Patología Vol. 18 pp 167-181
Impreso en México

CYSTIC FIBROSIS IN MEXICAN CHILDREN
A Report of 32 Cases in 3260 Consecutive Pediatric Autopsies

Eduardo López-Corella, Cecilia Ridaura-Sanz, Guillermo López-Cervantes
Department of Pathology, Instituto Nacional de Pediatría DIF, México City (ELC, CRS)
Department of Pathology, Hospital del Niño DIF del Noroeste, Hermosillo, Son. Mexico (GLC)
Address for reprints:
Dr. López Corella, Servicio de Patología, Instituto Nacional de Pediatría DIF
Insurgentes Sur 3700-C, México 22, D.F. MEXICO.

SUMMARY

Cystic fibrosis accounted for 0.98% of 3260 consecutive pediatric autopsies collected over ten years. The patients ranged from newborn to four years of age. Pancreatic pathology was the criterion for selection and the possible significance of different patterns of pancreatic damage is discussed. Two cases had segmentary biliary cirrhosis and portal fibrosis was found in eleven patients. Lung abscess and/or bronchiectasis were present in twelve patients. The accuracy of the clinical diagnosis, low in the early years, improved as more cases were identified at autopsy. Cystic fibrosis should be expected in populations with caucasian admixture such as Latin Americans and our findings, as well as others in the regional literature reviewed herein, support this prediction. Lack of awareness of the disease, intercurrent environmental pathology and the early mortality of affected children are probably the reasons for its infrequent identification in Latin America. (Patología (Méx) 18: 167-181, 1980).

RESUMEN

La mucoviscidosis representó el 0.98% de 3260 autopsias pediátricas consecutivas recolectadas a lo largo de diez años. La distribución por edad de los pacientes se extendió desde recién nacidos hasta la edad de cuatro años. El criterio de selección fue la alteración del pancreas y se discute el posible significado de los diferentes patrones de daño pancreatico encontrados. La patología encontrada en otros órganos fue: cirrosis biliar segmentaria en dos pacientes, fibrosis portal moderada en once y bronquiectasias y/o abscesos pulmonares en doce. El diagnóstico clínico de mucoviscidosis fue establecido con mayor frecuencia a medida que se fueron informando en la autopsia casos con este tipo de patología. Es de esperar un número significativo de casos de mucoviscidosis en poblaciones con mezcla de caracteres caucásicos como la latinoamericana y nuestros hallazgos, así como otros en la literatura médica de la región y que aquí se comentan, apoyan esta predicción.
La falta de conocimiento sobre la enfermedad, la patología intercurrente relacionada con el medio y con las condiciones socioeconómicas así como la temprana mortalidad de los niños afectados son probablemente las razones para su excepcional identificación en America Latina.

INTRODUCTION

Cystic fibrosis (Mucoviscidosis), acknowledged as the most common lethal or semi-lethal genetic disease among the Caucasian population, has been sparingly mentioned in Latin American children. Recent comprehensive reviews[1-4] summarizing the impressive amount of knowledge collected over the last decades give abundant epidemiologic information on white populations and mention the poorly known but clearly lower incidence among non-whites, including American Indians, Africans, Japanese, Malaysians, etc. Latin American populations are not mentioned. This is surprising in view of the fact that Latin American mestizo, stock probably represents the world's most numerous population group of mixed European ancestry. This paucity of information is in large measure to be blamed on the Latin American medical community that has not produced the necessary figures. Reference is seldom made to cystic fibrosis in the Latin American medical literature and the disease is widely believed to be extremely infrequent. Isolated reports to the contrary have not received adequate attention[5-8] and quantitative data are scarce[9-16].

It is the purpose of this paper to report on the autopsy incidence of cystic fibrosis in a Mexican pediatric hospital and to suggest the reason for its poor impact on medical thinking in Latin America.

MATERIAL AND METHODS

The Instituto Nacional de Pediatría DIF (formerly "Hospital del Niño IMAN") is a 350 bed general pediatric hospital serving mostly the low income population in southern metropolitan Mexico City up to the age of 18 years. Both urban and rural populations are represented. It covers all pediatric specialties, has an annual admission rate of 7 600, attends approximately 25 000 patients a year in the outpatient clinic and has an annual mortality rate of about 580 deaths. Permission to perform autopsies is actively sought for all deceased patients, including those dead on arrival, about 350 autopsies are performed each year amounting to 60% of the overall mortality. Autopsies are in no way selected in terms of their "clinical interest" although some selection is introduced by differing policies as to patient admission and discharge by the different clinical departments.

This study is based on 3 260 consecutive autopsies performed between December 1970 and September 1980. Cases selected displayed diffuse pancreatic changes diagnostic of cystic fibrosis beyond all reasonable doubt. The changes observed are those widely recognized and recently reviewed by Oppenheimer and Esterly[17] and include inspissated secretions, fibrosis and atrophy. Patients with meconium ileus were included regardless of pancreatic histology. Criteria for selection were set deliberatly strict in order to select a group of cases with a high certainty of diagnosis. Cystic fibrosis is defined by abnormal sweat electrolytes and pathologic changes may not be absolutely pathognomonic. Several cases with changes considered suggestive of cystic fibrosis, even with strongly supportive clinical histories or with typical features in other organs but without conclusive pancreatic changes were not included in the present study. With these criteria we feel justified in stating that this selec-

tion represents a minimal figure of anatomically documented cases of cystic fibrosis in our autopsy material.

Clinical histories, slides, wet tissue, gross photographs and a complete autopsy protocol were available in all cases. A detailed clinical and pathologic description of case material lies beyond the scope of this paper. Emphasis will be on frequency, but other selected features will be briefly mentioned.

RESULTS

General information on frequency, age and sex distribution.- Thirty two cases of cystic fibrosis occuring in 3 260 autopsies represent a frequency of 0.98%. All of our patients were less than 6 years of age and accounted for 1.2% of all cases up to this age. Twenty-seven cases were under one year of age likewise representing 1.2% of all autopsies in this age group. Our oldest patient was 4 years of age. Twelve patients were less than one month old, of these four had meconium ileus and another had yeyunal atresia.

Twenty-one of our patients were boys and eleven were girls. This male/female ratio of 1.9 exceeds the 1.3 male to female ratio in our autopsy population up to the age of six. This male predominance did not hold for cases of meconium ileus in which 3 of the 4 were female.

Selected pathological features.- All cases had changes in mucous glands of the respiratory and digestive systems consistent with cystic fibrosis.

Pancreas: Diffuse pancreatic changes of cystic fibrosis were present in all cases including those with meconium ileus. Representative fields of pancreatic histology are documented for each case in Figs. 1-32.

Two patterns of pancreatic involvement were identified. In a minority of the cases (1, 10, 15, 23, 24, 32), there was preferential involvement of large ducts with the production of thick calculous casts of secretion; in all these cases small ducts and acini were also involved although to a lesser degree. Patients with changes only in large ducts were not included in the series because of the possibility of an obstructive process unrelated to cystic fibrosis. In twenty six cases both large and small ducts as well as acini were involved with thick inspissated secretions forming calculous structures in eight of the cases. Sixteen cases in this group had involvement of a moderate degreee (2, 7, 8, 9, 11, 12, 13, 17, 18, 22, 24, 25, 26, 28, 30, 31), whereas ten cases (3, 4, 5, 6, 14, 16, 19, 20, 21, 27) were found with advanced changes. Of the four cases with meconium ileus, two (12, 22) each aged 3 days, showed moderate involvement and two (3, 5) aged 8 and 4 days, showed advanced changes. Table 1 correlates the degree of pancreatic damage with the age of the patients.

Liver: The features of liver tissue in 31 of the 32 patients were evaluated separately with regards to portal changes, fatty infiltration and cholestasis.

TABLE 1

PANCREATIC CHANGES IN CYSTIC FIBROSIS

Correlation of severity with age.

LESION	AGE 0-1 mo.	1-12 mos.	Over 12 mos.	TOTAL
Moderate	10(2)*	4	2	16
Advanced	2(2)*	7	1	10
Calculous	0	4	2	6
TOTALS	12	15	5	32

* Numbers in parenthesis refer to cases with meconum ileus

TABLE 2

LIVER PATHOLOGY IN CYSTIC FIBROSIS

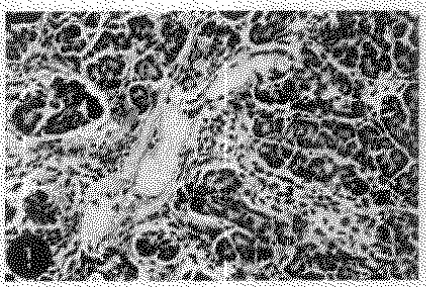
Correlation with age and pancreatic involvement

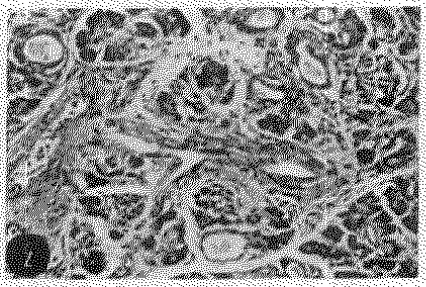
HEPATIC LESION	CASES	0-1 mos	1-12 mos	Over 12 mos	PANCREATIC INVOLVEMENT Moderate	advanced	calculous	Fatty liver
Biliary cirrhosis	2	1	1	0	0	2	0	0
Portal Fibrosis	11	3	6	2	5	2	4	4
Non Specific	18	8	7	3	10	6	2	6
TOTAL	31	12	14	5	15	10	6	10

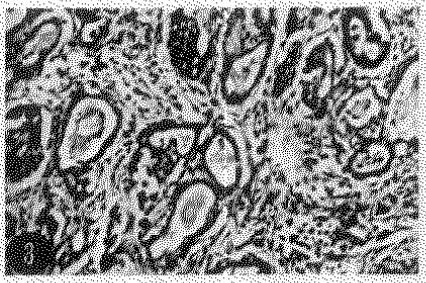
TABLE 3

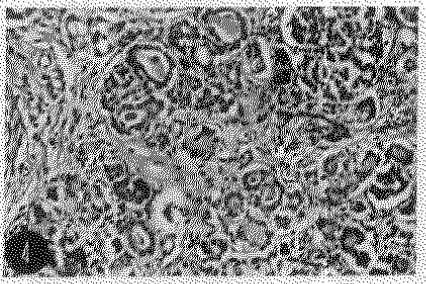
PULMONARY PATHOLOGY IN CYSTIC FIBROSIS

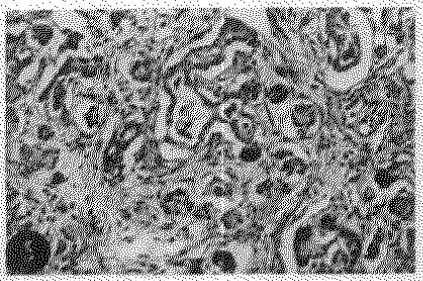
	AGE 0-1 mo	1-12 mos	Over 12 mos	TOTAL
Bronchiectasis	0	5	2	7
Abscess	0	4	1	5
Bronchopneumonia	5	3	1	9
Normal	4	0	1	5
Unrelated	3	3	0	6
	12	15	5	32

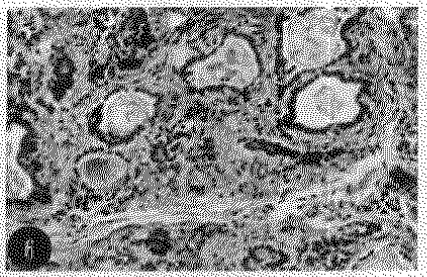


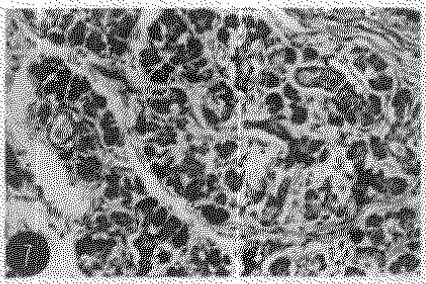


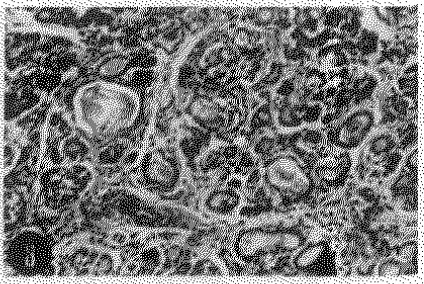


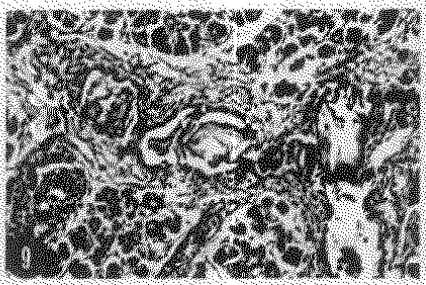


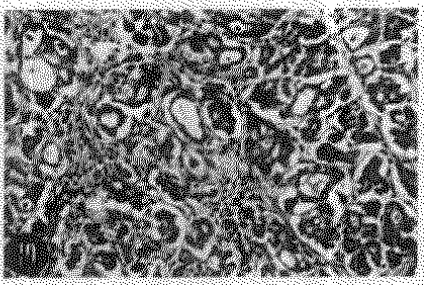


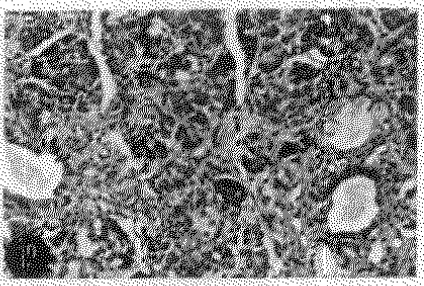


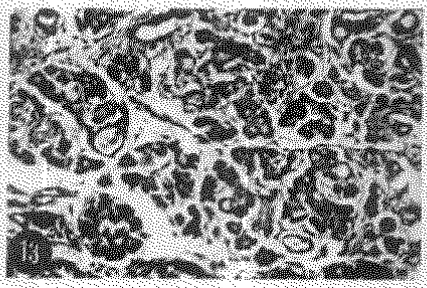


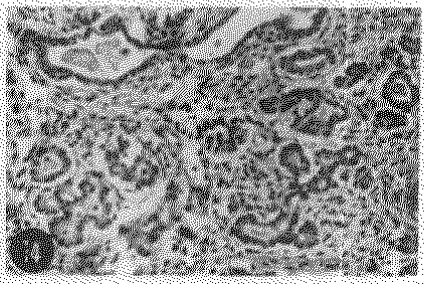


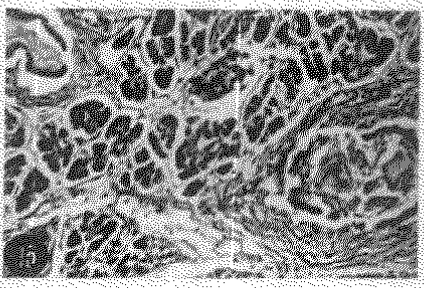


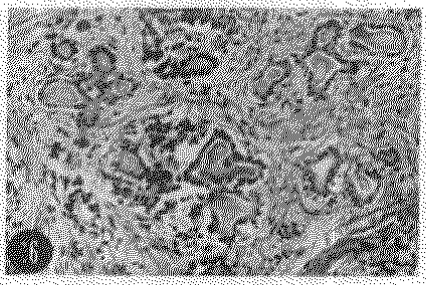


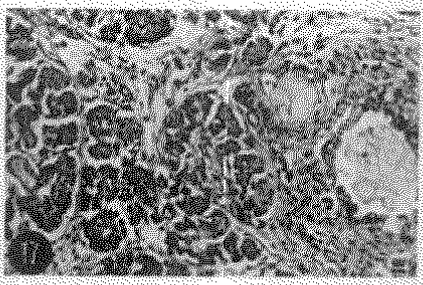


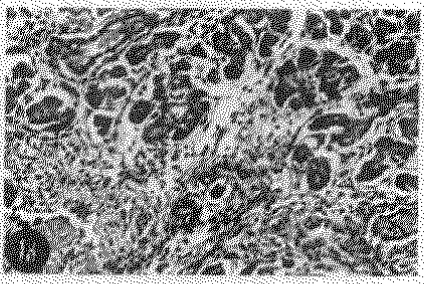


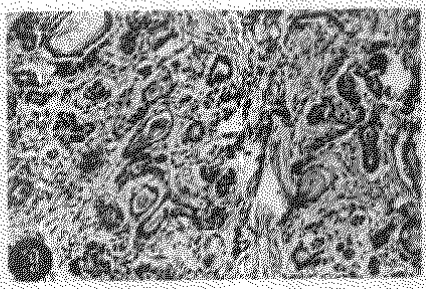


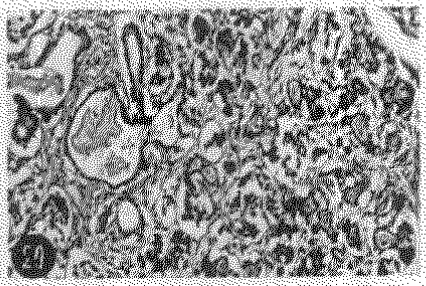


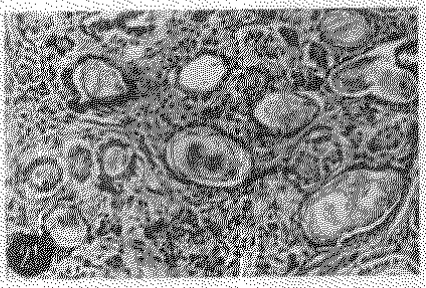


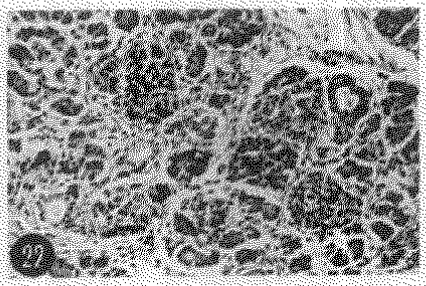


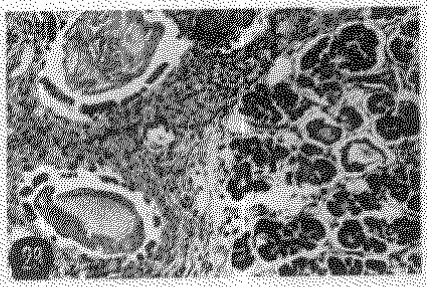


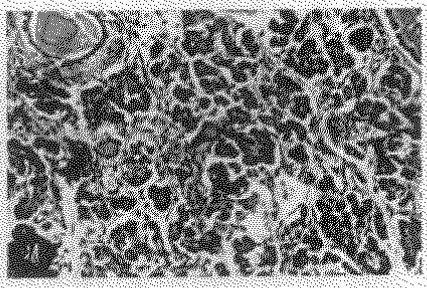


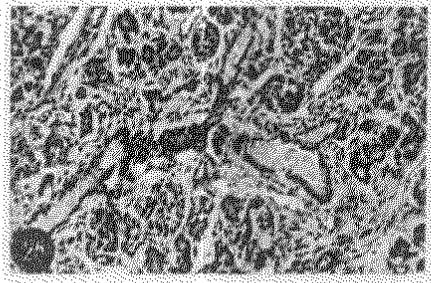


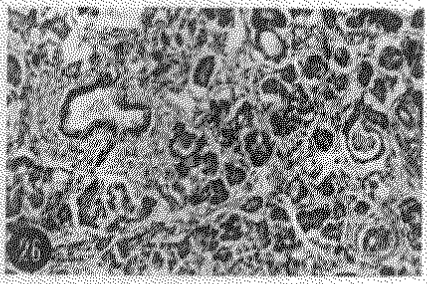


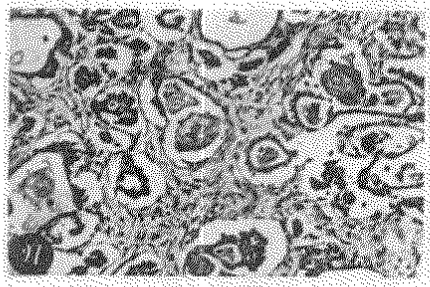


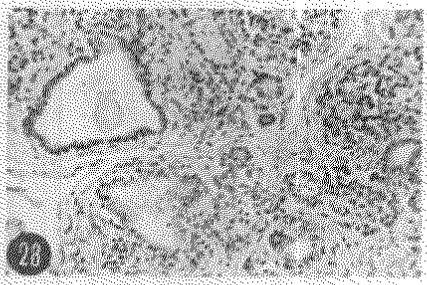


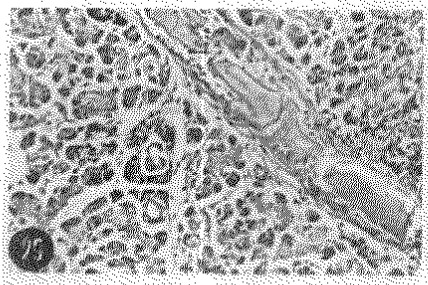


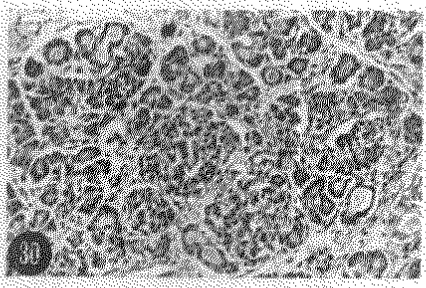


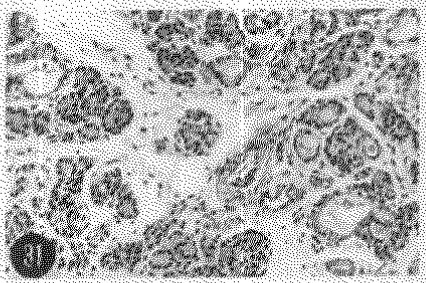


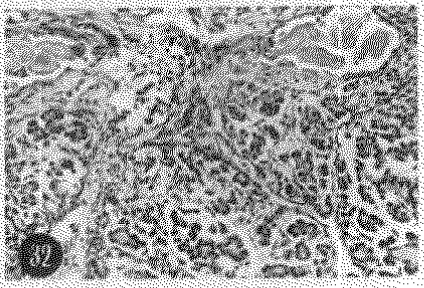












Figs. 1-32. Representative fields of pancreatic histology for each case, numbered consecutively according to case number (Hematoxilin and eosin. 160X).

a) Portal changes. Segmentary biliary cirrhosis, observed in two cases, was characterized by portal fibrosis with bile duct proliferation, occasionally joining several portal triads and with bile stasis of varying degrees. Portal fibrosis of moderate degree irregularly affecting portal triads with or without cholestasis was present in eleven cases. The other eighteen patients revealed no significant portal pathology.

b) Fatty infiltration. Massive diffuse fatty change of the large droplet type, probably related to malnutrition, was present in ten cases and did not parallel other liver abnormalities.

c) Cholestasis. Diffuse cholestasis involving canaliculi and/or bile ducts was present in 15 cases; eleven of these had portal changes of the types mentioned above. In only two cases was portal fibrosis with bile duct proliferation present without cholestasis.

d) Other liver changes. Large bile ducts from the porta hepatis were available for study in 17 cases. In ten of them, the ducts revealed thick eosinophilic material and bile pigment. Four of the patients also had irregular portal fibrosis in the peripheral triads. In on case an "accesory" lobe with bile ducts and goblet cell metaplasia/hyperplasia (case 14) was present; it was not possible to ascertain whether it was an hamartomatous malformation or an acquired process related to cystic fibrosis.

The hepatic changes did not correlate closely with the degree of pancreatic involvement, with patient age or with the presence or abscence of fatty infiltration (Table 2).

Lung: Twenty of our patients had important pulmonary inflammatory changes of the type expected in this disease. In seven, bronchiectasis were documented; three of these also had abscess formation. Five other patients presented with lung abscess or with micropustular changes and nine had bronchopneumonic changes only. Of 18 cases for which post-mortem cultures of the lung were available, staphylococci were grown in 9 and pseudomonas in 4; two of the latter also cultured staphylococci. Five patients had essentially normal pulmonary histology other than inspissated secretions and six more had diverse pathologic processes not closely related to cystic fibrosis; they included hemorhage, bronchitis, bronchopulmom ry

dysplasia, mild interstitial inflammation and candidiasis as part of a Candida sepsis. Table 3 summarizes the age range of the different varieties of pulmonary disease,

Male Genital System: Testicular and paratesticular tissue was evaluated in all male children. Three of them, aged 5 days, 5 and 13 months revealed no abnormalities. The other eighteen had diverse changes in epididymis and vas deferens including distortion, dilatation, inspissation and hypoplasia or atresia. Changes ranged from mild (4 cases) to moderate (8 cases) to severe (6 cases) including atresia or extreme hypoplasia of the vas deferens.

Salivary Gland: Nine cases had sufficient submaxillary gland tissue for evaluation. Two of them showed a normal histology and the rest had fibrosis and inspissated secretion with ductal dilatation ranging from moderate (4 cases) to severe (3 cases).

Clinical Diagnosis.- The correct diagnosis of cystic fibrosis was arrived at in nine of the thirty-two patients. Of the first fifteen cases, seen between 1970 and 1976, the only patients with correct diagnoses included three with meconium ileus and one patient aged four months with a clinical diagnosis of cystic fibrosis documented elsewhere by sweat electrolytes and who was seen terminally in this hospital. From mid 1976 (case 16) on, the disease was correctly diagnosed in five patients and documented by sweat electrolytes in two of them. Fourteen of the remaining 23 patients had a clinical diagnoses of gastroenteritis, respiratory infection or a combination of both. Three patients died with neonatal sepsis and single cases had clinical diagnoses of meningitis, tuberculosis, respiratory distress syndrome of the newborn, yeyunal atresia, congenital malformations and amibiasis.

DISCUSSION

The finding of a low but significant incidence of cystic fibrosis in an autopsy series in Mexico is buttressed by several publications in the Latin American literature mentioning this fact either explicitly or incidentally. An autopsy incidence of almost 1% for cystic fibrosis is in the general range of figures in other series in this region as contrasted to the 2-4% autopsy incidence in children's hospitals in the United States[18]. In Mexico, Armendares et al[13] report an incidence of 0.64% in pediatric autopsies and Gracia-Medrano and Velasco-Cándano[10] of 1.03% in autopsied newborns. In autopsies of all ages, Colon Rivera and Blasini in Puerto Rico[11] mention a figure of 0.32% and López-Vidaurre of 0.28% in Guatemala[12]. Castillo de Ariza et al[14] refer to a 1.15% frequency in a pediatric autopsy series from the Dominican Republic. By extrapolation from autopsy figures, Sifontes et al[15] have calculated an incidence of 1 in 8000 live births in Puerto Rico. This is clearly lower than the 1:000 to 1:4000 incidence recorded for the United States and several northern European countries, but clearly above the rates of 1:17 000 to 1:90 000 mentioned for Blacks and Orientals[1]. Although considered a disease related to the Caucasian genetic pool, cystic fibrosis should not be surprising in our autopsy material. The significant presence of white genetic markers among non-white populations has been documented[19, 20]. Lisker et al[21, 23] based on

their studies on lactase and blood group markers, estimate a 42% admixture of Caucasian genes in a typical Mexican mestizo population which comprises the overwhelming majority of the total population of Latin America. Furthermore, they report 15-25% of Caucasian markers in populations considered predominantly indian in ethnic background. From this, a lower but by no means negligible rate of cystic fibrosis among Latin American populations would be hardly unexpected.

As might be expected from a population in which the disease is not widely recognized and seldom diagnosed clinically, our patients were younger than those in autopsy series from countries with higher incidence rates[17]. Our finding of a slight male predominance is of unknown significance but has also been observed in other series[2] and a slight female predominance in meconium ileus is mentioned in the classic papers of Holsclaw et al[24] and of Donnison et al[25] but is not present in the series reported by Oppenheimer and Esterly[26]. As has been amply documented in the literature, and with due caution with the small sample size, pancreatic affliction seems to be progressive, older children being more severly affected than newborns. The significance, if any, of the calculous pattern of pancreatic involvement found in some of our cases is not clear. Data from the observation of Kopito et al[27] and from Oppenheimer and Esterly[17] would indicate that larger ducts are the primary sites afflicted and that progression of the disease results in greater dilatation of large ducts and eventually virtual disappearance of smaller structures. In our cases, the usual pattern as observed in twenty-six cases appeared to follow this sequence of events. However, the six cases considered as calculous would seem to be variants of morphological expression inasmuch as they appeared with higher frequency in older children and advanced changes in larger ducts coexisted with mild damage of peripheral structures. It may be surmised that in contrast to children from developed countries in whom continued medical assistance extends the natural course of the disease until death supervenes usually due to severe chronic pulmonary disease, children from poor countries rapidly die with electrolyte inbalance as a strong contributing factor to infection, enteric or pulmonary, and the intrinsically less affected survive the longest. Thus, patterns of pancreatic involvement possibly masked in children from developed countries might be discerned in patients dying earlier in the course of the disease.

With regard to liver pathology, there appeared in patients with a calculous pattern in the pancreas a tendency to develop hepatic portal fibrosis; four of six cases showed this association. The appearance of portal fibrosis in these patients was independent of malnutrition per se inasmuch as no association was noted with fatty transformation of the liver.

The findings in the lung were as expected, with newborns being less severely affected and older children presenting with more serious pathology such as abscess and bronchiectasis. The bacteriology of respiratory infection with staphylococci outnumbering pseudomonas also corresponds to the expected pattern in patients with relatively few bouts of pulmonary infection rather than to those with prolonged, repeatedly treated lung disease in which peculiar

pseudomonas strains predominate. The findings in male genital system are those expected in these groups and the findings in salivary glands conform to the known pathology of cystic fibrosis.

The controversy of cystic fibrosis as a genetically homogeneous versus heterogeneous disease is as yet unresolved[1, 28]. If the differences suggested by this study in sex distribution, patterns of pancreatic inolvement and population frequency are real, they can be added to other findings suggesting differences in the nature of the disease among different populations. Stern et al[29] have suggested a different and more benign course of cystic fibrosis among Blacks. Sifontes et al[15] have pointed out peculiarities in the clinical course of the disease among Puerto Rican children; some of these differences are clearly environmental, related in part to a tropical setting, but an inherent diversity of the disease may also be at play. These fragmentary pieces of evidence could be placed on the side of a multiple loci pathogenesis for the disease.

A marked difficulty in establishing the clinical diagnosis becomes evident in this series, particularly in the early cases before sufficient experience was gained from the unexpected emergence of cases at autopsy. This difficulty probably derives from the high regional incidence of diseases that can mask cystic fibrosis on one hand or imitate it on the other. Pediatric infectious diseases, both pulmonary and enteric, are widespread. Thus the Latin American pediatrician is forced to discriminate between cystic fibrosis and an overwhelming majority of cases which closely mimic it and are the result of the malnutrition/infectious disease complex. Moreover, in this environment, underlying functional alterations derived from the exocrine dysfunction of cystic fibrosis would aggravate morbidity from environment-related infection and malnutrition. Therefore it is quite likely that many of these patients die undiagnosed at the time of the early clinical manifestations and, given the progressive nature of the pathologic changes, even at autopsy the full-blown picture may not appear. In this respect it is worth mentioning that the age range of our patients differs markedly from that in other countries where the disease is promptly recognized and the patients have access to medical care[16].

The Latin American pathologist also encounters peculiar difficulties in identifying the disease. Aside from the well known differential diagnoses which include pancreatic changes of uremia, steroid effects and the combination of neutropenia and pancreatic fibrosis described by Shwachman[30], individual cases have to be discerned from those with intestinal pathology secondary to repeated enteric infections and from pancreatic changes attributable to dehydration producing inspissation on one hand and to malnutrition producing fibrosis and atrophy on the other.

It is the role of the pathologist to point out the emergence of these cases so that the clinician can document the disease with the appropriate clinical studies in other patients. This should lead to a more timely diagnosis and management of the patients as well as to

more reliable statistics of occurence than can be obtained from the admittedly limited source of an autopsy series.

REFERENCES

1. Wood, R.E., Boat, T.F., Doershuk, D.F.: Cystic Fibrosis. Am. Rev. Resp. Dis. 113: 833, 1976.

2. di Sant Agnese, P.A. Talamo, R.C.: Pathogenesis and physiopathology of cystic fibrosis. N. Eng. J. Med. 277: 1287/1344/1399, 1967.

3. di Sant Agnese, P.A., Davis, P.B.: Research in cystic fibrosis. N. Eng. J. Med. 295: 481, 1976.

4. Conneally, P.M., Merrit, A.D., Pao-Lo Yu: Cystic fibrosis: population genetics. Tex. Rep. Biol. Med. 31: 639, 1973.

5. Gómez-Martínez, S., Riojas-Davila, U.: Correlación clínico radiológica de 18 casos de Mucoviscidosis en niños. Rev. Mex. Pediat. 39:213, 1968.

6. Cuellar, A., Rangel, L., Aleman, P., Gomez, S., Frenk, S.: Mucoviscidosis. Descripción de un caso con especial atención al diagnóstico y tratamiento. Rev. Mex. Pediat. 40: 477, 1971.

7. Aristizabal-Duque, G., Leal-Quevedo, F.J., Ruiz-Vence, E., Franco-Ramírez, G.: Actualización sobre mucoviscidosis. Bol. Med. Hospital Infantil 35: 65, 1978

8. García-Hernández, N., Espinosa-Said, L. Haua-Kuri, J., López-Almaraz, Y: Fibrosis quística en el adulto. Prensa Med. Mex. 43: 289, 1978.

9. Puffer, R.R., Serrano C.V.: Características de la Mortalidad en la Niñez. Organización Panamericana de la Salud. Publicación científica No. 262, 1973, Washington, pp 234-235.

10. Gracia-Medrano P., Velásco-Cándano, L.: Fibrosis quística del pancreas en el recién nacido. Ginecol. y Obstet. de Méx. 20:811, 1965.

11. Colon-Rivera, E.S., Blasini, R.: Mucoviscidosis. Bol. Asoc. Med. P. Rico 47:487, 1955.

12. López-Vidaurre, M.: Enfermedad fibroquística crónica del pancreas. Comunicación de 19 casos del Hospital Roosevelt. Tesis de Médico Cirujano. Universidad de San Carlos de Guatemala, Guatemala, 1970.

13. Armendares, S., Cortés, R., De la Rosa, L.: El componente genético en la mortalidad infantil. Rev. Invest. Clin. (Méx) 26: 3, 1974.

14. Castillo de Ariza, M., Ravelo-Marchena, M.E., Vargas M.A., Sánchez, C.M.: Enfermedad fibroqústica del pancreas. Revisión de 13 casos. Arch. Dom. Ped. 15:175, 1979.

15. Sifontes, J.E., Rodriguez, F., Mayol, P. Ménendez, R., Alicea E., Velez, W.: Fibrosis quística en Puerto Rico. Bol. Asoc. Med. P. Rico 69: 251, 1977.

16. Ramírez-Mayans, J.A., Pedroza, A., López-Corella, E., Mora, M.A.Arriaga, J., Rivera-Echegoyen, M.: Manifestaciones gastrointestinales de mucoviscidosis en niños. Acta Pediat. Mex. (en prensa).

17. Oppenheimer, E.H., Esterly, J.R.: Pathology of cystic fibrosis. Review of the literature and comparison with 146 autopsied cases. Perspect Pediatr. Path. 2: 241, 1975.

18. di Sant'Agnese, P.: Cystic fibrosis in Vaughan, V.C., McKay, R.J., Behrman, R.E. (eds) Nelson Textbook of Pediatrics. Eleventh edition. W.B. Saunders, Co. Philadelphia London Toronto, 1979, p. 1989.

19. Reed, T.E.: Caucasian genes in American Negroes. Science 165:762, 1969.

20. Nei M., Roychoudhury, A.K.: Gene differences between caucasian, negro and japanese populations. Science 177: 434, 1972.

21. Rodríguez H., Rodríguez E. de, Loría A., Lisker, R.: Studies on several genetic hematological tratis of the mexican population. V. Distribution of blood group antigens in Nahuas, Yaquis, Tarahumaras, Tarascos and Mixtecos. Human Biol. 35: 350, 1963.

22. Steinberg, A., Cordoba, M., Lisker, R.: Studies on several genetic hematological traits of Mexicans. XV. The Gm allotypes of some indian tribes. Amer. J. Hum. Genet. 19: 747, 1967.

23. Lisker, R., López-Habib, G., Daltabuit, M., Rostenberg, I., Arroyo, P.: Lactase deficiency in a rural area of Mexico, Am. J. Clin. Nutr. 27: 756, 1974.

24. Holsclaw, D.S., Eckstein, M.A. Nixon, H.H.: Meconium ileus. A 20 year review of 109 cases. Amer. J. Dis. Child 109: 101, 1965.

25. Donnison, A.B, Shwachman, H., Gross, R.E.: A review of 164 children with meconium ileus seen at the Children's Hospital Medical Center, Boston, Pediatrics 37:833, 1966.

26. Oppenheimer, E.H., Esterly, J.R.: Cystic fibrosis of the pancreas. Morphologic findings in infants with and without diagnostic pancreatic lesions. Arch. Pathol. 96: 149, 1973.

27. Kopito, L.E., Shwachamn, H., Vawter, G.F., Edlow, J.: The pancreas in cystic fibrosis; chemical composition and comparative morphology. Pediat. Res. 10: 742, 1976.

28. Changus, J.E., Pitot, H.C.: Cystic fibrosis. A dilemma in the metabolic pathogenesis of genetic disease. Arch. Pathol. Lab. Med. 100:7, 1976.

29. Stern, R.C., Doershuk, C.F., Boat, T.F., Tucker, A.S., Primiano, F.P., Matthews L.W.: Course of cystic fibrosis in black patients. J. Pediatr. 89: 412, 1976.

30. Shwachman, H., Diamond, L.K., Oski, F.A., Khaw, K.T.: The syndrome of pancreatic insufficiency and bone marrow dysfunction. J. Pediatr. 65: 645, 1964.