ENZYME NOMENCLATURE

THE Commission of Editors of Biochemical Journals (J. T. Edsall (*president*), W. V. Thorpe (*secretary*), A. Dillmann, W. A. Engelhardt, Y. Raoul, E. C. Slater), appointed by the International Union of Biochemistry (IUB), wishes to direct attention to the recently published *Enzyme Nomenclature*[1], which is the report of the IUB Standing Committee on Enzymes.

The draft of this report was considered by a joint meeting of the Standing Committee and the IUB Commission of Editors of Biochemical Journals in Rome in February 1964. The version agreed to by that joint meeting was adopted by the Council of the IUB at its meeting in New York on July 27, 1964, and designated *Recommendations* (1964) *of the IUB on the Nomenclature and Classification of Enzymes*.

The report of the Standing Committee on Enzymes is based on the report of the IUB Commission on Enzymes[2], adopted by the General Assembly of the IUB in Moscow on August 16, 1961. The changes made by the Standing Committee in the report of the Commission on Enzymes are of four types: (*a*) additions of new enzymes, and, where necessary, new sub-groups to accommodate them; (*b*) correction of definite errors in the first edition; (*c*) changes in the nomenclature itself to meet criticisms which had been put forward; (*d*) addition of systematic names in some cases where the original Commission put forward only trivial names.

The chapter on the nomenclature of the cytochromes was revised by a special committee set up for this purpose. The chapter in the new report includes proposals for the nomenclature of haem compounds and haemoproteins in general.

Since the publication of the Report of the Commission on Enzymes in 1961, many of its recommendations have been widely used in scientific journals and text-books. Most biochemical journals urge authors to follow most of the recommendations even if they do not insist on all. Some journals already require the procedure suggested in Chapter 6, p. 29, that when an enzyme is the main subject of a paper or abstract, its code number (preceded by the letters *EC*), systematic name and source should be given at its first mention; thereafter the trivial name may be used. Enzymes which are not the main subject of the paper or abstract should be identified at their first mention by their code numbers. When the paper deals with an enzyme which is not yet in the Enzyme Commission's list, the authors may introduce a new systematic name and/or a new trivial name, both formed only according to the recommended rules, but a number should be assigned only by the IUB.

An addition to the new report is the inclusion in the index of names which have been in frequent use but which are no longer recommended. It was often difficult to find in the old report the new name of an enzyme known to the reader only by its old name. Many enzymologists may note with regret that the name by which they have long known a favourite enzyme is printed in italics in the index, indicating that it is not recommended. For example, fumarase (*EC* 4.2.1.2) is replaced by fumarate hydratase as trivial name (systematic name, L-malate hydro-lyase). Those who are irritated by this change should perhaps pause to think how many students first coming across the name fumarase might legitimately think that it catalyses the hydrolytic splitting of fumaric acid. Those who shed muramidase-containing tears on reading the first report may now rejoice that the old name lysozyme (*EC* 3.2.1.17) has been restored, whereas *muramidase* is now relegated to the list of disapproved names.

The chapter on enzyme units has received only one alteration. In the first report a standard temperature of 25° C was suggested, but this is now changed to 30° C because of the ambient laboratory temperature prevailing in many countries. No biochemical journals insist on the use of the Enzyme Commission's unit (*U*) of enzyme activity (the amount which will catalyse the transformation of 1 μmole of the substrate per min under standard conditions). However, this unit is to be strongly recommended and some journals suggest conversion of data in terms of the new unit when the paper has to be returned to the author for other revisions. The derived units specific activity (*U*/mg) and molecular activity (*U*/μmole enzyme) are also to be recommended. Where inconvenient numbers would otherwise be involved, terms such as milli-unit (m*U*), kilo-unit (K*U*) or, for those who specialize in small activities, nano-unit (n*U*) or pico-unit (p*U*).

The IUB Commission of Editors of Biochemical Journals would particularly like to direct the attention of authors to the recommendation that enzyme assays be based wherever possible on measurements of initial rates of reaction in order to avoid complications due, for example, to reversibility of reactions or to the formation of inhibitory products. Many papers are submitted in which kinetic parameters are calculated on the basis of data in which the initial rate was not measured. The substrate concentration should be, wherever possible, sufficient for saturation of the enzyme, so that the kinetics in the standard assay approach zero order. Where a distinctly sub-optimal concentration of substrate must be used, the Michaelis constant should be determined where feasible so that the observed rate may be converted into that which could be obtained on saturation with substrate.

The chapter on the symbols of enzyme kinetics is unchanged. The recommended symbols, v (velocity), V (v at infinite substrate concentration), K_m (Michaelis constant, that is, substrate concentration where $v = V/2$), K_s (substrate constant, that is, dissociation constant of the reaction $E + S \rightleftharpoons ES$), K_i (inhibition constant, that is, dissociation constant of the reaction $E + I \rightleftharpoons EI$), and k for rate constant are widely used. The recommended numbering of rate constants for enzyme systems involving consecutive steps, namely:

$$E + S \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} ES \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} EP \underset{k_{-3}}{\overset{k_{+3}}{\rightleftharpoons}} E + P$$

has not been widely adopted, and editors are still reluctant to request authors to make the extensive alterations to the typescript which would often be necessary.

The chapter on the classification and nomenclature of cytochromes has been completely rewritten. The term cytochromoid, introduced in the previous report to describe haemoproteins with haemoglobin-like structure and a reactivity with ligands which do not react with cytochrome *c*, has been set aside. It is now proposed that these non-haemochrome haemoproteins should be considered as variant *c*-type cytochromes. To indicate that a haem *c* prosthetic group is not in a haemochrome linkage, a dashed symbol, c'_1, is recommended. This chapter also defines a number of haem compounds and contains much useful information on the chemistry of these compounds and of haemoproteins. The individual cytochromes are now described in greater detail and some cytochromes appearing in the previous list have been dropped. Cytochromes c_4 and c_5 are now brought under cytochrome c_2. Cytochrome *f* is given the name cytochrome c_6, although no doubt it will continue to be called cytochrome *f* as well. Cytochrome d_1 (a_4) and a number of *C* cytochromes have been dropped. Indeed, the capital letters, introduced in the first report to describe a cyto-

chrome at a certain stage of the investigation, have been dropped.

The chapter on the terminology of enzyme formation does not appear in the new report. Part of it (formation from precursors) has been added to the chapter on classification and nomenclature of enzymes.

The chapter on the nomenclature of the nicotinamide nucleotide co-enzymes is an abbreviated version of part of the chapter on the nomenclature of coenzymes in the first report. The sections on ubiquinone or coenzyme *Q* and on coenzyme *A* have been omitted, since these compounds have been considered by the IUPAC (International Union of Pure and Applied Chemistry)–IUB Joint Commission on Biochemical Nomenclature, which maintains close contacts with the IUB Commission of Editors of Biochemical Journals. Ubiquinone (coenzyme *Q*) has been considered in a report on the nomenclature of quinones with isoprenoid side-chains (see, for example, ref. 3). This report makes two alternative recommendations for the naming of ubiquinone (coenzyme *Q*), namely: (1) the name be ubiquinone-*n* and the abbreviation *Q*-*n*, where *n* is the number of isoprenoid units in the side-chain; (2) the name be ubiquinone Q_n and the abbreviation Q_n. No changes in the name coenzyme *A* (Co*A*, CoASH) are proposed.

One of the more controversial recommendations of the Enzyme Commission was the use of the name nicotinamide adenine dinucleotide (NAD) and nicotinamide–adenine dinucleotide phosphate (NADP) instead of DPN and TPN. Many criticisms were received by the Standing Committee on Enzymes. These received careful consideration, but the Committee decided that the original arguments as set out in Chapter 4 of the *Report of the Commission on Enzymes* were sufficient to warrant no interference being made with their decision.

The editorial boards of some biochemical journals have encountered strong opposition from their authors to the replacement of the DPN–TPN nomenclature. Although the IUB Commission of Editors of Biochemical Journals has endorsed the new nomenclature, two of the larger journals represented in the Commission have been unable to enforce it, and have permitted the two systems to stand side by side.

In the first report, the Commission on Enzymes recommended two alternative systems of designating the reduced forms of NAD and NADP acting as substrates for enzyme reactions. The two systems were formulated $NAD^+ \rightarrow NADH + H^+$, and $NAD \rightarrow NADH_2$. The latter formulation was used in the enzyme list. In the new report the two forms are referred to simply as 'NAD' and 'reduced NAD' in the enzyme names and in the chemical equations illustrating the reaction catalysed by the enzyme in question. On the other hand, the IUPAC–IUB Commission on Biochemical Nomenclature has recommended that the abbreviations NAD and NADP should be used only when the state of oxidation of the compounds need not be specified. The oxidized and reduced forms of the coenzymes should be designated by NAD^+ ($NADP^+$) and NADH (NADPH), respectively. These may be used in an equation as follows:

$$NAD^+ + XH_2 \rightleftharpoons NADH + H^+ + X$$

For this reason, some journals will permit and even prefer the designation of an enzyme such as *EC* 1.6.99.3 by NADH: (acceptor) oxidoreductase (systematic name) and NADH dehydrogenase (trivial name) rather than by the names reduced-NAD: (acceptor) oxidoreductase and reduced NAD dehydrogenase, respectively, which appear in the new report. This is in conformity with current practice.

Because of difficulties with indexing, the use of chemical formulae in enzyme names has been prohibited, for example, *EC* 1.11.1.6 (catalase), which was given the systematic name $H_2O_2 : H_2O_2$ oxidoreductase in the first edition, has now been changed to hydrogen-peroxide : hydrogen-peroxide oxidoreductase. (Some journals may object to placing a hyphen between the two parts of a chemical name, which, according to the conventions of chemical nomenclature, do not have a hyphen in the English language.)

On the other hand, standard abbreviations for compounds of importance in biochemistry, as accepted by the IUPAC–IUB Commission on Biochemical Nomenclature, have been used in enzyme names, for example, ATPase (*EC* 3.6.1.3 and 3.6.1.8). Indeed, more use could possibly have been made of standard abbreviations, and editors will not object when these are used in enzyme names, for example, glutathione : hydrogen-peroxide oxidoreductase (*EC* 1.11.1.9) could be written GSH : hydrogen-peroxide oxidoreductase, and the systematic name of glutathione reductase (*EC* 1.6.4.2) can, in the opinion of the Commission of Editors, be legitimately written NAD(P)H : GSSG oxidoreductase instead of the longer name, reduced NAD(P) : oxidized-glutathione oxidoreductase.

The new report repeats the statement of the first report that abbreviations for names of enzymes, for example, GDH, should be strongly discouraged. While the Commission of Editors endorses this statement, and many journals rigorously enforce the prohibition of abbreviations for the names of enzymes, it must be recognized that such abbreviations are widely used, especially in clinical chemistry. It may soon be necessary to rationalize and standardize this practice rather than to ban it.

The most important change in the enzyme list is the reclassification of hydrogenases (Group 1.12), oxygenases (Group 1.13) and hydroxylases (Group 1.14). Errors in the first list have been corrected and many new enzymes added. The list now contains 875 enzymes.

It is obvious that the further purification of enzymes and advances in our knowledge of the mechanism of reactions catalysed by specific enzymes may soon make the recommended nomenclature no longer acceptable in certain cases. The present basis of classification is functional because sufficient chemical knowledge is absent. When more becomes known about the nature of active sites and amino-acid sequences, a chemical classification may become possible.

It is also clear that not everyone will agree with the classification and nomenclature of all the 875 enzymes. Editors of biochemical journals will carefully and sympathetically consider reasoned requests by an author to depart from the recommended nomenclature, and will forward them to Prof. E. C. Webb, who has been designated by the Council of the IUB to assemble such comments. Indeed, the Standing Committee on Enzymes received and considered many criticisms from authors which were transmitted by the editorial boards of various biochemical journals. If the editorial board agrees with the arguments brought forward by an author, it will allow him to depart from the recommendations of the enzyme report. It would be desirable to state the reasons for this departure in the text of the paper or in a footnote.

It should be added, however, that the experience of editors is that many authors have not grasped the basis of the nomenclature recommended by the Commission on Enzymes, namely that an enzyme should be named according to the reaction which it catalyses. Since the specificity of enzymes is not absolute, some arbitrariness in naming the substrate is inevitable. The principles followed by the Commission on Enzymes in choosing between different possibilities are given in Rule 14, p. 32, of the new report. Since it appears that few authors are fully aware of the implications of this rule, it might be useful to consider it in more detail. The long-known enzyme succinate dehydrogenase (*EC* 1.3.99.1) is given the systematic name succinate : (acceptor) oxidoreductase, even though it also catalyses the oxidation of a number of α-monosubstituted succinates. On the other hand, alcohol dehydrogenase (*EC* 1.1.1.1) is named alcohol : NAD oxido-

reductase, because it acts on a wide range of alcohols. Lactate dehydrogenase (*EC* 1.1.1.27) is named L-lactate : NAD oxidoreductase, even though it reacts quite rapidly with NADP as well as with NAD. However, the most commonly occurring glutamate dehydrogenase (*EC* 1.4.1.3) is named L-glutamate : NAD(P) oxidoreductase (deaminating), because it reacts readily with both NAD and NADP (see Rule 16). The aldehyde dehydrogenases give special difficulties. No less than 18 are listed in Group 1.2.1 (with NAD or NADP as acceptor). Of these, 14 are named in terms of a specific hydrogen donor, while in the others the donor is given simply as aldehyde. This should not be taken to mean that the 14 are absolutely specific for a single aldehyde. Of the 18 enzymes, NAD is given as acceptor for 8, NADP for 6 and both nucleotides for 4.

There are many discrete enzymes, differing in amino-acid composition, physical properties and enzyme kinetics, all of which have to be named aldehyde : NAD oxidoreductase (*EC* 1.2.1.3). At present these must be distinguished by source, such as organism, tissue and cell component. The IUB Commission of Editors of Biochemical Journals has set up a sub-committee to consider the problems of nomenclature posed by recent research on the nature of isoenzymes and enzyme sub-units.

[1] *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.* Pp. v+219. (Elsevier Publishing Co., Amsterdam, 1965). 2.50 dollars.

[2] *Report of the Commission on Enzymes of the International Union of Biochemistry*, 1961 (Pergamon Press, Oxford, 1961).

[3] *Biochim. Biophys. Acta*, **107**, 5 (1965).

INTERNATIONAL COMMITTEE ON LABORATORY ANIMALS

THE International Committee on Laboratory Animals held its third international symposium at Dun Laoghaire, near Dublin, during September 6–17 under the general title, "The Husbandry of Laboratory Animals"*. The Committee, while well known to those professionally engaged in laboratory animal science, appears to be largely unknown to the users of laboratory animals. It was, however, the users, who, acting through their international unions, set up the Committee. It seems appropriate, therefore, that a general report of the Committee and its work should be made to laboratory animal users on this occasion.

History. Ten years ago two independent initiatives towards an international organization were being made. One was by the International Union of Biological Sciences and the other by the Council for International Organizations for Medical Sciences working in association with Unesco. In December 1956 these organizations met and recommended the establishment of the International Committee on Laboratory Animals. The International Union of Physiological Sciences joined soon after, and the Committee was established as an inter-union committee; experts, who were heads of laboratory animal centres, were co-opted. Unesco provided most of the financial support and was represented on the Committee by an observer. Two other unions have since joined—the International Union against Cancer and the International Union of Biochemistry.

The growth of the Committee's activities was such that by 1961 a revised constitution was necessary. Laboratory animal centres or committees had been established in many countries to co-ordinate work in the field and act as information centres. It seemed important to associate these bodies with the International Committee. The Committee now consists of the union members and national representatives, numbering twenty-seven, coming from all parts of the world. The final authority rests with the governing body, which consists of all the union representatives together with an equal number of national representatives; the World Health Organization is represented by an observer. In effect this is an equal division between the users and the laboratory animal experts. The detailed work is done by an executive committee of individual experts.

The financial support from Unesco was only temporary and in 1962 it ended. The Committee is most grateful to Unesco. The World Health Organization has now undertaken to support the work of the Committee, and to that Organization also the Committee is deeply grateful.

Activities. Surveys of the production and utilization of laboratory animals have been carried out and published in relation to twenty-one countries. This has enabled the problems to be assessed and has provided a strong stimulus to the development of national centres dealing with problems connected with laboratory animals. Another major factor in such development has been the visits, made under Committee auspices, of the officers and other experts to many countries to give advice on laboratory animal problems. Up to the present time this advice has been mainly concerned with the development of healthy supplies of small mammals. Similarly, other activities have been concentrated in this direction. Thus, efforts have been made to improve technician training, and notes on training courses have been published in the *International Committee on Laboratory Animals Bulletin* which is published twice a year. Scholarships have been awarded to a number of workers in the field, and this has enabled them to work for a time in one of the established centres, in this way helping the development of new centres elsewhere.

Two previous international symposia have been held on "Living Animal Material for Biological Research" and "The Problem of Laboratory Animal Disease". These, together with that just held, have provided a forum for the discussion of a range of scientific problems connected with the supply of healthy animals, in particular small mammals.

Besides the basic problems of improving the health, nutrition and handling of animals, two other general fields have always been on the Committee's programme. The first of these concerns more specialized questions related to the breeding of small mammals. This side of the work has included a bibliography (now taken over by the publishers of the *Zeitschrift für Versuchstierkunde*—Gustav Fischer Verlag, Jena, German Democratic Republic) and the preparation of lists of agreed definitions. These are slow steps towards the difficult task of designating primary type colony centres and listing the primary type colonies being maintained. The difficulty in this task lies in specifying strains in such a way that the designations have real meaning.

The Committee is one concerned with laboratory animals of all kinds and not simply small mammals. One of its early aims was to establish world lists of sources of laboratory animals, especially lower vertebrates and invertebrates. This aim has so far proved very difficult to achieve and, with the concentration of effort on standards of care in animal houses for small mammals, little has yet been done in this field. This has caused some concern, and the governing body has now put on record its hope that some advance in the non-mammalian field may take place in the next three years.

In all these fields of activity this international organization is primarily a channel of communication between national organizations, and the latter have, as one of their functions, the giving of information not only to those

* The proceedings are being published by Academic Press.