

**Chapter 21**

**Fibrocalculous pancreatopathy**

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## Summary

*Fibrocalculous Pancreatopathy is an enigmatic disease. In this article, I discuss my experience with examining the histological spectrum of these cases, over several decades. In some cases, especially the advanced stages of the disease, the pathology is quite characteristic. However, in a proportion of cases, the disease process seems to have reached a static phase, or a phase of arrest. These cases of arrested disease need to be studied in detail as they could provide interesting insights into the pathogenetic factors involved in the disease, and thereby offer new therapeutic targets for studying the illness.*

## Introduction

Fibrocalculous pancreatopathy was known earlier as fibrocalculous pancreatic diabetes (FCPD). As the name points out this is a type of diabetes where there is significant fibrosis of the parenchyma of pancreas and in addition, the ductal system reveals calculi. The term fibrocalculous pancreatic diabetes is preferred to fibrocalcific pancreatic diabetes, for this is an illness that is not associated with tissue calcification. This disorder has been noted in other developing countries. In India the disorder initially appeared to be almost restricted to southern parts.

Clinically these cases first present below the age of 30 years. Many of them present during the first decade of their life with recurrent attacks of abdominal pain and symptoms pointing to diabetes mellitus. The patients are poorly built and nourished with other features of malnutrition. The patient's blood examination shows moderate to severe hyperglycemia and usually requires insulin for control. Ketosis may or may not be present. There will be some amount of 'C' peptide secreted by the gland.

Radiographic demonstration of calculi in the ductal system of pancreas will confirm the diagnosis. Presence of stones in the pancreas can also be confirmed by ultrasonography. There seems to be two stages of this disorder. One is identified as "advanced" stage, while the other one is called "arrested". Cases of advanced disease will have classical symptoms and they will die of complications of diabetes. Cases of arrested diseases

will not manifest with diabetes and may die of some other disease. Subjects with arrested disease are detected accidentally by radiologists or by pathologists in autopsy room.

### **Gross Pathology**

Several workers have studied and described the features of the organ in this disorder. Pancreas is markedly shrunken in size, shape is distorted. The normal lobular appearance is lost. The capsule is thickened and opaque. Hence, the organ looks like a sac or bladder. There are no adhesions to the surrounding tissues and the consistency varies from cystic to hard. The tissue is tough to cut. Unopened specimens when examined radiologically show multiple stones in the ducts. Some of the specimens show radio-opacity of the mucoid material in addition to the stones. The duct can be probed easily through ampulla of Vater. On opening the organ along with the main duct one finds markedly dilated ducts and ductules. The parenchyma is reduced to a capsule-like structure. The ducts and ductules are filled with abnormal mucoid secretions. This material is thick and viscid. It may be transparent like mucus or could be cloudy. Stones are usually submerged in this mucoid material. There are no strictures. There is no area where the stones are blocking the lumen tightly. The dilatation is marked. At times, ducts show cystic dilatations. Ductal surface is smooth, shiny and free from any projections. At places the surface looks like parchment paper. At no point do the ducts show thickening of their walls. The stones vary in size. They could be as small as sand granules or as big as two centimeters in their length. Most of the stones have the configuration of the ducts. But they are not impacted. They are cylindrical or oval. Their ends are blunt. Occasionally the ends are faceted. Surface of stones could be granular, sticky or smooth. Some stones are light and moldable. They could be termed "putty stones". The color also varies. Some are dirty white and others chalky white.

### **Microscopy**

Microscopic examination reveals extensive fibrosis. Fibrosis is universal and not limited to one zone or area. It is intra and inter lobular. There is no periductal fibrosis, capsule is thickened. Small islands of parenchyma

are noted in fibrous bands. Fibrous tissue irregularly dissects the surviving lobules. The acini are markedly reduced in number. Wherever they are seen, they show some pink secretory material in the lumen. The acinar cells look smaller in size. The intercalated ducts show mild dilation with pink secretion. The intra lobular and inter lobular ducts are also less in number but dilated. They are bundled together to form clusters giving an apparent look of ductal proliferation. The lining epithelium of the ducts shows goblet cell metaplasia. The larger ducts in contact with stones show squamous cell metaplasia. The lumen of the ducts show inspissated, lamellated secretory material. At many places these mucoid plugs show layers of calcification. Acute or chronic inflammatory cells may be found in the mucoid secretions. The inflammatory cells are seen in the walls of the ducts in the periductal and parenchymatous areas. Lining epithelium may be denuded.

Islets of Langerhans are very distinctly seen in the background of sparse acini and ducts. Islets are found even in the hyalinised fibrous bands. At places they are almost strangulated. In some areas they are found in clusters of 10 to 20 islets. This seems almost like aggregation of portal triads in cirrhosis of liver. The cells in the islets look normal in size and appearance. The normal proportion of beta and alpha cells is also maintained. Nesidioblastosis is found much reduced. In short, total insular mass is decreased. No specific inflammation of islets to be identified as insulitis is noted.

Previously inflammation of pancreas was suspected. These observations made were on totally burnt out cases. However, Geeverghese had observed inflammation in the pancreas. As the workers studied the organs of patients in the early phases of disease, they confirmed the existence of inflammation. The inflammation noted in the organ is more a reaction to the damage done to pancreas. Therefore, one should not draw a conclusion of inflammation as a precipitating cause of this disease. Inflammation in this disorder comes at the time of the end-stage destruction of the pancreas and not at the beginning of the lesion.

The inflammatory cells are of mixed cellular type. Moreover, lymphocytes and plasma cells predominate. Occasionally lymphocytes are found forming germinal centers. Some nerve bundles are seen surrounded by

lymphocytes. Fibrous bands are also studded with lymphocytes. Inflammatory cells are noted in the lumen of ducts. In this disorder, only lithiasis is evident in the ducts and never parenchymal calcification. Similarly there is one more statement in the WHO report describing "Periductal" fibrosis. This again is to be corrected. In this disorder some how periductal fibrosis is minimal or absent. Therefore, the ducts are so much stretched and sac like or cystic. The fibrosis noted in this entity appears more in the parenchyma. Before venturing to explain pathogenesis it is necessary to understand the physiological facts about pancreatic exocrine secretions. Acinar cells secrete the enzymes in the form of zymogen granules. The granules are released into the lumen of the acini. This secretion, rich in enzymes, is viscid and slightly acidic. The flow of this material is very slow in the acini and also in the ducts. There is no peristalsis in the pancreatic ducts. The reason for absence of peristalsis is that there are no muscles in the wall of the ducts. Normally the secretion of exocrine part of pancreas should flow into the duodenum. For this, nature has designed a flushing system.

The epithelial cells of intercalated ducts and ductules are known to secrete very thin watery fluid, which is alkaline in reaction. The rate of secretion of this fluid is so fast that it can be called as a jet of fluid. This watery secretion is jetted into the lumen of acini and tubules. As a result, the viscid material gets diluted and easily flows into the main duct and finally into the lumen of the duodenum. This fluid is rich in calcium and contains a protein, identified by Sarles and Bernard. This protein is named as 'Lithostathine S' and keeps the calcium in soluble state in the pancreatic juice. Whenever there is lack of lithostathine, calcium will get precipitated. Furthermore, if this protein is degraded to lithostathine H<sub>2</sub>, it becomes insoluble and becomes fibrillar material. This material is also called as pancreatic stone protein (PSP) or pancreatic fibrillar protein (PFP). On the surface of such fibrillar protein calcium gets deposited. This is the genesis of pancreatic stones. Therefore, pathogenesis of pancreatic stones is different from lithiasis elsewhere.

There are several changes related to the pancreatic juice abnormalities: flow of the juice is sluggish, stagnation and stasis sets in, the intraluminal pressure increases and finally, there is distention and stretching up of acini, intercalated ducts, ductules and ducts.

With the knowledge of physiology and pathological findings one is inclined to think in the following lines about the probable pathogenesis of FCPD. Primary lesion appears to be in the epithelial cells of intercalated ducts and intralobular ductules. Still unknown or unidentified etiological agents act on these cells. These cells get damaged. As a result the watery alkaline secretion of these cells will be absent or reduced. The flushing out system fails. The enzymes secreted in the lumen of the acini are not drained. Pressure increases in the acini. Acinar cells stop functioning. Gradually they undergo pressure and disuse atrophy. The death of acinar cells invites inflammation and replacement fibrosis. The already secreted enzyme rich material gets pent up in the ductules and ducts. Therefore, abnormal secretory mucoid material in the lumen stretches the ducts and ductules. This secretion irritates the lining epithelium of ductal system. The result is metaplasia of ductal epithelium.

The primary injury to the ductal epithelial cells may also lead to inadequate secretion of lithostathine S protein. Whatever amount of lithostathine S is present in the secretion may get degraded to lithostathine H<sub>2</sub> which is insoluble in neutral or acidic pH. So this protein moiety gets precipitated in the ducts and ductules as protein casts. Marked reduction of lithostathine S automatically precipitates calcium carbonate in the pancreatic juice; thus there will be calcium precipitation on the surface of the mucoid proteinaceous casts. This gives eggshell like structure. Over this shell a coat of secretory material is formed. Again a layer of calcium carbonate precipitates.

Repetition of such a process forms lamellated stones in the lumen of the ducts. In those places where mucoid material is less abundant, calcium carbonate may continue to get precipitated without alternating layers of mucoid material. Such stones will be hard. Yellow or dirty yellow color of pancreatic stones can be due to mix up of epithelial cells. The over stretched ducts may give way at places allowing the secretory material to leak. This will be another cause of inflammation and fibrosis, in the intra and! interlobular places. So far the pathological changes observed in the gland could be traced out easily. Regarding the endocrine part of pancreas one can think as follows. As the inflammation and replacement fibrosis continues, acinar tissue

disappears. The existing islets of Langerhans will be left out in their places. Therefore, one may find the islets even in the fibrous bands. Disappearance of acinar tissue and contracting fibrosis seems to cluster up the islets in groups. These islets, either left out singly, or found in clusters, are surrounded by less vascular collagenised fibrous tissue. This may hinder the transport of secreted insulin to the blood circulation. Gradually deficiency of insulin is brought in. As the fibrosis continues, the diabetes becomes more and more severe. Because of disappearance of normal ductal epithelium natural processes of nesidioblastosis is hindered. Thus total insular mass is reduced.

The exocrine part will be reduced in mass. Hence, malnutrition starts manifesting. The chronic inflammation in the pancreas will explain the prominence of nerve bundles, ganglion cells, endarteritic changes, etc. This hypothesis was proposed as early as 1980 by the author. But pathogenesis of lithiasis was not explained satisfactorily. The identification of lithostathine S in normal pancreatic juice by Sarles and Bernard has given a scope to explain this aspect too. Now the etiological factor to initiate this pathology remains to be searched: nutritional deficiency, a viral infection or a toxin.

### **The enigma of the “arrested” FCPD**

At this juncture the discussion and understanding of arrested FCPD could be meaningful. These cases are really quite interesting. Usually patients with this disorder do not suffer from diabetes mellitus. They lead a normal life. The calculi in the pancreas are detected in routine X-ray examination or they are detected at autopsy accidentally. Macroscopically the pancreas shows a segmental involvement. The segment could be in any part of the pancreas. The ducts in the involved area show mild dilatation and small stones in the lumen. The parenchyma drained by those particular tributaries is fibrosed and shrunken. That part will be firm to feel and tough to cut. No abnormal juice is found in the ducts as seen in advanced cases of FCPD. Rest of the pancreas looks totally normal. Microscopy reveals mild dilation of ducts and fibrosis of parenchyma in shrunken part. These cases of arrested FCPD appear as an incomplete answer to an unknown problem. Their occurrence in the general population suggests that certain

etiological factors act on the pancreas to precipitate FCPD. The factor or factors start acting on a part of pancreas for some time and then they are withdrawn. Rest of the pancreas continues to function normally. Hence only a small segment of pancreas is affected.

Chart 1. Probable pathogenesis and pathology of FCPD

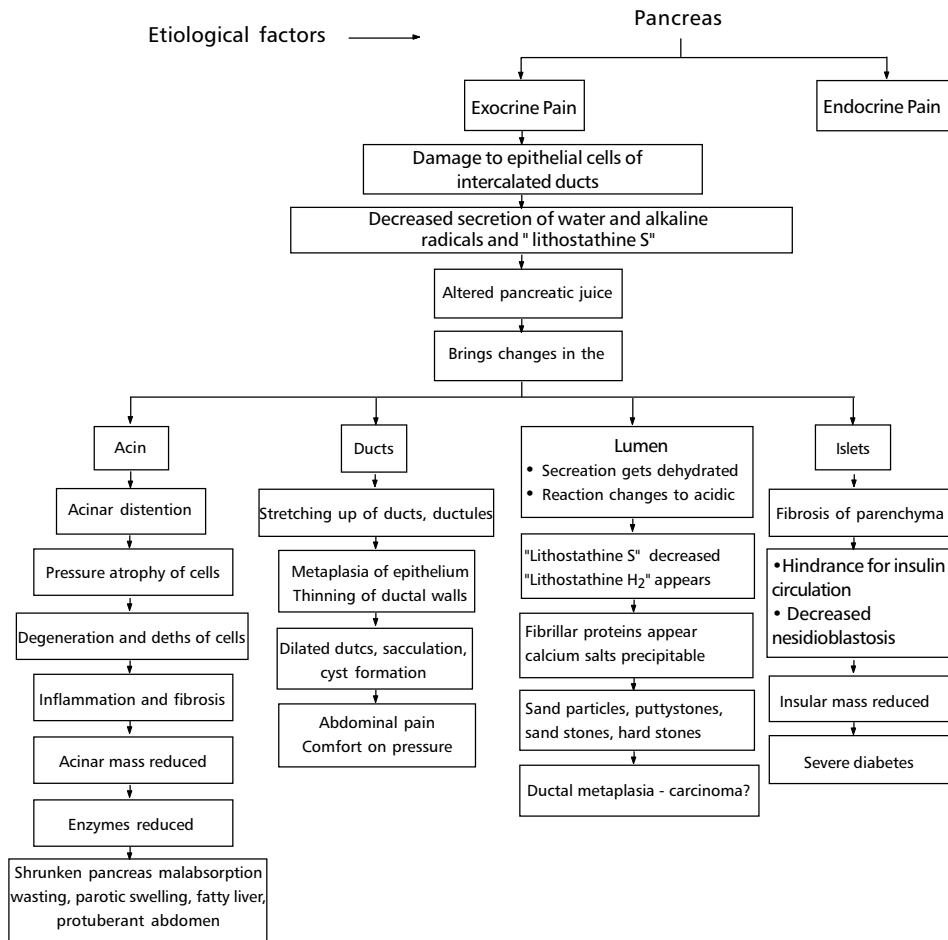


Fig. 1. Plain X-ray of upper abdomen. Note: Radio-opaque stones in the duct of pancreas.



Fig. 2. Autopsy specimen of pancreas and duodenum from a case of FCPD. Note: Loss of normal lobular pattern of pancreas. The organ looks like a bladder. Few adhesions are seen. Nodularity is seen. Consistency varied from cystic to stony hard.

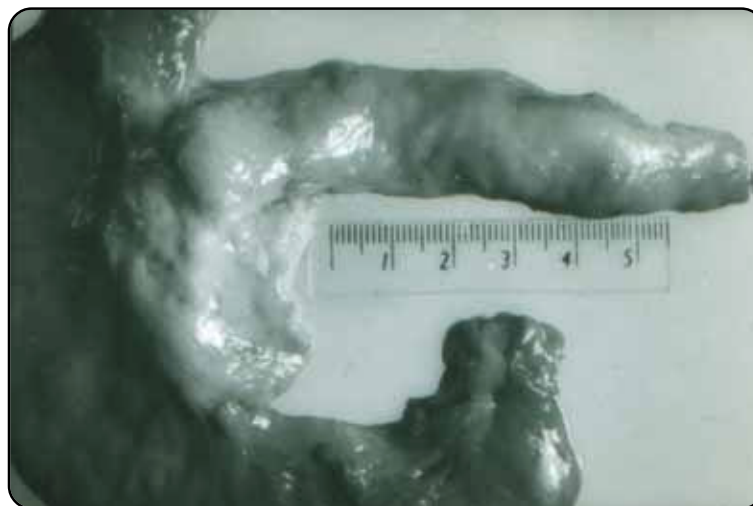


Fig. 3. Specimen of pancreas. Main duct is cut open. Large stones are seen from head to tail. Parenchyma is reduced to a flat ribbon. Main duct is markedly dilated. Opening of dilated tributaries can be seen.



Fig. 4. Specimen of pancreas along with duodenum. Close up view. Note: normal look of ampulla of Vater. Plenty of stones in the main duct.

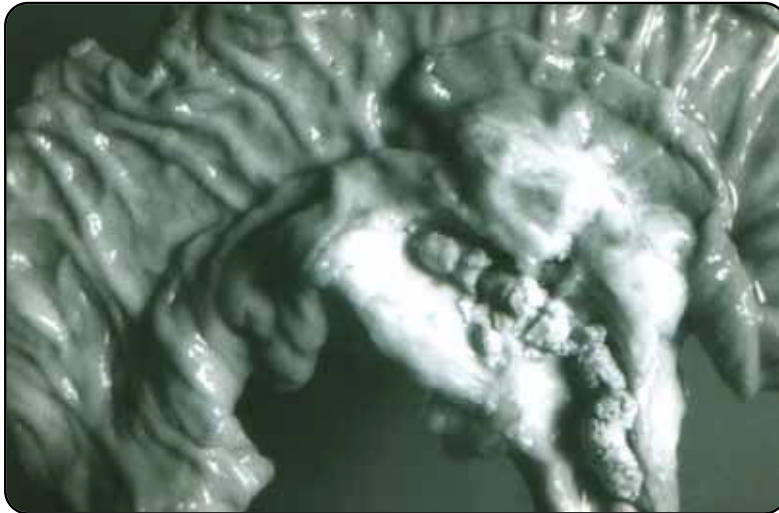


Fig. 5. Specimen of pancreas and duodenum.  
Dilated duct with stones. Litmus paper is to show acidic reaction of mucus.

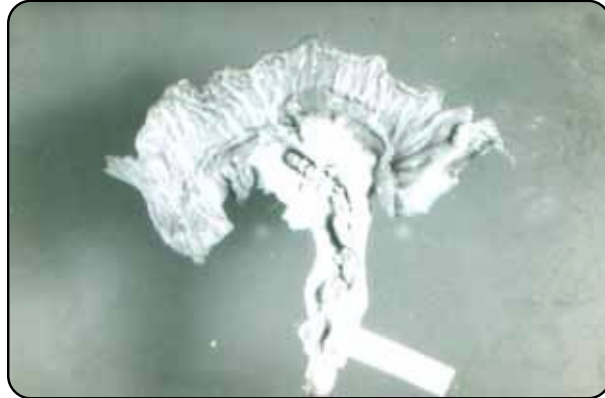


Fig. 6&7. Sections from pancreas from a case of FCPD. ( H & E. 100X).  
Dilated duct with denuded epithelium. Lumen shows formation of microscopic stone. There are inflammatory cells.

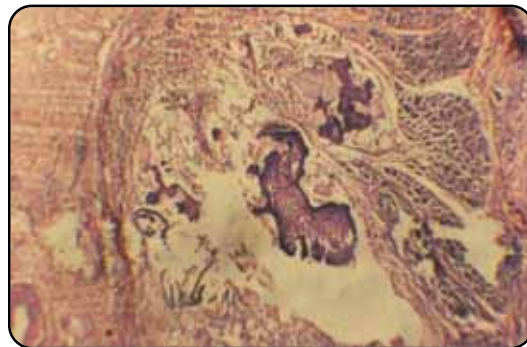
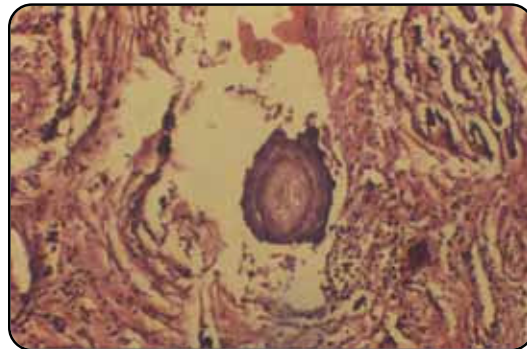


Fig. 8. Autopsy specimen of pancreas.  
Dilated duct, large stones. Plenty of mucus submerging the stones.  
Mucous is opalescent.

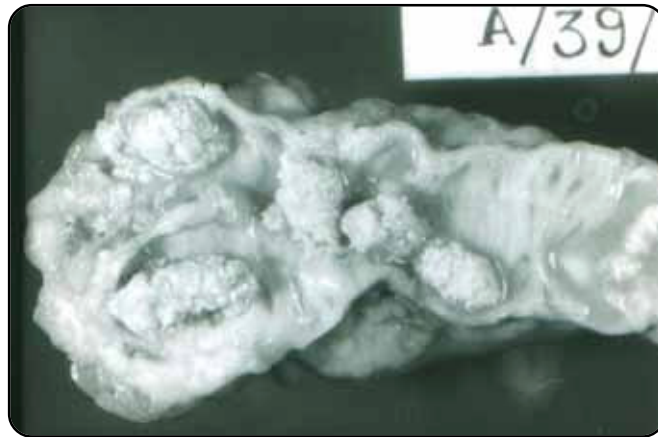


Fig. 9. Section from pancreas of a case of FCPD. (H & E - 100 X).  
Tiny lobule, plenty of fibrous tissue. Dilated ducts and ductules.

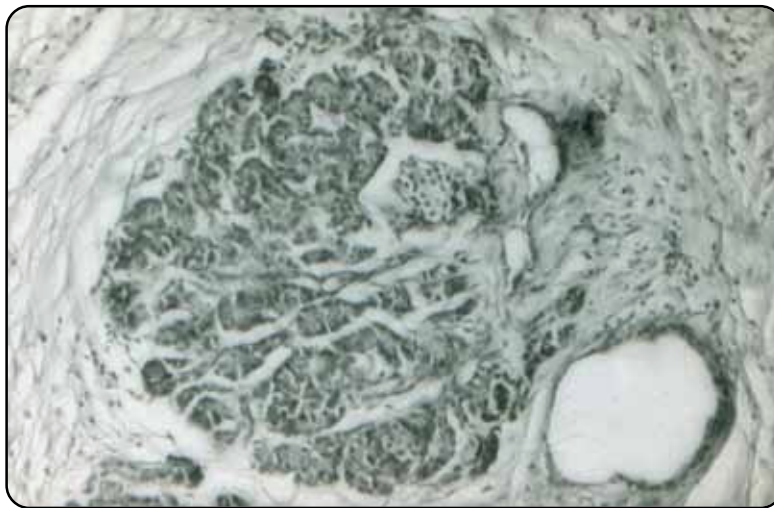


Fig. 10 & 11. Section from pancreas of a case of FCPD (H & E - 100 x)  
Fibrosis, aggregation of islets of Langerhans.

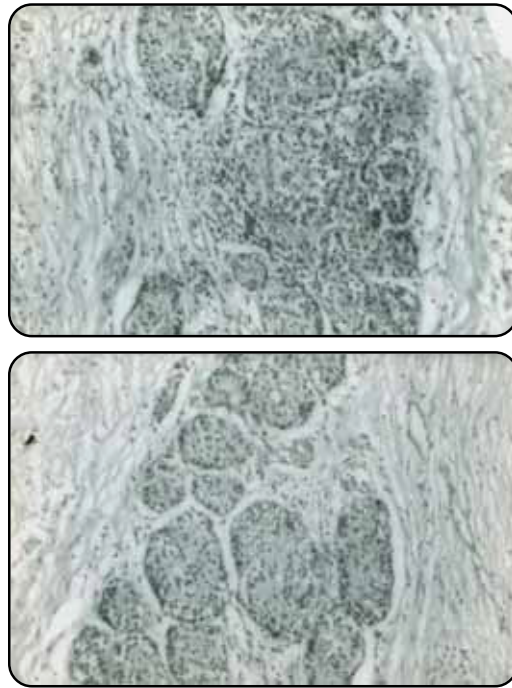


Fig. 12. Section from pancreas of a case of FCPD (H & E 100 x).  
Fibrous tissue. Nesidioblastosis seen around the ductules.

