quantity in human or animal biological fluids.

Nevertheless, manufacturers use these materials for calibration of their "master calibrator lot", but the uncertainty budget (GUM) of the values assigned to these WHO reference materials is unknown. Assuming that these uncertainty budgets become known in the future, that uncertainty should then be further propagated through the calibration hierarchy down to the results reported for a patient's sample (3).

The second analytical issue is the question of whether the available and used reference materials for category A and category B are commutable with the quantity (quantities) in the biological fluids? This question merits attention because the validity of calibration and other measurement exercises depends on it. However, this aspect is hardly ever addressed, for example, in WHO documents.

The biased results of measurements of category B quantities and the issue of commutability for category A as well as for category B analytes have important impacts on the uncertainty of measurement results.

The third issue relates to clinical decision-making: what is the effect on clinicians and the clinical decision process of reporting a measurement result for a patient's sample with the uncertainty budget calculated according to, e.g., GUM? Will clinicians understand it? Will it improve their efficacy and efficiency? GUM was elaborated by representatives of a host of international organizations; it is meant to be applicable to all scientific measurements, be they physical or chemical. The concept of uncertainty of measurement in laboratory medicine was incorporated in the "traceability" document (3), and it plays a role in the obtaining of accreditation by medical laboratories (5, 6). It then is important to ask whether medical associations in, for example, the US, Europe, and Japan have been consulted on this matter? If so, what are the problems perceived by our medical colleagues? As far as I am aware, to date no such attempt has been made. If that is true, are not laboratorians merely satisfying analytical and metrologic requirements? Should we not defer reporting the uncertainty of measurements of patients' samples until it is accepted clinically as useful and beneficial to patient care?

References

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Genetic Effects on Serum Concentrations of Serum Amyloid A Protein

To the Editor:

MacGregor et al. (1) reported a twin-study of the genetic contribution to baseline serum concentrations of two acute-phase proteins, C-reactive protein and serum amyloid A protein (SAA). In their discussion, they stated that no studies had been reported of associations between particular isoforms and different baseline values of SAA. Although twins were not used as subjects, we earlier reported genetic effects on SAA serum concentrations.

Acute-phase SAA is divided into two major isotypes, SAA1 and SAA2, which are coded at different loci. The dominant isotype, SAA1, consists of six allelic variants (SAA1.1 to SAA1.6) (2). In the Japanese population, three major alleles, SAA1.1 (52Val, 57Ala), SAA1.3 (52Ala, 57Val), and SAA1.5 (52Ala, 57Val), which differ from each other in SAA1 exon 3 structure, appear with approximately equal frequencies (0.30–0.35). Among 280 healthy Japanese (3), the mean serum SAA concentrations in SAA1.1 homozygotes, SAA1.5 heterozygotes, and non-SAA1.5 carriers were 5.7, 4.1, and 2.2 mg/L, respectively (analyzed after logarithmic conversion of the raw data). The mean SAA concentration (SD range) was 4.5 (2.6–7.8) mg/L in SAA1.5 carriers, whereas that in noncarriers was 2.2 (1.4–3.6) mg/L (P < 0.001). The SAA/C-reactive protein ratio was significantly higher in SAA1.5 carriers than in noncarriers in Japanese patients with rheumatoid arthritis (4). More recently we reported that human recombinant SAA1.5 protein is cleared from the circulation more slowly than other isoforms in mice (5). Differences in plasma clearance may therefore be one of the possible factors responsible for such genetic effects.

The differences in SAA isoforms are not likely to be attributable to a method effect of the analytical method because we used an assay (6) that has been confirmed by polyacrylamide gel electrophoresis analysis (7).

SAA1 allele frequencies in the United Kingdom have been reported to be 0.76, 0.19, and 0.05 for SAA1.1, SAA1.5 (originally considered as SAA1.2), and SAA1.3, respectively (8). It is predicted that ~35% of the English population (individuals homozygous and heterozygous for SAA1.5) have a tendency to have higher SAA serum concentrations.

As MacGregor et al. (1) noted, SAA may have some role in atherogenesis. We are also interested to
learn whether the genetic effects causing the differences in serum SAA concentrations have any associations with atherogenic diseases.

References

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