Research Fellowships in Pulmonary and Critical Care

In a recent editorial written by Dr. Block (November 2001), he takes issue with American Lung Association (ALA) procedures that are designed to maximize the likelihood that fellows who receive research training awards pursue research careers, and therefore do not support clinical training. We respond that the reasons for these procedures are straightforward and compelling.

We receive many more qualified applications than we can award. The funds received by the national ALA to support fellowships are designated for support of research. Our advisory committees have long taken the position that these monies are best used by supporting the training and work of researchers early in their careers, prior to their becoming competitive for National Institutes of Health support. A recently completed study of the effectiveness of this approach showed that 85% of awardees continued their work in research and many had become leading scientists. Thus we believe that the program has been highly successful and that use of these funds for goals other than advancing research would not be keeping faith with our supporters—the American public. In this spirit, most state and local Lung Associations follow the procedures set by the national ALA.

Let us now turn to the substantive issue, people power in pulmonary and critical care medicine. Block pointed out that the recently completed Committee on Manpower of Pulmonary and Critical Care Societies (COMPACCs) study predicts an inadequate supply of pulmonary and critical care specialists in the relatively near future. This may well be the case. However, given the collective size of clinical training programs, ALA support could only increase the pool of trainees to a very limited degree. The major funding for graduate medical education is provided by the federal government through the Medicare program and through other governmental vehicles in a few states. Any significant increase in external support for subspecialty training in pulmonary and critical care medicine will require changing the policies of these programs. The ALA Scientific Advisory Committee will soon undertake a review of the COMPACCs study. If, as seems likely, we concur with the findings and recommendations, we stand ready to work with interested professional societies and others to make the case to governmental agencies and the American public.

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Atrial Mechanical Performance Following Internal and External Cardioversion of Atrial Fibrillation

Its Relationship to Peripheral Embolization and Acute Cerebrovascular Accident

Atrial fibrillation (AF) is the most common persistent and intermittent arrhythmia seen in clinical practice. A recent large cross-sectional study by Go et al found a prevalence of AF of 0.95% in study patients ≥ 20 years old. The prevalence ranged from 0.1% in individuals < 55 years old to 9% in patients > 80 years old. These investigators estimated that there are currently 2.3 million adults with AF in the United States and that, since the prevalence is age related, this number could increase to somewhere between 5 million and 6.3 million by 2050. The implications of this problem are many and include the financial burden associated with treatment, effects on quality of life, and an increased risk of other medical conditions, such as heart failure and throm-
boembolism. The most potentially devastating associated problem is embolic cerebrovascular accident (CVA).

The Atrial Fibrillation Investigators found that the incidence of CVA in patients with AF averages 5%/yr in those who are not treated with anticoagulation. The rate varies among those with AF, depending on the presence or absence of other medical conditions. These investigators identified independent risk factors for CVA through multivariate analysis of pooled data. They found previous CVA or transient ischemic attack, increased age, history of hypertension, and diabetes mellitus to significantly increase the risk of CVA in patients with AF. Patients in their study were classified into risk categories based on the presence or absence of these risk factors. The investigators found that the event rate in those with AF ranged from 1% in patients < 65 years old with no risk factors, to 8.1% in patients > 75 years old with one or more risk factors. Most of these strokes are secondary to stasis-induced thrombi within the left atrial appendage that subsequently embolize. The risk of CVA is greatly reduced with use of anticoagulation therapy. The risk reduction in patients treated with warfarin has been shown to be approximately 68%.

Therapy for AF falls in two broad categories: (1) ventricular rate control and anticoagulation, or (2) cardioversion to sinus rhythm and maintenance of sinus rhythm with pharmacologic agents. Almost all would agree that every patient should have an attempt to restore regular rhythm with either electrical or pharmacologic cardioversion. This can be done with antiarrhythmic medication administered prior to cardioversion or immediately following. All would agree that the sooner cardioversion can be undertaken, the greater the likelihood of success and also the greater the likelihood of a persistence of regular rhythm.

Two major complications of cardioversion are thrombogenesis and atrial stunning, both of which predispose to thromboembolism. Thrombi usually form in the left atrial appendage, which is the only portion of the left atrium that is trabeculated. When functioning normally, the appendage contracts both longitudinally and circumferentially to express blood from its cavity. During fibrillation, blood is not actively expressed from the left atrial appendage and thrombus forms in the interstices of the trabeculae. These thrombi may embolize, especially after return of normal atrial function. Approximately 75% of initial emboli lodge in cerebral vasculature causing a CVA; 70% of such emboli result in severe neurologic disability or death. Bjerkelund and Orning found a 6.8% incidence of embolic events in patients with atrial arrhythmias who were not anticoagulated prior to direct-current cardioversion and who had a return to normal sinus rhythm. Patients in the comparative group, who were receiving anticoagulation, were noted to have a 1.1% incidence of embolic events after return to normal sinus rhythm. If AF has been present for < 48 h, anticoagulation is not necessary. If AF has been present for > 48 h or for an unknown period, then the patient should receive anticoagulation therapy. It is unclear whether the thrombogenicity of cardioversion is due to electrical injury to the atrial myocardium, the stunning of the atria, or both.

Postcardioversion CVAs occur most frequently within 2 to 3 days of the procedure, but may occur as long as 2 to 3 weeks after the procedure. There are two reasons for this: (1) the mechanical contraction of the left atrium may be delayed, and (2) it may take 2 to 3 weeks for thrombus that has formed in the left atrial appendage to become adherent to the wall of the appendage. The most recent recommendations for anticoagulation in patients undergoing elective cardioversion in whom the arrhythmia has been present for > 48 h are: (1) therapeutic warfarin (target international normalized ratio, 2.5; range, 2.0 to 3.0) anticoagulation for 3 weeks before elective cardioversion, and (2) anticoagulation for 4 weeks after successful cardioversion.

Recent studies have shown that transesophageal echocardiographically guided cardioversion may offer a safe alternative to these recommendations. The Assessment of Cardioversion Using Transesophageal Echocardiography Investigators studied a conventional approach to cardioversion vs an approach of transesophageal echocardiography (TEE) after diagnosis of AF with treatment guided by the results of that echocardiogram. Patients in whom no intracardiac thrombi were detected by TEE were treated with short-term anticoagulation and external direct-current cardioversion within 24 h to 5 days. Anticoagulation was continued for 4 weeks after cardioversion in both groups. The results showed no significant difference in the rate of embolic events between the two groups. There were, however, significantly fewer hemorrhagic events in the TEE-guided group. There was also a greater rate of successful restoration of sinus rhythm and shorter time to cardioversion in the TEE-guided group.

Another technique for cardioversion is internal electrical cardioversion. This technique utilizes catheter-based electrodes that are placed within the cardiac chambers and provide low-energy atrial defibrillation. Since extracardiac tissue is bypassed, the delivered electrical potential is greater. For this reason, the success rate of cardioversion by this technique should be superior to external cardioversion. Lévy et al. found that this method of cardio-
version was more effective than external cardioversion with no increase in complications. It was also shown to be effective in patients in whom external cardioversion was unsuccessful. Therefore, despite the potential for the complications associated with any invasive procedure, this procedure will continue to be utilized in patients who are deemed less likely to respond to external cardioversion or who have undergone unsuccessful external cardioversion.

In this issue of CHEST (see page 13), Lehmann et al report a randomized study of external vs internal cardioversion. They measured the time to return of “basal” atrial contraction of right and left atria using echocardiographic techniques and assessed tissue injury using enzymatic measurements. They found that there was no difference in the time of return to normal atrial mechanical performance. They found that the left atrium often remained stunned beyond day 7, with a return to basal function by day 28. They also found that the return to basal function of the right atrium was almost immediate. Finally, they found no evidence of significant cardiac tissue injury with either internal or external cardioversion. Given a propensity for both right and left atrial thrombus formation in patients with AF, there is the potential for pulmonary embolism, in addition to CVA. Therefore, the current American College of Chest Physicians’ recommendations for anticoagulation prior to and following electrical cardioversion seem vindicated.

Although the findings of this well-conducted study seem quite concise, the number of patients studied was relatively small and further studies are needed to corroborate these findings. Further studies are also indicated to determine if these findings apply to patients with atrial flutter, and whether patients with atrial flutter who are atrially paced into sinus rhythm also have atrial stunning and a propensity for thrombus formation and embolization. As further studies are reported, it may be possible to further refine therapy and increase the safety of cardioversion.

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Of Time and Experience

Sarcoidosis Revisited

Sarcoidosis, an immunopathogenic inflammatory disease of unproven etiology and universal organ involvement, has generated a vast literature. We have a good understanding of its clinical and laboratory manifestations, and a consensus exists that symptomatic and/or significantly organ-impairing disease can be treated. Certain questions continue to be addressed, however, in much of the literature, with no clearer answers today than existed 25 years ago, as a recent revisit of the proceedings of an early international symposium on sarcoidosis held in New York in 1975 made eerily apparent: Are there acceptable substitutes for systemic corticosteroids? Are they useful early in therapy, or only when steroids have proven ineffective or cannot be discontinued without relapse, or have caused morbidity? How can the course and outcome of a particular patient be...
predicted? What is the optimum dose and duration of therapy? Unquestionable advances in imaging and in understanding and measurement of immune and inflammatory processes have not answered these questions.

Certain observations made 3 decades ago still provide useful guidelines. Although rates of relapse have varied (the highest being 70%), there was a consensus that relapse did not occur until prednisone dosage was decreased to 10 to 15 mg/d. Most manifestations of this multiorgan disease are detectable within the first year of observation. The time of onset of chronic sarcoidosis cannot be specified, making any attempt at a prognostic timeline tenuous.

The likelihood of ultimate remission is great (60 to 80% spontaneous remission) in stage I (mediastinal/hilar lymphadenopathy alone on standard radiographs) and stage II (adenopathy with infiltrate; 50 to 70% often with therapy), especially if the disease is acute in onset. Remission is much less likely (< 30%) in stage III (infiltrates alone) and virtually nil in stage IV (radiographic evidence of fibrosis, including bullae, microcysts, and retraction). Nevertheless, even patients with long-standing fibrotic disease may improve with therapy, and such patients deserve a trial. While symptoms, radiographic abnormalities, and vital capacity (VC) are likely to improve (in as many as 75% of patients treated), improvement in diffusion capacity of the lung for carbon monoxide (DLCO) is far less likely (< 33% in the same large study); when it does improve, it is often much later. Improvement in pulmonary function may prevent or delay cor pulmonale, one of the major mechanisms of mortality in sarcoidosis. An early investigation (1971) of pulmonary circulation in patients with sarcoidosis found that increased pulmonary vascular resistance, increased pulmonary artery pressure, and reduced cardiac index all correlated with impairment in DLCO. More recent techniques have demonstrated the correlation between right ventricular function and total lung capacity. Despite favorable remission rates for the most common presentations of pulmonary sarcoidosis, mortality of chronic disease is appreciable, life expectancy is shortened, with 75% of deaths occurring before the age of 60 years, and radiographic abnormalities often persist a lifetime.

Are we accumulating sufficient experience to answer one of the most critical and long-standing questions: Does therapy, whatever its short-term benefits, affect the long-term status of sarcoidosis patients? Previous randomized prospective trials showed no differences in treatment arms, but enrolled patients with no or minimal symptoms and impairment whose prognosis without treatment would be favorable. More recently, the British Tho-
an improved functional outcome,” provides a second scientific basis for treatment, that long-term as well as short-term benefits may be achieved. It also demonstrates the contribution of a nationwide cooperating system of sarcoidosis centers, and supports a therapeutic effect from inhaled steroids.

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Of Mycetomas and Men

Aspergillus is a ubiquitous fungus found in soil, water, and decaying matter. It is readily airborne and causes a variety of respiratory conditions, including allergic bronchopulmonary aspergillosis, parenchymal tissue invasion, and mycetoma. Mycetomas have long been recognized to occur in patients with preexisting pulmonary disease that results in focal destruction of lung tissue, leading to the formation of an intraparenchymal cavity. An early English postmortem report of a pulmonary mycetoma described “a soft velvety mass...firmly attached to the wall of the cavity. Under the microscope it exhibited a distinct mycelium...”1 It became widely recognized that individuals with healed tuberculous cavities were at risk for development of fungus balls. As the incidence of tuberculosis declined, mycetomas were identified with greater frequency in individuals with advanced sarcoidosis, pneumoconiosis, and bullous emphysema.2

With the rise of transplant medicine, Aspergillus has become a scourge, with invasive parenchymal infection afflicting 5 to 8% of solid-organ transplant recipients, and having 50 to 100% mortality. In some centers, it has been a leading cause of posttransplant death. Most Aspergillus infections after any solid-organ transplant occur in the lung, and the transplanted lung is particularly vulnerable to Aspergillus. Since the pathogen is airborne, the lung is the only transplanted organ in direct contact to Aspergillus. Moreover, the transplanted lung has a diminished cough reflex, an abnormal mucociliary clearance, and a bronchial anastomosis that is the site of local inflammation promoting Aspergillus colonization. All of these reasons predispose the post-lung transplant patient to Aspergillus infection. However, little is known about the consequences of pretransplant mycetomas (usually caused by Aspergillus), which are generally considered a strong relative contraindication to transplantation. Given the high mortality associated with invasive Aspergillus and lung transplantation, it would stand to reason that an individual with a dense, focal inoculum of Aspergillus organisms, ie, a fungus ball, might be at increased risk for posttransplant fungal disease.

This month a report by the transplant group at Duke University retrospectively reviewed the clinical course of 9 of 303 lung transplant recipients found to have a mycetoma in an explanted lung. Six of nine patients were identified preoperatively as having a mycetoma on chest radiograph or CT scan. One of these, their first patient, was not treated preemptively with antifungals and died 20 days postoperatively. Another patient had Aspergillus growing from pleural fluid 3 weeks prior to transplant, and died in the operating room from sepsis. Apart from these two deaths (both, admit the authors, involving bad judgment), there was only one death in the remaining four patients with preoperatively known mycetomas, at 24 months after operation, due to noninfec-
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. 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, 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. 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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References

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. 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. Therefore, use of BHR as a “gold standard” will underestimate sensitivity.

Recognizing these limitations, many studies have...
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. A review 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 have also suggested a relationship between atopy and asthma severity. Atopy is also related to degree of BHR. 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.

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. 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. 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. 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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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\textsuperscript{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,\textsuperscript{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.\textsuperscript{5} Adding credence to this clinical approach are numerous studies\textsuperscript{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.\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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

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complaints, including difficulty initiating sleep, nocturnal awakenings, and early morning awakenings.

How could GER be related to such an apparent diversity of respiratory and neurobehavioral symptoms? In attempting to establish any relationship between symptoms of GER, or the actual occurrence of GER, and other symptoms such as snoring and chronic cough, it should be recognized that heartburn is a very common symptom that can easily overlap with a variety of other symptoms by chance alone. Establishing a cause-effect relationship among phenomena that occur commonly is quite difficult and requires a sophisticated statistical approach. That is, snoring and heartburn are obviously extremely common, and would therefore be expected by chance alone to occur in a fairly significant portion of any randomly selected population. In their study, the authors report that all the differences noted, except for the relationship between GER and morning cough, were significant after adjusting for possible confounding factors such as gender, age, smoking, BMI, and symptoms related to sleep-disordered breathing. Another somewhat more precise approach, not utilized in this study, would be to analyze the concurrent occurrence of two symptoms in time, such as wheezing and the occurrence of GER. This would require a signal detection analysis to assess whether the occurrence of the two (or any two) symptoms are occurring together with a frequency greater than chance.14

GER is a phenomenon that has been believed to be largely caused by an incompetent lower esophageal sphincter. Thus, a defective lower esophageal sphincter (< 10 mm Hg) would much more easily allow the retrograde flow of gastric contents under a circumstance of a somewhat enhanced pressure gradient between the abdominal cavity and the thoracic cavity. Thus, given the extreme negative pressures created by airway obstruction in patients with OSA, it would be a reasonable assumption that this patient population would be at considerable risk for the occurrence of nocturnal GER and its attendant complications. In addition, obesity would also be a putative risk factor by enhancing the pressure gradient via increased intra-abdominal positive pressure. Since obesity is also clearly a risk factor for OSA, and the current study, as well as the others by this research group, has established a clear relationship between symptoms of nocturnal GER and those commonly associated with OSA (snoring and daytime sleepiness), it would be postulated that there is a strong relationship between the occurrence of obstructive apneic events during sleep and the concomitant occurrence of GER. Furthermore, the resolution of GER by treating patients with contin-

Several studies16,17 have been done to assess the simultaneous occurrence of GER and OSA, with negative results. No study employed an appropriate signal detection analysis referred to above. In one study by Graf and colleagues,16 OSA was determined only by a drop in the oxygen saturation by approximately 4%. Using this as an identifier for OSA, they simultaneously monitored esophageal pH in order to detect episodes of GER. They found no significant difference between mild and severe groups of OSA in terms of percentage of esophageal acid contact time, and they concluded that there was no obvious relationship between obstructive events and GER. They did, however, note that 80% of their patients showed an increase in GER. This study has the additional flaw of not adequately identifying all episodes of OSA, since determining OSA events only by the determination of reductions in oxygen saturation by 4% will not identify a number of relatively mild obstructive events. A similar study by Penzel et al17 utilized more traditional polysomnography to determine episodes of OSA. In their study, they identified the occurrence of 69 episodes of sleep-related GER, and 38 of these were noted to occur during polysomnographically documented sleep. Virtually all of these were associated with polygraphically identified arousal responses. Although they indicated that GER has a very high incidence in the OSA population, they could not establish any significant relationship between GER and OSA events. Thus, the pressure gradient hypothesis discussed herein is not supported by either of these studies. In a somewhat more definitive study, Ing and colleagues18 studied a group of patients with polysomnography documented OSA compared to a group of control subjects, with regard to the simultaneous occurrence of obstructive events and GER as monitored by esophageal pH. They found that patients with OSA have significantly more GER events than control subjects, but only slightly more than half of the reflux events were noted to be temporally related to apneas or hypopneas. They subsequently subjected both groups to continuous positive airway pressure treatment that resulted in a reduced reflux event in both groups. Reflux therapy with a histamine-2 blocker reduced arousal responses but had no effect on the apnea-hypopnea index in patients with OSA. The authors concluded that GER does not appear to be caused by OSA but may be involved in the pathogenesis of arousal responses. The latter is a particularly important clinical observation, since studies9,10 from our laboratory have suggested that arousal responses are critical in the clearance of acid infused into the distal esophagus during sleep.
Although obesity would appear to be a condition that overlaps both OSA and GER, Gislason and his colleagues have shown that GER appears to be a risk factor independent of BMI. Furthermore, one study has shown no effect of weight loss on the occurrence of GER. Again we have the overlapping occurrence of two very common medical conditions, which does not appear to show any obvious cause-effect relationship.

The study by Gislason and colleagues did not address two respiratory complications of GER that have considerable clinical relevance. Chronic cough, for example, is a common clinical problem that has been related to GER. Although this is a complicated and difficult area in which to establish a cause-effect relationship, there are some suggestive data. Jacob et al. for example, have shown that a patient with laryngopharyngitis can be distinguished from a group of patients with esophagitis by the increase in proximal esophageal acid contact time during sleep. Furthermore, some studies have shown that in patients with symptoms of chronic cough and GER, prolonged acid suppression therapy will markedly improve chronic cough (see Irwin and Zawacki for a review of this topic). Secondly, pulmonary aspiration is certainly the most serious and dangerous complication of sleep-related GER. Depressed consciousness is clearly a risk factor for pulmonary aspiration, and it has been demonstrated that the risk of pulmonary aspiration is substantially increased under conditions of depressed consciousness. Lastly, an interesting study has recently been published by Tobin and colleagues which overlaps both OSA and GER, Gislason and his colleagues have shown that GER appears to be a risk factor independent of BMI. Furthermore, one study has shown no effect of weight loss on the occurrence of GER. Again we have the overlapping occurrence of two very common medical conditions, which does not appear to show any obvious cause-effect relationship.

In conclusion, Gislason and colleagues have provided some extremely interesting and provocative data that suggest that a common and relatively benign event such as GER occurring in the waking state can become a significant and potentially dangerous condition when it occurs during sleep. This extends our knowledge of sleep as a significant and important phenomenon in understanding not only the importance of sleep-related GER, but our overall understanding of the myriad of manifestations of sleep-related breathing disorders.

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Hospice and Pulmonary Medicine

In that portion of the Hippocratic Corpus called the "Art," physicians were warned not to treat patients "who are overmastered by their disease" at the end of life, realizing that in most cases medicine was powerless.\(^1\) In the pre-Socratic era, before the discovery of hemlock, euthanasia meant psychologically preparing a dying patient for a good death because there were no medications to alleviate physical pain or painlessly end life. Times have changed. The scientific advances of the last 2,000 years have not only given us a rational understanding of how to treat the physical suffering of the dying, but have changed our attitude about involvement in the dying process. That medicine has become more actively involved in the dying process can be seen not only in our changed notion of euthanasia, which now implies active participation in patients' deaths, but also in the hospice and palliative-care movements.

Hospice, from the Latin hospitium, literally means a guest house.\(^2\) Hospices > 1,500 years ago were havens for travelers, the poor, and the sick. In early medieval times, the term began to be applied only to a place where travelers rested on their journey. They were often built in impassable and uninhabited areas such as mountain passes. Like euthanasia, the meaning of hospice has changed. It is no longer a place of refuge for the traveler, but rather a form of care intended to comfort the dying and their loved ones. Hospice care can be given at home, the place where most patients wish to die, or it can be given in a specialized care facility. As noted in this issue of CHEST (see page 220), there are now > 3,000 accredited hospices in the United States caring for > 500,000 patients a year. Most hospices are run by nonprofit organizations, but that is changing.

Hospice is a response to the advances of civilization. In prior centuries, we died unexpectedly and at a younger age, often from infectious diseases. In our modern era, only about 10% of us die suddenly, while most will die from a life-threatening disease after either a prolonged period of deterioration with a short "terminal" phase, eg, lung cancer, or a slow decline periodically associated with life-threatening crises, eg, COPD.\(^3\)

The demographics of hospice sites and users are not surprising. Most hospice care is given in the home (78%).\(^4\) Fifty-five percent of hospice users are women, and most are > 65 years old, white, married or widowed, and have a caregiver.\(^5\) As it has probably been for all time, end-of-life decision making and the burden of caring for hospice patients falls largely on women.\(^4,5\) Dying men tend to have their wives caring for them, while dying women are more likely to be cared for by a child or child-in-law. The presumed reason for this difference is that many husbands precede their wives in death. Not everyone who enters a hospice program stays in it until death. Almost 20% are discharged from their initial hospice program for reasons that range from transfer to another hospice program to a return to live with family or nonfamily loved ones.\(^4\)

From a disease perspective, cancer is the most common admitting diagnosis to hospice, while the most common nonneoplastic diagnosis is heart disease.\(^4\) Patients with lung diseases are second only to patients with circulatory diseases in the nonneoplastic category. If we add patients with pulmonary cancers and COPD together, they represent approximately 20% of hospice patients.\(^4\) Considering that noncancerous lung diseases are the fourth most common cause of death, it is surprising that more isn’t written about hospice and these lung diseases.

The lung cancer patient and end-stage COPD patient differ dramatically in the minds of chest physicians, nurses, and therapists when thinking about end-of-life care. The lung cancer patient’s last few months of life generally follow a relentless, predictable downhill course, with most caregivers conscientiously referring their patient to a home hospice program in a timely manner.

In contrast, physicians have a much harder time predicting the nearness of death of the severe COPD patient. In the Study to Understand Prognoses and Preference for Outcomes and Risks of Treatment, just 2 days before the deaths of their COPD patients, the physicians estimated a > 40% chance that their patients would live > 6 months.\(^6\) This prediction occurred while the patients were hospitalized. In another part of the same study, using extremely narrow inclusion criteria for predicting that the patients would die within 6 months of their date of assessment (a Health Care Financing Administration [HCFA] criteria for hospice admittance), approximately 50% outlived the prediction.\(^7\) It is this unpredictability that makes chest physicians reluctant to recommend hospice for COPD patients.

It seems that there are only two outcomes to the present dilemma of not being able to predict which noncancer, end-stage lung disease patients should be admitted to hospice. The first is that we eventually develop criteria that more accurately predict death in patients with COPD and interstitial lung diseases. Should this occur, physicians’ comfort levels with...
sending these patients to hospice would rise along with the number of referrals. Present criteria are largely, but not exclusively, based upon scientific measurements of lung function that, as previously noted, have not proven particularly accurate. In this issue of CHEST, Abrahm and Hansen-Flaschen propose three new criteria based less on physiologic measurements and more on responses to therapeutic trials and quality of life. They deserve serious consideration.

If adequate predictors of death within 6 months cannot be found for these patients and others who confound predictions, eg, dementia, then HCFA will have to either accept the fallibility of physician judgment and reimburse hospice programs for longer than expected care, or limit care. It is fashionable at this point in an editorial (the mention of financing health care) to raise the specter of limiting resources to care for patients. While it is true that Medicare already sets a cap on the amount that it will pay per patient per year for hospice care, it is unlikely that a federal agency would ever systematically terminate care to dying patients already in hospice programs because they outlived their expected life span. Society would not tolerate such insensitivity, nor should it. Rather, it is the hospice programs that take the financial risk by accepting Medicare funding and trying to live within their budgetary constraints.

The early hospice was a refuge for the traveler through unknown lands. At the end of our lives, we will all make such a journey. It is our task as physicians to try to understand when to tell our patients that it is time to begin their journey, and then to be their faithful companions.

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