tious causes. Hence, patients with known contained mycetoma disease, treated preoperatively, had quite acceptable outcome.

It is of interest that three of the nine mycetomas found in explanted lungs were not seen on CT scans at 2 months, 6 months, and 9 months preoperatively. Presumably, these mycetomas progressed in the intervening time or might have been difficult to detect. Given the authors' conclusions (that mycetomas should be treated as a form of septic lung disease mandating bilateral lung transplant, and that pretransplant treatment with antifungal agents is helpful), perhaps repeat CT scan(s) may be indicated while awaiting transplant, at least in the sarcoidosis population at highest risk for mycetoma development. In an era of increasing waiting times, initial CT screening may not be enough.

Notably, there were only three fungal infections in the explanted lungs of the remaining 294 patients (including 69 patients with cystic fibrosis): one invasive pneumonitis and two airway colonizations. This low colonization incidence is in contrast to studies in cystic fibrosis patients, who commonly have pretransplant Aspergillus colonization (52% in one series), but are not at increased risk for posttransplant invasive Aspergillus infections, even without antifungal treatment.[3–5] However, six of nine patients with mycetomas in the Duke series suffered from sarcoidosis, a known risk factor for mycetoma. This predisposition may be due to the altered expression of natural killer inhibitory receptors on T cells of patients with sarcoidosis,[6] considered a possible cause of the disease as well as predisposition to some infections. General conditioning may also be part of the explanation for differing outcomes: cystic fibrosis transplant recipients tend to be young and with strong cough muscles; patients with mycetomas more often are chronically debilitated.

The authors point out that posttransplant survival in patients with sarcoidosis is less than for other disease states, but the survival difference is small.[7,8] Relatively few patients have undergone lung transplantation for sarcoidosis (1 to 2% of all lung transplants), and hence it is difficult to accurately categorize risks within such a small group. Nonetheless, this study of a handful of patients is helpful to point out some caveats: beware of aspergillomas in sarcoidosis patients, transplant only contained disease, and treat with long-term antifungals.

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Epidemiology of Asthma

Severity Matters

How should asthma be defined in population studies? The question is deceptively simple, and its answer remains elusive. Since questionnaires are the most practical tools to use in screening populations for asthma, much attention has focused on developing survey definitions of asthma based on questionnaires. In general, the approach to validating such definitions has been to assess the ability of individual questions and combinations of questions to predict which individuals in a population have either clinical diagnoses of asthma or nonspecific bronchial hyperreactivity (BHR) to agents such as histamine or methacholine.[1] Unfortunately, physicians' diagnoses of asthma and BHR are not particularly good "gold standards" for identification of asthma. It is likely that a physician's diagnosis of asthma underdetects subclinical mild asthma. Thus, using it as a "gold standard" will tend to underestimate the specificity of a questionnaire. In contrast, BHR is present in many people without asthma.[1–3] Therefore, use of BHR as a "gold standard" will underestimate sensitivity.

Recognizing these limitations, many studies[1,4–6]

have assessed the ability of questionnaires to predict a physician's diagnosis of asthma and/or BHR. In general, questions about ever having asthma, ever having asthma diagnosed by a physician, and having wheezing during the previous 12 months have been the questions with best sensitivity and specificity for prediction of the flawed "gold standards." Thus, responses to these questions are often used in survey definitions of asthma. In this issue of *CHEST* (see page 135), Ponsonby et al report a study suggesting that evaluation of severity can be used to classify into subsets individuals identified by questionnaire to have symptoms of asthma or the disease itself. The study is a cross-sectional survey for asthma conducted in 1999, evaluating children aged 8 to 10 years from randomly selected schools in the Australian Capital Territory. Children of the same age presenting in 1999 to the only three hospitals in the Australian Capital Territory able to manage acute pediatric asthma were also evaluated. For all of these children, asthma was identified using a questionnaire and atopy by a panel of allergy skin tests. Among those reporting wheezing in the previous 12 months, a stronger relationship was noted with atopy for those reporting > 12 episodes of wheezing in the last 12 months than for those reporting 1 to 3 episodes in the last 12 months (odds ratios [ORs], 8.70 vs 3.27, respectively). Atopy was also found to be more strongly associated with 1999 hospital attendance for asthma than with ever having had asthma (ORs, 16.95 vs 2.09, respectively). The proportion of "asthma-ever" attributable to atopy was 33%, while for hospital attendance in 1999, this proportion was 89%. Based on these findings, the authors suggest that atopy contributes more to frequent or severe asthma than to infrequent or mild asthma.

These findings are consistent with those of other studies. The important association of atopy with childhood asthma is well accepted.[7] A review[8] of studies relating atopy to asthma notes that in cross-sectional studies conducted exclusively or predominantly in children, the proportion of cases attributable to atopy varied from 25 to 63%, with a weighted mean of about 38%. Previous studies[8] have also suggested a relationship between atopy and asthma severity. Atopy is also related to degree of BHR.[9,10] Conversely, in patients having wheeze in the previous 12 months, BHR is related to both atopy and measures of disease severity such as peak flow variability.[11]

Thus, it has become increasingly apparent that populations identified by survey definitions of asthma based on self-report of asthma or asthma symptoms are a heterogeneous population. This population can be further subdivided into more homogenous subsets. Those with mild or inactive disease are less likely to be atopic or exhibit BHR. In contrast, those with more severe disease are more likely to be atopic and exhibit BHR. It has already been proposed that measurement of BHR can be used in combination with questionnaire responses to define subpopulations of asthmatics.[3,11] Perhaps it will also prove useful to define subpopulations based on severity of disease using questions such as those in the wheezing module of the International Study of Asthma and Allergies in Childhood questionnaire.[12] This approach has already been applied to evaluation of asthma prevalence, documenting that increases in the prevalence of asthma diagnosis and symptoms in Sheffield, UK, between 1991 and 1999 were confined to mild symptoms.[13] Identification of more homogeneous asthmatic subpopulations should also facilitate population studies addressing issues such as asthma pathogenesis and effectiveness of preventive interventions such as allergen avoidance.

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Sleep-Related Breathing Disorders

Is It All About Apnea?

It is generally accepted that sleep represents a period of abnormal or unstable respiration, largely manifest as either obstructive or central apnea. Recognition of the clinical significance and ubiquity of these phenomena has driven the widespread proliferation of sleep laboratories largely dedicated to studying sleep apnea. The clinical presentation of obstructive sleep apnea (OSA) is well-known to clinicians and includes obesity, snoring, and daytime hypersomnolence. The article in this issue of *CHEST* (see page 158) by Gislason and colleagues has drawn our attention to another sleep-related phenomenon that may also be exacerbating and/or contributing to sleep-related breathing disorders, *ie*, gastroesophageal reflux (GER). They have shown a strong relationship between respiratory symptoms and sleep-related heartburn, and they have shown in other publications[1,2] the relationship of sleep-related heartburn to symptoms of OSA such as snoring and obesity. It would appear from this research, and other outcomes that have been published from the European Community Respiratory Health Survey, that sleep-related GER may be another one of those "things that go bump in the night." In the current article, the authors establish a strong coincidence of asthmatic and other respiratory symptoms occurring in individuals who report symptoms of GER (*ie*, heartburn and belching) occurring at least 1 to 2 nights per week. A strong correlation, however, or even a robust odds ratio does not establish a causal relationship. Are there data available that would suggest that these events may have an underlying common cause or linkage?

Clearly, there is a body of literature accumulating suggesting a relationship between GER and asthma. In studies by Sontag and colleagues,[3,4] they have established a very high incidence of GER (confirmed via 24-h pH monitoring) in a large group of unselected asthmatics, and they have also demonstrated that 39% of asthmatics were shown to have esophagitis. The clinical relevance of these findings and the physiologic mechanisms have been studied. There are numerous studies that show that the treatment of asthmatic patients, particularly those who seem to have refractory and/or nocturnal symptoms, can be improved by the administration of standard acid-suppression therapy to treat GER.[5] Adding credence to this clinical approach are numerous studies[6,7] that have shown a bronchoconstrictive response to distal esophageal acid mucosal contact. In fact, there are data to suggest that other respiratory symptoms and disorders of the upper airway can be linked to the occurrence of GER.[8] With symptoms other than asthmatic symptoms, the rational is not as clear-cut, and it would seem that higher risk is associated with the prolongation of acid clearance during sleep. Studies[9–11] from our laboratory have shown that the risk of this is greater during sleep secondary to the suppression of normal clearance mechanisms, such as salivation and swallowing. In fact, in a recent study[11] from our laboratory, we have documented that the proximal migration of minute amounts of acid infused into the distal esophagus is significantly facilitated during sleep.

From a purely clinical prospective, it would seem rational to assume that in individuals with difficult-to-manage asthmatic symptoms, and the occurrence of nocturnal heartburn, treatment with acid-suppressing drugs such as proton pump inhibitors would have a salubrious effect on asthmatic symptoms. Although the report by Gislason and colleagues does not specifically address daytime heartburn symptoms, it does support the previously reported data[12] that suggest that nocturnal heartburn is a useful clinical symptom in determining the presence of esophageal disease. However, one should not succumb to the easy logic that the absence of heartburn rules out or precludes GER as a potential contributor to asthmatic symptoms. Harding and colleagues[13] have shown as many as 63% of asthmatics without reflux symptoms have significant GER. Accordingly, Gislason and colleagues have noted that individuals from this random population who had nocturnal heartburn were more than twice as likely to have a valid diagnosis of asthma compared to those who did not. These differences remained significant after appropriate adjustments for gender, age, body mass index (BMI), and other symptoms related to sleep-disordered breathing such as snoring. In the current study and two related studies[1,2] published by the same group of investigators, they have described nocturnal GER as an independent risk factor for snoring, daytime sleepiness, and a variety of sleep