Tuberculosis, Nontuberculous Lung Infection, Pleural Disorders, Pulmonary Function, Respiratory Muscles, Occupational Lung Disease, Pulmonary Infections, and Social Issues in AJRCCM in 2004

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NONTUBERCULOUS LUNG INFECTION

Lung Infections

HIV infection. In the setting of HIV infection, the clinical implications of the American Thoracic Society (ATS) diagnostic criteria and the significance of an isolated positive culture for Mycobacterium kansasii from respiratory specimens stay unknown. Marras and coworkers (1) studied HIV-infected patients with M. kansasii cultured from respiratory secretions at one institution. Of 127 patients, 33% fulfilled ATS disease criteria. Twenty-nine percent received at least three active drugs for 3 months or more, and 53% died. In survival analysis, a low CD4 lymphocyte count and positive-smear microscopy were associated with mortality, whereas antiretroviral and antimycobacterial treatments were associated with survival. ATS criteria did not predict mortality. Thus, the authors concluded that withholding therapy in HIV-infected patients with positive growth of M. kansasii from respiratory specimens should only be considered in those with negative-smear microscopy, few positive cultures, and mild immunosuppression.

Host defenses. Smoking has been shown to reduce antibacterial activity of macrophages and delay bacterial clearance from the lung. To examine the effect of cigarette smoke on inflammatory processes in the lung, Drannik and colleagues (2) exposed mice to 6 to 8 weeks of cigarette smoke and then inoculated pulmonary activity of macrophages and delay bacterial clearance from the lung, Drannik and colleagues (2) exposed mice to 6 to 8 weeks of cigarette smoke and then inoculated them intranasally with Pseudomonas aeruginosa to assess lung bacterial load and inflammatory response during the following 48 hours, as compared with sham-exposed animals. Bacterial loads were higher during the first 24 hours in smoke-exposed animals; neutrophil and mononuclear cell counts were also higher, as well as proinflammatory cytokines (tumor necrosis factor α, interleukin 1β and 6) levels, myeloperoxidase, and proteolytic activity. Administration of inactivated bacteria resulted in similar inflammatory response in cigarette- and sham-exposed animals. These results suggest that cigarette smoke results in an altered lung inflammatory response associated with delayed clearance of bacteria.

Macrolides have been shown to modulate the inflammatory response and may attenuate lung inflammation and improve lung function in patients with cystic fibrosis. In a model of chronic P. aeruginosa infection, Tsai and colleagues (3) examined the effect of azithromycin (20 mg/kg for 3 days starting at time of bacterial challenge) on lung inflammatory response to determine the mechanisms underlying this anti-inflammatory effect. Although lung bacterial clearance was unaffected by therapy, a marked reduction in neutrophil accumulation in the lung, and a 25 to 35% reduction of tumor necrosis factor– and keratinocyte-derived chemokine lung levels were noted at 3 days in comparison to untreated infected mice. In further in vitro experiments, the authors determined that preincubation of neutrophils with azithromycin (or clarithromycin) markedly attenuated their chemotactic response to both chemokine-dependent and chemokine-independent chemoattractants, most likely through reduced expression of the kinase 1 and kinase 2 (ERK-1/2 MAPK) intracellular signal transduction pathway. Thus, independently of any potential effects on bacterial protein synthesis and virulence factors, macrolides markedly affect neutrophil lung recruitment during chronic bacterial-mediated inflammation.

Pneumonia. New molecular techniques are promising tools for diagnosing infection with emerging pathogens. In a high-risk group of 111 patients (76% of whom had immunosuppression, including 57 lung transplant recipients), Garbino and colleagues (4) examined the incidence and clinical impact of respiratory viral infection. Respiratory viruses (influenzae, parainfluenzae, respiratory syncytial virus [RSV], rhinovirus, metapneumovirus, and coronavirus) and atypical pathogens (Chlamydiae, Mycoplasma, and Legionella) were looked for in bronchoalveolar lavage (BAL; n = 148) using reverse transcriptase–polymerase chain reaction and cultures. Respiratory viruses and/or atypical pathogens were recovered in 36 of 117 (33%) samples from patients presenting with symptoms suggesting respiratory tract infection, and only 2 of 31 (6%, p < 0.01) control patients without such symptoms. In the former group, 31 had viruses (mostly rhinovirus and RSV) identified by reverse transcriptase–polymerase chain reaction only, and only three by cell culture; concomitant bacterial/fungal infection were identified in 8 of 39 virus-positive and 12 of 78 virus-negative samples in that group. There was no apparent impact of viral infection on mortality or rejection rate, but deteriorating lung function (FEV1) that persisted 3 months or more after the infectious episode was documented in lung transplant recipients (17 of whom had viral infection documented by reverse transcriptase–polymerase chain reaction). The authors concluded that respiratory virus can be frequently identified in patients hospitalized with respiratory tract infection and may be associated with morbidity, especially...
in lung transplant recipients. These findings should be interpreted carefully in view of possible viral persistence and reactivation.

In lung transplant recipients, rejection and infection have been associated with the occurrence of bronchiolitis obliterans syndrome and rapid deterioration of lung function. To further examine the relationship between cytomegalovirus (CMV) infection, rejection episodes, bronchiolitis obliterans syndrome, and survival, Tampl and colleagues (5) examined a cohort of 341 patients who received a lung transplant from 1987 to 2001 and who were followed up for 6 months or more. All patients had transbronchial biopsies. CMV pneumonia was confirmed histopathologically and treated with ganciclovir, and was often preceded by a rejection episode within 3 months. The cumulative survival rate did not differ in patients with (n = 151) or without (n = 190) CMV pneumonia, and was 70 and 74% (3 years) and 58 and 63% (5 years), respectively. Corresponding cumulative incidence rates of bronchiolitis obliterans syndrome were 48 and 44% at 3 years and 71 and 62% at 5 years; there was no association of bronchiolitis obliterans syndrome or survival with any combination of donor/recipient serologic status for CMV. The authors concluded that treated CMV pneumonia is not associated with bronchiolitis obliterans syndrome or survival and suggested that previous assessments may have been confounded by the association between acute rejection and CMV infection.

**OCCUPATIONAL LUNG DISEASE**

The mode of transmission of rhinovirus remains under debate. To gain further insight into this question, Myatt and coworkers (6) attempted to detect rhinovirus in an office environment and related their findings to air supply, using CO2 concentration as a surrogate for air supply, using CO2 concentration as a surrogate for air supply, and reverse transcriptase–polymerase chain reaction to detect virus in air samples collected weekly in three offices in Boston. Of 181 filters from air samples analyzed, 32% were positive for picornaviruses. The recovery of picornaviruses was associated with a weekly average CO2 concentration of 100 ppm or more. In addition, a virus with the same sequence was recovered from both air samples and an occupant having respiratory symptoms during the same week. Thus, airborne transmission of rhinoviruses may occur in buildings with low outdoor air supply, and their occupants may be at increased risk of exposure to infectious droplets from a fellow occupant.

The ATS (7) published a statement on nonmalignant diseases related to asbestos, including asbestosis, nonmalignant pleural abnormalities (pleural effusion, pleural plaques, and diffuse pleural fibrosis), and airflow obstruction. This expert statement consists of a review and update of the 1986 statement. It provides diagnostic criteria and guidelines for documenting that these criteria are met, and discusses the implications of diagnosing subclinical forms of nonmalignant asbestos-related disorders.

Hoppin and colleagues (8) evaluated the odds of wheeze in the past year among 20,898 farmers from the Agricultural Health Study, a cohort of pesticide applicators in Iowa and North Carolina. Driving diesel tractors was associated with increased odds of wheezing of 1.31, with a significant duration–response relationship. Activities involving solvent exposure, particularly daily painting, were also associated with increased odds of wheezing.

Schenker and coworkers (9) performed a survey in 338 Costa Rican farm workers to test the hypothesis that chronic, low-level exposure to paraquat (a pneumotoxic herbicide) causes interstitial fibrosis. No clinically significant restrictive impairment or reduction in diffusing capacity for carbon monoxide were observed. However, an association between cumulative paraquat exposure and oxygen desaturation during maximal cardiopulmonary exercise suggested that paraquat may lead to subclinical gas exchange abnormalities.

Verougstraete and coworkers (10) evaluated pulmonary function changes over a period of 13 years in 122 workers from a Belgian cobalt refinery. Cobalt exposure contributed to a small excess decline in FEV1 over time, but only in association with smoking. No influence of a specific HLA polymorphism (HLA-DQ glu69) was detected.

Newman and colleagues (11) followed up a cohort of beryllium-sensitized subjects at 2-year intervals using BAL and repeated transbronchial lung biopsies to determine progression to chronic beryllium disease. Granulomatous inflammation in lung tissue developed in 17 (31%) of 55 sensitized individuals within 1.0 to 9.5 years; the other 38 subjects remained beryllium-sensitized without disease after a follow-up time of 1.7 to 11.6 years. Progressors were more likely to have worked as machinists.

Maghni and colleagues (12) assessed 133 subjects with occupational asthma 0.5 to 20.8 years after cessation of exposure by questionnaire, airway caliber, methacholine test, and induced sputum. Subjects with no improvement in methacholine responsiveness more frequently had evidence of airway inflammation (sputum eosinophils > 2%, neutrophils > 61%), suggesting that failure to improve after cessation of exposure to an agent causing occupational asthma is associated with airway inflammation at follow-up.

In a pulmonary perspective, Mudway and Kelly (13) performed a meta-analysis of data obtained from human chamber studies and derived simple linear relationships between ozone dose (determined by concentration, minute ventilation, and duration of exposure) and pulmonary inflammation, as assessed by neutrophils or proteins in BAL, in normal subjects.

Gryparis and coworkers (14) investigated the effects of daily ambient ozone concentrations on mortality in 23 cities or areas in Europe in the Air Pollution and Health: a European Approach, or APHEA2, project. No significant effects were observed during the cold half of the year. For the warm season, an increase in the 1-hour ozone concentration by 10 µg/m3 was associated with a 0.33% increase in the total daily number of deaths, 0.45% in the number of cardiovascular deaths, and 1.13% in the number of respiratory deaths. The corresponding figures for the 8-hour ozone concentration were similar. The associations with total mortality were independent of SO2 and particulate matter with aerodynamic diameter less than 10 µm (PM10), but were somewhat confounded by NO2 and CO. Individual city estimates were heterogeneous for total and cardiovascular mortality (larger effects were observed in southern cities).

Kim and colleagues (15) conducted a school-based, cross-sectional study using a parental questionnaire (n = 1,109) in the San Francisco Bay Area in 2001. Although pollutant concentrations (measured at 10 school sites during several seasons) were relatively low, the prevalence of reported respiratory symptoms was related to the spatial variability in traffic-related pollutants.

In 28 older Boston residents, DeMeo and coworkers (16) investigated the association between PM2.5 and oxygen saturation, as measured with a peripheral oxygen saturation monitor during a 12-week repeated measures study, using a rest and exercise protocol. PM2.5 was associated with small reductions in oxygen saturation during nonexercise periods, particularly in participants taking β-blockers, suggesting the occurrence of subtle particulate-related pulmonary vascular and/or inflammatory changes.

Riediker and coworkers (17) investigated the effects of in-vehicle, roadside, and ambient PM2.5 in nine young, healthy, nonsmoking, male North Carolina highway patrol troopers on 4 successive days. In-vehicle PM2.5 (average of 24 µg/m3), but not ambient and roadside PM2.5, was associated with changes involving inflammation and coagulation (blood lymphocytes, neutrophils, C-reactive protein, von Willebrand factor) and car-
diac rhythm (ectopic beats, next-morning heart beat cycle length, and heart rate variability).

Schaumann and coworkers (18) instilled 100 μg of PM2.5 suspensions, collected simultaneously from two German locations with differing degrees of air pollution, into contralateral lung segments of 12 healthy volunteers. Particles from both locations increased the number of leukocytes in BAL performed 24 hours later, but only the particles from the smelter area, which contained a higher concentration of transition metals, induced a significant influx of monocytes, an increased oxidant radical generation by BAL cells, and higher concentrations of interleukin 6 and tumor necrosis factor α in BAL.

Goto and colleagues (19) instilled PM2.5 (500 μg/ml) or supernatants of particle-exposed alveolar macrophages into the lungs of rabbits, and found that this led to increased circulating immature neutrophil (band cell) counts in the blood and a shortened transit time of monocytes through the bone marrow. They concluded that exposure to atmospheric PM2.5 stimulates the production of mediators by alveolar macrophages, leading to an accelerated release of monocytes from the bone marrow.

In mice, Park and colleagues (20) evaluated the role of complement in the development of airway hyperresponsiveness and inflammation 8 hours after acute O3 exposure (2 ppm for 3 hours). The depletion of complement by injection of cobra venom factor or its inhibition by an inhibitor of complement was necessary for the development of airway hyperresponsiveness, the influx of neutrophils, and the increase in BAL protein. Thus, activation of the complement system follows acute O3 exposure and is important in the development of airway hyperresponsiveness and neutrophilia. However, this neutrophil response does not appear necessary for the development of airway hyperresponsiveness, because depletion of BAL neutrophils was without effect on hyperresponsiveness.

Hollingsworth and coworkers (21) investigated the requirement of Toll-like receptor 4 (TLR4) in mice for pulmonary responses to aerosolized LPS, particulate matter (residual oil fly ash), and ozone. TLR4-deficient mice (C57BL/6, TLR4−/−) were unresponsive to inhaled LPS, but they did respond like wild-type mice to instilled residual oil fly ash or acute ozone exposure. However, after subchronic ozone exposure, these mice were protected against the development of airway hyperresponsiveness despite a robust inflammatory response. The requirement of TLR4 for pulmonary inflammation depends on the nature of the toxin and exposure conditions.

Johnson and colleagues (22) found that repeated and prolonged (up to 7 weeks) intranasal exposure of mice to house dust mite extract, but not ovalbumin, elicited severe and persistent eosinophilic airway inflammation. The lymphocyte response in the lung was characterized by helper T-cell type 2 (Th2-)–associated cytokines. There was evidence of airway remodeling with goblet cell hyperplasia, collagen deposition, and peribronchial accumulation of contractile tissue, as well as airway hyperreactivity to methacholine. After cessation of exposure, airway inflammation resolved fully and airway hyperreactivity resolved partly, but the remodeling changes did not resolve after 9 weeks.

Kondo and coworkers (23) inoculated naive mice intranasally with murine bone marrow–derived dendritic cells pulsed with mite allergen and/or infected with RSV, and then challenged these mice with mite allergen. RSV infection of allergen-pulsed dendritic cells resulted in a shift of the immune response from Th2 to Th1 in vitro, as well as abrogation of the allergic airway inflammation in vivo.

Verbanck and colleagues (24) revisited the value of the multiple breath washout test to evaluate smoking-related small airways disease. They found significant changes in indices of phase III of the nitrogen slope (S_{exp} and S_{in}) and in diffusing capacity for carbon monoxide in smokers from more than 10 pack-years onwards (i.e., before the presence of significant spirometric changes). In more advanced stages of smoking-induced lung disease, differential patterns of S_{exp} and S_{in} were found to be characteristic of the presence of parenchymal destruction.

He and colleagues (25) studied glutathione S-transferase (GST) polymorphisms in 1,098 whites with the lowest FEV1 (63% predicted) and the highest FEV1 (92% predicted) at the beginning of the Lung Health Study. Homozygosity for GSTP1 105Val was significantly more frequent in the low- than in the high-function group (13.2 vs. 9.3%; odds ratio 1.69), and was associated with a faster lung function decline in the high-function group. The frequencies of GSTM1, GSTTI null genotypes were similar between the high- and low-function groups, but subjects with the GSTTI null genotype had a faster decline of lung function in the low-function group. There was a significant interaction of GSTTI genotype and pack-years on lung function.

Upton and coworkers (26) investigated whether maternal and personal smoking synergize to increase airflow limitation. Maternal smoking was inversely associated with FVC and FEV1, irrespective of personal smoking. It was inversely associated with FEV1/FVC, forced midexpiratory flow rates, and residual FEV1 in current smokers, but not in never- or former smokers. The authors estimated that 10 cigarettes/day of maternal smoking increased the prevalence of chronic obstructive pulmonary disease by 1.7 in never-smokers without asthma.

Joad and colleagues (27) exposed guinea pigs from 1 to 6 weeks of age to environmental tobacco smoke. Environmental tobacco smoke exposure significantly enhanced citric acid–induced cough and bronchoconstriction. These effects were attenuated by a neurokinin-1 receptor antagonist injected in the nucleus tractus solitarius.

Butler and coworkers (28) analyzed the relation between dietary intake at baseline and new onset of cough with phlegm (ascertained by telephone interview) in a population-based longitudinal study of 63,257 middle-aged Chinese men and women in Singapore. Nonstarch polysaccharides, total fruit, and soy isoflavones had strong negative associations with the incidence of cough with phlegm (n = 571) after adjustment for age, sex, dialect group, total energy intake, and smoking, suggesting that a diet high in fiber from fruit and, possibly, soy foods may reduce the incidence of chronic respiratory symptoms.

In a rat model, Bechara and colleagues (29) showed that chronic ethanol ingestion increases lung expression of transforming growth factor β1. During endotoxemia, more biologically active transforming growth factor-β1 protein is released into the alveolar space in ethanol-fed rats than in control-fed rats, thus disrupting the normally tight epithelial barrier. This could contribute to the increased risk of acute respiratory distress syndrome in alcoholic patients.

### PLEURAL DISORDERS

#### Treatment

To determine if streptokinase was a useful addition to the treatment of empyema, Diacon and coworkers (30) designed a randomized, controlled, blinded trial that enrolled patients after meeting defined criteria for empyema (i.e., “frank pus”) or if they had a complicated parapneumonic effusion (i.e., a pH < 7.0 or < 7.2 with evidence of loculation on chest X rays or ultrasound examination). All patients received ultrasound-guided tube thoracostomy and, 24 hours later, were started on normal saline rinses with or without 250,000 IU of streptokinase. There were 22 patients in each group. One patient from each group died. No differences in treatment success or referral for
surgery were seen within the first 3 days, but after 7 days, patients receiving streptokinase had a greater clinical success rate (82 vs. 48%, p = 0.01) and fewer surgical referrals (45 vs. 9%, p = 0.02) (5). Although this result has been suggested by numerous case series, this study represents the first randomized controlled trial and, as such, is the first to define the utility of intrapleural streptokinase.

Noppen and colleagues (31) used aerosolized fluorescein along with autofluorescent thoracoscopy to localize the lung region where air leaks are occurring in the setting of recurrent spontaneous pneumothorax. In addition to suggesting a practical therapeutic advance, this report raises interesting speculations regarding the source of the leak in patients with this problem. Previously, leaks have generally been believed to occur from ruptured blebs located near the apical visceral pleura. The findings in this report suggest that other lung regions may be more important sites of leakage.

Respiratory failure after talc pleurodesis has been well described in the literature. In two prospective, controlled studies, Maskell and colleagues (32) addressed the hypothesis that this effect is related to an inflammatory response generated to talc particles less than 15 μm. In a prospective study comparing “mixed talc” (the standard preparation used in the United States and the United Kingdom, with ~ 50% talc < 15 μm) with tetracycline, the authors noted greater lung and systemic inflammation with the talc preparation. A second, randomized study compared pleurodesis with mixed talc or “graded talc” (talc with majority of particles < 10 μm removed and a mean particle size of > 25 μm, the preparation generally used in Europe). Mixed talc resulted in a greater increase in A-a gradient, a higher proportion of patients developing fever, and greater systemic inflammation than graded talc. Clinical outcomes with the two preparations were generally similar. These clever studies confirm that pleurodesis with mixed talc results in a greater systemic inflammatory response than tetracycline or graded talc. Talc particles smaller than 15 μm may play a prominent role in this detrimental response.

PULMONARY FUNCTION TESTING, DIAGNOSTIC METHODS, AND BRONCHOSCOPY

Equipment and Techniques
In this clinical commentary, Magder (33) reviewed the physiologic interactions of respiratory variations in arterial pulse pressure in light of the concerns about the safety of pulmonary arterial catheterization.

Because the ATS and the European Thoracic Society differ with respect to what represents acceptable reproducible results on spirometry, Enright and colleagues (34) characterized the reproducibility of spirometry in 18,000 patients who were sent for testing because of concerns for respiratory problems. Currently, the ATS requires that the prebronchodilator FEV1 and FVC be within 200 ml. The European Thoracic Society requires the differences to be within 5% or 100 ml. The authors found that 90% of patients had FEV1s within 120 ml (6.1%), FVCs within 150 ml (5.3%), and peak expiratory flows within 0.8 L (12%). They concluded that the current ATS criteria for reproducibility were too lenient.

Measurement of the arteriovenous CO2 difference and CO2 accumulation in tissues has been proposed as a clinically useful indicator of inadequate tissue oxygenation, based on the assumption that the hydrogen ions generated as a result of anaerobic metabolism are buffered by bicarbonate, generating CO2. Gutierrez (35) used a mathematical model to analyze CO2 exchange and found that increases in CO2 occur from either reductions in blood flow (i.e., ischemic hypoxia) or from decreases in arterial Po2 (i.e., hypoxic hypoxia). The model also suggested that tissue CO2 concentrations increase if transfer of CO2 from the tissues to the blood were impaired. The authors, an earlier proponent of measuring gastric mucosal CO2, now concludes that finding an increase in CO2 in tissues or venous blood is neither a sensitive nor a specific marker for tissue hypoxia.

Epidemiologic and Genetic Studies
The rate of loss of pulmonary function is well described in patients with chronic obstructive pulmonary disease, but the cause of this loss in function, and the explanation for why only 10 to 20% of smokers lose lung function over time, is not known. Wang and colleagues (36) used a preexisting database composed of patients between 15 and 54 years of age who were followed up for a 24-year period. They found that the maximal attainable FEV1 occurred 5 years later in men than in women, that smoking at an early age and the presence of airway hyperresponsiveness were independently associated with 5% reductions in the maximal attainable FEV1, and that patients with blood eosinophilia and respiratory symptoms also had reductions in the maximum attainable FEV1. These adverse effects on lung growth contribute to the changes in lung function over time that are seen in patients with chronic obstructive pulmonary disease.

Ciliary Function
Primary ciliary dyskinesia (PCD) is an autonomic recessive disorder characterized by abnormalities in ciliary structure and function, leading to chronic upper and lower respiratory tract symptoms. Noone and coworkers (37) assessed the diagnostic and phenotypic features in a cohort of 110 subjects suspected of having PCD. PCD was diagnosed in 78 of these subjects by a combination of compatible clinical features, together with tests of ciliary ultrastructure and function. Predominant phenotypic features of the disease were chronic rhinitis/sinusitis (100%), recurrent otitis media (95%), neonatal respiratory symptoms (73%), and situs inversus (55%). In older patients (> 30 years) with PCD, P. aeruginosa and nontuberculosis mycobacteria were present in 15 and 10% of patients, respectively. All of the subjects had defects in ciliary structure, which occurred in the outer dynein arm in 66% of patients. Compared with normal subjects, nasal nitric oxide production was low in PCD (19 ± 17 vs. 376 ± 124 nl/minute). The authors suggested that rigorous clinical ciliary phenotyping together with measurements of nitric oxide are useful in the diagnosis of PCD.

A case report by Stannard and colleagues (38) indicated that the diagnosis of primary ciliary dyskinesia, associated with a circular ciliary beat pattern in three siblings, was consistent with a ciliary transposition defect, where a peripheral microtubule doublet is transposed to the center of the ciliary axoneme to replace the absent central microtubule pair. The reported sibling ultrastructural analysis of the cilia revealed an absence of the central microtubule pair only. This variant of pattern transposition with a circular ciliary beat pattern has not been previously described.

Review Articles
In this occasional essay, West (39) summarized important discoveries pertaining to gas exchange over the last century, including the following: the discovery of respiratory gases; why it was initially believed that oxygen was secreted from the lungs into the blood (as opposed to moving by diffusion as suggested by studies); the description of the diffusion capacity, and its separation into two components; the concept of ventilation-perfusion inequality; Riley’s method for measuring Po2 and Pco2; multiple inert gas elimination technique; O2 and CO2 electrodes; and arterial oximetry.
PULMONARY INFECTIONS

Viral

RSV has been associated with delayed chronic and recurrent respiratory diseases. Viral latency (e.g., viral genomic RNA) and persistence (e.g., viral messenger RNA) have been documented in humans, but their mechanisms are still poorly understood. Schwarze and coworkers (40) studied antiviral immune responses using reverse transcriptase–polymerase chain reaction in a mouse model of infection with human RSV (14). The authors demonstrated that, although RSV could not be detected in BAL beyond Day 14 after infection, the following occurred: (1) RSV RNA encoding for surface and matrix viral proteins and for two nonstructural genes (which may have specific anti-IFN effects) persisted up to 100 days after initial infection in homogenized lung tissues of infected mice, (2) neutralizing antibody and memory cytotoxic T-cell activity were unaltered in mice with and without persistent infection, and (3) infective virus was recovered after a 30-day protocol of combined depletion of CD4 and CD8 T cells initiated 150 days after infection. These results suggest that RSV, rather than mutating to evade host defenses, can persist in some immunologically privileged sites (possibly neuronal or lymphoid cells) within the lungs and be reactivated after immunodepression.

Pathophysiology

Angiotensin-converting enzyme agents have been suggested to prevent the occurrence of respiratory tract infection. To support this hypothesis, Ohkubo and coworkers (41) examined rates of pneumonia in treatment and placebo groups within a post hoc analysis of a large (n = 6,105 patients), randomized, controlled trial of one such agent testing the effect of routine lowering of blood pressure in patients with a history of stroke or transient ischemic attack. Pneumonia occurred in 261 patients (4.3%) during a mean follow-up of 3.9 years; the pneumonia rate was 19% lower in patients receiving angiotensin-converting enzyme therapy (3.8 vs. 4.7%, p = 0.09). Only in patients of Asian origin was the relative reduction more pronounced (47%, p = 0.009). However, the authors were unable to relate this effect to the differing distribution of angiotensin-converting enzyme polymorphisms recorded among the various ethnic populations included in the study.

Strategies used during mechanical ventilation have been shown to interact with the severity of and inflammatory response to lung infection. van Kaam and colleagues (42) studied the effect of surfactant deficiency and ventilation using the “open lung concept” on the severity of infection during experimental Group B streptococcal pneumonia in mice. As compared with 100% survival and 0% bacteremia in healthy mice challenged with Group B streptococci receiving conventional ventilation with 4 cm H2O positive end-expiratory pressure and Vr 6.0 to 7.0 ml/kg, surfactant-depleted mice (after whole lung lavage) had a 80% mortality at 5 hours and 12 of 13 had bacteremia. Administration of 300 mg/kg exogenous surfactant before Group B streptococcal pneumonia attenuated hypoxemia, bacteremia, and mortality of animals during conventional mechanical ventilation, whereas the open lung approach (positive end-expiratory pressure 10 cm H2O) markedly improved hypoxemia and decreased bacteremia rate. The combination of exogenous surfactant and lung protective ventilation protected mice from both bacteremia and mortality. The findings suggest that minimizing alveolar collapse with exogenous surfactant or protective ventilation attenuates bacterial growth, translocation, and sepsis during lung infection.

RESPIRATORY MUSCLES

Pathophysiologic Studies in Patients and Volunteers

Exercise and peripheral muscles. During exercise at a constant work rate above the lactic acid threshold, oxygen consumption fails to plateau but continues to rise slowly. This slow component correlates closely with the rise in lactate in normal subjects. To determine if oxygen consumption during constant work-rate exercise could rise after 3 minutes in the absence of a rise in lactate, Ong and colleagues (43) studied five patients with McArdle’s disease (myophosphorylase deficiency) and phosphofructokinase deficiency (Tarui’s disease) who cannot increase plasma lactate during exercise because they cannot convert glycogen to lactate in skeletal muscle. Patients and normal subjects performed a 6-minute duration constant work-rate exercise test with 14 to 17% of peak oxygen consumption. During this low-intensity exercise, oxygen consumption reached a steady state by 3 minutes in both groups. Lactate rose slightly in control subjects, but not in patients. During high-intensity exercise, oxygen consumption rose from the third to the sixth minute and to a similar extent in control subjects and patients, whereas over the same period, lactate rose from 2.68 (1.10–5.00) to 5.39 (2.70–10.00) mmol/L in control subjects, but did not rise in the patients. These studies show that the slow component of oxygen consumption during heavy exercise is not dependent on lactic acidosis.

Structure and Histology

In this pulmonary perspective, Mitzner (44) discussed the validity of the various roles proposed for airway smooth muscles, including peristalsis, to assist exhalation and mucus propulsion and in the fetal lung to generate fluid pressure, the promoting of lymphatic and venous flow, ventilation-perfusion matching, protection for the peripheral lung and airway structure, stabilizing airways, enhancing the effectiveness of cough, and optimizing anatomic dead space volume.

Pharyngeal muscles that restrict or dilate the airways are believed to be important in the pathogenesis of sleep apnea. Kuna (45) used pharyngeal airway fiberoptic imaging in 10 decerebrate cats to determine the effect of selective pharyngeal muscle activation on airway shape. Anteroposterior and lateral diameters were measured in the rostral oropharynx, caudal oropharynx, and velopharynx at intraluminal pressures from 6 to –6 cm H2O with and without bilateral stimulation of the medial hypoglossus, lateral hypoglossus, whole hypoglossus, glossopharyngeus, and pharyngeal branch of vagus nerves. The increased diameter with increasing pressure was greater in the anteroposterior dimension at all three airway levels. With stimulation of the hypoglossal and glossopharyngeal nerves, there were greater increases in the lateral than in the anteroposterior diameter in all three regions. These studies show that selective activation of pharyngeal muscles in cats frequently results in greater changes in lateral than anteroposterior airway diameter and that these effects are dependent on airway region and cross-sectional area.

Respiratory Muscle Involvement in Clinical Disorders

To explore explanations for why patients with cystic fibrosis have an exercise capacity that is reduced out of proportion to changes in spirometry or nutritional status, Divangahi and colleagues (46) tested the hypothesis that the inflammation associated with chronic P. aeruginosa infection caused diaphragm and limb muscle weakness. The group produced chronic infection in mice and found that it was associated with diaphragm weakness, but there was no evidence of limb muscle weakness or of an association with the resulting pulmonary inflammation. Although a number of theoretic explanations for these curious findings were proposed, the explanation remained speculative. If these
and ELISPOT. The participants had brief duration of exposure to adult contacts of a pregnant woman with smear-positive multi-drug-resistant TB, using a T-cell–based assay, the enzyme-linked immunospot (ELISPOT) reaction method, demonstrated that 19% of all patients at an epidemiologic field site in Cape Town were simultaneously infected with Beijing and non-Beijing strains, and 57% of patients infected with Beijing strain were also infected with a non-Beijing strain. Multiple infections were more frequent in retreatment cases (23%) as compared with new cases (17%), but were not associated with sex, age, or smear-positivity grading. The authors concluded that multiple infections are likely to be frequent, thus implying high reinfection rates and absence of efficient protective immunity conferred by the initial infection. This finding impacts the understanding of epidemiology of TB in high-incidence areas, as well as that of vaccine development.

Clustering of disease cases with *M. tuberculosis* isolates showing identical restriction fragment length polymorphism patterns are presumed to result from disease transmission. In a prospective, population-based study in the Netherlands, van Deutekom and coworkers (52) combined molecular methods with meticulously obtained epidemiologic information to determine why many clustered cases cannot be detected earlier. Of 481 patients, 29% fell into 43 clusters, suggesting recent transmission in 20%. Of the clustered patients, 14% had no epidemiologic links, whereas 86% had such links. However, only 24% were identified early and 61% were missed/undetected. Thus, the authors concluded that, using conventional TB control strategies, the opportunities for earlier identification of such links remain limited.

Molecular epidemiology has revealed significant transmission of *M. tuberculosis* after casual contact with infectious index cases. Richel and coworkers (53) investigated such transmission after brief exposure using a T-cell–based assay, the enzyme-linked immunospot (ELISPOT) for IFN-γ. The 41 neonate and 47 adult contacts of a pregnant woman with smear-positive multi-drug–resistant TB were studied by tuberculin skin testing (TST) and ELISPOT. The participants had brief duration of exposure to the index patient only (mean 6.0 hours, range 0–65 hours). Seventeen individuals were ELISPOT-positive, and the results correlated significantly with three of four predefined measures of TB exposure. For each hour of sharing room air with the index case, the odds of a positive ELISPOT result increased by 1.05. Only four individuals were TST-positive, and TST results did not correlate with exposure. The authors concluded that the ELISPOT assay, but not TST, demonstrates quite extensive nosocomial transmission of multi-drug–resistant TB after brief exposure, with implications for prevention.

To study the association of smoking and TB, Leung and coworkers (54) followed up a cohort of 42,655 elderly subjects from 2000 through 2002. A total of 286 cases with active TB (186 culture-confirmed) were found. The annual TB notification rates were 735, 427, and 174 per 100,000 among current smokers, ex-smokers, and never-smokers, respectively (p < 0.001). The trend in TB risk persisted after control of background characteristics using Cox proportional hazards analysis (adjusted hazard ratios 2.63: 1.41:1). A statistically significant dose–response relationship was observed with respect to active TB and culture-confirmed disease. Smoking accounted for 32.8, 8.6, and 18.7% of the TB risk among males, females, and the whole cohort, respectively. The authors concluded that these findings have implications in expanding the armamentarium for TB control.

TB is an important infectious disease in HIV-infected subjects. Corbett and coworkers (55) hypothesized that rapid presentation may be a general feature of TB associated with HIV infection that limits the impact of HIV on the point prevalence of TB. They performed a cross-sectional HIV and TB disease survey with retrospective and prospective follow-up. HIV prevalence among a population of systematically recruited miners was 27%. TB incidence was much more strongly HIV-associated (incidence rate ratio 5.5) than the point prevalence of undiagnosed TB (odds ratio 1.7). For smear-positive TB, 78% of cases were HIV-negative, and point prevalence of TB was nonsignificantly lower in miners who were HIV-positive (odds ratio 0.8). The calculated mean duration of smear positivity before diagnosis (point prevalence/incidence) was substantially shorter for HIV-positive than HIV-negative patients with TB (0.17 vs. 1.15 years). The authors concluded that HIV infection has considerably less impact on the point prevalence of TB than on incidence of TB, probably because of increased presentation and case-finding rates from rapid disease progression. The difference in duration of smear positivity may have major implications for TB control prospects in areas with high HIV prevalence.

Jasmer and colleagues (56) evaluated cases of recurrent TB in two prospective clinical trials: a randomized study of two regimens for the last 4 months of treatment (n = 1,075) and a study of a twice-weekly rifabutin-containing regimen for HIV-infected patients with TB (n = 169). Isolates at diagnosis and from positive cultures after treatment completion underwent genotyping using IS6110 (with secondary genotyping for isolates with less than six copies of IS6110). Of 85 patients who had a positive culture after completing treatment, 6 (7.1%) were classified as false-positive cultures by a review committee blinded to treatment assignment. Of the remaining 75 cases with recurrent TB and genotyping data available, 72 (96%; 95% confidence interval, 88.8–99.2%) paired isolates had the same genotype; only 3 (4%; 95% confidence interval, 0.8–11.2%) had a different genotype and were categorized as reinfection. The authors concluded that recurrent TB in the United States and Canada, countries with low rates of TB, is rarely caused by reinfection with a new strain of *M. tuberculosis*.

**Diagnosis of TB**

In light of the limitations in utility of the TST to detect latent *M. tuberculosis* infection, a new diagnostic test, the Quanti-
FERON-TB, has been introduced. This test measures the release of IFN-γ from whole blood mononuclear cells on stimulation with purified protein derivative. Brock and coworkers (57) used the modified test, through employing antigens ESAT-6 and CFP-10 instead of purified protein derivative to circumvent the confounding effect of the bacille Calmette-Guérin (BCG) vaccine, to detect infection in contacts in a TB outbreak at a Danish high school. The majority of the contacts were BCG-unvaccinated. The authors thus found an excellent agreement (94%) between the TST and QuantiFERON-TB. In contrast to blood test based on purified protein derivative, the novel test was shown to have performance uninfuenced by the vaccination status of the subjects studied.

The concentration and size distribution of infectious aerosols produced by patients with pulmonary TB have not been previously documented. Fennelly and coworkers (58) developed a method, using a chamber with microbial air samplers, to collect and quantify culturable cough-generated aerosols of \( M. \) \( \text{tuberculosis} \). Such collected aerosols produced positive cultures in 25% of patients with smear-positive pulmonary TB. The culture-positivity rate declined rapidly within 3 weeks of effective treatment. Although the size distributions of these aerosols were variable, they mostly fell into the respirable range. The authors concluded that the feasibility of quantification of viable cough-generated aerosols offers a new approach to gauge the infectiousness and transmission of \( M. \) \( \text{tuberculosis} \) and other airborne pathogens.

The TST for diagnosing \( M. \) \( \text{tuberculosis} \) infection can be confounded by the effect of BCG vaccination or exposure to nontuberculous mycobacteria. Two \( M. \) \( \text{tuberculosis} \)-specific antigens, CFP-10 and ESAT-6, have been discovered. Mori and coworkers (59) examined the use of these two antigens in a whole blood IFN-γ assay for diagnosing TB in BCG-vaccinated individuals. Using a combination of responses to these antigens, the specificity of the test for the low-risk group was found to be 98.1%, and the sensitivity for patients with \( M. \) \( \text{tuberculosis} \) infection was 89.0%. The authors concluded that the whole blood IFN-γ assay using CFP-10 and ESAT-6 was highly specific and sensitive for \( M. \) \( \text{tuberculosis} \) infection, and was unaffected by BCG vaccination status.

**Treatment of TB**

Chan and coworkers (60) updated their 1993 report on treatment of multi-drug–resistant TB with respect to two new therapeutic approaches: surgical resection and fluoroquinolone antibiotics. With these two additions, the group produced successful results in 75% of patients (compared with 56% in the initial report), and mortality decreased from 22 to 12%. Accordingly, this therapeutic approach should now become the standard for treating multi-drug–resistant disease.

Jasmer and colleagues (61) compared the effects of directly observed versus self-administered treatment for TB and found that patients who self-administered their treatment had lower rates of cures (88.6 vs. 97.8%, \( p < 0.002 \)) and a higher mortality rate (5.5 vs. 0%, \( p < 0.002 \)). Although the study was not randomized, 44% of the patients receiving self-administered therapy had risk factors for nonadherence (e.g., positive sputum cultures, history of homelessness, illicit drug use, HIV infection, alcohol abuse, history of incarceration, \( < 21 \) years of age, infirmity severe enough to affect the patient’s ability to self-administer medications) that should have resulted in them receiving therapy under direct supervision.

A goal of developing new anti-TB drugs is to further shorten the required duration of chemotherapy. A new drug that improves the sterilizing activity of current regimens would reduce the duration of therapy without sacrificing efficacy, thereby enhancing treatment success rate and cost-effectiveness in utilization of health care resources. The new 8-methoxy fluoroquinolone, moxifloxacin, has potent activity against \( M. \) \( \text{tuberculosis} \) in vitro. Using the murine model, Nuermberger and coworkers (62) found that the combination of moxifloxacin, rifampin, and pyrazinamide reduced the time needed to eradicate \( M. \) \( \text{tuberculosis} \) from the lungs of infected mice by up to 2 months, when compared with the standard regimen of isoniazid, rifampin, and pyrazinamide. The authors concluded that these findings suggest the usefulness of combined use of moxifloxacin, rifampin, and pyrazinamide in shortening the course of chemotherapy for TB.

After the demonstration in the murine model that rifampin, moxifloxacin, and pyrazinamide in combination could shorten the time to negative cultures by up to 2 months compared with the standard regimen of rifampin, isoniazid and pyrazinamide, Nuermberger and coworkers (63) performed a second study in the same model to explore whether substitution of moxifloxacin for isoniazid would allow a shorter duration of treatment. The mice were assessed for relapse after treatment with combination therapy for 3, 4, 5, or 6 months. Although no relapse was observed among mice treated for at least 4 months with the moxifloxacin-containing regimen, mice treated with the isoniazid-containing standard regimen required 6 months of treatment to suppress relapse. For mice treated with rifampin, moxifloxacin, and pyrazinamide, similar efficacy was noted whether pyrazinamide was administrated for 1 month, 2 months, or the entire duration of therapy. The authors concluded that the combined use of rifampin, moxifloxacin, and pyrazinamide may substantially shorten the duration of therapy required to cure TB, and that the full benefit of pyrazinamide may be realized after just a month of treatment.

As a randomized controlled trial to assess the risk factors for early relapse of TB can be extremely difficult to perform because of its scale required, Chang and coworkers (64) conducted a nested case-control study to look for such risk factors. On matching 113 cases with 226 control subjects in a conditional logistic model, thrice-weekly treatment increased the risk of relapse in comparison with daily treatment (odds ratio 3.92), while prolonging both intensive and overall treatment by 50% or more protected against relapse (odds ratio 0.24). Cavitation was also found to be a risk factor for relapse. The authors concluded that further studies are required to identify ways of reducing the risk of relapse of TB under treatment program settings.

Administration of rifampin alone constitutes an alternative to the use of isoniazid as therapy for latent TB infection. Menzies and coworkers (65) conducted an open-label randomized trial on consenting patients of a respiratory hospital, for whom treatment for latent TB infection had been recommended. A patient received either daily self-administered rifampin for 4 months or daily self-administered isoniazid for 9 months. Among patients receiving rifampin, 91% took 80% of doses, and 86% took more than 90% of doses within 20 weeks, compared with 76 and 62% who took 80 and 90%, respectively, of doses of isoniazid within 43 weeks (relative risks: 80% of doses, 1.2; 90% of doses, 1.4). Adverse events resulted in permanent discontinuation of therapy for 3% of patients taking rifampin and 14% of patients taking isoniazid. Only three patients developed hepatitis—all were receiving isoniazid. The authors found that treatment completion was significantly better with 4 months of rifampin, and major adverse effects were somewhat lower. They concluded that further studies are warranted for assessing the safety and efficacy of the 4-month rifampin regimen.

Reichman and associates (66) discussed the potentially advantageous role of 4 months of treatment with rifampin in latent TB infection in a review article. Rifapentine is a long-acting cyclopentyl rifamycin suitable for use in once-weekly regimens for treatment of TB. Weiner
and coworkers (67) investigated the pharmacokinetics of this drug at dosages of 600, 900, and 1,200 mg during continuation-phase therapy in 35 patients with TB. Mean area under the plasma concentration-time curve (AUC(0-infinity)) increased significantly with dose: 296, 410, and 477 mg/hour/ml at 600, 900, and 1,200 mg, respectively. Fifty-four percent of patients had total plasma concentrations of rifapentine and of desacetyl rifapentine detected for more than 36 hours after clearance of concurrently administered isoniazid. Serious adverse reactions of therapy were infrequent (3%) and not linked with higher rifapentine AUC(0-infinity) or peak concentration. The authors concluded that the pharmacokinetic data support further trials to delineate the optimal dose of rifapentine for treatment of TB.

References

1. Marras TK, Morris A, Gonzalez LC, Daley CL. Mortality prediction in pulmonary tuberculosis from the discoveries and events that correlated with a decrease in mortality to the origins of the BCG vaccine, streptomycin, para-aminosalicylic acid (PAS), and isoniazid. In addition, the author describes the response to Robert Koch’s announcement that he found the causative organism, the effects of HIV infection and directly observed treatment, and the catastrophic results of the U.S. Congress’ policies that were intended to save money but ended up increasing the incidence of TB and of drug-resistant TB many-fold.

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Reviews

In two occasional essays, Murray (68, 69) summarized the history of TB, from the discoveries and events that correlated with a decrease in mortality to the origins of the BCG vaccine, streptomycin, para-aminosalicylic acid (PAS), and isoniazid. In addition, the author describes the response to Robert Koch’s announcement that he found the causative organism, the effects of HIV infection and directly observed treatment, and the catastrophic results of the U.S. Congress’ policies that were intended to save money but ended up increasing the incidence of TB and of drug-resistant TB many-fold.

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