contrary, that it may be harmful. This is in contrast to previous studies.

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REFERENCES

Arturson, G., and Wallenius, G. (1964). *Scand. J. clin. lab. Invest.*, **16**, 81.
Askrog, V., and Fossaberg, E. (1965). *Ugeskr. Læg.*, **127**, 965.
Bloch, E. H. (1955). *Amer. J. med. Sci.*, **229**, 280.
Bryant, M. F., Bloom, W. L., and Brewer, S. S. (1963). *Amer. Surg.*, **29**, 256.
Enger, E., Julsrud, A. Chr., and Kirkeby, K. (1963). *Acta med. scand.*, Suppl. No. 397.
Gelin, L. E., Sölvell, L., and Zederfeldt, B. (1961). *Acta chir. scand.*, **122**, 309.
—— and Thorén, O. K. A. (1961). Ibid., **122**, 303.
Langsjoen, P. H. (1965). *Tex. St. J. Med.*, **61**, 92.
—— Falconer, H. S., Sanchez, S. A., and Lynch, D. J. (1963). *Angiology*, **14**, 465.
Lindén, L. (1964). *Svenska Läk.-Tidn.*, **61**, 2300.
Long, D. M., Myer, M. W., Brown, E. B., and Lillehei, C. W. (1962). *Amer. J. Cardiol.*, **10**, 695.

Life-table for Cystic Fibrosis

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Life-tables can be of value in assessing the social problem which a disease presents and in evaluating the success of different methods of treatment. Two methods of constructing a life-table are available if a hospital series is used: (1) entering the patient from the age at proved diagnosis, and (2) entering the patient from birth. The first method will probably overestimate mortality, especially when diagnosis tends to be made shortly before death. The second will probably underestimate mortality, except in surveys of specific geographical areas in which all patients with the disease may be expected to be ascertained.

Cystic fibrosis is the commonest autosomal recessively determined disease of childhood. The best estimate of incidence in children of European stock is probably that of Danks, Allan, and Anderson (1965), which gives an incidence of approximately 1 in 2,400 live births.

Source of Case Material

A survey has been made of 498 children attending the Hospital for Sick Children between 1943 and midsummer 1964 who were coded in the hospital records as suffering or possibly suffering from cystic fibrosis. One further case was identified from a search of the post-mortem index, giving a total of 499 cases. Of these cases 399 were coded as suffering from cystic fibrosis and 100 from cystic fibrosis presenting with meconium ileus. Below are given the clinical and laboratory data resulting from the invesigation.

1. Cystic Fibrosis Not Presenting as Meconium Ileus

Examination of the case material disclosed pronounced variation in both the presence and the degree of characteristic clinical features. The diagnostic laboratory data consist of tests of tryptic activity of the duodenal juice or the sodium content of the sweat. As would be expected for cases collected over a period of more than 20 years, one or both tests had not always been carried out.

The variability both in clinical manifestation and in laboratory data is of potential importance in the construction of a life-table for the disease. Where laboratory data were not available the diagnosis was more likely to be correct in those cases in which the clinical manifestation was typical than in those in which it was not. Assay of the tryptic activity of the duodenal juice is not as reliable a confirmatory test as is the concentration of sodium in the sweat. For these reasons the patients were divided into four primary groups, according to the presence or absence of the two laboratory tests and to the results. Each of these groups was then subdivided according to the clinical manifestations.

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Classification on Laboratory Test Findings

Assay of the tryptic activity of the duodenal juice before 1952 was carried out by the method of Andersen and Early (1942). From 1952 until 1962 the method of Horsfield (1952) was used, and subsequently that of McGowan and Wills (1962). Inability to digest gelatin at a titre of 1:100 of the juice in the case of the two former methods, and a tryptic activity of the juice of less than 7 units by the latter method, were regarded as confirmatory. In all instances where the *p*H of the juice was stated to be below 7, or "acid," the results of the test have been excluded.

Prior to 1959 estimation of the sodium content of the sweat was determined by the method of Shwachman, Higgins, and Dooley, as quoted by Shwachman and Leubner (1955), and subsequently by the method of Gibson and Cooke (1959). By either method a sodium level of 70 mEq/K or L, or greater, was considered confirmatory.

The results of the pilocarpine iontophoresis method have been accepted only in those instances where the weight of sweat obtained was at least 100 mg. McKendrick (1962) discussed the effect of age on the sodium content of the sweat and concluded that, in infancy, levels as low as 50 mEq/l. offer strong evidence of the disease. In the present series there were seven patients in whom the sodium content of the sweat was found to lie between 50 and 70 mEq/l. Of these, four were below the age of 1 year at the time of estimation, and their diagnosis has therefore been accepted as having been confirmed. Laboratory data obtained from tests done at other hospitals were not used in the classification of cases.

The four primary groups were as follows:

1. Diagnosis first confirmed by the sodium content of the sweat —93 cases. (In 21 the diagnosis was subsequently also confirmed by the tryptic activity of the duodenal juice. In seven cases the tryptic activity of the duodenal juice was non-confirmatory.)

2. Diagnosis first confirmed by the tryptic activity of the duodenal juice—163 cases. (In 39 the diagnosis was subsequently also confirmed by the sodium content of the sweat.)

3. Diagnosis not confirmed by either test, since neither test was done—105 cases.

4. Diagnosis regarded as not confirmed by laboratory tests—27 cases: duodenal juice confirmatory but sweat test non-confirmatory, 2 cases; duodenal juice non-confirmatory, sweat test not done, 17 cases; sweat test non-confirmatory, duodenal juice not examined, 6

cases ; sweat test and duodenal juice both non-confirmatory, 2 cases. These 27 cases are hereinafter excluded.

The 11 remaining patients of the 399 studied were not diagnosed until post-mortem examination.

Classification on Symptoms and Signs

The patients were classified as showing typical or atypical signs of involvement of the respiratory and alimentary systems. The results of this classification for groups 1, 2, and 3 are given in Table I.

TABLE I.—*Classification of Patients on Symptoms and Signs, Showing the Number of Patients in Groups 1, 2, and 3 Thought to Have Either Typical or Atypical Involvement of the Respiratory and Intestinal Tract*

Respiratory tract: / Intestinal tract:	Typical / Typical	Typical / Atypical	Atypical / Typical	Atypical / Atypical	Total
Group 1 (diagnosis first confirmed on sweat)	68	17	5	3	93
Group 2 (diagnosis first confirmed on duodenal juice) ..	138	13	7	0	158*
Group 3 (no laboratory confirmation)	87	7	3	8	105
Total	293	37	15	11	356

* The 5 patients in this group in whom the diagnosis was disproved at necropsy have been excluded.

The respiratory tract was considered to have been typically involved if there was a history of infection of the lower respiratory tract of a frequency and/or severity which obviously exceeded that which might have been expected in a normal child. In those instances, however, where the child died before the age of 2 years the respiratory tract was considered to have been typically involved, even though respiratory infections were not frequent, provided the child presented with and died from an infection of the lower respiratory tract.

Respiratory-tract involvement was regarded as atypical if lower respiratory infection was unusually mild or infrequent, or if it was absent. Of the 26 children having little or no infection of the respiratory tract seven were below the age of 3 years when last seen.

A survey of the case material disclosed wide variation in those bowel symptoms which characterize the disease. In some instances the stools were greasy and offensive but not frequent, while in others they were frequent and pale though not apparently offensive. In view of these difficulties the intestinal tract was regarded as having shown evidence of typical involvement if it was apparent from the frequency and/or nature of the stools that there was a marked degree of dysfunction of the digestive and absorptive process in the small intestine. The intestinal tract was thought to have shown atypical involvement if the evidence of bowel abnormality was minimal or apparently absent.

Discussion of Certainty of Diagnosis

The degree of certainty of diagnosis was highest for patients in group 1. So far as is known cystic fibrosis is the only disease, other than Addison's disease (Conn, 1949), in which the sweat sodium is raised to the level which has been accepted as confirming the presence of cystic fibrosis. All 13 patients in this group who came to necropsy were histologically proved to be suffering from the disease. In all of these the clinical data were thought to be typical of the disease, while in the remaining two they were thought to be atypical.

The certainty of diagnosis for patients in group 2 was more limited. There are several anomalies and diseases of the pancreas, other than cystic fibrosis, in which the tryptic activity of the duodenal juice is either diminished or absent. Of the 54 patients in group 2 who came to necropsy five were histologically proved not to be suffering from the disease. In four of these the clinical data were thought to be typical of the disease, and in one they were thought to be atypical. None of the cases disproved at necropsy had had a sweat test. The causes of death and the histology of the pancreas for these five patients are given in Table II. It is possible that a similar proportion, about 1 in 10, of the 51 deceased patients of the group who did not come to necropsy, and of the 58 patients who were still living, were also not suffering from cystic fibrosis.

TABLE II.—*Necropsy Findings For the Five Cases Proved Not to be Suffering from Cystic Fibrosis*

Case	Clinical Data	Necropsy Findings
1	Typical	Aplasia of the exocrine pancreas. Cerebral haemorrhage. Thrombocytopenic purpura
2		Advanced interstitial pancreatitis. Confluent bronchopneumonia (*E. coli*). Ectopic right kidney with multiple dysplastic foci. Ectopic gastric mucosa and normal pancreas in ileum. Urachal cyst
3		Chronic interstitial pancreatitis. Periarteritis nodosa. Gangrene of right foot
4	,,	Mild cystic malformation of the pancreas. Marasmus and steatorrhoea
5	Atypical	Normal pancreas. Marasmus: steatorrhoea

In group 3 all 36 patients who came to necropsy were proved on histological examination to be suffering from cystic fibrosis. In 33 instances the clinical data were thought to be typical, while in three instances they were regarded as atypical.

2. Meconium Ileus

In the present series the diagnosis in all but two of the cases of meconium ileus was either confirmed by post-mortem histological examination or supported by the histology of the gut removed at operation. Of the two cases which had not had histological confirmation of the diagnosis one was subsequently confirmed by a sweat test ; in the other there was no acceptable laboratory confirmation, but since operation the disease had run a typical clinical course.

Construction of Life-tables and Results :

1. Cystic Fibrosis Not Presenting as Meconium Ileus

The five cases in group 2 in which the diagnosis of cystic fibrosis was disproved at necropsy have been excluded from the life-tables.

It was possible to ascertain the present status of all except five of the 367 patients diagnosed as suffering from cystic fibrosis, not presenting as meconium ileus, who thus remain available for a life-table. Of the five patients whose present status it has not been possible to ascertain one is in group 1, two are in group 2, and two are in group 3. They were entered in the life-tables as surviving up to whatever date they were last known to be alive.

Life-tables with Patients Entering at Diagnosis

Of the 367 patients remaining a further 11 were excluded from those life-tables in which a patient was entered at the age of diagnosis, since these patients were not diagnosed until necropsy. They are, however, included in the life-tables in which a patient was entered at birth.

For the life-tables entering patients at diagnosis entry is made at the patient's age when the diagnosis was first confirmed by one of the two laboratory tests, or, if neither of the tests had been done, at his or her age on the date of clinical diagnosis. In the few instances where the patient had been diagnosed previously elsewhere the age of the child when first seen at the hospital was taken as the age of entry.

Exclusion of the patients in groups 1, 2, and 3 who did not show typical clinical manifestations made no appreciable difference to the life-tables.

In the life-table for group 3 the derived life expectancy had to be calculated by using an arbitrary figure of 500 patients alive at the start of the first year. This procedure was necessary because prior to the first year the number of deaths exceeded the number of patients estimated to be at risk, on the assumption that a patient entering the table within a given period of days or weeks is at risk for half that period.

The life-tables for groups 1 and 2 did not differ significantly, but that of group 3 showed an appreciably shorter life expectancy. The reason why many of the patients in group 3 had not had laboratory tests was that they were too ill when first seen and died before the test could be undertaken. Thus this group contained a proportion of severely affected children, who by selection are necessarily absent from groups 1 and 2. The post-mortem data for group 3 suggest that the degree of certainty of diagnosis in the group is high. The best indication of life expectancy for the disease available from the present series is probably that derived from a life-table that includes the patients of groups 1, 2, and 3. The life expectancy per 1,000 derived from this table is given in column 1 of Life-table A. Since there was no appreciable difference in life expectancy between the sexes, the life expectancy is shown irrespective of sex.

Two additional life-tables, entering patients at diagnosis, have been constructed. The first of these contains all the patients of groups 1, 2, and 3 who were diagnosed during 1943–54 inclusive, and the second those diagnosed during 1955–64. The life expectancies per 1,000 derived from these tables are given in column 1 of Life-table B.

Life-tables with Patients Entering at Birth

A life-table has also been constructed in which patients were entered at birth. This table contains all the patients of groups 1, 2, and 3. The life expectancy per 1,000, irrespective of sex, derived from it is given in column 2 of Life-table A.

Two additional life-tables have been constructed in which patients were entered at birth. These compare the periods 1943–54 and 1955–64. The life expectancies per 1,000 derived from these tables are given in column 2 of Life-table B.

LIFE-TABLE A.—*Cystic Fibrosis Not Presenting as Meconium Ileus*

Age	Column 1. Groups 1, 2, and 3. Patients Entered at Diagnosis—356		Column 2. Groups 1, 2, and 3, and 11 Patients Diagnosed at Necropsy. No. Entered at Birth—367	
	Effective No. at Risk	Proportion of 1,000 Alive at Start of Each Period	Effective No. at Risk	Proportion of 1,000 Alive at Start of Each Period
Months:				
0–	2·0	1,000	366·5	1,000
1–	19·0	1,000	361·0	997
3–	49·0	684	346·0	969
6–	75·0	475	327·0	916
9–	92·5	374	312·0	871
Years:				
1–	113·0	342	288·5	849
2–	130·5	266	259·5	773
3–	134·5	236	233·5	728
4–	131·5	201	209·5	666
5–	131·5	189	190·0	641
6–	123·5	176	163·5	607
7–	108·5	153	137·5	548
8–	100·5	138	120·5	504
9–	94·0	131	107·0	483
10–	86·0	123	93·5	456
11–	75·0	112	79·5	417
12–	65·0	105	67·0	391
13–	54·0	89	55·0	333
14–	42·0	86	42·5	321
15–	33·5	74	33·5	276
16–	26·5	67	26·5	251

LIFE-TABLE B.—*Cystic Fibrosis Not Presenting as Meconium Ileus, Showing the Life Expectancy per* 1,000 *and Comparing the Periods* 1943–54 *and* 1955–64

Age in Years	Column 1 Entered at Diagnosis		Column 2 Entered at Birth	
	1943–54	1955–64	1943–54	1955–64
0–	1,000	1,000	1,000	1,000
1–	277	392	805	889
5–	121	260	534	741
10–	83	149	379	522
15–	54	63	246	259

2. Meconium Ileus

Ascertainment of the present status of the patients presenting with meconium ileus is complete.

Life-table with Patients Entering at Diagnosis

In the life-table for meconium ileus in which a patient was entered at diagnosis entry was made at the child's age on the date on which primary surgery for the condition was performed. Only those children whose primary operation was performed at the hospital, and in whom the diagnosis was either substantiated by or made at that operation, have been included. These criteria necessitated the exclusion of 15 of the 100 cases of meconium ileus. Of the excluded cases four were not diagnosed until necropsy, four died before operation, and in five instances operation was performed at other hospitals, the children being subsequently seen here because they developed complications. The remaining two cases have been excluded, since a definitive diagnosis of meconium ileus was not made at operation, though it later became apparent that both were suffering from cystic fibrosis. The life expectancy per 1,000 derived from the life-table in which patients were entered at diagnosis is given in column 1 of Life-table C. Since there was no appreciable difference in life expectancy between the sexes, the figures given are irrespective of sex.

Life-table with Patients Entering at Birth

A life-table has been constructed in which a patient was entered at birth. None of the 100 cases of meconium ileus has been excluded. The derived life expectancy from this table is given in column 2 of Life-table C.

Discussion

1. Cystic Fibrosis not Presenting as Meconium Ileus

The life-table for cystic fibrosis not presenting as meconium ileus, in which patients were entered at birth, probably under-

LIFE-TABLE C.—*Meconium Ileus*

Age	Column 1. Patients Entered at Diagnosis—85		Column 2. Patients Entered at Birth—100	
	Effective No. at Risk	Proportion of 1,000 Alive at Start of Each Period	Effective No. at Risk	Proportion of 1,000 Alive at Start of Each Period
Day:				
0–	8·0	1,000	100·0	1,000
1–	24·0	1,000	97·5	1,000
2–	42·0	792	92·0	949
3–	58·5	717	86·0	887
4–	66·0	680	81·5	825
5–	65·5	649	78·0	795
6–	65·0	609	75·0	754
7–	61·0	609	70·0	754
14–	47·5	509	54·5	625
Months:				
1–	31·0	327	36·0	407
3–	20·0	169	24·0	215
6–	15·0	127	19·0	170
9–	12·0	102	16·0	143
Years:				
1–	11·0	102	15·0	143
2–	9·5	102	13·5	143
3–	7·0	102	11·0	143
4–	5·0	102	8·5	143
5–	4·0	82	6·5	126
6–	3·0	82	5·0	107
7–	1·5	55	3·5	86
8–	0·5	18	2·0	61
9–	—	—	0·5	—

estimates mortality, because it necessarily does not take into account those who did not present at hospital. The pathogenesis of the disease is such that these patients are likely to have been more rather than less severely affected, and died either undiagnosed or before referral to hospital. The life expectancy derived from this table, given in column 2 of Life-table A, shows that by the end of the first year of life approximately 3 out of 20 children had died. By the end of the fifth year about one-third of the children were dead. At the end of the tenth year rather over a half, and by the end of the fifteenth year nearly three-quarters were dead. Only 10 children survived to the twentieth year. The oldest patient in the series died at the age of 23 years. The life-table suggests that mortality is highest between the third and ninth months of life, and this will be true unless there are a number of patients dying undiagnosed before the third month.

The life-table in which patients were entered at diagnosis will almost certainly overestimate mortality, because in the majority of instances the patients came under observation as sick children, and some were already moribund when diagnosis was made. Column 1 of Life-table A shows that by the end of the first year about two-thirds of the children had died. At the end of the fifth year over four-fifths were dead. By the end of the tenth year nearly nine-tenths were dead.

The true life expectancy for the disease will probably lie between that derived from the table in which the patients were entered at birth and that in which they were entered at diagnosis. If the life-table in which the patients were entered at diagnosis is modified so that there is a comparable proportion of 1,000 patients alive at the end of the first year as there is at the end of the first year in the table entering the patients at birth, then there is much less difference in the life expectancy between the two tables in the ensuing years. This observation suggests that the difference between the two life-tables is largely due to the different estimate of the mortality in the first 12 months of life. It is of interest that the life-table in which patients were entered at diagnosis indicates that very few children suffering from cystic fibrosis, without meconium ileus, present in the first month of life.

A comparison of the life expectancies for the years 1943–4 and 1955–64, derived from both the life-tables in which the patients were entered at diagnosis and those in which they were entered at birth, show an appreciable increase in the life expectancy in the latter group. The fact that this trend is present both in the tables in which patients were entered at diagnosis and those in which they were entered at birth suggests that the improvement in life expectancy in the more recent years is due to improved treatment rather than to earlier ascertainment of patients. It is of interest that this recent improvement was maintained up to the age of 10 years but was no longer apparent at 15.

2. Meconium Ileus

The presentation of meconium ileus is such that the vast majority of cases will come to hospital. Thus the modification of the life expectancy derived from the life-tables for cystic fibrosis not presenting as meconium ileus, due to cases which were not ascertained, will not occur to any great degree in the life-tables for meconium ileus. Since in all except one instance surgery was performed during the first week of life, there is less difference between the life expectancies for meconium ileus derived from the life-table in which patients were entered at birth and those in which patients were entered at diagnosis.

The life expectancy for meconium ileus derived from the life-table in which patients were entered at birth shows that by the end of the first week of life a quarter of them had died. By the end of the second week of life over a third were dead. At the end of the first month over a half, and at the end of the third month three-quarters of the children were dead. Only 15 children survived to the first year of life. The oldest survivor of the series was aged 9 years. The life expectancy derived from the life-table in which the patients were entered at diagnosis differs little from that in which they were entered at birth, except between the first and second day of life. The 15 cases excluded from the life-table in which patients were entered at diagnosis happen to have a relatively long life-span. The life-table in which patients were entered at diagnosis does, however, give a more accurate picture of surgical mortality. Surgical survivors are defined by Holsclaw, Eckstein, and Nixon (1965) as those children who survive one month after initial surgery. On these criteria, column 1 of Life-table C shows that the surgical mortality in the present series is approximately 67%.

Summary

A survey has been made of 499 children attending the Hospital for Sick Children who were diagnosed as suffering from cystic fibrosis; 399 cases presented without neonatal intestinal obstruction and the remainder with meconium ileus. The difficulties of diagnosis in the former group are discussed.

The series of life-tables have been constructed for each of the two groups of presentations of the disease: one entering the affected child at diagnosis, the other from birth. The true life expectancy for the disease will probably lie between the two estimates provided by the different methods of entry to the life-tables.

The life-table for cystic fibrosis not presenting as meconium ileus with patients entering at diagnosis shows that by the end of the first year of life over two-thirds of the children had died. At the end of the fifth year over four-fifths were dead. By the end of the tenth year nearly nine-tenths were dead.

The life-table for cystic fibrosis not presenting as meconium ileus with patients entered from births shows that by the end of the first year of life approximately one-seventh of the children had died. By the end of the fifth year about one-third were dead. At the end of the tenth year rather over a half, and by the end of the fifteenth year nearly three-quarters were dead.

The life-tables for meconium ileus show that by the end of the first week of life a quarter of the children had died. At the end of the second week over a third were dead. By the end of the first month over a half, and at the end of the third month three-quarters, were dead.

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References

Andersen, Dorothy H., and Early, Marialuise, V. (1942). *Amer. J. Dis. Child.*, **63**, 891
Conn, J. W. (1949). *Arch. intern. Med.*, **83**, 416.
Danks, D. M., Allan, J., and Anderson, C. M. (1965). *Ann. Hum. Genet.*, **28**, 323.
Gibson, L. E., and Cooke, R. E. (1959). *Pediatrics*, **23**, 545.
Holsclaw, D. S., Eckstein, H. B., and Dixon, H. H. (1965). *Amer. J. Dis. Child.*, **109**, 101.
Horsfield, A. (1952). *J. med. Lab. Technol.*, **10**, 18.
McGowan, G. K., and Wills, M. R. (1962). *J. clin. Path.*, **15**, 62.
McKendrick, T. (1962). *Lancet*, **1**, 183.
Shwachman, H., and Leubner, H (1955). *Advanc. Pediat.*, **7**, 249.