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Is Normal “Normal”?  

Ever since introduction of the biochemical profile (eg, SMAC, SMAC 12, Hycel 17), the problem of the isolated abnormal test occurring in an otherwise normal patient has been a source of concern.

Dr. Lester Kobylak’s paper in this issue, “Elevated serum transaminase as a presenting clue for precirrhotic hemochromatosis,” suggests that such findings should not be dismissed. However, this advice should be tempered with knowledge of how normal ranges are derived and what they mean.

Clinical chemistry laboratories receive many questions about apparently spurious elevations of certain tests, particularly enzyme assays. Often these occur in the evaluation of apparently healthy people who are asymptomatic. Two questions I am often asked by clinicians about isolated abnormal biochemistry values are: 1) What could they mean? and 2) What further testing should I do?

To answer these questions requires a discussion of “normal” and “reference” ranges. We no longer use the term “normal range,” but rather the terms “reference intervals” or “desired ranges.” Normal range encompasses 95% of the normal population. By this definition, the normal range is determined by calculating the mean (X) and standard deviation (SD) of data generated from at least 120 healthy people. Thus, the usual normal range is simply X ± 2 SD. Test results of some normal individuals fall outside this range, and occasionally those of unhealthy individuals fall within this range. Accordingly, it is important to think of these ranges as guidelines or “reference intervals.”

The further point may be made that in some cases “normal” may not be healthy. Cholesterol and uric acid are examples. At Henry Ford Hospital we now use 140-220 mg/dl as a “desired range” for serum cholesterol rather than the 150-300 mg/dl which has been the “normal range” for many years. The 150-300 mg/dl range previously used had been obtained from a healthy or asymptomatic population.

Isolated elevation of a single parameter in a biochemical profile with twenty variables on a healthy patient may not mean an abnormality. Certainly, a value greater than 2 SD but within 3 SD of the mean value need not be interpreted as an indication of disease in the absence of any other suspicious observations. In general, abnormalities of three or more related parameters, even slightly outside the reference range, should be evaluated by repeat testing. Should the abnormalities persist, other diagnostic tests should be used. A single significant abnormality should be repeated along with other tests to help define the unexpected abnormal result. The criteria of significant abnormalities are: 1) most enzymes—one-and-a-half times the upper limit of normal; 2) most other tests—greater than 3 SD of the mean of the reference range. To determine 3 SD, divide the mean of the reference range by four and add to the upper limit of the range.

An important example of this concept is testing for lactic dehydrogenase (LDH). Most clinicians have encountered spurious elevations of LDH, in the range of 200-250 IU/L (normal 100-200 IU/L), and most have learned to ignore this phenomenon. However, isolated significant elevation of LDH (>300 IU/L) is often a sensitive indicator of metastatic disease.

Finally, clinicians should appreciate significant shifts or trends that occur over a period of time in a patient’s laboratory data although the values may remain in the normal range. Serum creatinine and creatine phosphokinase (CPK) assays provide us with two relevant examples. Our reference ranges for these two tests are 1.5 mg/dl and <190 IU/L, respectively; but a change in creatinine from 0.8 mg/dl to 1.4 mg/dl in a short time is consistent with developing renal disease even though both values are “normal.” A change in CPK from 50 to 150 over a few hours is highly suggestive of myocardial infarction even though the values still fall within our normal range.

The cases reported in this issue by Dr. Kobylak demonstrate the importance of evaluating unexpected test elevations in biochemical screening in order to differentiate between spurious and truly abnormal results.

For further discussion of the problem, the reader is referred to Galen RS, Gambino SR, “Beyond normality: The predictive value and efficiency of medical diagnosis” (New York: John Wiley and Sons, 1975).

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