

NOMENCLATURE FOR HUMAN IMMUNOGLOBULINS^{1, 2}

Definition of Immunoglobulins.

Immunoglobulins are proteins of animal origin endowed with known antibody activity, and certain proteins related to them by chemical structure and hence antigenic specificity. Related proteins for which antibody activity has not been demonstrated are included—for example, myeloma proteins, Bence-Jones proteins and naturally occurring subunits of the immunoglobulins.

Immunoglobulins are not restricted to the plasma but may be found in other body fluids or tissues, such as urine, spinal fluid, lymph-nodes, spleen, etc. Proteins may occur which fulfil the above requirements but which have widely differing physicochemical properties such as electrophoretic mobility, sedimentation coefficient, and diffusion coefficient, and different chemical properties such as carbohydrate content, amino-acid composition of polypeptide chains, etc. Immunoglobulins do not include the components of the complement system.

Terminology.

Advances in biological and chemical studies of immunoglobulins have emphasized the need for a nomenclature and classification to meet new requirements. Terminology should be based on the identification of the polypeptide chains which by complementation make up the molecule. This principle should allow a precise description of different molecules. In addition, broader terms are needed for grouping classes of molecules with common physicochemical and biological characteristics. This can be achieved by minor modifications of current terminologies.

¹ This memorandum was drafted by the signatories (see pages 150-151) following discussions held during the WHO Meeting on Nomenclature of Human Immunoglobulins that took place on 29-30 May 1964 in Prague, just before the International Symposium on the Cellular and Molecular Basis of Antibody Formation.

Requests for reprints should be addressed to: Immunology, World Health Organization, Palais des Nations, Geneva, Switzerland.

² *Bull. Org. mond. Santé* 30, 447-450, 1964.

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The following notation for immunoglobulins provides:

- (a) an abbreviated notation to designate the major classes of immunoglobulins;
- (b) terms to designate the polypeptide chains of the immunoglobulin molecules.

Whenever possible terms already in common usage have been retained.

Abbreviated Notation.

Two symbols for immunoglobulins are considered to be appropriate. The logical abbreviation for the term immunoglobulin would be the symbol Ig. Since the symbol Ig may present some difficulties in verbal communication and, furthermore, since the symbol γ has been commonly employed to designate the immunoglobulins, both symbols γ and Ig are recognized as appropriate. These symbols should be accompanied by a capital letter designating a specific class of immunoglobulin, for example, γ G, γ M ... IgG, IgM ..., as noted below. The symbol should *not* be followed by arabic numbers, which in the past have been used to indicate electrophoretic mobilities.

The following symbols proposed for major classes of immunoglobulin molecules are based on differences associated with heavy chains.

<i>Present usage</i>	<i>Proposed usage</i>
γ , γ S γ , 6.6S γ , γ_2 γ_{ss}	γ G or IgG
β_2 A, γ_1 A	γ A or IgA
γ_1 M, β_2 M, 19S γ , γ -macroglobulin	γ M or IgM

The following symbols are proposed for types of molecules identified by the properties of light chains.

<i>Present usage</i>	<i>Proposed usage</i>
Type I, 1, B	Type K
Type II, 2, A	Type L

Notation for Polypeptide Chains.

Two major groups of polypeptide chains are now recognized as occurring in immunoglobulin molecules:

- (a) The L or B chains (Mol. wt. about 20,000) are at this time the only subunits known to be common to the three major classes of immunoglobulins;

(b) The H or A chains (Mol. wt. about 50,000) determine the distinctive properties of each class.

It is suggested that the terms L and H, and A and B to denote chains be discarded, in view of the more precise terminology proposed below. For simplicity, however, it is advisable to designate two major groups of polypeptide chains by the terms "light" and "heavy". The designation of these polypeptide chains may be revised as new evidence accumulates. For example, the possibility that the "heavy" chain is in fact several chains has been considered. Until definite proof of this hypothesis that the heavy chain is composed of two or more chains is provided, the heavy chain will be considered as a single chain in the following description.

(a) *Heavy chains*. It is proposed that the heavy chains be designated by small Greek letters corresponding to the Roman capital letters used for the immunoglobulin classes.

<i>Immunoglobulin class</i>	<i>Heavy chain</i>
γ G or IgG	γ (gamma)
γ A or IgA	α (alpha)
γ M or IgM	μ (mu)

It is recognized that the symbol γ has been used in two different designations. No ambiguity should occur, however, since γ is not used alone in either case. The symbol is always used in association with either the word immunoglobulin or chain, for example:

" γ G-immunoglobulin" for the class of immunoglobulin, and
 " γ -chain" for the polypeptide chain.

Use of the term γ -chain (rather than another Greek letter) to designate the heavy chain of the IgG or γ G-immunoglobulin molecule preserves an association with the distinctive properties of this major component within the immunoglobulin system.

(b) *Light chains*. Two forms of light chain (Type I and Type II) are recognized as occurring in man. To conform with the use of Greek letters for distinctive polypeptide chains, the following symbols are proposed:

<i>Present usage</i>	<i>Proposed usage</i>	
	<i>Abbreviated notation for immunoglobulins</i>	<i>Notation for light chains</i>
Type I	Type K	κ (kappa)
Type II	Type L	λ (lambda)

(c) *Molecular formulae.* The proposed system is similar to that in use for haemoglobin. Some typical formulae would be:

<i>Present usage</i>	<i>Abbreviated notation for immunoglobulins</i>	<i>Molecular formulae</i>
$\gamma S\gamma$ - type I	γGK or $IgGK$	$\gamma_2 \kappa_2$
$\gamma S\gamma$ - type II	γGL or $IgGL$	$\gamma_2 \lambda_2$
$\gamma_1 A$ - type I	γAK or $IgAK$	$\alpha_2 \kappa_2$
$\gamma_1 A$ - type II	γAL or $IgAL$	$\alpha_2 \lambda_2$
$\gamma_1 M$ - type I	γMK or $IgMK$	$(\mu_2 \kappa_2)_n^*$
$\gamma_1 M$ - type II	γML or $IgMK$	$(\mu_2 \lambda_2)_n^*$
Urinary globulin composed of light chains		κ_2 and λ_2 (if in the dimer form)

If it is desirable to indicate that the protein is a myeloma protein, Bence-Jones protein, etc., this information can be added in parentheses after the formula.

Classes and Subclasses.

There may be different degrees of molecular association within an immunoglobulin class, and this distinction may be made by the terms dimers, trimers and polymers of a particular unit. In addition the sedimentation coefficient or the molecular weight may be cited.

It may become necessary to recognize a new class of immunoglobulins when molecules containing a novel heavy chain are discovered. This new heavy chain should differ from the presently known heavy chains to the same extent that the latter differ from one another. Similar principles should be applied to the differentiation of new light chains. When new polypeptide chains are characterized, they should be designated with a new small letter of the Greek alphabet. If new immunoglobulins contain chains which can be recognized as members of presently known classes even though they differ in some significant detail, then it may become necessary to define them as new *subclasses*. Until adequate characterization of such novel polypeptide chains is achieved, it is suggested that a non-committal designation be used, and enclosed in parentheses as illustrated below. Terms indicative of origin, such as geographical names and the names of patients, could be used. For example, a

* n in this case may be 6.

newly found immunoglobulin with the characteristics of class G, thought to be a new subclass, if identified in Prague, could be designated IgG(Pr). If several such components are identified simultaneously, a combination of abbreviated words and numbers could be used— γ G(Pr-1), γ G(Pr-2), etc.

When new immunoglobulins, which can be recognized as subclasses, have been well characterized, they will be indicated by the symbol of the major class followed by a small Roman letter (IgAa, IgAb), to be read as A subclass a. Similarly, the new chain responsible for the subclass should be indicated as α a, α b, etc.

The WHO Reference Center for Immunoglobulins is being established at the Institute of Biochemistry, Lausanne, Switzerland, and investigators are encouraged to consult the Centre concerning notation of new immunoglobulins.

Fragments.

The term "fragment" is reserved for portions of the molecule obtained as a result of the cleavage of peptide bonds. Proteolytic enzymes produce heterogeneous groups of fragments which nevertheless can be distinguished by immunological and chemical properties. It is useful to name these fragments, but it is stressed that a single designation does not imply homogeneity.

Fragments Produced by Digestion with Papain.

<i>Present usage</i>	<i>Proposed usage</i>
A, C, S (I, II)*	Fab-fragment (antigen-binding)
B, F (III)*	Fc-fragment (crystallizable)
A piece	Fd-fragment

If it is necessary to specify the chain from which fragments are derived, the name of the chain may be subscripted—for example, Fc_γ or Fd_γ. For 5S fragments obtained by pepsin digestion and having two antibody sites, the notation would be F(ab')₂. The univalent pepsin fragments should be designated as Fab'. If possible details of molecular formulae may be appended. For fragments derived from immunoglobulins without known antibody activity, the same notation should be used.

* The parentheses enclose terms used for fragments in the rabbit.

Immunoglobulins in Proliferative Disorders of Lymphocytic or Plasmacytic Cells.

It is suggested that the distinctive proteins related to the immunoglobulins be classified as "discrete components" or "pathological proteins", and that they be classified further in relation to the corresponding normal protein. It is recognized that at this time no decision can be made as to whether these are large amounts of normally present immunoglobulins or abnormal proteins related to them.

In the abbreviated notation, these proteins should not be classified precisely in the absence of an appropriate clinical diagnosis. In patients with multiple myeloma or macroglobulinaemia they should be termed: (a) G myeloma or A myeloma globulin; (b) M-macroglobulin (Waldenström); (c) light-chain protein or Bence-Jones protein depending on the thermosolubility properties associated with them; (d) heavy-chain proteins with the appropriate class designation.

As is the case for normal immunoglobulins, the notation for polypeptide chains can be used regardless of the disease process with which they are associated. This provides for those instances where relatively homogeneous immunoglobulins are associated with pathological states other than those mentioned above. Under those circumstances the diagnosis can be listed separately.

Nomenclature of Immunoglobulins in Other Species.

In the nomenclature of immunoglobulins of different species, it is recommended that the same principles used in devising a nomenclature for human immunoglobulins be applied. As many criteria as possible, for example, immunological cross-reactivity, estimation of molecular weight, carbohydrate content and biological properties, should be employed to establish whatever similarities in chemical structure may exist between animal and human immunoglobulin classes.

For example, in animal sera the use of γ M or IgM is recommended for a class of immunoglobulins with molecular weight of the order of magnitude of 10^6 . In addition, other properties of the human γ M or IgM—such as high carbohydrate content, dissociation by mercapto-ethanol, and antigenic relationship—should be considered.

Notation for Genes, Genotypes and Allotypes.

As a logical consequence of the criteria followed for outlining the above proposed terminology, the gene notation should be based on the

specification of the molecular subunit controlled by the gene in question. For immunoglobulins, unusual genetic situations may occur, such as somatic mutation, repeats, etc., posing problems which at the moment cannot be precisely foreseen. Moreover, identification of individual variants under genetic control has been limited until now to variants detected by serological reagents (Gm groups, allotypes). The problem of genetic terms related to immunoglobulins, as well as terms for serological variants, would best be dealt with by a committee of investigators active in the field of immunoglobulins, and representing different disciplines (genetics, immunology, protein chemistry).

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