ative exposure in this investigation, are reported to be the most common bacterial contaminants of metalworking fluids.\textsuperscript{10-12} From an epidemiologic perspective, the observation of precipitins such as those identified by Bernstein and colleagues does not equate with disease, but precipitins are an excellent marker of exposure. At least one other immunologic study of workers exposed to highly Pseudomonad contaminated metalworking fluid (in that case \textit{Pseudomonas pseudoalcaligenes}) found exposure-related IgG antibodies to the bacteria in workers' sera, but reported no evidence of HP in that cohort.\textsuperscript{12}

There continue to be many unanswered questions about the causes, natural history, and clinical management of HP in general.\textsuperscript{13} The role of agents other than thermophylic bacteria and the impact of high levels of exposure (characteristics that typify metalworking aerosols) are particularly interesting factors that, as they come to be better understood, may challenge widely held assumptions about HP. One example may be the relative predominance of certain lymphocyte subsets in this group of diseases.\textsuperscript{14} The report of Bernstein and colleagues provides a signpost pointing us toward an important avenue of future research in what may become an all too common occupational lung disease.

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\section*{The Quest for Normal Values}

The risk associated with extrapolating linear regressions outside the range of data on which they were based is presumably well known to the readers of CHEST. Some predictions of pulmonary function when extrapolated to short geriatric subjects yield negative values, which if issued on a computer-generated report would embarrass most pulmonary function laboratory directors. In this issue of CHEST (see page 663), Enright and associates have provided normal values for the age group 60 to 85, a rapidly increasing segment of our white population that has been seriously underrepresented in previous studies. Interestingly, the data from this study agree closely with linear extrapolations into this age range from the most commonly used studies.\textsuperscript{1} The subjects in this study were volunteers carefully screened to exclude history of symptoms or diseases which might impair cardiopulmonary function. Strictly, these results should apply only to this population of Northern European ancestry who for the most part were lifelong residents of the urban nonindustrial Upper Midwest. However, similarities between these studies and other white populations in the United States and Europe support wider applicability, particularly in the absence of other data. The chief clinical application of normal values is to identify individuals outside the normal range. Discrepancies between normal value studies can be problematic. An individual could be diagnosed as having mild airways obstruction or normal lung function with the same FEV\textsubscript{1} and FVC when compared to different normal values studies. Over the years, the science of normal value studies has improved. Initial studies were performed on patients hospitalized for diagnoses other than lung disease, but undoubtedly included many heavy smokers, patients with other diseases that impair pulmonary function, and individuals who by today's
standards would be diagnosed as having airways obstruction. Refinements in instrumentation, standardization of methodology beginning with the original Snowbird Conference in 1977, and careful attention to population selection has resulted in more recent studies yielding comparable predictions as illustrated in the figures in the current study by Enright et al.

Some residual differences remain. The study by Enright and colleagues reports significantly higher peak expiratory flows than other studies. This almost certainly is the result of quality control software which was used in this study and which emphasizes maximizing peak expiratory flow rates. The study by Crapo et al predicts higher FEV1 for men, but not for women than the current or other recent studies cited by Enright et al. It is not clear whether this difference is totally due to the population sampled or whether methodologic differences contribute. Once a threshold of expiratory effort is achieved, further increases in expiratory effort produce reductions in FEV1 because of the effect of intrathoracic gas compression.3 This effect is directly proportional to lung volume and expiratory muscle strength, and therefore, would be more prominent in men than women. The largest FEV1 and the FEV1 associated with a maximal effort are equally reproducible1 but may be substantially different. Inclusion of submaximal efforts in the construction of a composite best spirogram results in significantly higher FEV1 than directly measured.4

Subtle differences in mean predictions due to combination of population and methodology are very small relative to the between-subject variability. In the current study, the difference between the mean value and the lower limit for normal FEV1 and FVC is comparable to the changes that occur over 15 to 25 years with aging. This vexing variability greatly reduces the sensitivity of these measures for the detection of abnormalities. A person starting at the upper fifth percentile would have to experience more than a 40% reduction in FEV1 to reach the lower limit of normal. A fair amount is known about the causes of the variability in maximal flow as a function of lung volume that produces this great variability. FVC, the difference between TLC and RV, is a function of lung size, and FEV1 is highly correlated with FVC. For a given height, lung size varies with body habitus. A 1.8 m, 94.9 kg mesomorph will have a larger lung volume than a 1.8 m, 65.5 kg ectomorph of the same age. Body mass is not a good additional predictor because for any given body habitus, obesity reduces TLC due to mass loading of the trunk. Measurements of chest size cannot be used because rib-cage volume changes with pathology induced changes in lung volume. To my knowledge, no studies have been done of other parameters such as ring or shoe size which might correlate with body habitus.

The primary determinant of maximal flow and residual volume in adults is lung elastic recoil. Reductions in recoil appear to be the primary determinant of the reduction in both vital capacity and FEV1 with age. Differences between biologic and chronologic aging rates may contribute to the variability of flow in the elderly, but it is unlikely to be the major determinant because although the fractional variability may increase, the absolute variability is not substantially different in young adults. Muscle strength should be a determinant of lung capacity and thus a potential predictor of FVC, although in the Minnesota study, this correlation was present only in those individuals in the lowest quartile of FVC.

If lungs were aerodynamically similar, flow would scale with volume, and FEV1/FVC would be constant except for the differential effect of age on volume and flow. Although FEV1 and FVC are highly correlated, there is a great deal of variability in FEV1/FVC or other indices of relative emptying rate in all ages. This is maintained because during fetal development, airways rise from different primordial tissues than the alveolar tissue which is responsible for most of the volume and elasticity of the lung. Airway size may develop independently of lung parenchymal size. This has been termed dysnaptic growth.6 Therefore, for a given lung elastic recoil and volume, there is considerable variability in maximal flow. There is no known biologic marker to predict maximal flow based on genetic airway size to increase the sensitivity of flow measurements for disease detection.

In summary, in spite of recent advances in documenting normal values for lung function from growth and development through senescence, the sensitivity and specificity of these measures are limited by the large between-individual biologic variability. Our understanding of the structural and functional determinants of normal variability has not resulted in improved normal predictions. Serial changes in lung function remain a far more sensitive means of detecting early disease than isolated measurements.

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REFERENCES

Tuberculosis Chemoprophylaxis and Physicians

In the past 2½ decades a significant body of evidence has shown, unequivocally, that isoniazid (INH) chemoprophylaxis markedly reduces the risk of developing active tuberculosis (TB), especially for recently infected individuals.1 Isoniazid, however, has been uncommonly associated with clinically significant hepatitis and rare fatalities have been reported, especially in older adults. As a result, guidelines for administration and monitoring of INH chemoprophylaxis have been devised with the intent of minimizing the risk of toxicity.2

Despite the above knowledge, however, one wonders if anyone out there is really listening. Studies show us that physicians may be the worst offenders. Data from surveys3 show that, as few as 8% of tuberculin-reacting physicians have taken isoniazid chemoprophylaxis for their own skin test conversion, let alone complete a fully prescribed course! Although the reasons for this are not clear, it is likely that when it comes to practicing what we should be preaching, in the depths of our subconscious the imp/angel paradigm of logic most likely warps and wobbles our decision-making.

The Paradigm May Unfold As Follows

Angel: “Your lifetime chances of getting active disease once infected can be as high as 10%. Why, you can spread disease to your loved ones! You might die of it if you don’t prevent it. It makes rational individual sense and it is good public health policy to take INH for a few months. The medical literature supports its effectiveness. Besides, you should practice what you preach . . . .”

Imp: “Don’t listen to that public health rubbish . . . they’re more worried about the masses than about you, as an individual. Who cares if every once in a while somebody dissolves their liver with INH, as long as the proletariat is protected from spreading TB to the world? Your lifetime chances of getting TB are only as low as 4%. You have no symptoms, why risk getting sick from a medicine? Remember in second year of medical school, they said INH is bad for your liver as you get older . . . ? It must be important, because it is on every board exam . . . besides, you can’t drink alcohol while you’re on it; it also makes you sleepy . . . and you probably shouldn’t take any medications if you’re thinking of getting pregnant, anyhow. Besides, remember that nurse last year who was put on INH and died even after a liver transplant? Or how about that family doctor who got sued for giving INH to a patient and then the patient missed his appointment and got hepatitis? Who needs the hassle? If I were you, I wouldn’t take that stuff, and I wouldn’t push it on any of your patients!”

Sound Familiar?2

Given this imp/angel paradigm, is it any wonder that physicians may be reluctant to prescribe INH chemoprophylaxis to patients, especially for those who are older and asymptomatic? In their prospective study published this month in CHEST, Sorresso and coworkers (see page 706) point out that isoniazid chemoprophylaxis is sorely underutilized in older, tuberculin-reactive contacts in the state of Tennessee. They found that only half of tuberculin positive contacts over age 50 ever received INH chemoprophylaxis. Moreover, of 829 people who were unequivocally candidates for chemoprophylaxis, only 30% ever truly completed a full course. Therefore, a meager one in three individuals in this group received the true benefit of tuberculosis prevention by INH, and this is in the very same age group where the incidence of active TB was 17.8/100,000, or nearly double that of the general population! Why? Their questionnaire data indicated that nearly two-thirds of physicians cited the reason for not starting INH chemoprophylaxis in these older patients was solely the result of “fear” of age-related side effects.

So where does the answer lie? Is INH chemoprophylaxis safe? The answer is “Yes,” (with a qualitative “most likely”), in defined subpopulations, including the elderly. A recent decision-analysis reevaluating previous decision analyses concluded that if the INH-associated case-fatality rate is less than 1%, and if the TB-associated case-fatality rate is greater than 7% in a population under age 35, then INH chemoprophylaxis is beneficial, and safe.4 Decision analyses have also been devised for chemoprophylaxis in the elderly.5 Moreover, Stead and coworkers6 found that in elderly recent-tuberculin converters in a nursing home population in Arkansas, the risk of developing active tuberculosis without chemoprophylaxis clearly outweighed the risk of INH-associated hepatitis. In the present study by Sorresso and co-workers, no cases of those over age 50 started on INH chemoprophylaxis developed hepatitis, although 7% had elevated liver function tests. Since their study did not address how many cases