Familial hypercholesterolemia (FH) is an inherited disorder characterized by hypercholesterolemia due to high plasma levels of low density lipoproteins (LDL), xanthomatosis, and premature coronary heart disease (CHD). It is one of the most common single-gene disorders resulting from mutations in the gene coding for the LDL receptor. The disorder is transmitted in both heterozygotes and homozygotes, and the frequencies have been estimated at 1 in 500 and one in a million, respectively. These population frequencies are remarkably similar in most countries: United States, England and Wales, Norway, Denmark, and Japan; Lebanon and white Afrikaaners from South Africa are exceptions and have a remarkably higher prevalence of FH. In the French-Canadian population of the province of Quebec, although no prevalence figures are available, it has been our collective experience that heterozygote FH patients constitute an unusually large proportion of Lipid Clinic patients. Because of the difficulties involved in conducting a large-scale epidemiological survey, a census of homozygous patients throughout the province of Quebec was undertaken. In this report, we present data on the high prevalence of FH among French Canadians, based on the frequency of contemporary homozygotes and assuming that the study population is in Hardy-Weinberg equilibrium.

Methods

Patients

Twenty-six patients with homozygous FH from 21 families were documented by the Lipid Clinics in 1988: 20 patients were seen at Laval University Medical Center in Quebec City and 14, at four clinics in metropolitan Montreal; eight patients were documented by more than one clinic. Of the 26 homozygotes, 22 were born in the province of Quebec, three in New Brunswick, and one outside Canada, in Lebanon. We used 1981 Canada census figures to estimate gene frequencies; accordingly, the two patients not alive in 1981 and one patient born after 1981 were not included. Thus, in the present study, data are derived from 19 patients born in the province of Quebec to 16 families of French-Canadian origin. Fourteen families produced one homozygote each. In one family, there were two homozygous siblings and in another, three. When the prevalence of homozygous FH was estimated, the population of French Canadians in the province of Quebec at the time of the 1981 census was approximately 5.3 million. This number was used to estimate the prevalence of heterozygotes with FH.

Plasma lipoprotein fractions were prepared by the combined use of ultracentrifugation and heparin-manganese precipitation. Plasma was centrifuged at 40,000 rpm in a Beckman 50.3 rotor at a density of 1.006 g/ml for 18 hours. Tubes were sliced, and the very low density lipoprotein fraction was removed. The infranatant...
### Table 1. Clinical Features of 19 Homozygotes with Familial Hypercholesterolemia Living at Time of 1981 Census

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<th>Case</th>
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*Age at time of the 1981 Canada census. AC=Arcus corneae, XTLA=xanthelasma, SM=systolic aortic ejection murmur, MI=myocardial infarction, L=living. Cases linked by brackets are siblings.*

(d>1.006 g/ml) was used for LDL and high density lipoprotein (HDL) determinations after LDL precipitation by addition of heparin and manganese chloride. The cholesterol and triglyceride concentrations in plasma and lipoprotein fractions were quantified on an AutoAnalyzer AA-II (Technicon Instruments Corp, Tarrytown, NY) as previously described. Plasma apoprotein (apo) B levels were determined by rocket immunooassay as reported previously.

### Results

#### Clinical and Biochemical Features of Homozygotes

Diagnostic criteria for the homozygous phenotype were: 1) plasma cholesterol levels above 550 mg/dl, 2) appearance of xanthomas at an early age, 3) detection of hypercholesterolemia in both parents. All subjects met the first two criteria; 14 cases also met the third. In cases 13 and 16, the father had died of early CHD. In cases 5 and 14, neither parent had cholesterol values available, but the probands had died of CHD at ages 11 and 20, and hypercholesterolemia was documented in several first-degree relatives. In case 3, the data on the father had documented hypercholesterolemia, but the value was not available.

The cohort consisted of 11 female subjects and eight male subjects with an average age of 15 years (range of 1 to 26 years). Only five subjects were younger than 10 years old. The clinical features of this cohort (Table 1) were typical of the homozygous state. Tendon and tuberous xanthomas were present in all patients; interdigital and other planar xanthomas were present in all but two patients. Arcus corneae were observed in six persons and xanthelasma, in three persons. Another prominent feature was an audible aortic ejection murmur in 13 patients. Angina pectoris was diagnosed in nine patients and myocardial infarction, in seven patients. Five patients died from sudden death due to CHD; their ages ranged from 11 to 27 years.

The concentration of plasma cholesterol (Table 2) showed a more than twofold variation among the homozygotes (mean, 854 mg/dl; range, 557 to 1532 mg/dl). There was no correlation between presence of CHD, age at death, and plasma cholesterol concentrations. Plasma levels of apo B and LDL cholesterol were increased; HDL cholesterol levels were lower than normal. Plasma triglyceride levels (72 to 355 mg/dl) were normal or moderately elevated.

The concentrations of plasma lipids and lipoproteins are given as maximum and minimum levels (Table 2) observed in each homozygote since first consultation. The minimum values are those obtained under various pharmacological or nonpharmacological treatments. All patients received lipid-lowering drugs alone or in combination. The lipid-lowering drugs used were cholestyramine, clofibrate, gemfibrozil, mevinolin, niacin, and probucol. The nonpharmacological approaches used were portacaval shunt in cases 4, 5, 7, 8, and 18, partial ileal bypass in case 13, and LDL-apheresis in cases 4 and 16. Of all the treatments, LDL-apheresis was the most effective in lowering plasma cholesterol levels. The lowest HDL cholesterol levels were observed during probucol administration.
Prevalence of Familial Hypercholesterolemia

The present population of the province of Québec is 6.4 million, 83% of whom (5.3 million) are descendants from approximately 8000 immigrants from northern and western France who settled in Canada between 1608 and 1763.19 The 19 homozygotes from 16 families in this study were all of French-Canadian origin. Thus, the minimum prevalence of homozygotes among French Canadians in the province of Québec was 3.6 per million. Using this figure, we estimated the frequency of the allele (q) for FH as 0.0018708. The frequency of the normal allele p, is 1-q=0.9981292. Thus, the frequency of FH heterozygotes is about 4 per 1000.

The geographical location of homozygotes in the province of Québec is shown in Figure 1, and the data on the population frequency estimates of the FH gene are presented in Table 3. Of the 19 homozygotes, 17 were located in northeastern Québec, which has a population of about 1.6 million, mostly of French descent and with very little crossbreeding from people of other origins. Thus, in northeastern Québec (regions 01, 02, 03, and 09), the prevalence of homozygotes is 1 in 100,000, and the frequency of FH heterozygotes is 1 in 154, with a regional range varying from 1 in 81 to 1 in 208.

Discussion

The frequency of homozygotes with FH in the French-Canadian population of Québec is much higher than that reported in populations elsewhere.1 Two other regions of the world have high frequencies: Lebanon2 and South Africa.9 The frequency of heterozygotes in most studies1 is generally estimated at 1 in 500 except in Lebanon and South Africa, where, based on the number of homozygotes and using the Hardy-Weinberg equation, the estimated frequencies of heterozygotes are 1 in 1714 and 1 in 100,9 respectively. Based on similar calculations, we estimated the heterozygote frequency of FH as ~1 in 270 in the province of Québec. Due to the high concentration of homozygotes, mainly in northeastern Québec, the minimal estimated frequency of FH in this region was 1 in 154, and even as high as 1 in 81 in one region. The exceptionally high gene frequencies in Lebanese and Afrikaaners were attributed to founder effects in comparatively isolated communities and were maintained by a high incidence of consanguineous marriages. The geographic, historical, and demographic characteristics of the population of northeastern Québec also suggest random genetic drift in the form of a founder effect as likely explanation for the higher gene frequency of FH.

The settlement of the present Québec territory was begun in the early 17th century (1608 to 1763) around Québec City.18,19 During that period, 8527 immigrants arrived from northern and western France and settled in the Saint Lawrence Valley (Figure 1). The population growth after that was the result of an unusually high birth rate, at times as high as 50 to 60 per 1000 per year with
very little immigration. Today, there are approximately 5.3 million French Canadians, of which 1.6 million inhabit northeastern Québec. The first migrations to eastern Québec were along the Saint Lawrence Valley and later extended inland. The lack of further immigration and high fertility rates contributed to the high incidence of genetic disorders: cystic fibrosis, Sipple's syndrome, tyrosinemia, vitamin D-dependency rickets, spastic ataxia, and myotonic muscular dystrophy. Some of these disorders are more specific to Saguenay-Lac Saint-Jean. From the geographical distribution of FH homozygotes, it is reasonable to assume that more than one gene mutation may be responsible for the clinical manifestation of FH. Recently, a large deletion of more than 10 kilobases from the 5' end of the gene for the LDL receptor was shown to occur in 63% of the French-Canadian heterozygotes and was also detected in 4 of 7 homozygotes. One homozygote, who had inherited one copy of the 5' deletion and one copy of another LDL receptor mutation, which has not yet been characterized (JL Goldstein, personal communication). The characterization of other mutation(s) in the LDL receptor gene will be helpful to establish the precise gene frequencies of these mutations, their geographical distribution, and their relation to migratory pathways in northeastern Québec.

The mean plasma cholesterol level of 854 mg/dl was similar to reported values of 728 mg/dl from Lebanon, 678 mg/dl from the United States, 713 mg/dl from Japan, and 786 mg/dl from South Africa. The mean plasma cholesterol concentration of 359 mg/dl in the parents was approximately half that of the homozygotes and similar to our previously reported findings in French Canadians. Nevertheless, marked heterogeneity in both plasma and LDL cholesterol was observed in this cohort, as has also been reported extensively in previous studies. In the pres-
ent study, 5 of the 17 homozygotes died of sudden death due to acute CHD, which is the prime cause of early death in these patients. Although the mean age at death of 21 years is comparable to that in Japanese (20 years) and Afrikaners (19 years), it is important to point out that only one subject in this study died before age 20 as compared to four of seven and four of six, respectively, in the studies cited above. In our cohort, the age at death was not related to plasma cholesterol levels, nor were there differences in plasma cholesterol levels between subjects with clinical CHD (824 mg/dl, n=10) and those without symptoms (890 mg/dl, n=9). However, differences in LDL cholesterol levels have been reported between subjects with and without myocardial ischemia.24,25 These authors also reported that the heterogeneity in CHD was associated with the LDL receptor activity status (negative/defective) of the patients. Perhaps studies in homozygotes of the same ethnic origin will address this question more thoroughly.

The concentration of HDL cholesterol reported in several studies in homozygotes9,22,25,26 has been consistently lower than in controls. The mean HDL cholesterol concentration of 37 mg/dl was relatively higher than the previously reported values of 34 mg/dl,22 28 mg/dl,25 and 20 mg/dl.26 A much smaller relative decrease in HDL cholesterol in heterozygotes was also documented in several studies.13,22-27 In the present cohort of homozygotes, the concentration of HDL cholesterol was significantly lower in subjects with myocardial infarction than in those without clinical manifestations of CHD (X±SD, 30.7±4.5, n=6 vs. 44.3±9.1, n=7; p<0.01). Whether HDL particles play any role in the clinical course of CHD in FH homozygotes merits further investigation. Since HDL cholesterol concentrations are consistently lower in homozygotes of various ethnic origins, it is likely that HDL metabolism is modulated by tissue cholesterol overload due to the primary accumulation of LDL particles.

Acknowledgments

This study was made possible by the efforts of the Collaborative Research Group on Familial Hypercholesterolemia (CRGFH), which convened for the first time in Chicoutimi on October 24, 1987. This consortium involves four universities (Laval, McGill, Montreal, and Quebec-Chicoutimi). The founding members are: Gérard Bouchard, Jean Davignon, Marc De Braekeleer, Margaret Gradie, Claude Laberge, Sital Moorjani, Blanche Leblanc, Habi T, et al. Heterozygous familial hypercholesterolemia in Japan. Am J Med 1978;65:290-297


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