Genetic and Environmental Contributions to Cholesterol and Its Subfractions in 11-Year-Old Twins

The Medical College of Virginia Twin Study


We conducted a cross-sectional analysis of the genetic and environmental contributions to the variance of lipoprotein cholesterol and its subfractions in children during early adolescence. Univariate path analysis was used to determine the relative contributions of genes, individual environment, and family environment to these measures in 233 11-year-old Caucasian twin pairs. For high density lipoprotein, high density lipoprotein₂, low density lipoprotein, very low density lipoprotein, and triglycerides, a model that incorporated genes and individual environmental variation but not common environment was sufficient to explain the variation. Different magnitudes of genetic effects were seen for total cholesterol in boys and girls. High density lipoprotein showed different magnitudes by sex for genetic and individual environmental effect. Intermediate density lipoprotein was the only cholesterol subfraction in which shared, or common, environment was found to make a statistically significant contribution to the variation. (Arteriosclerosis and Thrombosis 1991;11:844–850)

Heart disease tends to cluster in families. Certain rare genetic disorders such as familial hypercholesterolemia that are poorly responsive to dietary and other environmental changes are responsible for only a small fraction of the prevalence of coronary heart disease. The genetic contribution versus the environmental effects of other lipid and lipoprotein abnormalities to the familial aggregation of cardiovascular disease is less well known, yet broad public health recommendations have been made both for children and adults of both sexes to reduce their cholesterol intake. Plasma concentrations of low density lipoprotein (LDL) cholesterol have been shown to be directly related to the risk of cardiovascular disease in adults. High density lipoprotein (HDL) cholesterol has shown an inverse relation. A key question concerns the extent to which environmental differences account for variation in lipoprotein cholesterol concentrations in children because the efficacy of alternative intervention strategies could depend on the issue.

To explore, in early-pubertal children, the genetic and environmental contributions to variation in cholesterol and its major subfractions, HDL (including HDL₂ and HDL₃), intermediate density lipoprotein (IDL), LDL, and very low density lipoprotein (VLDL) cholesterol and triglycerides, we measured these variables in 233 11-year-old Caucasian twin pairs and obtained point estimates of the additive genetic, shared environmental, unique environmental, and sex-specific genetic effects on these traits.

**Methods**

From school rosters we ascertained 233 Caucasian twin pairs living in Virginia who represent an unbiased volunteer sample of the central Virginia twin population. The twins were examined at times as near to their 11th birthdays as possible. Informed consent for the institutionally approved protocol was obtained from the twins and their parents. Zygosity was assessed by questionnaire, dermatoglyphic analysis, and testing of the twins and their parents for the ABO, Rh, MNS, Kell, Duffy, Kidd, and P systems. Lipoprotein cholesterol measures were determined by vertical-spin ultracentrifugation. By use of a set of 853 control samples, the following means and standard deviations were observed for the lipid subfractions: for HDL, 36.2±1.6;
Sex twin pairs are shown in Figure 1, with the parameter covariances. An illustrative path model for an unlike-sex twin pair is designated as twin 1 and the female as twin 2. To test analysis, a variety of alternative causal models were formulated that could readily be represented by path diagrams. We included unlike-sex pairs in an overall analysis to provide an opportunity to test the possibility that the set of genes that influences a particular variable in males may be different from the set of genes that influences that variable in females. The LISREL program was used in the analysis. The program LISREL uses the techniques of structural equation modeling to investigate the causal relations between sets of unmeasurable variables (e.g., genetic effects, shared environmental effects, etc.) and observed variables (e.g., serum cholesterol level). For the present analysis specifically, a multisample analysis was performed in which the covariance matrices of the observed data were compared with those predicted by a set of plausible models. A $\chi^2$ goodness-of-fit statistic provides a measure of how well a particular model is supported by the data. In addition, maximum-likelihood estimates are calculated for each model parameter.

The preliminary statistical work was performed with the SAS computer package. Male/female mean differences were assessed by a pooled $t$ test analysis, which accounted for different variances in the two groups. The basic data summary statistics for our maximum-likelihood testing are the variance/covariance matrixes for the sex/zygosity groups. These provide us with replicate estimates of individual variances (i.e., for twin 1 and twin 2), together with the covariances between members of a twin pair, or a total of three statistics for each class of twins. Pearson product-moment correlations summarized the twin–twin covariation by zygosity and sex type. Within like-sex twin pairs, the first-born twin was consistently designated as twin 1 and the cotwin as twin 2. In the unlike-sex twin pairs, the male cotwin was designated as twin 1 and the female as twin 2. To pool correlation coefficients within a zygosity group across sex types and to test for homogeneity among the coefficients, a $Z$ score procedure outlined by Steele and Torrie was used. Because the parameter estimation techniques used in this study assume that variables are normally distributed, all of the variables were adjusted by a logarithmic transformation before analysis. A variety of alternative causal models were formulated that could readily be represented by path diagrams to explain the observed variances and covariances. An illustrative path model for an unlike-sex twin pair is shown in Figure 1, with the parameter estimates from the analysis of serum cholesterol. The phenotypes of the twins ($T_m, T_f$) are modeled as if they were determined by additive genetic effects ($G_m, G_f$), environmental effects common to both twins ($C_m, C_f$), and environmental effects specific to each twin ($E_m, E_f$). The subscripts m and f are used to represent the possibility of sex-specific effects.

The $\chi^2$ goodness-of-fit statistic provides a measure of how well a particular model is supported by the data. In addition, maximum-likelihood estimates are calculated for each model parameter.

The algorithm for selecting the best model was as follows. The $\chi^2$ goodness-of-fit statistic of the best-fitting model with $p$ parameters was subtracted from the $\chi^2$ statistic for the best-fitting model with $p-1$ parameters. This difference is itself a $\chi^2$ statistic with one degree of freedom. If its value was greater than 3.841 (the critical value for $p=0.05$), then we concluded that the model with $p$ parameters was "better" than the model with $p-1$ parameters. The process was repeated until all the consecutive groups of models were compared. These difference $\chi^2$ values appear in Table 3.

### Results

The means and standard deviations for the untransformed cholesterol, lipoprotein cholesterol sub-

![Figure 1. Path diagram for full model with parameter estimates from cholesterol analysis. Additive genetic, common environmental, and specific environmental effects are allowed to exert different effects on the male and female twin. $r_h$ represents correlation between genetic effects in male and female twins. $r_e$ represents correlation of effects of shared (common) environment on male and female twins. In this example, parameter estimates for the genetic effects $h, h'$ differ. Because $r_e=1$ in the best model for cholesterol, the same genes are thought to affect cholesterol regulation in boys and girls. Specific environmental effects are equal ($_e, e')$. No common environmental effect is detected ($e, e'=0$). $T_m, T_f$, phenotypes in male and female twins, respectively; $E_m, E_f$, environmental effects specific to each twin; $G_m, G_f$, additive genetic effects.](http://atvb.ahajournals.org/Downloadedfrom)
fraction, and triglyceride measures are given for the twin pairs in Table 1. Boys at age 11 years had higher total HDL cholesterol levels than did girls. This was due to the HDL₁ cholesterol subfraction. Girls had a slightly more advanced Tanner sexual maturity stage than did boys (2.19±0.94 versus 1.72±0.63) at age 11.

Pearson correlation coefficients for the transformed variables by type (twin 1 versus twin 2) are shown in Table 2. The monozygotic twin measurements were highly correlated, whereas lower correlations were seen for dizygotic twins. Differences between the sex types within zygosity groups were not statistically significant.

The model-fitting results for serum cholesterol are presented in Table 3 and serve to illustrate how the three-parameter model was considered to be the better of the two. The inclusion of a fourth parameter (see model 30) did not result in a significantly better fit; therefore, hh’e was considered to be the best model.

For each variable, Table 4 shows the most parsimonious model, its goodness-of-fit statistic, and model parameter estimates with associated standard errors. Also included for each variable is a model that represents the best-fitting model modified to include the shared-environment effect (c). Maximum-likelihood parameter estimates are expressed as percentages of the total phenotypic variance due to the three main sources: genes (h²), shared environment (c²), and unique environment (e²). The goodness-of-fit χ² given tests the agreement between observed and predicted twin correlations. A large χ² indicates that the postulated model, even when all the parameters are included, does not provide an adequate explanation for the data. Our estimation and model-fitting procedure takes account of all the information contained in the variances as well as family covariances, provides a systematic decision procedure for the selection of adequate but parsimonious models, and then provides maximum-likelihood estimates of the parameters that take proper account of the precision

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<th>HDL₃</th>
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<th>LDL</th>
<th>VLDL</th>
<th>Trig</th>
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HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; VLDL, very low density lipoprotein cholesterol; Trig, triglycerides (all in mg/dl).

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<th>Twin pairs (n)</th>
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<th>HDL₃</th>
<th>IDL</th>
<th>LDL</th>
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HDL, high density lipoprotein cholesterol; IDL, intermediate density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; VLDL, very low density lipoprotein cholesterol; Trig, triglycerides; MZ, monozygotic; DZ, dizygotic.
with which individual statistics are known. The lack of inclusion of a particular effect in our best-fitting model does not imply that the effect was zero, but rather that it could not be shown to be statistically significantly different from zero. For example, only for IDL did the inclusion of shared environment (c) result in a significantly reduced $\chi^2$.

For HDL, HDL2, LDL, VLDL, and triglycerides, when shared environment was included in the model its estimate was less than 0.05%.

Different magnitudes of genetic effects were seen for boys and girls for total serum cholesterol. The best-fitting model included $rh=1$, that is, the same genes were involved in the effects in boys and girls. The contribution of these effects, however, was somewhat greater in girls than in boys (79.9% versus 71.2%).

Although HDL3 is the major quantitative component of total HDL, different magnitudes by sex were found for genetic and unique environmental effects in HDL3 but not in HDL2 or total HDL. In particular, the contribution of additive genetic effects to HDL3 variation was 48.3% in girls and 73.0% in boys. For total cholesterol, the best-fitting model involved the same genes in boys and girls.

### Table 3. Model-Fitting Results for Serum Cholesterol

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* $e$, unique environment; $h$, genes; $r$, correlation between genetic effects in male and female twins; $c$, shared environment; $<=$ = = best model.
LDL was the only cholesterol subfraction for which shared, or common, environment was found to make a statistically significant contribution to variation, given the power of the study. Whereas additive genetic effects explained slightly more variation than did common environmental effects (37.6% versus 34.4%), the contribution of unique environmental effects was similar to that in the models for other cholesterol subfractions.

### Discussion

Our study question centered on the amount of variation in cholesterol subfractions of early-pubertal children that is likely to be significantly influenced by genetic factors and environmental intervention. No other study has examined the genetic and environmental contributions to variation in lipoprotein cholesterol fractions and triglycerides in as large a group of juvenile twins of the same age. Some of the discrepancies among previous studies may be accounted for by differences in the populations studied, differences in the ages studied, differences in measurement adjustment and estimation methods, or a combination of these causes. Other studies have used the technique of segregation analysis, particularly in families with various hyperlipidemias, to look for the specific involvement of major genes or specific alternative models in lipoprotein cholesterol variation.\(^9\)\(^{10}\) The extent to which modification in diet, for example, may be able to modify cholesterol levels at different ages is undoubtedly subject to some genetic limitation. Estimates of heritability from twin studies may often be higher than those estimated from nuclear families in which ages will necessarily differ. In particular because of age differences, gene expression in siblings will only be correlated for that proportion of the genetic effect expressed at different ages. Age-regression adjustments cannot remove this limitation of cross-sectional data for subjects of different ages.

Although the age ranges varied, sibs in the New York study\(^11\) and in the Tecumseh study\(^12\) showed remarkably similar correlations for total cholesterol, 0.37 and 0.35, respectively. Doubling these values would yield heritability estimates of 0.74 and 0.70. Our pooled dizygotic correlation of 0.39 would, if consistent in isolation, yield a heritability estimate of 0.78. Several studies with different samples have estimated \(h^2\) and \(c^2\) for serum lipid and lipoprotein measurements. In adult Swedish twins, Weinberg et al\(^13\) found that \(h^2=0.74\) and \(c^2=0.06\) for total serum cholesterol. In adults and children of Japanese ancestry living in Hawaii, Rao et al\(^14\) found that \(h^2=0.49\) and \(c^2=0.04\). Sing and Orr\(^15\) studied children and adults in Tecumseh, Mich., and found that \(h^2=0.58\) and \(c^2=0.2\) for total serum cholesterol. Estimates derived from school-age children in Bogalusa\(^16\)

<table>
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<th>(p)</th>
<th>Sex group</th>
<th>Additive genetic (%)</th>
<th>Shared environmental (%)</th>
<th>Unshared environmental (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol</td>
<td>hh'c*</td>
<td>7.2</td>
<td>0.8</td>
<td>Male</td>
<td>71.2 ± 10.7</td>
<td>...</td>
<td>28.8 ± 3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female</td>
<td>79.9 ± 10.7</td>
<td>...</td>
<td>20.2 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>hh'ce</td>
<td>7.2</td>
<td>0.8</td>
<td>Male</td>
<td>69.1 ± 22.6</td>
<td>2.0 ± 20.2</td>
<td>28.9 ± 3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female</td>
<td>78.4 ± 17.1</td>
<td>1.4 ± 14.1</td>
<td>20.2 ± 2.4</td>
</tr>
<tr>
<td>HDL</td>
<td>he*</td>
<td>8.5</td>
<td>0.8</td>
<td>Both</td>
<td>76.3 ± 8.0</td>
<td>...</td>
<td>23.7 ± 2.7</td>
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<tr>
<td></td>
<td>hce</td>
<td>8.5</td>
<td>0.8</td>
<td>Both</td>
<td>76.3 ± 8.0</td>
<td>0.0 ± t</td>
<td>23.7 ± t</td>
</tr>
<tr>
<td>HDL(_2)</td>
<td>he*</td>
<td>21.0</td>
<td>0.1</td>
<td>Both</td>
<td>67.6 ± 7.8</td>
<td>...</td>
<td>32.4 ± 3.8</td>
</tr>
<tr>
<td></td>
<td>hce</td>
<td>20.7</td>
<td>0.1</td>
<td>Both</td>
<td>59.4 ± 18.4</td>
<td>8.2 ± 17.0</td>
<td>32.5 ± 4.0</td>
</tr>
<tr>
<td>HDL(_3)</td>
<td>hh'ee*</td>
<td>18.2</td>
<td>0.1</td>
<td>Male</td>
<td>73.0 ± 11.1</td>
<td>...</td>
<td>27.0 ± 4.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female</td>
<td>48.3 ± 11.0</td>
<td>...</td>
<td>51.7 ± 8.1</td>
</tr>
<tr>
<td>VLDL</td>
<td>he*</td>
<td>13.5</td>
<td>0.4</td>
<td>Both</td>
<td>71.1 ± 7.9</td>
<td>...</td>
<td>28.9 ± 3.6</td>
</tr>
<tr>
<td></td>
<td>hce</td>
<td>13.5</td>
<td>0.3</td>
<td>Both</td>
<td>71.1 ± t</td>
<td>0.0 ± t</td>
<td>28.9 ± t</td>
</tr>
<tr>
<td>LDL</td>
<td>he*</td>
<td>12.6</td>
<td>0.5</td>
<td>Both</td>
<td>84.7 ± 7.9</td>
<td>...</td>
<td>15.3 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>hce</td>
<td>12.6</td>
<td>0.4</td>
<td>Both</td>
<td>84.7 ± t</td>
<td>0.0 ± t</td>
<td>15.3 ± t</td>
</tr>
<tr>
<td>IDL</td>
<td>he*</td>
<td>12.8</td>
<td>0.5</td>
<td>Both</td>
<td>72.6 ± 7.8</td>
<td>...</td>
<td>27.4 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>hce*</td>
<td>8.3</td>
<td>0.8</td>
<td>Both</td>
<td>37.6 ± 14.6</td>
<td>34.4 ± 14.5</td>
<td>28.0 ± 3.3</td>
</tr>
<tr>
<td>Trig</td>
<td>he*</td>
<td>8.3</td>
<td>0.8</td>
<td>Both</td>
<td>68.0 ± 8.2</td>
<td>...</td>
<td>32.0 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>hce</td>
<td>8.3</td>
<td>0.8</td>
<td>Both</td>
<td>68.0 ± t</td>
<td>0.0 ± t</td>
<td>32.0 ± t</td>
</tr>
</tbody>
</table>

*Best-fitting model.
†Because an estimate was close to zero, no standard errors could be computed.

HDL, high density lipoprotein cholesterol; VLDL, very low density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; IDL, intermediate density lipoprotein cholesterol; Trig, triglycerides; h, genes; e, unique environment; c, shared environment.
yielded $h^2 = 0.88$ and $c^2 = 0.05$. While shared environmental effects were not detectable in our study, additive genetic effects explained more than 70% of the variation in total serum cholesterol. The size of the genetic effect was somewhat greater in females than males. This may be consistent with the girls' slightly more advanced Tanner stage at age 11.

Investigators in Bogalusa had demonstrated a more marked decrease in total cholesterol for boys than girls in the early teenage years. The beginning of the rise toward adult levels appeared to occur in girls at about age 14 and in boys at about age 16.17 Hewitt et al18 found stronger correlations between parents and offspring for cholesterol at younger rather than at older ages (>15 years), but the sib correlations did not change appreciably in the childhood years. Longitudinal follow-up will enable us to see whether there is evidence, at different ages, for different genes' influencing cholesterol in boys and girls as they progress through adolescence. These studies will also tell us whether, at the same age, different sets of genes are active in boys and girls. While shared environment might be expected to become more dissimilar in the teenage years (e.g., differing diets), it is also possible that its contribution to variation could become augmented with advancing age.19

For HDL and HDL$_2$, a very simple model that allowed only for the additive effects of genes and environment unique to the individual was sufficient to explain the observed twin data. The contribution of shared environment in creating variation between families for these variables could not be distinguished from zero. There was no statistically significant evidence that the effects of genes and environment depended on gender at 11 years of age in these twin pairs. Others have estimated the heritability of HDL to range from 0.28 to 0.59.14,20-23 In a small sample of adult twins, Kuusi et al23 found an $h^2$ of 0.56 for HDL$_2$ and of zero for HDL$_3$. We found an $h^2$ of 0.68 for HDL$_3$ and evidence for a significant genetic effect of different magnitudes for HDL$_1$ in boys and girls. Although the HDL subfractions are metabolically interrelated, most variation in HDL cholesterol is due to the HDL$_2$ subfraction.24 We had previously shown a significant negative correlation between height/weight and HDL$_3$ levels in girls.3 The need to include differing magnitudes for additive genetic and unique environmental effects in the best-fitting model may relate to size and sexual maturity differences present at age 11. Multivariate analysis will be useful in clarifying whether the genes that influence body size are specific to body size or whether they share influence on other cardiovascular variables such as left ventricular mass.25

IDL was the only cholesterol subfraction in which we demonstrated an important contribution for shared environment in the 11-year-old twins. IDL, also known as the VLDL remnant, is derived from the liver-produced VLDL after triglycerides are removed. Some IDL is removed from the circulation in the liver, and the remainder is transformed into LDL. We have found no analogous studies that examined the genetic and environmental contributions to IDL variation. IDL has been shown to be influenced by obesity and smoking.26,27 As an intermediate between VLDL and LDL, it may be somewhat surprising to demonstrate a large common environmental effect not present in its precursor or breakdown product. On the other hand, the presence of a significant $c^2$ may suggest that environmental changes, for example, in smoking and weight, could modify IDL.

Observed variation in LDL and VLDL levels was explained by a simple model that allowed only for the additive effects of genes and unique environment. For LDL, others have demonstrated an $h^2$ from 0.390 to 0.624 and a $c^2$ from 0.012 to 0.118 in different populations. For VLDL, $h^2$ has ranged from 0.339 to 0.58 and for $c^2$ from 0.12 to 0.012.14,16,20 We observed a larger $h^2$ for LDL (0.85) than for VLDL (0.71).

We were also able to demonstrate a major contribution of additive genetic effects to triglyceride variation in these 11-year-old children. In the Hawaii and Cincinnati lipid studies, Rao et al14,20 found genetic heritabilities of 0.235 and 0.194 and cultural heritabilities of 0.059 and 0.149 for triglyceride values. Morrison et al28 found persistence of close sibling correlations in hypertriglyceridemic family units during the period of shared common household environment. Christian et al29 found a heritability of 0.68 in adult male twin pairs. Our high heritability value for triglycerides ($h^2=0.68$) may again be a function of a uniform age group. Our findings are thus far limited to Caucasian children. Laskarzewski et al30 found increased measures of within-family resemblance for HDL alone of all lipids and lipoproteins in blacks. We intend to analyze black children when our sample size allows comparison of black children increases.

No models that ignored the effect of genes fit the data. Feinleib et al31 found little or no genetic variability in male veteran twin pairs for total cholesterol, HDL, and LDL, while Vogler et al32 found that the common family environment contributed less than 10% of the variance for HDL, LDL, and VLDL. Although lipid and lipoprotein levels may track fairly well in children,33,34 we cannot predict that the explanatory models for these measures will remain the same into adulthood. We did see a significant negative relation between a positive family history for cardiovascular disease and HDL in an earlier study of these twins; however, even though the genetic variability may be the same in adults and children, the genes that contribute to the variables could differ.35

The presence of significant genetic effects in all the measured lipids and lipoproteins raises questions about the expectations for the success of traditional environmental interventions such as universal dietary changes at age 11 years. Dietary intervention studies have, on average, shown a 15% reduction of LDL cholesterol. Five-year follow-up of a small group of obese children receiving family-based behavioral treatment showed a sustained small increase in the HDL cholesterol level.36 This is consistent with our
finding of environmental variance in these measures. It will be necessary to follow these twins longitudinally to see whether these effects and their relative magnitudes persist throughout adolescence as lipid and lipoprotein levels approach values typical for adults. Multivariate analysis of lipoproteins and anthropometric measures over time in twins of both sexes should enable us to better assess the contributions of innate biologic variability, changing environments, and their interaction. Moreover, the longitudinal aspect of this study, combined with the analysis of data on the parents of our subjects, will help us to more directly address these important questions.

Acknowledgments

We acknowledge the technical expertise of A. Cook, L. Stevenson, B. Toms, K. Vincent, C. Dickens, W. Smith, M. Blanchard, and P. Winter and appreciate the insights of John Hewitt and Lindon Eaves.

References


Key Words • cholesterol • cardiovascular risk • lipoprotein cholesterol • genetics • twins
Genetic and environmental contributions to cholesterol and its subfractions in 11-year-old twins. The Medical College of Virginia Twin Study.
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Arterioscler Thromb Vasc Biol. 1991;11:844-850
doi: 10.1161/01.ATV.11.4.844

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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