*THE EVOLUTIONARY ORIGINS OF THE IMMUNOGLOBULINS**

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There is general agreement that the evolutionary origins of appropriately related proteins are reflected by homologies in amino acid sequence.[1, 2] With the increasing knowledge of the structure and function of the different classes of immunoglobulins, it is now possible to consider the evolutionary relationships among these proteins. Although several kinds of studies have given some insight into the evolution of immunoglobulins,[3–5] comparison of amino acid sequences among the major types of L and H chains may provide a clearer picture of immunoglobulin evolution. Now that a considerable portion of the amino acid sequence of the F_c fragment of rabbit IgG has been established,[8] the sequence of L chains as observed in Bence-Jones proteins[5–7] can be compared with a part of the sequence of the H chain. It is the purpose of this report to present this comparison, and on the basis of the observed homology in sequence, to propose a scheme for the evolution of the immunoglobulins. The nomenclature for the immunoglobulins proposed by the World Health Organization (*Bull. World Health Org.*, **30,** 447 (1964)) will be used here.

Amino Acid Sequence of a Portion of the F_c Fragment of Rabbit Heavy Chains.— The sequence of 161 residues of the F_c fragment of H chain is given in Table 1. The proof for this sequence has been summarized in an earlier report[8] and will be documented fully in future publications. Since the exact number of residues in F_c chain or H chain remains unknown, the sequence in Table 1 is numbered arbitrarily from the COOH-terminal glycyl residue of heavy chain.

Comparison of Amino Acid Sequences of F_c Fragment and Bence-Jones Proteins.— Table 2 compares the sequence of a K-type Bence-Jones protein[6, 7] with the established portion of the sequence of F_c fragment (Table 1). Forty-two identical residues are in the same position in these sequences, which is equivalent to 25 per cent of the total positions (168) compared. In addition, 42 residues also possess amino acid side chains which are similar chemically. These are considered to be "conservative"[9] replacements that may not alter markedly the conformation of a protein. Those residues which are identical, or are considered to be similar, are underlined in the table and account for 50 per cent of the sequence. The homology shown in Table 2, with respect to identical residues, is not as great as that found between the α and β chains of human hemoglobin[1] or between the pancreatic zymogens.[2] On the other hand, the total number of identical plus similar residues is in accord with the corresponding values for the hemoglobin chains and the zymogens, which are 51 per cent and 53 per cent, respectively. Perhaps the smaller number of identical residues reflects the fact that the two polypeptides are derived from different animal species. For example, the prolyl residue in position 157 in F_c fragment is a lysyl residue in bovine heavy chains, as judged by sequence analysis of bovine glycopeptides.[10] Whereas proline at position 157 is not homologous

TABLE 1

AMINO ACID SEQUENCE OF A PORTION OF THE F_c REGION OF RABBIT HEAVY CHAIN

160 150 Cbh 140
-Thr-Ala-Arg-Pro-Pro-Leu-Arg-Glu-Gln-Gln-Phe-Asp-Ser-Thr-Ile-Arg-Val-Val-Ser-Thr-Leu-Pro-
130 120
Ile-Ala-His-Glu-Asp-Try-Leu-Arg-Gly-Lys-Glu-Phe-Lys-CyS-Lys-Val-His-Asp-Lys-Ala-Leu-Pro-
110 100
Ala-Pro-Ile-Glu-Lys-Thr-Ile-Ser-Lys-Ala-Arg-Gly-Glu-Pro-Leu-Glu-Pro-Lys-Val-Tyr-Thr-Met-
90 80
Gly-Pro-Pro-Arg-Glu-Glu-Leu-Ser-Ser-Arg-Ser-Val-Ser-Leu-Thr-Cys-Met-Ile-Asp-Gly-Phe-Tyr-
70 60
Pro-Ser-Asp-Ile-Ser-Gly-Val-Try-Glu-Lys-Asp-Gly-Lys-Ala-Glu-Asp-Asp-Tyr-Lys-Thr-Thr-Pro-
50 40 30
Ala-Val-Leu-Asp-Ser-Asp-Gly-Ser-Try-Phe-Leu-Tyr-Ser-Lys-Leu-Ser-Val-Pro-Thr-Ser-Glu-Try-
20 10
Gln-Arg-Gly-Asp-Val-Phe-Thr-CyS-Ser-Val-Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Glu-
1
Lys-Ser-Ile-Ser-Arg-Ser-Pro-Gly-COOH

TABLE 2

HOMOLOGY IN THE SEQUENCE OF BENCE-JONES PROTEIN (K-TYPE) AND F_c CHAIN*

160 (Lys) 150 Cbh
Thr-Ala-Arg-Pro-Pro-Leu-Arg-Glu-Gln-Gln-Phe-Asp-Ser- Thr-Ile- Arg-Val- Val- Ser-Thr-Leu-
Gly- Val-Pro-Ser- Arg-Phe-Ser- Gly-Ser- Gly-Phe- -Gly-Thr-Asp-Phe-Thr-Phe-Thr-Ile- Ser-
57 60 70a 70b 70c 71

140 130
Pro- Ile- Ala- His-Glu-Asp-Try-Leu-Arg-Gly-Lys-Glu- Phe-Lys-CyS-Lys-Val-His- Asp-
Gly-Leu-Gln-Pro-Glu-Asp- -Ile- -Ala- Thr-Tyr-Tyr- -CyS-Gln-Gln-Tyr-Asp-Thr-Leu-
80 90

120 110
-Lys- Ala-Leu-Pro-Ala- Pro-Ile-Glu-Lys- -Thr-Ile-Ser-Lys-Ala-Arg-Gly- Glu-Pro-Leu-Glu-
Pro-Arg-Thr-Phe-Gly-Gln-Gly- -Thr-Lys-Leu-Glu-Ile- -Lys- -Arg-Thr- -Val- Ala-Ala-
100 110

100 90
Pro-Lys-Val-Tyr-Thr-Met-Gly-Pro-Pro- -Arg-Glu-Gln-Leu-Ser- Ser-Arg-Ser- Val-Ser-Leu-Thr-
Pro-Ser- Val-Phe- -Ile- Phe-Pro-Pro-Ser-Asn-Glu-Gln-Leu-Lys-Ser-Gly-Thr-Ala-Ser-Val- Val-
120 130

80 70
CyS-Met-Ile- Asp-Gly-Phe-Tyr-Pro-Ser- Asp-Ile- Ser-Val-Gly-Try- -Glu-Lys- Asp-Gly-Lys-
CyS-Leu- Leu-Asn-Asn-Phe-Pro-Tyr-Arg-Glu-Ala-Lys-Val-Gln-Try-Lys- Val-Asp-Asn-Ala- Leu-
140 150

60 50
Ala- Glu-Asp-Asp-Tyr-Lys-Thr-Thr-Pro-Ala- Val-Leu-Asp-Ser- -Asp-Gly-Ser-Tyr-Phe-Leu-
Gln-Ser- Gly- Asn-Ser- Gln-Glu- Ser- Val-Thr-Glu-Gln-Asp-Ser-Lys -Asp-Ser-Thr-Tyr-Ser- Leu-
160 170

40 30 20
Tyr-Ser-Lys-Leu-Ser- Val- Pro-Thr-Ser-Glu-Try-Gln-Arg-Gly-Asp-Val-Phe-Thr-CyS-Ser- Val-
Ser- Ser-Thr-Leu-Thr-Leu-Ser- Lys-Ala-Asp Tyr-Glu-Lys-His- Lys- Val-Tyr-Ala- CyS-Glu-Val-
180 190

10 1
Met-His-Glu-Ala- Leu-His-Asn-His- Tyr-Thr-Glu-Lys-Ser-Ile- Ser- Arg-Ser- Pro-Gly- COOH
Thr- His-Gln-Gly-Leu- Ser- Ser- Pro- Val- Thr- -Lys Ser-Phe-Asn-Arg-Gly-Glu-CyS-COOH
200 210 212

* The top sequence on each line is F_c chain; the lower sequence on each line is Bence-Jones protein, K-type, Ag (Putnam, F. W., K. Titani, and E. Whitley, Jr., *Proc. Roy Soc.* (*London*), *Ser. B*, in press).

to arginine at position 58 in Bence-Jones protein, lysine, at position 157 in F_c fragment, is quite similar to the corresponding arginine in Bence-Jones chain.

The introduction of gaps into the sequence in Table 2 was made initially in order to accommodate a maximum number of identical and similar residues. In the immunoglobulin chains under consideration here, the credibility of the gaps in-

TABLE 3

COMPARISON OF PORTIONS OF F_c FRAGMENT WITH K- AND λ-TYPE BENCE-JONES PROTEINS

	13	1
F_c fragment	Asn-His-Tyr-Thr-Glu-Lys-Ser- Ile- Ser- Arg-Ser- Pro-Gly- COOH	
	201	212
Bence-Jones protein (K)	Ser- Pro-Val- Thr- Lys-Ser- Phe- Asn-Arg-Gly-Glu-CyS-COOH	
	201	213
Bence-Jones protein (λ)	Ser- Thr-Val- Glu-Lys-Thr-Val- Ala- Pro-Thr-Glu-CyS-Ser-COOH	
	103	93
F_c fragment	Leu-Glu-Pro-Lys-Val-Tyr-Thr- Met-Gly-Pro-Pro-	
	109	118
Bence-Jones proteins (K)	Ala-Ala-Pro-Ser- Val-Phe- Ile- Phe-Pro-Pro-	
	109	118
Bence-Jones proteins (λ)	Ala-Ala-Pro-Ser- Val- Thr- Leu- Phe-Pro-Pro-	

troduced into the sequences has been strengthened by knowledge of the amino acid sequence of portions of the λ-type Bence-Jones proteins,[5] as shown in Table 3. The gaps between positions 204 and 205 in the Bence-Jones protein are exactly accommodated by the sequence of F_c chain. A comparable situation is evident on comparison of residues 93–103 in F_c fragment with residues 109–118 in the two types of Bence-Jones proteins.

The gaps in sequence shown in Table 2 are clearly more numerous toward the amino terminal portion of these sequences. Perhaps this reflects the fact that the Bence-Jones proteins possess variant and invariant sections. Residues 107–212 are nearly identical among all Bence-Jones proteins (K-type) examined thus far, whereas at least 32 interchanges at 21 different positions are known between residues 1 and 106.[6] Further sequence studies on rabbit light chains or human heavy chains may reveal sequences which are more closely homologous.

Evolutionary Relationships between Light and Heavy Chains of IgG.—The homology between a considerable section of the sequence of F_c fragment and Bence-Jones protein suggests that the genes for L and H chains of IgG may possess a common ancestor. To evaluate this conclusion, it becomes essential to consider the fact that the H chain contains about twice the number of amino acids as the L chain. Therefore, the question arises, which of the two chains, L or H, gave rise to the other? For several reasons it is most plausible to conclude that the gene for L chain, by a process of duplication, gave rise to the gene for H chain. First, mutations of this type are known in the human haptoglobins.[11] In this case a single gene, which controls the sequence of 75 residues in the α-polypeptide, $Hp1\alpha$, appears to have duplicated to produce a gene which determines the sequence of a chain 140 residues in length ($Hp2\alpha$).

Second, if duplication of the type observed in the haptoglobins occurred, then the H chain should have an internal homology, such that the sequence of the F_c region of H chain should be homologous to the F_d region. Without the sequence of the F_d region, it is impossible to test this conclusion. However, on examination of the sequence information available (Table 1), an internal homology in F_c chain was found as shown in Table 4.

Clearly, the homology between residues 1–57 and 106–161 represents sufficiently large segments of sequence so that it appears to be significant. Only three gaps are required to place residues 1–57 and 106–161 in the alignment shown. Seventeen residues or 29 per cent of the residues compared are identical, whereas 13 residues, or 22 per cent of the residues compared, possess similar side chains. A total of

TABLE 4

INTERNAL HOMOLOGY IN F_c CHAIN

	161 (Pro) (Glu) 150 Cbh
Residues 106–161	-Thr-Ala-Arg-Pro-Pro-Leu-Arg-Glu-Gln-Gln-Phe-Asp-Ser-Thr-Ile- Arg- Val-
	57 50
Residues 1–57	-Asp-Tyr-Lys-Thr-Thr-Pro- Ala-Val- Leu-Asp-Ser- Asp-Gly-Ser- Tyr-Phe-Leu-
	140 130
Residues 106–161	Val- Ser-Thr-Leu-Pro-Ile- Ala-His- Glu-Asp-Try-Leu-Arg-Gly-Lys-Glu-Phe-
	40 30
Residues 1–57	Tyr-Ser-Lys-Leu- Ser- Val-Pro-Thr-Ser- Glu-Try-Gln-Arg-Gly-Asp-Val- Phe-
	120
Residues 106–161	Lys-CyS-Lys-Val- -His-Asp-Lys-Ala-Leu-Pro-Ala- Pro- -Ile- Glu-Lys-
Residues 1–57	Thr-CyS-Ser- Val-Met-His-Glu- -Ala-Leu-His-Asn-His-Tyr-Thr-Glu-Lys-
	106
Residues 106–161	-Thr-Ile-Ser-Lys-Ala-Arg-Gly-
	1
Residues 1–57	Ser- Ile-Ser-Arg-Ser- Pro-Gly-COOH

TABLE 5

INTERNAL HOMOLOGY IN BENCE-JONES PROTEIN

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1                                          10                                  (Ala) 20
H2N-Asp-Ile- Gln-Met-Thr-Gln-Pro-Ser- Ser-Ser- Leu-Ser- Ala- Ser- Val- Gly-Asp-Arg-Val-Thr-
Ala- Pro-Ser-Val- Phe- Ile- Phe-Pro-Pro-Ser-Asn-Glu- Gln-     -Leu-Lys-Ser- Gly-Thr-Ala-Ser-
110                                        120

(Leu)                                30                           35                 40
Ile-Thr-CyS-Gln-Ala- Ser- Gln(                                  )Leu-Asn-Try-Tyr-Gln-Gln-Gly-Pro- Lys-
Val-Val- CyS-Leu-Leu-Asn-Asn-Phe-Pro-Tyr-Arg-Glu-Ala- Lys-Val- Gln-Try-Lys-Val- Asp-
130                                  140

                               50                (Ala)          60
Lys- Ala-Pro- Lys-Ile- Leu-Ile- Tyr-Asp-Ala- Ser-Asn-Leu-Glu-Thr-Gly-Val-Pro- Ser-Arg-Phe-
Asn-Ala-Leu-Gln-Ser-Gly-Asn- Ser- Gln- Glu-Ser-             -Val-Thr-Glu-Gln-Asp-Ser-Lys-Asp-
150

                          70a  70b  70c                                              80
Ser-Gly- Ser- Gly-Phe-Gly-Thr-Asp-Phe-Thr-Phe-Thr-Ile- Ser- Gly-Leu-Gln-Pro-Glu-    -Asp-
Ser-Thr-Tyr-Ser- Leu-Ser- Ser-                 -Thr-Leu-Thr-Leu-Ser- Lys-Ala-Asp-Tyr-Glu-
   170                                                       180

                                      90
                                      (Leu)          (Thr)          (Pro)
Ile- Ala-Thr-Tyr-Tyr-     -CyS-Gln-Gln-Tyr-Asp-Thr-Leu-Pro- Arg-Thr-Phe-Gly-Gln-Gly-
Lys-His-Lys- Val- Tyr-Ala-CyS-Glu-        -Val- Thr-His- Gln-Gly- Leu-Ser- Ser- Pro-Val-
          (Leu) 190                                               200

               (Phe)              109
Thr-Lys-Leu-Glu-Ile- Lys-Arg-Thr-Val- Ala-
Thr-Lys-Ser-      -Phe-Asn-Arg-Gly-Glu-CyS-COOH
                            210       212
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51 per cent of the residues are similar or identical, a value which compares favorably with that exhibited by Bence-Jones protein and F_c fragment (Table 2).

The data in Table 4 suggest that the F_c region of H chain is composed of two homologous halves, and that each half is about 106 residues in length. Surprisingly, this length of sequence is about equal to that of the "variant" and "invariant" halves of Bence-Jones protein. Thus, if H and L chain genes evolved from a common L chain gene and the two halves of H chain are homologous, as well as the two halves of F_c fragment, then one may expect to find an internal homology in L chains, or Bence-Jones protein. To test this, the two halves (residues 1–109 and residues 110–212) of a K-type Bence-Jones protein[8] are compared as shown in Table 5.

TABLE 6

HOMOLOGY IN SEQUENCES OF K AND λ-TYPE BENCE-JONES PROTEINS

	1									10									18
K-chain	-H_2N-Asp-	Ile-	Gln-	Met-	Thr-	Gln-	Pro-	Ser-	Ser-	Ser-	Leu-	Ser-	Ala-	Ser-	Val-	Gly-	Asp-	Arg-	
K-chain	-Ala-	Pro-	Ser-	Val-	Phe-	Ile-	Phe-	Pro-	Pro-	Ser-	Asn-	Glu-	Gln-		-Leu-	Lys-	Ser-	Gly-	Thr-
λ-chain	-Ala-	Pro-	Ser-	Val-	Thr-	Leu-	Phe-	Pro-	Pro-	Ser-	Ser-	Glu-	Glu-		-Leu-	Gln-	Ala-	Asn-	Lys-
	110									120									127

	80								90 (Leu)				94		
K-chain	-Asp-	Ile-	Ala-	Thr-	Tyr-	Tyr-	-CyS-	Gln-	Gln-	Tyr-	Asp-	Thr-	Leu-	Pro-	Gly-
K-chain	-Glu-	Lys-	His-	Lys-	Val-	Tyr-	Ala-	CyS-	Glu-		-Val-	Thr-	His-	Gln-	Arg-
λ-chain	-Lys-	Ser-	His-	Arg-	Ser-	Tyr-	Ser-	CyS-	Gln-		-Val-	Thr-	His-	Glu-	Gly-
	185					190									198

	97		100				(Ile)			109		
K-chain	-Gly-	Pro-	Gly-	Thr-	Lys-	Leu-	Glu-	Phe-	Lys-	Arg-	Thr-	Val-	Ala-
K-chain	-Ser-	Pro-	Val-	Thr-	Lys-	Ser-		-Phe-	Asn-	Arg-	Gly-	Glu-	CyS-COOH
λ-chain	-Ser-	Thr-	Val-	Glu-	Lys-	Thr-		-Val-	Ala-	Pro-	Thr-	Glu-	CyS-Ser-COOH
	201										212		

These sequences were also aligned with the aid of gaps, which give considerably more opportunity for homology. As written, there are 17 identical residues (15% of the sequence) and 18 similar residues (21% of the sequence). Thus, 36 per cent of the total residues compared are identical or similar.[12] Whether this homology is valid remains to be established, but it gains support from two sources: (1) knowledge of the sequence differences among K-type Bence-Jones proteins[6, 7] and (2) the preliminary sequence data on λ-type Bence-Jones proteins.[5] At least 21 of the first 106 residues have been shown to differ among the K-type Bence-Jones proteins examined thus far. At seven of these positions, the nature of the different amino acids which vary supports the homology shown in Table 5, since each replacement is more homologous with the corresponding residue from the other half of the chain. Comparison is made in Table 6 of sections of the sequence given in Table 5, with known segments of λ-chain sequence. At each of the following positions, λ-chain possesses residues homologous to corresponding positions in the opposite section of K-chain: 10 vs. 120; 16 vs. 125; 17 vs. 126; 18 vs. 127; 88 vs. 193; 91 vs. 194; 104 vs. 207; and 107 vs. 210. Possibly, the extensive variation which occurs within residues 1–106 of Bence-Jones proteins precludes the possibility of ever detecting a more exact homology between the two halves of Bence-Jones protein.

The degree of internal homology in F_c fragment and Bence-Jones protein may be most easily explained, as shown in Figure 1, by assuming that the genes for H and L chains possessed a common ancestor which controlled a sequence of about 106 residues. By a process of duplication, similar to that known for one of the haptoglobin genes, the gene for a chain of about twice the size was formed. By a second duplication of the gene for this primitive L chain, the gene for H chain was formed. If this were the case, then each half of light chain should be homologous to four segments of heavy chain, with each segment containing about 110 residues. From the sequence data available, this prediction may be tested as shown in Table 7, which compares the homology of two sections of Bence-Jones protein with two corresponding sections of F_c chain. The homology among these sequences seems to be significant. As written, residues in 58 positions can be compared. Of these

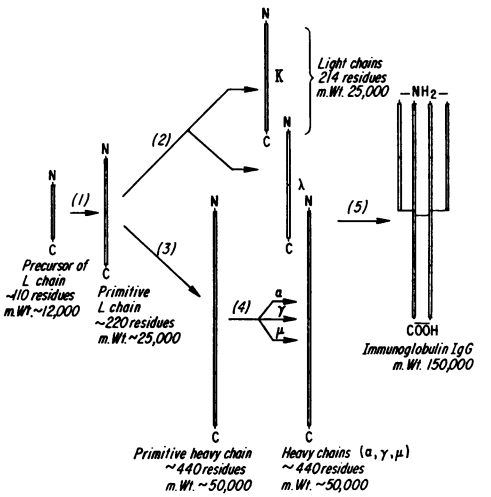

FIG. 1.—A tentative scheme for the genetic origins of the immunoglobulins.

58 positions, 14 show identical residues between either of the three sections of the Bence-Jones chains and at least one of the two sections of the F_c fragments. On the same basis, 25 residues possess similar side chains. Thus, about 67 per cent of all residues between the three Bence-Jones segments are homologous to residues in the two segments of F_c fragment.

Conclusions.—The hypothetical scheme for the evolution of the immunoglobulins as given in Figure 1 is sufficient to explain the observed homology between the F_c region of H chain and the L chain (Bence-Jones protein). This scheme not only accounts for the common ancestry of the K- and λ-types of L chain proposed earlier by Milstein,[5] but also provides a plausible explanation for the common ancestry of L and H chains. Once the gene for a primitive H chain arose, it would be possible by further mutations to obtain genes for the three unique heavy chains. This is in accord with the proposal made earlier[4] that the α and μ chains may possess a common ancestor. Of interest also is the fact that the L and H chains can be roughly divided into six equivalent segments, two in L chain and four in heavy chain, all of which may be homologous to one another. This type of segmentation of IgG was first proposed by Singer and Doolittle[4] but receives much stronger support from the sequences shown in Table 7. It will be of interest to see whether the sequences from the F_d region of H chain as they become available will support this view of immunoglobulin structure.

Finally, it must be emphasized that the present proposal for the evolution of the immunoglobulins should be considered only as a working hypothesis. For example, Hood *et al.*[16] have recently suggested that the invariant region of Bence-Jones protein may be controlled by a single gene, and the variable portions by any one of many different genes. By some means, the two polypeptide products of these genes are united so as to form a single light chain. Perhaps a similar type of genetic control of the variant and invariant sections of H chain would also be expected. If the genetic control of L and H chains is shown to be in accord with this proposal, then the scheme in Figure 1 must be modified. Nevertheless, the

TABLE 7

HOMOLOGY AMONG CORRESPONDING SEQUENCES OF H AND L CHAINS

F_c (106–161)	161 Thr-Ala- Arg- Pro- Pro- (Pro) Leu-Arg-Glu- Gln-Gln-Phe- Cbh Asp- Ser- Thr-Ile- Arg-Val- Val-Ser- Thr-Leu-Pro- Ile- Ala-
F_c (1–57)	57 Asp-Tyr-Lys- Thr-Thr-Pro-Ala- Val-Leu-Asp- Ser- Asp- Ser- Gly-Tyr-Phe-Leu-Tyr-Ser- Lys-Leu-Ser- Val-Pro-
K-BJ (161–212)	161 Val-Thr-Glu- Gln-Asp-Ser- Lys-Asp-Ser-Thr- Phe-Ser- Leu-Ser- Ser- -Thr-Leu-Thr-Leu-Ser- 180
K-BJ (55–109)	55 Glu-Thr-Gly- Val-Pro- 60 Ser- Arg-Phe-Ser-Gly- Ser- Gly- Phe-Gly-Thr- 70a Asp- 70b Phe- 70c Thr-Phe-Thr-Ile- Ser- Gly-Leu-
F_c (106–161)	His-Glu- Asp- Try-Leu-Arg-Gly-Lys-Glu-Phe- Lys-CyS-Lys-Val- -His- Asp-Lys- Ala- Leu-Pro- Ala- Pro-
F_c (1–57)	Thr-Ser- Glu- Try-Gln- Arg-Gly-Asp-Val-Phe- Thr-CyS-Ser- Val- -Met-His- Glu -Ala- Leu-His- Asn-His-Tyr-
K-BJ (161–212)	Lys-Ala- Asp-Tyr-Glu- Lys-His- Lys-Val- 190 Tyr- Ala-CyS- -Glu- -Val-Thr- His- Gln-Gly-Leu- 200 Ser- Ser- Pro-Val-
K-BJ (55–109)	Gln-Pro- Glu- -Asp- 80 Ile- Ala-Thr-Tyr-Tyr- -CyS-Gln-Gln-Tyr- 90 Asp-Thr-Leu-Pro-Arg-Thr-Phe-Gly-Pro-Gly-
λ-BJ (185–213)	185 Lys-Ser- His-Arg-Ser-Tyr- 190 Ser- CyS- -Gln- -Val-Thr- His- Glu-Gly( )201 Ser-Thr-Val-
F_c (103–161)	Ile- Glu-Lys-Thr-Ile- Ser- Lys-Ala-Arg- 106 Gly-
F_c (1–57)	Thr-Glu-Lys- Ser- Ile- Ser- Arg-Ser- Pro- 1 Gly- COOH
K-BJ (161–212)	Thr-Lys-Ser- -Phe-Asn-Arg- 210 Gly-Glu- 212 CyS-COOH
K-BJ (55–109)	100 Thr-Lys-Leu-Glu- (Ile) Phe-Lys-Arg-Thr-Val- 109 Ala-
λ-BJ (185–213)	Glu-Lys-Thr- -Val- Ala-Pro- 210 Thr-Glu- CyS- 213 Ser-COOH

homology among the two halves of L chain and the two halves of F_c fragment indicates a common ancestry of the genes controlling these portions of immunoglobulins. Thus, the many aspects of antibody structure and function which remain obscure prevent formulation of a complete picture. As explanations of these problems are provided, the proposals of immunoglobulin evolution put forth here may require revision. Until that time, however, the present scheme may provide a useful working model, not only for immunoglobulins but also for the evolution of other proteins which contain polypeptide chains of both "light" and "heavy" types.

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