Biological Variability of 26 Clinical Chemistry Analytes in Elderly People

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Analytical, within-subject, and between-subject components of variation were estimated for 26 clinical chemistry analytes from duplicate analyses of 10 specimens collected from 27 healthy elderly subjects over a period of 20 weeks. Within-subject variations were similar to those generated previously by us in younger subjects. We conclude, therefore, that homeostasis is not compromised by age alone, and biological variability does not increase simply with age. All analytes except serum water had marked individuality, showing that conventional population-based reference values are of limited utility. The critical differences required for two results to be significantly ($P \leq 0.05$) changed are not the same as those that prompt action by clinicians. Although heterogeneity of within-subject variation does exist, we believe that the critical differences generated will be useful in routine clinical decision making.

Additional Keyphrases: variation, source of • geriatric chemistry

A large proportion of hospitalized patients and those seeking primary health care are elderly people, and the number of elderly persons in the population continues to increase (1). It has been suggested that: (a) homeostatic mechanisms may become diminished in the aging process (1), (b) there is an apparent increase in biological variability with age (2), and (c) biological variation is least between ages 30 and 50 years (3).

Despite the fact that data on biological variation have been used for many purposes in clinical chemistry—including setting of analytical goals (4), deciding the significance of changes in serial results (5), and assessing the utility of conventional population-based reference values (6)—most information has been obtained on young subjects. Williams et al. (7), investigating biological variation in three groups, ages 18–35, 36–55, and >56 years, found little change with increasing age. However, elderly people have not been studied in detail.

To examine hypotheses a–c, we assessed the analytical and biological components of variation for a range of serum analytes in a cohort of healthy elderly adults over a period of 20 weeks. To more clearly study the effect of age, we assessed a variety of analytes for which we had already generated data on within-subject and between-subject variation in young subjects, using exactly the same analytical methods and instrumentation, and sources of reagents, that we had used previously. The analytes we studied were those of value in assessing salt/water homeostasis, renal function, liver function, bone function, lipid metabolism, the immune system, carbohydrate metabolism, and pancreatic function: sodium, potassium, chloride, urea, creatinine, calcium, phosphate, proteins, albumin, alkaline phosphatase (EC 3.1.3.1), and bilirubin (8); cholesterol, triglycerides, and apolipoproteins (apo) A-I and B (9); immunoglobulins G, A, and M, and $\kappa$ and $\lambda$ light-chains (10); glucose (11); fructosamine (12); amylase (EC 3.2.1.1) and lipase (EC 3.1.1.3) (13); and osmolality and water (14).

Materials and Methods

Subjects and Specimens

The subjects were selected from the National Health Service (NHS) register of patients of a U.K. urban general practice. The study had ethical approval.

The inclusion criteria were that the subjects should be ages 70 years or older, living at home independently, and requiring no help with feeding, toileting, or maintaining hygiene. The exclusion criteria removed patients with any chronic medical condition, including dementia, a history of gastrointestinal surgery, or current drug therapy.

After detailed review of the medical records of the practice, 32 subjects were invited by a letter from their own general practitioner to participate in the study. The research nurse then visited each subject to discuss the study, verified that the inclusion criteria were fulfilled, and confirmed the absence of dementia by the use of a structured questionnaire.

At 14-day intervals, 12 mL of venous blood was collected from each subject, generally on 10 occasions. It was verified each day that the subjects were fasted, that no therapy had been instituted, and that lifestyle had not changed. The nurse collected the specimens between 0700 and 0900 h from seated subjects by conventional venepuncture with minimal stasis. The specimens were transported to the laboratory within 1 h; sera were separated by centrifugation (3000 x g, 15 min) and stored at −30 °C until analysis.

Analytical Methods

Instruments. The instruments used were the SMAC continuous-flow analyzer (Technicon Instruments Corp., Tarrytown, NY 10591) for sodium, potassium, chloride, urea, creatinine, calcium, phosphate, proteins, albumin, bilirubin, and alkaline phosphatase; a Cobas Fara centrifugal analyzer (Roche Products, Welwyn Garden City, Herts., U.K.) for cholesterol, triglycerides, apo A-I and apo B, IgG, IgA, IgM, $\kappa$ chains, $\lambda$ chains, glucose, amylase, and lipase; a Rotochem IIa centrifugal analyzer (Aminocon, Silver Spring, MD 20910) for fructosamine; and a Roebelg automatic micro-osmometer (Herman Roebeling, Berlin, F.R.G.) for osmolality.

Reagents. Reagents for the SMAC were purchased from Technicon (Basingstoke, Hants., U.K.); for cholesterol and lipase from Boehringer Corp. London, Ltd., (Lewes, East Sussex, U.K.); for triglycerides from Roche Products; for apo A-I and apo B from Orion Diagnostics (Espoo, Finland); for IgG, IgA, IgM, $\kappa$ chains, and $\lambda$ chains from Kallestad Diagnostics (Austin, TX 78701); for glucose from Beckman RIIC Ltd. (Risley, Warrington, U.K.); and for amylase from Behringwerke AG (Marburg, F.R.G.).

Methods. Standard Technicon methodology was used with the SMAC. Cholesterol was assayed by the cholesterol ester-
Triglycerides by formazan production from idonitrotetrazoli-

um chloride; apolipoproteins, immunoglobulins, and light-

chains by immunoturbidimetry; glucose by the hexokinase/

glucose-6-phosphate dehydrogenase method; fructosamine

exactly as described previously (12); amylose by hydrolysis

of 4-nitrophenylmaltopentaoside/hexaoside substrate, lipase

by turbidimetry; osmolality by freezing-point depression;

and water by the osmometric method of Faye and Payne

(15).

Analytical Strategy

At the time of analysis of each analyte, all specimens were

allowed to thaw at room temperature, and assayed in the

smallest number of analytical batches possible. The speci-

mens were assayed in no specific sequence in duplicate in

separate batches. The same lots of reagents, standards, and

quality-control materials were used throughout, and all

analyses of a particular analyte were performed by the same

analyst.

Database and Statistical Analysis

During the study, four subjects decided not to participate

further, and one other subject was excluded because of

initiation of antibiotic and diuretic therapy. The database

therefore comprised results from 27 subjects, 14 men and 13

women, between 70 and 83 years of age.

We examined the data rigorously at various strata before

performing statistical analysis. Each pair of results was

examined for differences; if, on the basis of the imprecision

of the method, unexpected differences (> ± 2 SD) existed,

the analyses were repeated, and the results not apparently

aberrant were substituted. The results for each analyte for

each subject were then examined against the reference

values in use in the laboratory; if all results were outside

such values, we excluded all of that subject's results, be-

cause we wished to study healthy, elderly subjects. The

mean and parametric standard deviation (SD) were calcu-

lated for each analyte, and if any result exceeded ± 2 SD

from the mean, both results for that specimen were exclud-

ed. Before we determined immunoglobulins and light-

chains, we assayed by serum protein electrophoresis (Multi-

trac agarose electrophoresis, Ciba Corning Diagnostics, Hal-

stead, Essex, U.K.) the first specimen taken from each

individual; further determinations were not performed if an

expert reviewer considered that any abnormality was pre-

sent.

The remaining results were subjected to nested analysis

of variance to dissect the total variance into analytical

(\(SD_a^2\)), within-subject (\(SD_w^2\)), and between-subject (\(SD_b^2\))

components.

Results and Discussion

The number of results included in the nested analysis of

variance; the mean values; and analytical, within-subject,

and between-subject variations (as coefficients of variation)

are shown in Table 1.

Comparison of Elderly and Younger Subjects

Table 2 shows the within-subject variation generated in

this study, and the data previously obtained by us for

younger subjects, ages 20–53 years. These sets of results

can be compared directly because the same methods, instrumen-
tation, and sources of reagents were used.

The ratios of the CV, called Q by Hölsel (16), are shown in

\[ Q = \frac{CV_{within}}{CV_{between}} \]

Table 1. Data Points, Mean Results, and Calculated Components of Variation

<table>
<thead>
<tr>
<th>Analyte</th>
<th>No. *</th>
<th>Mean</th>
<th>CV_{within} %</th>
<th>CV_{between} %</th>
<th>CV_{total} %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>518</td>
<td>141.8 mmol/L</td>
<td>0.75</td>
<td>0.86</td>
<td>0.88</td>
</tr>
<tr>
<td>Potassium</td>
<td>518</td>
<td>4.45 mmol/L</td>
<td>2.0</td>
<td>4.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Chloride</td>
<td>516</td>
<td>107.2 mmol/L</td>
<td>0.95</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Urea</td>
<td>516</td>
<td>5.94 mmol/L</td>
<td>2.5</td>
<td>10.3</td>
<td>13.4</td>
</tr>
<tr>
<td>Creatinine</td>
<td>516</td>
<td>93.8 μmol/L</td>
<td>2.8</td>
<td>4.3</td>
<td>18.3</td>
</tr>
<tr>
<td>Calcium</td>
<td>500</td>
<td>2.36 mmol/L</td>
<td>0.95</td>
<td>1.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Phosphate</td>
<td>516</td>
<td>1.19 mmol/L</td>
<td>1.7</td>
<td>4.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Alanine</td>
<td>518</td>
<td>67.5 g/L</td>
<td>1.2</td>
<td>2.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Albumin</td>
<td>518</td>
<td>43.0 g/L</td>
<td>1.3</td>
<td>2.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>518</td>
<td>9.1 μmol/L</td>
<td>6.0</td>
<td>16.5</td>
<td>27.8</td>
</tr>
<tr>
<td>Alk. phos.</td>
<td>516</td>
<td>88.0 U/L</td>
<td>1.9</td>
<td>6.5</td>
<td>24.4</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>452</td>
<td>6.30 mmol/L</td>
<td>1.9</td>
<td>5.8</td>
<td>11.0</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>486</td>
<td>1.47 mmol/L</td>
<td>3.4</td>
<td>15.3</td>
<td>27.8</td>
</tr>
<tr>
<td>Apo A-1</td>
<td>522</td>
<td>1.17 g/L</td>
<td>2.3</td>
<td>6.6</td>
<td>13.8</td>
</tr>
<tr>
<td>Apo B</td>
<td>522</td>
<td>1.05 g/L</td>
<td>1.9</td>
<td>8.3</td>
<td>25.7</td>
</tr>
<tr>
<td>IgG</td>
<td>392</td>
<td>9.47 g/L</td>
<td>3.5</td>
<td>6.2</td>
<td>16.5</td>
</tr>
<tr>
<td>IgA</td>
<td>394</td>
<td>2.24 g/L</td>
<td>3.6</td>
<td>8.6</td>
<td>36.8</td>
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<tr>
<td>IgM</td>
<td>396</td>
<td>0.92 g/L</td>
<td>3.7</td>
<td>9.3</td>
<td>34.9</td>
</tr>
<tr>
<td>κ chains</td>
<td>370</td>
<td>7.59 g/L</td>
<td>2.2</td>
<td>6.1</td>
<td>17.7</td>
</tr>
<tr>
<td>λ chains</td>
<td>390</td>
<td>4.37 g/L</td>
<td>2.1</td>
<td>5.4</td>
<td>20.6</td>
</tr>
<tr>
<td>Glucose</td>
<td>512</td>
<td>5.21 mmol/L</td>
<td>2.4</td>
<td>4.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Fructosamine</td>
<td>276</td>
<td>2.19 mmol/L</td>
<td>2.9</td>
<td>4.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Amylase</td>
<td>530</td>
<td>65.8 U/L</td>
<td>1.6</td>
<td>10.8</td>
<td>32.1</td>
</tr>
<tr>
<td>Lipase</td>
<td>498</td>
<td>120.0 mmol/L</td>
<td>8.8</td>
<td>14.0</td>
<td>17.8</td>
</tr>
<tr>
<td>Osmolality</td>
<td>476</td>
<td>289.0 mmol/L</td>
<td>0.5</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Water</td>
<td>438</td>
<td>0.95 g/L</td>
<td>1.9</td>
<td>3.8</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Analytical variation (CV_{within}), within-subject variation (CV_{between}), and between-subject variation (CV_{total}).

No. of analytical results subjected to ANOVA.

Table 2. Q\(^2\), for Q > 1, and 1/Q\(^2\), for Q < 1, are equivalent to the
F-statistic for comparison of variances. For five analytes, the
CV_{within} of the elderly subjects was statistically the same as
in the younger subjects; for 11 analytes, it was larger
(P <0.05); and for nine, it was smaller (P >0.05). However,
we think that it is useful also to compare data for both
groups with all previously published estimates of CV_1
generated from studies performed over a period longer than
one week. Such estimates have been tabulated by Ross (17)
and Fraser (18), and their ranges are shown in Table 2. In
general, the data found by us for both groups fall within
these ranges.

We conclude that within-subject biological variation in
healthy elderly people is not different from that in younger
subjects, confirming the suggestions that can be drawn from
the data of Williams et al. (7). Moreover, this finding refutes
the suggestions that homeostatic mechanisms become di-
minished in elderly people (1), that biological variation is
least between the ages of 30 and 50 years (3), and that
biological variability increases with age (2). An important
consequence is that desirable standards of analytical per-
formance for analytical methods are the same for specimens
from elderly and younger subjects; therefore, the plethora of
data available on biological variation, which have been used
to set analytical goals (18) by the statistical theories of
Harris (19), can be applied ubiquitously.

Our findings also provide further evidence that, as we
have suggested earlier (10, 12, 20), valid estimates of data
on within-subject variation can be generated from circum-
scribed studies on small groups of young, healthy subjects.

Indices of Individuality

Conventional population-based reference values are of
utility only when the within-subject variability exceeds the
between-subject variability. More formally, Harris (6) has
shown that only when CV<sub>y</sub>/CV<sub>x</sub> of the index of individuality, is >1.4 are reference values of use.

The indices of individuality for the analytes investigated are listed in Table 3. Except for serum water, they all have indices of individuality <1.4. For 12 of the analytes, the indices are <0.6, which demonstrates (9) that conventional reference values have extremely limited utility.

This high degree of individuality means that, for most analytes, subjects can have values that are very unusual for them but that still lie within the population-based reference limits. Thus the analytes examined in this study, although commonly assessed in clinical chemistry laboratories, will be of limited use in the diagnosis of early or latent disease. We therefore consider it a waste of resources to use such tests as general population-screening tests, or in admission profiles. Interestingly, the only analyte having low individuality, i.e., serum water, is not used for diagnoses but only to investigate the possibility of factitious hyponatremia (15).

### Critical Differences

Although commonly requested clinical chemistry tests are likely to be of little value in diagnosis of minor illness, in practice most tests requests to laboratories are made for the purpose of monitoring patients (21). In that context, it is vital to know the magnitude of change in serial results from an individual that makes a difference statistically significant. Such changes are due to analytical and within-subject variation; for \( P \leq 0.05 \), the critical difference is 2.77 \((CV<sub>x</sub> + CV<sub>y</sub>)^{1/2}\) (5). The critical differences are also listed in Table 3.

The question arises as to whether clinicians appreciate the magnitude of these critical differences. The results of a recent survey of the opinions of clinicians (22) allow calculation of the median percentage of critical differences considered to be clinically important. In asymptomatic patients, the median changes that would prompt action by physicians for 10 analytes were, except for triglycerides, higher than the critical differences. In contrast, in acute situations, changes of 13.3%, 16.6%, 16.7%, 28.6%, and 20.0% were considered significant for bilirubin, calcium, creatinine, phosphate, and urea, respectively, whereas these values are very different from the objectively calculated critical differences. We therefore suggest that educating physicians as to what constitutes a significant change is warranted, and we have attempted this through teaching medical students with a simple textbook (23). Moreover, these findings cast further doubt on the validity of deriving analytical goals for precision based on the views of clinicians.

### The critical differences detailed in Table 3 are valid only if all subjects have the same within-subject variation. This aspect can be investigated by calculation of an index of heterogeneity, calculated as the CV of \((SD<sub>x</sub> + SD<sub>y</sub>)^{1/2}\) divided by the theoretical CV if no heterogeneity existed, namely \((2/(n - 1))^{1/2}\), where \( n \) is the average number of specimens collected from each subject (24). The indices of heterogeneity are listed in Table 3. Because these are all \( >1.45 \) (1.00 + (22/n)^{1/2}) except for potassium, phosphate, proteins, and fructosamine, we conclude that the heterogeneity of within-subject variation is general. Therefore, although the critical differences documented in Table 3 may be used as a simple single figure to guide clinical decision making, they are not ubiquitously valid. More complex approaches, which require more data, such as those advocated by Harris and Yasaka (25) and Boyd and Harris (26), may be worthy of future investigation. We also consider it of interest to examine the biological variation of hospitalized elderly subjects, given

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### Table 2. Within-Subject Variations (CV<sub>y</sub>) of Elderly and Younger Subjects, Ratio of Variations, and Results of Previous Studies

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Elderly subjects</th>
<th>Younger subjects</th>
<th>Q*</th>
<th>Previous studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>0.9</td>
<td>0.7</td>
<td>1.29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(17, 18)</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.8</td>
<td>5.4</td>
<td>0.89</td>
<td>3.5 - 6.3</td>
</tr>
<tr>
<td>Chloride</td>
<td>1.2</td>
<td>1.0</td>
<td>1.00</td>
<td>1.1 - 2.1</td>
</tr>
<tr>
<td>Urea</td>
<td>10.3</td>
<td>13.9</td>
<td>0.74&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9.5 - 16.4</td>
</tr>
<tr>
<td>Creatinine</td>
<td>4.3</td>
<td>4.1</td>
<td>1.05</td>
<td>2.5 - 6.3</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.6</td>
<td>2.1</td>
<td>0.76&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.0 - 2.6</td>
</tr>
<tr>
<td>Phosphate</td>
<td>4.8</td>
<td>8.3</td>
<td>0.58</td>
<td>3.4 - 13.0</td>
</tr>
<tr>
<td>Proteins</td>
<td>2.6</td>
<td>3.1</td>
<td>0.84&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.2 - 3.3</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.6</td>
<td>2.2</td>
<td>1.18&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.5 - 4.2</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>16.5</td>
<td>19.2</td>
<td>0.86&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18.7 - 26.0</td>
</tr>
<tr>
<td>Alk. phos.</td>
<td>6.5</td>
<td>9.8</td>
<td>0.66&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.5 - 8.6</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>5.8</td>
<td>4.9</td>
<td>1.18&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.1 - 7.9</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>15.3</td>
<td>17.5</td>
<td>0.87&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17.5 - 27.3</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>6.6</td>
<td>4.7</td>
<td>1.40&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>Apo B</td>
<td>8.3</td>
<td>7.3</td>
<td>1.14</td>
<td>—</td>
</tr>
<tr>
<td>IgA</td>
<td>6.2</td>
<td>4.4</td>
<td>1.41&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.7 - 5.0</td>
</tr>
<tr>
<td>IgM</td>
<td>8.6</td>
<td>5.0</td>
<td>1.72&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.4 - 5.4</td>
</tr>
<tr>
<td>k chains</td>
<td>9.3</td>
<td>5.9</td>
<td>1.58&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.1 - 6.1</td>
</tr>
<tr>
<td>glucose</td>
<td>4.7</td>
<td>4.8</td>
<td>0.98</td>
<td>5.6 - 13.2</td>
</tr>
<tr>
<td>fructosamine</td>
<td>2.9</td>
<td>5.3</td>
<td>0.55&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>Amylase</td>
<td>10.8</td>
<td>9.0</td>
<td>1.20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.8 - 8.7</td>
</tr>
<tr>
<td>Lipase</td>
<td>14.0</td>
<td>11.0</td>
<td>1.27&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>Osmolality</td>
<td>0.8</td>
<td>1.9</td>
<td>0.42&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>Water</td>
<td>3.8</td>
<td>2.5</td>
<td>1.52&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
</tr>
</tbody>
</table>

*Q*: ratio of CV<sub>y</sub> in elderly subjects to CV<sub>y</sub> in younger subjects.

*CV<sub>y</sub>* significantly (\( P < 0.05 \)) greater in elderly than in younger subjects.

*CV<sub>y</sub>* significantly (\( P < 0.05 \)) less in elderly than in younger subjects.

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### Table 3. Indices Derived from Data on Biological Variation

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Index of individuality</th>
<th>Critical difference, %</th>
<th>Index of heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>0.98</td>
<td>3.2</td>
<td>2.73</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.71</td>
<td>14.4</td>
<td>1.39</td>
</tr>
<tr>
<td>Chloride</td>
<td>0.77</td>
<td>4.3</td>
<td>1.76</td>
</tr>
<tr>
<td>Urea</td>
<td>0.77</td>
<td>29.4</td>
<td>1.59</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.23</td>
<td>14.1</td>
<td>3.08</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.58</td>
<td>5.2</td>
<td>1.47</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.36</td>
<td>14.2</td>
<td>1.28</td>
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<td>Proteins</td>
<td>0.75</td>
<td>7.3</td>
<td>1.21</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.74</td>
<td>8.1</td>
<td>1.55</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.59</td>
<td>48.6</td>
<td>1.92</td>
</tr>
<tr>
<td>Alk. phos.</td>
<td>0.27</td>
<td>18.7</td>
<td>2.41</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.53</td>
<td>16.9</td>
<td>1.80</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.55</td>
<td>43.3</td>
<td>1.74</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>0.70</td>
<td>19.5</td>
<td>2.02</td>
</tr>
<tr>
<td>Apo B</td>
<td>0.32</td>
<td>23.7</td>
<td>3.15</td>
</tr>
<tr>
<td>IgG</td>
<td>0.37</td>
<td>19.7</td>
<td>1.80</td>
</tr>
<tr>
<td>IgA</td>
<td>0.23</td>
<td>25.9</td>
<td>2.82</td>
</tr>
<tr>
<td>IgM</td>
<td>0.27</td>
<td>27.8</td>
<td>1.59</td>
</tr>
<tr>
<td>k chains</td>
<td>0.34</td>
<td>17.9</td>
<td>2.20</td>
</tr>
<tr>
<td>lambda</td>
<td>0.26</td>
<td>16.1</td>
<td>2.01</td>
</tr>
<tr>
<td>Glucose</td>
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<td>14.7</td>
<td>3.37</td>
</tr>
<tr>
<td>Fructosamine</td>
<td>1.21</td>
<td>15.0</td>
<td>1.15</td>
</tr>
<tr>
<td>Amylase</td>
<td>0.34</td>
<td>30.3</td>
<td>2.47</td>
</tr>
<tr>
<td>Lipase</td>
<td>0.78</td>
<td>45.7</td>
<td>3.18</td>
</tr>
<tr>
<td>Osmolality</td>
<td>0.93</td>
<td>2.7</td>
<td>1.85</td>
</tr>
<tr>
<td>Water</td>
<td>52.58</td>
<td>11.8</td>
<td>2.03</td>
</tr>
</tbody>
</table>

*Index of individuality calculated as CV<sub>y</sub>/CV<sub>x</sub>, critical difference as 2.77 (CV<sub>x</sub> + CV<sub>y</sub>)<sup>1/2</sup>; and index of heterogeneity as ratio of CV of (SD<sub>x</sub> + SD<sub>y</sub>)<sup>1/2</sup> to \((2/(n - 1))^{1/2}\), where \( n \) is the number of specimens per subject. A, I, and G represent analytical, within-subject, and between-subject components of variation.
that the spectrum of within-subject variation may differ in
different acute clinical situations (26), although consider-
able evidence suggests that the magnitude of this is not
affected by chronic stable disease (18).

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