External Quality-Control Survey of Cholesterol Analyses Performed by 12 Lipid Research Clinics

Kenneth Lippel,1 Susan Ahmed,2 John J. Albers,3 Paul Bachorik,4 Richard Muesing,5 and Carole Winn6

We report accuracy and precision achieved in the automated analysis for cholesterol in a long-term multilaboratory study, presenting and evaluating the significance of data accumulated by 12 Lipid Research Clinics (LRC's) in the analysis of 18 unknown surveillance pools during three years. The average bias for all pools and for 13 AutoAnalyzer II (Technicon Instruments Corp., Tarrytown, N.Y. 10591) instruments in the 12 clinics was −0.41% (range −1.2 to +0.3%), as compared to values established by reference methodology. The regression equation relating observed cholesterol values (y) to reference values (x) was: y = 0.035 + 0.977x. The bias varied from pool to pool (−2.3 to +5.3%), positive biases being observed for pools with cholesterol concentrations <1.4 g/liter, and negative biases for those pools with higher concentrations. Total standard deviations ranged between 25 and 75 mg/liter, and total CV's for most individual instruments were between 1 and 3%. Of the variability for a particular pool, <20% was due to differences among instruments, and within- and between-run variabilities were approximately equal. These trends were the same as those previously observed [Clin. Chem. 23, 1744 (1977)] in the analysis of bench control pools of known cholesterol concentration.

Additional Keyphrases: interlaboratory performance · continuous-flow analysis · variation, source of

Results of automated analyses performed by 12 Lipid Research Clinics (LRC) laboratories on bench control pools of known cholesterol concentration have been described previously (1). Here, we report the results of blind analyses for cholesterol, performed on external surveillance pools with cholesterol concentrations ranging from 0.59 to 3.49 g/liter.

Materials and Methods

The preparation of primary standards, bench control pools, and calibration pools, and the procedures used by the LRC laboratories for cholesterol analysis and for the calibration of the continuous-flow analyzer (AutoAnalyzer II) have all been described previously (1, 2). Reference cholesterol concentrations were determined by the method of Abell et al. (3) at the Center for Disease Control (CDC), Atlanta, Ga.

Preparation and Labeling of Surveillance Pools

The CDC prepared surveillance pools, tested them for homogeneity, labeled them with target values, and monitored them for stability (4). The target values for these pools were established by replicate analyses by the method of Abell et al. (3). Six vials from each pool were analyzed in duplicate in a run. A total of 72 to 180 analyses was done on samples from each pool in six to 15 runs, to minimize cycling effects. Each run included samples from both a high- and a low-concentration bench control pool with mean values established previously by replicate analyses according to the method of Abell et al. (3). If the mean value of either the high- or low-concentration pool exceeded three standard deviations—for the high pool, 2.58 ± 0.05 g/liter; for the low pool, 1.58 ± 0.04 g/liter—then the run was declared "out-of-control" and rejected. The target value for each surveillance pool was the mean of values from all runs that were "in-control."

The CDC documented the stability of the target values for the surveillance pools by analyzing duplicate samples of each pool in at least 16 different analytical runs, according to the method of Abell et al. (3), and then comparing means of these results to the original mean. The first set of pools (B, D, E, G, H, J, L, M, and Q) was analyzed at CDC from October 1973 to January 1975 and the second set of pools (A, C, F, I, K, N, O, P, and R) from January 1975 to March 1976. During the two time periods the clinics were also analyzing samples from the different sets of pools. The coefficient of variation (CV) averaged 2.2% (1.5 to 2.5%); the average deviation from the target values was 34 mg/liter (+10 to +60 mg/liter), and the average per cent deviation from the target values was +1.5% (0.4 to 2.2%) for the sets of pools analyzed during the first time period.

1 National Institutes of Health, National Heart, Lung, and Blood Institute, Lipid Metabolism Branch, Federal Building, Room 308, Bethesda, Md. 20014. (To whom requests for reprints should be addressed.)
2 Georgetown University Medical School, Washington, D.C. 20007.
3 University of Washington, Seattle, Wash. 98104.
4 Johns Hopkins University, Baltimore, Md. 21205.
6 Center for Disease Control (CDC), Atlanta, Ga. 30333.

Other members of the Laboratory Methods Committee who participated in this survey included: Herman Arnett, M. T., Washington University, St. Louis, Mo.; Harris Reeder, Ph.D., Baylor College of Medicine, Houston, Tex.; Carl Breckenridge, Ph.D., University of Toronto, Toronto, Canada; Mary E. Dempsey, Ph.D., University of Minnesota, Minneapolis, Minn.; Gerald Hillerman, B.S., MT(ASCP), Oklahoma Medical Research Foundation, Oklahoma City, Okla.; Lillian Karlson, Stanford University, Stanford, Calif; Gerald Kessler, Ph.D., Washington University, St. Louis, Mo.; Kanta Kubo, M.S., University of Minnesota, Minneapolis, Minn.; Byron Kuchuk, Ph.D., Center for Disease Control, Atlanta, Ga.; Mauro Nave, M.S., Baylor College of Medicine, Houston, Tex.; Donald Puppione, Ph.D., University of California, San Diego, Calif.; Louis Smith, Ph.D., Baylor College of Medicine, Houston, Tex.; Paula Steiner, B.A., University of Cincinnati, Cincinnati, Ohio; Charles Stewart, Ph.D., Center for Disease Control, Atlanta, Ga.; John Turner, M.D., University of California, San Diego, Calif.; Russell Warnick, M.S., University of Washington, Seattle, Wash.; Stuart Weidman, Ph.D., Washington University, St. Louis, Mo.; Donald Wiebe, Ph.D., University of Iowa, Iowa City, Iowa; and Peter Wood, Ph.D., D.Sc., Stanford University, Stanford, Calif.

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period. The bench control pools analyzed in this time period averaged about 1% high, as compared to the established values. For the second time period, the CV averaged 1.7% (1.2 to 3.3%), the average deviation was -6.7 mg/liter (-20 to +10 mg/liter) and the average per cent deviation was 0.5% (0 to 1.4%). The quality control pools did not indicate any bias for this time period. There was no significant difference between the means used to establish the target values and the means determined from the monitoring runs.

**Standardization of Lipid Determinations**

Before becoming operational, each LRC laboratory met the requirements of a lipid standardization program (1, 2), which consisted of three phases: Phase I, an initial evaluation; Phase II, a standardization phase involving a more intensive evaluation of the laboratory’s performance; and Phase III, the ongoing surveillance phase.

The concentrations of external surveillance pools analyzed during Phases II and III were not known by the laboratories. During Phase III two bench control pools were analyzed in quadruplicate in each analytical run and six surveillance samples were analyzed in one run each week for four weeks of the month. Laboratories meeting the criteria for accuracy and precision were redesignated annually as “standardized” (1, 2). All 13 LRC instruments remained standardized during the first three years of Phase III external surveillance reported here.

**Analyses of Surveillance Pools**

Each month’s set of 24 samples came from three different pools, eight samples per pool. Nine different pools with cholesterol concentrations ranging from 0.59 to 3.49 g/liter were analyzed during each surveillance year. The nine pools used during the first year of surveillance were labeled B, D, E, G, H, J, L, M, Q; the second-year pools were A, C, E, G, I, J, K, N, R; the third-year pools were A, C, F, I, K, N, O, P, R. Thus, pools B, D, H, L, M, and Q were used only in year 1, pools E, G, and J were used in years 1 and 2; pools A, C, J, K, N, and R were used in years 2 and 3; pools F, O, and P were used only in year 3. The results presented here are based on surveillance data from all runs in all laboratories except for data from “out of control” runs and data from eight additional samples which were considered to be outliers.

**Results**

The data presented were evaluated in terms of accuracy (agreement with the reference method target value), precision (reproducibility), and comparability (agreement among laboratories).

**Accuracy**

Analytical accuracy depends on three systematic factors: type of instrument, instrument variation, and serum pool bias. The accuracy achieved in the surveillance program was evaluated in these terms.

**Individual instrument bias.** Bias estimates and their standard errors for each instrument and pool combination are compiled in Table 1. The per cent bias averaged over pools for each instrument is summarized in the last column of the table. The overall average instrument per cent bias was -0.41%. Some bias trends were observed for individual instruments. For pools with concentrations <2.9 g/liter, instruments 2, 5, and 10 showed biases higher than the average. Instruments 3, 8, 9, and 12 showed biases relatively lower than average. Averaged over all pools, however, the individual instrument average per cent bias range was relatively narrow: -1.2% (instrument 9) to +0.3% (instrument 2). The variation in bias observed among the 13 instruments is illustrated in Figure 1.

**Systematic type of instrument bias.** Table 1 summarizes the systematic biases exhibited by the AutoAnalyzer II instruments for each of the surveillance pools. The overall bias as well as the biases observed on individual instruments are plotted in Figure 1 as a function of the cholesterol concentration of the individual pools, as determined by the method of Abell et al. (3).

The bias appears to be concentration-dependent. Positive biases were observed for pools A and B, which had cholesterol concentrations of 0.59 g/liter and 1.34 g/liter, respectively. Negative biases were observed for all other pools, whose cholesterol concentrations ranged from 1.46 to 3.49 g/liter. The largest negative biases were observed for the pools with the highest concentrations of cholesterol (i.e., >2.9 g/liter). The average bias over all pools and all instruments was 0.41% below reference values.

The 10 334 cholesterol concentration data points from 13 instruments and 18 pools were used to estimate the coefficients of the best-fitting regression line relating observed cholesterol values (y) to reference values (x). The resulting regression equation was: \( y = 0.035 + 0.977x \). Based on the estimated line, the bias decreased from +34 mg/liter at a concentration of 0.50 g/liter, to +1 mg/liter at a concentration of 1.50 g/liter, and continued to decrease to -45 mg/liter at 3.50 g/liter.

**Serum pool bias.** Pool bias is defined as the difference between the cholesterol value for a particular serum pool as measured by the AutoAnalyzer II in the LRC laboratory, and the target value for that pool, as determined at CDC by the method of Abell et al. (3). Some variability both with respect to the magnitude of the bias and the agreement among instruments was observed for the different pools on the various AutoAnalyzer II instruments. The downward trend of the bias as a function of concentration, which was noted previously, was probably not pool-related. There were differences among pools at very similar concentrations, however. For example, as shown in Figure 1, the overall bias of pools L and M (concentrations = 2.87 and 2.91 g/liter) was much less than that of pools N and O (concentrations = 2.96 g/liter), and the bias of pool Q (concentration = 3.23 g/liter) was much greater than that of pool R (concentration = 3.49 g/liter). The agreement among instruments also varied considerably from pool to pool; for example, pools I, K, and O showed very good agreement among instruments, whereas values obtained for pool M were more variable.

**Precision**

Table 2 gives nested analysis of variance components (5) based upon pooled data from all AutoAnalyzer II instruments. Separate analyses were performed for each pool. Each standard deviation is the square root of the corresponding variance component. The “df” column refers to the degrees of freedom for each source of variation, as would be found in an ANOVA table. A large “df” indicates high statistical precision of the estimates of the standard deviations. The “Components %” column indicates the relative magnitudes of the among-instruments, between-run and within-run variance components. The “Components %” is computed as 100 \( \times (\text{V.C.} / \text{T.V.C.}) \), where V.C. is the among-instruments, between-run, or within-run variance component, and T.V.C. is the “total” variance component.

**Total variability.** The overall total standard deviation listed in Table 2 is the square root of the sum of the among-instruments, between-run, and within-run variance components and is an estimate of the standard deviation of a single determination of a sample from the specified pool. The overall total
standard deviation ranged from 32 mg/liter (pool A) to 74 mg/liter (pool Q). The standard deviation generally increased with concentration.

For the individual instrument analyses, the total standard deviation is the square root of the sum of the between- and within-run variance components for that instrument and is an estimate of the standard deviation of a single determination of a sample from the specified pool for the specified instrument. The individual instrument total standard deviations ranged from 18 mg/liter (instrument 6, pool A) to 0.123 g/liter (instrument 1, pool Q).

Using the individual instrument-pool total standard deviation, we derived a linear regression equation to estimate the coefficients of the best-fitting line relating standard deviation to the reference method cholesterol concentration. The best-fitting line was: standard deviation = 0.022 + 0.010 (reference method cholesterol concentration), i.e., the standard deviation at any concentration was 1% of the concentration + 22 mg/liter. The total CV—which is a measure of relative variability, i.e., variability relative to the reference method cholesterol concentration—is defined as: \( CV = \frac{\text{total standard deviation/target value}}{100\%} \times 100\% \). The instrument-pool CV's, plotted in Figure 2, averaged about 2% at cholesterol concentrations ranging from 2.0 to 3.5 g/liter; most of the individual instrument CV's ranged between 1 and 3%. At cholesterol concentrations of <2.0 g/liter, the CV's tended to increase with decreasing cholesterol concentrations, to a maximum of about 5% at a cholesterol concentration of 0.51 g/liter.

Within-run variability. The overall “within-run” standard deviation is the pooled (over runs and instruments) estimate of within-run variability, i.e., a measure of the variability among the essentially identical samples from the same pool in one run. The overall within-run standard deviations ranged from 20 mg/liter for pool A to 52 mg/liter for pool Q (Table 2).

The individual within-run standard deviation is the pooled (over runs) estimate of within-run variability for the specified instrument. The individual instrument within-run standard deviations ranged from 10 mg/liter (instrument 8, pool C and
Table 2. Among-Instruments, Between-Runs, and Within-Run Variance Components for Each Pool

<table>
<thead>
<tr>
<th>Pool</th>
<th>Concentration g/l</th>
<th>df</th>
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<th>Components %</th>
<th>df</th>
<th>SD g/l</th>
<th>Components %</th>
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<th>Components %</th>
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<td>16.4</td>
<td>375</td>
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<td>42.2</td>
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<td>10.9</td>
<td>194</td>
<td>0.028</td>
<td>46.1</td>
<td>196</td>
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<td>371</td>
<td>0.030</td>
<td>55.5</td>
<td>380</td>
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<td>30.0</td>
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</tr>
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<td>100.0</td>
<td>11</td>
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<td>16.1</td>
<td>154</td>
<td>0.030</td>
<td>53.9</td>
<td>163</td>
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<td>14.8</td>
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between-run variability. The overall “between-run” standard deviation is a pooled (over instruments) measure of run-to-run variability. The overall between-run standard deviation ranged from 21 mg/liter for pool A to 51 mg/liter for pool Q (Table 2).

The individual instrument between-run standard deviation is a measure of run-to-run variability for the specified instrument. The between-run standard deviation ranged from 1 to 99 mg/liter for individual instrument-pool combinations. Most between-run standard deviations fell between 10 and 50 mg/liter.

Instrument Comparability

The “among-instruments” standard deviation (Table 2) is a measure of instrument comparability. As mentioned previously, total standard deviations, representing the standard deviation of a single determination on a sample from a specified pool, ranged from 32 to 74 mg/liter. An average of 10% of this variability (2 to 20%) was due to differences among instruments. Most of the variability occurred within and between days on a single instrument.

For every pool, the among-instruments standard deviation was smaller than the within- and between-run standard deviations. The between-run variability (48.4%) was similar in magnitude to the within-run variability (41.4%).

Discussion

The LRC laboratories attempted to minimize bias and variability of cholesterol analyses by using identical instrumentation and aliquots of common primary standard solutions, as well as common bench control, standardization, surveillance and calibration pools. They also used the same sequence of standards and common procedures for instrument start-up, instrument calibration, and analysis. However, different reagent sources were used by the individual laboratories (1, 2).

The results indicated good agreement among instruments;
the average cholesterol bias for the 13 instruments was -0.41% (range -1.2 to +0.3%). The degree of bias varied from pool to pool, ranging from +5.3% on pool A (concentration 59 mg/liter) to -2.9% on pool O (concentration 2.96 g/liter). The bias was concentration dependent, with positive biases observed at concentrations <1.4 g/liter and negative biases observed at higher concentrations (the higher the concentration, the greater the magnitude of the negative bias).

Part of this trend in biases may have been caused by carryover effects from patient samples in the tray position preceding that of the surveillance pools. For example, the carryover from a patient sample with a cholesterol value of 2.0 g/liter to a pool with a low-cholesterol concentration such as pool A, would result in a positive bias. Conversely, the carryover effects from that same sample would cause a negative bias in samples from pools such as N to R, which had cholesterol concentrations >2.5 g/liter. This is essentially what was observed. Pools with cholesterol concentrations of 1.5 to 2.5 g/liter would be influenced only slightly by these carryover effects and the biases observed for samples in this concentration range were quite low.

In general, we found that the magnitude of the biases for these surveillance pools was of the same order as that reported previously (1) for our bench control pools.

The two bench control pools with low-normal cholesterol concentrations of 1.66 and 1.71 g/liter produced biases of -11 and -23 mg/liter, respectively (1). The estimated biases observed for external surveillance pools D and E, which had approximately the same cholesterol concentrations, were -6 and -15 mg/liter, respectively. Similarly, the biases observed for the two bench control pools with high-normal cholesterol concentrations (2.51 and 2.63 g/liter) were -42 and 2 mg/liter, respectively (1). These biases were in the same range as the biases of -9 and -22 mg/liter observed for external surveillance pools J and K, the cholesterol concentrations of which were 2.45 and 2.70 g/liter, respectively.

We observed that the various pools behaved differently on the 13 instruments, with very close agreement among instruments for pool O and more variable results for pool M. In addition, a stronger negative bias was observed for some pools than for others in the same concentration range. This finding is not surprising, because pools are biological materials that may vary in properties among themselves and may also change differently as they age.

The overall total standard deviation increased with increasing cholesterol concentration. Most total standard deviations were between 25 and 75 mg/liter, in agreement with the average of <40 mg/liter reported for the bench control pools (1).

As observed for the bench control pools (1), the run-to-run variance compared favorably with the within-run variability, often accounting for less than 50% of the total variability. This shows that run-to-run variability for most instrument-pool combinations was tightly controlled, which we attributed to our use of accurately prepared standards and common calibration pools. Even more impressive than the small run-to-run variability was the small instrument-to-instrument variability. The AutoAnalyzer II instrument-to-instrument variability was substantially smaller than the average within-run and between-run variability for every surveillance pool, which presumably resulted from the use of the same calibrators and standards by all of the laboratories. This finding confirmed the results observed for the internal quality-control pools (1) and demonstrated impressive comparability among the 13 instruments. The small instrument-to-instrument variability also suggested that the source of reagents contributed minimally to variation, since each LRC laboratory used its own source of reagents.

The magnitude of the among-instruments, between-run and within-run standard deviations was slightly higher than the corresponding results for the bench control pools (1). For bench control pools having low cholesterol concentrations, the total standard deviation was estimated at 33 to 37 mg/liter, whereas that estimated for analogous external surveillance pools was 59 mg/liter. The total standard deviation for bench control pools with higher cholesterol concentrations was 39 mg/liter, as opposed to 45 mg/liter for the external pools (2). Increased variability is usually observed in measurements on unknown value samples as compared to those on known value samples. However, a recent study (6) reported no difference between results obtained with masked and unmasked specimens, which supports our observation of approximately equal variability for bench control and external surveillance samples. Also, the accuracy and precision achieved by the LRCs in analyzing unknown surveillance pool samples for cholesterol compares favorably with the accuracy and precision achieved by other national and international standardization programs (7).

The basic requirement for comparing cholesterol distributions in different populations is a well-standardized laboratory measurement. Although cholesterol values collected by different laboratories are often difficult to compare due to lack of standardization (8-11), we have shown here that the LRC Program achieved a high degree of accuracy, precision, and interlaboratory comparability by vigorously standardizing all laboratory procedures and continuously monitoring laboratory performance by internal as well as by external surveillance. More importantly, the practicality of collecting accurate, precise, and comparable data from several laboratories engaged in collaborative studies has been demonstrated.

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Director, Central Electrocardiographic Laboratory: L. Thomas Sheffield, M.D.

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