Reports

Nomenclature of the Nicotinamide Nucleotide Coenzymes

The nomenclature of the nicotinamide nucleotide coenzymes has been a subject of long-standing disagreement, and unanimity has not yet been reached. Several different systems are in use to varying extents.

Included with other subjects in the terms of reference of the Enzyme Commission of the International Union of Biochemistry (*1*) is the nomenclature of enzymes and of coenzymes, and during the past three years the commission has been giving careful and detailed consideration to the question of coenzyme nomenclature, in an effort to reach a generally acceptable solution. The question has also been considered by the Biological Chemistry Nomenclature Commission of the International Union of Pure and Applied Chemistry. A summary of the points involved and the reasons for the recommendations of the commissions may be of interest.

Present position. The situation that has to be faced is that, except perhaps in the United States, there is no unanimity about the naming of the two coenzymes. Four different systems are in use, although to very different extents, and the special difficulty of the position arises from the fact that the system that is most used is that to which there are the strongest objections from the chemical point of view. The four systems are (i) cozymase and phospho-cozymase, (ii) codehydrogenase I and codehydrogenase II (or codehydrase I and codehydrase II, terms used by some Continental writers), (iii) coenzyme I and coenzyme II (abbreviated to CoI and CoII), and (iv) diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN). The first system is probably the least used, the fourth the most used, at present. None of these systems is satisfactory, the first three because they are uninformative, the last because it is incorrect, as a number of reviewers have pointed out (*2, 3*).

There is rather more consistency among the journals than there is among authors of books and reviews. The *Journal of Biological Chemistry*, which had previously used both cozymase and coenzyme I (systems i and iii), first used diphosphopyridine nucleotide (system iv) about 1940; it has continued to do so, along with cozymase and coenzyme I until about 1950, and as the sole form after that date. The *Biochemical Journal* used the names cozymase and coenzyme I, and did not permit use of diphosphopyridine nucleotide, until as recently as 1953, but since then it has used the last name almost entirely. The index of *Chemical Abstracts*, however, still uses codehydrogenase I (system ii) rather than DPN.

DPN, TPN. There would be no objection whatever to the use of the names diphosphopyridine nucleotide and triphosphopyridine nucleotide if they did not indicate chemical structures, but the main objection is, in brief, that not only do they fail to give the structure of the coenzymes properly, but they are the chemical names of other compounds. It is somewhat like using the name "methyl acetate" for pyruvate; the name indicates a structure, but it is the wrong structure.

The names are derived from, though not the same as, names introduced by Warburg (*4*) in 1936 as convenient descriptions. The term "pyridine nucleotide" was used, quite legitimately, to distinguish this class of compounds from purine nucleotides such as the adenine nucleotides. To distinguish the coenzymes from each other they were described as "the diphospho-" and "the triphospho-pyridine-nucleotide," at first with the definite article, but this was almost immediately dropped and the terms were thereafter used as names, in the German forms "Diphospho-Pyridinnucleotid" and "Triphospho-Pyridinnucleotid."

"Diphospho-." In 1939 F. G. Fischer (*2*), in his review of the subject, pointed out that these names, though concise, were incorrect. According to chemical terminology, "phospho-*X*" denotes *X* combined with an additional phosphate group; but a "nucleotide" already includes a phosphate group; thus a "diphospho-(di)nucleotide" would contain four phosphate groups, and not two as does the coenzyme. Fischer suggested that, especially in relation to the accepted names of the analogous flavin nucleotides, the names "Pyridine-Adenine-Dinucleotide" and "Phospho-Pyridine-Adenine-Dinucleotide" would be clearer. They would have the advantage of showing that the compounds are dinucleotides containing adenine, which was not indicated by the earlier names. Probably because of the outbreak of war in the same year, these suggestions did not receive the attention they deserved.

"Triphospho-." It was at first believed that the three phosphate groups of TPN were joined in line, as in ATP, so that the relationship between the two coenzymes would be analogous to that between ADP and ATP. When the true structure of TPN was determined in 1950 by Kornberg and Pricer (*5*), it was found to be a monophosphodinucleotide, so that the prefix "triphospho-" became less appropriate.

"Diphosphopyridine-." Perhaps the most serious objection arose when the names became Anglicized—first, I believe, about 1940 in the United States. The form used by Warburg, namely "Diphospho-Pyridinnucleotid," was clearly intended to be taken in the sense of diphospho (pyridinenucleotide), as shown by the hyphen and the capital P. The introduction of a space before "nucleotide" gave a form with quite a different meaning. The name "diphosphopyridine nucleotide" means, quite unambiguously, a nucleotide of diphosphopyridine, that is, a substance of the structure diphosphopyridine—D-ribose—phosphate, and it is not surprising that biochemists have often been criticized by the organic chemists for using such names.

"Dihydrodiphospho-." For the reduced or dihydro- forms, DPN and TPN yield names beginning with the undesirable prefix "dihydrodiphospho-," which is a further objection.

"Pyridine-." One may properly use the term "purine nucleotides" for the whole class, but in referring to a particular nucleotide the name of the particular purine is used. One says "flavin-adenine dinucleotide" and not "flavin-purine dinucleotide." Correspondingly,

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Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [*Science* **125**, 16 (1957)].

the word "pyridine" ought not to be used for the names of particular nucleotides unless they are in fact nucleotides of pyridine itself. "Pyridine" should not be used when "nicotinamide" is meant. The coenzymes are nicotinamide compounds, and the corresponding pyridine compounds are inactive as coenzymes (*6*). The DPN system of nomenclature causes great difficulty in the rapidly expanding work on analogues of the coenzymes. If the nicotinamide nucleotides are called "pyridine nucleotides," what can one call the pyridine nucleotides? They surely cannot be called pyridine analogues of the pyridine nucleotides! The use of DPN forces the use in current literature of such terms as "pyridine-DPN" and APDPN (for acetyl-pyridine diphosphopyridine nucleotide), in which the word "pyridine" occurs twice, although there is only one pyridine ring in the compound. This is a very real difficulty.

"DNP." DNP is the accepted abbreviation for dinitrophenol, a reagent much used in studies on the coupling of biological oxidation and phosphorylation. Papers on DNP often contain many references to DPN, and the similarity makes them confusing and difficult to read.

"FMN, FAD, NMN,—?" Finally, the name diphosphopyridine nucleotide obscures the close and important analogy with the corresponding flavin compounds, shown in Table 1. Flavin-adenine dinucleotide (FAD) is the same substance, with the nicotinamide end changed into the flavin structure. Flavin mononucleotide (FMN) is the same without the adenylic acid half of the molecule. Nicotinamide mononucleotide (NMN) is the coenzyme without the adenylic acid. These three names and the corresponding abbreviations are quite generally accepted, and there is no suggestion that they should be changed. To complete the scheme we should expect NAD for nicotinamide-adenine dinucleotide, thus:

FMN	NMN
FAD	NAD

The use of DPN instead of NAD breaks the logic of the nomenclature.

Summary of objections. To recapitulate, the main objections to the name diphosphopyridine nucleotide are (i) the coenzyme is not a nucleotide of diphosphopyridine as the name indicates; (ii) the name indicates the presence of four phosphate groups instead of two; (iii) it does not indicate that the coenzyme is a dinucleotide or that it contains adenine; (iv) the coenzyme is not a nucleotide of pyridine but of nicotinamide; (v) the pyridine nucleotides, to which the name properly applies, are inactive as coenzymes; (vi) the use of the name for the nicotinamide compound makes it impossible to name the pyridine analogues satisfactorily; (vii) the combination "dihydrodiphospho-" in the name of the reduced form is undesirable; (viii) the name is out of line with the FMN, FAD, NMN sequence and obscures the close chemical analogy with the flavin compounds; (ix) the corresponding name triphosphopyridine nucleotide suggests a triphosphate structure rather than the actual monophospho-dinucleotide structure.

In view of the strong chemical objections, the Enzyme Commission felt itself unable to recommend the continued use of the DPN system of nomenclature, particularly as a satisfactory alternative is available. The difficulty is not a chemical one, for there is no doubt about what the substance is: it is nicotinamide-adenine dinucleotide. It is a psychological difficulty—that of bringing the correct name into use when an incorrect name has become well established. The commission fully realizes that it is taking a serious step in recommending a change, and that there is likely to be some opposition, perhaps especially in America, as there was in Britain when the form DPN replaced CoI. However, this moment, when a real effort is being made to bring the terminology of enzymology into order, is the right one for putting the coenzyme nomenclature right also. This is probably the last opportunity there will be for doing so; if it is not done now, there is not likely to be another chance.

Some workers feel that the whole matter should be left optional, so that authors should be free to use any system they wish. The difficulty facing the commission, however, was that, apart from the fact that they were given the task of dealing with coenzyme nomenclature, they also had to deal with the nomenclature of enzymes, and the names of a large number of enzymes depend on those of the coenzymes. They were therefore obliged to make a choice, in order to avoid the necessity for more than one systematic name for each of these enzymes.

NAD. They have therefore decided to recommend that both forms CoI and DPN be dropped, and that the coenzyme be known by its actual chemical name, nicotinamide-adenine dinucleotide, which may be abbreviated to NAD. It will be seen that this name avoids all the objections mentioned above, it indicates the structure of the compound, it brings out the analogy with FAD, and it makes it possible to name the analogues satisfactorily. The reduced form would be named dihydronicotinamide-adenine dinucleotide, which indicates correctly the part of the molecule that becomes reduced.

NADP. TPN (CoII) might be named phospho-nicotinamide-adenine dinucleotide, but this is undesirable, for "phospho-nicotinamide" is as incorrect as "diphosphopyridine," and the reduced form would again have the "dihydrophospho-" prefix. The recommended form "nicotinamide-adenine dinucleotide phosphate" (NADP) avoids both these objections, and the extra P clearly indicates the formation from NAD by the addition of a phosphate group.

Coenzyme analogues. With the NAD system, the naming of the analogues be-

Table 1. Structures of nicotinamide and flavin nucleotides.

Name and abbreviation	Structure
Nicotinamide mononucleotide (NMN)	Nicotinamide—D-ribose—phosphate
Cozymase Coenzyme I (CoI)	Adenine—D-ribose—phosphate
Diphosphopyridine nucleotide (DPN) Nicotinamide-adenine dinucleotide (NAD)	Nicotinamide—D-ribose—phosphate
Flavin mononucleotide (FMN)	isoalloxazine—ribitol—phosphate —flavin—
Flavin-adenine dinucleotide (FAD)	Adenine—D-ribose—phosphate isoalloxazine—ribitol—phosphate
Phospho-cozymase Coenzyme II (CoII)	Phosphate Adenine—D-ribose—phosphate
Triphosphopyridine nucleotide (TPN) Nicotinamide-adenine dinucleotide phosphate (NADP)	Nicotinamide—D-ribose—phosphate

comes relatively simple and straightforward. For example, the pyridine analogue would be called pyridine-adenine dinucleotide, which might be abbreviated to PAD if desired. The deaminated form is at present called "desamino-diphosphopyridine nucleotide," but this term gives little idea of its nature, since the part of the molecule which is deaminated (the adenine) is not mentioned in the name. The obvious name for it is nicotinamide-hypoxanthine dinucleotide (NHD). The analogue of TPN in which the phospho- group is attached to the 3′-position instead of the normal 2′-position is at present called "3′-triphosphopyridine nucleotide," a name which surely cannot be taken as indicating only one phosphate group attached to the 3′-position. The new system would give the natural name nicotinamide-adenine dinucleotide 3′-phosphate, perhaps abbreviated to NAD3P. Other analogues should cause no great difficulty. Abbreviations for the analogues are not being officially suggested; these are merely given as personal suggestions to illustrate the great advantages of the NAD system.

Possible objections. It remains to consider whether the names now proposed for the coenzymes are in strict accordance with chemical terminology.

"Nucleotide." Can NMN and FMN strictly be termed nucleotides? If the definition of a nucleotide is restricted to substances that can be obtained from nucleic acids (that is, to purine and pyrimidine nucleotides), they cannot, because of the different bases present. Probably, however, nobody would wish to narrow the definition in this way, and it is much more reasonable to use the term to denote the chemical structure:

base—pentose—phosphate

Clearly NMN qualifies as a nucleotide.

The case of FMN is not so clear, for two reasons. In the first place, it contains not ribose but ribitol, so that the —CHOH— group in position 1 of the ribose is represented by a —CH_2— group in the flavin. However, the term "nucleotide" is also applied to the deoxyribonucleotides, in which the —CHOH— group in position 2 of the ribose is replaced by a —CH_2— group. It is not unreasonable, therefore, to make the term cover both modifications, although the change in the 1-position is the more important, since it prevents ring formation. In actual fact, the flavin compounds have been universally called nucleotides for well over 20 years, and there is no suggestion that their nomenclature should be changed.

In the second place, the term "flavin" includes not only the base but the ribitol as well. Therefore the term "flavin nucleotide" must be understood as referring to a nucleotide containing flavin, rather than a nucleotide "of" flavin in the sense in which NMN is a nucleotide of nicotinamide.

"Dinucleotide." Finally, can NAD and FAD be strictly termed dinucleotides? A purist might hold that the term implies that the two mononucleotides are linked in the same way as the nucleotides in nucleic acid, by a 3′-5′-linked phosphate group. However, it would seem reasonable to consider a compound formed by the simple union of two mononucleotides to be a dinucleotide, particularly since the two classes of dinucleotides differ only in the point of attachment of a single bond.

"Dipeptide" has been cited as an analogy where the term implies a definite point of linkage, but the analogy is not a valid one. A dipeptide is not formed by the union of two monopeptides, and the name is clearly based on different principles. A truer analogy would be "disaccharide," which is used for a compound formed by joining two monosaccharides, without respect to the point of attachment.

Substances of the FAD type have been called dinucleotides ever since their first discovery, and it is the only name available. It has probably appeared far more often in the literature in this sense than in the sense of the 3′-5′-linked compounds, and it would be unreasonable now to restrict its use to the latter type.

Conclusion. Such are the reasons which have led the Enzyme Commission of the International Union of Biochemistry to recommend the use of NAD and NADP. The Biological Chemistry Nomenclature Commission of the International Union of Pure and Applied Chemistry has also decided, after considering the possible alternatives, to recommend these names in place of the existing systems. Preliminary experience has shown that, even by those whose first reaction is to express a preference for the retention of DPN, the new names are very quickly found to be attractive and satisfactory. It is hoped that when they become the official recommendations of both international unions, journals will give a lead in their adoption.

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11 October 1960

Sustained Swimming Speeds of Dolphins

Abstract. Observations of four large groups of dolphins suggest that they are able to swim at a sustained speed of 14 to 18 knots. The blackfish are able to maintain speeds of about 22 knots, and one killer whale seemed able to swim somewhat faster. This implies that the apparent coefficient of surface friction remains approximately constant for dolphins from 6 to 22 ft long, as is the case for rigid bodies.

Since Gray (*1*) called attention to the anomalously high speed of dolphins (or porpoises) in 1936 and presented the case of a dolphin clocked at 33 ft/sec (about 19.7 knots), there have been a number of reports of similar high speeds of swimming. However, very little information on the sustained speeds of which these animals are capable has been published. On the basis of the various assumptions made, the speeds reported indicate a work rate per pound of muscle between 5 and 10 times that measured for terrestrial mammals, including man and the horse. However, data for terrestrial mammals (*2*) show that such mammals, by going into oxygen debt, can sustain work rates up to 100 times the basal metabolic rate for very short periods of time, and there seems to be a good possibility that many of the observations reported were of dolphins doing the equivalent of a 100-yard dash.

The lack of information in the scientific literature on the sustained speed capability of dolphins prompted us to have observations made through the cooperation of the Matson Navigation Company and Alexander Anderson, navigating officer of the S.S. *Monterey*. Printed forms were provided the observers for recording the time and location of observations, the speeds and relative positions of ships and dolphins, and the duration of sightings. Also included were seven sketches of species likely to be encountered on the trip from California to Australia, together with common names and lengths at maturity.

Most of the observations were made in the Southern Hemisphere while the