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THE INTERNATIONAL FEDERATION OF CLINICAL CHEMISTRY (IFCC) AND REFERENCE METHODS

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Abstract—The International Federation of Clinical Chemistry (IFCC) is working in the field of reference methods in clinical chemistry through several Expert Panels of the Committee on Standards. The reference methods concept of IFCC and proposals for definition of terms in the field of clinical chemistry developed by the Expert Panel on Nomenclature and Principles of Quality Control will be discussed in detail. A description will be given of the way in which recommendations are prepared on reference methods and how consensus within the community of clinical chemists is reached. Special examples from the work of the Panels on proteins, bilirubin, enzymes, and quality control, will be given. The cooperation of IFCC with other international scientific organizations and with the World Health Organization is important for the wide acceptance of reference methods. Progress and problems in this field will be reported.

1. INTRODUCTION

The "Standardization of Diagnostic Methods and Materials (WHA 27.62)" resolution passed by the WHO General Assembly in May 1974[1] once more underlined the need for standardization in the field of clinical chemistry. There is no doubt among clinical chemists that it is clinical chemical methods in particular which urgently call for standardization.

This is due primarily to the noncompatibility of the results of clinical chemical analyses.[2] The resulting reexamination cost places a substantial burden on health services. The evaluation of quality control data shows that this lack of compatibility can be traced mainly to insufficient accuracy of the analytical methods employed. By improving accuracy one would also simultaneously increase the diagnostic reliability of examinations. Boutwell and Mather,[3] in a summary statement given at the International Conference on Standardization of Diagnostic Materials held in Atlanta in June 1973, stressed the urgency of a "concerted effort" both at national and international levels. For the field of standardization of clinical chemical methods, it is above all the International Federation of Clinical Chemistry (IFCC) that is called upon.[4] Therefore, the following describes the way in which the IFCC contributes to standardization and its stance with regard to the question of standardizing clinical chemical methods.

2. STRUCTURE AND FUNCTION OF THE IFCC

To explain the nature of the decision-making process within the IFCC, it is necessary to give a brief description of that organization's structure and bodies (see Fig. 1). The standardization functions are performed by the Committee on Standards, which directs and coordinates the work carried out by the Expert Panels. Six Expert Panels are currently at work; two more have been newly established. The exchange of information among the Expert Panels and the national member societies is effected by Associate Members, who are appointed by the national societies.

Within the IFCC, certain mechanisms have been developed to prepare recommendations on the basis of a scientific consensus. This process is aimed at an international recommendation reflecting to the "state-of-the-art," and one which will gain widespread approval among clinical chemists. A recommendation of this kind will also be a prerequisite for adoption at a national level. The targets pursued by the IFCC in the field of standardization are far-reaching and go beyond the standardization proper of analytical methods (Table 1).

3. STANDARDIZATION OF CLINICAL CHEMICAL METHODS

To put it simply, there are two ways of standardizing clinical chemical methods:

3.1 Declaring a customary method to be the standard method, or,

3.2 Standardization on the basis of accuracy.

The first approach is based on the notion that the results of clinical chemical analyses will become comparable when all laboratories use the very same method under a compulsory protocol. Regardless of any errors inherent in the method specified, relatively little effort is needed to achieve conformity. This approach certainly does not correspond to, nor allow for advances in the "state-of-the-art" of clinical chemistry.

The second approach calls for the development of methods that permit analytical results to reflect to the necessary degree the "true value"; i.e. methods of an excellent and known accuracy. The IFCC has decided in favor of the latter mode of standardization.

3.1.1. *Prerequisites for a standardization of methods.* For standardization based on accuracy to be successful, certain requirements, now to be described, must be met.

Methods cannot be described and assessed unambiguously unless one has pertinent criteria. The Expert Panel on Nomenclature and Principles of Quality Control (EP-NPQC) has given this issue its close attention and proposed the criteria listed in Table 2, for the description and assessment of methods.[5] An attempt has been made to define accurately each term.

Starting with these criteria, the Expert Panel EP-NPQC has also tried to define various categories of methods. Such definition would seem to be imperative since at present the most varying terms and expressions coexist without any clear distinction. The basis chosen for the classification of methods was accuracy. This is the only way of achieving objectivity. The Expert Panel EP-NPQC

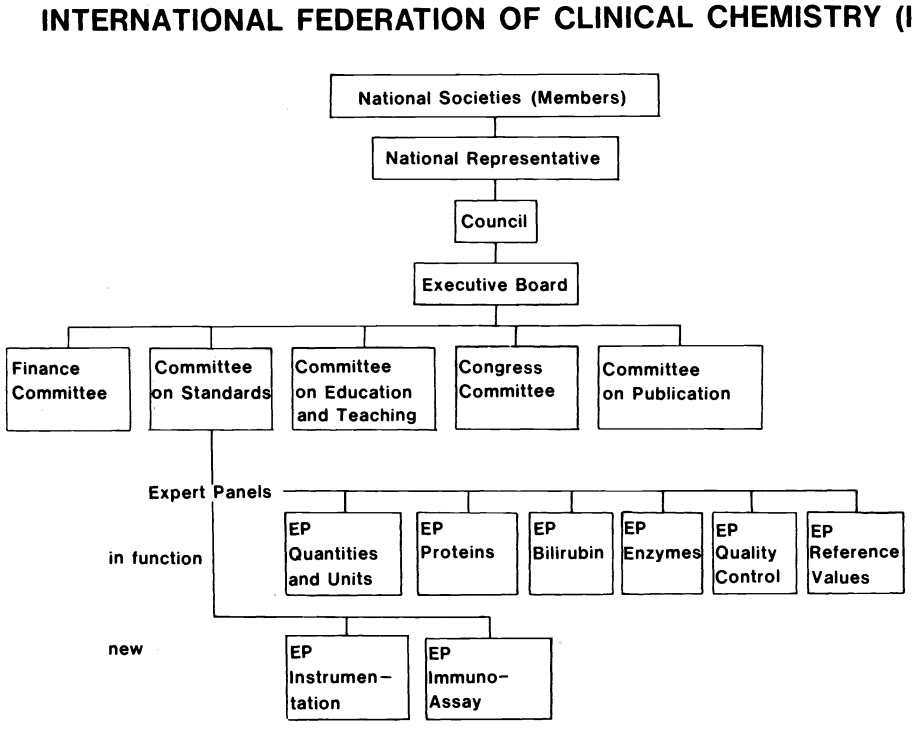

Fig. 1. Structure of the International Federation of Clinical Chemistry.

Table 1. Goals of standardization in clinical chemistry

Methods
Instruments
Quantities and units
Standard (calibration) materials
Quality control
Reference values

Table 2. Criteria for description and assessment of methods

Reliability
Precision
Accuracy and specificity
Sensitivity
Practicability
Speed
Cost
Technical skill requirements
Dependability
Safety

Table 3. IFCC-CS, expert panel on nomenclature and principles of quality control. Proposal for categorizing analytical methods

Term	Concept	Value obtained for calibration or control material
Definitive method	No known source of inaccuracy (inaccuracy = 0)	Definitive value (best known approximation to "true" value)
Reference method	After exhaustive testing: inaccuracy = $0 \pm \delta$; δ negligible (as compared to between-laboratories' imprecision)	Reference value (stated or certified)
Method with known bias	Known bias δ as determined	
Method with undetermined bias	Bias not known	Assigned value (stated or certified)

distinguishes four types according to degree of accuracy (Table 3):[6]

(a) A *definitive method* is one which, after exhaustive investigation, is found to have no known source of inaccuracy or ambiguity. The result obtained is termed the *definitive value* and is the best known approximation to the "true value." An example is the isotope dilution-mass spectrometry method for determining calcium in serum (Cali, Bowers and Young[7]).

(b) A *reference method* is one which after exhaustive investigation has been shown to have negligible inaccuracy in comparison with a definitive method. An example is the determination of calcium in serum by atomic absorption spectroscopy (Cali, Bowers and Young[7]). Since there may be alternative reference methods for the same analyte, the reference to the publication should always be given. The *reference method value* (which may be stated or certified) is that derived from a set of results obtained by a reference method.

(c) A *method with known bias* is one in which the amount of bias has been established (for example, by comparison with a reference method). The result it gives with a standard or control sample is termed an *assigned value* (which may be stated or certified) and its confidence limits should be given. The amount of bias may depend, e.g. on concentration or on the presence of interfering materials. Results are accurate if appropriate corrections are made.

(d) A *method with unknown bias* is one of unknown accuracy, and the results obtained are called *assigned values* (stated or certified).

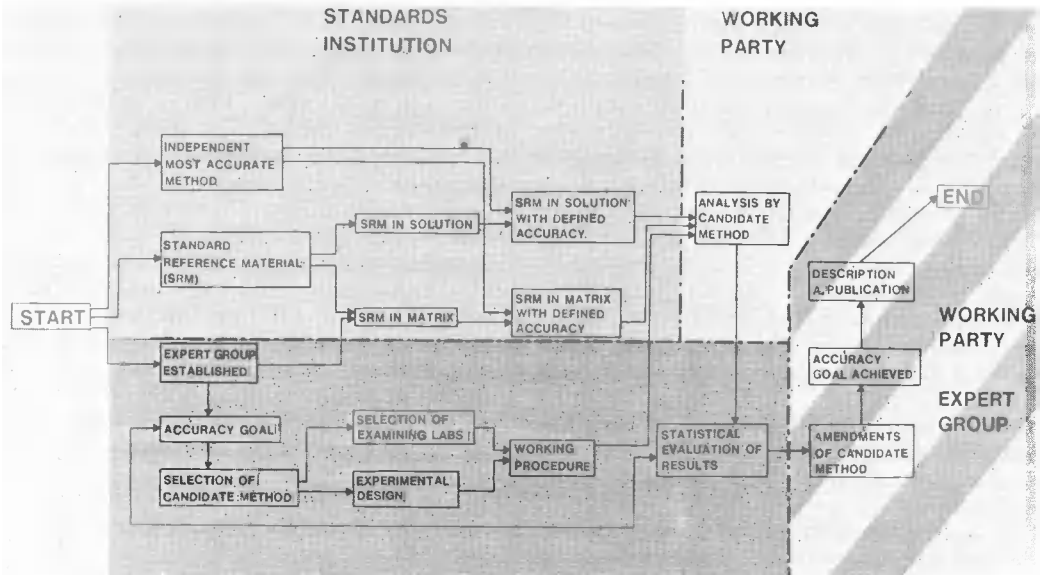

Fig. 2. Development of a reference method by means of the reference materials and methods concept.

The above proposals were accepted as "working definitions" at an Expert Discussion Meeting on Reference Materials and Methods in Clinical Chemistry (Munich 1974).[8]

The definitions given are not universally applicable. For example, the determination of enzymes must be treated as a special case, insofar as catalytic activity is determined rather than the direct measurement of the active centers.

3.1.2 *Goals of the IFCC Committee on Standards.* With reference to the categories of methods described above, the goals of the IFCC Committee on Standards in the field of the standardization of clinical chemical methods can be explained as follows:

The Committee on Standards has as its primary responsibility the assessment and promulgation of recommendations for *reference methods.* The methods recommended should in every respect meet the state-of-the-art. Furthermore, a broad international consensus among clinical chemists must be achieved. The recommendations are then submitted to the WHO as proposals for international reference methods. (In this connection, it should be noted that the reference method definition used by the WHO is a more general one.)†

3.1.3 *Development of reference methods.* The development of reference methods for clinical chemical analysis is at present in its initial stage. In his preceding contribution to this symposium, Cali[10] pointed out the prerequisities and difficulties and reported on the state of the development. Special mention should be made once more of the necessity of developing reference materials together with the methods.

For reference methods to be developed in larger numbers, one needs a rational and efficient technique. As an example, Fig. 2 is a graph of the technique worked out by the US National Bureau of Standards (NBS) under Cali's direction.[11] This procedure can be adopted where a definite method was previously developed. In the case of the NBS' calcium reference method, the procedure shown has been very successful.

3.1.4 *Role of the IFCC committee on standards in the development of reference methods.* The schematic shown in Fig. 2 is a clear indication that the development of a reference method is an extraordinarily expensive process. No single laboratory nor, indeed, any single group or organization can in the long run pay these expenses themselves. Nor is the IFCC in a position to provide the necessary resources. Therefore, the development of reference methods will have to be achieved through close cooperation at an international level.

Because of the structure described at the beginning as well as the great variety of opportunities to gather information at national and international levels, the IFCC is able to play a specific and effective role in the process of developing reference methods. Two different ways are possible:

by gathering and communicating information; for this purpose, a Reference Materials and Methods Office was established at the Committee on Standards.

by preparing recommendations based on an international scientific consensus; the procedure developed from this purpose within the IFCC will be described in more detail below.

3.1.5 *Procedure for the preparation of IFCC recommendations.* Figure 3 is a schematic diagram of the IFCC procedure for the preparation of recommendations.

A draft and the first revision of a recommendation is the responsibility of the Expert Panel. To ensure speedy handling, the size of each Expert Panel is limited to a maximum of six members. When a first draft of a recommendation is submitted, it is sent to the Associate Members with a request for their opinions. Each Associate Member then has that draft discussed in greater detail within their own national societies. At the same time, the draft is also sent to the other Expert Panels as well as to the Committee on Standards for comment. To ensure that the draft is made known to all scientists interested, it is published on the IFCC pages of *Clin. Chim. Acta.*

†WHO Document LAB/75.2:[9] Reference method denotes a clearly and exactly described laboratory procedure which in the opinion of a recognized authority provides sufficiently accurate and precise laboratory data that can be used to assess the validity of other laboratory methods.

Based on the suggestions and comments received, the Expert Panel then prepares a second draft to be passed on to the Committee on Standards and, finally, to the Executive Board. The final decision is taken by vote within the Council of the IFCC. The multi-stage procedure described, with the participation of the national societies, ensures recommendations based on a broad consensus. To reach this goal, it is clearly understood that the treatment will require a substantial period of time, usually several years.

As the first Expert Panel, the EP Enzymes has completed the first part of a "Methods for the Measurements of Catalytic Activity of Enzymes" recommendation.[12] Other recommendations will follow in the near future.

3.1.6 *Application of the IFCC recommended reference methods.* The question is frequently put, "For what applications are the IFCC recommended reference methods intended?"

The comparatively heavy expenses involved in the development and implementation of reference methods would seem to indicate that their use as routine methods is unsuitable in many cases. Rather, the main area of reference method application is:

examination of new routine methods (refer to the detailed notes in the "Assessment of Analytical Methods for Routine Use" Provisional Recommendation prepared by EP-NPQC[6]);
analysis of reference material to be used both in internal and external quality control, usually in the form of matrixed reference materials. (A "Calibration and Control Materials" Provisional Recommendation is being prepared by the EP-NPQC[13].)

3.1.7 *Standardization of methods for routine use.* Recommendations concerning the standardization of methods for routine use cannot be included in the primary functions of the IFCC Committee on Standards, because the use of these methods will depend largely on prevailing local conditions. Workload, equipment, and personnel, etc. of laboratories will have a bearing on the selection of a routine method. The IFCC Committee on standards has the responsibility for recommending reference methods and materials for the examination of those methods, as well as providing advice on how examination should be performed.

In order to be able to select suitable candidate methods from the great variety of methods described, larger-scale use should be made of the "selected methods principle," which was first employed in the United States. Meanwhile, other national societies, among them various European societies, are attempting to proceed in a similar way. The IFCC Committee on Standards might well assist in the sense of coordinating these efforts.

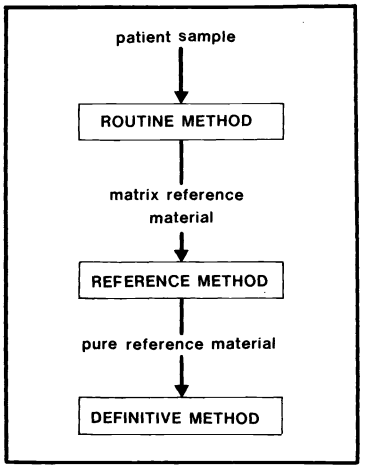

Fig. 4. Tracing back accuracy to definitive methods.

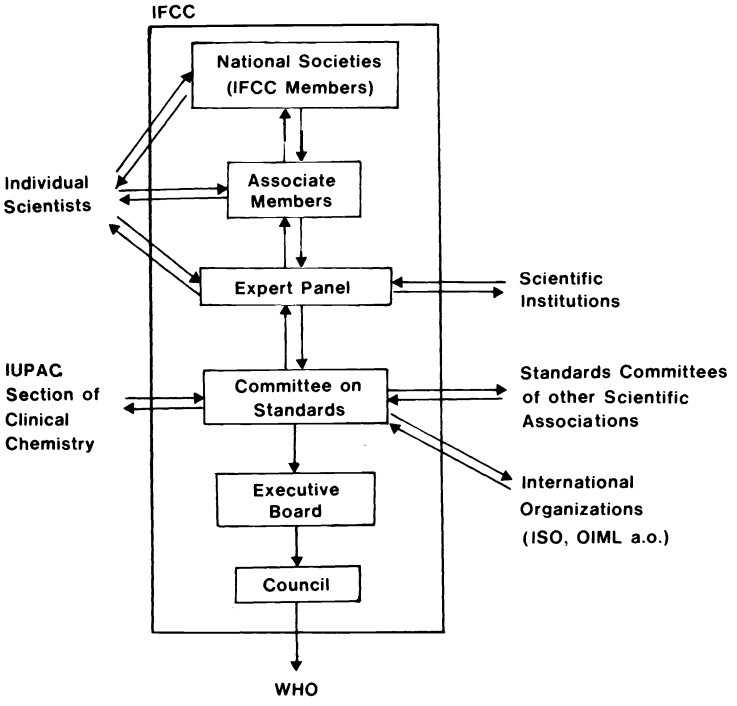

Fig. 3. Procedure for development of recommendations by IFCC.

The goal of these joint efforts should be to use suitable reference materials (matrixed samples) to provide traceability from the routine methods, through the reference methods, finally to the definitive method (Fig. 4).

4. CONCLUSION

It would seem that, in the field of clinical chemistry, the time has come to approach the issue of standardizing analytical methods at an international level. If such standardization is to meet the state-of-the-art, then it will have to be based on accuracy. That road is long and expensive. It can only be mastered through the cooperation of scientists, scientific institutions, and national and international scientific organizations. The International Federation of Clinical Chemistry, through its Committee on Standards, is in a position to contribute both to the coordination of international efforts in this area and to the preparation of recommendations that meet with the broad consensus of the community of clinical chemists.

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