Interaction of Two Lipid Disorders in a Large French-Canadian Kindred


This study investigates the pedigree of 508 individuals over five generations identified by an individual with hypertriglyceridemia, familial hypercholesterolemia, and a lipoprotein electrophoretic phenotype. The sample of 378 living individuals studied extensively for risk factors and disease status was distributed among maternal (170) and paternal (176) relatives and the codescendants (32) of the index case. It was found that the distributions of the plasma lipid and lipoprotein abnormalities in the different subsets of the kindred were consistent with the presence of two separate hereditary lipid disorders: familial hypercholesterolemia on the paternal side and familial hyperprebetaIipoproteinemia on the maternal side. This combination of disorders with a possible contribution from factors influencing glucose metabolism was associated with a high frequency of hypercholesterolemia and its clinical manifestations and of cardiovascular morbidity among the codescendants. An interaction effect is suggested as an explanation for the unusually high prevalence of hyperlipidemia among the codescendants and for the presence of a lIb phenotype in the index case. (Arteriosclerosis 3:13–22, January/February, 1983)

Familial hypercholesterolemia (FH) is characterized by a very high plasma low density lipoprotein (LDL) cholesterol level, the presence of tendon xanthomas in some affected subjects, premature atherosclerosis, and a decreased number of cell surface LDL-receptors. Although plasma cholesterol in FH is always markedly elevated, plasma triglycerides and their major carrier, very low density lipoproteins (VLDL), may be either normal (FH IIA) or elevated (FH IIB). FH patients with the IIB phenotype represent a heterogeneous group since both environmental and genetic factors may be responsible for the superimposed hypertriglyceridemia. This study was initiated in an attempt to sort out these various influences in a proband with typical FH and the IIB phenotype and to establish the genetic etiology of the plasma lipid levels and lipoprotein patterns in a French-Canadian pedigree identified by such a proband.

This paper presents the description of the study and the initial analyses carried out. We identified 508 individuals in five generations and extensively studied 379 (four generations) who were alive. These individuals were distributed into four major subsets defined with respect to the index: 135 paternal relatives (P subset); 142 maternal relatives (M subset); 26 codescendants (C subset) which included his offspring, his siblings, and all of their offspring; and finally, 75 nonmembers who married into the pedigree (NM subset). The nonmembers were further subdivided according to the subset of the pedigree into which they married (i.e., P nonmembers).

We shall demonstrate in this paper that the adults and children in the different subsets that compose the pedigree differed markedly in the frequencies of lipoprotein abnormalities and clinical manifestations of atherosclerotic disease. It will be shown that the
Ilb phenotype of the index case and the distribution of lipid phenotypes in the different subsets are consistent with the presence of two separate, hereditary lipid disorders in this pedigree that are distinct from familial combined hyperlipidemia. This combination of disorders is associated with an increased frequency of hypercholesterolemia and its clinical manifestations and of cardiovascular morbidity in the C subset.

**Methods**

**Index Case**

The index case was selected from 26 potential probands with a type Ilb electrophoretic phenotype and a well documented diagnosis of xanthomatous FH. The criteria for selection included: the size of the pedigree, the availability of living relatives, the distribution of subjects between maternal and paternal relatives, the number of codecsendants, and the geographic dispersion of the individuals of the kindred.

The index case selected (III-7 in figure 1) was a French-Canadian police officer, born in Saint-André, New Brunswick, who had moved to a Montreal suburb at the age of 18, married at 23, and had seven children. His father was discovered to be hypercholesterolemic shortly before his death at age 57 of a myocardial infarction. This event prompted a family survey which revealed the presence of hypercholesterolemia in several of the index's siblings. Two months before his referral to our lipid clinic at age 36, the presence of hyperlipidemia (cholesterol, 365 mg/dl; triglycerides, 200 mg/dl) had been documented during hospitalization for atypical chest pain, anxiety, and gastrointestinal symptoms. Myocardial ischemia was indicated by an ECG during a two-step Master's test, and coronary atherosclerosis was demonstrated by a coronary angiogram. Shortly before we began to collect his genealogy in 1972, he sustained (at age 37) an acute anteroseptal myocardial infarction from which he recovered uneventfully.

He was of normal weight (77.6 kg) for his height (1.83 m). Bilateral xanthelasmas had been present for several years and were stable in size. He had arcus cornæae and xanthomas of the Achilles tendons bilaterally and of the extensor tendon of the middle right finger. His plasma cholesterol level at entry into our clinic in January 1971 was 370 mg/dl and his triglyceride level was 238 mg/dl. The plasma lipopro-

![Pedigree Diagram](http://atvb.ahajournals.org/)

**Figure 1.** Plasma lipids, age, and clinical manifestations of hyperlipidemia and atherosclerosis in the codecsendants and their spouses. The frequency and severity of the hyperlipidemia and of its clinical consequences are higher than expected from the inheritance of the two lipid transport disorders transmitted independently and militate in favor of genetic interactions (CHO-intol = carbohydrate intolerance).
tein cholesterol levels were 80 mg/dl for VLDL, 261 mg/dl for LDL, and 29 mg/dl for high density lipoproteins (HDL). He had an impaired glucose tolerance with a normal fasting glycemia of 102 mg/dl and values at 60 minutes of 222 mg/dl and at 120 minutes of 188 mg/dl. The major causes of secondary hyperlipidemias were excluded by a thorough clinical and laboratory evaluation.

**Definition of the Pedigree**

A complete genealogical chart, a description of the clinical variables studied, and the procedures used to sample and record data are available from the National Auxiliary Publications Service (NAPS). The distribution among subsets of the 378 living individuals studied (excluding the index) who spanned four generations and ranged in age from 6 months to 83 years is given in table 1. All the living first- and second-degree relatives of the index and over 75% of the living, more genetically distant relatives of the index were studied. For this study, adults were defined as those individuals who were 20 to 83 years old. All nonmembers were adults. There were 87 persons younger than 20 on the paternal side (49 females), 96 persons on the maternal side (44 females) and 19 persons among the descendants (8 females). The distribution of the 103 different households among subsets of the pedigree at the time of clinical and biochemical examinations is also given in table 1.

Genealogic records exist for the Acadians and most French-Canadian families. The mother and father of the index case were both descendants from a marriage which occurred in 1721. The index’s paternal grandparents were first cousins and the parents of the index’s maternal grandfather were cousins. Inbreeding coefficients (i.e., the probability that the two allies at a locus are identical by descent) for the index, his father and his maternal grandfather are 0.000732, 0.0625000, and 0.007812 respectively. No other evidence of consanguinity was identified in this pedigree.

**Clinical Evaluation**

A systematic clinical evaluation was carried out with four major aims: to measure the levels of known risk factors for healthy and diseased individuals, to record the clinical manifestations of atherosclerosis and of hyperlipidemia, to determine the presence of associated metabolic and cardiovascular diseases, and to assess the major influences on plasma lipid levels. The assessment of atherosclerosis, hypertension, diabetes, obesity and other clinical evaluations were carried out according to criteria that are defined in detail in NAPS.

**Sampling Procedure and Laboratory Methods**

Blood samples were obtained by venipuncture from an antecubital vein at the time of clinical evalua-

<table>
<thead>
<tr>
<th>Table 1. Number Examined and their Sex Distribution in the Various Subsets of the Pedigree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Members</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Nonmembers</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Households</td>
</tr>
</tbody>
</table>
type, taking into account the clinical setting. This
initial classification into normals and hyperlipidemias
was further documented by plasma lipoprotein analy-
yses. A few adults whose lipid levels were above the
cut-off points were later reclassified as unaffected as a
result of the lipoprotein analyses. Indeed, in some
instances elevated HDL-cholesterol was responsible
for the total plasma cholesterol exceeding the upper
limit of the normal range. Whenever there was a
discrepancy between the plasma lipids and lipopro-
tein measurements (for instance, normal plasma
triglycerides and elevated VLDL-cholesterol) at-
tempts were made to find the source of the discrep-
ancy. In a few instances this led to including some
individuals in an "unclassifiable" category.

Urine samples were tested immediately after void-
ing for the presence of blood, ketones, glucose, and
protein using a standard strip test procedure (Lab-
stix, Ames Company, Rexdale, Ontario).

Hypotheses and Statistical Methods

The index was not included in any of the analyses
reported here. We considered the distributions of
continuous variables and the class frequencies for
the categorical variables: 1) in the total sample of
individuals, 2) within the subsamples of adults and
children in the C, M and P subsets, and 3) in the
adults who made up the NM subset. The first general
hypothesis tested was that the medians of each
continuous variable and relative frequencies of the
classes of each categorical variable were similar for
adult members and for the nonmembers of the pedi-
gree. Other analyses tested the hypothesis that the
class frequencies and the medians were the same:
1) in the P, M and C subsets of adults and children, 2)
in the three subsets of spouses who married those
members and 3) between hyperlipidemic and normal
individuals.

A two-way analysis of frequencies tested the in-
dependence of subset assignment and each of the
discrete classifications: status of influences, electro-
phoretic type, presence or absence of clinical mani-
festations of hyperlipidemia, atherosclerosis, and
risk factors. The null hypothesis that two classifica-
tions are independent in their effects on the frequen-
cy of joint outcomes was tested by the likelihood ratio
of the probability of observing the two-way table un-
der the assumption of independence compared to the
probability of the observed table.

The null hypothesis that specified subsets have
equal medians against the alternative that at least
one of the subsets has a different median from at
least one other subset was also tested. If the null
hypothesis was rejected, multiple a-posteriori com-
parisons were made to identify statistically signifi-

cant contrasts. Because these data were not normal-
ly distributed and because the variability among
individuals was heterogeneous among the subsets
compared, we used the nonparametric Kruskal-Wall-

The tests using these nonparametric statistics are
conservative in that the actual level of significance is
smaller than the stated level when the variable is
normally distributed and there is homoscedasticity
among subsets. We chose the nonparametric ap-
proach for the interpretation of the data realizing that
both parametric and nonparametric approaches as-
sume independence of observations which may be
violated when pedigrees are sampled. Unless other-
wise noted, the statistical contrasts reported in the
results section were considered to be significant
when the expected differences would have occurred
by chance alone less than 5% of the time. Means,
rather than medians, are reported for comparability
to other studies.

Results

Among the 378 subjects examined, there were no
cases of hypothyroidism, high fever within the week
before the examination, nephrosis, active hepatitis,
obstructive liver disease, or uncontrolled diabetes
mellitus that would have necessitated resampling.
Among the 193 women, seven were pregnant, and
three of them were resampled at a later date when
their normal menstrual cycle had resumed. One was
hyperlipidemic but could not be resampled. Her lipid
values, as well as those of a child who did not fast,
were excluded from the study.

Of the 108 individuals, besides the pregnant wom-
en, who presented with one or more influences
known to affect lipid levels, none was considered to
need resampling. Two persons had major surgery
approximately 2 months before sampling but their
previously diagnosed hyperlipidemia persisted. One
subject had had a partial ileal bypass operation sev-
eral years earlier for the treatment of hypercholester-
olemia but was still hypercholesterolemic. Four sub-
jects were receiving a lipid-lowering agent, but the
therapy was not effective. One subject with doc-
umented hypercholesterolemia had sustained a
recent myocardial infarction within 1.5 months of
sampling and still had hypercholesterolemia. Of 34
subjects on a low fat diet, only two reported a recent
moderate weight loss, and the influence of this on
lipids was considered negligible. There were 19
women on oral contraceptives, 14 on estrogens, and
seven had had ovariectomies.

There were no differences between nonmembers
and adult members of the pedigree in average age,
height, weight, body mass index (BMI = weight over
height squared), blood pressure, glucose, and uric
acid levels. Furthermore, the mean levels of these
measures for adult members and nonmembers were
independent of the relationship of the subject to the
index. Similarly, when adjustments were made for
variations in age, there were no differences between
children of the various subsets for the other varia-
tables. The large number of children (53.3% of total
sample, 101 females and 101 males) accounted for
Table 2. Distribution of Electrophoretic Phenotypes and Percentage of Hyperlipidemia in the Subsets for Adults (Distribution for Children Is in Parentheses)

<table>
<thead>
<tr>
<th>Electrophoretic phenotype</th>
<th>Members</th>
<th>Nonmembers</th>
<th>Codescendant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paternal</td>
<td>Maternal</td>
<td>Codescendant</td>
</tr>
<tr>
<td>Normal</td>
<td>32(52)</td>
<td>25(75)</td>
<td>1(9)</td>
</tr>
<tr>
<td>Ila</td>
<td>9(17)</td>
<td>0(0)</td>
<td>3(9)</td>
</tr>
<tr>
<td>IIb</td>
<td>6(1)</td>
<td>3(0)</td>
<td>3(1)</td>
</tr>
<tr>
<td>IV</td>
<td>1(0)</td>
<td>13(2)</td>
<td>0(0)</td>
</tr>
<tr>
<td>V</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>0(9)</td>
<td>4(1)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16(18)</td>
<td>16(3)</td>
<td>7(10)</td>
</tr>
<tr>
<td>Percent</td>
<td>33.3(22.8)</td>
<td>35.6(3.7)</td>
<td>85.7(52.6)</td>
</tr>
<tr>
<td>Number not typed</td>
<td>0(8)</td>
<td>1(18)</td>
<td>0(0)</td>
</tr>
</tbody>
</table>
Table 3. Summary Statistics for Plasma Lipids and Lipoproteins (mg/dl)

<table>
<thead>
<tr>
<th></th>
<th>Nonmembers</th>
<th>Paternal &lt;20 years</th>
<th>Paternal ≥20 years</th>
<th>Maternal &lt;20 years</th>
<th>Maternal ≥20 years</th>
<th>Codescendant &lt;20 years</th>
<th>Paternal ≥20 years</th>
<th>Maternal &lt;20 years</th>
<th>Codescendant &lt;20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholesterol</strong></td>
<td>189 ± 40</td>
<td>226 ± 90</td>
<td>202 ± 38</td>
<td>341 ± 56</td>
<td>188 ± 64</td>
<td>154 ± 22</td>
<td>231 ± 77</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(100-334)</td>
<td>(126-456)</td>
<td>(146-300)</td>
<td>(212-380)</td>
<td>(118-344)</td>
<td>(108-214)</td>
<td>(120-368)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>121 ± 92</td>
<td>89 ± 47</td>
<td>132 ± 83</td>
<td>162 ± 107</td>
<td>55 ± 24</td>
<td>56 ± 40</td>
<td>65 ± 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VLDL-C</strong></td>
<td>25 ± 15</td>
<td>21 ± 12</td>
<td>31 ± 21</td>
<td>51 ± 31</td>
<td>21 ± 15</td>
<td>14 ± 8</td>
<td>16 ± 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2-73)</td>
<td>(4-66)</td>
<td>(6-108)</td>
<td>(20-90)</td>
<td>(2-78)</td>
<td>(1-46)</td>
<td>(8-30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LDL-C</strong></td>
<td>129 ± 33</td>
<td>169 ± 81</td>
<td>133 ± 29</td>
<td>252 ± 47</td>
<td>131 ± 61</td>
<td>108 ± 20</td>
<td>181 ± 73</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(63-231)</td>
<td>(83-382)</td>
<td>(59-206)</td>
<td>(149-299)</td>
<td>(45-281)</td>
<td>(70-149)</td>
<td>(72-299)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HDL-C</strong></td>
<td>36 ± 7</td>
<td>36 ± 9</td>
<td>39 ± 7</td>
<td>38 ± 11</td>
<td>36 ± 7</td>
<td>35 ± 6</td>
<td>38 ± 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C/HDL-C</strong></td>
<td>5.4 ± 1.2</td>
<td>6.6 ± 3.1</td>
<td>5.4 ± 1.1</td>
<td>9.9 ± 3.7</td>
<td>5.3 ± 1.7</td>
<td>4.5 ± 0.7</td>
<td>6.3 ± 2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3.5-8.5)</td>
<td>(3.8-18.4)</td>
<td>(3.6-8.7)</td>
<td>(4.9-16.7)</td>
<td>(3.0-9.6)</td>
<td>(3.1-6.8)</td>
<td>(3.3-9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LDL-C/HDL-C</strong></td>
<td>3.7 ± 1.0</td>
<td>5.0 ± 2.8</td>
<td>3.5 ± 0.9</td>
<td>7.2 ± 2.4</td>
<td>3.7 ± 1.6</td>
<td>3.1 ± 0.7</td>
<td>4.8 ± 2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.9-7.0)</td>
<td>(2.2-15.5)</td>
<td>(1.4-6.4)</td>
<td>(3.5-11.4)</td>
<td>(1.1-7.8)</td>
<td>(1.8-5.1)</td>
<td>(1.9-8.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± sd. Range is given in parentheses. VLDL-C = very low density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol.

mean for LDL/HDL (8.0). The hyperlipidemic maternal members had mean triglyceride levels 36 mg/dl above the mean for all hyperlipidemic adults (p < 0.001). Among hyperlipidemic children, the ranking of the C, P, and M subset means were similar to that observed for hyperlipidemic adult members.

In summary, these data suggest that the genealogical relationship of members to the index case (i.e., the subset) was not independent of their lipid and lipoprotein levels. While all differences were not statistically significant, all the lipid and lipoprotein levels were highest among C subset members. A similar pattern of elevated levels was seen in both the adults and children of the C subset. Likewise, for both adult members and children, those in the P subset had significantly higher mean cholesterol levels and significantly lower mean triglyceride levels than those in the M subset.

The distribution of lipid and lipoprotein levels among subsets was associated with the percentages of the individuals with major clinical manifestations of hyperlipidemia and atherosclerosis (table 4). For adults, the members of the pedigree differed significantly from nonmembers only in the percentage of tendon xanthomas (23.8% versus 0%). The distribution of clinical conditions among nonmember adults (table 4) was independent of the subset of the pedigree in which the marriage occurred. Among adults who were members, those in the C subset had significantly higher percentages of arcus corneae, xanthelasma, tendon xanthomas, CHD, and angina pectoris compared to the M and P subsets. For all the manifestations mentioned just above, the P subset members had higher relative frequencies than the M subset members. For children, only the percentages of cigarette and alcohol use varied significantly among subsets. No children in the C subset reported that they smoked and no children in either the P or M subsets reported alcohol use. Although not shown in table 4, hyperlipidemic adults had significantly higher percentages of arcus corneae, xanthelasma, tendon xanthomas, CHD, angina pectoris, MI, and use of alcohol (25%, 11%, 32%, 29%, 7%, 25%, respectively) compared to normolipidemic adults (5%, 2%, 0%, 4%, 4%, 4%, 1%, 12%, respectively).

Discussion

Typical cases of FH with tendon xanthomas, premature atherosclerosis, and cell surface LDL-receptor deficit may or may not exhibit hypertriglyceridemia. Although FH IIb shares many of the clinical and biological features of FH IIa, some differences be-
Table 4. Percentage of Individuals with Major Clinical Manifestations of Hyperlipidemia, Atherosclerosis, and Risk Factors for Coronary Heart Disease

<table>
<thead>
<tr>
<th>Arcus corneae</th>
<th>Xanthelasma</th>
<th>Tendon xanthomas</th>
<th>Coronary heart disease</th>
<th>Angina pectoris</th>
<th>Myocardial infarction</th>
<th>Peripheral atherosclerosis</th>
<th>Intermittent claudication</th>
<th>Obesity</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Smoking</th>
<th>Alcohol use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmembers</td>
<td>Members</td>
<td>All members &gt;20 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 75)</td>
<td>(n = 101)</td>
<td>(n = 101)</td>
<td>Paternal (n = 48)</td>
<td>Maternal (n = 46)</td>
<td>Codescendant (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.7</td>
<td>11.9</td>
<td>12.5</td>
<td>4.3</td>
<td>42.9</td>
<td>0.0</td>
<td>9.3</td>
<td>9.3</td>
<td>2.7</td>
<td>3.0</td>
<td>2.0</td>
<td>11.9</td>
<td>22.7</td>
</tr>
<tr>
<td>2.7</td>
<td>5.9</td>
<td>4.2</td>
<td>2.2</td>
<td>57.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>4.0</td>
<td>3.0</td>
<td>1.3</td>
<td>5.3</td>
<td>1.3</td>
</tr>
<tr>
<td>0.0</td>
<td>23.8</td>
<td>25.0</td>
<td>0.0</td>
<td>85.7</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>4.0</td>
<td>3.0</td>
<td>2.0</td>
<td>16.8</td>
<td>44.6</td>
</tr>
<tr>
<td>9.3</td>
<td>13.9</td>
<td>14.6</td>
<td>6.5</td>
<td>57.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.3</td>
<td>2.0</td>
<td>1.3</td>
<td>21.7</td>
<td>1.3</td>
</tr>
<tr>
<td>9.3</td>
<td>12.9</td>
<td>12.5</td>
<td>6.5</td>
<td>57.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>4.0</td>
<td>3.0</td>
<td>1.3</td>
<td>8.9</td>
<td>22.7</td>
</tr>
<tr>
<td>2.7</td>
<td>3.0</td>
<td>6.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>2.0</td>
<td>2.0</td>
<td>1.3</td>
<td>21.7</td>
<td>3.0</td>
</tr>
<tr>
<td>4.0</td>
<td>3.0</td>
<td>4.2</td>
<td>2.2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.3</td>
<td>2.0</td>
<td>1.3</td>
<td>5.3</td>
<td>22.7</td>
</tr>
<tr>
<td>22.7</td>
<td>16.8</td>
<td>14.6</td>
<td>21.7</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.3</td>
<td>3.0</td>
<td>1.3</td>
<td>22.7</td>
<td>1.3</td>
</tr>
<tr>
<td>1.3</td>
<td>3.0</td>
<td>2.1</td>
<td>4.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>4.0</td>
<td>3.0</td>
<td>1.3</td>
<td>12.8</td>
<td>22.7</td>
</tr>
<tr>
<td>5.3</td>
<td>8.9</td>
<td>8.3</td>
<td>8.7</td>
<td>14.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>8.9</td>
<td>5.3</td>
<td>1.3</td>
<td>8.9</td>
<td>8.9</td>
</tr>
<tr>
<td>44.6</td>
<td>38.6</td>
<td>35.4</td>
<td>41.3</td>
<td>42.9</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>20.0</td>
<td>12.9</td>
<td>14.6</td>
<td>14.6</td>
<td>14.6</td>
</tr>
</tbody>
</table>

The overall relative frequencies of the Types IIa, IIb and IV in adult relatives of the index case in the entire kindred are consistent with the expectation that one-third of the affected relatives would be of each type in familial combined hyperlipidemia. However, there are several reasons to reject the hypothesis that the segregation of these phenotypes in this pedigree is consistent with familial combined hyperlipidemia. First, data from the M and P subsets represent separate lipid disorders that are not typical of familial combined hyperlipidemia. First, data from the M and P subsets represent separate lipid disorders that are not typical of familial combined hyperlipidemia. The distribution of electrophoretic phenotypes among the progeny of 33 matings in the P subset (table 5) is explained...
The Type Mb individuals were likely the double heterozygote for the two mutants, one from the father and one from the mother. The Type lla phenotype represented the combination of normal genes at the two loci from the mother. Observed are consistent with the segregation of two separate loci. The normal individual (III-9, figure 1) were entirely by familial hypercholesterolemia (FH) determined by a dominant gene at a single locus. A ratio of 14 to 17 (hypercholesterolemic to normal) observed for the progeny of 12 matings in which one parent was hypercholesterolemic does not deviate significantly from the 1 to 1 ratio expected for a trait determined by a dominant gene. In contrast, none of the mating types in the M subset produced hypercholesterolemic progeny (table 5). The M subset gave a markedly different pattern of lipid phenotypes; only two children had abnormal electrophoretic phenotypes (table 2). We used an analysis of the continuous variability of lipid levels to test for the presence of a major segregating locus for familial hyperprebeta-lipoproteinemia (FHPB). Elston et al. suggest four criteria necessary to infer segregation at a major locus. One is that continuously distributed data, when considered as a random sample from some distribution, should fit a mixture of distributions significantly better than they fit a single distribution. The triglyceride values for all members of the M subset and their spouses were standardized for age, sex, and use of hormones using the Lipid Research Clinics population as a standard. Using the method of Day, we found that two normal distributions fit the standardized data significantly better than one. This preliminary finding is consistent with the hypothesis that genetic variability at one locus may contribute to the distribution of triglyceride levels.

A second reason to presume the presence of two heritable disorders in the M and P subsets is provided by a detailed examination of the codescendants (figure 1). If we assume: 1) that the father of the index case transmitted the type lla phenotype (tendon xanthomas, a high cholesterol level (425 mg/dl), and premature CHD) from the P subset to his offspring; 2) that the mother of the index case transmitted the Type IV phenotype (high triglyceride levels, diabetes, and a milder form of CHD) to her offspring; and 3) that these conditions are determined by two unlinked and nonpseudotistical heritable disorders, we would expect an equal number of offspring with Type lla hyperlipidemia with tendon xanthomas, Type IV with few clinical signs of hyperlipidemia and atherosclerosis, a mixture of IIa and IV (Type llb with severe disease), and the normal lipid phenotype. Although there was an excess of the Type II phenotype (7 of 8), the types of progeny observed are consistent with the segregation of two separate loci. The normal individual (III-9, figure 1) represented the combination of normal genes at the two loci that were transmitted from each of the singly heterozygous parents. The Type lla individuals represented the combination of a mutant gene determining hypercholesterolemia and a normal gene for triglyceride levels from the father and the combination of normal genes at the two loci from the mother. The Type llb individuals were likely the double heterozygotes for the two mutants, one from the father and one from the mother.

Even more striking than the distribution of electrophoretic phenotypes, were the extreme levels of the lipids and lipoproteins and the high frequency of clinical manifestations and atherosclerotic complications among these eight adults in the C subset who were all under age 40 when examined. Taken in combination with the data from the M and P subsets that support two heritable disorders, these data further support the hypothesis that the adults of the C subset represented the interactions between the effects of a gene determining hypertriglyceridemia and the effects of a gene for hypercholesterolemia. In the next generation in the C subset, one-half the children of the index case had normal triglycerides (three FH lla, one normal) even though the index’s spouse had hypertriglyceridemia with a Type IV pattern. Among the nieces and nephews of the index (IV, figure 1), Phenotype lla was present in nine of the 10 affected children. Since the mean age at the time of sampling was 9.5 years (No = 18) for this generation, it is probable that the hypertriglyceridemia was not expressed and that this trait may exhibit low penetrance as previously reported in FHPB. It is likely that the hypertriglyceridemia would eventually be expressed in children who had plasma triglycerides in the upper normal range either as Type IV (IV-5, figure 1) or as Type llb (IV-4, the twin of IV-3). It is also possible that the 2-year-old IV-19 with a cholesterol level of 194 might be eventually affected (Type IIa).

These interpretations of the distribution of information among the P, M, and C subsets are based on the assumptions that the father of the index who transmitted the hypercholesterolemia was not hypertriglyceremic, that no secondary causes accounted for the hypertriglyceridemia in the index case, and that the diabetic trait present on the maternal side did not account for a major part of the hypertriglyceridemia in the index. These assumptions are supported by a number of considerations. First, although plasma triglyceride levels for the father of the index (II-1, figure 1) were not available, his plasma cholesterol was very high, he had tendon xanthomas, he died at age 57 of a myocardial infarction, and most of his affected biological relatives had the lla phenotype (26 of 33, 79%). Therefore, it is reasonable to assume that he also had FH lla. Second, the index was not obese and he did not consume alcohol or large amounts of simple sugar in his diet at the time of the sampling. Thyroid, liver, and renal functions were normal and he was not taking any drugs or hormones. Third, only three of the 16 hypertriglyceridemic adults in the maternal subset had fasting glucose levels above 115 mg/dl, the level which is regarded by the National Diabetes Group as the limit defining impaired glucose tolerance. Two of these individuals had values below 125 mg/dl and the third (an aunt of the index) was a possible diabetic with a fasting glucose of 158 mg/dl. Because the 59-year-old mother of the index had an adult-onset diabetes requiring insulin, the index case could have inherited the diabetic trait. This is unlikely because his fasting glycemia level was normal. Although he had an abnormal
glucose tolerance, his normal fasting blood sugar in the absence of excess body weight was not likely to be the source of hypertriglyceridemia of the magnitude noted after a 12-hour fast.

Indeed, it has been shown that plasma free fatty acids, the substrate for liver synthesis of triglycerides, are not increased in subjects with glucose intolerance unless they are obese. Furthermore, no deficit in plasma or adipose tissue-lipoprotein lipase activity (the major catalytic enzyme for plasma triglycerides) is found in lean individuals until plasma glucose reaches or exceeds 150 mg/dl. This is not to say that glucose intolerance could not contribute to enhancing an inherited defect in triglyceride metabolism or increase the sensitivity of plasma triglyceride levels to dietary carbohydrates.

The high prevalence of abnormal glucose tolerance in patients ascertained for hypertriglyceridemia is well established and was to be expected on the maternal side where FHPB is present. On the other hand, it has been shown that the prevalence of diabetes is the same among normolipidemic and hypertriglyceridemic first-degree relatives of individuals with familial hypertriglyceridemia. This suggests that diabetes and hypertriglyceridemia have separate etiologies, although they may coexist in about 35% of subjects with familial hypertriglyceridemia.

In conclusion, the mild carbohydrate intolerance in the index case may have contributed in part, but not wholly, to his hypertriglyceridemia. There is no way to determine whether it could have contributed to enhancing the severity of the cardiovascular abnormalities in the codescendants by means other than increased plasma triglycerides (i.e., basement membrane changes, effect on collagen metabolism, or other mechanisms).

Inclusion, the distribution of lipoprotein phenotypes, as well as the concentrations of plasma lipids and lipoproteins in the various subsets, corroborates the fact that there is aggregation specifically for hypercholesterolemia (Type II, elevated LDL) on the maternal side and aggregation specifically for hyperbetalipoproteinemia (Type IV, elevated VLDL) on the maternal side. Adults with hypercholesterolemia in both the P and C subsets have children with elevated cholesterol levels. Matings of normals with hypercholesterolemics in the M subset did not give rise to hypertriglyceridemic children, and matings of normals with hypertriglyceridemics in the M subset did not give rise to hypercholesterolemic children. Finally, the index case had an LDL receptor site deficiency. These observations all suggest that the distribution of phenotypes in this pedigree is not consistent with the criteria currently used to define familial combined hyperlipidemia.

The nonrandom distribution of lipid and lipoprotein measures and of clinical manifestations among the subsets of this pedigree are more consistent, instead, with a hypothesis that the IIb phenotype in the index resulted from the combined inheritance of FH from the father and FHPB from the mother.

Acknowledgments

The generous collaboration of Christine Bertagna, Rémi Collin, Emmett Corbin, Marcel Faucournier, Michel Langelier, Michel Leblévre, Jacques LéLorier, Maurice A. Mishkel, Martine Ortin-George, Lewis D. Page, Elisabeth Reichel, and Fernand Roberge is gratefully acknowledged. The invaluable participation of Denise Brossard, Lise Demers, Lise Dubé, Gabrielle Fullum, Mireille Olivier, and Suzanne Quldou is deeply appreciated as well as the secretarial help of Danièle Amaud, Réjeanne Ouellet, and Anne Preston and the technical assistance of Lucie Boulet, Diane Giroux, Murielle Paquette, Nicole Patard, Stephen Rothwell, and Michel Tremblay.

References

5. Arsenault B. Histoire des Acadiens. Ottawa:LaMéac; 1978
6. Tanguay C. Dictionnaire génétique des familles Canadiennes. Montréal/Elyssé; 1975


30. Brunzell JD, Hazzard WL, Motulsky AG, Bierman EL. Evidence for diabetes mellitus and genetic forms of hypertriglyceridemia as independent entities. Metabolism 1975;24:1115-1121

Index Terms: Familial hypercholesterolemia • familial hyperprebeta1ipoproteinemia • plasma lipoproteins • xanthomas • atherosclerosis • field survey • genetics • cholesterol • triglycerides • diabetes
Interaction of two lipid disorders in a large French-Canadian kindred.
J Davignon, S Lussier-Cacan, A Gattreau, P P Moll and C F Sing

doi: 10.1161/01.ATV.3.1.13
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/3/1/13

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/