Classification and Nomenclature of Enzymes

The Commission on Enzymes of the International Union of Biochemistry recommends measures of standardization.

One of the problems that biologists and chemists alike are faced with is that of the nomenclature of the vast array of complex substances of which living tissues are composed, and in no field have these difficulties been greater than in relation to the enzymes and coenzymes that bring about the chemical changes on which life depends. Enzymology, although a relatively new science, is a rapidly growing one, and in recent years there has been a great increase in the number of enzymes newly described, the total number now known amounting to more than 700. In the past the naming of new enzymes had been largely left to the individual workers responsible for their discovery, and since, on occasion work had been proceeding simultaneously in different centers, it was not unknown for the same enzyme to be allotted different names by the different groups of workers; on the other hand, there were also cases in which the same name was chosen for different enzymes. These same difficulties applied to the nomenclature of the small-molecular coenzymes.

The units of enzyme activity and the conditions under which activity was measured for purposes of their standardization, and even the mathematical symbols used in the study of enzyme kinetics, differed in different laboratories, so that comparison of results on a quantitative basis was difficult and in some cases presented a real problem, as in the field of clinical biochemistry, where comparison of enzyme levels in body fluids is used extensively to assist in diagnosis and in the assessment of the effects of treatment.

Because of this chaos, the General Assembly of the International Union of Biochemistry (IUB) decided in August 1955, seven months after its establishment, that the first and most outstanding task requiring investigation at the international level was the whole problem of the proper classification and nomenclature of enzymes and coenzymes, and it was unanimously agreed that an International Commission on Enzymes should be set up.

The Section of Biological Chemistry of the International Union of Pure and Applied Chemistry (IUPAC) was informed of this decision, and it was agreed between the two unions that IUB should proceed immediately with the setting up of this commission, which was to have joint consultations with the existing IUPAC Commission on Biochemical Nomenclature. After circularizing the various national committees associated with IUB for their advice as to membership of the commission, M. Florkin, who was at that time president of IUB, called together a meeting in Paris, in July 1956, of an *ad hoc* committee for the purpose of establishing the commission. It was decided at this meeting that the commission should consist of ten full members and as many as four corresponding members, and that it should be empowered to set up and obtain advice from special subcommissions chosen to deal with special topics.

The members of the commission were chosen at this meeting on the advice of the *ad hoc* committee and were appointed by the Bureau of the Union. It was agreed that the terms of reference of the commission should be: "To consider the classification and nomenclature of enzymes and co-enzymes, their units of activity and standard methods of assay, together with the symbols used in the description of enzyme kinetics."

And finally it was agreed that the decisions reached by the commission were to be submitted to the Council of IUB for approval.

The commission, as set up, was composed of the following members: M. Dixon (United Kingdom, president), O. Hoffmann-Ostenhof (Austria, secretary), A. E. Braunstein (U.S.S.R.), S. P. Colowick (United States), P. A. E. Desnuelle (France), V. A. Engelhardt (U.S.S.R.), E. F. Gale (United Kingdom), A. L. Lehninger (United States), K. Linderstrøm-Lang (Denmark), and F. Lynen (Germany), with F. Egami (Japan) and L. F. Leloir (Argentina) serving as corresponding members. The desirability of having available a philologist to advise on questions of terminology was early recognized, and in 1957 H. Sykes Davies (United Kingdom) was appointed to the commission to assist in these matters. The only other change in membership was the appointment in 1959 of E. C. Webb (United Kingdom) to fill the vacancy caused by the death of K. Linderstrøm-Lang.

The following individuals kindly agreed to serve on the various subcommissions: G. B. Brown, P. P. Cohen, J. E. Falk, R. Hill, M. Kamen, D. Keilin, R. Lemberg, A. Meister, M. Morrison, R. K. Morton, H. Neurath, S. Paleus, G. Schmidt, E. L. Smith, E. H. Stotz, H. Theorell, and W. W. Wainio.

The commission met each year from 1956 to 1961, in a total of 32 sessions; two of these were joint meetings with the Biological Chemistry Nomenclature Commission of IUPAC and one was a joint meeting with a Committee of Editors of Biochemical Journals, set up by IUB. In addition, six meetings of various subcommissions were held, amounting in all to 30 sessions.

The commission finished its work in the spring of 1961, and its report was presented to the Council of IUB at its meeting in Moscow during the 5th International Congress of Biochemistry, in August 1961. The Council of the Union formally accepted the report, which has now been published as volume 20 of the "I.U.B. Symposium Series" (Pergamon, Oxford, 1961).

The report begins with a number of chapters setting out the various problems and explaining the basis on which

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This summary of the commission's recommendations has also appeared in *Nature*.

the final recommendations are made. It ends with a classified list of over 700 enzymes. They are divided, on the basis of the nature of the overall reaction catalyzed, into six main classes: oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. Each of these classes is further divided into a number of subclasses and sub-subclasses.

In its proposals for nomenclature the commission had to balance the need for a logical system, which would reduce some of the present confusion and which would identify the enzyme and indicate its action as exactly as possible, with the desirability of retaining, wherever possible, long-established and widely recognized names, particularly when no good purpose would be served by making a change. With this end in view the commission has proposed that each enzyme shall be given two names, a systematic name and a trivial or "working" name. The systematic name is based on a set of rules which can serve as a guide for the naming of new enzymes in the future. Since, in order to indicate the type of enzyme action, the systematic name must include the name of the substrate, and since many of the substrates have themselves long chemical names, it is inevitable that many of the systematic names will be too long and unwieldly for ordinary use. The trivial name, on the other hand, is short and suitable for general use, and is, in a great many cases, the name already in current use.

The commission has devised a four-figure system of numbering the classified enzymes, based on the nature of the reaction, which will precisely identify each enzyme as well as allow for the insertion of new enzymes into their appropriate class. It should have the additional advantage of serving as a coding system for mechanical or electronic indexing devices.

Nearly the whole of one chapter is given to a discussion of the nomenclature of the nicotinamide nucleotide coenzymes. At the present time four different systems are in use for naming these substances. Some of the names used—such as *cozymase, coenzyme I,* or *codehydrogenase I*—are unsatisfactory because they are uninformative, while the names *di- and triphosphopyridine nucleotide* are frankly incorrect and have rightly been criticized on the grounds that they give no true indication of the structure of these coenzymes but would be expected to refer rather to nucleotides of "diphosphopyridine" or "triphosphopyridine." It is proposed instead to make yet a further change and to call these compounds nicotinamide-adenine dinucleotide (NAD) and nicotinamide-adenine dinucleotide phosphate (NADP).

The various recommendations of the commission are summarized in chapter 9 of the report, as follows.

Summary of Recommendations

Enzyme Units

1) One unit (U) of any enzyme should be defined as that amount which will catalyse the transformation of 1 micromole of substrate per minute, or, where more than one bond of each substrate molecule is attacked, 1 microequivalent of the group concerned per minute, under defined conditions. Where two identical molecules react together, the unit will be the amount which catalyses the transformation of 2 micromoles per minute. The temperature should be stated, and where practicable should be 25°C. The other conditions, including *p*H and substrate concentration, should be optimal. In order to avoid inconvenient numbers, terms such as milli-unit (mU), kilo-unit (kU), etc., may be used.

2) Enzyme assays should be based wherever possible upon measurements of initial rates of reaction in order to avoid complications, and the substrate concentration should be sufficient for saturation of the enzyme, so that the kinetics approach zero order. Where a sub-optimal concentration of substrate must be used, the Michaelis constant should be determined so that the observed rate may be converted into that which would be obtained on saturation with substrate.

3) Specific activity should be expressed as units of enzyme per milligram of protein.

4) Molecular activity should be defined as units per micromole of enzyme at optimal substrate concentration, that is, as the number of molecules of substrate transformed per minute per molecule of enzyme.

5) When the enzyme has a prosthetic group or catalytic centre whose concentration can be measured, the catalytic power can be expressed as catalytic centre activity, i.e., the number of molecules of substrate transformed per minute per catalytic centre. The term "turnover number," which has been employed with various meanings, should no longer be used.

6) Concentration of an enzyme in solution should be expressed as units per millilitre.

Symbols of Enzyme Kinetics

7) In mathematical equations for enzyme kinetics, the symbols given in Appendix B of the Report* should be used for velocity, saturation velocity, Michaelis constant, substrate and inhibitor constants, and velocity constants.

8) All equilibria involving combinations of enzymes with substrates, inhibitors or products should be expressed in terms of dissociation constants rather than association constants.

9) The term "Michaelis constant" and the symbol K_m should be used only to denote the substrate concentration at which the velocity is equal to half the saturation velocity.

10) The terms "substrate constant" (K_s) and "inhibitor constant" (K_i) should be used to denote the equilibrium (dissociation) constants of the reactions $E + S = ES$ and $E + I = EI$ respectively.

11) The velocity constants of the individual steps involved in an enzyme reaction should be numbered as in the following example:

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

Thus k_{+n} will denote the velocity constant of the nth step in the forward direction, i.e., proceeding from substrate to product, while k_{-n} will denote that of the reverse reaction of the same step.

12) The velocity of an enzyme reaction should be denoted by v, and the value of v corresponding to saturation of the enzyme with substrate should be denoted by V.

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* *Recommended Symbols for Enzyme Kinetics.*
v, Velocity of reaction catalysed by an enzyme.
V, Value of v when the enzyme is saturated with substrate, as given by the Michaelis equation.
K_m, "Michaelis constant." Concentration of substrate at which $v = V/2$.
K_s, "Substrate constant." Equilibrium (dissociation) constant of the reaction $E + S \rightleftharpoons ES$.
K_i, "Inhibitor constant." Equilibrium (dissociation) constant of the reaction $E + I \rightleftharpoons EI$.
k_{+n}, k_{-n}, Velocity constants of the forward and backward reactions in the nth step of an enzyme reaction.

Nomenclature of Coenzymes

13) The nicotinamide nucleotide coenzymes should in future be known by their chemical names "nicotinamide-adenine dinucleotide" (NAD) and "nicotinamide-adenine dinucleotide phosphate" (NADP) respectively. The names "cozymase," "phosphocozymase," "coenzyme I" (CoI), "coenzyme II" (CoII), "diphosphopyridine nucleotide" (DPN), "triphosphopyridine nucleotide" (TPN), "codehydrogenase I," "codehydrogenase II" should no longer be used. The mononucleotide should continue to be known as "nicotinamide mononucleotide" (NMN).

14) The names "flavin-adenine dinucleotide" (FAD) and "flavin mononucleotide" (FMN) should be retained.

15) For the reduced form of NAD, two alternative abbreviations should be permitted, namely $NADH_2$ (corresponding to $FADH_2$) or, where it is desired to show the release of a H^+ ion in the reduction, $NADH + H^+$. However, when the latter form is used, the oxidized form should always be written as NAD^+; under no circumstances should the reduction be shown as a change from NAD to NADH. Similar forms should be permitted for NADP.

16) The name "coenzyme Q" should be dropped and the name "ubiquinone" used instead. This may be abbreviated as "UQ," and when it is desired to indicate the number of isoprene units in the side-chain a numerical suffix may be added thus, "UQ_{10}."

17) Although names of the form "coenzyme X" are not recommended, the name "coenzyme A" should be retained, in the absence of any practicable alternative. Two alternative abbreviations should be permissible, namely CoA for normal use or, where it is desired to indicate the thiol group, CoASH.

Classification and Nomenclature of Cytochromes

18) Cytochromes should be defined as haemoproteins whose principal biological function is electron and/or hydrogen transport by virtue of a reversible valency change of their haem iron.

19) The name "cytochrome" implies a single haemoprotein entity; the term "cytochrome system" should be used to denote any wider system in which one or more cytochromes, apart from cytochrome oxidase, are involved.

20) Cytochromes should be classified at present in four groups, according to the nature of their prosthetic haem groups, namely Cytochromes A, B, C, and D, containing formylporphyrin-iron, protoporphyrin-iron, a substituted mesoporphyrin-iron with covalent porphyrin-protein linkages, and dihydroporphyrin-iron respectively. The criteria for assignment to groups should be those given in Chapter 5 of the Report.

21) When a cytochrome contains haem groups of two different kinds attached to one specific protein, both groups should be shown in the name, e.g. "cytochrome CD."

22) Haemoproteins closely related to cytochromes, but with a haemoglobin-like spectrum and a reactivity with ligands which do not react with cytochrome *c*, should be called "cytochromoids."

23) There should be no sub-classification of groups A–D at present.

24) A newly discovered haemoprotein should not be classed as a cytochrome until it has been shown to come within the definition given in (18) above. It may temporarily be named on the pattern "haemoprotein 560 (Bacterium X)," where 560 is the wavelength in $m\mu$ of the α band of its spectrum.

25) When a haemoprotein is first established as a cytochrome, it should receive a provisional name of the type "cytochrome 560 (*Bacterium X*)." Efforts should then be made to establish its group; when this has been done provisionally, an interim name of the form "cytochrome B (560, *Bacterium X*)" should be given, in which the group is indicated by a capital letter. Finally, when the allocation has been clearly determined and its individuality properly established, it should be allocated an official final name, based on an italic small letter and a subscript number, e.g. "cytochrome b_1," and be included in the list of cytochromes (see Appendix C of the Report).

26) The names of the majority of already well-established cytochromes, including those used in the names of enzymes, should remain unchanged, since they will rank as final names.

27) Final names should only be allotted by authority, preferably by a Standing Committee, and not by individual workers.

28) It is recommended that the International Union of Pure and Applied Chemistry should be consulted about setting up a Standing Committee on Cytochromes, to decide on the inclusion of cytochromes within the different groups, to allot final names to cytochromes when necessary, to consider the establishment of new groups if needed, and to keep the list of cytochromes up to date.

Classification and Nomenclature of Enzymes

29) Names purporting to be names of enzymes, especially those ending in "-ase," should only be used for single enzymes. When it is desired to name a system containing more than one enzyme on the basis of the overall reaction catalysed by it, the word "system" should be included in the name, e.g. "the succinate oxidase system."

30) The basis for classification and naming should be the overall reaction catalysed, as expressed by the formal equation; this means that the intimate mechanism of the reaction, and the formation of intermediate complexes with the enzyme, will not be taken into account.

31) Systematic names cannot be given to enzymes until it is known what reactions they catalyse. This applies for example to any enzyme that is only known to catalyse an isotopic exchange.

32) The Commission recommends that the system of classification shown in Appendix D of the Report be approved; this divides enzymes into six main classes, each of which is divided into a number of sub-classes and sub-sub-classes, according to the nature of the reaction catalysed.

33) It also recommends that the enzymes should be coded on a four-number system intimately connected with the system of classification, as shown in Appendix D and Appendix E of the Report. On this system the first number indicates the main class, the second and third show the sub-class and sub-sub-class respectively, thus defining the type of reaction, and the fourth is the number of the enzyme within its sub-sub-class.

34) Once given, the number of an enzyme should remain attached to it as a permanent means of identification (unless it has been wrongly classified and has to be moved to another group). New enzymes should be placed at the end of the appropriate sub-sub-class, so that the numbering of the existing

enzymes therein will not be disturbed.

35) New enzyme numbers should be allotted only by authority (e.g. by future Enzyme Commissions or by a Standing Committee) and not by individual workers.

36) It is recommended that there shall be both systematic and trivial nomenclatures for enzymes; the systematic name will be formed in accordance with definite rules, and will identify the enzyme and indicate its action as precisely as possible; the trivial name will be sufficiently short for general use, and in a great many cases will be the name already in current use.

37) The systematic and trivial nomenclatures should be in accordance with the Rules (1) to (31) set out in Chapter 6 of this Report.

38) The systematic and trivial enzyme names given in the list in Appendix E of the Report should be used henceforth.

39) Where an enzyme is the main subject of a paper or abstract, it is recommended that its code number, systematic name (where a satisfactory name exists) and source should be given at its first mention in the text; thereafter the trivial name may be used.

40) Enzymes which are not the main subject should be identified at their first mention by their code numbers.

41) When the paper deals with an enzyme which is not yet in the Commission's list, the author may introduce a new systematic name and/or a new trivial name, both formed only according to the recommended rules.

42) A Standing Committee should be set up with power to approve the names of new enzymes, to allot enzyme numbers, to alter or delete existing names or numbers, and generally to keep the list of enzymes up to date.

Terminology of Enzyme Formation

43) In discussing enzyme formation evoked by the presence of chemical substances, the term "induction" should be used, rather than "adaptation," the enzyme-forming system should be described as "inducible" and the enzyme formed as "induced." "Sequential induction" should be used instead of "simultaneous adaptation" or "succcessive adaptation."

44) The names of enzyme precursors should no longer be formed by the use of the suffix "-ogen"; the prefix "pre-" should be used instead.

It will be apparent on reading the report that some of the recommendations made by the commission are far-reaching and fundamental. It will also be clear that they have been made only after lengthy consideration and debate by an internationally picked group of enzymologists, themselves active workers in the branch of biochemistry. Despite this, however, the Council of IUB, and also the members of the commission, fully realize that balanced and reasonable objections are likely to be raised to some, perhaps to many, of these recommendations. With this in mind, the Council of the Union, having accepted the report, decided to dissolve the existing commission, and to set up as an interim measure a Standing Committee on Enzymes, composed of S. P. Colowick, A. L. Lehninger, O. Hoffmann-Ostenhof, and E. C. Webb. The purpose of this standing committee is to receive criticisms, suggestions, and comments on the report; to list any newly discovered enzymes with a view to allotting them a provisional name and place in the classified Table of Enzymes; and, in addition, to take up any new problem that may arise in this field. As an example, the standing committee is already at work on the problem of naming and numbering iso-enzymes, a topic that is becoming of increasing interest to clinical biochemists. The report has also been passed to the International Commission of Editors of Biochemical Journals, which was set up by IUB last year under the presidency of J. T. Edsall (*Journal of Biological Chemistry*). It is hoped that comments from national committees for biochemistry and from editorial committees and other interested organizations or persons will be sent, if possible before 1 January 1963, to Dr. E. C. Webb, Department of Biochemistry, University of Queensland, Brisbane, Australia, who has agreed to act as secretary of the standing committee. When these have been received it is the intention of IUB to set up a second commission on enzymes in order to consider these comments and to incorporate changes, where desirable, in a second edition of the *Report*, which, it is hoped, may then serve as a generally acceptable, definitive document covering the nomenclature of enzymes and coenzymes.

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