COMmUnICATIOnS
To the Editor:

Communications for this section will be published as space and priorities permit. The comments should not exceed 350 words in length; with a maximum of five references; one figure or table can be printed. Exceptions may occur under particular circumstances. Contributions may include comments on articles published in this periodical, or they may be reports of unique educational character. Specific permission to publish should be cited in a covering letter or appended as a postscript.

The Normal Ranges in Spirometric Indices

To the Editor:

In their special communication entitled "Changes in Measured Spirometric Indices: What is Significant?" Pennock, Rogers, and McCaffree (Chest 1981; 80:97-99), presented an excellent discussion of what should be considered an abnormal change in the results of spiographic tests over a period of time. This is a serious problem which cries out for practical standards, especially among workers under mandated annual surveillance.

In the second paragraph, the statement was made that the usual definition of an abnormal value is one that statistically would be expected in less than 5 percent of normal subjects. The authors then claimed that in a Gaussian population "this represents values that are more than 1.65 times the coefficient of variation below the mean." However, this is based on looking only at the lower tail of the distribution. The normal range is ordinarily defined in terms of both tails of the distribution so that there is 2.5 percent in each tail and the critical value should be twice the coefficient of variation. I see no a priori reason for applying a different definition to the normal change of spirometric indices.

False positives are troublesome, especially in screening procedures, and they should be kept to a minimum. With this in mind, a lower limit of normal which yields only 2.5 percent false positives should be better than one which yields 5 percent false positives.

The importance of this viewpoint can be illustrated with a hypothetical example. If one were to perform spiographic testing on 10,000 workers of which 500 (5 percent) truly had abnormality, a lower limit of normal set at 1.65 times the coefficient of variation would yield almost as many false positives (9,500 x 0.05 = 475) as true positives (500) if we assume that the spirogram would identify every one of the true positives, an unlikely assumption. In my opinion, based on more than 30 years of experience in screening, this degree of false positivity is undesirable when dealing with people who do not think they are sick. Much unwarranted anxiety can be generated by so many false positives, not to mention hostility.

Another point I would like to make concerns the misuse of the term "confidence limits." In biostatistics, 95 percent confidence limits are the limits within which the mean of the entire target population (all the people about whom we want to draw conclusions based upon inference from a sample) will be found with a theoretic probability of 0.95. It describes the degree of certainty with which a sample mean reflects the population mean, given certain assumptions. The coefficient of variation, on the other hand, describes the dispersion in the distribution of observed values in a sample group, such as the one studied by Morris. It is used to provide a definition of upper and lower critical values of the normal range, values which can be called normal limits. It is not uncommon to find the term "confidence limits" substituted for the term "normal limits" in the medical literature, but such misuse leads to confusion.

William Weiss, M.D.
Professor of Medicine,
Hahnemann Medical College and Hospital,
Philadelphia

To the Editor:

Dr. Weiss' thoughtful letter is a good example of the type of discussion relative to predicted normals that we hoped would be generated in response to publication of our communication.

The problem of defining respiratory impairment or range of normality from measurements on a population of normal subjects has been variously addressed. Ranges have been defined artfully using a mix of clinical experience and approximations of statistical principles. It may be useful at this point to review the basis of the statistical contribution to these definitions.

Let us, for the sake of simplicity, examine the hypothetic measured FVC of 100 normal individuals of the same sex, height and age. We certainly would not expect each of these 100 to have an FVC exactly equal to the values predicted from the mean measurements on normal subjects. There will be some scatter; some will be higher, some will be lower.

The statistical term that measures the amount of scatter is the standard deviation. About 68 of the 100 will have FVCs within the mean ± 1 standard deviation: 90 percent or 90 within ± 1.64 SD and 95 within ± 2 SD (Fig 1).

Let the mean FVC for this hypothetical group be 5.0 L and the SD 0.6 L. Suppose, now, this group of 100 normal subjects disperses and seeks evaluation in your offices. How can we define a range of normal without calling "too many" of these normals abnormal? If we choose a lower limit of 4.4 L (mean - 1 x SD) 16 of the 100 normal subjects will be called abnormal. A lower limit of 4 (mean - 1.64 x SD) gives five subjects false labels and 3.8 yields 2-3 (2.5) false calls.

The most common procedure is to accept five false positives out of 100. We chose in our communication to use this criterion of 1.64 times the standard deviation.

Dr. Weiss states that on the basis of his experience in interpreting pulmonary function screening tests, false positivity is undesirable because it generates unwarranted patient anxiety. He then says that it is preferable for him to choose a lower limit of normal which produces only 2.5 percent false positives. The example he uses to illustrate the

Figure 1. Normal distribution curves illustrating the number (out of 100) of subjects with FVC within (striped area) below (shaded) and above (clear) the specified number of standard deviations.
The importance of this viewpoint is entirely appropriate and we agree with his conclusion.

On the other hand, it is informative to examine this decision about choice of a normal range from another perspective. Let us ask the question, "How can we define a range of normal without calling 'too many' normals abnormal?" Suppose, for example, the 100 hypothetic normal subjects discussed previously all were one of equally hypothetical identical twin pairs. Moreover, these 100 other twins have all been exposed to an environmental toxin that uniformly reduced their FVC by 20 percent. These twins also come to your offices for evaluation of pulmonary function.

The results of their studies for FVC are shown in Figure 2. Each individual has lost 20 percent of his FVC so that the total curve is left shifted 20 percent. The mean of these "restricted" twins is now at the FVC which marked the 1.64 \times SD limit of their normal twins or 4 L. Fifty "restricted" twins will have FVC higher than 4 L. If the 4 L cutoff for abnormal is used, 50 of these twins will be misdiagnosed. (If the 3.8 L or 2 SD cutoff had been used an even greater number would be misdiagnosed.) If loss of 20 percent of FVC is medically significant, 50 or more of these twins would, for example, be denied special respiratory care following abdominal surgery.

The basis for interpretive conclusions must be based upon clinical criteria, using statistical definitions to help. If I must disagree with Dr. Weiss it would be with the phrase, "the normal range is ordinarily defined ..." This ordinary definition is a statistical one and has no basis in what may or may not be important clinically. The normal range needs to be defined by the physician in the clinical setting.

Bernard E. Pennock, Ph.D., Associate Professor of Medicine; Robert M. Rogers, M.D., F.C.C.P., Professor of Medicine and Anesthesiology; Gregory R. Owens, M.D., Assistant Professor of Medicine; and Kenneth M. Unger, M.D., F.C.C.P., Assistant Professor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh

Figure 2. Distribution of FVC for 100 normal subjects of the same sex, height and age and the distribution for their 100 "twins" with 20 percent reduction in FVC ("restricted"). Striped region represents misdiagnosed "restricted" subjects.

References

Usual Interstitial Pneumonia following Texas A2 Influenza Infection

To the Editor:

I was pleased to note that the authors of the paper "Usual Interstitial Pneumonia following Texas A2 Influenza Infection" (Chest 1981; 80:123-26) considered the possibility that the lesion found in their case 1 might have been a manifestation of oxygen toxicity. However, it was disappointing to see that they discounted this concept because of the absence of hyaline membranes and capillary proliferation. The purpose of this communication is to call the authors' attention to a more recent article describing the evolution of lesions with time in patients with adult respiratory distress syndrome. In this article it was shown that hyaline membranes become less conspicuous with time, probably because they are progressively replaced by fibrosis. The fibrosis occurs mainly along alveolar ducts, which are also the major site of the hyaline membranes, and produces a characteristic pattern of branching, linear bundles of interstitial fibrosis. The photomicrograph of the biopsy from case 1 of Pinsker et al is strikingly similar to several of those in our article. This appearance was found in every one of the 25 cases whose therapy course was two or more weeks in duration. Reasons for considering it to be the result of oxygen exposure were discussed. The lesion is sufficiently characteristic to permit separation of such cases from cryptogenic fibrosing alveolitis on the basis of morphology alone. Only nine of the 25 cases had begun with a viral illness. Therefore, the lesion should not be considered as a direct result of viral pneumonitis. Case 2 in the article by Pinsker and associates does not appear to have this pattern of fibrosis and may indeed represent the sequel of a viral infection.

The survival of a patient with pulmonary fibrosis such as their case 1, documented by biopsy, is very surprising, but has been observed on several previous occasions. We have also observed one such case and another was presented as a clinical pathological conference. This last case was also thought by the authors to represent a late stage in evolution of an infectious process, in this instance, Legionnaires' disease.

Philip C. Pratt, M.D., F.C.C.P., Duke University Medical Center, Durham

References

Communications to the Editor: 659