NORMAL? - TIS OR IT ISN'T?

Pages with reference to book, From 254 To 256

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*When vomiting tumbles down like rain, Normal? Orfalse ranges once again?**

About Normal ranges. A personal view.

John Smith has a blood urea nitrogen (B.U.N.) of 22 mg/dl and, as other renal function tests show, is doing very nicely. Malik Ahmed also has a B.U.N. of 22 mWdl as has Khalid el-Sheikh but unfortunately, if they did but know it, the latter two may eventually be investing their life-savings in kidney machines as their renal functions have already diminished by at least 50%. Supposing, our three friends have each serum alkaline phosphatase levels of 140 lU/L. John Smith has probably been enjoying his Saturday (and other) evenings out too much, over the years; Malik Ahmed is jaundiced and may have hepatitis; but providing he does not trip over his thobe and break his neck, Khalid el-Sheikh can probably continue doing the sword-dance on festive occasions for years to come, at least on this account. With a serum CPK level of 250 lUlL, J.S. would be laughing, but MA. should give up cricket and K. el-S his sword-dance, after all. On opening a laboratory in Pakistan, 99.9% of owners/supervisors either grab the nearest clinical chemistry textbook (published in the West) or if the lab. is fortunate enough to have purchased an autoanalyser such as the Beckman Astra Ideal, has the following normal ranges[1] printed on the laboratory report form, e.g. B.U.N. 5-25 mg/dl, alkaline phosphatase 26-88 lUlL, CPK 22-268 IU/L, amongst others. The director of the Alka Mist Laboratory, Karachi, which Malik Ahmed patronises bought the autoanalyser and did precisely this. Hence Malik Ahmed has been given a false sense of security concerning his renal and cardiac functions, but he may indeed have hepatitis, and if the laboratory in Riyadh, to which Khalid el-Sheikh went did likewise he is unaware about a cardiac and a growing renal problem but is probably horrified to an unnecessary extent about his overindulgence with the eau-de- Cologne. After their initial stages of development, these two laboratories should have determined their own normal ranges which would have been something ‘With sincerest apologies to WeHcome Pakistan Ltd. and to Marzine. like the following. For the Alka Mist Lab.: B.U.N. 6-16 mgfdl, alkaline phosphatase 28-124 lUlL, CPK 17- 176 lUlL. For the laboratory in Riyadh[2]: B.U.N. 7-19 mg/dl, alkaline phosphatase 43-154 lUlL, CPK 30-210 lUlL etc. The ten year old son of Malik Ahmed had a series of tests done, including alkaline phosphatase, at the Alka Mist Laboratory. He was not jaundiced but his level was 298 lUlL. The normal range found for a Pakistani boy of his age would have been in the order of 125-405 lUlL because of continuing and rapid bone growth, and therefore his level is in fact normal. (Malik Ahmed’s wife would have fitted into a lower normal range than her husband - less exposure to the sun and slower bone turn-over). For a given test the normal range may not only be dependent on ethnic group as the above illustration shows, and perhaps also on age and sex, but also on methodology and instrumentation and possibly on variations in overall social status of the patient population. Below are the normal ranges for serum inorganic phosphate and sodium for adults derived by the Aga Khan University Clinical Laboratories and the Pakistan Medical Research Council, Research Centre, both in Karachi. Methodology was the same for sodium but different for phosphate. Inorganic phosphate 2.7-4.8 and 0.32-6.6 mg/dl respectively. Sodium 136-148 and 132-164 mEq/L respectively. Clearly, each clinical chemistry laboratory should establish its own normal range for each of its tests, by age and sex if necessary, adhering strictly to the recognised procedure for that test and to relevant factors such as diet, fasting or otherwise, posture, time of day or menstrual cycle, etc., as necessary; to ensure the minimum degree of stress or stasis and that each subject is clinically normal and healthy. It is not sufficient to establish a normal range for Pakistanis or for Karachiites but each laboratory must have that for its own patient population. It may need revision from time to time. Even when established, for some tests patient results may require

modifications e.g., a serum calcium level may need tobe adjusted for the serum albumin level, and creatinine clearance often needs adjustment for the body surface area (via height and weight). Otherwise, would you expect either a healthy toddler or Mike Tyson to faliwithin the normal range 100-130 ml/min/1.73 m2? When it comes to an enzyme estimation, inter-laboratory variations in normal range almost always occur because different methodologies introduce additional variables such as unit derivation, substrate variation, time and temperature of incubation, pH, etc. It is dangerous to compare two results, each from a different laboratory or even from the same laboratory using two different methods. Every clinical chemist must be familiar with the following scenario. A patient had a serum a-amylase estimation done at the Alka Mist Laboratory, which had by then established its own normal range. He then went to the Aga Khan University and the laboratories issued the result 481 lU/L (Normal range, N.R., 112-509)*. He accused the A.K.U. Laboratories of issuing rubbishy results and verbally stated that the result from the Alka Mist Lab. was only 150 but could not remember the normal range and was, expectedly, unaware of the method used. A.K.U. laboratories estimate serum a-amylase activityby either of two methods, depending on the workload at the time or the degree of urgency: a starch turbidimetric method on the Beckman Astra Ideal autoanalyser (N.R. 51-126 lUlL) or the Roche amylochrome method (N.R. 112- 509 dye units/dl). As it happens, the Alka Mist Lab. uses neither method, but a starch iodide method, N.R. 60-160 Somogyi units. Both laboratory results were accurate. Laboratory test results should supplement the clinician's fmdings and add another piece towards the completion of the clinical jigsaw puzzle. Diagnosis should NOT be made principally on the results of laboratory tests. Unfortunately, this abominable American practice is creeping in here as well as in U.K., probably owing to laziness or incompetence among certain members of the profession. I have seen diagnostic comments on computerised printouts from certain laboratories in U.S.A. based entirely on the test results which should have earned the clinical chemist/chemical pathologist a one-way ticket to Alcatraz! If the patient had ndt had a myocardial infarct before the test, he probably would have had one after! Let us remember one or two facts about the term "normal range" or "reference interval" as it should really be called. If, in the determination of a normal range, the Interestingly, a normal range for Westerners by this method is 45-200 dye units/di distribution of the individual results is Gaussian, the normal range may generally be taken as the mean plus or minus two standard deviations. Thus 21/2% of the clinically normal population is below the normal range and 2 1/2 % is above. If the distribution is log-Gaussian or totally non-Gaussian, these percentages may be different but, in general, about 5% of adlinically normal population is biochemically abnormal. Similarly, part of a diseased population sometimes falls within the normal range. Consider the term "normal range" when talking about serum cholesterol or triglyceride levels. A normal range for 20-24 year old male Pakistani is of the order 115-266 mg/dl. Although all subjects were clinically normal at the time of determination, a sizeable proportion of them had levels of over 200 mg/dl and unless remedial action is taken, many will prematurely develop cardiovascular problems and are therefore "at risk". The need of treatment is often difficult for such an individual to understand if he knows his level lies within the normal range and his cooperation is often impossible to obtain. (Patient: "Why do I needtreatment when mylevelis only 220 mg/dl and up to 266 is normal ?!"). Let us have a reductio ad absurdum. The normal range for serum copper in Kansas City, Kansas, was found to be 80.9-208.3pgldl[4] and that in Kansas City, Missouri 95.3-248.9*[4]. Does this mean that the copper level of someone moving to and fro across the state boundary will go up and down like a yoyo or that a person with a level of 230 pg/dl will alternate between bouts of an Indian childhood cirrhosis-like syndrome and normality? Abnormal patient results, particularly if marginally abnormal, should be viewed objectively and open-mindedly as not all variables can always be taken into account when determining the normal range. Except in a minority of cases, there is no substitute for a clinician's skill in fmally obtaining the correct clinical picture from all the available pieces of evidence. This brings us to another essential requirement for every clinical Laboratory. QUALITY CONTROL. Every laboratory should participate in a systematic, precise, and

accurate programme of internal and external (internationally assessed) quality control. Manufacturer's ranges for their control sera are no substitute for this. Not only dpes participation in such schemes give complete confidence to all concerned with regards to the accuracy of reported results but it is an essential pre-requisite for embarking on a normal range exercise. -But this should be a topic for another editorial.

REFERENCES

1. Beckman Instruments S.A., Astra Abstracts, Geneva, Switzerland, 1984.
2. El-Hazmi, M.A.F. and Manser, W.W.T. A manual of biochemiMiy services, Riyadh, King Saud University, 1982.
3. Tietz, N.W. Fundamentals of Qinical Chemistry. ed. Philadelphia, Saunders, 1983, p. 54.
4. Varsiech, J. and Correlis, it Normal levels of trace elements in human blood plasma or serum. Anal. Chim. Acta, 1980; 217-254.