Evolution at Two Levels in Humans and Chimpanzees

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Evolution at Two Levels in Humans and Chimpanzees

Their macromolecules are so alike that regulatory mutations may account for their biological differences.

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Soon after the expansion of molecular biology in the 1950's, it became evident that by comparing the proteins and nucleic acids of one species with those of another, one could hope to obtain a quantitative and objective estimate of the "genetic distance" between species. Until then, there was no common yardstick for measuring the degree of genetic difference among species. The characters used to distinguish among bacterial species, for example, were entirely different from those used for distinguishing among mammals. The hope was to use molecular biology to measure the differences in the DNA base sequences of various species. This would be the common yardstick for studies of organismal diversity.

During the past decade, many workers have participated in the development and application of biochemical methods for estimating genetic distance. These methods include the comparison of proteins by electrophoretic, immunological, and sequencing techniques, as well as the comparison of nucleic acids by annealing techniques. The only two species which have been compared by all of these methods are chimpanzees (Pan troglodytes) and humans (Homo sapiens). This pair of species is also unique because of the thoroughness with which they have been compared at the organismal level—that is, at the level of anatomy, physiology, behavior, and ecology. A good opportunity is therefore presented for finding out whether the molecular and organismal estimates of distance agree.

The intriguing result, documented in this article, is that all the biochemical methods agree in showing that the genetic distance between humans and the chimpanzee is probably too small to account for their substantial organismal differences.

Indications of such a paradox already existed long ago. By 1963, it appeared that some of the blood proteins of humans were virtually identical in amino acid sequence with those of apes such as the chimpanzee or gorilla (1). In the intervening years, comparisons between humans and chimpanzees were made with many additional proteins and with DNA. These results, reported herein, are consistent with the early results. Moreover, they tell us that the genes of the human and the chimpanzee are as similar as those of sibling species of other organisms (2). So, the paradox remains. In order to explain how species which have such similar genes can differ so substantially in anatomy and way of life, we review evidence concerning the molecular basis of evolution at the organismal level. We suggest that evolutionary changes in anatomy and way of life are more often based on changes in the mechanisms controlling the expression of genes than on sequence changes in proteins. We therefore propose that regulatory mutations account for the major biological differences between humans and chimpanzees.

Similarity of Human and Chimpanzee Genes

To compare human and chimpanzee genes, one compares either homologous proteins or nucleic acids. At the protein level, one way of measuring the degree of genetic similarity of two taxa is to determine the average number of amino acid differences between homologous polypeptides from each population. The most direct method for determining this difference is to compare the amino acid sequences of the homologous proteins. A second method is microcomplement fixation, which provides immunological distances linearly correlated with amino acid sequence difference. A third method is electrophoresis, which is useful in analyzing taxa sufficiently closely related that they share many alleles. For the human-chimpanzee comparison all three methods are appropriate, and thus many human and chimpanzee proteins have now been compared by each method. We can therefore estimate the degree of genetic similarity between humans and chimpanzees by each of these techniques.

Sequence and immunological comparisons of proteins. During the last decade, amino acid sequence studies have been published on several human and chimpanzee proteins. As Table 1 indicates, the two species seem to have identical fibrinopeptides (3), cytochromes c (4), and hemoglobin chains [alpha (4), beta (4), and gamma (5, 6)]. The structural genes for these proteins may therefore be identical in humans and chimpanzees. In other cases, for example, myoglobin (7) and the
This method indicates that the sequences of human and chimpanzee the average degree of difference between the amino acid replacement. The amino acid sequences already mentioned is not yet complete. By applying the microcomplement fixation method to large proteins, however, one can obtain an approximate measure of the degree of amino acid sequence difference between related proteins (9). This method indicates that the sequences of human and chimpanzee albums (10), transferrins (11), and carbonic anhydrases (4, 12) differ slightly, but that lysozyme (13) is identical in the two species (Table 1) (14). Based on the proteins listed in Table 1, the average degree of difference between human and chimpanzee proteins is 19 x 1000 = 7.2 amino acid sites per 1000 substitutions. That is, the sequences of the human and chimpanzee polypeptides examined to date are, on the average, more than 99 percent identical.

Electrophoretic comparison of proteins. Electrophoresis can provide an independent estimate of the average amino acid sequence difference between closely related species. We have compared the human and chimpanzee polypeptide products of 44 different structural genes. Table 2 indicates the allelic frequencies and the estimated probability of identity at each locus. The symbol $S_i$ represents the probability that human and chimpanzee alleles will be electrophoretically identical at a particular locus $i$, or

$$S_i = \frac{1}{L} \sum_{j=1}^{A_i} x_{ij} y_{ij}$$

where $x_{ij}$ is the frequency of the $j$th allele at the $i$th locus in human populations, and $y_{ij}$ the frequency of the $j$th allele at the $i$th locus in chimpanzee populations for all $A_i$ alleles at that locus. For example, Table 2 indicates the frequencies of the three alleles (A, A', A'') at the acid phosphatase locus for human and chimpanzee populations. The probability of identity of human and chimpanzee alleles at this locus, that is, $S_i$ is (0.29 x 0) + (0.68 x 1.00) + (0.03 x 0), or 0.68.

Of the loci in Table 2, 31 code for intracellular proteins; 13 code for secreted or extracellular proteins. In general, the intracellular proteins were analyzed by starch gel electrophoresis of red blood cell lysates, with the buffer systems indicated in the table and stains specific for the enzymatic activity of each protein. For a few intracellular proteins (cytochrome c, the hemoglobin chains, and myoglobin), amino acid sequences have been published for both species, so that direct sequence comparison is also possible. Most of the secreted proteins were compared by acrylamide gel electrophoresis of human and chimpanzee plasma (15). The electrode chamber contained tris(hydroxymethyl)aminomethane (tris) borate buffer, pH 8.9; acrylamide gel slabs were made with tris-sulfate buffer, pH 8.9. Gels were stained with amido black, a general protein dye. The identification of bands on a gel stained with this dye poses a problem, since it is not obvious, particularly for less concentrated proteins, which protein each band represents. We determined the electrophoretic mobilities of the plasma proteins by applying the same sample to several slots of the same gel, staining the outside columns, and cutting horizontal slices across the unstained portion of the gel at the position of each band. The protein was eluted separately from each band in 0.1 to 0.2 milliliter of an appropriate isotonic tris buffer (9) and tested for reactivity with a series of rabbit antiserums, each specific for a particular human plasma protein, by means of immunoelectrophoresis and immunodiffusion in agar (15, 16). The results of this analysis are shown in Fig. 1.

Some of the secreted proteins were compared by means of other electrophoretic methods as well. Albumin and transferrin were surveyed by cellulose acetate electrophoresis; and $\alpha_1$-antitrypsin, Gc-globulin (group-specific component), the haptoglobin chains, lysozyme, and plasma cholinesterase were analyzed on starch gels, with the buffers indicated in Table 2.

The results of all electrophoretic comparisons are summarized in Fig. 2. About half of the proteins in this survey are electrophoretically identical for the two species, and about half of them are different. Only a few loci are highly polymorphic in both species (see 17).

The proportion of alleles at an "average" locus that are electrophoretically identical in human and chimpanzee populations can be calculated from Table 2 and Eq. 3, where $L$ is the number of loci observed:

$$S = \frac{1}{L} (S_1 + S_2 + \ldots + S_L) = 0.52$$

![Fig. 1. Separation of human and chimpanzee plasma proteins by acrylamide electroophoresis at pH 8.9. The proteins are: 1, $\alpha_2$-macroglobulin; 2, third component of complement; 3, transferrin; 4, haptoglobin; 5, ceruloplasmin; 6, $\alpha_2$-glycoprotein; 7, Gc-globulin; 8, $\alpha_1$-antitrypsin; 9, albumin; and 10, $\alpha_1$-acid glycoprotein. The chimpanzee plasma has transferrin genotype Pan CC; the human plasma has transferrin genotype Homo CC and haptoglobin genotype 1-1. The direction of migration is from left to right.](attachment:image.png)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Amino acid differences</th>
<th>Amino acid sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinopeptides A and B (3)</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Cytochrome c (4)</td>
<td>0</td>
<td>104</td>
</tr>
<tr>
<td>Lysozyme (13)</td>
<td>~0</td>
<td>130</td>
</tr>
<tr>
<td>Hemoglobin a (4)</td>
<td>0</td>
<td>141</td>
</tr>
<tr>
<td>Hemoglobin b (4)</td>
<td>0</td>
<td>146</td>
</tr>
<tr>
<td>Hemoglobin $\alpha_2$ (5, 6)</td>
<td>0</td>
<td>146</td>
</tr>
<tr>
<td>Hemoglobin $\alpha_4$ (5, 6)</td>
<td>0</td>
<td>146</td>
</tr>
<tr>
<td>Hemoglobin $\delta$ (5, 8)</td>
<td>1</td>
<td>146</td>
</tr>
<tr>
<td>Myoglobin (7)</td>
<td>1</td>
<td>153</td>
</tr>
<tr>
<td>Carbonic anhydrase (4, 12)</td>
<td>~3</td>
<td>264</td>
</tr>
<tr>
<td>Serum albumin (10)</td>
<td>~6</td>
<td>580</td>
</tr>
<tr>
<td>Transferrin (11)</td>
<td>~8</td>
<td>647</td>
</tr>
<tr>
<td>Total</td>
<td>~19</td>
<td>2633</td>
</tr>
</tbody>
</table>

Table 1. Differences in amino acid sequences of human and chimpanzee polypeptides. Lysozyme, carbonic anhydrase, albumin, and transferrin have been compared immunologically by the microcomplement fixation technique. Amino acid sequences have been determined for the other proteins. Numbers in parentheses indicate references for each protein.
In other words, the probability that human and chimpanzee alleles will be electrophoretically identical at a particular locus is about one-half.

Agreement between electrophoresis and protein sequencing. The results of electrophoretic analysis can be used to estimate the average number of amino acid differences per polypeptide chain for humans and chimpanzees, for comparison with the estimate based on amino acid sequences and immunological data. To calculate the average amino acid sequence difference between human and chimpanzee proteins, we need first to estimate the proportion (e) of amino acid substitutions detectable by electrophoresis. Electrophoretic techniques detect only amino acid substitutions that change the net charge of the protein observed. Four amino acid side chains are charged at pH 8.6: arginine, lysine, glutamic acid, and aspartic acid. The side chain of histidine is positively charged below approximately pH 6. The proportion of accepted point mutations that would be detectable by the buffer

<table>
<thead>
<tr>
<th>Locus (i) and allele (j)</th>
<th>Human (xij)</th>
<th>Chimpanzee (yij)</th>
<th>Probability of identity (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid phosphatase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3.1.3.2); N = 86</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AP0</td>
<td>0.29</td>
<td>0</td>
<td>0.68</td>
</tr>
<tr>
<td>AP0</td>
<td>0.68</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>AP0</td>
<td>0.03</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Adenosine deaminase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3.5.4.4); N = 22</td>
<td></td>
<td></td>
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<tr>
<td>ADA0</td>
<td>0.96</td>
<td>0</td>
<td>0</td>
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<td>ADA0</td>
<td>0.04</td>
<td>1.00</td>
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<tr>
<td>ADA0, ADA0, ADA0</td>
<td>0</td>
<td>1.00</td>
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</tr>
<tr>
<td>Adenylate kinase</td>
<td></td>
<td></td>
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<tr>
<td>(2.7.4.3); N = 86</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AR0</td>
<td>0.98</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>AR0</td>
<td>0.02</td>
<td>0</td>
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<tr>
<td>Carbonic anhydrase</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>I or II (4.2.1.1); N = 111</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Cytochrome c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esterase A,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3.1.1.6); N = 111</td>
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<td></td>
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</tr>
<tr>
<td>E0</td>
<td>1.00</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E0</td>
<td>0</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>E0, E0</td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esterase B,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3.1.1.1); N = 111</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>E0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Glutathione reductase</td>
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<tr>
<td>(1.6.4.2); N = 64</td>
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<tr>
<td>GSR0</td>
<td>0.97</td>
<td>1.00</td>
<td>0.97</td>
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<tr>
<td>GSR0</td>
<td>0.01</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>GSR0</td>
<td>0.02</td>
<td>0</td>
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</tr>
<tr>
<td>Hemoglobin α chain; N = 108</td>
<td></td>
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<td></td>
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<tr>
<td>Hb00</td>
<td>1.00</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Hb00</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Comments and references:

- Red cells; six subunits, each 43,000 MW; ~370 aa; phosphate, pH 7.0; and tryptic peptides of human and chimpanzee common variants.
- Red cells; two subunits, each 50,000 MW; ~430 aa; tris-citrulline, pH 7.0, starch electrophoresis (62, 109); chimpanzee protein faster (62)
<table>
<thead>
<tr>
<th>Locus (i) and allele (j)</th>
<th>Allele frequency</th>
<th>Probability of identity ( (S_j) )</th>
<th>Comments and references‡</th>
</tr>
</thead>
</table>
| Hemoglobin \( \beta \) chain; \( N = 108 \)  
\( Hb^a \) | 0.99 0.99 | 0.98 | Red cells; 16,000 MW; 146 aa; tris-glycine, \( pH \) 8.4, cellulose acetate electrophoresis (7); amino acid sequences of \( \beta \) chains identical (65); chimpanzee \( Hb^a \) electrophoretically identical to human \( Hb^a \) (66) |
| Hemoglobin \( \alpha_\gamma \) chain | 1.00 1.00 | 1.00 | Fetal red cells; 16,000 MW; 146 aa; amino acid sequence of human and chimpanzee \( \gamma \) chains identical; \( \alpha_\gamma \) and \( \beta_\gamma \) are products of different structural genes, differ at residue 136; A, alanine; G, glycine (67) |
| Hemoglobin \( \delta \gamma \) chain | 1.00 1.00 | 1.00 | Red cells; 16,000 MW; 146 aa; human and chimpanzee electrophoretic mobilities identical, but one amino acid difference at position 125: humane \( \delta \), methionine; chimpanzee \( \delta \), valine (8) |
| Lactate dehydrogenase H \( (1.1.1.27); N = 74 \) | 1.00 1.00 | 1.00 | Red cells; \( H \) and \( M \) subunits each 34,000 MW; 330 aa; citrate-phosphate, \( pH \) 6.0, starch electrophoresis (69); three intermediate bands of five-band, tetrameric electrophoretic pattern have different mobilities for humans and chimpanzees, because of difference in \( M \) polypeptide (70) |
| Lactate dehydrogenase M \( (1.1.1.27); N = 74 \)  
\( ldh \ M^a \) | 1.00 0 | 0 | Red cells; two subunits, each 34,000 MW; 330 aa; see LDH for procedures; polymorphic in some human populations (71) |
| Malate dehydrogenase \( (cytoplasmic) \) \( (1.1.1.37); N = 88 \) | 1.00 1.00 | 1.00 | Red cells; tris-citrate, \( pH \) 6.8, starch electrophoresis (72) distinguishes \( M^a \) human and chimpanzee enzymes, no difference with tris-EDTA, \( pH \) 9.3, electrophoresis (56, 73) |
| Methemoglobin reductase \( (1.6.99); N = 86 \)  
\( MR^1 \) | 1.00 0 | 0 | Red cells; tris-citrate, \( pH \) 6.8, starch electrophoresis (72) distinguishes human and chimpanzee enzymes, no difference with tris-EDTA, \( pH \) 9.3, electrophoresis (56, 73) |
| Myoglobin | 1.00 1.00 | 1.00 | Muscle; 16,900 MW; 153 aa; tryptic and chymotryptic peptides of cyanmethemoglobin electrophoretically identical at \( pH \) 8.6 (74), but at position 116, human has glutamine, chimpanzee has histidine (7) |
| Peptidase A \( (3.4.3.2); N = 63 \)  
\( PepA^1 \) and \( PepA^2 \)  
\( PepA^a \) | 0.99 1.00 | 0.99 | Red cells; two subunits, each 46,000 MW; ~400 aa; tris-maleate, \( pH \) 7.4 starch electrophoresis, leucyl-glycine substrate (65); \( PepA^1 \) and \( PepA^a \) not distinguishable in red blood cell lysates (75) |
| Peptidase C \( (3.4.3.2); N = 63 \)  
\( PepC^1 \)  
\( PepC^a \) | 0.99 1.00 | 0.99 | Red cells; 65,000 MW; ~565 aa; see peptidase A for procedures; polymorphism in human populations (78) |
| Phosphoglucomutase 1 \( (2.7.5.1); N = 168 \)  
\( PGM^1 \) | 0.77 0.26 | 0.20 | Red cells; subunits \( PGM^1 \) and \( PGM^2 \) each 62,000 MW; ~540 aa; tris-maleate-EDTA, \( pH \) 7.4, starch electrophoresis (16, 55, 61, 77) |
| Phosphoglucomutase 2 \( (2.7.5.1); N = 168 \)  
\( PGM^2 \) | 0.04 0.74 | 0.04 | Red cells; two subunits, each 40,000 MW; 350 aa; see G6PD for procedures; chimpanzee allele electrophoretically identical to human "Canning" variant (55) |
| 6-Phosphogluconate dehydrogenase \( (1.1.1.44); N = 86 \)  
\( PGDA \) | 0.96 0 | 0.04 | Red cells; two subunits, each 66,000 MW; 580 aa; tris-citrate, \( pH \) 8.0, starch electrophoresis (56); chimpanzee protein has slower mobility, both cathodally migrating (78) |
| Phosphohexose isomerase \( (5.3.1.9); N = 86 \)  
\( PH^1 \)  
\( PH^a \) | 1.00 0 | 0 | Red cells; two subunits, each 66,000 MW; 580 aa; tris-citrate, \( pH \) 8.0, starch electrophoresis (56); chimpanzee protein has slower mobility, both cathodally migrating (78) |
<p>| Superoxide dismutase A ( (indophenol oxidase) ) ( (1.15.1.1); N = 64 ) | 1.00 1.00 | 1.00 | Red blood cells; two subunits, each 16,300 MW; 158 aa (68); see phosphoglucomutase for procedure |
| Triosephosphate isomerase A ( (5.3.1.1) ) | 1.00 1.00 | 1.00 | Fibroblasts: dimers 48,000 MW; each polypeptide 248 aa (79); ( \beta ) polypeptide found only in hominoids. |
| Triosephosphate isomerase B ( (5.3.1.1) ) | 1.00 1.00 | 1.00 | See triosephosphate isomerase A |</p>
<table>
<thead>
<tr>
<th>Locus (i) and allele (j)</th>
<th>Allele frequency</th>
<th>Probability of identity</th>
<th>Comments and references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human* (xi)</td>
<td>Chimpanzee (yi)</td>
<td>(Si)</td>
<td></td>
</tr>
<tr>
<td><strong>Secreted proteins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1-Acid glycoprotein</td>
<td>0.32</td>
<td>0.02</td>
<td>Glycoprotein in plasma; carbohydrate &gt; 50 percent; 44,100 MW; 180 aa; acrylamide electrophoresis, pH 8.9 (see text); polymorphism in human populations detectable at pH 2.9 (80); isoelectric point is 1.82 for human and chimpanzee proteins, but proteins differ by quantitative precipitin analysis (81)</td>
</tr>
<tr>
<td>(orosomucoid); N</td>
<td>0.68</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Albumin; N = 123</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AlbA</td>
<td>0.00</td>
<td>0.00</td>
<td>Plasma; 46,000 MW; ~580 aa; tris-citrate, pH 5.5, cellulose acetate electrophoresis; acrylamide electrophoresis, pH 8.9; chimpanzee protein slower mobility, immunological difference detected by microcomplement fixation (10, 42); rare polymorphic alleles in human populations (82)</td>
</tr>
<tr>
<td>AlbB</td>
<td>1.00</td>
<td>0.00</td>
<td></td>
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<tr>
<td>α1-Antitrypsin; N = 123</td>
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<tr>
<td>PrA</td>
<td>0.95</td>
<td>0.00</td>
<td>Plasma; eight subunits, each 17,000 MW; ~150 aa; acrylamide electrophoresis, pH 8.9; possible adaptive significance of polymorphism in human populations (84)</td>
</tr>
<tr>
<td>PrB</td>
<td>0.03</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>PrC</td>
<td>0.02</td>
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<tr>
<td>PrD</td>
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<td>Ceruloplasmin; N = 123</td>
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<td>CpA</td>
<td>0.01</td>
<td>1.00</td>
<td>Plasma; total MW 240,000; acrylamide electrophoresis, pH 8.9; polymorphism in human populations detectable by high voltage electrophoresis (85)</td>
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<td>CpB</td>
<td>0.98</td>
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<tr>
<td>CpC</td>
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<tr>
<td>Third component of</td>
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<td>complement; N = 123</td>
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<td>C3rA</td>
<td>0.12</td>
<td>0.00</td>
<td>Plasma; two subunits, each 25,000 MW; ~220 aa; acrylamide electrophoresis, pH 8.9; human C3 2-2 and chimpanzee protein similar on acrylamide, chimpanzee slightly faster on starch or immunoelectrophoresis (86)</td>
</tr>
<tr>
<td>C3rB</td>
<td>0.87</td>
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<tr>
<td>component; N = 206</td>
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<tr>
<td>GcA</td>
<td>0.74</td>
<td>0.00</td>
<td>Plasma; α1 chain is 8,900 MW; 83 aa; α2 chain is 16,000 MW; 142 aa; β chain is 36,000 to 40,000 MW; ~330 aa; acrylamide electrophoresis, pH 8.9; borate-NaOH well buffer and tris-citrate gel buffer, pH 8.6, starch electrophoresis (56); chimpanzee electrophoresis, pH 8.9; polymorphism in human populations (88)</td>
</tr>
<tr>
<td>GcB</td>
<td>0.76</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>GcC</td>
<td>0.02</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Haptoglobin α chain; N = 300</td>
<td>0.36</td>
<td>0.00</td>
<td>Plasma; α1 chain is 8,900 MW; 83 aa; α2 chain is 16,000 MW; 142 aa; β chain is 36,000 to 40,000 MW; ~330 aa; acrylamide electrophoresis, pH 8.9; borate-NaOH well buffer and tris-citrate gel buffer, pH 8.6, starch electrophoresis (56); chimpanzee Hp shares six human Hp 1-1 and eight Hp 2-2 antigenic determinants; Hpβ evolved since human-chimpanzee divergence (87)</td>
</tr>
<tr>
<td>HpA</td>
<td>0.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>HpB</td>
<td>0.64</td>
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</tr>
<tr>
<td>HpC</td>
<td>0.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Haptoglobin β chain; N = 300</td>
<td>1.00</td>
<td>1.00</td>
<td>See haptoglobin α chain</td>
</tr>
<tr>
<td>Lysozyme</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LysA</td>
<td>1.00</td>
<td>0.00</td>
<td>Milk; 14,400 MW; 130 aa; starch gel electrophoresis, pH 5.3 (88)</td>
</tr>
<tr>
<td>LysB</td>
<td>0.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>α2-Macroglobulin; N = 123</td>
<td>1.00</td>
<td>0.00</td>
<td>Plasma; four subunits, each 196,000 MW; acrylamide electrophoresis, pH 8.9; X-linked antigenic polymorphism observed in human populations (89) but not detectable by electrophoreses; human and chimpanzee proteins immunologically indistinguishable (14)</td>
</tr>
<tr>
<td>XmA</td>
<td>1.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>XmB</td>
<td>0.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Plasma cholinesterase (3.1.1.8); N = 111</td>
<td>1.00</td>
<td>0.00</td>
<td>Plasma; four subunits, each ~87,000 MW; see esterase A, for procedures; chimpanzee protein has four components with faster mobilities than analogous human components (15)</td>
</tr>
<tr>
<td>E1*</td>
<td>0.01</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>E1**</td>
<td>0.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Transferrin; N = 133</td>
<td></td>
<td></td>
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<tr>
<td>Homo: TfA</td>
<td>0.99</td>
<td>0.00</td>
<td>Plasma; 73,000 to 92,000 MW; ~650 aa; acrylamide electrophoresis, pH 8.9; tris-glycine, pH 8.4, cellulose acetate electrophoresis (77, 90)</td>
</tr>
<tr>
<td>TfB</td>
<td>0.01</td>
<td>0.00</td>
<td></td>
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<tr>
<td>TfC</td>
<td>0.00</td>
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<tr>
<td>TfG</td>
<td>0.00</td>
<td>0.02</td>
<td></td>
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</tbody>
</table>

* Allelic frequencies for human populations are calculated from data summarized by Nei and Roychoudhury (28). Sample sizes generally greater than 1000. Only alleles with frequency > 0.01 are listed. The relative sizes of racial groups were estimated to be Caucasian, 45 percent; Black African, 10 percent; and Mongoloid (combined), 45 percent. † See Eq. 2 in text. § Given in this column are: the tissue used, polypeptide chain length, electrophoretic conditions, and references to previous studies on people and chimpanzees, Genetics, population, and physiological studies of most human red cell and plasma proteins are summarized by Giblett (56) or Harris (91); studies of plasma proteins are summarized by Schultz and Herrmann (92). References are for additional studies of chimpanzee or human proteins. ¶ Not included in identity calculations. || Notation for the chimpanzee alleles at the PGM locus differs in published surveys. Ours is as follows: PGM,M* (which is chimpanzee PGM,); of Goodman and co-workers and PGM,M* of Schmitt and co-workers is the allele with lowest electrophoretic mobility; PGM,1 (which is human PGM,); the chimpanzee PGM,1; of Schmitt, and the chimpanzee PGM,1 of Goodman is intermediate; and PGM,9 (found only in human populations) has the fastest mobility.
First, more changes may appear in DNA than in proteins because of the redundancy of the code and consequently the existence of third-position nucleotide changes which do not lead to amino acid substitutions. The nature of the code indicates that if first-, second-, and third-position substitutions were equally likely to persist, then about 30 to 40 percent of potential base replacements in a cistron would not be reflected in the coded protein; that is, 1.4 to 1.7 base substitutions would occur for each amino acid substitution (27). However, it is likely that a larger proportion of the actual base substitutions in a cistron are third-position changes, since base substitutions that do not affect amino acid sequence are more likely to spread through a population. In addition, many of the nucleic acid substitutions may have occurred in regions of the DNA that are not transcribed and are therefore not conserved during evolution. Proteins analyzed by electrophoresis, sequencing, or microcomplement fixation techniques, on the other hand, all have definite cellular functions and may therefore have been conserved to a greater extent during evolution.

Genetic Distance and the Evolution of Organisms

The resemblance between human and chimpanzee macromolecules has been measured by protein sequencing, immunology, electrophoresis, and nucleic acid hybridization. From each of these results we can obtain an estimate of the genetic distance between humans and chimpanzees. Some of the same approaches have been used to estimate the genetic distance between other taxa, so that these estimates may be compared to the human-chimpanzee genetic distance.

First, we consider genetic distance estimated from electrophoretic data, using the standard estimate of net codon differences per locus developed by Nei and Roychoudhury (28). Other indices have been suggested for handling electrophoretic data (29) and give the same
Nei and Roychoudhury's standard estimate of genetic distance between humans and chimpanzees can be written:

\[ D = D_{nc} - \frac{D_c + D_H}{2} \]  
(8)

where

\[ D_{nc} = - \log S \]

\[ D_c = - \log \left( \frac{1}{L} \sum_{i=1}^{L} \sum_{j=1}^{L} x_{ij}^2 \right) \]

\[ D_H = - \log \left( \frac{1}{L} \sum_{i=1}^{L} \sum_{j=1}^{L} y_{ij}^2 \right) \]

according to the notation of Table 2 and Eqs. 2 and 3. Therefore, \( D \) is an estimate of the variability between human and chimpanzee populations (\( D_{nc} \)), corrected for the variability within human populations (\( D_H \)) and within chimpanzee populations (\( D_c \)). \( D_c \) and \( D_H \) are also measurements of the degree of heterozygosity in human and chimpanzee populations (30).

Based on the data of Table 2, \( D_{nc} \) is 0.65, \( D_c \) is 0.02, and \( D_H \) is 0.05, so that:

\[ D = 0.62 \]  
(9)

In other words, there is an average of 0.62 electrophoretically detectable codon differences per locus between homologous human and chimpanzee proteins.

This distance is 25 to 60 times greater than the genetic distance between human races (28, 31). In fact, the genetic distance between Caucasian, Black African, and Japanese populations is less than or equal to that between morphologically and behaviorally identical populations of other species. In addition, these three human populations are equally distant from the chimpanzee lineage (Fig. 3).

However, with respect to genetic distances between species, the human-chimpanzee \( D \) value is extraordinarily small, corresponding to the genetic distance between sibling species of \( Drosophila \) or mammals (Fig. 4). Nonsibling species within a genus (referred to in the figure as congeneric species) generally differ more from each other, by electrophoretic criteria, than humans and chimpanzees. The genetic distances among species from different genera are considerably larger than the human-chimpanzee genetic distance.

The genetic distance between two species measured by DNA hybridization also indicates that human beings and chimpanzees are as similar as sibling species of other organisms. The differences in dissociation temperature, \( \Delta T \), between reannealed human DNA and human-chimpanzee hybrid DNA is about 1.1°C. However, for sibling species of \( Drosophila \), \( \Delta T \) is 3°C; for congeneric species of \( Drosophila \), \( \Delta T \) is 19°C; and for congeneric species of mice (\( Mus \)), \( \Delta T \) is 5°C (32).

Immunological and amino acid sequence comparisons of proteins lead to the same conclusion. Antigenic differences among the serum proteins of congeneric squirrel species are several times greater than those between humans and chimpanzees (33). Moreover, antigenic differences among the albumins of congeneric frog species (\( Rana \) and \( Hyla \)) are 20 to 30 times greater than those between the two hominoids (34, 35). In addition, the genetic distances among \( Hyla \) species, estimated electrophoretically, are far larger than the chimpanzee-human genetic distance (36). Finally, the human and chimpanzee \( \beta \) chains of hemoglobin appear to have identical sequences (Table 1), while the \( \beta \) chains of two \( Rana \) species differ by at least 29 amino acid substitutions (37). In summary, the genetic distance between humans and chimpanzees is well within the range found for sibling species of other organisms.

The molecular similarity between chimpanzees and humans is extraordinary because they differ far more than sibling species in anatomy and way of life. Although humans and chimpanzees are rather similar in the structure of the thorax and arms, they differ substantially not only in brain size but also in the anatomy of the pelvis, foot, and jaws, as well as in relative lengths of limbs and digits (38). Humans and chimpanzees also differ significantly in many other anatomical respects, to the extent that nearly every bone in the body of a chimpanzee is readily distinguishable in shape or size from its human counterpart (38). Associated with these anatomical differences there are, of course, major differences in postural (see cover picture), mode of locomotion, methods of procuring food, and means of communication. Because of these major differences in anatomy and way of life, biologists place the two species not just in separate genera but in separate families (39). So it appears that molecular and organismal methods of evaluating the chimpanzee-human difference yield quite different conclusions (40).

An evolutionary perspective further illustrates the contrast between the results of the molecular and organismal approaches. Since the time that the ancestor of these two species lived, the chimpanzee lineage has evolved slowly relative to the human lineage, in terms of anatomy and adaptive strategy. According to Simpson (41):

Pan is the terminus of a conservative lineage, retaining in a general way an anatomical and adaptive facies common to all recent hominoids except Homo. Homo is both anatomically and adaptively the most radically distinctive of all hominoids, divergent to a degree considered familial by all primatologists.

This concept is illustrated in the left-hand portion of Fig. 5. However, at the macromolecular level, chimpanzees and humans seem to have evolved
at similar rates (Fig. 5, right). For example, human and chimpanzee albumins are equally distinct immunologically from the albumins of other hominoids (gorilla, orangutan, and gibbon) and human and chimpanzee DNA's differ to the same degree from DNA's of other hominoids. As shown on the right, both protein and nucleic acid evidence indicate that as much change has occurred in chimpanzee genes as in human genes.

for evolutionary changes in gene regulation.

Although humans and chimpanzees have rather similar chromosome numbers, and respectively, the arrangement of genes on chimpanzee chromosomes differs from that on human chromosomes. Only a small proportion of the chromosomes have identical banding patterns in the two species. The banding studies indicate that at least 10 large inversions and translocations and one chromosomal fusion have occurred since the two lineages diverged. Further evidence for the possibility that chimpanzees and humans differ considerably in gene arrangement is provided by annealing studies with a purified DNA fraction. An RNA which is complementary in sequence to this DNA apparently anneals predominantly at a cluster of sites on a single human chromosome, but at widely dispersed sites on several chimpanzee chromosomes. The arrangement of chromosomal sites at which ribosomal RNA anneals may also differ between the two species.

Biologists are still a long way from understanding gene regulation in mammals, and only a few cases of regulatory mutations are now known. New techniques for detecting regulatory differences at the molecular level are required in order to test the hypothesis that organismal differences between individuals, populations, or species result mainly from regulatory differences. When the regulation of gene expression during embryonic development is more fully understood, molecular biology will contribute more significantly to our understanding of the evolution of whole organisms. Most important for the future study of human evolution would be the demonstration of differences between apes and humans in the timing of gene expression during development, particularly during the development of adaptively crucial organ systems such as the brain.

Summary and Conclusions

The comparison of human and chimpanzee macromolecules leads to several inferences:

1) Amino acid sequencing, immunological, and electrophoretic methods of protein comparison yield concordant estimates of genetic resemblance. These approaches all indicate that the average human polypeptide is more than 99 per-
cent identical to its chimpanzee counter-
2) Nonrepeated DNA sequences differ more than amino acid sequences. A large proportion of the nucleotide differences between the two species may be ascribed to redundancies in the genetic code or to differences in non-transcribed regions.
3) The genetic distance between humans and chimpanzees, based on electrophoretic comparison of proteins encoded by 44 loci is very small, corresponding to the genetic distance between sibling species of fruit flies or responding to the genetic distance between human and chimpanzees. This indicates that macro-molecular sequence and Structure (National Biomedical Research Foundation, Georgetown Univ., Medical Center, Washington, D.C., 1972), vol. 5.
14. A variety of immunological techniques have been used to compare chimpanzee proteins with those from human counterparts (17, 18, 29), haptoglobin and C. A. Leone, Comp Biochem.

Physiol. 38, 437 (1969); M. Goodman and G. W. Moore, Nature 201, 19 (1971); K. Bauer, Humangenetik 17, 253 (1973). The immunodiffusion techniques employed in these studies are sensitive to small differences in amino acid sequence and are microsorptions in which G. F. Prager, A. C. Wilson, J. Biol. Chem. 246, 5978 (1971). Nevertheless, their results are generally consistent with those in Table 1. The few cases of large antigenic differences between human and chimpanzees proteins are not probably indicative of large sequence differences. For example, the haptoglobin difference reported by Prager and Leon is due mainly to the fact that the haptoglobin of chimpanzees is nearly twice the length of the haptoglobin 1 polypeptide (J. A. Black and G. H. Dixon, Nature [London] 273, 586 (1978)). Human haptoglobin 1 is immunologically very similar to chimpanzee haptoglobin (J. Javid and H. H. Fuhrmann, Am. J. Hum. Genet. 207, 496 (1971)). The immunoglobulin differences reported by Bauer (12) may be due to comparison of peptide chains that are not strictly homologous. In addition, Bauer's chain conflict results with quantitative studies which detected no immunological difference (A. J. Wang, J. E. Cronin, A. Epstein, H. H. Fudenberg, Biochem. Genet. 1, 347 (1968)). Furthermore, the factor difference that Bauer reported might result from the fact that the chimpanzees in his studies were not as highly inbred as the human lacking X factor.
18. See figure 9.3 in Dayhoff (4). We determined the proportion of amino acid substitutions causing a change during vertebrate evolution for several additional proteins: cytochrome c, lysozyme, myoglobin, a and B hemoglobin chains, triosephosphate dehydrogenase, acid fucokinase, growth hormone, trypsin, and insulin. The average for these proteins is 0.27. Our estimate of 0.16 for hemoglobin alone is very similar to that of Boyer et al. (S. H. Boyer, A. N. Noyes, C. F. Timmons, R. A. Young, J. Hum. Evol. 1, 515 (1972)), who calculated that the ratio between electrophoretically silent and electrophoretically detectable alleles in primates is about 5.5; that is, about 15 percent of the amino acid substitutions in pri-
19. A negative binomial variable may better describe the distribution of charged amino acids would have affected the net charge of the protein and would, therefore, be detectable by electrophoresis.
22. N. R. Kallenbach and S. D. Droit, Bio-
28. The average heterozygosity estimates for the loci in this study, as calculated from comparable heterozygosity estimates for human and chimpanzees, indicate that there are at least three reasons for the difference between the heterozygosity estimates for humans and chimpanzees. First, many more humans than chimpanzees have been surveyed at each locus, so that the variability estimate for humans is biased in favor of it is based on alleles present at low frequency in human populations. Second, there are many more humans than chimpanzees alive today, living in a greater variety of environments and with a larger number of gene pools. As a result, rare, and perhaps advantageous frequencies in human population. Thus, probably most important, the chimpanzees in comparable for study are based on even fewer gene pools and are highly inbred in many cases. Hence, the discrepancies in real population size and sampling techniques between human and chimpanzees populations probably account for the greater number of polymorphic loci, the larger number of alleles at polymorphic loci, and the higher average heterozygosity estimates in human populations.
36. G. H. Bourne, Ed., The Chimp-
questionable whether organismal classifications should be revised on the basis of protein evolution and organismal evolution. In situ annealing studies have been performed with RNA complementary to purified human satellite DNA [K. W. Jones, J. Prosser, G. Carneve, E. Ginelli, M. Bobrow, D. J. Weatherall, and J. B. Cleag, The Thalassemia Syndromes (Blackwell, Oxford, 1973)]. Additional references can be drawn from the comparison of human and chimpanzee macromolecules; some of these will be discussed elsewhere.


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