Serum Phospholipids

Genetic and Environmental Influences

By Louis E. Schaefer, M.D., David Adlersberg, M.D., and Arthur G. Steinberg, Ph.D.

Serum phospholipid levels were determined in 1,067 healthy persons aged 2 to 77 years. Phospholipid levels increased with age but in a different way for each of the sexes. The age-sex changes of serum phospholipids were similar to those observed for serum cholesterol. Correlation coefficients in members of 156 families indicated that the genetic factor is of importance in determining the serum phospholipid level in health. Because of the age-sex variations of serum phospholipid and serum cholesterol levels, no single arbitrary line can be drawn between normal and abnormally elevated levels of these 2 serum lipid fractions.

There is increasing evidence that atherosclerosis is a problem with many facets. Extensive investigative work is being conducted on the role of abnormal lipid metabolism as well as carbohydrate and protein metabolism in atherosclerosis. Factors such as thrombogenesis, blood coagulation, fibrinolysis, arterial wall injury, intimal hemorrhage, and others are also subjects of intensive study.1, 2 Most investigators, however, are mainly concerned with the part played by lipids in the genesis of atherosclerosis. At one time these studies centered around serum cholesterol and cholesterol metabolism. In recent years the interest in this field has been focused on aspects of lipids and lipoproteins other than cholesterol. For example, it is believed by some that the concentration of triglycerides in the serum may be an important factor in atherogenesis.3 It has been shown in animals that in serum triglycerides results in a 2° elevation of serum cholesterol and phospholipid.4 Neutral fat transport and metabolism may thus be important in atherogenesis. The role of the nonesterified fatty acids in lipid transport and their possible relationship to carbohydrate metabolism have been investigated.5, 6 In the study of dietary factors related to atherogenesis, the effect of saturated versus unsaturated fats is being carefully watched.7

In this connection the role of serum phospholipid deserves consideration. Its presence in atheromatous plaques and its synthesis in the arterial wall are well established.8 Elevations or depressions of serum cholesterol are usually associated with changes in a similar direction of levels of serum phospholipid.9, 10

In contrast to extensive studies on serum cholesterol in relation to age, sex, endocrine factors, and such environmental factors as dietary, climatic, and occupational influences, relatively little information is available concerning corresponding changes of serum phospholipid. A detailed discussion of our present knowledge will be presented later.

It seemed profitable, therefore, to investigate systematically the levels of serum phospholipid in a normal population sample. The twofold purpose of the study was to establish possible relationships between age, sex, and serum phospholipid level, and to assess the relative importance of genetic versus environmental influences determining serum phospholipid levels in a healthy population.

Materials and Methods

The sample included 1,067 normal persons, 516 men and 551 women, aged 2 to 77. Among these were 156 families, consisting of 156 fathers, 156 mothers, and 268 children of these parents.

The 1,067 persons studied were part of the total sample of 1,236 persons of a healthy and unselected group of New York City employees.
TABLE 1.—Ethnic Origin, Race, and Religion of Population Studied

<table>
<thead>
<tr>
<th>Population</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic Origin</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>38</td>
</tr>
<tr>
<td>Ireland</td>
<td>25</td>
</tr>
<tr>
<td>England, Scotland</td>
<td>17</td>
</tr>
<tr>
<td>Germany</td>
<td>6</td>
</tr>
<tr>
<td>Scandinavian countries</td>
<td>3</td>
</tr>
<tr>
<td>Poland</td>
<td>3</td>
</tr>
<tr>
<td>France</td>
<td>3</td>
</tr>
<tr>
<td>Spain</td>
<td>2</td>
</tr>
<tr>
<td>Hungary</td>
<td>2</td>
</tr>
<tr>
<td>All others</td>
<td>1</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>98</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>2</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
</tr>
<tr>
<td>Catholic</td>
<td>71</td>
</tr>
<tr>
<td>Protestant</td>
<td>20</td>
</tr>
<tr>
<td>Jewish</td>
<td>9</td>
</tr>
<tr>
<td>Moslem</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Living in Staten Island, New York, who were investigated for the incidence and mode of transmission of idiopathic hypercholesteremia. A history was taken and a physical examination was performed on each person. The serums were analyzed for phospholipid by the Sperry modification of the Fiske-Subbarow method and for total and esterified cholesterol by the Sperry-Schoenheimer method.

Ethnic origins, race, and religion of the persons studied are reproduced from a previous publication for the sake of completeness (table 1).

The overwhelming majority of these persons consumed a mixed American diet of the usual protein, carbohydrate, and fat content, similar in its composition to that described by Epstein et al. for the working population in New York City.

**SERUM PHOSPHOLIPID LEVELS**

Analysis of the data shows that serum phospholipid level varies with age in a manner similar to serum cholesterol. In males, the serum phospholipid level remains essentially constant through age 20 years, it rises sharply for the next 12 years (to age 32), and then it remains essentially constant until age 60 years (table 2). In females the serum phospholipid level remains constant until age 32 years and then rises gradually for the next 28 years until age 60. Our data are not exten-

**SCHAEFER, ADLERSBERG, STEINBERG**

TABLE 2.—Changes in Serum Phospholipid Level with Age in Males and Females

<table>
<thead>
<tr>
<th>Age interval (yr.)</th>
<th>No.</th>
<th>b*</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-20</td>
<td>158</td>
<td>-1.323</td>
<td>.05</td>
</tr>
<tr>
<td>20-32</td>
<td>60</td>
<td>5.010</td>
<td>.001</td>
</tr>
<tr>
<td>32-60</td>
<td>298</td>
<td>0.338</td>
<td>.10</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-32</td>
<td>264</td>
<td>-0.296</td>
<td>.10</td>
</tr>
<tr>
<td>32-60</td>
<td>287</td>
<td>2.137</td>
<td>.001</td>
</tr>
</tbody>
</table>

*The average annual change of serum phospholipid level in mg./100 ml. is represented by the coefficient b in the regression equation \( Y = a + bX \) where \( X \) = age in years and \( Y \) = serum phospholipid level.

†Probability that observed value of \( b \) is an estimate of an annual change which is zero.
TABLE 3.—The Mean or Predicted Level and Upper Five Per cent Values of Serum Phospholipids

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean</th>
<th>Upper 5% Level</th>
<th>Age</th>
<th>Mean</th>
<th>Upper 5% Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-20</td>
<td>227.2</td>
<td>295.3</td>
<td>27</td>
<td>268.7</td>
<td>335.5</td>
</tr>
<tr>
<td>20</td>
<td>233.7</td>
<td>300.4</td>
<td>28</td>
<td>273.7</td>
<td>340.5</td>
</tr>
<tr>
<td>21</td>
<td>238.7</td>
<td>305.4</td>
<td>29</td>
<td>278.8</td>
<td>345.5</td>
</tr>
<tr>
<td>22</td>
<td>243.7</td>
<td>310.4</td>
<td>30</td>
<td>283.8</td>
<td>350.5</td>
</tr>
<tr>
<td>23</td>
<td>248.7</td>
<td>315.5</td>
<td>31</td>
<td>288.8</td>
<td>355.5</td>
</tr>
<tr>
<td>24</td>
<td>253.7</td>
<td>320.5</td>
<td>32</td>
<td>293.8</td>
<td>360.5</td>
</tr>
<tr>
<td>25</td>
<td>258.7</td>
<td>325.5</td>
<td>32</td>
<td>282.5</td>
<td>364.2</td>
</tr>
<tr>
<td>26</td>
<td>263.7</td>
<td>330.5</td>
<td>60</td>
<td></td>
<td>65.2</td>
</tr>
</tbody>
</table>

*Based on 158 males between ages 2 and 20 years (r = 41.4).
†Means for ages 20 to 32 predicted from regression equation in table 2.
‡Based on 298 males aged 32 through 60 years inclusive (r = 49.6).
§Based on 264 females aged 2 to 32 inclusive (r = 42.3).
¶Means for ages 32 to 60 inclusive based on regression equation in table 2.

which serum phospholipids were determined for the mother and at least 1 child, but not for the father (“incomplete” families).

There were 5 “complete” families in which the father was hyperphospholipemic, and 5 in which the mother was hyperphospholipemic. Two (13 per cent) of the 15 children in these families were also hyperphospholipemic. There were 253 children in the remaining 146 “complete” families in which neither parent was hyperphospholipemic. Ten (4 per cent) of these children, 1 in each of 10 different families, were hyperphospholipemic. The difference between the frequency of hyperphospholipemia among the children of these 2 sets of families is not significant: it is, however, in the direction one would expect if there were a genetic component in the determination of hyperphospholipemia.

Correlation analyses similar to those undertaken for the cholesterol levels were computed for the phospholipid levels to check further on a possible genetic component. The correlation coefficients are shown in table 4.

The correlation between the serum phospholipid levels of mothers and fathers is essentially zero while that between fathers and their children, mothers and their children, and between siblings are each significantly different from zero and very similar to each other (upper part of table 4). There is no suggestion in these data, as there was in the data for serum cholesterol, that the correlation coefficient between father and child is lower than that between mother and child. Nevertheless, for completeness we have computed the correlation coefficients between father and son, father and daughter, mother and son, and mother and daughter. These correlation coefficients will be found in the lower portion of table 4. The presence of an important sex-linked genetic component in the determination of a character would lead to a relatively low correlation between father and son, a higher correlation between father

TABLE 4.—Correlation Coefficients* between the Serum Phospholipid Levels of the Indicated Pairs

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother-father</td>
<td>156</td>
<td>-0.147</td>
<td>&gt;.80</td>
</tr>
<tr>
<td>Father-child</td>
<td>287</td>
<td>0.2055</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mother-child</td>
<td>309</td>
<td>0.2089</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sibling-sibling</td>
<td>100</td>
<td>0.2232</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>Father-son</td>
<td>139</td>
<td>0.1785</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>Father-daughter</td>
<td>148</td>
<td>0.2355</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mother-son</td>
<td>152</td>
<td>0.3118</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mother-daughter</td>
<td>157</td>
<td>0.1024</td>
<td>&lt;.20</td>
</tr>
</tbody>
</table>

*All phospholipid levels were converted to equivalent levels for males aged 20 (as determined by the regression equation) to eliminate factors of age and sex.

†Intraclass r based on first and second siblings only.
and daughter, which would be essentially equal to that between mother and daughter, and a still higher correlation between mother and son. The data in the lower portion of table 4 show an unexpectedly wide scatter of values, but do not support the hypothesis of an important sex-linked component in the genetic causation of the serum phospholipid level.

The correlation between mother and daughter is the lowest of the 4 and the sequence thereafter in order of increasing values is father and son, father and daughter, mother and son. None of these 4 correlation coefficients differs significantly from any of the others. The greatest difference is between the correlation coefficients for mother and daughter and mother and son, and this difference has a probability greater than .05 of having arisen as a result of sampling. We must, therefore, consider the variation among the 4 correlation coefficients as chance phenomena.

The absence of a correlation between the serum phospholipid levels of the parents and the presence of a significant positive correlation between the serum phospholipid levels of parents and child, and sibling and sibling are evidence of an important genetic component in the determination of serum phospholipid levels.

**Relation Between Serum Cholesterol and Serum Phospholipid Level**

The relation between serum cholesterol level and serum phospholipid level was determined from blood samples from 499 males and 510 females. There is a very high correlation between serum cholesterol and serum phospholipid levels in both males and females (.72 and .74 respectively, table 5). Within statistical limits, the correlation coefficients may be considered to be the same. The regression of serum phospholipid level on serum cholesterol level is statistically significant both for males and females. For each rise of 1 mg. per cent of serum cholesterol there is a rise of 0.72 mg. in males and 0.68 mg. in females of serum phospholipid. Within statistical limits these regression coefficients may be considered to be the same. In the light of the high correlation between serum cholesterol level and serum phospholipid level it is not surprising to find that the genetic analyses of these 2 variables parallel each other closely.11

Although high the correlation coefficients are considerably less than unity, hence a large amount of variation of the observed value about the predicted value of phospholipid level may be expected. A correlation coefficient of .72 accounts for only about 52 per cent of the variation around the mean, the remainder of the variation being due to sampling. Examination of the data for the 689 individuals in the 201 families in this study who were tested for serum cholesterol and serum phospholipid levels confirms this expectation. Ten had hypercholesteremia and hyperphospholipemia by our standards; 19 had hypercholes- teremia, but not hyperphospholipemia; while 20 had hyperphospholipemia, but not hypercholesteremia. In each of the latter 39 individuals the "normal" value is in the upper range of normal.

**Discussion**

Only limited information is available concerning the influence of age, sex, environmental and hereditary factors on serum phospholipid levels of healthy persons. Almost no information is obtainable on levels in childhood and adolescence, or even among adults in significant numbers. Peters and Man15 concluded that there was no effect of age and sex on serum phospholipid among 108 persons studied. Foldes and Murphy17 reached the same conclusions. Gertler et al.18 compared average phospholipid levels of normal control subjects and patients with coronary artery disease. They concluded that the difference between the 2 groups was significant, but did not evaluate their observation material.
SERUM PHOSPHOLIPIDS

in regard to age and sex. Epstein et al.\textsuperscript{15} could not discern a clear-cut trend in phospholipid levels in relation to age and sex. Lindholm\textsuperscript{19} investigated serum lipids in 102 males and 93 females between the ages of 20 and 91. The phospholipid levels increased steadily with age in women, whereas in men this increase was seen only until age 50. Statistical criteria could not be applied to these data because of the small number of subjects. Table 6 summarizes the available information concerning serum phospholipid levels in normal persons.

Most investigators have been interested in serum phospholipids in disease, particularly atherosclerosis; in the relationship of serum phospholipids to cholesterol and other lipids; in influencing the level under experimental conditions; and in studies of phospholipid synthesis and turnover.

It has been shown that atheromatous plaques contain about 20 per cent phospholipid.\textsuperscript{8} Serum phospholipid levels can be raised in animals by feeding cholesterol\textsuperscript{20} and by injecting certain detergents,\textsuperscript{21} and in man and animals by administration of steroid hormones.\textsuperscript{22} Patients with atherosclerosis have, as a group, higher phospholipid levels than control subjects and higher cholesterol: phospholipid ratios.\textsuperscript{18} It has been maintained that serum phospholipid stabilizes serum cholesterol and keeps it in solution.\textsuperscript{23} It has been shown that the effect of certain (unsaturated) dietary fats on serum lipids is manifest in the lowering of serum cholesterol, and to a lesser extent of serum phospholipid.\textsuperscript{24} Thus, more attention has been paid to the pathologic implications of phospholipid metabolism than to the variations of this lipid in the serum of healthy persons.

The present study indicates that serum phospholipid levels of healthy persons consuming a mixed diet increase with age in males earlier in life than in females. They are similar to the age-sex changes previously described for serum cholesterol, but of lesser magnitude. The levels of serum cholesterol and of serum phospholipid are distributed throughout this population as continuous variables. Our data also indicate the existence of a genetic factor determining serum phospholipid levels in healthy people.

The positive parent-child and sibling-sibling correlations and the negative mother-father correlations support the concept that serum phospholipid levels are genetically determined, probably in the same manner as serum cholesterol levels. These data further indicate that the common environment shared by a family does not lead to common serum phospholipid levels, unless blood relationship exists. Thus, such factors as diet cannot be the only factor in determining serum lipid levels of healthy persons.

On the basis of our admittedly limited data the responsible gene or genes are probably not sex-linked.

Hyperphospholipemia usually occurs in the presence of hypercholesteremia. A change of 1 mg. in serum cholesterol is accompanied by a change in the same direction of serum phospholipid amounting to 0.70 mg. Since this correlation occurs at all ages in both sexes a higher cholesterol: phospholipid ratio may be expected in hypercholesteremic than in normocholesteremic states. The importance of

<p>| Table 6.—Serum Phospholipid Concentrations in Normal Persons* |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Yr.</th>
<th>No. &amp; Sex</th>
<th>Age Range</th>
<th>Mean in mg./100 ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyd</td>
<td>1933</td>
<td>8 female ‘young’</td>
<td>196</td>
<td></td>
</tr>
<tr>
<td>Page et al</td>
<td>1935</td>
<td>66 male</td>
<td>—</td>
<td>181</td>
</tr>
<tr>
<td>Peters and Man</td>
<td>1943</td>
<td>108 mixed</td>
<td>10-68</td>
<td>220</td>
</tr>
<tr>
<td>Foldes and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murphy</td>
<td>1946</td>
<td>20 mixed</td>
<td>20-35</td>
<td>228</td>
</tr>
<tr>
<td>Kornrerup</td>
<td>1950</td>
<td>73 male</td>
<td>19-96</td>
<td>173</td>
</tr>
<tr>
<td>Ahrens</td>
<td>1950</td>
<td>20 mixed</td>
<td>21-38</td>
<td>219</td>
</tr>
<tr>
<td>Goldbloom</td>
<td>1952</td>
<td>15 mixed</td>
<td>22-72</td>
<td>218</td>
</tr>
<tr>
<td>Peterson</td>
<td>1952</td>
<td>21 male</td>
<td>20-55</td>
<td>208</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27 female</td>
<td>17-52</td>
<td>250</td>
</tr>
<tr>
<td>Swahn</td>
<td>1953</td>
<td>10 mixed</td>
<td>10-57</td>
<td>218</td>
</tr>
<tr>
<td>Gertler and Oppenheimer</td>
<td>1954</td>
<td>22 male</td>
<td>18-35</td>
<td>193</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 female</td>
<td>18-35</td>
<td>228</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 male</td>
<td>65-86</td>
<td>258</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 female</td>
<td>65-86</td>
<td>258</td>
</tr>
<tr>
<td>Lindholm</td>
<td>1956</td>
<td>102 male</td>
<td>20-91</td>
<td>245</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93 female</td>
<td>20-91</td>
<td>252</td>
</tr>
</tbody>
</table>

*Adapted from data of Lindholm.\textsuperscript{19}
the raised cholesterol/phospholipid ratio in atherosclerotic persons with hypercholestere-
mia is, therefore, open to question.

The problem arises as to the definitions of normophospholipemia and hyperphospho-
lipemia. One is confronted here with a situation similar to that encountered in the defini-
tion of normocholesteremia and hypercholesteremia. Since serum phospholipid levels vary
with age and sex, no single arbitrary line can be drawn between normal and elevated serum
phospholipid levels. It is suggested, therefore, that the upper 5 per cent levels (table 3) of each age and sex group may be utilized for this purpose. Future studies will estab-
lish the possible clinical importance of such a delineation.

**Summary**

Serum phospholipid levels were studied in a healthy population sample in New York City including 1,067 persons, 516 males and 551 females, aged 2 to 77 years. Among these
were 156 families consisting of 156 fathers, 156 mothers, and 268 children of these par-
ents.

Serum phospholipid levels of healthy per-
sions increase with age but in a different way
for each of the 2 sexes. In males the level remains practically constant until age 20, rises
sharply to age 32, and then remains constant
until age 60. In females the level remains
constant until age 32 and then rises gradually
until age 60. These age-sex changes of serum
phospholipid are similar to those observed for
serum cholesterol but they are of lesser mag-
nitude. The data indicate the existence of a
genetic factor determining serum phospholip-
id levels in healthy persons.

A study of correlation coefficients of serum
phospholipid revealed negative mother-father
and positive parent-child and sibling-sibling
correlations. These observations indicate that
common environment in a family does not re-
sult in common serum phospholipid levels un-
less blood relationship exists, and that diet
cannot be the only factor in determining se-
rum phospholipid levels of healthy persons.

Because of the age-sex variations of serum
phospholipid and serum cholesterol levels, no
single arbitrary line can be drawn between
normal and abnormally elevated levels of
these 2 serum lipid fractions. The levels are
distributed as continuous variables. The upper
5 per cent levels of each age and sex group
may be utilized to characterize hyperphospho-
lipemia and hypercholesteremia, respectively.

**Summario in Interlingua**

Le nivello de phospholipido seral esseva
studiate in un segmento representativa del
population del Citate New York, incluse 1.067
individuos de sanitate normal, 516 masculos
e 551 femininas, de etates de inter 2 e 77 annos.
Se trovava inter illes 156 gruppos fa-
nial, i.e. 156 patres, 156 matres, e lor 268
pueros e pueras.

Le nivello de phospholipido seral in indi-
viduos normal monta con le avantiamento del
etate, sed non identicamente in le 2 sexos. In
masculos le nivello remane practicamente con-
stante usque al etate de 20 annos Postea illo
monta acutemente usque al etate de 32 annos
pro remane de novo constante usque al etate
de 60 annos. In femininas le nivello remane
constante usque al etate de 32 annos e monta
gradualmente usque al etate de 60 annos. Le
variationes secundo sexo e etate in le nivello
de phospholipido seral es simile a illos obser-
vate pro cholesterol seral, sed lor magnitude
es minor. Le datos indica le existentia de un
factor genetic que determina le nivello de
phospholipido seral in individuos normal.

Un studio de coefficientes de correlation pro
le nivello de phospholipido seral reveleva un
correlation negative inter matre e patre e un
correlation positive inter parente e progenie
e inter fraterno e fraterno. Iste observation-
es indica le milieum comun de un familia
non resulta in commun nivello de phospholip-ido seral, excepte sub conditiones de consan-
guineitate, e que le dieta non pote esser le
sol factor in le determinacion del nivello de
phospholipido seral in individuos normal.

A causa del variationes secundo sexo e etate
in le nivello seral de phospholipido e de cho-
lesterol, il non es possible fixar un sol linea
de demarcazione inter nivello normal e supra-
normal pro iste 2 fractiones lipidic del sero. In omne gruppo de etate e de sexo, le plus alte 5 pro cento del mesuraciones pote esser usate pro characterisar hyperphospholipemia e hypercholesterolemia, respectivamente.

REFERENCES

Serum Phospholipids: Genetic and Environmental Influences
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