press (see ref. 61).

extensive review of the literature. These criteria (Table III) have been generally accepted by other workers in the field.[43,73]

12. COMPLICATIONS

Complications of FCPD may arise from diabetes mellitus as well as from chronic pancreatic disease.

A. Complications Due to Diabetes

It was earlier believed that, being a secondary form of diabetes, microvascular complications may not be seen in FCPD. Recent studies[17,33,74,75–78] have shown that microangiopathy does occur in FCPD patients. In one study,[36] FCPD patients were compared with a group of Type 2 diabetic parents (matched for duration). It was found that the prevalence of retinopathy, nephropathy or neuropathy was similar in FCPD patients and Type 2 diabetic patients. More detailed studies using sensitive techniques established the occurrence of retinopathy,[76–78] neuropathy[74] and left ventricular dysfunction[75] in FCPD patients. More recently, the occurrence of autonomic neuropathy has also been documented.[79,80]

In contrast, the occurrence of macroangiopathic complications, namely coronary artery disease, strokes or peripheral vascular disease, is very uncommon in FCPD patients.[81] This is not surprising, considering the younger age of the patients and the leanness. Moreover, FCPD patients have low serum cholesterol, low-density lipoprotein (LDL) cholesterol and serum triglyceride levels.[36,82]

B. Complications Due to Pancreatic Disease

Complications due to chronic pancreatitis include pseudocysts, pancreatic abscess and

Table II. Heterogeneity (variability) in fibrocalculous pancreatic diabetes

1. Symptoms	Asymptomatic, marked symptoms
2. Carbohydrate intolerance	Normal GTT, IGT Overt diabetes
3. β-cell reserve	Good Poor Negligible
4. Response to therapy	Diet alone Oral agents Insulin
5. Proneness to ketosis	Ketosis resistant Ketosis prone
6. Exocrine dysfunction	Only after provocative tests Clinical steatorrhoea
7. ERCP	Absent to mild ductal changes Marked ductal changes (more common)
8. Pancreatic size	Normal to swollen (early stage) Shrunken to size of a thumb
9. Histopathology	Mild changes Marked changes: (more common) Extensive fibrosis Ductal dilatation Multiple calculi Lipidosis; lipoatrophy

Table III. Criteria for fibrocalculous pancreatic diabetes (FCPD) (Mohan *et al.*[33,52,72])

1. The patient should originate from a "tropical" country
2. Diabetes should be present
3. Evidence of chronic pancreatitis must be present: Pancreatic calculi on abdominal X-ray or at least *three* of the following:
   (a) Abnormal pancreatic morphology on sonography/CT scan
   (b) Recurrent abdominal pain since childhood
   (c) Steatorrhoea
   (d) Abnormal pancreatic function test
4. Absence of other causes of chronic pancreatitis, i.e. alcoholism, hepatobiliary disease, primary hyperparathyroidism, etc.

ascites. Patients may present with obstructive jaundice, which can either be due to stenosis of the common bile duct, a stone obstructing the passage or associated carcinoma of the pancreas. Recent studies[12,83,84] suggest that FCPD could be a premalignant condition. Current evidence[83] suggests that the risk for developing pancreatic carcinoma is higher in FCP than in temperate zone pancreatitis, although the reasons for this are not clear.

C. Life Expectancy, Survival and Causes of Mortality

Few studies have reported on the long-term survival data in FCPD. In a recent study[85] it was noted that long-term survival of patients with FCPD is quite good, with several patients surviving 25–30 years after the onset of diabetes. The majority of deaths were associated with diabetes-related causes, with diabetic nephropathy accounting for 40%. Severe infections, pancreatic cancer and other chronic pancreatitis-related causes also contribute to the mortality of FCPD patients.[82,85,86]

13. MANAGEMENT

Both aspects of FCPD, namely diabetes and chronic pancreatitis, need specialized management and close follow-up.

A. Diabetes

The treatment of diabetes is mainly directed at the control of hyperglycaemia and prevention of complications. The principles of diet and exercise are the same as for other types of diabetes except that a more liberal calorie and protein intake may be advised because of the features of undernutrition and leanness.

Oral hypoglycaemic agents may be tried in cases with mild diabetes and relatively early in the course of the disease, when the general health is satisfactory. As discussed earlier, insulin is required in the vast majority of patients.

B. Chronic Pancreatitis

Pancreatic enzymes help to reduce steatorrhoea and may indeed even alleviate pancre-

atic pain in some cases. More often, however, the pain is severe and intractable and is not relieved even by powerful analgesics. At this stage, surgical intervention is indicated. The role of surgery in FCPD has recently been reviewed.[87–90] Sphincterotomy, side-to-side pancreatico-jejunostomy (Puestow's procedure) and end-to-side pancreatico-jejunostomy (Duval's procedure) have been tried with fairly good results.[88–90] Many of these procedures are beneficial with respect to alleviation of pain, although some patients may experience a relapse. There are some reports which suggest that after surgery the mean daily insulin requirement may decrease.[18,25,34] It is more likely that the changes are transient and the diabetic status appears to be largely unaffected by surgery. There is, however, improvement of general health and the quality of life, particularly in patients who fail to gain weight despite good diabetes control.

14. AETIOLOGY AND PATHOGENESIS

The aetiopathogenic mechanisms for FCPD remain unclear. Malnutrition and cyanogenic alkaloids (derived from cassava or other food items) have often been incriminated as aetiological factors. Recently, "oxidant stress" has been proposed as a mechanism in pancreatic damage. These are briefly reviewed below.

A. Malnutrition

Clinical evidence of malnutrition at the time of diagnosis of FCPD suggested that malnutrition could be a factor in the aetiology of FCPD.[6,7,17,91–93] However, malnutrition at presentation may well be secondary to severe exocrine and/or endocrine pancreatic deficiency.[33,43] Protein–calorie malnutrition has been shown to produce pancreatic changes as well as glucose tolerance and insulin deficiency in experimental animals[94,95] but it rarely leads to permanent diabetes. Moreover, pancreatic calculi have virtually never been described in patients with kwashiorkor or marasmus. Recent work suggests that rather than overt protein and calorie deprivation, micronutrient deficiency could be a more important predisposing factor (see below). The possible role of malnutrition in FCPD and other forms of diabetes seen in the tropics has been elegantly reviewed.[51]

B. The Cassava Hypothesis

McMillan and Geevarghese[96] observed the geographical occurrence of FCPD in areas where the tuber cassava (tapioca, manihot) is consumed as a staple food and suggested a causative role for cassava in the aetiology of this condition. Cassava contains 95% starch, 0.4% protein and also contains cyanogenic glycosides, linamarin and lotustralin. It has been suggested that dietary deficiency of sulphur-containing amino acids like methionine and cystine could hamper the detoxification of cyanide to thiocyanate and thus lead to high levels of "free" cyanide which might be toxic to β-cells. Studies in rats by the same group showed that cyanide administration could lead to transient hyperglycaemia but not to permanent diabetes. There are, however, several lines of evidence against the cassava hypothesis. Many studies[66,97] have shown that there is no excess of cassava intake in patients with FCP. Recent studies in Africa[98] failed to find FCPD in areas where cassava is eaten as a staple food but this could be related to differences in processing or cooking of the tuber. Experimental studies on cassava have led to conflicting results. Akpan *et al.*[99] showed evidence of glycosuria and decreased glucose-induced insulin release in rats, but the studies of Pushpa[100] were not conclusive. A recent study[101] showed that in rats fed on cassava diets for up to one year no evidence of either diabetes or chronic, pancreatitis was noted, while a study in dogs showed evidence of pancreatic damage.[102] In summary, while the cassava theory is certainly interesting, its role in the causation of FCPD remains speculative at the present time. More studies on cassava and other foodstuffs which may contain cyanogenic or other toxic products should be done in areas where FCPD is endemic.

C. Do Genetic/Familial Factors Play a Role?

Familial clustering of FCP has been described by several workers.[17,18,103,104] In a large series,[104] 12% of parents and 21% of siblings of FCPD patients showed evidence of FCPD, while 21% of parents and 11% of siblings had previously undiagnosed non-insulin-dependent diabetes (NIDDM). The latter could be explained by the high background prevalence of NIDDM in India.[105] In the absence of a specific genetic marker, it is difficult to say if these results reflect a genetic transmission or a shared environmental factor. Recently, in collaboration with Dr Hitman's group at London, it has been observed that about 40% of FCPD patients have the HLA-DQ-B haplotype which is usually associated with IDDM.[106] Another 40% of FCPD patients showed an association with the class 3 allele of the insulin gene, which is similar to the association seen in NIDDM patients. These studies provide evidence for a genetic susceptibility to FCPD but obviously more studies are needed to confirm these findings.

D. Oxidant Stress and Antioxidant Deficiency

The work of Braganza at Manchester has suggested that, like chronic pancreatitis in the UK, FCP could also be related to oxidant stress mediated by heightened cytochrome P-450 activity.[107,108] In studies with the Manchester group evidence of increased exposure to xenobiotics, especially polycyclic aromatic hydrocarbons (cigarette, kerosene and firewood smoke and vehicular fumes), was found in FCP patients.[109] This was associated with elevated theophylline clearance (a marker for cytochrome P-450 activity).[110] Further studies[111] showed evidence of antioxidant deficiency, particularly of vitamin C and β-carotene in Madras FCP patients and control subjects compared to Manchester subjects. The levels of selenium and vitamin E were not significantly different between the two groups.

E. Lithostatine (Pancreatic Stone Protein)

Investigations by Sarles and co-workers in Marseilles[112,113] have shown that deficiency of

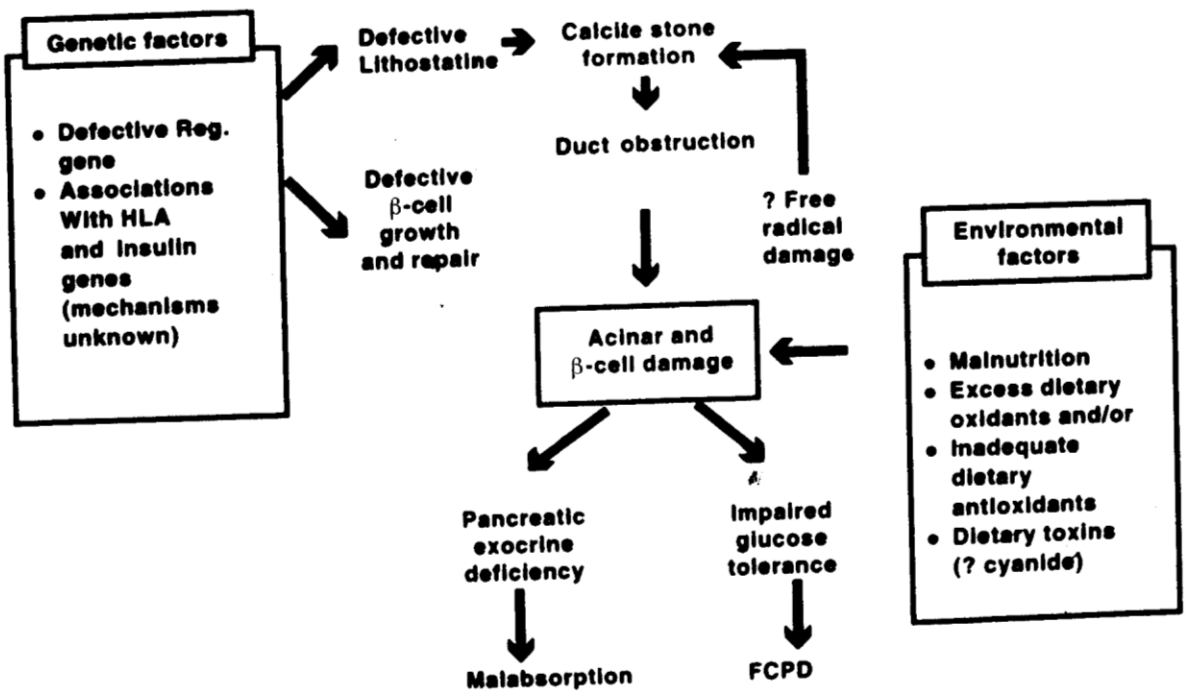

Figure 10. Hypothesis for aetiopathogenesis of FCPD. Reproduced with permission from *Pickup's Text Book of Diabetes* published by Blackwell Science Ltd. (see ref. 116).

pancreatic stone protein (PSP), also known as lithostatine or Reg protein, could be one of the mechanisms responsible for chronic pancreatitis in temperate zones. There is very little data on the role of lithostatine in FCP. Recently, the gene for lithostatine, also known as Reg gene, has been cloned.[114] In collaboration with Dr Graham Hitman's group at London, we looked for mutations of the Reg gene in FCPD patients but the results were essentially negative.[115]

It is possible that on a background of genetic susceptibility, deficiency of macro- or micronutrients may make the pancreas vulnerable to toxic injury. When the susceptible individual is then exposed to toxic agents like cyanogenic glycosides (e.g. cassava) or polycyclic aromatic amines (e.g. smoke, petrol, diesel fumes, chemicals), this could lead to toxic pancreatitis either via the cytochrome P-450 system or through other unidentified pathways (Figure 10).[116]

15. PLACE OF FCPD IN THE NEW CLASSIFICATION OF DIABETES

At an international workshop on "Diabetes peculiar to the tropics" held recently at Cuttack in India, a Consensus Statement emerged regarding the place of FCPD in the classification of diabetes.[73] FCPD was earlier classified under MRDM in the WHO Study Group Report on diabetes.[1] Since malnutrition does not appear to be an essential feature of FCPD, it was recommended at the Cuttack meeting that FCPD should not be classified under MRDM but instead considered as diabetes secondary to tropical chronic pancreatitis. These recommendations have been accepted by the recent Expert Committee on Classification of Diabetes[2] and FCPD has now been reclassified under "Diseases of exocrine pancreas".

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