IUPAC-IUB Commission on Biochemical Nomenclature

The Nomenclature of Multiple Forms of Enzymes*

Recommendations (1971)

Recommendations on the nomenclature of multiple forms of enzymes were made by a subcommittee set up by the International Union of Biochemistry and were published in 1964 in a number of journals (1). Since that time, there have appeared a large number of publications in this field; some hundreds of enzymes have been shown to exist as heteromorphs. It seemed appropriate at this time to review the earlier recommendations (1) in the light of current knowledge. For that purpose, the IUPAC-IUB Commission on Biochemical Nomenclature (CBN) set up a subcommittee consisting of G. Brewer, O. Hoffmann-Ostenhof, R. S. Holmes, P. Karlson (Convenor), B. Keil, G. B. Kitto, C. L. Markert, C. J. Masters, F. Moyer, J. Scandalios, C. R. Shaw, E. C. Slater, R. Tashian, and E. C. Webb. The subcommittee reported to CBN, the report was discussed, and the following recommendations were finally adopted.

I. DEFINITION OF ISOZYMES OR ISOENZYMES

The 1964 Committee recommended (1) that "multiple enzyme forms" in a single species should be known as isoenzymes (or isozymes). It is known that enzymes catalyzing essentially the same reaction may differ in various ways, as shown in Table I. In this table, some prominent examples are also listed.

According to the original definition, which was meant to be purely operational, all of these multiple forms should be termed "isozymes" or "isoenzymes." However, most biochemists feel that the term "isoenzymes" should be restricted to those forms arising from genetic control of primary protein structure. Genetically determined differences in primary structure are the reason for the multiplicity in Groups 1 to 3 of Table I, but not in Groups 4 to 7. Indeed, scientists working on conjugated or derived enzymes do not use the isoenzyme terminology for characterization of their multiple forms.

It is therefore recommended:

1. The term "multiple forms of the enzyme . . ." should be used as a broad term covering all proteins possessing the same enzyme activity and occurring naturally in a single species.

2. The term "isoenzyme" or "isozyme" should apply only to those multiple forms of enzymes arising from genetically determined differences in primary structure, and *not* to those derived by modification of the same primary sequence.

Nevertheless, the term "isozyme" or "isoenzyme" is being used as an operational term in dealing with enzyme proteins with the same catalytic activities but separable by suitable methods (*e.g.* electrophoresis) and where knowledge of the nature of multiplicity is lacking. These terms should not be used in cases in which other multiple forms, *e.g.* conjugated or derived, are primarily under study.

The present recommendations deal only with isoenzymes and genetic variants.

TABLE I

Multiple forms of enzymes

Artifacts occurring during preparation are outside the scope of this document.

Group	Reason of multiplicity	Example
1	Genetically independent proteins	Malate dehydrogenase in mitochondria and cytosol
2	Heteropolymers (hybrids) of two or more polypeptide chains, noncovalently bound	Lactate dehydrogenase
3	Genetic variants (allelic)	Glucose-6-phosphate dehydrogenase in man
4	Proteins conjugated with other groups	Phosphorylase *a* and *b*
5	Proteins derived from one polypeptide chain	The family of chymotrypsins arising from chymotrypsinogen
6	Polymers of a single subunit	Glutamate dehydrogenase of mol wt 1,000,000 and 250,000
7	Conformationally different forms	All allosteric modifications of enzymes

II. NOMENCLATURE OF ISOZYMES OR ISOENZYMES

The earlier committee (1) recommended that individual isoenzymes (isozymes) should be distinguished and numbered on the basis of electrophoretic mobility, with the number 1 being assigned to that form having the highest mobility toward the anode.

Of all of the means available to indicate the different properties of isoenzymes (electrophoresis, chromatography, kinetic cri-

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teria, chemical structure, etc.), electrophoresis is most widely used for the following reasons:

a. It is still extremely important in the study of enzyme heterogeneity to avoid any artifactual consequences of the handling or "purification" of enzymes, and zone electrophoresis is one procedure in which the resolution of individual protein species is not unduly influenced by their application in the original state (*i.e.* as tissue homogenates, etc.).

b. The degree of resolution is another factor of prime importance in this field, and resolution by electrophoretic procedures is generally more effective than other methods of protein separation.

c. Electrophoresis offers the advantages of rapidity and broad applicability.

The recognition of these facts and the consequent wide utilization of electrophoretic procedures by workers in this field has built up a substantial literature on the subject and has facilitated communication and reference.

Other alternatives suggested for the distinction of isoenzyme forms include kinetic criteria and structural data. While kinetic criteria are extremely valuable as an adjunct to investigations of enzyme multiplicity, they cannot provide information on the extent of heterogeneity. With regard to structural criteria, it has long been the hope of many workers in the field that the interrelationships of multiple forms might soon be delineated in chemical terms. However, such information is available only for very few enzyme systems, so that it would not be useful at this stage to make general recommendations about isoenzyme nomenclature based on structural considerations. When structural details are available, a system similar to that used for hemoglobin, in which the polypeptide chains are represented by Greek letters, could be used. [The use of upper case Roman letters (as have been used for lactate dehydrogenase and aldolase) would be more acceptable.]

Isoenzymes (isozymes) or their subunits should not be labelled on the basis of tissue distribution (*e.g.* brain type, heart type) since confusion can arise on account of species variation; homologous forms may occur in altogether different tissues in other species.

It is therefore recommended:

3. In naming isozymes (isoenzymes), the normal enzyme name (either systematic or trivial) (2) should be used, followed by a number. The numbers should be allotted consecutively, preferably on the basis of electrophoretic mobility under defined conditions, with the lower numbers given to the forms with the higher mobility towards the anode. In photographs or diagrams of electrophoretic results, the anode should be oriented to the top or right-hand side of the page.

4. Where complex isoenzyme (isozyme) patterns occur, with major groups each composed of several different electrophoretic zones, the numbers may be used to designate the major groups, with subscript lower case letters used consecutively for the individual subzones (1_a, 1_b, 1_c, 2_a, 2_b, etc.).

5. For unambiguous identification of particular isozymes (isoenzymes), additional parameters such as molecular weight, stability, or subunit structure should be given where available. Subunits may be denoted by upper case Roman letters or lower case Greek letters, but not by terms based on tissue distribution.

III. NOMENCLATURE OF GENETICALLY VARIANT ENZYMES

In the case of genetic variants, a flexible and open system is desirable. The chief consideration is that the investigator recognize that the new variant that he describes will probably not be the last one discovered, and, in the case of some enzymes, a very large number may eventually be found.

A special committee on the nomenclature of glucose-6-phosphate dehydrogenase in man (of which more than 50 genetic variants are known) was convened by the World Health Organization, and the report of its recommendations was published in abbreviated form in several journals (3); it forms the basis for certain of the recommendations presented here.

This report considers only the naming of the variant enzymes; it does not consider the designation of genotype and phenotype symbols, since these have been standardized by several appropriate genetic groups and differ somewhat among various organisms. The name of the enzyme variant can be readily adapted to the appropriate genetic terminologies.

It is therefore recommended:

6. In naming genetic variants, the normal enzyme name (either systematic or trivial) should be used, followed by a trivial name for the variant. This can be of any sort provided that it is sufficiently adaptable. A suitable system (as has been used for glucose-6-phosphate dehydrogenase) is to use the name of the town, university, country, etc., where the variant was discovered. The use of superscript letters or numbers is considered acceptable initially, but, once it is apparent that more than a few variants are being found, the trivial nomenclature should be initiated, to avoid using the same letter for two different variants.

7. When two variants originally considered as different are subsequently discovered to be identical, the name first used for that variant should then be accepted, the other one being discontinued.

REFERENCES

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2. *Enzyme nomenclature: recommendations (1964) of the International Union of Biochemistry on the nomenclature and classification of enzymes, together with their units and the symbols of enzyme kinetics.* Elsevier Publishing Company, Amsterdam, 1965.
3. *Biochem. Genet.*, **1**, 198 (1967).

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