acetaminophen, salicylamide, isoniazid, etc., is not surprising, in view of the effect we reported at what we judged to be usual concentrations, and the clinician must surely be wary of these.

Since the first reports concerning such substances in patients, there has been a concentrated effort at YSI to understand the mechanism of interference and to deal with it. Two approaches—(a) a means for determining in vitro that such a substance is present in the specimen and (b) a means for removing it prior to assay for glucose—have been found feasible but judged impracticable in the clinical situation for reasons of the cost and time required. Meanwhile, we have made promising advances toward immobilized-enzyme membranes that diminish the effects of such interfering substances to innocuous levels. This work is still incomplete, but there is reason to hope that such membranes will be available during this calendar year.

References


Henry E. Sostman
Vice President, Product Integrity
Yellow Springs Instrument Co., Inc.
Yellow Springs, OH 45387

Estimating Biological Variation In Diagnostic Tests

To the Editor:

In any reference population, the variation in results about the reference median is due to analytical and biological variation (1-6). Analytical variation is routinely estimated as the coefficient of variation (CV)A of stable quality-control material (3). Biological variation has been estimated by complicated statistical techniques (4) but is ignored in routine practice for lack of a convenient estimate. Glick described random analytical variation as a percentage of the reference range (6). We suggest a similar treatment as a convenient description of biological variation.

From (CV)A we can obtain (SD)A, the standard deviation of random analytical variation at the reference median:

\[(SD)_A = \frac{(CV)_A \cdot \text{reference median}}{100}\]

In a symmetrical reference range, the difference between the actual 95% reference range and (4(SD)A) would be an estimate of biological variation. But because reference ranges are not necessarily symmetrical, and because results have different interpretations on either side of the reference median, the estimate of biological variation should be specific for results that are above or below the reference median. We suggest as a specific estimate of biological variation, the difference, \[|\text{reference limit} - \text{reference median}| - 2(\text{SD})_A\], where | | indicates absolute value.

The accuracy of this difference as an estimate of biological variation depends on the accuracy of limit and median reference results. Both parameters vary with method, technique, and population. It has been recommended that the 95% reference limits be set at the 2.5th and 97.5th percentiles of a reference population made up of at least 120 subjects (7).

It would be convenient to know, for any given test, what percentage of total variation is biological variation (% BV). We suggest that this term can be estimated as the percentage of the range between the reference median and reference limit that is occupied by our expression for biological variation:

\[
%BV = \left(\frac{100 \cdot (\text{reference limit} - \text{reference median}) - 2(\text{SD})_A}{\text{reference limit} - \text{reference median}}\right)
\]

where reference limit refers to either the 2.5th or 97.5th reference percentile. The term %BV is convenient to calculate, offers a quantitative estimate of biological variation, and is comparable among different tests irrespective of the magnitude of the result or the units of measurement.

The smaller %BV, the better is our ability to detect a change in an individual's test relative to the reference range. Just as methods have been proposed to determine acceptable limits of analytical variation (8, 9), so also should we begin to establish such criteria for biological variation. Unacceptable levels of biological variation would indicate that the reference population should be subdivided according to one or more of the factors that determine biological variation, such as sex, race, age, diet, or time of sampling (2). We suggest that use of %BV may be helpful in establishing uniform limits of acceptable biological variation.

References


Douglas Dix
Patricia Cohen
Samad Barzegar
Dept. of Biol. and Health Sciences
Univ. of Hartford
West Hartford, CT 06117

Interference of “Intralipid” with Measurement of Total Serum Proteins in the Du Pont aca is Removed by Trichlorofluoromethane

To the Editor:

We recently observed that determination of total protein (7) in some sera with the Du Pont aca gave concentrations equal to, or even lower than, the albumin concentrations. Control measurements of total protein both by multichannel clinical analyzer (Technicon SMA 12/60) (2) and the manually performed biuret reaction (3) gave normal ratios for total protein/albumin. Albumin is measured by the bromcresol green method in both the SMA and the aca; a modification of the biuret method is used in estimating total protein in the aca.

The sera with unusually low total protein/albumin ratios were all from critically ill patients who were receiving