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Clinico-Pathological Evaluation of 37 Cases of Cystic Fibrosis of the Pancreas in Infancy at Necropsy*

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Cystic fibrosis of the pancreas (mucoviscidosis) is a hereditary disease due to generalized dysfunction of the exocrine glands. It is frequent in children but is rare in adolescents and young adults. In fully manifested cases there is chronic pulmonary disease, pancreatic enzyme deficiency, abnormally high sweat electrolyte levels and, at times, cirrhosis of the liver. Partial involvement of the organs or glandular systems may lead to variations in clinical patterns.[1] Cystic fibrosis was first described as a distinct entity by Fanconi in 1936 and by Anderson in 1938.[2,3] Recent literature suggests that control of pulmonary infection, maintenance of good nutrition and adequate vitamins prolong the life of patients up to the age of 42 years,[4] although the number of such cases is not high.

The incidence of this disease varies in different countries; it ranges from 1/1000 to 1/3500 in live births.[3-5] A study carried out among live births in Turkey found the incidence to be 1/3000.[6]

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A few clinically diagnosed cases have previously been reported from our country.[7] The present study reviews autopsied cases with cystic fibrosis of the pancreas and evaluates the incidence of age and sex distribution, parental consanguinity, associated conditions and histopathological findings.

Materials and Methods

Five hundred and twenty five non-consecutive complete necropsies were selected from among those performed at Hacettepe Children's Hospital between the years of 1968 and 1974. Cystic fibrosis of the pancreas was diagnosed in 37 of the 525 necropsies. Data was collected from the patients' charts and additional sections from various tissues were studied.

Each pancreatic section was stained with hematoxylen-eosin, PAS (periodic acid-schiff), and trichrome methods. Furthermore, sections from the liver tissues were stained with Prussian blue for hemosiderin pigment. In statistical evaluation of age and sex distribution, the Chi square method was used.

Findings

A total of 37 cystic fibrosis cases were diagnosed histopathologically from 525 necropsies. Twenty four of these were male and 13 female. All of these were below the age of 2 years. Age and sex distribution of the cases are indicated in Tables I and II. It was noted that most of the cases were within the first 3 months of life. Excepting one case, all were diagnosed at autopsy. This finding suggests that when death occurs during the neonatal period or early infancy, the diagnosis of

TABLE I

AGE DISTRIBUTION OF CASES WITH CYSTIC FIBROSIS OF THE PANCREAS FROM 525 NECROPSIES

Age	Number of Necropsies	Number of Cases	Percentages of Cases
0 – 30 days	211	21	9.9
1 – 3 months	67	9	13.4
3 – 6 months	57	4	7.01
6 – 11 months	36	2	5.5
1 – 2 years	49	1	2.04
2 – 17 years	105	0	0
Total	525	37	7.04

TABLE II

SEX DISTRIBUTION OF CASES WITH CYSTIC FIBROSIS OF THE PANCREAS WITHIN 525 NECROPSIES

Sex	Number of Necropsies	Number of Cases	Percentages of Cases
Female	197	13	6.6
Male	328	24	7.3
Total	525	37	7.04

cystic fibrosis of the pancreas is necessarily based on autopsy findings.[8] Fourteen of the 37 cases had consanguinity among the parents and 10 cases had histories of sibling death.

Ten patients was admitted to hospital with complaints of respiratory system disorders. In eight cases the main complaints were of gastrointestinal system origin. Hypoalbuminemia was found in three cases. Co-existing diseases and malformation in the studied group are indicated in Table III.

TABLE III

COEXISTING DISEASES AND MALFORMATIONS IN 37 CASES WITH CYSTIC FIBROSIS

Diseases and Malformations	Number of Cases
Iso-immunization (ABO, Rh Incompatibility)	6
Undescended Testis	5
Anal Atresia	3
Congenital Heart Disease	3
Hydrocele	2
Meckel's Diverticulum	2
Pes Equinovarus	2
Down's Syndrome	1

Histopathologically, varying severity of changes in the pancreas was a common feature; all cases showed dilatation of acini and ductules and eosinophilic secretory precipitation. In 16 cases, varying degrees of fibrosis in the periductal and perilobular areas of the pancreas were found. There was increased mucus secretions, dilatation, flattening of epithelium

and precipitation in glands of the larynx and trachea in 30 cases, in Brunner and Lieberkühn's glands of gastro-intestinal system in 10 cases, and in salivary glands in 9 cases (Figures 1-4).

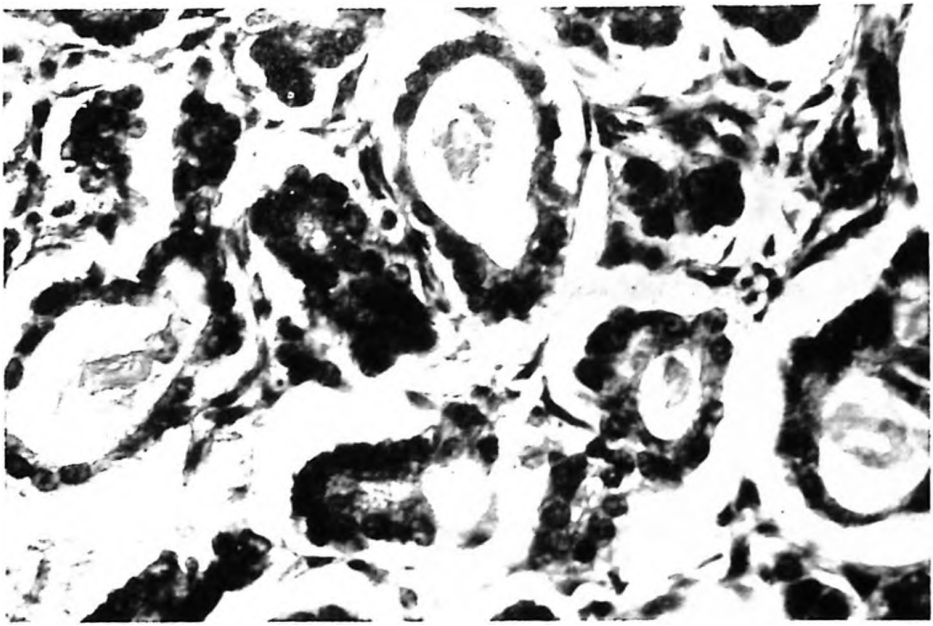

Figure 1
Pancreas: Cystic dilatation of the acini and precipitation of secretions of their lumina (Hematoxylin-eosin x 250).

Various pathological changes were observed in the lungs of all cases. These were bronchopneumonia in 28 cases, emphysema in 25, atelectasis in 19, bronchiolectasia in 12, abscess in 5 and bronchitis and bronchiolitis in 4 cases (Figures 5 and 6). Enlargement of pulmonary conus of the heart, flattening papillary muscles with right-sided heart dilatation, were noticed in 14 cases.

The liver revealed a fatty deposition in 18 cases and 14 had regional fibrosis in the perilobular areas. There was a slight degree of proliferation of the bile ducts in 9 cases. Focal biliary cirrhosis was seen in 3 cases only (Figure 7). Varying degrees of hemosiderin deposits were present in the livers of 30 cases.

Although the post-mortem examination was delayed a week in 7 cases in the studied group, intestinal mucosa and the villi were remarkably well preserved in all cases including these, without any evidence of autolysis.

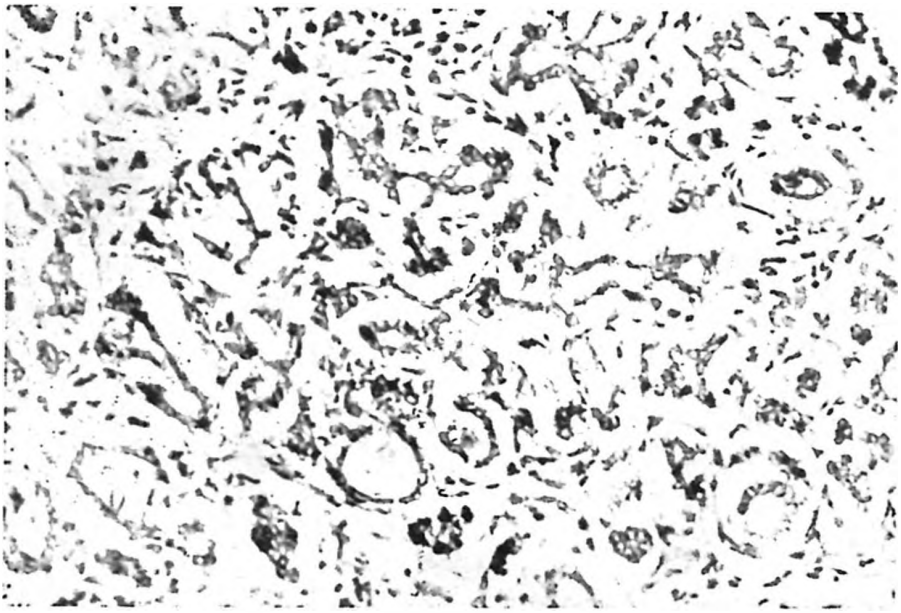

Figure 2

Pancreas: Cystic dilatation of the acini and minimal and interstitial fibrosis (Hematoxylin-eosin x 150).

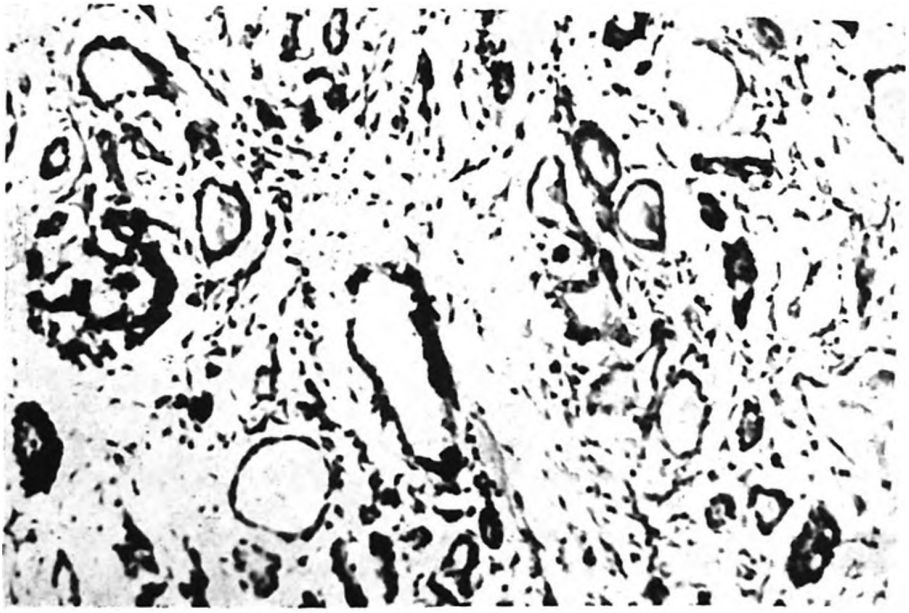

Figure 3

Pancreas: Mild interstitial fibrosis (Hematoxylin-eosin x 150).

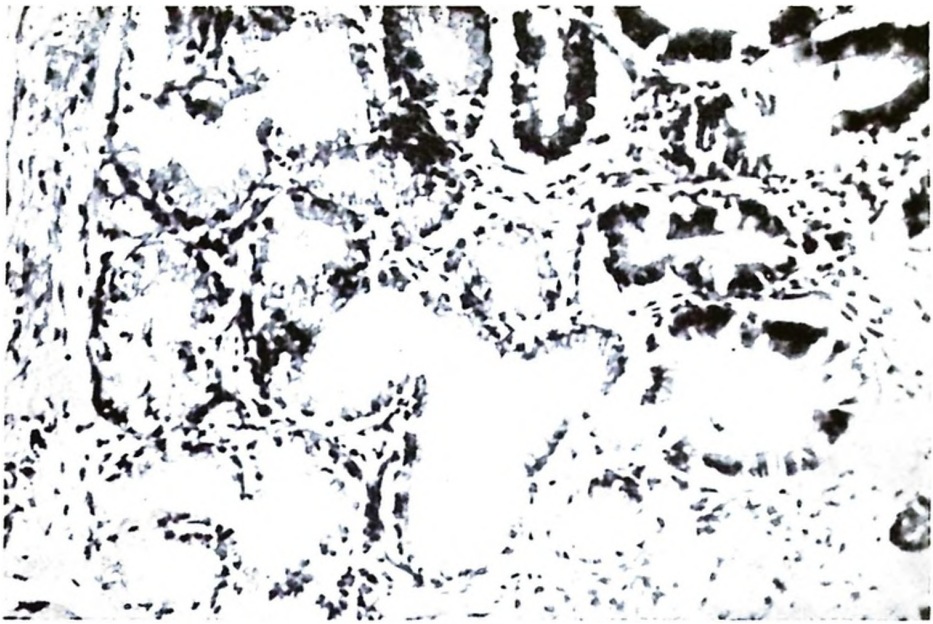

Figure 4
Duodenum: dilatation in Brunner's glands (Hematoxylin-eosin x 200).

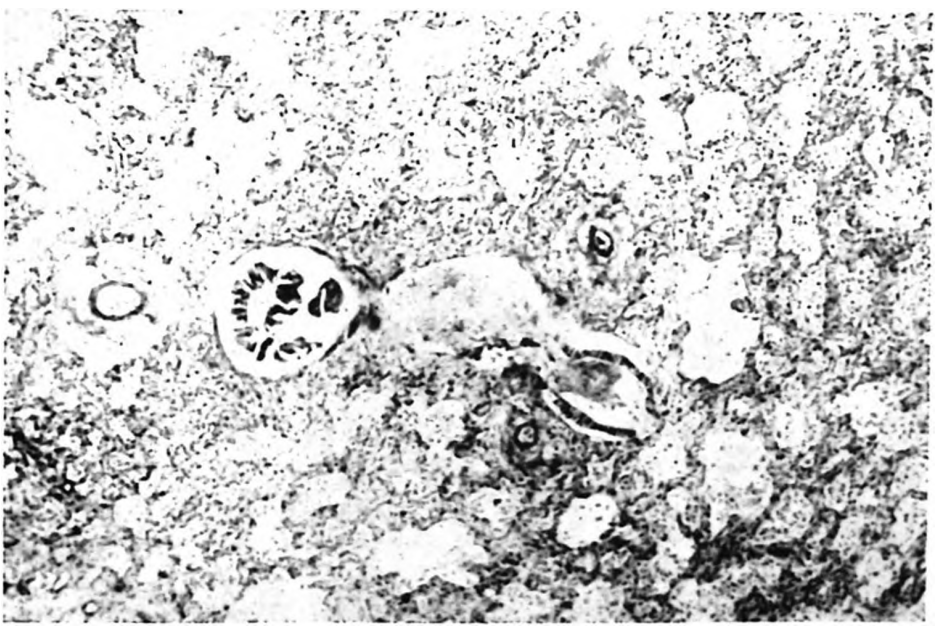

Figure 5
Lung: Bronchopneumonia and obstructive bronchiolectasia (Hematoxylin-eosin x 75).

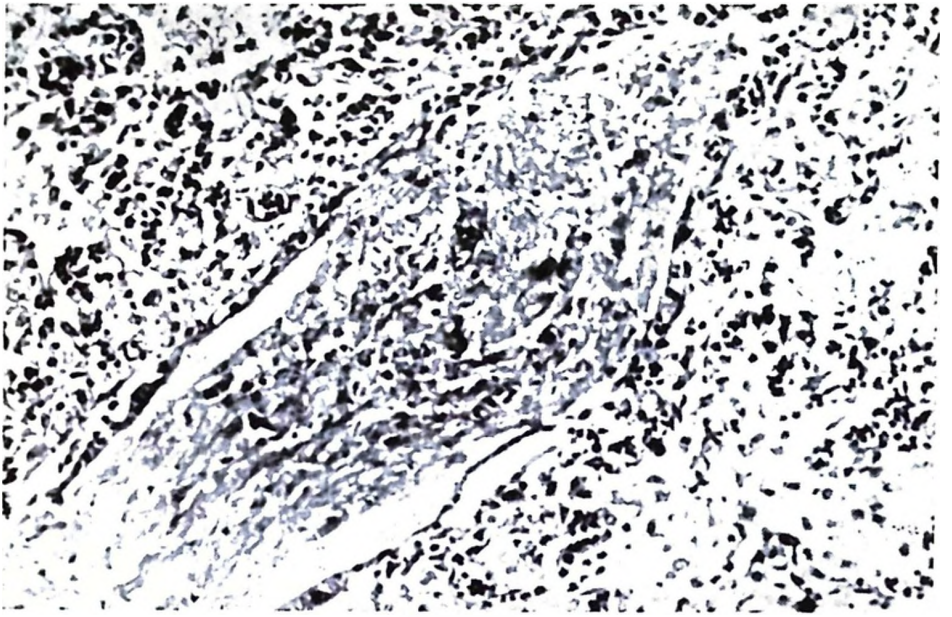

Figure 6
Lung: Obstructive bronchiolitis under high magnification (Hematoxylin-eosin x 200).

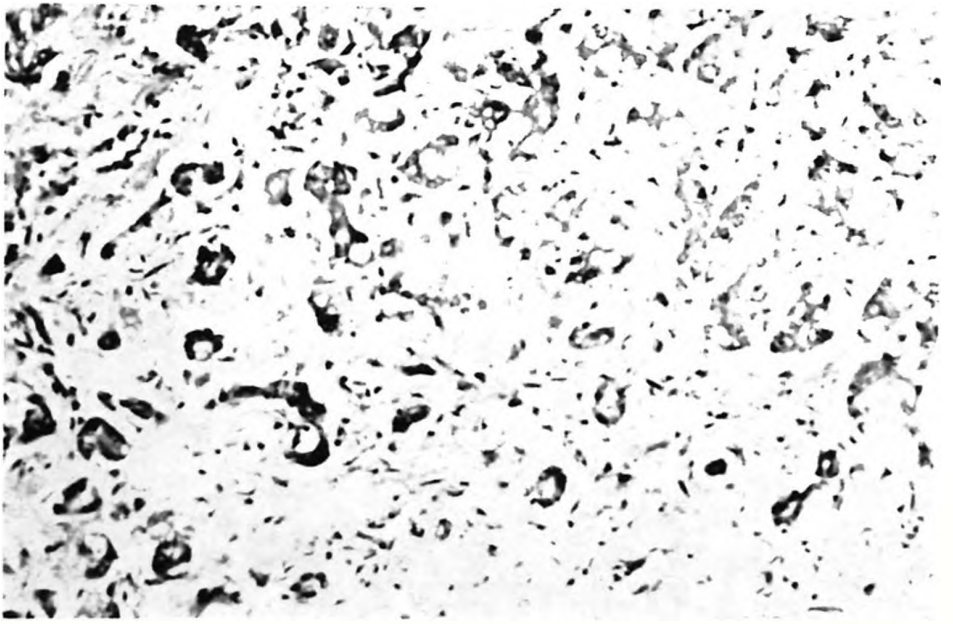

Figure 7
Liver: Prolification of the bile ducts and early cirrhosis.

Sections were obtained from the reproductive gonads of all males and an increased amoung of fibrosis was observed in the interstitial tissues in 7 out of 24 cases.

In 4 cases there was generalized cytomegalo virus infection which showed typical cells.

Discussion

The incidence of cystic fibrosis of the pancreas at necropsy ranges from 2 to 4 % in literature.[9-11] In our autopsy study in which the cases were all infants the incidence was found to be 7 %. The high incidence of disease and the age range of patients may be due to a variety of conditions such as high frequency of marriages among relatives, which is reported to be 20 % in the Turkish population,[12] poor nutrition, poor care of infants, frequent infections and the low socio-economic background of patients. Infants affected by such factors usually become critically ill and perhaps preclude the early clinical diagnostic studies.

Although it has been reported that this disorder occurs more frequently in males than in females,[13, 14] generally no sex difference is accepted in the incidence. No statistically significant correlation with the patients' sex was demonstrated in our series.

Chronic pulmonary disease dominates the clinical picture in cystic fibrosis.[9, 15, 16] In our group, all cases had some pulmonary system findings at autopsy and in 10 of these the initial clinical symptoms seemed to be pulmonary.

Symptoms of malabsorption and infections of the gastro-intestinal tract were present in 8 cases; thirteen cases had both complaints and findings of respiratory and gastro-intestinal system disorders.

About 5 to 10 % of patients with cystic fibrosis have meconium ileus.[8, 9, 17] Furthermore, intussusception, volvulus and ileal atreasia are seen in patients with cystic fibrosis.[8, 18, 19] Three cases with anal atresia and 2 cases with Meckel's diverticulum were observed in our series. The cases with meconium ileus were excluded from this study.

Rectal prolapse, inquinal hernia, hydrocele and undescended testis coexist with cystic fibrosis.[7, 8, 20, 21] In our series there were 2 cases with hydrocele and 5 with undescended testis.

Prolonged jaundice, ABO and Rh incompatability are frequently reported in cystic fibrosis of the pancreas.[22-24] Six cases with isoimmunization were noticed in our study. Associated Down's syndrome is

reported more frequently than should be expected with cystic fibrosis.[5] In our series, there was only one case of Down's syndrome in which the diagnosis was confirmed by chromosomal analysis.

Generally, serum proteins levels are normal in cystic fibrosis but edema secondary to hypoproteinemia has been reported.[9, 25, 26] In our study, hypoproteinemia was found in 3 cases.

In two cases, cystic dilatation of acini were confined to the pancreas, one of which was a twin. The other twin showed dilatation of mucous glands in other organs in addition to the pancreatic changes. Kwashiorkor, thymus dysplasia and chronic uremia were excluded from this study since these disorders may cause pancreatic acini changes which resemble cystic fibrosis of the pancreas.[8, 27, 28]

Microscopically, the lung findings revealed a similarity to the findings of patients in the same age group in literature.[9, 10, 15, 16, 29, 30]

Recognition of corpulmonale was less than expected and this could be explained by the fact that our patients died in the early months of life, before the development of such a disorder. Incidence of focal biliary cirrhosis is reported as 2 to 20 % and this abnormality was seen in 3 of our cases.

A varying degree of hemosiderin pigment was found in the liver of 30 out of 37 cases. Hemosiderosis in liver was also found by others,[29] which may be due to metabolic dysfunction caused by the disorder.

Dilatation and distention in mucous glands of gastro-intestinal tract are seen in cystic fibrosis;[30, 31] in our group, it occurred in 10 cases. Interestingly, even though the post-mortem examinations were delayed a week in 7 cases, all of these cases showed well preserved intestinal mucosa, which may be due to pancreatic achylia.[27]

The absence of vas deferens has also been reported in cystic fibrosis.[32-34] It was not observed in any of our cases and the cause of this might be the technique of the post-mortem examination employed in our series. Interstitial fibrosis in the epididymis was noticed in 7 cases, however. Viral and fungal infections were also reported in cystic fibrosis of the pancreas and in our study there were 4 generalized cytomegalo virus infections and 2 generalized deep fungus infections due to Candida.

Summary

The clinical and morphological findings of 37 cases of cystic fibrosis of the pancreas from 525 full, but non-consecutive necropsies are presented. All of these 37 cases were diagnosed at post-mortem examination. The autopsy incidence was 7 % and none of the cases was beynod two

years of age. Morphological findings revealed varying severities in organ involvement in all cases, with absence of fibrosis of the pancreas in some. In only two cases histopathological changes seemed to be confined to the pancreas. This study suggests that cystic fibrosis plays a considerable role in infant deaths in our country and in most if not all cases the diagnosis must necessarily be based on postmortem studies.

REFERENCES

1. di Sant'Agnese, P.A.: Cystic fibrosis. Textbook of Pediatrics. Edited by Nelson, W.E., Vaughan, V.C., and McKay, R.S. W.B. Saunders Co. 1969, p. 856.
2. Guide to Diagnosis and Management of Cystic Fibrosis. Cystic Fibrosis Foundation, Atlanta, Ga., 1971, p. 1.
3. Hall, B.D., and Simpkiss, M.J.: Incidence of Cystic Fibrosis. Proc. 5th Int. Cystic Fibrosis Conf. Churchill College, Cambridge, 1969, p. 82.
4. Wright, S.W.: Racial Variations in the Incidence of Cystic Fibrosis. Proc. 5th Int Cystic Fibrosis Conf. Churchill College, Cambridge, 1969, p. 91.
5. Warwick, W.J.: Infant screening for cystic fibrosis, a critical review of methods and results. Proc. 13th Int. Congr. of Pediatrics, Vienna, 1971, p. 101.
6. Gürson, C.T., Sentel, H., Gürkan, M., and Pala, S.: Newborn screening for cystic fibrosis with the chloride electrode and neutron activation analysis. Helv. Paediat. Acta. 28: 165, 1973.
7. Hatemi, N.: Kistik Pankreas Fibrozu. Medicina, Roche, 2: 1972.
8. Oppenheimer, E.H., Eateryly, B.J.R.: Cystic fibrosis of the pancreas. Morphologic findings in infants with and without diagnostic pancreatic lesions. Arch. of Pathol. 96: 149, 1973.
9. di Sant' Agnese, P.H.: Cystic fibrosis. Am. Fam. Physician 7: 102, 1973.
10. di Sant'Agnese, P.A., Talome, P.C.: Pathogenesis and physiopathology of cystic fibrosis of the pancreas. New Eng. Med. J. 277: 1287, 1344, 1399, 1967.
11. Morison, J.E.: Foetal and neonatal pathology. 2nd ed., Butterworths Co., London, 1963. p. 305.
12. Say, B., Tunçbilek, E., Balcı, S., et al.: Türk Halkında Çeşitli Kongenital Malformasyonların Görülme Sıklığı. Hacettepe Üniversitesi Tıp Fakültesi ve Ankara Doğumevi Müşterek Araştırması. 1971, p. 27.
13. Danks, O.M., Allen, J., and Anderson, C.M.: Genetic study of fibrocytic disease of pancreas. Ann. Human Genet. 28: 323, 1965.
14. Smoller, M., and Assia, D.Y.: Studies on genetic mechanism of cystic fibrosis of pancreas. Am. J. Dis. Child. 98: 277, 1959.
15. Siassi, B., Moss, J.A. and Dooley, R.R.: Clinical recognition of corpulmonale in cystic fibrosis. J. of Pediatr. 78: 794, 1971.
16. Esterly, J.R., Oppenheimer, E.H.: Observations on cystic fibrosis of the pancreas; pulmonary lesions. Johns Hopkins Med. J. 122: 94, 1968.
17. Thomaidis, T.S., Arey, J.B.: Intestinal lesions in cystic fibrosis of pancreas. J. of Pediatr. 63: 444, 1963.
18. Hodson, W.J.: Intestinal obstruction in an adult suffering from mucoviscidosis. Brit. J. Surg. 56: 472, 1969.

19. Seliger, G., Firooznia, H., and Genieser, N.S.: Intestinal obstruction on adult with cystic fibrosis. Digestive Disease. 27: 10, 1972.
20. Schwachman, H., and Holschlow, D.: Examination of the appendix at laparotomy as a diagnostic clue in cystic fibrosis. J. of Pediatr. 286: 1300, 1972.
21. Holsclaw, D.S.: Increased incidence of inguinal hernia, hydrocele uand undescended testicle in males with cystic fibrosis. Pediatrics. 48: 442, 1971.
22. Taylor, W.F., and Ququndah, B.Y.: Neonatal jaundice associated with cystic fibrosis. Am. J. Dis. Child. 23: 161, 1972.
23. Volman, H.B., France, W.F., and Walis, P.G.: Prolonged neonatal jaundices in cystic fibrosis. Arch. Dis. Child. 46: 805, 1971.
24. Rickham, p. p., and Johnson, J. H.: Neonatal surgery. Butterworths Co., London, 1969, 366.
25. Milunsky, A.: Cystic Fibrosis and Down's Syndrome. Pediatrics. 42: 501, 1968.
26. Lee, P.A. et al: Hypoproteinemia and anemia in infants with cystic fibrosis. J. A.M.A. 288: 585, 1974.
27. Tınaztepe, K., Tınaztepe, B., Say, B.: Pancreatic Changes associated with cases of thymic dysplasia. Turkish J. Pediatr. 17: 19, 1975.
28. Castleman, B., Scully, R.E.: Intestinal pneumonities after a renal transplantation. New Eng. J. Med. 288: 570, 1973.
29. Porta, E. A., Steni, A. A. and Patterson, P.: Ultrastructural changes of the pancreas and liver in cystic fibrosis. Am. J. Clin. Path. 42: 451, 1964.
30. Esterly, N. B., Oppenheimer, E. H.: Observation on cystic fibrosis of the pancreas. A. J. Dis. Child. 123: 200, 1972.
31. Falchuk, Z. M. and Taussig, L. M.: IgA synthesis by jejunal biopsies from patients with cystic fibrosis and hereditary pancreatitis. Pediatrics. 51: 49, 1973.
32. Valmen, H. B., France, N. E.: The vas deferens in cystic fibrosis, Lancet. 2: 566, 1969.
33. Kaplan, F., Shwachman, H., Perlumutter, A. D., Rule, A., Khaw, K. T., Holschlaw, D. S.: Reproductive failure in males with cystic fibrosis. New Eng. J. Med. 279: 65, 1968.
34. Holschlaw, D. S.: Cystic fibrosis and fertility. Brit. Med. J. 3: 356, 1969.