



Asthma

The Epidemic Has Ended, or Has It?

All truths are easy to understand once they are discovered;
the point is to discover them.

Galileo Galilei (1564–1642)

Asthma, a chronic inflammatory lung condition with acute episodes of bronchoconstriction and exacerbation, is associated with considerable patient morbidity, a diminution of productivity, and an increase in health-care utilization. Throughout the 1980s and 1990s, there was a clear perception that asthma prevalence was increasing. This perceived trend prompted concern about a possible “asthma epidemic.” Worldwide efforts to promote awareness about asthma diagnosis, prevention, and treatment followed the publication of these concerns.¹ In the United States, the Healthy People 2010 initiative² has clearly targeted improving asthma care, awareness, and education as key objectives.

In this issue of *CHEST* (see page 1993), Vargas et al report on asthma trends in Mexico from 1991 to 2001, analyzing health claims data from a nationwide database representing approximately one third of the Mexican population. Asthma incidence (*ie*, newly diagnosed asthma cases determined by first-time family physician visits), emergency department visits for asthma, and hospital discharges with asthma listed as a primary diagnosis steadily increased from 1991 to 1995. This increment was followed by a plateau (from 1995 to 1997) and a subsequent decline (from 1997 to 2001). It appears that in Mexico, at least for a third of the population with health insurance, there is an early trend toward decreased health-care utilization by asthmatic patients. This may, in part, be due to a decrease in the incidence of asthma in this population. Can the same be said about the incidence of asthma in the United States and other countries? Are we continuing to observe a worldwide increase in asthma incidence or has the asthma epidemic truly stabilized, and perhaps even decreased? Moreover, are we even using the proper tools to detect any changes in the trend? The answers to these questions are conflicting, in

part due to the lack of uniformity in definitions and the nature of epidemiologic survey tools used to monitor asthma trends.

The principal source of data for the estimation of asthma prevalence in the United States is the National Health Interview Survey (NHIS),³ a multipurpose health survey conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention, to study the health of the civilian, noninstitutionalized, household population of the United States. The NHIS undergoes periodic revision, to reflect the changing nature of the population and to improve sampling techniques, with the last major revision having been done in 1997. The revised questionnaire evaluates both the lifetime and attack prevalence of asthma. Respondents or their proxies are asked whether they ever have received a diagnosis of asthma by a health professional in their lifetime and, if so, whether they had experienced an asthma attack or episode in the preceding 12 months. In 2001, an additional question pertaining to “current asthma” prevalence was added to the survey. Those with a “yes” response to “being diagnosed with asthma in their lifetime” also were asked whether they still had asthma. This question is similar to the one asked in the 1982 to 1996 NHIS survey, except the current questionnaire measures the respondent’s recall of physician-diagnosed asthma, not self-reported asthma symptoms.

Due to survey revisions, the responses on questionnaires from 1997 onward are not directly comparable to those given prior to 1997. Thus, during the time period examined by Vargas et al, we do not have a continuous estimate of asthma prevalence trends in the United States and cannot draw any comparisons to data reported from Mexico. Furthermore, unlike the asthma incidence estimates reported for the Mexican population, none of the national survey tools employed in the United States measure asthma incidence. Another distinction that precludes a comparison between existing asthma trends for the United States and the current study in *CHEST* is the heterogeneity of the Hispanic population in the United States. The 1998 to 2001 lifetime asthma prevalence rates for Hispanic Americans, while increasing, were lower than those of non-Hispanic whites and blacks. Within Hispanic sub-

groups, there are interesting differences, with Puerto Ricans having higher asthma rates, morbidity rates, and mortality rates than other Hispanic groups, including Mexicans.^{4,5} This may be due to differences in lung function and responsiveness to bronchodilators, in addition to environmental variations.⁴

Despite our inability to compare trends between the two countries, the question remains, "Is the asthma epidemic over in the United States?" The even more difficult question to ask and answer is "What of the asthma epidemic worldwide?" Reports^{6–10} regarding asthma prevalence and incidence in various countries, drawn from a wide range of age, ethnic, and racial backgrounds, are conflicting. While some parts of the world (*eg*, Rome, Italy; Saskatchewan, Canada; and Melbourne, Australia) have reported a decrease in asthma incidence, especially in children, other areas (*eg*, Saudi Arabia; South Australia; and Patras, Greece) continue to notice an increasing trend in asthma prevalence and health-care utilization. Due to differences in case definitions, survey techniques, periods of study, and population characteristics, none of these studies are easily comparable. At present, there seems to be no clear indication that the worldwide asthma epidemic is ending.

To discover the answer in the United States, we must examine trends reported for "lifetime asthma" and "attack rate" prevalence from 1997 to June 2003. The final results are not yet completely available for 2002 and 2003. In addition, sufficient time has not passed since the 2001 addition to the NHIS to comment on "current asthma prevalence" trends. Between 1997 and 1999, the lifetime asthma prevalence rate decreased by approximately 6% (96.6 per 1,000 persons in 1997 to 90.9 per 1,000 persons in 1999) but increased again by 25% by 2001 (113.4 per 1,000 persons in 2001).⁵ As with lifetime asthma prevalence, the asthma attack rate decreased by 7.4% from 1997 to 1999 (41.8 per 1,000 population in 1997 to 38.6 per 1,000 population in 1999) but then increased significantly by 10% (42.6 per 1,000 population) in 2002. Results for the first half of 2003 indicate an asthma attack rate of 40.1 per 1,000 population.³ Interestingly, despite a recent increase in lifetime asthma prevalence, estimates from the National Hospital Discharge Survey suggest a decline in the number of hospital discharges for asthma from 1988 to 2000. Similarly, mortality rates declined over the same time period.⁵

In summary, during the 1980s and early 1990s asthma prevalence trended upward in the United States followed by a brief, but nonsustained, decline from 1997 to 1999. The 2001 NHIS data suggest that there has been a net increase in lifetime asthma prevalence in the United States since 1997. Thus, any conclusions about the end of the asthma epidemic in

the United States are premature. And unlike Galileo's statement, in the case of asthma there remains much speculation about the reasons for this continued increase in prevalence.^{10,11} Regardless of cause, there is no doubt that asthma remains a significant health-care problem. In absolute numbers, asthma has been diagnosed in millions of people in the United States and worldwide, and many continue to experience considerable morbidity and mortality. Continued surveillance of asthma prevalence, morbidity, and mortality worldwide is necessary to guide the implementation of asthma risk reduction programs, to judiciously direct the use of limited health-care resources, and to gauge the effectiveness of existing management programs.

Shirin Shafazand, MD, MS, FCCP
Gene Colice, MD, FCCP
Washington, DC

Dr. Shafazand is an Assistant Professor and Dr. Colice is a Professor, The George Washington University, and both are affiliated with the Washington Hospital Center.

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Correspondence to: *Shirin Shafazand, MD, MS, FCCP, Washington Hospital Center, 110 Irving St NW, Room 2A-38D, Washington, DC 20010-2975; e-mail: shirin.shafazand@medstar.net*

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Influenza Vaccination in Vulnerable Populations

People with asthma and COPD are considered to be at risk for complications of influenza. This disease has been responsible for a major increase in morbidity and mortality during epidemic periods, especially in such patients. As early as 1848, the founder of modern concepts of medical surveillance, William Farr, estimated that 41% of the population of London died due to bronchitis or pneumonia.¹ Each year, an average of 20,000 people die of influenza-related illness in the United States.² Influenza and pneumonia were the seventh leading cause of death in 2000.³

Vaccination remains the primary preventive strategy. Recommendations for annual influenza vaccination in COPD patients come from evidence indicating the efficacy and cost-effectiveness of vaccination in decreasing the rates of hospitalization, pneumonia, and deaths among the elderly and people with high-risk conditions. Yet, there have been few prospective, placebo-controlled, double-blind studies designed to assess the efficacy of the vaccine. Ethical issues pose a difficulty in using the design in high-risk patients.⁴ A practical problem arises with the requirement to vaccinate a sufficient number of individuals with the vaccine or placebo in order to detect a statistically significant difference between the two arms of such a study. In addition, the study is best conducted during an influenza epidemic. The antigenic properties of the vaccine strains should match those of strains that are likely to circulate during the epidemic in order for it to be efficacious. Most studies attempting to address these issues have been conducted over short periods and have yielded contradictory results. To complicate matters, some physicians still believe that the vaccine itself can induce exacerbations, and some hesitate to recommend vaccination in patients with allergic asthma,⁵ especially in those who are allergic to chicken protein. Many patients are not convinced that the vaccine is helpful. Yet, not only is influenza vaccination effective in decreasing morbidity and mortality, but it can also save costs.⁶

In order to clarify some of these issues concerning vaccination in patients with COPD, Wongsurakiat and colleagues describe in this issue of *CHEST* (see page 2011) a 16-month study performed at a university hospital in Thailand. They evaluated the protective effects of a trivalent split-virus vaccine in 62 elderly patients with COPD by analyzing the number and severity of episodes of total acute respiratory illness (ARI), and in episodes of influenza-related ARI, and comparing the results to 63 near-age-matched and sex-matched patients who received placebo. Severity of

illness was classified as outpatient treatment, hospitalization, and the need for assisted ventilation. They found that the overall incidence of influenza-related ARI in the vaccinated group was less than one fourth that in the placebo group. The effectiveness of vaccination was not influenced by the severity of COPD (as assessed by FEV₁), comorbid diseases, age, gender, or current smoking status. By contrast, as expected, there was no difference in the incidence or severity of total ARI between the vaccinated and placebo groups. A key finding was that none of the vaccinated patients required mechanical ventilation because of influenza-related ARI. By contrast, all the unvaccinated patients with moderate-to-severe COPD who were hospitalized because of influenza-related ARI needed assisted ventilation. The effectiveness of the vaccine was reflected by high antibody rates following vaccination, particularly in response to the influenza A strain. Considering that the burden of influenza-related disease represented by COPD is heavy, the clinical relevance of this investigation is significant.

In addition to the elderly and individuals with chronic illnesses such as COPD, vaccination is recommended for health-care providers and others who might transmit the virus to those at risk.^{7,8} Both the National Asthma Education and Prevention Program⁹ and the Centers for Disease Control and Prevention¹⁰ recommend that individuals with asthma receive annual influenza vaccinations. Despite these recommendations, only about 21% and 45%, respectively, of persons with asthma aged 18 to 49 years and 50 to 64 years reported being vaccinated from 1999 to 2001 in National Health Interview Surveys.¹¹ Influenza is a common disease in children. During epidemics, the attack rates approximate 40% in preschool children and 30% in school-age children.^{12,13} The latter group is the main source that introduces the virus into households. Healthy children < 1 year of age are hospitalized for influenza illness at rates similar to those for high-risk adults.¹² Despite recommendations by professional organizations, one study¹⁴ found that only 9% of children with asthma had received vaccination in the period from 1993 to 1995. In a large, retrospective cohort study, Neuzil et al¹⁵ found that among healthy young children there were excess numbers of hospitalizations for acute cardiorespiratory conditions, outpatient visits, and filling of antibiotic prescriptions during a 20-year period when influenza virus was circulating in the community.

The report of Wongsurakiat and colleagues is particularly timely in light of the recent emergence of a new avian strain of influenza A virus in Asia as a potentially serious epidemic that could have global implications. Thailand is among the countries that initially reported illnesses and deaths resulting from fowl-to-human transmission, which resulted in the government-

decreed slaughter of millions of chickens as the only means of controlling the spread of the virus. Person-to-person transmission of this new, more virulent avian virus, possessing the H5N1 antigenic subtype, has yet to be documented. An antigenic shift resulting from the replacement of the hemagglutinin and sometimes the neuraminidase antigens with novel subtypes that have not been present in human viruses for a long time, however, could lead to increased human susceptibility to infection from birds. The incorporation of the hemagglutinin of the avian virus into that of a more common H3N2 or H1N1 type can lead to interhuman transmission with the potential for a pandemic.¹⁶ The identification of a new subtype would require the timely preparation of its corresponding influenza vaccine. This may be problematic in the case of new antigenic variants that may not replicate well in eggs, as was the case with the A/Fujian strain that was in circulation from 2003 to 2004.¹⁶ Rapid production of vaccine in mammalian cells could be an alternative, or genetically produced viruses with better growth characteristics in eggs could be another option. Whatever the methods used, the study of Wongsurakiat and colleagues clearly demonstrates the importance of the timely production and administration of vaccine in preventing life-threatening complications in large, susceptible populations.

*Ahmet Baydur, MD, FCCP
Los Angeles, CA*

Dr. Baydur is Professor of Medicine, Division of Pulmonary and Critical Care, Department of Medicine, Keck School of Medicine, University of Southern California.

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Correspondence to: Ahmet Baydur, MD, FCCP, Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Keck School of Medicine, University of Southern California, GNH 11-900, 2025 Zonal Ave, Los Angeles, CA 90033; e-mail: baydur@hsc.usc.edu

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Asthma and Obesity

A Real Connection or a Casual Association?

Scientists have long suspected an association between overweight and asthma to be likely.¹⁻⁴ The common assumption is that weight gain occurs because many asthmatic patients avoid exercise since physical activity can trigger their symptoms. The term *overweight* was defined as a body mass index (BMI) of 25 to 29.9 kg/m², while *obesity* was defined as a BMI of ≥ 30 kg/m².² Interestingly, during the last 3 decades the incidences of both obesity and asthma have shown a steady raise, with the incidence of asthma more than tripling during that period. Currently, it is estimated that 97 million adults in the United States are overweight or obese and that 5.3% of US adults are affected by asthma.² In addition to asthma, obesity substantially raises the risk of mor-

bidity from other diseases such as hypertension, type 2 diabetes mellitus, coronary heart disease, stroke, sleep apnea, and respiratory problems.²

Probably one of the most pervasive issues in the relation of obesity and asthma is the relation between airway hyperresponsiveness (AHP) and changes in BMI. While many studies have supported the possible association between obesity and asthma, the scientific literature remains divided regarding the relation between AHP and changes in BMI.

Multiple previous studies⁵⁻⁹ have attempted to answer that question through either population-based or cohort studies. A large population-based study⁹ utilized the data of 11,277 participants in the European Community Respiratory Health Survey (ECRHS). It demonstrated a rise in AHP with the increase in BMI in men (ECRHS slope decrease, 0.027 for each unit increase in BMI; 95% confidence interval, -0.044 to -0.010; $p = 0.002$),⁸ but not in women (ECRHS slope decrease, 0.014; 95% confidence interval, -0.033 to 0.005; $p = 0.41$). However, the study was not designed to allow for the follow-up of a possible variation in AHP with changes in BMI. In a more recent study from Finland, Stenius-Aarniala et al⁷ evaluated the effect of 14 weeks of controlled dieting on obese asthmatic patients. At the end of the dieting, there was a statistically significant increase in both FEV₁ ($p = 0.009$) and FVC ($p = <0.001$), but not in the peak expiratory flow ($p = 0.06$) of the study group compared to the control group. Even after one year, the differences in FEV₁ and FVC remained statistically significant ($p = 0.02$ and 0.001 respectively). However, the study had no account of group airway responsiveness to methacholine challenge either prior to or after the dieting period.

In this issue of *CHEST*, Aaron and colleagues (see page 2046) investigate the possibility that an intensive weight loss program may improve the severity of adult-onset asthma in obese women. They performed a prospective study for up to 6 months in 58 women with a BMI of $> 30 \text{ kg/m}^2$. By utilizing Pearson correlation coefficients, they described a possible relation between weight change and unadjusted changes in FEV₁, FVC, provocative concentration of a substance causing a 20% fall in FEV₁, and St. George Respiratory Questionnaire score. The authors concluded that although weight loss can improve the lung function of obese women, such a change appeared to be independent of changes in airway reactivity.

The study by Aaron et al had a unique approach to the obesity-asthma relationship. Indeed, in order to evaluate such a relationship, the study and control populations underwent a structured dietary program, followed by broncho-provocation challenge (BPC)

testing and responding to an asthma symptoms questionnaire. Through that approach, they were able to demonstrate a favorable response to dietary therapy in the form of positive changes in BPC test results. In addition, by electing to include the lower quartile of the cohort who lost weight as their control group, they were able to adjust for possible selection bias by including obese patients who had no access to a weight reduction program.

However, few caveats should be considered when analyzing their conclusion. First, they did not account for other possible unrecognized or unappreciated cofactors that may account for the statistical improvement in BPC test results noted. For example, obesity may increase the risk of gastroesophageal reflux disease, which may then trigger latent asthma. The possible reduction in severity of gastroesophageal reflux disease, with the reported dietary control and weight loss, may result in a decline of the asthma symptoms with subsequent improvement of the BPC test results. In addition, the short follow-up period precluded any firm conclusion about the long-term changes in BPC test results in patients in the study group, who might increase their BMI over time. Finally, since obesity commonly reduces functional residual capacity by $\geq 500 \text{ mL}$, weight loss in the study group may account for the reported changes in the BPC testing results rather than having a direct effect on the airways.^{10,11}

In summary, while obesity and asthma remains two of the fastest growing and most pervasive public health problems in developing countries, the question remains whether the relation of asthma to obesity is a real connection or just a casual association. Large prospective studies and randomized population-based studies are needed to determine the prevalence of such an association, and the possible relation between AHP and variations in BMI. Indeed, such studies might support the counter opinion that different mechanisms other than AHP are responsible for the development of obesity-associated dyspnea and that asthma might be overdiagnosed in the portion of the population that is overweight.

*Elamin M. Elamin, MD, MSc, FCCP
Springfield, IL*

Dr. Elamin is Associate Professor of Medicine, and Director, Critical Care Medicine, Division of Pulmonary and Critical Care Medicine, Southern Illinois University.

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Correspondence to: Elamin M. Elamin, MD, MSc, FCCP, Associate Professor of Medicine, Southern Illinois University, Director, Critical Care Medicine, Division of Pulmonary and Critical Care, PO Box 19636, Springfield, IL 62794-9636; e-mail: eelamin@siumed.edu

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QT Dispersion

Much Ado About Something?

The QT interval, in its basic form, is a seemingly simple concept. Defined as the interval from the beginning of the QRS complex to the end of the T wave on a surface ECG, the QT interval represents the period of global ventricular depolarization and subsequent repolarization.¹ Prolongation of the QT interval due to inherited ion channel abnormalities or due to drugs or metabolic abnormalities has been associated with an increased incidence of ventricular arrhythmias. In addition, experimental studies^{2–4} have demonstrated that regional differences in repolarization facilitate reentry and the development of ventricular arrhythmias. Heterogeneous ventricular repolarization was recognized from surface ECGs as early as 1934.⁵ Over a decade ago, the difference between the longest and shortest QT intervals on a standard 12-lead ECG (QT dispersion) was forwarded as a simply measured marker for vulnerabil-

ity to ventricular arrhythmias and risk for sudden cardiac death.⁶ A number of publications followed, and currently there are >1,000 articles in the literature on QT dispersion. However, the exact physiologic mechanism and true clinical utility of QT dispersion have been the subject of intense debate over the past several years.^{7–9}

QT dispersion is measured as the difference between the maximal and minimal QT intervals.^{6,9,10} While the definition is straightforward, its accurate measurement becomes quite complex. First determining the end of the T wave can often be difficult, particularly if the T wave is of relatively low amplitude. Five “experts” were asked to measure the onset of the QRS complex and the end of the T wave in 250 ECGs from both normal and abnormal hearts without QT interval prolongation or bundle-branch block.¹¹ The interexpert variation for the QRS onset was 6.5 ms, but the variation for the end of the T wave was 30.6 ms with an intraindividual variability of 8 ms. Several computer algorithms have been developed to accurately and reproducibly localize the end of the T wave, but have not been associated with any significant improvement in reproducibility over manual techniques.^{12,13} Unfortunately, increasing paper speed or amplifying the signals do not aid in measuring the T wave end point.¹⁴ In general, interobserver and intraobserver variability of QT dispersion measurements can be as much as 30 to 40%.^{9,15} Second, it is not clear whether QT dispersion measurements must be corrected for rate. Several large studies^{16,17} have demonstrated the potential clinical utility of QTc dispersion, but a recent clinical study¹⁸ in 35 patients demonstrated that QT dispersion is independent of heart rate. Since elevated heart rate itself is associated with increased risk of death in the general population, analysis of QT dispersion should probably not be rate corrected to eliminate the influence from an additional variable.^{18,19} Third, the specific number of leads required for measurement of QT dispersion has not been formally defined. Initial studies in QT dispersion used body surface potential mapping (BSPM) with 100 to 200 unipolar precordial ECGs to identify differences in ventricular repolarization. A subsequent study by Cowan et al¹⁰ found that the values obtained from the surface 12-lead ECG were similar to those obtained by BSPM. However, since only two of the six frontal plane leads are actually recorded while the other four are derived mathematically, many clinical studies have used only six unipolar precordial leads or eight leads (two frontal plane leads and six precordial leads). The T wave generally shortens and decreases in amplitude from precordial leads V₂ to V₆ to reach minimal values in aVL due to tissue attenuation from air in the lungs. Recent

studies suggest that using a specific combination of “quasiorthogonal” leads (aVF, V₁, and V₄; I, aVF, V₂, and V₄) may provide sufficient QT dispersion data for analysis.²⁰ However, at this time no standardized method for acquiring QT dispersion exists.

Even if consistent and standardized measures could be obtained, it is also clear that QT dispersion provides only a correlate of global ventricular repolarization rather than directly identifying small regions of heterogeneous repolarization. An experimental study²¹ has demonstrated that the peak of the T wave rather than the end of the shortest QT interval coincides with initial ventricular repolarization. The shape of the T wave and the interval between the peak of the T wave and the end of the T wave contain most of the information on differences in regional ventricular depolarization. QT dispersion correlates with but is not a direct measure of heterogeneous ventricular action potential durations.²² An analysis²³ suggests that the shape of the T wave vector of repolarization is the main determinant of QT dispersion.

Given the methodologic problems associated with QT dispersion measurements, it is not surprising that normal values for QT dispersion have not been well defined. Generally values between 30 ms and 60 ms are considered normal. In an analysis⁹ of 8,455 healthy subjects from 51 studies, mean QT dispersion ranged from 11 ± 10 to 71 ± 7 ms. The weighted mean ($\pm$ SD) from all of the studies was 33 ± 20 ms. Several large prospective studies have evaluated the use of QT dispersion in well-defined populations without recognized cardiac disease. In the Rotterdam Study,¹⁶ 5,812 adults > 55 years old were followed up for 4 years. Subjects with QTc dispersion > 60 ms had a twofold risk for cardiac death or sudden death and a 40% increased mortality risk when compared to those subjects with a QTc dispersion < 30 ms. In the Strong Heart Study¹⁷ of 1,839 American Indians aged 45 to 74 years, QTc dispersion > 58 ms was identified in 4.1% of the population and was associated with a 3.4-fold increased risk for cardiovascular death.

Several studies have evaluated the use of QT dispersion in specific patient populations with hyperlipidemia, coronary artery disease, heart failure, and diabetes mellitus. The West of Scotland Coronary Prevention Study²⁴ evaluated 6,595 middle-aged men with moderately raised cholesterol but no prior myocardial infarction; QT dispersion > 44 ms was associated with a 36% increased risk death or non-fatal myocardial infarction, but because the sensitivity was 8.8% and the specificity was 93.8%, the cut-off provided little predictive value. Although retrospective studies^{25,26} have suggested that QT dispersion provides prognostic information after

myocardial infarction, in the only prospective study²⁷ to date QT dispersion provided no prognostic information in 280 patients after myocardial infarction. The prognostic value of QT dispersion has also been evaluated in patients with congestive heart failure with mixed results.^{28–31} In a retrospective study²⁹ of 2,265 patients with an ejection fraction < 0.40 a QT dispersion > 35 ms was associated with a 5-year mortality rate of 58%, compared to 45% in patients with a QT dispersion of < 35 ms. The Losartan Heart Failure Survival Study³⁰ evaluated 3,152 patients > 60 years old, New York Heart Association class II–IV, and ejection fraction < 0.40 . In the 986 patients with interpretable ECG tracings, baseline QT dispersion was 86 ± 31 ms. Using a prespecified QT dispersion cutoff of > 80 ms, no prognostic information was obtained from QT dispersion measurements. In a retrospective study³² of 219 patients with diabetes mellitus, increased QT dispersion was associated with an increased incidence of myocardial ischemia and left ventricular hypertrophy.

The possible relationship between QT dispersion and pulmonary disease has been previously described. In a small study,³³ patients with COPD had higher QT dispersion values than age-matched control subjects (COPD, 58 ± 10 ms; control subjects, 38 ± 8 ms). In addition, COPD patients with episodes of nonsustained ventricular tachycardia had higher QT dispersion values (67 ± 10 ms) than those without ventricular tachycardia (55 ± 8 ms). Nakamura and colleagues (see page 2107) extend this relationship by their finding that QT dispersion in patients with obstructive sleep apnea is significantly increased during sleep when compared to awake (sleep, 65 ± 15 ms; awake, 51 ± 13 ms; $p < 0.0001$). In addition, treatment with continuous positive airway pressure (CPAP) significantly decreased QT dispersion (awake, 56 ± 13 ms; CPAP, 51 ± 11 ms). Although the findings are statistically significant, as is common in many studies evaluating QT dispersion, the individual data points overlap significantly, thus limiting the clinical utility of QT dispersion measurements.

Obstructive sleep apnea can be associated with both bradyarrhythmias and tachyarrhythmias.^{32–34} In a study³⁴ of 458 patients undergoing sleep studies, arrhythmias were noted in 58% of patients with apneic episodes compared to 42% in patients without apnea. Two studies^{35,36} have demonstrated that ventricular ectopy is particularly common in patients with sleep apnea and left ventricular dysfunction. In a study of 47 patients with left ventricular ejection fraction ≤ 0.40 and sleep apnea, > 25 episodes of nonsustained ventricular tachycardia were observed in those patients with severe sleep apnea during 24-h ambulatory ECG monitoring.³⁵ In a prospective

study³⁶ of 29 men with severe sleep apnea, left ventricular ejection fraction ≤ 0.45 , and treated with continuous positive airway pressure, the 16 “responders” had a significant reduction in the frequency of premature ventricular contractions ($66 \pm 117/\text{h}$ vs $18 \pm 20/\text{h}$) and couplets ($3.2 \pm 6/\text{h}$ vs $0.2 \pm 0.21/\text{h}$).

The mechanism for increased ventricular irritability associated with obstructive sleep apnea and the salutary effects of CPAP are not known. Nakamura and colleagues provide intriguing data that heterogeneity of ventricular repolarization may be a possible mechanism for this finding. However, the vagaries of QT dispersion measurement prevent any fundamental conclusions to be reached. It may be that other measures of repolarization such as microvolt T wave alternans, T wave repolarization vectors, or direct measurement of regional monophasic action potentials will confirm that regional ventricular repolarization differences are an important pathophysiologic mechanism for the close relationship between ventricular arrhythmias and sleep disorders.

Alex Chen, MD

Fred M. Kusumoto, MD

Albuquerque, NM

Dr. Chen is a Cardiology Fellow for the Department of Medicine, University of New Mexico. Dr. Kusumoto is Associate Professor of Clinical Medicine, Cardiology Division, Department of Medicine, University of New Mexico, and Director of Electrophysiology and Pacing Service, Cardiology Department, Lovelace Medical Center.

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Correspondence to: Fred M. Kusumoto, MD, Electrophysiology and Pacing Service, Cardiology Department, Lovelace Medical Center, 5400 Gibson Blvd SE, Albuquerque, NM 87108; e-mail: fred.kusumoto@lovelacesandia.com

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Atrial Fibrillation

Nonpharmacologic Therapies Coming of Age

Atrial fibrillation is a common arrhythmia present in 0.4% of the population. Its prevalence increases with age and in the presence of structural heart disease. Although seldom life threatening, it is associated with morbidity primarily related to symptoms, thromboembolism, and heart failure. Once patients experience recurrent episodes of atrial fibrillation, pharmacologic rhythm control (maintenance of sinus rhythm) is at best partly effective. However, when patients are relatively symptom free, a strategy of heart rate control in atrial fibrillation is equivalent to one of rhythm control in terms of quality-of-life measures and all-cause mortality, although superior in reducing hospitalization.¹ In either strategy, anticoagulation should be maintained in patients at high risk of thromboembolism.

For the symptomatic patient, the main reason to pursue restoration and maintenance of sinus rhythm is to improve perceived quality of life.² Antiarrhythmic drugs are useful but have limited long-term efficacy. In the Canadian Trial of Atrial Fibrillation, 31% of patients treated with amiodarone and 63%

treated with sotalol or propafenone had recurrence of atrial fibrillation at a mean follow-up of 16 months. In addition, adverse effects forced the discontinuation of amiodarone in 18% of patients and of sotalol or propafenone in 11% of patients.³ Such disappointing results with antiarrhythmic drugs have prompted the development of a number of nonpharmacologic approaches designed to cure atrial fibrillation. These techniques generally have two aims: (1) to isolate foci of triggers of atrial fibrillation, and (2) to ablate critical areas of atrial tissue that serve as substrates for reentrant fibrillatory wavefronts. The pulmonary veins in the posterior left atrium contain sleeves of electrically active tissue capable of rapidly firing and triggering atrial fibrillation. In 1998, Haisaguerre and colleagues⁴ reported that radiofrequency ablation to isolate electrically the pulmonary veins from the atrial tissue could eliminate atrial fibrillation in a select group of patients with trigger-mediated atrial fibrillation. Pulmonary vein isolation is particularly suited to patients without obvious structural heart disease and paroxysmal atrial fibrillation, in whom rapid firing from sleeves of muscle within the origin of the pulmonary veins may act as the sole mechanism for atrial fibrillation. Catheter ablation can eliminate atrial fibrillation in 60 to 70% of such patients.

Persistent or established atrial fibrillation, however, is often associated with structural heart disease such as hypertensive or valvular heart disease. Progressive atrial enlargement and fibrosis is a common pathologic finding. Here, elimination of pulmonary venous triggers of the arrhythmia alone does not appear to be as effective because other mechanisms for initiation and maintenance of atrial fibrillation appear to be operative. In theory, atrial fibrillation is composed of multiple reentrant wavelets that require a critical mass of electrically contiguous tissue for propagation. The surgical maze procedure pioneered by Cox et al⁵ based on this premise, created a series of surgical incisions in the left and right atria to segment atrial musculature to prevent fibrillatory wave propagation, yet allow conduction of sinus impulses to the AV node for normal sinus node driven ventricular activation. The procedure has been rendered surgically less complex through various iterations of the technique. The current iteration, termed the *Cox III maze procedure*, is successful in maintenance of sinus rhythm in > 90% of patients.⁶ Increasingly, surgeons are embracing a simpler modification termed the *mini-maze procedure*, in which incisions are confined to posterior left atrial tissue, where pulmonary vein triggers reside and the complex anatomy lends itself to reentry. A recent study by Todd et al⁷ showed that the posterior left atrial tissue was critical for maintenance of atrial

fibrillation in patients with lone atrial fibrillation, and when successfully isolated would not allow the re-initiation of atrial fibrillation. Another report from Pappone et al⁸ indicates that increasing volume of posterior left atrial tissue ablated corresponds favorably with clinical success. These and other data are congruent with the mounting evidence that atrial fibrillation is predominantly a left atrial arrhythmia.⁹

At most centers, surgical cure of atrial fibrillation requires open-heart surgery on cardiopulmonary bypass with its attendant risk of morbidity and mortality (1 to 2% risk of death, 1 to 2% risk of stroke). Consequently, there is limited acceptance of the surgical maze for "lone" atrial fibrillation. The bulk of surgical maze procedures are currently performed in patients undergoing concomitant cardiac surgery. In this issue of *CHEST* (see page 2129), Chen et al report on the results of the radiofrequency maze in 81 patients undergoing surgery for mitral valve disease. Instead of surgical incisions, radiofrequency current delivered through hand-held probes can achieve linear lesions in the atrial tissue akin to surgical incisions. The use of radiofrequency energy shortens procedure time and abbreviates the period of cardiopulmonary bypass. In the series of Chen et al, 65 patients (84%) were noted to be in sinus rhythm at a mean follow-up of 38 months. This is commendable considering that these were patients with long-standing mitral valve disease and established atrial fibrillation. A left atrial size > 57 mm was predictive of patients who failed to convert and/or maintain sinus rhythm.

A question with this and other surgical reports of successful surgical treatment of atrial fibrillation is whether restoration of sinus rhythm is tantamount to zero risk for thromboembolism. Can we safely discontinue chronic anticoagulation in patients conventionally defined as being at high risk for a stroke from atrial fibrillation? In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial,¹ despite apparently successful maintenance of sinus rhythm with antiarrhythmic drug therapy, high-risk patients still carried a significant risk of thromboembolism when anticoagulation was discontinued. The risk remains mainly because many patients continue to have bouts of asymptomatic atrial fibrillation undetected by physicians. In addition, not all patients who undergo the surgical maze procedure regain normal left atrial contractility.¹⁰ Impaired left atrial contractility may be a risk for thromboembolism. In theory, ligation of the left atrial appendage, which is an essential component of surgical treatment of atrial fibrillation, should minimize stroke risk. Current surgical experience appears to substantiate this theory,⁶ but randomized trials are lacking. A reasonable recommendation at this time would be to use ambulatory monitoring to confirm

sinus rhythm at periodic intervals over a 3- to 6-month period and confirm echocardiographic evidence for left atrial activity prior to discontinuation of anticoagulation. High-risk patients should probably continue anticoagulation if tolerated.

The current challenge for invasive cardiac electrophysiologists is to develop a minimally invasive technique to treat atrial fibrillation in patients who do not require concomitant cardiac surgery and with a success rate that approaches that of the surgical maze procedure. In this respect, the catheter-based left atrial ablation technique developed by Pappone et al¹¹ shows promise. This procedure emulates the surgical mini-maze technique of posterior left atrial modification, but with the major advantage of being percutaneous. Adverse event rates, including stroke and cardiac tamponade, are approximately 1%. Pappone et al¹² recently reported on their experience with > 1,000 left atrial ablation procedures and a success rate of 75 to 80% in maintaining sinus rhythm over 3 years. Additionally, the data of Pappone et al¹² suggest that patients may enjoy improvement in quality of life, risk of stroke, and survival. Although this seems at odds with the results of the AFFIRM trial, it may be that the left atrial modification procedure is more effective in maintaining sinus rhythm than antiarrhythmic medication with its attendant risks. Randomized trials are needed to evaluate this hypothesis in symptomatic patients.

The current "gold standard" for preventing future episodes of atrial fibrillation is the surgical maze procedure. Minimally invasive endoscopic cardiac surgery with aid of robotic arms and without the need for cardiopulmonary bypass surgery will clearly enhance the acceptance of surgical techniques for the cure of atrial fibrillation in patients who do not need cardiac surgery otherwise. Percutaneous techniques and tools are evolving to make left atrial modification easier, safer, and more efficacious. Atrial fibrillation is an arrhythmia that is expected to increase in prevalence with the growing age of our population. As the procedure success rates and safety profiles continue to improve, it is likely that the ability to perform left atrial modification procedures for the prevention of atrial fibrillation will become a necessary and commonly held skill for both cardiac electrophysiologists and cardiac surgeons.

Roy M. John, MD, PhD
Gregory Michaud, MD
Burlington, MA

Dr. John is Director, Cardiac Electrophysiology Laboratory, and Dr. Michaud is Director, Atrial Fibrillation Center, Lahey Clinic Medical Center, Burlington, MA. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

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Legionella Pneumonia

The Spectrum Continues to Expand

It has been almost 2 decades since landmark studies demonstrated the presence and importance of a previously undescribed organism causing pneumonia.^{1,2} Within several years the etiology, epidemiology, diagnosis, and treatment became better

understood, and the importance of species of *Legionella* other than *Legionella pneumophila* became recognized. Coincident with this was the demonstration of *Legionella* in clinical situations other than community-acquired lower respiratory infection. It became appreciated as a cause of nosocomial pneumonia,³ and became associated with illness outside of the lower respiratory system that included but were not limited to surgical site infections, pericarditis, and intraocular infection.⁴

Pneumonia continues to be the most common and important manifestation of infection with *Legionella*. Historically, pneumonia caused by this organism was generally considered to be moderate to severe, with mortality 10 to 15%, and higher if appropriate therapy was delayed.⁵ Reasons for this degree of severity remain incompletely understood, but are likely to include the following: (1) testing only in patients hospitalized with serious illness, and (2) the increasingly recognized feature of legionellosis coexisting with other bacteria (eg, *Streptococcus pneumoniae*) independently associated with substantial morbidity and mortality.^{6,7}

Yu and colleagues (see page 2135) have identified 97 persons (4% of total) meeting laboratory and clinical criteria for *Legionella* pneumonia through a pharmaceutical database of patients enrolled in six prospective trials for community-acquired pneumonia (CAP). Although study designs varied among the trials, patients identified with legionellosis met criteria for pneumonia and demonstration by either culture or serology for this pathogen. Levofloxacin was investigated in therapy against a variety of comparators. Dose, route, and duration of treatment varied among studies. That levofloxacin was effective in treatment of legionellosis is not surprising, and should not be considered the major importance of their article. Newer fluoroquinolones have long been recognized as effective agents for this disease, and are generally considered one of the antimicrobials of choice because of excellent *in vitro* and clinical activity, ease of administration, IV and oral bioequivalence, and activity against most other CAP pathogens.⁸ What becomes more appealing about this investigation is that one third of patients were young and did not have expected comorbidities generally associated with *Legionella* pneumonia. Additionally, almost two thirds had mild-to-moderate disease, and mortality in the entire population of patients with *Legionella* treated with levofloxacin was nil. This reinforces recommendations in most CAP guidelines^{8,9} to employ agents in outpatients that include activity against “atypical” pathogens (historically anticipated to be *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*).

The above commentary is similar to what has been

the case with pneumococcal pneumonia, where the spectrum includes severities from mild (eg, "walking pneumonia") to overwhelming. And while there may be an anticipated cadre "typical" for disease, it is well appreciated that it occurs in patients of all ages, and in those without obvious comorbidities. Also similar to pneumococcal pneumonia is the appreciation that we can often treat with shorter antibiotic courses than was generally appreciated and what has been historically recommended. The current investigation, on account of protocols not specifically aimed at therapy for legionellosis, utilized durations of treatment as little as 5 days with generally excellent outcomes, although numbers are small. Indeed, almost 20% of patients were treated with this short duration, similar to recommendations for management of uncomplicated pneumococcal pneumonia in patients with good initial response.⁸ Recently, other data have demonstrated the effectiveness of azithromycin in 25 patients hospitalized with CAP caused by *L pneumophila*.¹⁰ Mean duration of IV plus oral therapy was < 8 days, with good outcomes. Although the pharmacokinetics and pharmacodynamics of azithromycin are dissimilar to those of the fluoroquinolones, this report adds further substance to the concept of shortened therapy for this disease.

It would have been valuable for Yu and colleagues to have analyzed pooled information about legionellosis in the control populations from the databases that were investigated. As an example in one of these studies, two thirds of a small number of patients with *Legionella pneumonia* had satisfactory outcomes despite receiving only cephalosporins.¹¹ An analysis of larger numbers of similar patients could have helped place the results of the current study in better perspective, and perhaps provided further information about the natural history of this infection.

Richard B. Brown, MD, FCCP
Springfield, MA

Dr. Brown is Chief, Infectious Disease Division, Baystate Medical Center, Springfield; and Professor of Medicine, Tufts University School of Medicine, Boston, MA. The author is on speakers bureaus for Ortho McNeil and Pfizer Pharmaceuticals.

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Correspondence to: Richard B. Brown, MD, FCCP, Chief, Infectious Disease Division, Baystate Medical Center, 759 Chestnut St, Springfield, MA 01107; e-mail: richard.brown@bhs.org

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Cytokines

The Tomb Markers of the ICU

A study¹ reported that severe sepsis accounts for > 215,000 deaths annually from a total population of approximately 750,000 patients, which means a mortality rate of 29%. Multiple other reports quote a range between 25% and 50%. Mortality levels may be much higher in the developing world. Such high mortality has led to widespread research and the expenditure of billions of dollars. This has led to a great deal of progress in the last few years in our understanding of the molecular and genetic factors that affect the pathophysiology of sepsis and severe illness. This ability to leave the whole-organism model to now study the cellular model has led to introduction of many possible treatment options.² With the release by the pharmaceutical industry of activated protein C, we now have targeted therapy toward specific cellular functions, which are modulated by the systemic inflammatory response and cytokine levels.³ This avenue of therapy will only expand in the next few years as multiple clinical trials come to completion.

Despite the wealth of information of cytokine

modulation of sepsis, organ failure, and severe illness, there has been no widespread introduction in clinical practice of the laboratory evaluation of these cytokines as disease markers. We routinely evaluate glucose levels, electrolyte levels, tumor markers, and hundreds of other levels to diagnosis disease and treat patients. No modern ICU would treat a patient with severe ARDS without the use of oxygen saturation and blood gases to titrate mechanical ventilation.

In this issue of *CHEST*, we have two reports of the use of cytokines as markers of illness: Cardier and coworkers (see page 2238), who report on the levels of tumor necrosis factor (TNF)- α /TNF receptor I (TNFRI) and Fas ligand/Fas in sepsis; and a report by Vincent and coworkers (page 2232), who report on the TNF-2 allele and survival from cardiogenic shock. These articles illustrate how these markers may have a future in clinical practice much as routine laboratory values did at the start of the last century. Both articles showed how specific levels of cytokines can play a role in patient outcome, transforming growth factor- β 1 being predictive of survival in cardiogenic shock, and increased levels of TNFRI and Fas as important markers of the severity of sepsis in the other. Both articles measured and evaluated TNF- α one of the most commonly measured cytokines in research. TNF- α has been implicated in myocardial depression associated with septic shock,⁴ as well in the pathogenesis of heart failure. The study by Vincent et al showed that the TNF-2 allele of the TNF- α promoter is a strong independent factor associated with better survival from cardiogenic shock. The clinical implication cannot be understated, in that if we can identify patients with cardiogenic shock with the TNF-2 allele we may be able to provide them with more aggressive therapy or transfer them to university centers where they may have improved outcomes. TNF- α levels in the study by Cardier et al, as in several other studies,^{5,6} found no correlation in mortality in patients with severe sepsis, which suggests that although TNF- α plays an important role in the pathogenesis of sepsis, it may not be a good marker or predictor of mortality in severe sepsis. TNF- α levels can also be greatly affected by the support provided in the ICU. Our group⁷ showed how there can be a loss of compartmentalization of TNF- α in the lung and can affect systemic levels based on the mode of mechanical ventilation. This varied utility of one common cytokine marker shows how specific cytokine levels can be used in specific patient populations and why further investigation of the utility of each cytokine must be investigated in critical illness.

Cardier et al have added to our database on how specific cytokines affect the systemic inflammatory

response and may lead to specific aspects of organ failure. Cell death by apoptosis may play an important role in the pathogenesis and development of multiple organ dysfunction syndrome in patients with sepsis syndrome.⁸ He showed that there are differential patterns in the circulating levels of apoptosis-associated molecules between severe sepsis and sepsis. The key marker seems to be serum levels of death-receptors TNFRI and Fas. They reported that serum levels were higher in patients who died than those who survived, which may suggest that serum Fas levels may constitute an important marker not only for severity but also for survival. This supports other reports that up-regulation of Fas has been reported in both experimental models of sepsis and in the patients. This may support a future avenue of investigation: the genetic mapping of these patients to see if some patients are genetically primed to be high cytokine releasers.

The investigations in this issue and the many others published investigations are creating the markers and guideposts to unlock the physiology of sepsis and organ dysfunction. As we move forward in our understanding of these important cellular modulators, we believe we will utilize specific laboratory tests to classify patients and use them as markers to modulate therapy and predict outcome. It is important that other investigators begin to study these and other cytokines and measure their levels in patient populations. The genetic variation in the expression of these cytokines must also be expanded. This wide spread use of this basic science data will in the future lead us to further investigations of cell dysfunction. With these data in large homogeneous groups of patients, investigators may be able to develop specific therapies to target increases of cytokines that may be unique to a disease or trigger. They may be also able to identify patients with genetic phenotypes that place them at risk for activation of cytokine cascades, much as patients with specific genetic phenotypes are at risk for specific diseases.

We believe that this may be a fruitful pathway to investigate therapies instead of the current pattern of large multicentered studies over varied ICU patient populations. Many of these studies failed to have overall positive outcomes, but did have small groups of patients who were responders.¹ This ability to measure levels and titrate therapy to specific end points seems like a logical avenue to treat illness. A basic example of this has been the control of glucose levels in patients both with chronic diabetes and in patients with low levels of insulin with sepsis.^{2,9} With tight control of glucose levels, we have improved both morbidity and mortality. This time-tested way to evaluate and treat patients may hold true in this new century as we explore the cellular response of

illness and trauma. Evidence-based medicine is highly suited in the practice of ICU if we use these cytokine markers to develop protocols and treatments that will modulate specific cellular dysfunction. This will tell us if elevations of some cytokines are destructive or protective. We must develop easy, economical assays for cytokines and introduce them to widespread clinical practice. Once they are used in such widespread practice, there will be exponential growth in our ability to care for patients. The field of cellular medicine will only grow as more and more investigation and physicians in clinical practice add to our growing understanding of how specific patients react to specific stimuli and how these physiologic responses are regulated.

Peter J. Papadakos, MD, FCCP
Rochester, NY

Jack J. Haitzma, MD, PhD
Rotterdam, the Netherlands

Dr. Papadakos is Director, Division of Critical Care Medicine, Department of Anesthesiology, University of Rochester; and Dr. Haitzma is Visiting Research Fellow, University of Rochester, and Researcher, Erasmus University.

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Correspondence to: Peter J. Papadakos, MD, FCCP, Director, Division of Critical Care Medicine, Department of Anesthesiology, University of Rochester, Rochester, NY 14642; e-mail: peter_papadakos@urmc.rochester.edu

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SARS, Pneumothorax, and Our Response to Epidemics

In late 2002, the severe acute respiratory syndrome (SARS) coronavirus (CoV) jumped from feral animals to humans in the Guangdong province of China. This CoV strain had the capacity to spread from person to person, and many of the infected people became severely ill with SARS. The official toll from the multifocal epidemic that ensued was 8,422 cases and 816 deaths on five continents.¹ This startling epidemic demonstrated the continuing risk of zoonotic diseases for humans and the awesome potential for emerging diseases to wreak havoc around the globe. SARS brought several ethical issues associated with new, severe epidemic diseases into sharp focus.

In this issue of *CHEST* (see page 2345), Sihoe et al describe an important clinical feature of SARS, and they raise an important ethical issue that faces clinicians caring for patients with new infectious diseases. Clinical details were reported for six cases of spontaneous pneumothorax that occurred among 356 patients with SARS at two Hong Kong hospitals, an incidence of 1.7%. Secondary pneumothorax developed in other patients who were receiving mechanical ventilation or who had catheters inserted into veins near the pleura. Two of the six patients had pneumomediastinum, an uncommon but characteristic sign of SARS.²

In these six cases, pneumothoraces were bilateral in three patients, mechanical ventilation was indicated in three patients, and two patients died. Air leaks or recurrences occurred in all four patients who accepted chest tubes; the other two patients refused chest tubes. These air leaks took 14 to 31 days (mean of 23.5 days) to resolve. The concentrations of peripheral leukocytes and serum lactate dehydrogenase in patients with SARS and pneumothorax were greater than in other patients with SARS in Hong Kong, which supported the clinical perception that pneumothorax was associated with more severe disease. These complications reflected the severe pathologic changes in lung tissues and strong pulmonary and systemic inflammatory responses that accompany SARS.³

All six patients reported in this issue had received glucocorticoids. This reflected the opinions of several clinicians around the world who believed that early treatment with glucocorticoids improves outcomes from SARS.³ Glucocorticoid therapy may have interfered with lung healing in ways that predisposed to pneumothorax in these patients. The risk of this complication may be acceptable if in fact glucocorticoids improve outcomes in most patients,

but a properly controlled trial of the use of glucocorticoids in SARS has not been done.

The six patients reported by Sihoe et al were managed conservatively. Several had complications that are considered indications for thoracoscopic repair in patients with primary pneumothorax, including bilateral pneumothorax, recurrent pneumothorax, or persistent air leaks.⁴ None of the patients had procedures to repair their pneumothoraces. Several reasons for avoiding surgical repair were discussed, including reluctance on the part of two patients to accept invasive procedures, severe illness in some patients, and the risk of spread of SARS CoV within the operating room from patients to operating room staff.

That concern for the risk for operating room staff dissuaded physicians from repairing air leaks raises an important ethical issue for physicians. The responses of physicians who have faced risks from contagion throughout history have been mixed. Many physicians fled epidemics of plague that swept repeatedly across Europe.⁵ During an epidemic of yellow fever in Philadelphia in 1793, some physicians stayed and performed heroically while others fled.⁵ As medicine became a rigorous scientific discipline in the twentieth century, physicians gained increased respect and power, and the medical profession became more cohesive and developed integrated, widely accepted ethical codes. A social contract developed between physicians and society, whereby in return for substantial income, high social prestige, and professional autonomy, physicians are expected to go to great lengths to provide optimal care even in perilous times.⁶ This social contract exists throughout the world. Section 29.1 of the Professional Code and Conduct for the Guidance of Registered Medical Practitioners of the Medical Council of Hong Kong reads in part, "All patients, including those with serious contagious/infectious diseases, are entitled to timely and appropriate investigations and treatment."⁷ The American Medical Association Declaration of Professional Responsibility reads in part, "We, the members of the world community of physicians, solemnly commit ourselves to: . . . (3) Treat the sick and injured with competence and compassion and without prejudice; and (4) Apply our knowledge and skills when needed, though doing so may put us at risk. . . ."⁸

Early during the AIDS epidemic, some physicians refused to provide care or perform invasive procedures for patients with HIV infection or AIDS. Many responded by reaffirming that all patients, including those with HIV infection or AIDS, deserve the best possible care.^{5,9,10} The AIDS epidemic made clear that providers do not always know when patients have latent or subclinical infections, and this led to

adoption of universal precautions whereby reasonable infection control practices are followed for all patients.

During the SARS epidemic, the expectation that optimal care would be provided for all patients was fulfilled by thousands of providers. It was clear early on that cases were occurring in health-care workers. By the end of the epidemic, approximately 30% of reported cases were in health-care workers, and some died.¹¹ We know now that the primary mode of spread was by respiratory droplets, but that fomites and aerosolized feces also spread the virus under some circumstances. The rate of spread from most people with SARS to household or casual contacts was only moderate. Occasionally, large numbers of people became infected from single ill individuals, so called "superspreading events" that remain poorly understood. The potential for spread was substantial within the health-care setting, but we know now that intensive but widely available, practical infection control measures effectively prevented transmission.¹²⁻¹⁴ A case control study in Hong Kong found that personnel who used gowns, masks, and gloves, and washed their hands regularly did not come down with SARS while other personnel who were less scrupulous did become ill.¹⁴ In multivariate analysis, wearing masks (N95 or surgical masks) was the single practice that seemed to be protective. By analogy, other frightening epidemic viral diseases like Ebola or Lassa fever have spread from patients to health-care workers when modern infection control practices have not been followed or have not been possible because of lack of resources in underdeveloped countries. However, when supplies and equipment widely available in developed countries have been provided and infection control practices have been followed, health-care workers have been protected.¹⁵⁻¹⁷

During the SARS epidemic, providers were at risk from emergency departments to ICUs.¹⁸ Providers at greatest risk included those who cared for undiagnosed patients and those who cared for patients who were breathing and coughing without masks or endotracheal tubes that could contain their secretions. There may be substantial risks to those who perform bronchoscopy.¹⁹ It seems likely that the risks of performing invasive procedures in a well-equipped operating room are not substantially greater than the risks to personnel in many other settings and may be less. In an operating room, patients who would undergo thoracic surgery would likely be intubated and secretions could be contained fairly effectively. It seems unlikely that most surgical procedures would generate substantial aerosols that could not be contained and would pose a risk to operating room staff.

The ethical questions surrounding whether surgical procedures should be performed in patients with SARS are distinct from the decision about whether they would benefit patients. The striking inflammation and necrosis that occurs in lungs, especially those with pneumothorax may decrease the success rate or lead to new leaks. The success rate of pneumothorax repair should be studied if sufficient numbers of SARS cases occur in the future.

The clinical and ethical decisions faced by health-care workers, public health workers, and others during the SARS epidemic were difficult and had to be made in the face of a frightening epidemic. However, epidemics of new and emerging diseases are sufficiently common that we should use the lessons learned from this and other situations to help prepare ourselves for future challenges.^{20–22} In the SARS epidemic and others like it, the risk was greatest to providers before it was clear that they were faced with a new disease. When it became clear that people were faced with a new transmissible disease and after strict infection control practices were implemented, those who followed these practices were protected. Optimal care of patients with a new infectious disease may entail invasive tests or surgical procedures. Rational steps should be taken to reduce risks whenever possible. If multiple management or treatment options are available and they can be expected to result in equivalent, optimal patient outcomes, options that pose lesser risks to health-care providers should be selected. The overriding principle for our patients and our profession is that that we must provide the best possible care to patients. Informed by the lessons of SARS and other epidemic or emerging diseases, we can be comforted by the fact that adherence to reasonable infection control practices available in modern clinics or hospitals will protect us very well.

Gregory A. Filice, MD
Minneapolis, MN

Dr. Filice is Chief of the Infectious Disease Section, Medical Service, Veterans Affairs Medical Center and Associate Professor, Department of Medicine, University of Minnesota. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

Correspondence to: Gregory A. Filice, MD, Infectious Disease Section (111F), Veterans Affairs Medical Center, Minneapolis, MN 55417; e-mail: filic001@umn.edu

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