J Clin Epidemiol Vol. 41, No. 6, pp. 583–591, 1988
Printed in Great Britain.

0895-4356/88 $3.00 + 0.00

A COMPARISON OF SURVIVAL, GROWTH, AND PULMONARY FUNCTION IN PATIENTS WITH CYSTIC FIBROSIS IN BOSTON AND TORONTO

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(*Received in revised form* 23 *September* 1987)

Abstract—Two cystic fibrosis (CF) clinic populations of similar size and age distribution were compared with respect to growth, pulmonary function, and survival. Height and weight measurements were made on 499 patients in Boston (mean ± SD age 15.9 ± 9.6, range 1 month to 45 years) and on 534 patients in Toronto (mean ± SD age 15.2 ± 8.3, range 1 month to 43 years). Males constituted 57% in the Boston group, 58% in Toronto. Pulmonary function test results were recorded for 64% of the Boston patients and 77% of the Toronto patients. Survival curves for the period 1972–1981 generated by the CF Patient Registry were compared.

Patients in Boston tended to be shorter than patients in Toronto. This pattern was seen in both sexes in the 10–20 year age groups. Toronto males also weighed more than Boston males. Mean forced expiratory volume in one second (FEV_1) was not different in Boston and Toronto CF patients whether expressed as a percent of predicted or in litres by age groups. Median age of survival in Boston was 21 years, in Toronto 30, the two curves showing a marked separation from age 10. Although progressive pulmonary disease is the major cause of mortality in cystic fibrosis, the differences in growth and survival in these two patient groups, with very similar age-specific pulmonary function, suggest further examination of nutritional guidance and intervention in CF, especially regarding the traditional restriction of dietary fat.

INTRODUCTION

Cystic fibrosis (CF) is a recessively inherited genetic disease, characterized by abnormalities of exocrine secretions, particularly in the sweat gland, the lungs, and the pancreas. The incidence of CF in Caucasian populations is estimated as one in every 2000 live births [1]. Incidence in non-Caucasians is much rarer, with estimates around 1/20,000 in blacks, 1/100,000 in Orientals. Long term survival of patients with cystic fibrosis has improved dramatically over the last 40 years [2]. However even now some 15–20% of children with CF in the U.S. and Canada die before their tenth birthday with some combination of the pulmonary and gastrointestinal symptoms typical of CF. On the other hand there are ever-increasing numbers of patients in their 20s, 30s and 40s, many of whom live relatively normal lives in spite of long-term, gradually progressive, obstructive lung disease.

Because the clinical course of CF is so variable, large numbers of patients must be followed over long periods of time in order to evaluate the effects of chronic treatment and other environmental factors. Prospective follow-up with appropriate control groups is the best way to demonstrate whether or not a particular treatment or practice is beneficial. However cross-sectional studies of large, well-documented groups of patients can be very useful for suggesting hypotheses and delineating patterns for further investigation. In this study the characteristics of two large clinic populations in

Supported by a grant from the Canadian Cystic Fibrosis Foundation

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Boston and Toronto were examined in order to define the modern CF population, to describe similarities and differences in the two groups, and to suggest further epidemiological and clinical investigations.

METHODS

Children's Hospital in Boston and The Hospital for Sick Children (HSC) in Toronto both have well established clinics for the care of cystic fibrosis patients, as well as research and training programs in CF. All patients who were seen in either centre in 1982, for routine care of CF, were included in this study, including those who died or who transferred out of the clinic later in the year.

Height, weight, age, and sex were recorded for each patient, at the time of a regular clinic visit. The results of pulmonary function tests were also recorded if done within 6 months of the clinic visit. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were recorded in litres. Percent of predicted values for sex and height were computed for each patient using HSC pulmonary function laboratory standard equations. Percentile height and weight, and weight as a percentage of ideal for height were computed for each patient using the tables of Tanner *et al.* [3]. Information regarding age at diagnosis, ethnic origins, and residental distance from clinic was retrieved from patient charts. Ethnic distributions in the metropolitan areas of Boston and Toronto were compiled from Census publications for U.S. 1980 and Canada 1981.

Both clinics submit annual status reports on each CF patient to the CF Patient Registry in Rockville, Maryland [4]. Life tables are constructed from age-specific death rates during observation periods of 1, 5, and 10 years. Details have been reported [2]. Each patient contributes 1 year of exposure in each year of age that he was seen during the observation period. The resultant cumulative survival curves represent the mortality in the population during that period. A 10 year observation period is necessary in order to observe a reasonable number of deaths in each clinic for estimates of age-specific mortality rates.

Registry reports also include summaries of patients who are newly diagnosed, and those who transfer in or out of each clinic each year. Patients who transfer out of a clinic in a given year are excluded from that clinic's survival data for that year, only if they were not seen during the year. A report on the data for a particular clinic is sent to the clinic director, along with national summaries. Registry reports for the observation period 1972–1981 have been used to describe survival patterns in the U.S. and Canada, and in Boston and Toronto, because population distributions in the clinics in 1982 were the result of the diagnosis and mortality patterns during 1972–1981.

In order to test the association between nutritional status and mortality, and to assess the potential selection bias due to differential transfer rates in the two clinics, the 1982 anthropometric and pulmonary function data of those patients who died or who transferred out during 1982 or 1983 were compared to the data of those who remained.

RESULTS

Boston and Toronto are two North American cities of similar size and climate. In the 10 year period leading up to 1982, both clinics had similar stable patterns of diagnosis and treatment of CF patients. Presenting symptoms, complications, and therapeutic practices have been described [5–7]. In the Registry reports for 1972–81 data, the average annual number of newly diagnosed patients was 28 in Boston, 21 in Toronto. The average annual numbers of patients transferring into the Boston and Toronto clinics were 44 and 16 respectively; transferring out were 42 and 11; and dying were 25 and 9. The net results were a decrease in the Boston clinic population of approximately 5 patients per year, and an increase in Toronto of 17 patients per year.

In 1982 both clinics drew approximately 50% of their CF patients from an area within 50 miles of the clinic, 20–25% from 50–100 miles, 20% from 100–200 miles, and 5–10% from distances greater than 200 miles. Patients' addresses were distributed in all socio-economic areas in both clinics. Twenty-five percent of the Boston patients came from outside the state, while only 2% of Toronto patients came from another province. However Ontario covers a much larger area than does Massachusetts. Both clinics provided primary CF care for a large majority of the CF patients living within 100 miles (Boston 85%, Toronto 90%). Neighbouring clinics of both centres are much smaller and there is a similar probability of very ill patients or those with complications being re-

Table 1. Characteristics of the CF clinic populations in 1982 in Boston and Toronto

	Boston	Toronto
Number of patients	499	534
Percent male/female	57/43	58/42
Age (yr)		
Mean ± SD	15.9 ± 9.6	15.2 ± 8.3
Range	0–45	0–43
Age at diagnosis (yr)		
Mean ± SD	3.1 ± 4.9	3.1–5.1
Median (range)	1.1 (0–39)	0.9 (0–34)

ferred to the specialized pediatric hospitals of this study.

Ethnic origins were not available in most patient charts. The information available, supplemented by clinic staff members' knowledge of the patients, suggested similar distributions. A majority of families were of Irish or British descent, followed by smaller groups of French, Italian or Greek background, and smaller still numbers originating in other European countries. There was one Black patient in Toronto and three in Boston. The metropolitan population percentages of Black, Asian, and Hispanic heritage were different in Boston (22.5, 2.9, 6.5) and Toronto (2.5, 6.3, 2.8). But the ethnic distributions of the Caucasian populations were very similar. Family origins reported by Census respondents in Boston and Toronto respectively were: 48 and 50% British or Irish, 10 and 10% Italian, 2 and 3% French, 2 and 3% German, 1 and 3% Portuguese, 2 and 2% Polish, 1 and 2% Greek, 2 and 0.2% Russian, 0.2 and 2% Ukrainian, 0.2 and 1% Dutch. All other groups were represented by less than 1% in both cities.

Table 1 summarizes the patient groups in the two clinics in 1982. There were 499 patients in Boston, 534 in Toronto. The mean age in Toronto was slightly less than in Boston but both clinics followed all their patients regardless of age so that the age range was similar. Median and range of age at diagnosis were comparable. The percentage of patients who were male was also similar. The age–sex distributions in the two clinics are shown in Fig. 1. The Boston clinic on the left shows a fairly smooth distribution, with some patients clearly not yet diagnosed in the youngest age group. The effect of mortality is seen in decreasing percentages, especially of females, at ages over 20.

The Toronto clinic had a somewhat younger population, the percentage of patients dropping off rather sharply in the 25–30 age group. This drop does not reflect patients leaving the clinic group, through excess mortality, transfers, or loss-to-follow-up, but may well reflect the fact that the Toronto clinic has only been in operation since the early 1960s.

The CF Patient Registry Reports have noted for several years that the survival curve for Canadian centres looks better than that for U.S. centres [4]. Figure 2 shows the Registry survival curves for the U.S. and Canada, as well as for Boston and Toronto, for the 1972–1981 period, for patients with normal birth, excluding approximately 10% of the patients in each clinic who presented in the neonatal period with meconium ileus. Historically these patients had

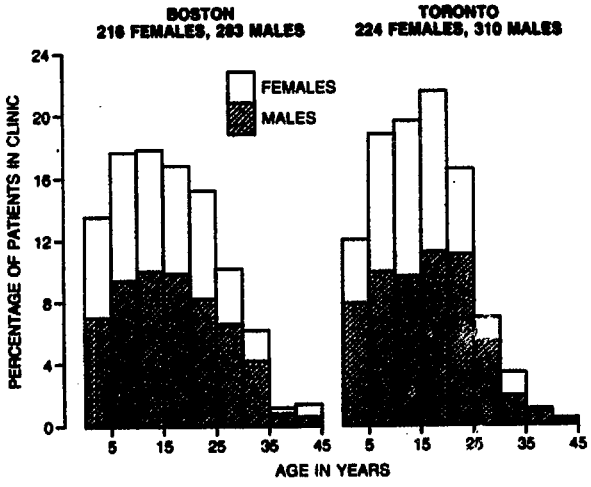

Fig. 1. Distribution of CF patients according to sex and 5-year age groups in the Boston and Toronto clinic populations.

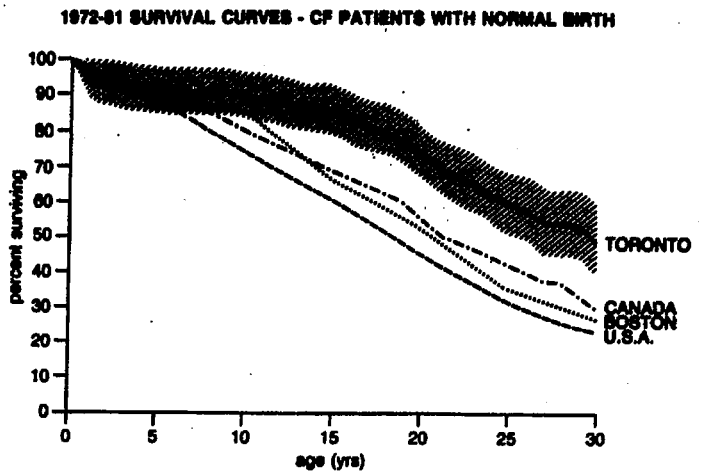

Fig. 2. Survival curves 1972–81 for patients without meconium ileus at birth in Toronto and Boston, and in all CF care centres in Canada (including Toronto) and U.S.A. (including Boston).

greatly increased infant mortality, so their survival was reported separately. Confidence limits of 95% are shown around the Toronto curve to give an idea of the variability in the estimates of both centre curves.

The Canada and U.S. curves separate gradually from the earliest ages so that 50% or median survival in the U.S. group is to age 19, in the Canadian group to age 21. Both Boston and Toronto curves show better survival than the respective national curves, but after age 10, the Toronto curve shows markedly better survival than Boston. Median age of survival is 30 years in Toronto, 21 years in Boston.

Figure 3 shows height for males plotted against age. The dotted lines in the background are the 3rd, 50th and 97th percentiles for normal subjects. Toronto means ± 2 SD at the midpoint of each year of age are joined by solid lines, Boston means ± 2 SD by dashed lines. In displaying the entire age and height range on one figure, patterns at some points become obscured. However the major population similarities and differences are clear. Under the age of 8 and over 25 the Boston and Toronto lines are not distinguishable. Between the ages of 10 and 25, the dashed Boston line is consistently below the solid Toronto line, except at age 17.

Mean percentile height was compared by t-test in the whole population and in 5 year age groups. The Boston male average was at the 33rd percentile, significantly shorter than the Toronto male average at the 42nd percentile ($p < 0.001$). The difference was due to highly

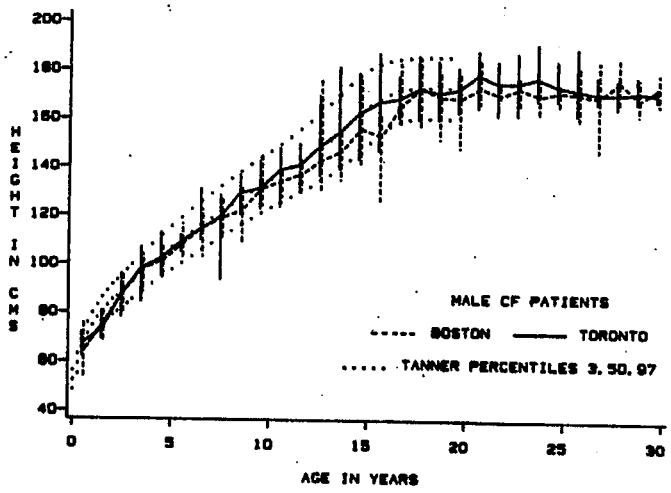

Fig. 3. Heights of male CF patients in Boston and Toronto, mean ± 2 SD at each year of age.

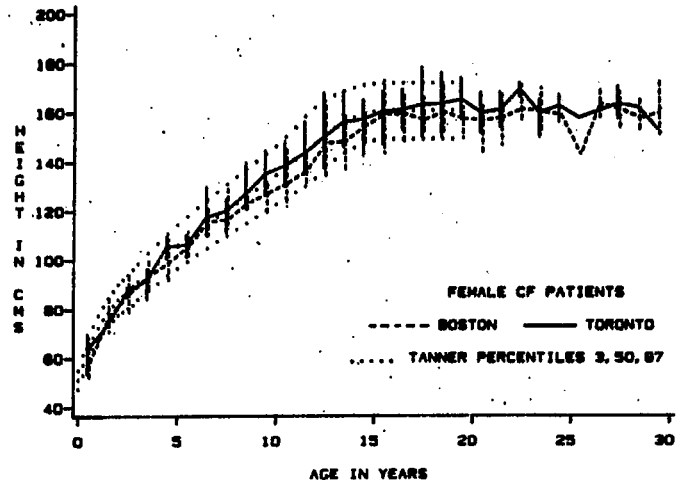

Fig. 4. Heights of female CF patients in Boston and Toronto, mean ± 2 SD at each year of age.

significant differences in the 10–15 and 20–25 age groups. The other age groups did not show significant differences. Figures 3–6 show the data only up to age 30, since after that age, there was no suggestion of clinic differences. Mean values fluctuated in the fashion seen here from ages 25–30.

Figure 4 shows the mean height at each age for females in Boston and Toronto. Like the males, Toronto females had heights that averaged around the 44th percentile, Boston around the 33rd. Boston females are significantly shorter than Toronto females in the 5–10, 10–15, and 15–20 year age group ($p < 0.01$) there being no significant difference under age 5 or over age 20. There is only one female in each clinic at age 25 so no standard deviation is shown, and what looks like a large difference has a relatively small effect on the age group mean.

In Fig. 5 the weights for male patients in Boston and Toronto show the same pattern as seen in the heights. The standard deviations for weight are wider than for height, the CF weights ranging far below normal at most ages. The Boston 17 year old males displayed excellent weight to match their height, but as with height the male percentile weights in Boston were significantly lower than in Toronto in the 10–15 and 20–25 year olds ($p < 0.01$), the population average at the 35th percentile in Boston, the 43rd percentile in Toronto.

The weights for females shown in Fig. 6 demonstrate a different pattern for Toronto

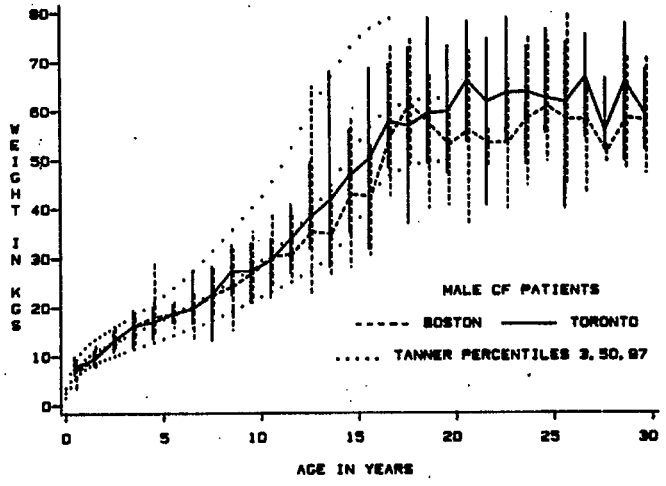

Fig. 5. Weights of male CF patients in Boston and Toronto, mean ± 2 SD at each year of age.

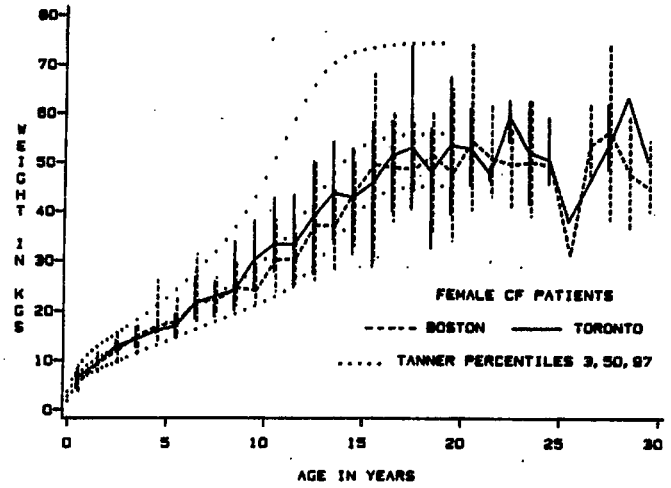

Fig. 6. Weights of female CF patients in Boston and Toronto, mean ± 2 SD at each year of age.

females. While they appear to have better weight percentiles than Boston females in age group 10–14, in fact this difference is not significant, and certainly at all other ages there is no consistent pattern of better weight in either group. The population average for weight percentile was 29 in Boston, 31 in Toronto. Again the two patients at age 25 show a dramatic but isolated effect.

When weight was calculated as a percentage of the ideal weight for an individual's height the Boston females had a significantly ($p < 0.001$) better mean weight for height, at 97%, than the Toronto females whose average weight for height was 93. For males in both clinics, mean weight for height was 100%, significantly better than females in Boston ($p < 0.05$) and Toronto ($p < 0.001$). Poor weight for height in Toronto female patients, especially over the age of 15, has been reported previously [5] and may be related to the difference in survival between males and females in Toronto. Survival curves by sex, for Boston patients were not available during this analysis, but the proportions of males seen in the age–sex distribution would suggest better survival for males.

Table 2 shows the mean values of forced expiratory volume in one second, FEV_1, which is a good indicator of airway obstruction over a wide range of clinical severity [8]. FEV_1 in CF patients is usually presented as a percent of predicted for sex and height, but since height differed significantly in Boston and Toronto over a large age range, Table 2 also shows mean FEV_1 in litres. There were no significant clinic differences in any age group or combination of age groups, suggesting that the surviving patients in both Boston and Toronto had comparable lung function for their age and sex. The statistical power of the comparisons of mean percent predicted values, in separate or pooled age groups, was similar to that for the corre-

Table 2. Forced expiratory volume in one second (FEV_1), mean ± SD, by sex and age group in Boston and Toronto

		Females			Males		
Age	Clinic	N	FEV_1 % pred.	FEV_1 litres	N	FEV_1 % pred.	FEV_1 litres
5–9	Boston	25	102 ± 28	1.23 ± 0.35	37	87 ± 25	1.24 ± 0.38
5–9	Toronto	34	89 ± 21	1.32 ± 0.47	40	89 ± 19	1.40 ± 0.33
10–14	Boston	33	82 ± 30	1.73 ± 0.71	40	78 ± 27	1.75 ± 0.77
10–14	Toronto	51	77 ± 22	1.73 ± 0.60	47	74 ± 20	1.80 ± 0.57
15–19	Boston	26	69 ± 32	2.00 ± 1.02	36	80 ± 27	2.82 ± 1.06
15–19	Toronto	49	65 ± 24	1.97 ± 0.84	59	73 ± 28	2.69 ± 1.11
20–29	Boston	40	61 ± 27	1.70 ± 0.78	52	51 ± 26	1.96 ± 1.06
20–29	Toronto	31	63 ± 26	1.85 ± 0.74	79	58 ± 28	2.28 ± 1.10
30–45	Boston	9	48 ± 29	1.42 ± 0.85	19	55 ± 26	2.33 ± 1.27
30–45	Toronto	10	45 ± 26	1.35 ± 0.85	13	44 ± 16	1.79 ± 0.69

Table 3. Mean ± SD values of age, percentile height and weight, and % predicted FEV_1 for CF patients in Boston and Toronto in 1982. Those who died or transferred out in 1982–83 are compared to those who remained

Clinic	Status	N	Age (yr)	Height %ile	Weight %ile	FEV_1 % pred.
Boston	Died	25	21.1 ± 8.7**	31 ± 25	8 ± 11***	34 ± 24*
	Transferred	87	17.6 ± 9.4*	36 ± 28	33 ± 31	67 ± 30
	Remained	385	15.1 ± 9.6	32 ± 28	33 ± 30	74 ± 32
Toronto	Died	34	18.3 ± 6.9*	33 ± 29*	14 ± 20***	33 ± 17***
	Transferred	36	14.8 ± 8.8	49 ± 29	44 ± 30	73 ± 25
	Remained	464	14.9 ± 8.3	43 ± 29	39 ± 28	73 ± 25

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ for Student's t-test of the difference between the mean for patients who died or transferred and the corresponding mean for the remaining patients.

sponding comparisons of height and weight percentiles, since the magnitude and variance of these measures were very similar.

Of the patients seen in 1982, the numbers who died or transferred out of each clinic during 1982 or 1983 are shown in Table 3. Mean values of age, percentile height and weight, and FEV_1 % predicted for these patients are compared to those of the remaining patients. In both clinics, the patients who died within 1 or 2 years were older, and had significantly reduced nutritional and pulmonary measures. More than twice as many patients tranferred out of the Boston clinic than the Toronto clinic. However in both clinics the mean values of the transferring patients were very similar to those of the remaining patients, except that in Boston the patients transferring tended to be older.

DISCUSSION

Boston and Toronto are two large centres for CF care and research with similar numbers of patients who were distributed similarly with respect to age, sex, and ethnic background, and who had comparable lung function. However Boston patients were significantly shorter than Toronto patients, and Toronto male patients maintained significantly better weight. Previous reports from Boston [9] and Toronto [10] indicated that patients in both clinic groups showed a notable lack of psychological or social pathology, compared with earlier descriptions in CF. Although data on family income or employment was not collected in this study, the patients' residential addresses represented all socioeconomic sectors in the two cities.

The fact that the very young children and the long surviving adult patients in both centres had similar heights and weights suggests that the differences between ages 5 and 25 are probably not due to differences in ethnic mix. Although there are many components of treatment that may have differed in the two centres over the last 20 years, the general approach has been the same, stressing prophylactic therapy to avoid respiratory illness and gastrointestinal malfunctioning, with aggressive treatment of acute pulmonary infections. However the approach to diet and pancreatic supplementation was radically different between the two centres. In the early 70s Crozier [6] from Toronto advocated a high fat, high calorie diet with up to 20 or 30 pancreatic enzyme capsules per meal, whereas Shwachman [7] from Boston advocated a low fat, high calorie diet with much less pancreatic enzyme capsules per meal. This restriction of dietary fat was standard treatment in other North American CF clinics. It is possible that the height and weight differences presented in this report are the result of these different treatment regimes, and that improved growth and nutrition have contributed to better survival in the Toronto patients.

Testing this hypothesis would involve more than the usual number of problems inherent in long term clinical trials. The treatment to be evaluated is inextricably bound up with culture and lifestyle. Even if random allocation to two groups—high and low dietary fat were to be accepted, only general guidelines for each diet could be given since it would be unrealistic to prescribe specific foodstuffs or quantities for each patient over several years. An ethical issue arises since the accepted mode of treatment has historically been the restriction of a normal healthy diet, but the present study demonstrates that one large CF clinic population has achieved exemplary patient growth and survival without recommending the traditional restricted diet.

Other possible factors must be considered that may contribute to differences in the Boston and Toronto CF patients. Canadian patients have had greater access to medical care pro-

grams that minimize the financial burden of hospitalization and prescribed drugs. Thus Toronto patients may be healthier because of better health care delivery. Alternatively, the Boston clinic population may have an underrepresentation of relatively healthy patients because of costs associated with attendance and compliance in clinic programs. Two to four times as many patients do not return for care each year in the Boston clinic, compared to the Toronto clinic. However there was no evidence in the 1982 patients that those transferring out of the clinic were healthier. Since a similar number were reported transferring in and out each year in the 1972–81 Registry data, this pattern may suggest more population mobility in Boston than in Toronto, or more clinic-switching because of the greater proximity of alternatives.

Another possible factor may be the distribution and virulence of viruses and bacteria in different geographic regions causing differential morbidity and mortality in susceptible patient groups. The most notable differences in respiratory disease therapy have been the more prevalent use of inhaled bronchodilators in Toronto and the use of mist tents in Boston but not in Toronto since 1972. Such environmental and treatment factors would be expected to cause at least as great a differential in pulmonary status as in growth in patients with CF. Yet there was no evidence that the Toronto patients had better pulmonary function values. Both pulmonary function and weight were significantly reduced in the Boston and Toronto patients who died within 1 or 2 years of their 1982 measurements. It is not possible in this cross-sectional study to say whether the poor weight was secondary to lung disease or whether it contributed independently to mortality. However poorer growth in the surviving Boston patients in 1982 cannot be attributed only to worse lung disease, since FEV_1 in each age group was similar to that in the Toronto patients.

There is no good explanation why females with CF had poorer weight and greater mortality in both centres in comparison with the males. It is too simplistic to suggest that females are unable to ingest sufficient calories or tend to be less compliant with therapy than males. One recent study [11] based on 28-day food records of nine male and six female patients in the Toronto clinic, found that both the males and females had energy intakes, and fat intakes in particular, that were similar to those of their adolescent counterparts in a regional health survey. The average intake for the females was 98% of the Canadian Recommended Daily Nutrient Intake whereas that of the males was 109%. It is possible that the increase in hormone secretion associated with menarche interferes with the immunological defense mechanisms in the lung of CF females facilitating progressive pulmonary involvement and subsequent mortality.

Several studies [12–14] have shown that late nutritional intervention can result in some weight gain and temporary clinical improvement in severely malnourished CF patients. However there have been no studies showing an impact of nutritional intervention on long-term survival. Prospective studies of the effect on growth and survival of nutritional encouragement and intervention early in the course of the disease are clearly required. The growth and survival data for the Toronto clinic suggest that restriction of fat intake in the diet of CF patients is not necessary.

Both Boston and Toronto clinic groups show similar age and sex distribution of patients, similar median and range of age at diagnosis, and similar decline of pulmonary function with age. In these respects they probably represent the modern North American population of CF patients who have access to multidisciplinary care in CF centres. Prospective comparison of the Boston and Toronto groups has been undertaken in order to investigate longitudinally the cross-sectional differences that have been noted. Patient registries in both U.S. and Canada have recently expanded to include pulmonary and anthropometric measures, which will enhance the study of longitudinal patterns of mortality and morbidity in CF.

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