

# Restructuring of International Council for Standardization in Haematology (ICSH) in Asia

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## Abstract

Standardization and harmonization in Laboratory testing are a key issue in the midst of globalization era, because most of laboratory testing has been currently achieved with various kinds of automated systems. In the developed countries, automated systems with highly-regulated principles are commonly used in the routine laboratory. However, there are so many undeveloped and developing countries in Asia that diversity of testing levels can be observed in the area. Some laboratories use glass chamber method for blood cell counting, while other laboratory use semi-automated or fully automated analyzers for complete blood count. International standardization on Hematology is focused on the developed system but not for the developing system. Established standardized documents therefore would not be unsuitable for Asian societies. In the context, International Council for Standardization in Hematology (ICSH) changed its rules to adjust our Asian Societies and ICSH started to restructure the body. International ICSH society is divided into 5 region sub-groups. Asian area is able to possess one new sub-society, ICSH-Asia. Its reconstruction work has been just started with Asian colleagues, and we are now extending the new societies to discuss Asian problems on the quality of hematology testing.

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Scientific principles of standardization were first applied in hematology in 1963 when a small group of hematologists became aware of the confusion which occurred because of the different methods used for measuring hemoglobin and the lack of a universally accepted hemoglobin standard. One blood sample measured in a number of leading laboratories in Europe gave results between 100 and 180 g/l for hemoglobin. This unsatisfactory situation led to the foundation of International Council for Standardization in haematology (ICSH) in 1965 and an Expert Panel in Hemoglobinometry. The panel agreed that the most stable form of hemoglobin was hemiglobincyanide and a solution of this was adopted as a international standard with a defined molecular weight and an extinction coefficient of 11.0. The value of hemoglobin in this preparation was then calculated from the absorbance in a calibrated spectrophotometer.

At regular intervals a batch of the hemoglobin standard is prepared by ICSH for WHO and is available to national health authorities and ICSH committee members and also to manufacturers. Every batch is checked to ensure that it is valid; this checking is undertaken by a

number of leading laboratories in various countries. These laboratories check for contamination by ensuring that there is virtually no absorption at a wave length of 750 nm; maximum absorbance is at 540 nm and the ration of absorbance at 540:504 must be 1.6 +/- 0.1. The concentration of hemoglobin is calculated from the mean results obtained by these experts and this is the value assigned to the batch. After adopting this hemiglobincyanide method, there has been remarkable improvement in hemoglobinometry. In the UK, hemoglobinometry survey showed a remarkable reduction on the coefficient of variance from 7.6% in 1970s to low 1.3 in 1980s. External quality surveillances conducted by Japan Medical Association also show less than 1.3% in the hemoglobinometry in 1990s. This is probably the limit of accuracy with which this test can be performed in routine practice.

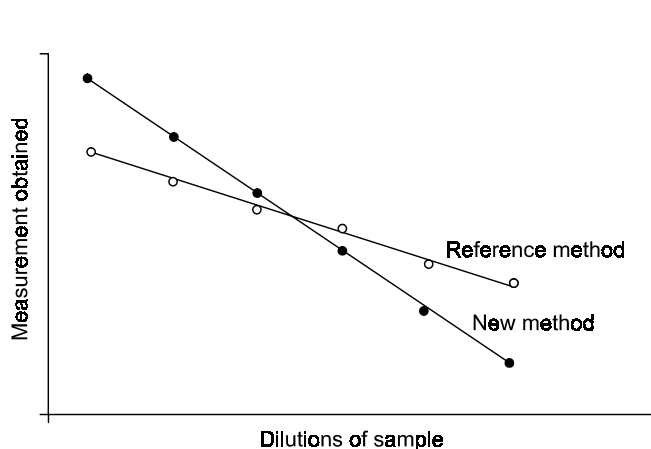
ICSH has a number of Expert Panels covering a wide range of hematological topics: Cytometry, Hemoglobinometry, Vitamin B12 and Folate, Iron, Diagnostic Tests with Radionucleotides, Abnormal Hemoglobins, Red Cell Enzymes, Stain and Staining Methods, Thrombosis and Hemostasis, Differential Leukocyte Counting, Platelet

Function Studies, Leukemia and Lymphoma Subtyping, Blood Rheology, Granulocyte Function, ESR, et al. (Lewis M, 1987). Specific Stain methods for leukemia cell identification, such as Peroxidase Stain Method and Esterase Stain Method were defined by Stain Method Panel chaired by Dr. Shibata A. What is then ICSH?

## 1. What is Standardization?

What exactly is a standard. Let us consider what is the objective of standardization. It is to obtain results for diagnostic tests which prove precision, accuracy, specificity and harmonization of results between different laboratories and also between instruments or methods in the same laboratory. In this context, standards may be materials or they may be standardized methods. When a standard is used to control accuracy of a cell counting system or any other test system, it is essential to ensure lineality of response. It is well known that some photoelectric colorimeters show lineality over a narrow range. One might be misled if the standard is defined at a point on the scale where, by chance, the reference method and a new method coincide (Figure 1). An example of this problem is illustrated in an evaluation of a new system for hemoglobinometry where the lineality of response was excellent at normal levels, but began to fail at higher reading of hemoglobin concentration (Figure 2). This indicates the need to have a range of standards at low and high values as well as at the intermediate level.

Material standards and method standards are equally important to achieve reliable laboratory measurement. Only by paying meticulous attention to technical detail is it possible to get reproducible results between laboratories. How often have we failed to repeat a procedure described in a published paper because the original author has left out some small but important aspect of the technique. This sort of problem occurred when an experimental process required the same to be heated to 50°C for exactly for 30minutes, but when the reagents



**Figure 1.** Comparison of new method and reference method illustrating major failure of harmonization except at one point.

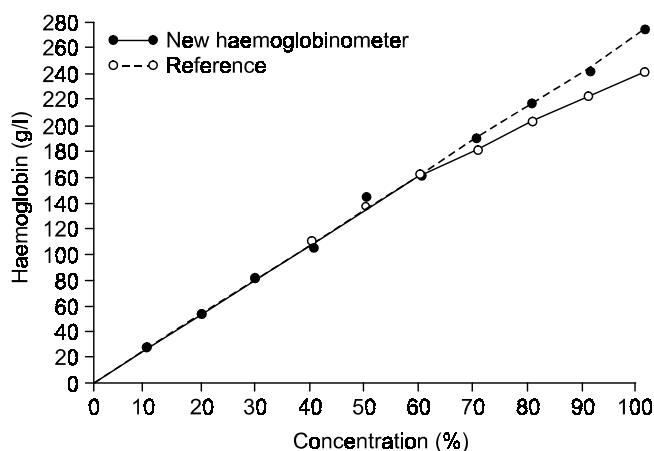
were put into plastic instead of in glass tubes it took a considerable proportion of that time for the reacting low temperature. Conversely cuvettes made of various plastic materials will take different time for reacting mixtures contained in the cuvettes to reach a required low temperature for measuring a kinetic reaction in a spectrophotometer [1].

Likewise, all of fundamental laboratory tests should be standardized to get internationally harmonized results.

## 2. Mission of ICSH

The purpose of ICSH is organized to promote the development of international standards needed to achieve international comparability of results of hematology analysis. Standards are related to specifications for biologic and chemical reagents for reference preparations, to reference methods, or reference procedures, to systems of nomenclature and classification, and to operating methods, controls and calibrators, for equipment and test procedures, and other related matters. The effort should result in harmonizing hematological data throughout the world.

The work of ICSH is based on international consensus. This ensures that all interested persons and organization take part in the decision making as both the profession and manufacturers are most likely to adopt procedures with which they agree. ICSH is controlled democratically by its Assembly. Each country in which there is a society of hematology or a national standardization committee for hematology or clinical pathology has the right to nominate a representative to the assembly. The assembly meets usually at international hematology congresses; the assembly appoints the Board and the board is responsible for the organization of expert panels. When a particular subject has been decided on, the members of the particular subject has been decided on, the members of the expert panel will undertake experimental work in their own laboratories,



**Figure 2.** Comparison of new haemoglobinometer and reference method. The new instrument compares well in the normal range but not at high values.

will take account of the view of manufacturers and will undertake critical review of previous work by others. This study will lead to the preparation of a document which is then reviewed by international contacts including WHO, International Standards Organization (ISO), NCCLS (National Committee for Clinical Standard Laboratory Standard), CEN (The Center for European Standards), International Society of Hematology (ISH), International Federation of Clinical Chemistry (IFCC), and other distinguished international authorities. In due course these consultations reach and an ICSH tentative standard is published. If this is approved by the assembly it is then promulgated as an ICSH standard, and in collaboration with WHO it may be adopted as an international biological standards [1,2].

### 3. Why Do We Need to Re-structure the ICSH?

Over 300 documents of ICSH standards have been released in the past 30 years and the standard have been effectively used internationally: e.g. Romanovsky staining. The staining has been used for the past 90 years virtually unchanged since the early years of the 20 century, until recently, when ICSH began to consider the problem why is it that the various stains differ in their staining intensity? Why does one batch of a stain suddenly give a different staining reaction to other batches of the same stain? What is the significance of the stain reactions of different cells? These problems were solved when the Expert Panel identified the specific chemical reactions between tissue and dye, and identified the factors which cause staining variation. It was found that only 2 components are required to produce the Romanovsky effect, namely Azure B and Eosin. However, the commercially available dyes are contaminated with a number of other dyes and metal salts. Studies by chromatography demonstrated that any one stain is likely to have as many as 10 different dyes in variable proportions- no wonder why text book illustrations are often quite different to what one sees under the microscope. ICSH has now published a reference method and has established a protocol for the specifications of manufactured stain to ensure their purity and consistency [3].

The most accurate and precise techniques serve no purpose without reliable collection of the blood specimen and maintenance of the stability of its composition until the analysis is undertaken. Recommendations on this were settled by cooperation between ISH and ICSH in 2001, and the document was publicized on International J of Hematology of the 2002 issues [4].

Needs of standardization will be understood from the above description, but why do we need to restructure ICSH? Recently almost all laboratory tests have been processed with automated analyzers, and data obtained by the analyzers show high accuracy and precision because of adoption of built-in type automated QC management systems. The testing system is familiar to people who are working in the modern laboratories. The high quality of hematology testing would be maintained

by contribution of ICSH, but the advantages of such standardization work are utilized just in advanced countries. Some of examples are described as follows for standardization needs in Asia:

#### 3.1. Case 1: *Thalassemia in Japan*

Many of patients with low MCV have been treated as iron deficiency anemia (IDA) in Japan because over 90 % of the low MCV patients are IDA in Japan. Doctors have less knowledge and less experience on thalassemia diagnosis. They think that low MCV anemia equals IDA, and they do not try to look for real causes of anemias. Incidence of thalassemia is low about 3-5/10<sup>6</sup> population in Japan, and most doctors do not suspect any thalassemia to the anemic condition although thalassemias are so common in the southeast Asia. This case indicates necessity of some standardized expert systems to diagnose thalassemias.

#### 3.2. Case 2: *Malaria in Japan*

Many people travel internationally in the midst of the current globalization era. Booming of the visit-to-foreign countries make patients with variety of imported infectious diseases increase. One of the problems is malaria. Many of Japanese youth get malaria infection when they visit Southeast Asian, and the disease is imported into Japan. The patients visit a hospital suffering from high fever. Japanese doctors sometimes misdiagnosed the disease because of no experience and no chance of malaria cases. According to Infection News released from the Ministry of Health and Welfare, 80 to 125 patients were found in the past 10 years. This case teaches us needs of education on malaria prevention.

#### 3.3. Case 3: *Thrombocytopenia in China*

A Chino-Japanese cooperative study was conducted in 2000 for getting hematological normal reference values in Chinese population using an automated hematology analyzer. They visited 3 places in China and summarized their data. One of rural town showed low platelet counts. The research group concluded that the people living there have racially low platelet count, and assumed that the habit of food intake might cause the count decrease. They visited the site next year, but the values were similar to those obtained the other sites. Then its conclusion was changed that the count would show some seasonal changes, although we cannot judge whether their conclusion was correct or not. This case would be a calibration and control issue for cell counting.

What ICSH is aiming at is good laboratory practice., which includes not only standardized test method but also normal reference value setting, instrumental calibration/control, laboratory management, staff education etc. Medical laboratories should be managed totally. To do good practice requires the use of selected equipment and selected methods to ensure efficient, effective and

economical laboratory tests. Total area of Asia is bigger than that of North America and Europe. Asia has 60% of total population on the earth. Some countries are rich, but others are poor. Less than 5% of Asian people can receive modern medical care, but 95% of them cannot get any sophisticated medical treatment. Some people are suffering from starvation, poverty and illiteracy. A diversity of medical system exists in the area. Medical testing also varies greatly in the area from high to low. To compare disease types and treatment methods internationally, however, we do need to get standardized harmonized test results under unequal testing conditions. European and American standards prepared for modern laboratory testing would be powerless and less effective. Disease types are different from those in western countries. All of such background should be taken into account for evaluating laboratory data. In other words, Asia should have its own standards, reflecting such diversity. In the context, ICSH assembly agreed to reform the ICSH organization to regionalize into 5 parts in the world in 2002. Following this decision, Asian colleagues started to form a sub-organization in Asia, ICSH Asia.

#### **4. Standardization and Harmonization Activities in Asia**

Laboratory services must be justified by availability of technology, equipment, capability of laboratory workers, practical relevance of the procedures, and ability to function within defined cost limits and assurance that laboratory is a safe place to work. Recent advances in laboratory hematology have been implemented in daily practice in many laboratories in all countries of Asia, although laboratory classes and data levels would differ in laboratory. The differences should give some difficulties to compare clinical data among Asian countries. Thus the state of the art of laboratory practice must be timely analyzed and problems relating the practice and safety of laboratory testing. Thus, we are organizing our ICSH-Asia with the following scope:

1. to review the status of laboratory practice in hematology in the countries of Asia,
2. to address questions related to the state of the art of quality control and assurance in hematology,
3. to develop guidelines for good laboratory practice in hematology,
4. to define quality of reference and quality control materials for standardization in hematology,
5. to stimulate international relationship/activities related to laboratory testing.

Good planning and management is required for organizing a new system. In the first, we had a preparatory meeting at the 5th Asian Conference of Clinical Pathology in Kochi on 13-14th Nov. 1998. The 1st Colloquium for Standardization in Laboratory Medicine was held on 19-20th Feb. 1999 in Jakarta Indonesia under the cooperative support of Japan Society of Promotion of Sciences and University of Indonesia. To the meeting we could have c. 150 participants from 7 Asian

countries. The Asian Network for Clinical Laboratory Standardization (ANCLS) was settled and Prof. Dr. Malamba T. Jr. of Philippine was elected as the 1st president of the society. We adopted there to discuss to organize ICSH-Asia, and Prof. Dr. Bunjaratvey A was designated as its chief organizer. Its proceeding was published as a special issue of *Southeastern J. of Tropical Medicine and Public Health* (Vol. 30, Suppl. 3, 1999). In 2001, its 2nd Meeting was held on 20-21st Oct. 2000 in Kobe under the support of Nakatani Foundation (President: Prof. Dr. Miwa S) and its proceeding was published as a *ICMR (The International Center for Medical Researches) Annals of Kobe University* (Vol. 20). In the meeting we decided to conduct an international external quality surveillance in Asia (AQuAS; Asian Quality Assurance Survey), and Prof. Dr. Lee NK of Korea University was designated as the chief conductor of the surveillance. The 3rd meeting was held in Singapore (President: Prof. Dr. Lee SH) on 16-17th Nov. 2001 under the cooperative support of National University of Singapore and Japan Society of Promotion of Sciences. Its proceeding will be published in the *Southeastern J. of Tropical Medicine and Public Health* in 2002. And The 4th Meeting will be held in Korea in Oct. 2002 by the hand of Prof. Dr. Lee KN of Korea University.

Each country has their External Quality Assurance Programs. Most of them are supported by governmental or semi-governmental bodies, and they examine over 30 items on chemistry and hematology tests, although resulting variation is influenced by their geometrical, economical, social and medical background. According to Dr. Lee's report [4,5], they performed the AQuAS with 7 countries. Twenty hospitals were chosen and chemistry and hematology materials were distributed 5 times by air. The results will be reported in the Seoul Congress of The International Society of Hematology.

Another action on standardization and harmonization in hematology is to organize national bodies of laboratory hematology from the seeds of ICSH-Asia. Thailand organized Thai Society for Quality Control for Laboratory Hematology in 1999, Japan founded Japan Society of Laboratory Hematology (JSLH) in 2000, and Korea founded Korean Society of Laboratory Hematology (KSLH) in 2002. Those societies were composed by doctors, medical technologists, and manufacturer scientists. They may be said to be more practical rather than academic.

On the basis of such activities, organizing movement of ICSH-Asia would be steadily stepping up year by year. And one unity will be founded in a couple of years with Asian colleagues.

#### **5. Conclusion**

The work of ICSH is never ending; every standardized method and all material standards must be continually critically evaluated by the appropriate expert panel; if necessary recommendations must be added to or amended; New Techniques for preparation and

checking of standards must be used as soon as they become available. Asian standards must be harmonized with ICSH international standards as possible as they can do. By this approach of dynamic standardization ICSH is able to make major contributions to the practice of hematology worldwide.

In order to reach our objectives, however, we will also require more assistance at governmental and industrial levels.

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