

Chapter 2

Tropical pancreatitis - what is happening to it?

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Summary

Tropical pancreatitis is an entity first described in the 1950s. Though it was originally seen in young malnourished subjects from the tropics, this pattern is showing a gradual change. Older, better nourished patients are now affected by the disease. Alcoholism has increased in the population, and as a result, alcoholic pancreatitis too has gone up. Etiology of this disease is still not clear. The authors examine various hypotheses of etiology of TP and advocate the concept wherein pancreatitis of different types may have common etiological factors, but in differing proportions. The interplay of the environmental and genetic factors determine the phenotype of the disease.

Introduction

Tropical pancreatitis (TP) is a form of chronic pancreatitis of the young, originally described from the tropics. Though Zuidema had described malnourished young diabetics with fibrosis and calcifications of the pancreas in 1955¹ and again in 1959², and similar patients were described by Shaper³ from Uganda, it was the report by Geevarghese⁴ of a large series of young patients with malnutrition, diabetes and pancreatic calculi from Kerala state in South West India that focused attention on this condition, peculiar to developing countries.

When our group started work on tropical pancreatitis at the Medical College Hospital, Trivandrum, Kerala state in India in 1972, patients suffering from this disease were a common sight in our hospital, which was a referral centre, drawing patients from all the neighbouring districts. The tools that were available to us to investigate these patients were few. We had no ultrasound, CT scan, ERCP, MRCP or EUS. There were no pancreatic function tests being done in our hospital and genetic studies had not yet come of age. In short, we had to depend mainly upon the clinical picture, a plain X-ray of the abdomen, blood sugar estimations, biopsies from surgical specimens or an occasional autopsy to diagnose our patients. We started a registry for chronic pancreatitis and started recording details of our patients, and during the ensuing years, some of the newer investigational modalities became slowly available to us.

The clinical picture of tropical pancreatitis patients in those early years were so striking, that we could, most of the time, observe them walking around the wards, and make a "spot diagnosis". They were mostly children, adolescents, or sometimes young adults, who had the common characteristics of malnutrition, deficiency signs, a cyanotic hue of the lips, bilaterally enlarged parotid glands, a pot belly, and sometimes, pedal edema (Figure. 1)

This classical picture, with an elevated blood glucose level and the demonstration of a pancreas studded with dense intraductal calculi on X-ray abdomen would clinch the diagnosis. As far as diagnosis was concerned, there was no need for further investigations. However, there was a subgroup of these patients who did not show pancreatic calculi at the time of presentation, of whom many subsequently developed them. In the initial stages, in the absence of further functional studies or imaging modalities, diagnosis in this subgroup posed some difficulty. Our early patients were an almost equal mix of males and females, with a slight male preponderance. The distinctive feature of these patients were the near absence of any history of alcohol abuse, and mostly, smoking, thus contrasting them from the "alcoholic calcific pancreatitis (AP)" of the West. They had no gallstones or other detectable causes of pancreatitis.

Ketosis occurred in 15% in our early series⁵. They had high blood sugar values, often in the ranges of 200-400 mg/dl, requiring generally, large doses of insulin for control, had a brittle diabetes, and were frequented by episodes of hypoglycemia. During the sixties and seventies, a number of reports started coming in from other Asian and African countries^{6,7,8}, and even from Brazil⁹ in South America, describing similar young malnourished diabetics with pancreatic calculi. The common denominator of the countries afflicted by this malady was their location in the tropics, poverty and poor standards of nutrition. Large segments of population in such countries also regularly consumed cassava (tapioca), a tuber containing starch almost exclusively, with negligible quantities of protein (and amino-acids) as their staple diet. This close association with tropics, poverty and malnutrition earned the disease synonyms such as "Nutritional pancreatitis", "Afro-Asian pancreatitis", "Juvenile pancreatitis", and "Tropical pancreatitis". At that time, these descriptive terms were useful to segregate such patients from the well-

recognized entity of “alcoholic pancreatitis”. This geographically descriptive term was also a reflection of the ignorance about the etiology or etiologies of this newly recognized disease. In the seventies and early eighties, we seldom saw patients of alcoholic chronic pancreatitis in our hospital. The following are results of studies in our early series (in the seventies and eighties) of nearly 250 patients with TP.

Clinical details

The male to female ratio in our patients was 1.6 :1. The mean age of presentation of the disease was 30.5 years in the calcific group and 22 years in the noncalcific group.⁵ This might indicate that calcification is a function of time. The clinical features of our patients are given in Table 1.

Pain was the commonest presenting symptom, closely followed by diabetes mellitus.

Table 1. Demographic and clinical features

	Calcific n=155	Non-calcific n=65
Age (mean) at presentation	30.5 (years)	22 (years)
M:F	2.7:1	1:1
Pain	84%	80%
Duration of pain	7.9 (years)	3.6 (years)
Diabetes	76%	81%
Duration of diabetes	6.0 (years)	4.8 (years)
Complications of diabetes	27%	46%
Steatorrhoea	72%	81%
Surgery	25%	15%

Retinopathy, peripheral neuropathy and nephropathy were common complications of diabetes¹⁰. (Table 2)

Table 2. Tropical pancreatic diabetes - complications

Complications	Percentage
Ketosis	15
Hypoglycemic episodes	20
K.W. Syndrome	10
Neuropathy	69
Retinopathy	34
Tuberculosis	5

Most patients of tropical pancreatitis died in their thirties as a result of nephropathy or infections. Many of them developed pulmonary tuberculosis. Some of our patients (10%) developed malignancy of the pancreas on follow up and succumbed to it. Nearly twenty five percent of patients with tropical pancreatitis in this series had to undergo surgery – mostly for intractable pain, occasionally for proven or suspected malignancy, pseudocysts or common bile duct obstruction.

In the early surgeries, there was no standardization of the surgical procedures and based on the operating surgeon's judgement, various procedures such as sphincterotomy or sphincteroplasty, often combined with scooping out of stones from an opened main pancreatic duct, drainage procedures, resections and splanchnicectomy were all employed.

Surgery

Out of a series of 64 patients operated upon, 47 had the surgery done for severe intractable pain. Nine had carcinoma pancreas complicating TP, 10 had obstructive jaundice (6 having associated carcinoma), 5 had pseudocysts and 2 pancreatic ascites. Eighty-six percent of patients had immediate pain relief and 68% remained pain free on follow up of up to 5 years⁵.

noncalcific pancreatitis and 2.75 ± 2.92 EQ/min/ml in those with calcific pancreatitis. Ninety percent of the TP patients showed subnormal (less than 12.4 EQ/min/ml duodenal tryptic activity and steatorrhea. No correlation was found between the severity of steatorrhea and the level of tryptic activity.

In a collaborative study with the group from Marseille¹¹, the exocrine pancreatic function after secretin-CCK stimulation was assessed in South Indian TP patients and French AP patients and matched South Indian and French controls. (Table 4).

Table 4. Comparison of biochemical parameters in pancreatic juice of South Indian (TP) and controls French patients (AP) and controls

	Indian CCP	A	TP	B	AP	Controls	C	D
Bicarbonate (mEq/L)	23.4 ± 4.4	S	60.4 ± 4.6		71.6 ± 4.8	40.8 ± 4.1	S	S
Calcium (mEq/L)	3.7 ± 0.3	S	3.2 ± 0.5	S	1.9 ± 0.2	2.4 ± 0.2	S	S
Amylase (UI/ml)	100.0 ± 35.4	S	205.2 ± 31.6		398.7 ± 94.3	241.4 ± 34.6	S	S
Lipase (UI/ml)	102.1 ± 34.9	S	957.0 ± 109.0		1089.3 ± 82.6	469.6 ± 76.2	S	S
Phospholipase (UI/ml)	1.8 ± 0.8	S	9.1 ± 1.2	S	21.4 ± 2.6	10.5 ± 2.4	S	S
Trypsin (UI/mL)	2.9 ± 0.9	S	19.2 ± 1.9		25.6 ± 1.4	7.7 ± 0.9	S	S
Chymotrypsin (UI/mL)	22.6 ± 8.4	S	118.1 ± 7.8	S	149.0 ± 11.5	73.7 ± 10.2	S	S
Lactoferrin (ug/mL)	19.4 ± 8.9	S	1.7 ± 1.6		0.1 ± 0.07	4.8 ± 2.3	S	S

Displayed values are mean \pm SEM

A. Indian CCP vs. Indian controls ($p < 0.05$); B. Indian controls vs. French controls ($p < 0.05$); C. Indian CCP vs. French CCP ($p < 0.05$); D. Indian CCP vs. French controls ($p < 0.05$)

S=significant

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We observed that the South Indian patients with TP had very low lipase and phospholipase levels in their pancreatic juice compared to French patients. Further, even the Indian controls exhibited markedly reduced enzyme secretions than their French counterparts. However, the calcium and lactoferrin levels, which have been thought to indicate pancreatic injury, were significantly higher in the Indian controls than in the French controls.

From these studies, we proposed that perhaps, among the malnourished population in the tropics, there existed a condition of "subclinical pancreatopathy"¹¹ that became overt when a second insult to the pancreas supervened.

Family studies

We did HLA studies in members of seven families with more than one patient of TP in each. Six of the seven families and eight of twelve patients shared the HLA AW19/AW10 haplotypes, suggesting a possible genetic role in the causation of this disease¹⁴. In a subgroup study, in the family members of 24 patients with calcific pancreatitis, there were 12 family members with TP, 16 with type 2 diabetes, and 1 with pancreatic cancer⁵. In the families of 15 patients with non-calcific pancreatitis, there were 3 members with pancreatic calculi, including a twin sister, 11 with type 2 diabetes and 1 with carcinoma pancreas. These findings pointed to a strong family background common to TP, type 2 diabetes mellitus and carcinoma pancreas, and possibly, a genetic predisposition.

Infection

In another study, we tested for antibodies against rubella, mumps, CMV and M-pneumoniae in the sera of patients with TP and controls and found that significantly more numbers of patients were tested positive for antibodies against mumps and CMV than the controls; however, in the case of M. pneumoniae, more controls than patients were tested positive¹⁵ (Table 5).

Table 5. Viral and M. pneumoniae antibodies in chronic pancreatitis

Agent		Total no. tested	No. +ve	Antibody titre		Chi square	P value
				<1:32	>1:32		
Rubella	Patients	51	41	1	40	-	-
	Controls	60	50	0	50	-	-
Mumps	Patients	52	46	21	25	19.07	<0.001
	Controls	45	44	40	4		
CMV	Patients	39	36	14	22	15.57	<0.001
	Controls	45	33	29	4		
M.pneumoniae	Patients	52	26	14	12	12.02	<0.001
	Controls	45	42	5	37		

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In the above study seriological evidence of current viral infection was present in 12 of our patients with chronic pancreatitis (4 with rubella, 2 with CMV, 4 with mumps and 3 with M.pneumoniae) as evidenced by a four to eight fold rise in antibody titres.

In yet another study, 66.7% of our TP patients showed coxsackie B antibodies in their serum¹⁶. Injection of extracts of pancreatic tissue and pure pancreatic juice, obtained during surgery, into suckling mice, did not yield any viral agents, nor did it produce any pancreatic lesions.

Immunity

Sera from 60 of our patients with TP and 20 normal controls were tested against a pancreatic antigen prepared in our laboratory for antipancreatic antibodies by a hemagglutination test. Sixty-nine of the patients (29%) tested positive for the antibodies against the pancreatic antigen, but none of the controls. We also failed to detect any autoantibodies in the sera of our patients on testing for a panel of autoantibodies¹⁷, apart from 6 patients tested weakly positive for parietal cell antibodies and one weakly positive for islet cell antibodies (Table 6)

Table 6. Anti-pancreatic and auto immune antibodies and C3 in tropical pancreatitis patients

Antibodies & Complement	Patients		Controls	
	No. tested	Positive	No. tested	Positive
Anti-Pancreatic Antibodies				
positive titre of >1/8 (Indirect hemagglutination test)	69	20	30	Nil
Autoantibodies				
Antinuclear	12	Negative	10	Negative
Smooth muscle	12	Negative	10	Negative
Antimitochondrial	11	Negative	10	Negative
Islet cell	11	Negative	10	1 weakly +ve
Parietal cell	24	6 weakly +ve	10	Negative
Thyroglobulin haemagglutinating	11	Negative	10	Negative
Adrenal	11	Negative	10	Negative
C3	11	Negative	10	Negative

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ERCP

ERCP findings in TP were reported for the first time by our group in 1985¹⁸. The ERCPs showed marked tortuosity, dilatation, stenosis, obstruction and cyst formation in the main pancreatic duct and finer branches with multiple large intraductal calculi and the findings were similar to, but more pronounced, than those described in alcoholic pancreatitis (Figure 2).

Calculi, protein plugs

In a study of pancreatic calculi from patients with TP, the stones were found to vary in size from large to small, were whitish or dirty brown, gritty or thorny, and adherent to the duct walls and were always intraductal. The stones were analyzed by scanning electron microscopy, atomic absorption spectrophotometry, chemical analysis, thermo-analytical methods, infrared spectrometry and X-ray diffraction. The chief constituent of the stones was found to be calcium carbonate, constituting 95 to 98 percent⁵. Crystallographic studies using X-ray diffraction revealed that the calcium carbonate existed as calcite.

Scanning electron microscopy revealed the presence of amorphous and crystalline material in the stones¹⁹. The crystals were of a rectangular form and were heaped one upon the other. Interlacing fibres of 3-5 microns were seen in between the deposits. These findings bear resemblance to that of one of two types of stones described by Harada in AP from Japan²⁰ (Fig 3).

Pure pancreatic juice and protein plugs from pancreatic duct collected during ERCP were studied under the electron-microscope and scanning electron microscope. Clumps of amorphous material deposited in the spaces between interlacing fibres were observed. There were deposits of varying sizes on the surface of the clumps as well as on the fibres. These protein plugs appear to form the nidus for deposition of calcium on and within its meshes with subsequent stone formation (Fig 4).

Chemical composition of pancreatic calculi was studied using atomic absorption spectrophotometry (Table 7).

Table 7. Trace elements in calculi from TP

Element	Mean \pm S.E. Mg/g dry weight
Calcium	379.4 \pm 0.8365
Copper	0.0256 \pm 0.0096
Magnesium	0.0176 \pm 0.0033
Cadmium	0.0058 \pm 0.0011
Iron	0.0306 \pm 0.0087
Manganese	0.0072 \pm 0.0006
Zinc	0.1552 \pm 0.0485
Cobalt	0.023 \pm 0.0007
Aluminium	0.0728 \pm 0.0044

The changing pattern of TP

The first author of this article has been actively involved in the care of patients and study and research in pancreatitis, and particularly on chronic pancreatitis of the tropics over a period of three decades. He has personally treated, recorded and followed up more than a thousand patients with tropical pancreatitis and has been a keen observer of the changing trends in the epidemiology and clinical course of this disease. These observations have brought to his attention several social, dietary and life-style changes that have occurred during the past thirty and odd years in Kerala state, where the highest prevalence of tropical pancreatitis has been recorded in the world, which could have influenced, to a great extent, the changing trends in the natural history and occurrence of the disease in the state¹⁹. It will be interesting to examine what these socioeconomic and lifestyle changes are and how these could have influenced the clinical presentation of this disease.

Firstly, people are more literate now (nearly 100%) and the standard of living has greatly improved²¹. There is better hygiene, as a result of better literacy and health awareness and standard of living. Cassava, which was an inexpensive poor man's diet, has been replaced to a large extent, by rice, through improved purchasing power and availability through

the public distribution system²². People eat more fish, meat and poultry. Medical facilities have remarkably improved and are more easily accessible than what obtained thirty years back. Diabetics are better cared for and more closely monitored, thanks to a parallel, or even more powerful network of private healthcare facilities. There are large numbers of specialists available in the all regions of the state, which is like an extended township. Early detection of diseases has become common. Facilities such as ultrasound and CT scan are now readily accessed, and even ERCP, MRCP and EUS are now available in the larger centres. The longevity in the state has risen dramatically, boasting of the country's best figures²¹. Along with this, on the negative side, alcoholism has become extremely common, and according to recent figures, Kerala's per head annual consumption of liquor is thrice that of the national average²³. Smoking is rampant. Pollution from factories, exhaust from motor vehicles, toxins from pesticides and adulteration of foodstuffs have phenomenally increased. Genetic studies are now available in a few major centres in the country and patterns of genetic mutations in diseases are being reported, particularly so in pancreatitis. In a vast country like India, geographical variations in the genetic make-up are expected. It is but natural that such social, dietary, life-style, and environmental changes, on a genetic background (that has many commonalities, but at the same time, with variety thanks to the size and heterogeneity of the population) would influence the pattern of several diseases. Perhaps, in the case of tropical pancreatitis, this is what must have been happening. The occurrence and extent of such influences, and the combination of factors that has wielded such influences, are still matters of speculation.

Study of a new cohort

In the light of the above observations, we compared a cohort of about 250 patients with chronic pancreatitis that we have prospectively followed up during the past 5 years to a cohort of 250 patients of chronic pancreatitis that was studied and followed up by the first author personally during the seventies and eighties, that is, 30 to 20 years earlier. Such comparison should be interesting and educative.

The current cohort of nearly 250 patients with chronic pancreatitis were seen and followed up by us at the Amrita Institute of Medical Sciences, Cochin, in Kerala state in India during the last 5 years. In our current series of 255 patients, 226 have chronic pancreatitis and 29 have recurrent acute pancreatitis. Pancreatic calculi were present in 213 of the chronic group and 13 were without calculi. Of the 29 patients with recurrent acute pancreatitis, 18 developed calcification during follow-up and they were included in the chronic pancreatitis group for the present analysis. Of these 18 patients, 11 were alcoholic and the rest gave no history of alcohol.

Among the non-alcoholic patients in our current cohort, 2 have hypertriglyceridemia and one hyperparathyroidism. Four patients have pancreas divisum. Eight patients have associated cirrhosis of the liver, of whom 7 are among the alcoholics. The demographic and clinical details of these patients are given in Table 8.

Table 8. Demographic and clinical details of new cohort of patients

Variables	Whole group of 244 patients	
	No.	%
Gender		
Male	170	69.6
Female	74	30.3
Socio-economic status		
Poor	34	15
Lower middle	116	51.1
Upper middle	72	31.7
Rich	05	2.2
Clinical features		
BMI		
18-25	70	69.3
<18	25	24.7
>25	5	4.9
Age of presentation	39.1 ± 12.87	
Age of onset of Pain	30.8 ± 14.56	
Age of onset of DM	36.2 ± 11.27	
Pain (n = 243)	233	95.9
Steatorrhea (n = 203)	94	38.4
Diabetes (n = 243)	145	59.7
Calcification	231	94.7
Duct dilatation (n = 225)	196	80.4
No. of alcoholics n=158 males	77	33.2 (among whole) or 48.7 among males
No. of smokers (n = 221)	75	33.9
Family history		
Diabetes (n=173)	87	50.2
Pancreatitis (n=158)	19	12
Ca pancreas	12	4

where n is the number of patients whose data is available

The majority of patients (70%) had a BMI within the normal range (mean 20.4; range 14.03 – 27.85), as compared to the BMI of 15.9; (range 9.6 – 21.07) of our cohort of 1984. Thus the majority of patients in the current series were moderately to well-nourished.

The predominant symptom is pain, which occurred in 95%. Nearly 60% of the patients are diabetics. Thirty eight percent of them have clinical steatorrhea.

The age of onset of disease, and the ages of presentation and duration of the main symptoms are given in table. It will be noticed that the age of presentation is more than one decade later than in the earlier series (Fig 5).

Forty nine percent of our male chronic pancreatitis patients consume alcohol. Of the whole group, including males and females, 33% are patients with alcoholic pancreatitis. For this study, we applied a threshold level of 80g of alcohol intake daily for 5 years. As opposed to our earlier series where 98% of patients (except 2 percent of alcoholic pancreatitis) had tropical pancreatitis, in the current series, nearly one third of our total number of patients, and nearly half of the male patients are suffering from alcoholic pancreatitis. In addition, 17 patients among the 'non-alcoholic' group are occasional or 'social' drinkers. This shows that alcoholic pancreatitis is on the rise in this state where we used to see earlier, almost exclusively, tropical pancreatitis. It is also possible that alcohol, in smaller amounts, as in the social drinkers, might be having an additive role, along with other dietary or environmental toxic factors, even in the causation of "idiopathic" or "tropical pancreatitis", as there is no real cut-off value for the harmful effects of alcohol²⁴.

Forty percent of the patients are smokers, and it was interesting to observe that 83 percent of the alcoholics were also smokers. The combined effect of alcohol and tobacco are known to contribute to the development of chronic pancreatitis²⁵, and even pancreatic cancer²⁶.

We compared the features of our alcoholic with the non-alcoholic group of patients. In the alcoholic patients, the age of onset and the age of presentation of the disease are both about a decade later than in the non-alcoholic group (Table 9).

Table 9. Comparison of age of onset and age of presentation between alcoholics and non-alcoholics

	Alcoholics	Non-alcoholics	p value
Age of presentation	45.4 ± 9.71	35.9 ± 2.92	0.000
Age of onset of pain	36.1 ± 13.49	27.4 ± 13.94	0.000
Age of onset of DM	41.53 ± 9.56	32.6 ± 10.4	0.000

The age of onset and presentation in the alcoholics are more or less same as those of alcoholic pancreatitis described in other reports. The nonalcoholic group is a mix of classical cases of tropical pancreatitis and idiopathic pancreatitis, which explains this age difference between the alcoholic and the nonalcoholic groups. We are also looking at any possible genetic differences between the alcoholic and the nonalcoholic pancreatitis groups.

Sixty percent of the patients are diabetics. The mean age of onset of diabetes is 36 years. The age of onset of pain and the age of presentation are about 7 years and 9 years later, respectively, in the diabetics as compared to the non-diabetic group, which is significant (Table 10). This raises the question whether TP and FCPD are two different diseases. However, this issue is still contentious and awaits further proof. It is also possible that these two conditions may be different expressions of the same disease.

Table 10. Comparison of age of onset and age of presentation between diabetes and non-diabetes groups

	Diabetes	Non-diabetes	p value
Age of presentation	40.54 ± 11.747	28.26 ± 10.68	0.000
Age of onset of pain	29.47 ± 15.16	20.77 ± 10.98	0.000

The diabetic patients had significantly more clinical steatorrhoea (47.2%) than the non-diabetics (24.4%; p 0.001). However, there is no correlation between diabetes, and pain, calcification or ductal dilatation (Table 11)

Table 11. Correlation between diabetes, pain, steatorrhea, calcification or ductal dilatation

		Diabetes		Non-diabetes		p value
		No.	%	No.	%	
No. of patients		145	59.7	98	40.3	
Pain	Yes	137	94.5	96	98	0.157
	No	8	5.5	2	2	
Steatorrhoea	Yes	59	47.2	19	24.4	0.001
	No	66	52.8	59	75.6	
Calcification	Yes	140	96.6	90	91.8	0.096
	No	5	3.4	8	8.2	
Duct dilatation	Yes	106	81.5	75	78.9	0.375
	No	24	18.5	20	21.1	

We searched for possible correlations between pain, and ductal dilatation, calcification or diabetes, but there was no correlation (Table 12).

Table 12. Correlation between pain, and ductal dilatation, calcification or diabetes

		Pain				p value
		Yes		No pain		
		No	%	No.	%	
Ductal dilatation	Yes	172	79.6	9	100	0.136
	No	44	20.4			
Calcification	Yes	220	94.4	10	100	0.571
	No	13	5.6			
Diabetes	Yes	137	58.8	08	80	0.157
	No	96	41.2	02	20	

Table 13 looks at correlations between ductal dilatation and pain, calcification or steatorrhoea. There was positive correlation between ductal dilatation and calcification.

Table 13. Correlation between ductal dilatation, and pain, calcification or steatorrhea

		Ductal dilatation				p value
		Yes		No		
		No.	%	No.	%	
Pain	Yes	172	95	44	100	0.136
	No	9	5			
Calcification	Yes	174	96	38	86.4	0.02
	No	7	4	6	13.6	
Steatorrhea	Yes	56	36.6	15	41.7	0.351
	No	97	63.4	21	58.3	

Nearly 50% of the patients consumed cassava in significant quantities. However, the mean daily intake of cassava was 171.8 SD 170.8g/day, which is much lower than the intake in our earlier cohort (370 g/day). This is because cassava has, to a large extent, been replaced by rice as the staple diet even among the poor in the state. The age of presentation, onset of pain and onset of diabetes mellitus were also about 3-4 years later in the cassava eaters than in the cassava non-eaters. However, these differences were not statistically significant.

There were 12 patients who developed malignancy in our current series of chronic pancreatitis. Apart from this, there were 9 cases of carcinoma pancreas complicating TP who directly attended the G.I. Surgery clinic. They are not included in this analysis of TP cases.

Our observations

What are our important observations on the changes that have occurred in tropical pancreatitis over the past 2- 3 decades? Firstly, the age of onset of the disease and the age of presentation have shifted to the right by a decade²⁷. The patients in the current series are better nourished than those in the earlier series. Malnutrition is now much less common. The diabetes mellitus is milder and is better controlled, often with diet and oral hypoglycemic drugs alone. The patients with TP eat less cassava now than their predecessors and, in addition, newer varieties of cassava with reduced cyanogenic content are available now. Alcoholism has

phenomenally increased in India in general, and in Kerala in particular, and as a result, we see many more cases of alcoholic pancreatitis now than earlier. A large number of the alcoholics are smokers too and there is the likelihood of an additive effect of smoking with alcoholism in the causation of pancreatitis. Patients of chronic pancreatitis live longer (many of them to fifties and a few, even to sixties), and fewer require surgery for relief of pain, as in a large number, pain can be controlled with medical treatment. However, because of increased longevity, and perhaps, as the effect of environmental and genetic factors, our patients develop malignancy more frequently. In our experience, the incidence of chronic pancreatitis has not come down in the state, but we feel that this impression is consequent on a comparative reduction in the number of the classical cases of "tropical pancreatitis" that we used to see earlier. There are now small series of cases reported from other parts of India, particularly Northern India, of "tropical pancreatitis" occurring in these regions^{28,29} Whether these cases truly conform to the "classical" features of "tropical pancreatitis", or they are simply "idiopathic pancreatitis" is a matter of speculation. It is noteworthy that almost all these populations are cassava non-eaters. If the cases of TP described from Northern India are true cases of TP, then it is an argument against cassava being a major etiological factor in TP. However, it has to be admitted that even in the heartland of tropical pancreatitis, Kerala, the classical picture of tropical pancreatitis is gradually fading and merging with the picture of idiopathic pancreatitis.

What causes tropical pancreatitis?

Now, we come to the important question, what causes tropical pancreatitis? We have to admit that, as of today, we do not know the exact cause/causes. The hypothesis that protein deficiency is the cause of TP held sway over a long period³⁰. Even though this is an attractive proposition, concrete proof is lacking to implicate protein deficiency as the sole, or even the major cause of TP³¹. The high carbohydrate content of cassava and its low protein value, together with its cyanogen content made the cassava hypothesis look a plausible one. Moreover, the close geographic association between cassava consumption and the prevalence of TP in many tropical countries support this hypothesis³². In dietary studies conducted by us in our earlier cohort of patients with

TP and age and sex matched controls from the same geographical region, the cassava intake did not show significant differences between the two groups (370 g/day Vs 309 g/day)¹⁰. Moreover, as mentioned earlier, TP is now reported from many parts of India where cassava is not consumed at all^{28,29}. Cyanogenic glycosides are tissue toxins, and it has been suggested that certain other foodstuffs consumed in these regions of India contain cyanogenic glycosides, or other similar tissue toxins. Tiescher and colleagues have also reported the absence of diabetes mellitus in rural West African population whose diet predominantly consisted of high starch cassava³³. Environmental toxins or pollutants also deserve attention as co-factors in the etiology. In fact, Braganza had proposed the "oxidant stress" theory of pancreatitis³⁴. According to this theory, the toxic effects of oxygen derived free radicals and lipoperoxidases can cause pancreatic damage. Exposure to xenobiotics, induction of detoxifying mixed function oxidases, and excess production of unmitigated metabolites and free radicals have been proposed to cause damage to cellular membranes. An imbalance between these toxic substances and antioxidants could lead to pancreatic injury. Deficiency of antioxidants such as vitamins A, C and E has been demonstrated in chronic pancreatitis³⁵. Alcohol itself has been shown to contribute to oxidant stress.

The observation by our pathologists that the pathological changes in the acini in TP are primarily an atrophy and that inflammatory changes are minimal, lend credence to a dietary etiology³⁶. Sandhyamani, from her observations on autopsy of patients with endomyocardial fibrosis and also from feeding experiments in bonnet monkeys described deposition of mucopolysaccharides (proteoglycans) in the walls of blood vessels and connective tissue and sclerotic changes in the blood vessels in different organs including the pancreas. She has dubbed these changes as a "muroid vasculopathy"^{37,38}. She attributes these changes to a dietary imbalance, or to be more precise, a high carbohydrate, low protein diet fed to her experimental monkeys. These changes were noticed irrespective of whether the source of the carbohydrate was cassava or corn starch. The findings in the pancreas in her autopsies in humans and in the experimental monkeys closely resemble the early changes in TP. It is noteworthy that in alcoholic pancreatitis in France, Sarles and colleagues observed that a high fat, high protein diet, and

next, a very low fat diet also, predisposed his patients to alcoholic pancreatitis²⁴. This also points to dietary imbalances as a cause for pancreatic damage. In our studies with the French group, we have recorded a high carbohydrate, low protein and very low fat diet in our patients from South India with TP^{11,39}. We had recorded our suspicion whether the low fat content in our TP patients would have made them more susceptible to develop pancreatitis. We also reported low pancreatic enzyme levels and high calcium and lactoferrin content in the pancreatic juice of even our normal controls and proposed the entity of a "subclinical pancreatopathy" in populations where the diets are not necessarily "inadequate", but are "unbalanced"¹¹. Such a subnormally functioning pancreas (with most likely, early structural changes too) must be prone to injury when another injurious agent/agents or insult supervenes. Even though there is no evidence so far that cassava could be a sole etiological agent for pancreatitis, its role as a cofactor (due to its cyanogen content) cannot be entirely ruled out. The fact that the poor and low middle class population of Kerala now eat lesser quantities of cassava than their predecessors and that the varieties that are cultivated and consumed now are less toxic ones could mean a lesser exposure to the cyanogen content than would have been the case earlier. This might partially explain the later age of onset of the disease now. In addition, there are cofactors now that were not significant a couple of decades earlier.

These cofactors could be consumption of moderate quantities of alcohol, smoking, environmental toxins or pollutants, oxidant stress or even an infection. As has been demonstrated in the case of the liver that even moderate alcohol consumption promotes oxidative stress in chronic hepatitis C (CHC) patients, suggesting a role for oxidative injury in the worsening of CHC evolution by alcohol⁴⁰, the pancreas also might be vulnerable to oxidant stress from moderate quantities of alcohol. These environmental stresses may be abetted and modified or facilitated by one or more mutations in genes such as SPINK 1, PRSS1, CFTR, or even some novel gene mutations as have been demonstrated^{41,42,43,44}.

The nature of the exposure to such combinations of injurious agents or factors, and the genetic make up of the individual, determine the type of pancreatitis one develops and also the phenotype. At one end of

this spectrum is the classical alcoholic pancreatitis; at the other, the classical tropical pancreatitis. In between these two, there could be a spectrum of a variety of manifestations of the disease depending on the combination of environmental stress and genetic make up. Thus, the etiology of chronic pancreatitis in general, and tropical pancreatitis in particular, we believe, is complex and multifactorial and may involve more than one environmental factor and may be modulated by polygenic influences. Alcohol, in doses less than that generally recognized to cause alcoholic pancreatitis, and varying degrees of smoking, may also add up as injurious agents, as seen in our intermediate group of so-called "social drinkers". In addition, the change in lifestyle that have occurred over the years in our state have resulted in a sizeable proportion of our chronic pancreatitis patients conforming to the definition of alcoholic pancreatitis. It should be noted that the majority of the alcoholics were smokers too.

A novel concept

Tropical pancreatitis is likely to be multifactorial, as the first author had observed 20 years ago⁴⁵, and perhaps, this is true for many other types of chronic pancreatitis. We believe, therefore, that the old sharp compartmentalization of alcoholic and tropical pancreatitis as two separate entities, poles apart, is now becoming slowly blurred. In alcoholic pancreatitis, even though alcohol is a predominant etiological factor, there are other possible co-factors such as smoking and diet (high fat, high protein diet) and genetic factors that contribute to hasten the onset of the disease process.

In the same way, in TP too the dietary imbalances (high carbohydrate high protein diet, low fat diet) and/or toxins in diet or atmospheric pollutants (xenobiotics), along with moderate amounts of alcohol and smoking and possible genetic influences are likely to be contributory to the pancreatic damage. Free radical stress should be a common factor for both TP and AP, though the causes may be different. We consider that in the case of TP, injurious agents such as alcohol, smoking dietary toxins, atmospheric pollutants and the resultant oxygen stress must be acting as the "second hit" on a pancreas that is already suboptimally functioning as a result of a "subclinical pancreatopathy". Both these

conditions (AP and TP) are two ends of a spectrum with a complex interplay of multiple injurious factors filling the gap between these extremes. And this intermediate region is represented by many patients in our current series of "tropical pancreatitis", which no more resembles the classical TP of old, but occurs in a more varied form in the not so young, fairly well-nourished, and occasionally alcoholic or smoking population whose diets may be unbalanced, who are exposed to a number of atmospheric or food toxins and who have varied genetic mutations or polymorphisms that make them prone to be victims of injury to their pancreas. Another region of this spectrum is occupied by the "idiopathic" type of pancreatitis. Thus, tropical pancreatitis is now moving closer to "idiopathic" pancreatitis, and the distinction between "idiopathic" and "tropical pancreatitis" is slowly fading and we are left fumbling to find new definitions for this enigmatic disease we now call "TP". This new paradigm compels us to shift our focus from searching for exclusive etiological factors for a chronic disease such as chronic pancreatitis, to a more broad and comprehensive understanding of a wide range of environmental toxins, dietary factors, environmental stresses, infections and genetic polymorphisms or mutations involving multiple genes, and also alterations in our genetic competence in handling such environmental stresses and challenges. We shall not consider chronic pancreatitis to result from a one-time "hit", but rather, occurring as a result of repeated and multiple insults to an organ that is made susceptible by different influences.

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Fig. 1. Picture of patient with tropical pancreatitis showing marked emaciation



Fig. 2. ERCP picture of tropical pancreatitis showing calculi, ductal dilatation, strictures and irregularity

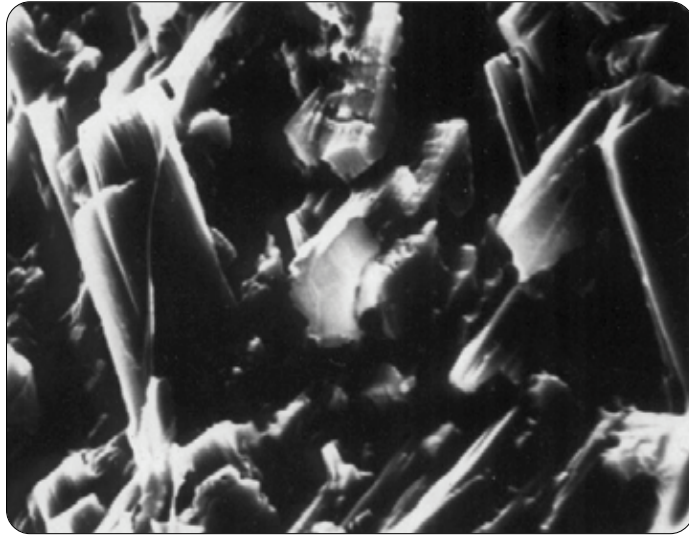


Fig. 3. Electron microscopy of pancreatic calculi from tropical pancreatitis showing heaps of calcium carbonate crystals

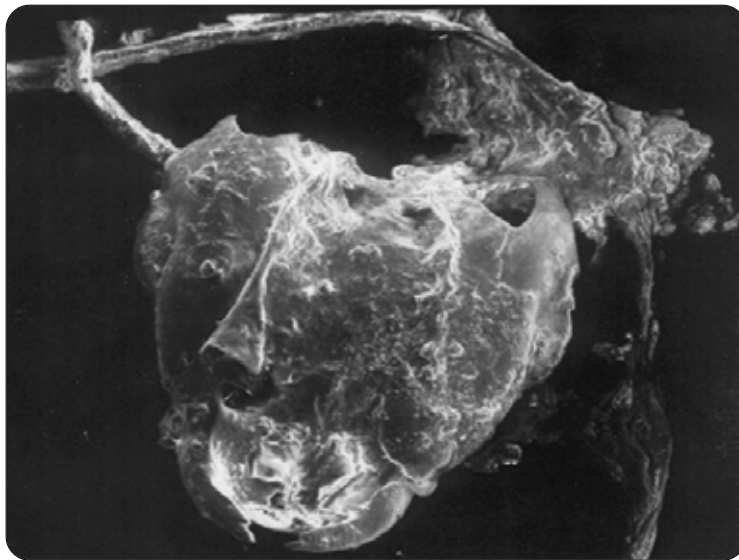


Fig. 4. Protein plugs from pancreatic duct showing fibres and amorphous deposits

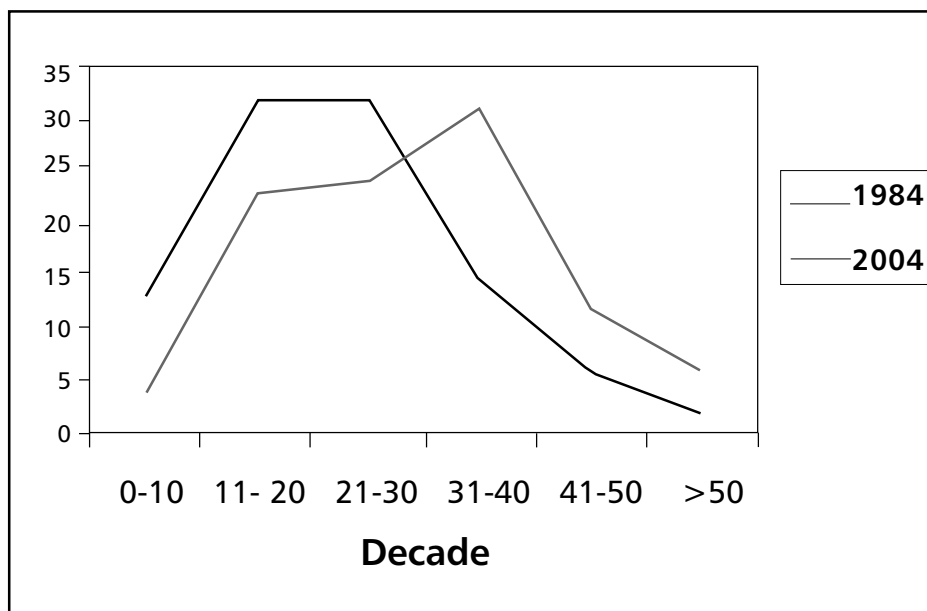


Fig. 5. Graph showing shift in the age of presentation of chronic pancreatitis patients

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