An Extension of the Nomenclature for Immunoglobulins[1,2]

Earlier proposals for the nomenclature of human immunoglobulins (1–4) have been generally accepted. Recent studies of the remarkable heterogeneity of immunoglobulins and of antibodies have produced additional findings on human immunoglobulins which require the extension of the existing terminology. Certain new terms are therefore proposed for well established properties of the structure and amino acid sequences of the heavy and light chains of these proteins. These additions to the terminology should help in defining those regions of antibody molecules responsible for their two major kinds of functions—*i.e.* the function of antigen binding and those other functions manifested by biological properties such as complement fixation.

DEFINITION OF REGIONS OF IMMUNOGLOBULIN MOLECULES

It is now clear that the polypeptide chains of immunoglobulins consist of two well defined regions which are here designated the "variable region" and the "constant region." The variable region has been so designated because of the diversity of its amino acid sequences, whereas the constant region is relatively invariant in molecules of the same class and type. It is recommended that the variable and constant regions be termed the "V region" and the "C region," respectively. It is proposed that the symbols "V_L" and "C_L" be generic terms for the variable and the constant regions of light chains and that "V_H" and "C_H" be generic terms for the corresponding regions of heavy chains. If it is desired to specify a particular class or subclass of heavy chain, the symbol "H" could be replaced by the symbol of the chain. For example, the C_H region of a heavy chain of a molecule of the IgG1 subclass would be designated "$C_{\gamma 1}$ region." Similarly, if it is desired to specify a particular type of light chain, the symbol "L" could be replaced by the symbol for the chain: for example, "V_κ region," "C_λ region."[3]

The exact length of these regions cannot be specified. In human light chains the V_L and C_L regions have about the same number of amino acid residues. For example, in the κ-chains so far studied the V_L regions consist of 107 to 113 residues beginning at the amino terminus and the C_L regions consist of the remaining 107 residues. Heavy chains have been less extensively studied than have light chains. For γ-chains the available data on complete sequences of human heavy chains show that the V_H region is of approximately the same length as the V_L region of the same molecule and that the C_H region consists of three linearly arranged adjacent regions which show homologies with C_L and with each other. Less extensive data on other human γ-chains and on rabbit γ-chains suggest that this will be a general finding in chains of the γ-class. It is therefore proposed that such regions in $\gamma 1$ heavy chains, for example, be named "homology region $C_{\gamma 1}1$," "homology region $C_{\gamma 1}2$," "homology region $C_{\gamma 1}3$," and so on, beginning with the homology region closest to the amino terminus of the chain. If similar homology regions are found in other classes, the appropriate chain symbol would be used, *e.g.* "homology region $C_\alpha 1$," "homology region $C_\mu 1$," etc.

NOMENCLATURE OF HALF-CYSTINYL RESIDUES

It is suggested that half-cystinyl residues be designated by Roman numerals, the 1st residue being that closest to the amino terminus. An Arabic numeral (to be placed as a subscript) corresponds to the number of the amino acid residue in the chain being described. This will satisfactorily permit the representation of intrachain and interchain disulfide bonds as well as of free sulfhydryl groups. Intrachain bonds can be designated, for example, "disulfide bond $\kappa(I_{23}\text{-}II_{88})$." Interchain bonds can be designated as follows: "disulfide bond $\kappa V_{214}\text{-}\gamma 1V_{200}$" and "disulfide bond $\gamma 1VI_{226}\text{-}\gamma 1VI_{226}$." In all matters of chemical terminology the rules of IUPAC-IUB (5) should be observed.

DEFINITION OF GROUPS AND SUBGROUPS

All variable regions associated with a light chain of given type are defined as a "group." Subdivisions may be distinguished within a group. These subdivisions are called "subgroups" and are designated by Roman numerals. In human κ-chain groups at least three discrete sets of sequences have been recognized. These are now called "Subgroup $V_{\kappa I}$," "Subgroup $V_{\kappa II}$," and "Subgroup $V_{\kappa III}$." Similarly, in human λ-chains at least five sets of sequences have now been recognized: these are called "Subgroup $V_{\lambda I}$," etc. The correspondence between the present usage and the proposed usage is shown in Table I. The subgroups have been designated I, II, and III, etc., in order of their frequency of occurrence in the chains which have so far been studied. This follows the nomenclature of subclasses of heavy chains of IgG, which are also numbered in order of frequency of occurrence (3). Prototype sequences of 20 residues of the subgroups beginning at the amino terminus are given in Table II of this paper.

DEFINITION OF CLASSES AND SUBCLASSES AND TYPES AND SUBTYPES

C_H and C_L regions show heterogeneity. This is the basis of the recognition of classes of heavy chains and types of light chains. Subdivisions of classes have previously been designated subclasses. It is proposed that similar subdivisions of types be designated "subtypes" and that the principles for their nomenclature should be the same as those for subclasses. The terms "classes" and "subclasses," "types," and "subtypes" specifically exclude differences arising from allelism.

[1] This memorandum was drafted by the signatories (see page 3034) following discussions held during a WHO meeting on the nomenclature of immunoglobulins that took place June 9 to 11, 1969, in Prague. A French version will be published elsewhere.

[2] Reprints are available from Waldo E. Cohn, Director, Office of Biochemical Nomenclature, NAS/NRC, c/o Biology Division, Oak Ridge National Laboratory, P. O. Box Y, Oak Ridge, Tennessee 37830.

[3] The symbol "L" has been suggested previously for the L type of immunoglobulins (1). The usage of the subscript "L", as in "V_L" and "C_L" is distinct: subscript "L" specifies light chains irrespective of type.

TABLE I

Light chain subgroups

Light chain[a]	Present usage	Proposed usage
κ-Chains	$S_{\kappa I}$, Tra, basic Group I	$V_{\kappa I}$
	$S_{\kappa II}$,[b] Smi,[b] basic Group III	$V_{\kappa II}$
	$S_{\kappa II}$,[b] Smi,[b] basic Group II	$V_{\kappa III}$
λ-Chains	I, $S\lambda_{II}$	$V_{\lambda I}$
	II,[b] $S\lambda_{I}$	$V_{\lambda II}$
	IV, other	$V_{\lambda III}$
	II,[b] $S\lambda_{III}$	$V_{\lambda IV}$
	III, other	$V_{\lambda V}$

[a] For references for the κ-chain see Hood *et al.* (6), Niall and Edman (7), and Milstein (8). For references for the λ-chain see Langer, Steinmetz-Kayne, and Hilschmann (9) and Hood and Ein (10).

[b] These subgroups were not further separated at the time of publication.

FORMULAS FOR IMMUNOGLOBULIN MOLECULES

The over-all structure of immunoglobulins may be represented by formulas. Thus, an IgG1 molecule with κ-light chains of Subgroup I could be written

$$[(V_{\kappa I}C_{\kappa})\ (V_{\gamma}C_{\gamma 1})]_2$$

If it is desired to include homology regions, this could be expanded to

$$[(V_{\kappa I}C_{\kappa})\ (V_{\gamma}C_{\gamma 1}1C_{\gamma 1}2C_{\gamma 1}3)]_2$$

Presence inside the square brackets indicates association of light and heavy chains, the formula for each of which is in parentheses. The subscript 2 outside the brackets indicates that the association of two such units forms the molecule. An IgM molecule with κ-light chains may be represented by use of the brace, as

$$\{[(V_{\kappa}C_{\kappa})(V_{\mu}C_{\mu})]_2\}_5$$

Formulas could be especially useful in representing certain γA immunoglobulins in which the two light chains are linked as $(V_{\kappa}C_{\kappa})_2$ and the heavy chains as $(V_{\alpha}C_{\alpha})_2$ to give

$$[(V_{\kappa}C_{\kappa})_2(V_{\alpha}C_{\alpha})_2]$$

IMMUNOGLOBULINS OF SECRETIONS

The IgA in the external secretions of man and several other species has a molecular structure characterized by the presence of an additional component which is lacking in IgA derived from serum. This additional component is sometimes encountered not bound to IgA. It is suggested that it be designated "secretory component" or "S component" and that other terms such as "transport piece" should not be used. The term "secretory" in the definition is not meant to imply any function but rather to indicate the characteristic association with secretions of IgA possessing this additional component.

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TABLE II

Prototype amino terminus sequences of subgroups of human κ- and λ-light chains

Subgroups	Sequence
	κ-Chains
$V_{\kappa I}$	Asp-Ile-Gln-Met-Thr-Gln-Ser-Pro-Ser-Ser-Leu-Ser-Ala-Ser-Val-Gly-Asp-Arg-Val-Thr-
$V_{\kappa II}$	Glu-Ile-Val-Leu-Thr-Gln-Ser-Pro-Gly-Thr-Leu-Ser-Leu-Ser-Pro-Gly-Glu-Arg-Ala-Thr-
$V_{\kappa III}$	Asp-Ile-Val-Met-Thr-Gln-Ser-Pro-Leu-Ser-Leu-Pro-Val-Thr-Pro-Gly-Glu-Pro-Ala-Ser-
	λ-Chains
$V_{\lambda I}$	*Glp-Ser-Val-Leu-Thr-Gln-Pro-Pro-[ ]-Ser-Val-Ser-Gly-Ala-Pro-Gly-Gln-Arg-Val-Thr-
$V_{\lambda II}$	Glp-Ser-Ala-Leu-Thr-Gln-Pro-Ala-[ ]-Ser-Val-Ser-Gly-Ser-Pro-Gly-Gln-Ser-Ile-Thr-
$V_{\lambda III}$	[ ]-Tyr-Val-Leu-Thr-Gln-Pro-Pro-[ ]-Ser-Val-Ser-Val-Ser-Pro-Gly-Gln-Thr-Ala-Ser-
$V_{\lambda IV}$	Glp-Ser-Ala-Leu-Thr-Gln-Pro-Pro-[ ]-Ser-Ala-Ser-Gly-Ser-Pro-Gly-Gln-Ser-Val-Thr-
$V_{\lambda V}$	[ ]-Ser-Glu-Leu-Thr-Gln-Pro-Pro-[ ]-Ala-Val-Ser-Val-Ala-Leu-Gly-Gln-Thr-Val-Arg-

* Glp is the residue derived from pyrollid-2-one 5-carboxylic acid.

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