Journal of Medical Genetics (1972). **9**, 33.

The Incidence and Genetics of Cystic Fibrosis

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Cystic fibrosis is a generalized disease of the exocrine glands, the aetiology of which is unknown. This and diabetes mellitus are the most frequent hereditary conditions known among white children (Table I).

Material

Data were obtained from the whole of Czechoslovakia for the period covering the past 8 years. There are 14 million inhabitants and 1·5 million live births were recorded from 1960 to 1967. During this period, 297 cases of cystic fibrosis have been diagnosed on the basis of clinical investigations and/or necropsy reports. All children with chronic diseases of any kind are registered and investigated regularly so that only those in whom symptoms were not manifest could have been missed. Furthermore, as 88% of all cases of cystic fibrosis are diagnosed during their first year of life and all children who die during their first year (at home or in hospital) are subject to necropsy by law, it is improbable that any significant number of cases could have been missed (Table II and Fig. 1).

It seems that the difference in incidence between the individual regions is too great to have arisen by chance and ethnic differences could not be the explanation. In consequence a varying standard of diagnostic and documentary care is probable. Only 2% of the cases in the regions with a high incidence (regions II, V, VII) were diagnosed after the first year of life whereas, in those with the lowest incidence (X, XI), 27% of the cases were detected later. Necropsy by law on all children who died before reaching the age of 15 years has already been mentioned. For these reasons, the incidence found in the regions with the highest numbers of cases (II, V, VII) is that which is to be considered relevant for the whole country. These three regions have 4,330,000 inhabitants and 490,000 live births have been recorded during the last 8 years. Among these, 147 cases of cystic fibrosis were diagnosed: the incidence of cystic fibrosis in Czechoslovakia may therefore be estimated as 30:100,000 live births (1:3300).

Type of Heredity

A number of basic papers have determined the heredity mechanism of cystic fibrosis to be of an autosomal recessive type (Carter, 1952; Childs, 1956; Steinberg and Morton, 1956; Steinberg *et al*, 1956; Crow, 1965). Several workers, however, have recently found a greater number of affected children in sibships than would correspond to this type of Mendelian inheritance (Baumann, 1958; Roberts, 1960; Bernheim *et al*, 1961; Mastella and Montenovesi, 1964). The disadvantage of most of these papers is that the type of statistical analysis used was usually not in accordance with the method of ascertainment. If these same types of analysis have been used in the present paper, it is only to enable comparison to be made with previous studies on the same subject (Table III).

Method of Ascertainment

Included in this study are 234 sibships with at least one affected member, derived from all paediatric departments in Czechoslovakia. In 44 families the patient was an only child and these families were excluded from the calculations; this left a total of 190 families but in only 135 of them could the number of affected members

TABLE I

ESTIMATES OF THE INCIDENCE OF CYSTIC FIBROSIS IN VARIOUS COUNTRIES

Cystic Fibrosis per Live Births	Country	Source
1:3800	Hawaii	Wright and Morton (1968)
1:3700	USA	Steinberg and Brown (1960)
1:3300	W. Germany	Vivell, Jacobi, and Münbach (1963)
1:3200	France	Bernheim *et al* (1961)
1:2900	England	Pugh and Pickup (1967)
1:2700	Czechoslovakia	Houštěk and Vávrová (1962 and 1967)
1:2500	Australia	Danks, Allan, and Anderson (1965)
1:2500	USA	Sultz, Schlesinger, and Mosher (1966)
1:2400	USA	Kramm *et al* (1962)
1:2400	England	Hall and Simpkiss (1968)

Received 25 September 1970.

TABLE II

INCIDENCE OF CYSTIC FIBROSIS IN REGIONS OF CZECHOSLOVAKIA IN THE PERIOD 1960–67

Region	No. of Inhabitants	Births	Ascertained Cases of Cystic Fibrosis	Incidence per 100,000 Live Births
I Prague	1,030,000	82,581	10	12·1 (1:8258)
II Central Bohemia	1,273,000	129,781	38	29·2 (1:3415)
III South Bohemia	655,000	74,998	9	12·0 (1:8333)
IV West Bohemia	862,000	103,681	14	13·4 (1:7416)
V North Bohemia	1,116,000	136,763	42	30·6 (1:3256)
VI East Bohemia	1,206,000	135,142	33	24·4 (1:4095)
VII South Moravia	1,940,000	223,338	67	30·0 (1:3300)
VIII North Moravia	1,759,000	144,000	27	18·7 (1:5346)
IX West Slovakia	1,854,000	181,349	36	20·0 (1:5037)
X Central Slovakia	1,375,000	213,430	20	9·3 (1:10,671)
XI Eastern Slovakia	1,204,000	208,748	11	5·2 (1:19,000)
Czechoslovakia	14,274,000	1,551,570	297	18·8 (1:5306)

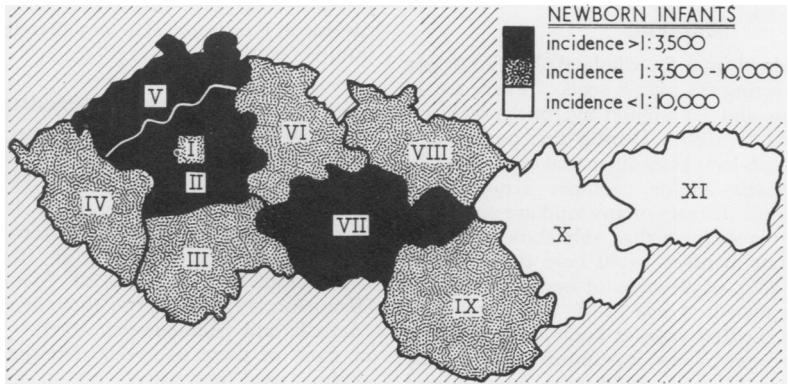

FIG. 1. The incidence of cystic fibrosis in Czechoslovakia (1960–67).

be reliably ascertained. Then we had to decide whether only those families could be included in which the exact number of sibs born up to the last year of the study had been checked. It is probable that, although a newborn affected child would be noticed, several newborn healthy sibs might not be recorded and this might wrongly increase the proportion of affected children. A follow-up study of this kind was performed in 1968 (the last year included in the present study) on 70 of the 190 families. The incidence of cystic fibrosis was, surprisingly, found to be higher in this group (55% affected children in 70 sibships) than in the whole group where 52% affected children were found. This result was considered to be sufficient grounds to allow this small error to be neglected and the calculations are therefore based upon 190 families (Table IV).

The method of ascertaining families by their affected children is called the 'truncate ascertainment method'. A group of sibships detected on the basis of clinical material never possesses the character of complete ascertainment as this postulates the investigation of every member of a given population or at least of every family with cystic fibrosis from the whole population within a certain period of time. Single ascertainment is, however, also out of the question, as with this method the chance of detection is proportional to the number of affected children in the family. In a country with a well-developed health service, every child with cystic fibrosis is sure to be detected and treated, ie, it will certainly become a propositus. Thus all affected children in urban areas are propositi: several children from rural districts, however, are treated only in small hospitals and do not reach the larger clinics unless they are severely ill or there are older affected sibs in the family.

Multiple ascertainment is therefore the method of choice and the methods used for estimating the type of heredity involved are those of Neel and Schull (1954), Vogel (1961), Penrose (1963), and Crow (1965).

Estimation of True Segregation Ratios in Sibships

A priori *Methods*. (1) Correction of total number of children (Bernstein, 1929). Estimated proportion of affected = 0·298 (30%).

(2) Correction of number of affected (Lenz, 1919; Hogben, 1946). D (observed affected—expected affected) = 47·8%; $\sigma = 7{\cdot}17$; $D/\sigma = 6{\cdot}6$ (see Table V).

(3) Percentage affected method (Macklin, 1938). Estimated proportion of affected = 43·3%.

TABLE III

OBSERVED AND ESTIMATED FAMILIAL INCIDENCE IN SIBSHIPS

	Baumann (1958)	Roberts (1960)	Bernheim *et al* (1961)	Mastella and Montenovesi (1964)	Present Series
No. of sibships	42	73	41	16	190
Total no. of children	139	225	128	40	574
No. affected	72	113	64	27	297
Observed percentage affected	51·8	50·2	50·0	67·5	51·7
Estimates of true percentage affected					
A priori method					
Expected	37·0	33·3	40·6	61·9	3·9
Observed—expected	14·8	16·9	9·4	5·6	47·8
σ	±3·7	±4·0	±3·5	±1·8	±7·2
D/σ	4·0	4·2	2·6	3·1	6·5
Macklin's (percentage affected) method ($p=0·25$)	—	39·8	—	—	43·3
Weinberg's simple sib method, percentage expected	—	—	38·0	61·0	4·10
Weinberg's proband method, percentage expected	—	30·0	—	—	32·4
Standard error					2·7
Weinberg-Just correction	30·9	—	—	45·8	27·8
Standard error	3·9	—	—	—	2·3

TABLE IV

DISTRIBUTION OF SIBSHIPS BY SIZE AND NUMBER OF RECESSIVES (CYSTIC FIBROSIS) IN A SIBSHIP

Sibship Size	Number of Recessives						Number of		
	1	2	3	4	5	6	Sibships	Recessives	Children
2	72 (34)*	16 (4)	—	—	—	—	88 (38)	104 (42)	176 (76)
3	30 (9)	27 (8)	4 (2)	—	—	—	61 (19)	96 (31)	183 (57)
4	5 (1)	11 (6)	3	1 (1)	—	—	20 (8)	40 (17)	80 (32)
5	2 (1)	4 (1)	—	1	1	—	8 (2)	19 (3)	40 (10)
6	3	1	1 (1)	1	—	1	7 (1)	18 (3)	42 (6)
7	—	—	1 (1)	—	—	—	1 (1)	3 (3)	7 (7)
8	1	—	1	—	—	—	2	4	16
9	—	—	—	1 (1)	—	—	1 (1)	4 (4)	9
10	—	—	—	1	—	—	1	4	10
11	—	—	—	—	1	—	1	5	11
Total	113 (45)	59 (19)	10 (4)	5 (2)	2 (0)	1 (0)	190 (70)	297 (103)	574 (188)

* The numbers of children controlled during 1967 (the last year of the study) are given in parentheses.

TABLE V

A PRIORI TEST FOR RECESSIVE MODE OF INHERITANCE

Sibship Size (s)	No. of Sibships (n)	Affected Sibs			Variance of Expected No.
		Observed	Expected for Assumed Incidence		
			$\frac{1}{4}$	$\frac{2}{5}$	
			$sn\,\frac{}{1-(\frac{1}{4})^s}$	$sn\,\frac{}{1-(\frac{2}{5})^s}$	
2	88	104	100·58	110·00	10·34
3	61	96	79·12	93·33	16·04
4	20	40	29·26	36·80	8·40
5	8	19	13·11	17·36	4·74
6	7	18	12·77	17·64	5·43
7	1	3	2·02	2·88	0·97
8	2	4	4·45	6·50	0·34
9	1	4	2·43	3·64	1·38
10	1	4	2·65	4·02	1·59
11	1	5	2·87	4·42	1·80
Total	190	297	249·26 $D_1=47·8$ $D_1/\sigma=6·6$	296·59 $D_2=0·4$	51·43 $\sigma=7·17$

TABLE VI

ANALYSIS OF 135 SIBSHIPS BY WEINBERG'S 'PROBAND METHOD'

Size of Family (s)	Number Affected (r)	Number of Propositi (n_a)	Number of such Sibships (n)	Total Number of Children	Total Number Affected	Total Number of Propositi (a)	a(r−1)	a(s−1)
2	1	1	47	94	47	47	0	47
2	2	1	10	20	20	10	10	10
2	2	2	3	6	6	6	6	6
3	1	1	22	66	22	22	0	44
3	2	1	12	36	24	12	12	24
3	2	2	5	15	10	10	10	20
3	3	1	2	6	6	2	4	4
3	3	2	1	3	3	2	4	4
4	1	1	3	12	3	3	0	9
4	2	1	9	36	18	9	9	27
4	2	2	2	8	4	4	4	12
4	3	1	3	12	9	3	6	9
4	4	2	1	4	4	2	6	6
5	1	1	3	15	3	3	0	12
5	2	1	3	15	6	3	3	12
5	4	1	1	5	4	1	3	4
6	1	1	1	6	1	1	0	5
6	2	1	1	6	2	1	1	5
6	3	1	1	6	3	1	2	5
6	4	1	1	6	4	1	3	5
6	6	1	1	6	6	1	5	5
7	3	2	1	7	3	2	4	12
10	4	1	1	10	4	1	3	9
11	5	1	1	11	5	1	4	10
Total	—	—	135	411	217	148	99	306

Corrected frequency of affected $p = \frac{\Sigma a(r-1)}{\Sigma a(s-1)} = 0{\cdot}324 = 32{\cdot}4\% \pm 2{\cdot}7\%$

$$\Sigma(p) = \pm\sqrt{\frac{\Sigma p(1-p)}{\Sigma a(s-1)}} = \pm 0{\cdot}027 = \pm 2{\cdot}7\%.$$

A posteriori *Methods*. (1) Simple sib method (Weinberg, 1928). Estimated proportion of affected = 41%.

(2) Maximum likelihood method (for k = 1 and Kaelin's tables).

p = 0·35 p′ = 0·4029
p = 0·40 p′ = 0·4009
p = 0·45 p′ = 0·4026.

(3) Method of discarding the singletons (Li and Mantel, 1968). Estimated proportion of affected = 0·40 (40%).

The above are examples of how different methods of ascertainment can result in widely different estimates of the proportion of affected subjects. It is interesting to note how the *a priori* estimate calculation is in agreement with an assumed incidence of $\frac{2}{5}$ at 40%.

Methods for Multiple Ascertainment (see Table VI).

Method for Single Ascertainment. Weinberg-Just's correction (Just, 1930) which gives a minimal estimate:

Total number of sibships N = 190
Total number of children T = 574
Total number of affected children R = 297

$$b = \frac{R-N}{T-N} = \frac{297-190}{574-190} = \frac{107}{384} = 0{\cdot}278$$

$$V(b) = \frac{ab}{T-N} = \frac{72{\cdot}2 \times 27{\cdot}8}{384} = 5{\cdot}22$$

Standard error of $b = \sqrt{5{\cdot}22} = 2{\cdot}285$

Proportion of affected = 27·8% ± 2·28%.

Discussion

It is essential that incorrect ascertainment methods be regarded as the cause of the fact that *a priori* and *a posteriori* methods give results which are incompatible with an autosomal recessive heredity mechanism (giving an average of approximately 40% affected individuals in sibships). A similar situation has also arisen in the work of other authors (see Table III).

Weinberg's proband method, which is the only one adequate for the type of ascertainment in question (multiple ascertainment) and Weinberg-Just's correction (single ascertainment) give a result of 32% and 28% affected members respectively. As, however, both these methods tend to give a lower limit of the estimate, it seems reasonable to seek an explanation for the higher proportion of affected members elsewhere: (1) manifestation of the disease in some heterozygotes, (2) heterogeny, (3) gametic selection (suggested by Professor Penrose), ie, a gametic advantage of the sperm carrying the gene for cystic fibrosis.

Summary

In the region surveyed, with 4,330,000 inhabitants, 490,000 live births were recorded during the 8-year period 1960–67. Of these live births, 147 were diagnosed as cases of cystic fibrosis. The incidence of the disease in Czechoslovakia is therefore 1 in 3300 live births.

There were 190 sibships in which more than one affected child was found and these were studied and

the proportions of healthy and affected members calculated. The results are in accordance with similar findings on the subject in that the condition does not seem to follow a simple autosomal recessive pattern, if complete ascertainment is assumed. Analysis by methods for multiple or single ascertainment, on the other hand, give results of 32% and 28% affected members respectively, and, although these are compatible with the autosomal recessive mechanism, the small proportion of affected individuals in excess of the expected number still remains to be explained.

The author wishes to express his sincere gratitude to Professor L. S. Penrose for his helpful criticisms of this paper and valuable suggestions for further research in this field.

He is also indebted to all the paediatricians who submitted some of their data, above all to Dr N. Šimanková (1st Pediatric Clinic, Prague), Dr V. Vávrová (2nd Pediatric Clinic, Prague), Dr P. Endler (Pediatric Department, Usti nad Labem), Dr J. Polákovi (Pediatric Clinic, Hradec Králové), Dr J. Filipová (Pediatric Clinic, Olomouc), Dr J. Michaličková (1st Pediatric Clinic, Bratislava), and Dr Boksajová (Košice).

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