

Year in Review

Tuberculosis, Lung Infections, and Interstitial Lung Disease in *AJRCCM* 2000

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TUBERCULOSIS

Genetic Susceptibility to *Mycobacterium avium-intracellulare* Infection

To determine why some patients with *Mycobacterium avium-intracellulare* pulmonary infection show deterioration and others do not, Kubo and coworkers (1) measured the frequencies of human leukocyte antigen (HLA) alleles in 64 cases and followed their short-term natural history. After a 30-month interval, 42% had deteriorated. No significant frequency of HLA-B or -C alleles was found in patients deteriorating or not deteriorating. In the patients who deteriorated, HLA-A26 was positive in 52% versus 21% of healthy controls. The authors conclude that HLA-A26 antigen may indicate immunogenetic susceptibility in patients with *Mycobacterium avium-intracellulare* infection who deteriorate.

It has been suggested that genetic variation in *NRAMP1* (the natural resistance-associated macrophage protein gene) may influence susceptibility to mycobacterial infection. Tanaka and coworkers (2) determined whether defects in that gene might explain susceptibility of two siblings in two families affected by pulmonary *Mycobacterium avium* complex disease. None of the strains of the organism was related epidemiologically to any of the others. In one patient, sequencing of *NRAMP1* revealed a nonconservative missense mutation at codon 419, which was heterozygous and not seen in his affected sibling. Variations similar to those in mice that confer susceptibility to the disease were not found. The authors conclude that alterations in the coding region of *NRAMP1* do not appear to explain susceptibility to *Mycobacterium avium* complex disease.

Because major histocompatibility complex molecules might play a role in susceptibility to pulmonary *Mycobacterium avium* complex infection, Takahashi and coworkers (3) investigated human leukocyte-associated antigen (HLA) phenotypes in patients with this disease. HLA phenotypes were tested in 59 patients with *Mycobacterium avium* complex infection and compared to Japanese control subjects. Compared to the controls, antigen frequencies in the patients were increased for HLA-A33 (29 versus 13%) and HLA-DR6 (51 versus 20%); the haplotype A33-B44-DR6 was also increased in the patients (24 versus 4%). The authors conclude that the

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development of pulmonary *Mycobacterium avium* complex infection is associated with specific HLA phenotypes.

Studies of Molecular Mechanisms in Tuberculosis

Because the release of interleukin-1 β and tumor necrosis factor- α from alveolar macrophages is important in the host defense against mycobacterial infection, Kuo and coworkers (4) determined whether nitric oxide is involved in their release. In alveolar macrophages of eleven patients with tuberculosis, the release of these proinflammatory cytokines was greater than in ten healthy controls; expression of their messenger RNAs was also upregulated. The nitric oxide inhibitor, *N*^G-monomethyl-L-arginine (L-NMMA), inhibited production of interleukin-1 β , tumor necrosis factor- α , and nitrite in the patients; it also depressed the expression of their mRNAs. Nuclear factor- κ B was highly expressed in the nuclei of the patients' alveolar macrophages, and the nitric oxide inhibitor inhibited it. Production of interleukin-1 β and tumor necrosis factor- α was attenuated by an inhibitor of nuclear factor- κ B. The authors conclude that enhanced generation of nitric oxide in the alveolar macrophages of patients with tuberculosis plays an autoregulatory role in amplifying the synthesis of proinflammatory cytokines, probably through activating nuclear factor- κ B.

Because interferon- γ is an important mediator of macrophage activation in controlling *Mycobacterium tuberculosis* and because interleukin-18 induces interferon- γ , Yamada and coworkers (5) measured their concentration in 43 patients with pulmonary tuberculosis and 25 healthy controls. Serum levels of interleukin-18 and interferon- γ were increased in the patients; the levels correlated with each other and with the level of disease. The authors conclude that interleukin-18 may contribute to the immune response in infection with *Mycobacterium tuberculosis*. An editorial commentary by Barnes and Wizel (6) accompanied this article.

Lipoarabinomannan is a component of the cell wall of *Mycobacterium tuberculosis*, which shares many properties with lipopolysaccharide and can induce the release of cytokines and chemokines. Juffermans and coworkers (7) assessed the effect of this substance on lung inflammation. In normal mice, lipoarabinomannan produced bronchoalveolar neutrophilia, and increases in macrophage inflammatory protein-2, keratinocyte, tumor necrosis factor- α , interleukin-1 α , and interleukin-1 β . Because interleukin-1 contributes to granuloma formation during mycobacterial infection, studies were also done in mice deficient in the interleukin-1 receptor. These animals developed less influx of granulocytes and lower levels of tumor necrosis factor- α than the wild-type mice. The authors conclude that lipoarabinomannan appears to stimulate innate immunity in infection with *M. tuberculosis* via mechanisms that involve interleukin-1 activity.

Matsuyama and coworkers (8) examined whether endothelial growth factor is associated with pulmonary tuberculosis. Serum levels were higher in 43 patients with active pulmonary tuberculosis than in 29 patients with old tuberculosis or 25 patients with acute bronchitis. In seven patients with active disease, the serum levels paralleled clinical improvement over six months. Resected specimens in three patients revealed vascular endothelial growth factor in alveolar macrophages surrounding the lesion. The authors conclude that vascular endothelial growth factor may contribute to the pathogenesis of pulmonary tuberculosis.

Epidemiology of Tuberculosis

To determine the incidence, risk factors, and transmission of tuberculosis in the homeless, Moss and coworkers (9) prospec-

tively followed 2,774 homeless persons. Between 1992 and 1996, 25 persons developed tuberculosis. Independent risk factors for tuberculosis were HIV infection, African-American or other nonwhite ethnicity, positive tuberculin skin test, age, and education. Clustering of restriction fragment length polymorphism (DNA fingerprinting), thought to represent recent transmission and rapid progression, was evident in 60% of cases overall, and in 77% of African-American cases and in 88% of HIV-positive cases. The authors conclude that the high rate of tuberculosis in the homeless is secondary to recent transmission in persons who are HIV-positive and nonwhite.

In Beijing, compulsory vaccination of newborns with bacillus Calmette-Guérin (BCG) began in 1952, reaching more than 95% of the population. In 1988, BCG vaccination was discontinued in Shun-yi County of Beijing. Zhang and coworkers (10) examined the trend in annual risk of tuberculous infection in that county. The prevalence of tuberculous infection was 1.4% in 1995, contrasted with 46% in 1950. The number of cases of tuberculous meningitis did not increase after the discontinuation of BCG. The authors conclude that discontinuation of BCG vaccination had no harmful effect.

Latent Tuberculosis Infection

Screening. The reference standard for purified protein derivative (PPD) used in tuberculin skin testing is PPD-S1. Because stock of PPD-S1 is almost depleted, a new standard, PPD-S2, has been developed. Villarino and coworkers (11) did a double-blind trial of these two standards in 69 patients with a history of culture-proven tuberculosis and in 1,189 subjects with a very low risk of tuberculosis. The two standards produced statistically indistinguishable results in both study groups. The authors conclude that PPD-2 is qualified to serve as the new U.S. reference standard for PPD tuberculin.

Among 529 subjects undergoing tuberculin skin testing, Al Zahrani and coworkers (12) asked, "Does the size of the reaction indicate a greater risk for tuberculosis?" Final diagnosis included 68 subjects with active tuberculosis and 274 with inactive tuberculosis. An induration of 5 mm or larger was more likely to indicate active or inactive tuberculosis. The size and frequency of indurations larger than 5 mm did not predict different outcomes. Reactions were not different between 121 BCG vaccinated subjects and 121 unvaccinated subjects. The authors conclude that in close contacts or in patients suspected of active tuberculosis, skin reactions less than 5 mm indicate a lower likelihood of active or inactive tuberculosis, but for reactions above that threshold, the size does not matter.

The cost-effectiveness of tuberculosis screening of immigrants has not been previously investigated. To address this issue, Dasgupta and coworkers (13) prospectively compared three methods—radiographic screening of all immigration applicants, surveillance for inactive tuberculosis in immigrants already arrived, and investigation of close contacts of active cases of tuberculosis—against a policy of passively diagnosed active tuberculosis. Over one year, the three programs detected 27 cases of active tuberculosis and prevented 14 future cases. Compared with passive case detection, close-contact investigation achieved a net savings of \$815 for each active case detected and treated, and of \$2,186 for each future active case prevented. The incremental cost of treating each case of active tuberculosis was \$39,409 for applicant screening, and \$24,225 for surveillance of newly arrived immigrants; the cost of preventing each case was \$33,275 for screening and \$65,126 for surveillance. The authors conclude that close-contact investigation resulted in net savings, whereas immigrant applicant screening and surveillance programs were less cost effective. An editorial commentary by Taylor and O'Brien (14) accompanies this article.

All immigrants to Canada undergo chest radiographic screening for tuberculosis, but its cost-effectiveness has never been evaluated. In three simulated cohorts of 20-year-old immigrants, Schwartzman and Menzies (15) modeled the cost-effectiveness of radiography and tuberculin skin testing for preventing tuberculosis. In the highest risk group (50% tuberculosis-infected, 10% HIV seroprevalence), radiography prevented 4.3% of expected cases and skin testing achieved a further 8% decrease. In the lowest risk group (5% tuberculosis-infected, 1% HIV seroprevalence), radiography prevented 8% of expected cases and skin testing achieved a further 4% decrease. To prevent one active case of tuberculosis, radiography screening cost \$3,943 Canadian in the highest risk groups and \$236,496 in the lowest risk groups. To prevent each additional case, skin testing cost \$32,601 in the highest risk group and \$68,799 in the lowest risk group. For immigrants from countries with a high prevalence of tuberculosis, radiographic screening is inexpensive and skin testing is much less cost effective. For immigrants from countries with a low prevalence of tuberculosis, both screening tools are extremely expensive and have negligible impact.

Risk, reactivation, and treatment. To assess outcomes among close contacts of patients with active tuberculosis, Marks and coworkers (16) identified an urban sample of 1,080 patients with smear-positive pulmonary tuberculosis and a median of four close contacts per patient. Of eligible contacts, 88% received tuberculin skin tests and 36% had positive reactions. Positive skin tests were more likely among household contacts and among contacts of patients with highly positive smears or cavitary tuberculosis. Of contacts with a positive skin test, 74% started treatment for latent tuberculosis infection and 56% completed it. The likelihood of completion was increased by directly observed treatment. The authors conclude that the high rate of positive skin tests among foreign-born contacts probably indicates prior infection or boosting rather than recent infection. This article is accompanied by an editorial commentary by Hopewell (17).

To determine the incidence of reactivation of latent tuberculosis, Marks and coworkers (18) studied a cohort of 15,489 predominantly Southeast Asian refugees to Australia between 1984 and 1994. On arrival, all had a clear chest x-ray and their tuberculin skin test was recorded. On follow up, 122 cases of tuberculosis occurred over 10.3 years (crude annual incidence, 76 per 100,000 person-years). The risk increased linearly as the size of the skin reaction increased above 10 mm. Among individuals with an initial reaction of at least 15 mm, the annual incidence was 213 per 100,000 in the first 3 years and it averaged 122 per 100,000 in the subsequent 10 years. The risk, and the relation of risk to skin reaction size, was unrelated to BCG status. The authors conclude that the incidence of tuberculosis is similar to that of the U.S. in the 1950s and 1960s.

Directly observed therapy. In 1,022 patients with a positive tuberculin skin test and old tuberculosis on chest x-ray who had not been previously treated, Jasmer and coworkers (19) compared two treatment regimens. Of 545 patients assigned to daily isoniazid for twelve months, 80% completed the course and 5% developed adverse effects. Of 477 patients assigned to four months of daily isoniazid and rifampin, 84% completed the course and 6% developed adverse effects. On a Markov model, both regimens increased life expectancy by 1.5 years. Compared with twelve months of isoniazid, four months of isoniazid and rifampin resulted in net incremental savings of \$135 per patient. The authors conclude that four months of isoniazid and rifampin is cost effective in the treatment of latent tuberculosis infection.

McNab and coworkers (20) compared two approaches to treating latent tuberculosis infection in Canadian plains Ab-

origines. From 1992 to 1995, 591 persons received directly observed treatment with isoniazid and rifampin twice weekly for six months. From 1986 to 1989, 487 persons received self-administered isoniazid every day for twelve months. Compliance was 82% with directly observed treatment and 19% with self-treatment. Over six years of follow-up, the rate of tuberculosis per 1000 patient-years was 0.9 for directly observed treatment and 9 for self-treatment. The authors conclude that six months of directly observed twice-weekly treatment with isoniazid and rifampin improves outcome in a population with poor compliance.

To assess adherence to isoniazid for latent tuberculosis infection, Matteelli and coworkers (21) did a prospective, randomized study of three regimens in 208 illegal immigrants to Italy. Of 82 subjects assigned to supervised treatment with 900 mg twice weekly, only 7% completed six months, and time to dropout was 3.8 weeks. Of 73 subjects assigned to unsupervised treatment with 900 mg twice weekly, 26% completed six months, and time to dropout was six weeks. Of 53 subjects assigned to unsupervised treatment with 300 mg daily, 41% completed six months, and time to dropout was 6.2 weeks. The authors conclude that the rate of completing isoniazid treatment by illegal immigrants was low, and that supervising the administration of the therapy reduced adherence.

If the frequency of drug administration could be reduced to once a week, implementing directly observed treatment (DOT) for *Mycobacterium tuberculosis* would be easier. Because the newly approved agent, rifapentine, offers potential, Daniel and coworkers (22) tested various once-weekly regimens in mice infected with *M. tuberculosis*. When mice were treated once weekly with rifapentine as a sole agent, all failed treatment and resistant bacilli emerged. The combination of rifapentine plus isoniazid was successful at six months when it was preceded by a two-month daily phase with isoniazid, rifampin, and pyrazinamide. When the initial daily phase was reduced to two weeks, once weekly treatment of rifapentine plus isoniazid was successful only if supplemented by agents at specific intervals. The authors conclude that a combined regimen containing rifapentine was effective only if preceded by intensive initial therapy or by subsequent addition of supplemental agents.

Targeted tuberculin testing and treatment of latent tuberculosis infection is discussed in an ATS statement (23).

Atypical Tuberculosis

Cullen and coworkers (24) reported a 33-year-old patient with cystic fibrosis who was thought to have colonization with *Mycobacterium abscessus* for 13 years. After infection became clinically apparent, review of histology revealed active infection from the onset. The authors conclude that indolent infection should be considered when mycobacteria are repeatedly isolated.

Diagnosis of Tuberculosis

Detection of acid-fast bacilli by sputum smear has a sensitivity of 45 to 75% for *Mycobacterium tuberculosis* recovered by growth in culture. Warren and coworkers (25) determined whether a minimum sputum volume of 5 ml would improve sensitivity. When 3,486 specimens were processed regardless of volume, sensitivity was 73%. When 1,846 specimens were processed using a minimum volume of 5 ml, sensitivity was 92%. All of 18 cases of tuberculosis were smear positive using 5 ml of sputum for testing, whereas 12 of 26 cases of tuberculosis were smear negative when a minimum volume was not required. The authors conclude that setting a minimum volume of 5 ml of sputum improves sensitivity of the acid-fast smear.

Among 500 consecutive patients referred for sputum induction for diagnosis of possible active tuberculosis, Al Zahrani and coworkers (26) prospectively studied the yield and clinical utility of a combination of diagnostic tests. A diagnosis of active tuberculosis was made in 60 patients. Sensitivity of the tests were: mycobacterial culture (using liquid [BACTEC] and solid media) 73%; polymerase chain reaction 42%; chest x-ray 67–77%; tuberculin testing 20%; and an ELISA serologic test 33%. Specificity of the tests were: mycobacterial culture 100%; polymerase chain reaction 100%; chest x-ray 66–77%; tuberculin testing 20%; and serology 87%. The authors conclude that no test has a sufficiently high sensitivity and specificity to accurately diagnose pulmonary tuberculosis, and that a combination of tests in conjunction with clinical evaluation is necessary.

Conde and coworkers (27) assessed the yield of sputum induction and bronchoalveolar lavage in the diagnosis of tuberculosis in a region with a high prevalence of tuberculosis and HIV infection. Of 251 patients, 143 (57%) had a diagnosis of tuberculosis; among these, 25 (17%) were HIV seropositive. Among 207 HIV-seronegative patients, agreement between sputum induction and bronchoalveolar lavage was 97% for acid-fast smear and 90% for mycobacterial culture. Among 44 HIV-seropositive patients, agreement between sputum induction and bronchoalveolar lavage was 98% for acid-fast smear and 86% for mycobacterial culture. The authors conclude that sputum induction provides a high yield in diagnosing pulmonary tuberculosis in patients with and without HIV infection.

In patients with suspected mycobacterial infection and a negative sputum smear, bronchoscopy is often performed. In 98 smear-negative patients (24 with active tuberculosis, 28 with cured tuberculosis, and 46 without TB), Hidaka and coworkers (28) applied the polymerase chain reaction combined with restriction fragment length polymorphism (PCR-RFLP). With positive cultures and radiographic improvement after antituberculous therapy as the reference standard, the sensitivity of the test was 70% for bronchoscopic brush, 76% for bronchoscopic washings, and 91% for both combined. The authors conclude that bronchoscopy combined with polymerase chain reaction-restriction fragment length polymorphism is a good diagnostic approach for diagnosing several species of mycobacterium.

Chan and coworkers (29) determined whether an antibody against lipoarabinomannan, a lipoglycan component of the mycobacterial cell wall, would help in the diagnosis of tuberculosis. In patients with active tuberculosis, sensitivity was 85 to 93%. Specificity was 100% in healthy young U.S. citizens, and 89% in an at-risk population. Five patients with active tuberculosis were smear negative but tested positive for the antibody. The authors conclude that the immunoassay for lipoarabinomannan is relatively sensitive and specific for active tuberculosis.

The diagnostic standards and classification of tuberculosis in adults and children are discussed in an ATS statement (30).

Treatment of Tuberculosis

Because patients vary in their response to treatment of pulmonary tuberculosis, Wallis and coworkers (31) determined whether use of a multivariate model could predict the likelihood of treatment failure in 42 patients with drug-sensitive tuberculosis. Two patients who showed an initial response later had a drug-sensitive relapse. Duration of culture positivity was best predicted by a model that included the concentration of *M. tuberculosis* antigen 85 in the sputum on day 14, days-to-positive in BACTEC culture medium on day 30, and extent of disease on baseline radiography. The authors conclude that

stratifying patients according to anticipated response to treatment may result in better outcome.

Other Issues in Tuberculosis

Tuberculosis is associated with a compromised immune system, particularly a failure of Th1 cytokine responses. Baker and coworkers (32) determined whether altered cortisol metabolism might contribute to the immune compromise. A shift towards active cortisol over inactive cortisone was found in 24-hour urine samples: the ratio of cortisol to cortisone was higher in 30 patients with active pulmonary tuberculosis (1.19) than in 14 patients with cured tuberculosis (0.89) or 23 healthy controls (0.78). The cortisol-to-cortisone ratio in bronchoalveolar fluid was 91% higher in patients with active disease than in healthy controls; the ratio in serum was not different. Conversion of oral cortisone to plasma cortisol was 34% higher in patients with active tuberculosis. The response of plasma cortisol to stimulation with adrenocorticotropic hormone and corticotropin-releasing hormone was normal. The authors conclude that peripheral metabolism of glucocorticoids, especially in the lung, is deviated toward the active metabolite, cortisol, in patients with active tuberculosis.

To determine the effect of age and diabetes on the appearance of chest x-rays in patients with pulmonary tuberculosis, Perez-Guzman and coworkers (33) studied 192 patients with pulmonary tuberculosis and diabetes and 130 patients with pulmonary tuberculosis alone. The proportion of patients with lower zone lesions increased progressively with age ($r = 0.89$), whereas the frequency of cavitation steadily decreased with age ($r = -0.79$). Diabetic patients had a high frequency of lower lobe lesions and cavitation in all age groups. The authors speculate that diabetic and older patients have a higher alveolar PO_2 in the lower lobes, favoring the development of lower lobe disease.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Animal Models

Because as many as 40% of HIV-infected individuals meet the criteria for alcoholism, Stoltz and coworkers (34) studied the separate and combined effects of *in vivo* viral infection and *in vitro* exposure to alcohol in rhesus macaques, some of which had been infected with the simian immunodeficiency virus (SIV). Stimulation of cultured alveolar macrophages with lipopolysaccharide increased the production of tumor necrosis factor- α protein in uninfected animals and in animals with terminal SIV infection; the response was depressed in macrophages of asymptomatic SIV-positive animals. When the alveolar macrophages were cultured in ethanol for two hours before administration of lipopolysaccharide, the increase in tumor necrosis factor- α was depressed by 50% in both SIV-positive and SIV-negative animals; this suppression occurred at a post-transcriptional level. The authors conclude that ethanol's depression of tumor necrosis factor- α production may contribute to infectious complications in HIV-infected individuals.

Studies of Molecular Mechanisms

Cryptococcus neoformans is a common cause of fatal fungal infection in AIDS, and alveolar macrophages are the initial cells of host defense. Jeong and coworkers (35) determined whether infection of alveolar macrophages by HIV would impair their anti-cryptococcal activity. Normal uninfected macrophages demonstrated innate fungicidal activity against *C. neoformans*. Infection of macrophages with HIV caused a reduction, or loss, of fungicidal activity. The decreased fungi-

cidal activity was not due to a cytotoxic effect of HIV, nor did HIV impair the binding or internalization of the fungus by the macrophages. The authors conclude that HIV-infection impairs the innate fungicidal activity of alveolar macrophages by a mechanism involving a defect of intracellular processing of microorganisms.

The recruitment of cytotoxic T lymphocytes into the lung plays a major role in clearing HIV from the lower respiratory tract. Agostini and coworkers (36) investigated the role of two CXC chemokines (interferon- γ -inducible protein-10 and Mig) in the lungs of eleven HIV-positive patients with high intensity T-cell alveolitis. These CXC chemokines stimulate migration of activated T cells and interact with a specific receptor (CXC receptor 3). Lymphocytes in the patients' bronchoalveolar fluid were CD8⁺ T cells, and expressed high levels of CXC receptor 3 and interferon- γ . T cells expressing CXC receptor 3 exhibited a high migratory capability when stimulated by CXC chemokines. The patients' alveolar macrophages bore the CXC chemokines, and secreted levels of ligands of CXC receptor 3 capable of inducing T-cell chemotaxis. The authors conclude that chemotactic ligands that bind CXC receptor 3 contribute to the accumulation of HIV-specific cytotoxic T lymphocytes in the lung.

***Pneumocystis carinii* Pneumonia**

General aspects. Improvements in therapy have altered the clinical manifestations of HIV infection and predictors of mortality from *Pneumocystis carinii* pneumonia. To provide a model for evaluating severity of illness, Arozullah and coworkers (37) analyzed data from 1,660 patients hospitalized with HIV-associated *P. carinii* pneumonia between 1995 and 1997. Inpatient mortality was 11%. A five-category staging system was developed using 3 variables: wasting, alveolar-to-arterial PO₂ gradient, and serum albumin. Mortality increased progressively from stage 1 (4%) to stage 5 (49%). The authors conclude that the staging system may prove helpful for assessing quality of care in future studies.

To determine whether HIV-associated pneumonia caused by *Pneumocystis carinii* or bacteria results in permanent changes in lung function, Morris and coworkers (38) prospectively followed 1,149 patients for 3.7 years. Pneumonia resulted in permanent decreases in FEV₁, FVC, FEV₁/FVC ratio, and diffusing capacity. The authors conclude that *P. carinii* and bacterial pneumonias in HIV-infected persons results in persistent airflow limitation.

Geographic clustering. Although animal studies demonstrate that *Pneumocystis carinii* is transmitted by the airborne route, the communicability is not known. To determine whether cases are geographically clustered, Dohn and coworkers (39) analyzed ZIP code areas of 118 HIV-infected patients presenting with a first episode of *P. carinii* pneumonia. Geographic clustering was observed for the cases, but not for 960 HIV-infected patients seen over the same period. The authors conclude that the data raise intriguing questions about exposure to exogenous sources of *P. carinii*. An editorial commentary by Beck (40) accompanies this article.

Geographic analysis has been used to study environmental or sources of various diseases, but it has not been applied to *Pneumocystis carinii* pneumonia. Morris and coworkers (41) analyzed data from cases with confirmed *P. carinii* pneumonia in HIV-infected persons and compared them with controls. Independent predictors of increased risk were lack of *P. carinii* prophylaxis and a CD4 cell count no higher than 50 cells per μ l. Subjects living in one ZIP code, 94102, had an 80% lower likelihood of *P. carinii* pneumonia. The authors conclude that residence in one geographic area of San Francisco was associ-

ated with a lower risk of *P. carinii* pneumonia than living in other areas of the city. An editorial commentary by Beck (40) accompanies this article.

Bacterial Pneumonia

To determine the factors associated with mortality in bacterial pneumonia in HIV-infected patients, Cordero and coworkers (42) did a one-year prospective study in 355 patients. Attributable mortality was 9.3%. Patients meeting the ATS criteria of severe disease had a longer hospital stay, longer duration of fever, and higher attributable mortality (13 versus 3.5%) than those that did not. A prognostic rule based on five criteria (shock, CD4⁺ cell count less than 100 per μ l, pleural effusion, cavities, and multilobar infiltrates) had a negative predictive value for mortality of 97%. The authors conclude that ATS severity criteria are valid in HIV-infected patients with bacterial pneumonia and that a prognostic rule can be used to identify patients requiring admission to hospital.

Pulmonary Hypertension

Because the clinical and histologic features of pulmonary hypertension in patients with HIV infection resemble those of primary pulmonary hypertension, Aguilar and Farber (43) treated six patients with continuous intravenous infusions of epoprostenol (prostacyclin) for up to 40 months. Acute infusions of epoprostenol caused a 16% decrease in mean pulmonary artery pressure, a 33% decrease in pulmonary vascular resistance, and a 37% increase in cardiac output. At one year, mean pulmonary artery pressure was 22% lower and pulmonary vascular resistance was 55% lower than baseline, while cardiac output was increased by 51%. The authors conclude that infusion of epoprostenol improved hemodynamic and functional status in six patients with HIV-associated pulmonary hypertension.

Highly Active Antiretroviral Therapy

The effect of highly active antiretroviral therapy (HAART) on the incidence of bacterial pneumonia had not been previously examined. Sullivan and coworkers (44) analyzed data from 1,898 HIV-infected patients with CD4 counts below 200 cells per mm³ followed between 1993 and 1998. Between early 1993 and late 1997, the incidence of bacterial pneumonias decreased by 60%. The risk of bacterial pneumonia was decreased with use of protease-inhibitor-containing regimens (relative risk [RR] 0.55), and it increased with lower CD4 cell counts (RR 2.22), injection drug use (RR 2.0), and previous *P. carinii* pneumonia (RR 3.88). The authors conclude that the introduction of combination antiretroviral therapy containing protease inhibitors has led to a dramatic decline in the incidence of bacterial pneumonia.

In the early 1990s, hospital survival in HIV-positive patients with *Pneumocystis carinii* pneumonia and respiratory failure was about 20%. Curtis and coworkers (45) assessed the outcome in patients from 71 hospitals in 1995–1997, when highly active antiretroviral therapy started to be used. Of 1,660 patients with confirmed or presumed *P. carinii* pneumonia, 9% received mechanical ventilation and their hospital survival was 38%. Patients who were taking prophylaxis against *P. carinii* before developing pneumonia were less likely to survive to discharge. The authors conclude that survival in patients requiring mechanical ventilation for *Pneumocystis carinii* pneumonia increased to 40% for 1995–1997.

The introduction of highly active antiretroviral therapy has dramatically decreased mortality and morbidity in HIV-infected patients. To determine the effect of the new therapy on the incidences of mycobacterial diseases, Kirk and coworkers

(46) analyzed data on over 7,000 patients participating in the EuroSIDA study. The incidence of *Mycobacterium tuberculosis*, in terms of cases per 100 person-years, decreased from 1.8 before September 1995 to 0.3 after March 1997, and the decrease in *Mycobacterium avium* was from 3.5 to 0.2. After adjusting for changes in CD4 cell counts and use of antiretroviral agents, the risk of *M. avium* complex decreased by 42% over time, whereas *M. tuberculosis* did not change. The authors conclude that the incidence of *M. tuberculosis*, and even more so *M. avium* complex, decreased markedly in HIV-infected patients between 1994 and 1999.

LUNG INFECTIONS

Host Defenses

Because viral and bacterial infections of the respiratory tract are often linked, Pang and coworkers (47) examined the influence of influenza virus on the secretion of lysozyme by sputum neutrophils obtained from 6 patients with bronchiectasis. After being infected with influenza virus A, neutrophils had a reduced capacity to secrete lysozyme but not myeloperoxidase. Inhibition was greater with A than with B strains of influenza. Bactericidal activity was also reduced by A but not by B strains. The authors conclude that impaired neutrophil function with decreased secretion of lysozyme and bactericidal activity may foster bacterial colonization in the respiratory tract following influenza infection.

To evaluate the immune activities of exudate macrophages in the pulmonary immune response, Kradin and coworkers (48) injected labeled, heat-killed *Listeria* into the trachea of Lewis rats. At 24 hours, macrophages from bronchoalveolar fluid were purified based on their expression of an antigen specific for rat macrophages. The macrophages were analyzed for uptake of *Listeria*, and were purified on the basis of intensity of staining. Bright-staining macrophages were the dominant mediators of phagocytosis when low doses of *Listeria* were administered but did not support proliferation of T lymphocytes. Dim-staining macrophages expressed more interleukin-1 and tumor necrosis factor, but less nitric oxide; they had excellent antigen-presenting cell activities for T cell responses. The authors conclude that a subset of dim-staining macrophages shows phenotypic and functional evidence of dendritic cell differentiation.

The degradation of the bronchial matrix by neutrophils is thought to be important in the pathogenesis of bronchiectasis. Shum and coworkers (49) determined whether neutrophils are capable of degrading lung matrix proteoglycans and whether proinflammatory mediators are involved. Rat bronchoalveolar proteoglycans were entrapped in polyacrylamide gel beads and served as a substrate for incubation with neutrophils from healthy volunteers combined with sputum sol from patients with bronchiectasis. Incubation of the sputum and neutrophils produced degradation of proteoglycans in excess of the sum of each on its own. The degradation of proteoglycans was completely inhibited by the addition of an antibody to tumor necrosis factor- α , and largely inhibited by Eglin C. The authors conclude that serine proteases secreted by neutrophils were mainly responsible for the degradation of proteoglycans and that secretion of the proteases was stimulated by tumor necrosis factor- α in the presence of cofactors in the sputum of patients with bronchiectasis.

Immunocompromised Host

In 63 patients with hematologic malignancy, White and coworkers (50) examined the usefulness of open lung biopsy. A specific diagnosis was found in 62% of biopsies. Therapy was

changed in 57% of patients, but in 69% of those with a specific diagnosis. Survival was higher at 90 days in patients with a specific diagnosis than in those with a nonspecific diagnosis. A specific diagnosis was less likely with a diffuse rather than focal radiographic abnormality (36 and 79%), and in patients with neutropenia, ventilator support, or having received chemotherapy in the preceding six months with an agent known to cause pulmonary toxicity. Specific diagnoses included inflammatory disorders (23%), infections (21%), and malignancy (18%). Complications occurred in 13%, and one patient died. The authors conclude that open lung biopsy has a significant yield and impact on the management of patients with hematologic malignancy.

Diagnosis of primary immunodeficiency is problematic because low levels of serum immunoglobulin occur in healthy subjects. Rodrigo and coworkers (51) determined whether the antibody response to *Haemophilus influenzae* type b-conjugated vaccine would discriminate between 22 patients with humoral immunodeficiency and 59 healthy subjects. Among the healthy subjects, 85% exceeded the threshold value for IgG antibody response to *Haemophilus*; 75% of 20 subjects who had received pneumococcal vaccine exceeded the threshold for IgG response to *Streptococcus pneumoniae*. All healthy subjects receiving both vaccines responded to at least one. No patient with humoral immunodeficiency responded to either vaccine. The authors conclude that measuring the antibody response to *Haemophilus influenzae* or pneumococcal vaccination may aid in the diagnosis of humoral immunodeficiency.

Diagnosis of Lung Infection

In a febrile patient with a cavitating lung tumor, it can be difficult to differentiate infection from tumor necrosis. In 22 patients with cavitating lung tumors, Liao and coworkers (52) performed transthoracic aspiration under ultrasound guidance. Microorganisms were isolated in six of seven febrile patients and in one of 15 nonfebrile patients. In five of the six febrile patients, culture results led to adjustment of antibiotics resulting in clinical improvement. The authors conclude that transthoracic aspiration helps to differentiate infection from tumor necrosis in cavitating lung tumors.

Standard virological methods can take 3–10 days to detect cytopathic effects of varicella-zoster infection in cell culture. Cowl and coworkers (53) described the use of polymerase chain reaction technique in a woman with leukemia to detect varicella-zoster infection within 24 hours of bronchoalveolar lavage. The patient responded to acyclovir therapy.

Pneumonia

To determine the role of apoptosis in the resolution of pneumonia, Kazzaz and coworkers (54) studied two models of bacterial pneumonia in rats. Infection with *Streptococcus sanguis* resolves over three weeks, whereas infection with *Streptococcus pneumoniae* type 25 progresses to fibrosis. During the acute stage, the pattern and extent of apoptosis was similar in both models, with the number of apoptotic nuclei increasing for four days. After eight days, major differences occurred. In the resolving model, apoptosis was limited primarily to an abscess at the base of the lung. In the nonresolving model, apoptosis was persistent. The authors conclude that the location and timing of apoptosis may determine whether pneumonia resolves or progresses to fibrosis.

In 49 patients admitted to hospital with community-acquired pneumonia, Arancibia and coworkers (55) determined the causes and prognostic implications of treatment failure. A definite cause of treatment failure could be identified in 65% of the patients. Treatment failures were mainly infectious in

origin, and included primary (19%), persistent (24%), and nosocomial infections (20%). Persistent infections arose mainly because of microbial resistance to agents initially selected. Associated mortality was 75% for persistent infections and 88% for nosocomial infections. On multivariate analysis, nosocomial pneumonia was the only cause of treatment failure associated with death (RR 16.7). The authors conclude that microbial resistance and diagnosing nosocomial pneumonia continue as the major challenges in managing patients admitted to hospital with community-acquired pneumonia.

Infection with *Pseudomonas aeruginosa* that is resistant to several antibiotics accounts for many episodes of nosocomial pneumonia. Hamer (56) described three patients with nosocomial pneumonia caused by multidrug-resistant *Pseudomonas aeruginosa*. Colistin, an abandoned agent, administered as an aerosol proved beneficial as supplemental therapy.

BRONCHIECTASIS

In 74 patients with bronchiectasis and *Pseudomonas aeruginosa*, but without cystic fibrosis, Barker and coworkers (57) did a double-blind, randomized trial of self-administered tobramycin, inhaled twice daily for four weeks. Two weeks after finishing treatment, *P. aeruginosa* was eradicated in 35% of the tobramycin group but in none of the placebo group. Investigators rated an improvement in the medical condition of 62% of the tobramycin patients and 38% of the placebo patients. Strains of *P. aeruginosa* resistant to tobramycin developed in 11% of the tobramycin group and in 3% of the placebo group. Change in FEV₁ did not differ in the two groups. The authors conclude that further evaluation of inhaled tobramycin in bronchiectasis is warranted.

Diffuse panbronchiolitis is associated with sinusitis, bronchiectasis and mucociliary dysfunction. Nakano and coworkers (58) measured nitric oxide in air samples directly from the nose in 8 patients with this disorder and in 15 healthy controls. Nasal nitric oxide was lower in the patients (69 versus 556 nl/min), and it did not change with erythromycin therapy. The authors conclude that diffuse panbronchiolitis is the third disease associated with reduced nasal nitric oxide levels, the others being cystic fibrosis and primary ciliary dyskinesia syndrome.

In four patients with early onset of severe bronchiectasis, Tsang and coworkers (59) found a previously undescribed ciliary defect. Numerous cystlike structures were present within the ciliary shafts.

In 150 consecutive adults with bronchiectasis identified with high-resolution computed tomography, Pasteur and coworkers (60) attempted to identify the underlying cause. Intensive investigation led to identification of a cause in 47% of cases. Causes identified were: early childhood pneumonia, pertussis, or measles (44 cases), immune defects (12 cases), allergic bronchopulmonary aspergillosis (11 cases), aspiration (6 cases), Young's syndrome (5 cases), cystic fibrosis (4 cases), rheumatoid arthritis (4 cases), ciliary dysfunction (3 cases), panbronchiolitis (1 case), and congenital defect (1 case). In 22 patients (15%), the cause identified had implications for prognosis and treatment.

INTERSTITIAL LUNG DISEASE

Idiopathic Pulmonary Fibrosis

Genetics. Fibrosing alveolitis (also known as idiopathic pulmonary fibrosis) is characterized by persistent inflammation and increased production of tumor necrosis factor- α , interleukin-1 β , and interleukin 1 receptor antagonist. Because a number of cytokine gene polymorphisms are associated with suscepti-

bility to inflammatory diseases, Whyte and coworkers (61) determined whether single base variations at position +2018 in the gene for interleukin-1 receptor antagonist (IL-1RN) and at position -308 in the gene for tumor necrosis factor- α (TNF- α) influence susceptibility to fibrosing alveolitis. Genotyping was performed on 88 cases and controls in England and on 61 cases and controls from Italy. For the allele on the gene for interleukin-1 receptor antagonist, the risk for fibrosing alveolitis in homozygotes was increased 10 fold in England and 2.5 fold in Italy. For the allele on the gene for tumor necrosis factor- α , the risk for fibrosing alveolitis in the carriers was increased 2 fold in England and 2.5 fold in Italy. The authors conclude that interleukin-1 receptor antagonist gene (+2018) allele 2 and tumor necrosis factor- α gene (-308) allele 2 confer increased risk of developing fibrosing alveolitis.

Histopathological subtypes. In 78 patients with clinicopathologic diagnoses of a wide spectrum of "lone" cryptogenic fibrosing alveolitis, also known as idiopathic pulmonary fibrosis, Nicholson and coworkers (62) evaluated the clinical significance of recent histologic reclassifications. Biopsy specimens were reclassified by two histopathologists (κ 0.49) as usual interstitial pneumonia 47%, nonspecific interstitial pneumonia 36%, and desquamative interstitial pneumonia/respiratory bronchiolitis-associated interstitial lung disease 17%. On follow-up over 42 months, 50 patients died: usual interstitial pneumonia 89%, nonspecific interstitial pneumonia 61%, and desquamative interstitial pneumonia 0%. Patients with desquamative interstitial pneumonia/respiratory bronchiolitis-associated interstitial disease responded more frequently to treatment than the other groups. The authors conclude that their findings confirm the prognostic value of subclassifying patients according to histopathologic pattern, and they caution that patients with nonspecific interstitial pneumonia do not necessarily have a good prognosis.

Because nonspecific interstitial pneumonia is distinguished from usual interstitial pneumonia by a relative lymphocytosis in bronchoalveolar fluid (and better prognosis), Park and coworkers (63) examined whether interleukin-6 contributes to the lymphocytosis. Lymphocyte numbers and levels of interleukin-6 were higher in seven patients with nonspecific interstitial pneumonia than in sixteen patients with usual interstitial pneumonia; the level of interleukin-6 correlated with the lymphocyte count ($r = 0.93$). The source of the interleukin-6 was the epithelial cells of the small airways and alveolar macrophages. The authors conclude that lymphocytosis in the bronchoalveolar fluid of patients with nonspecific interstitial pneumonia is associated with high levels of interleukin-6.

In patients with different forms of idiopathic pulmonary fibrosis, Miki and coworkers (64) compared the function of lung fibroblasts. Fibroblasts from five patients with usual interstitial pneumonia had 2.2 times greater contractility than did fibroblasts from five patients with nonspecific interstitial pneumonia; the increased contractility was consistent with enhanced F-actin content in the fibroblasts. Conditioned media of fibroblast cultures from patients with usual interstitial pneumonia enhanced the contractility of fibroblasts from normal lung; the media contained 2.4 times more fibronectin and 3.2 times more transforming growth factor- β 1 than did media from patients with nonspecific interstitial pneumonia. The increased contractility correlated with fibronectin ($r = 0.87$) and transforming growth factor- β 1 ($r = 0.94$). The authors conclude that fibroblasts from patients with usual interstitial pneumonia showed greater contractility than fibroblasts from nonspecific interstitial pneumonia.

Usual interstitial pneumonia. In lung biopsy specimens from 30 patients with usual interstitial pneumonia, Paakko

and coworkers (65) examined which cells synthesize tenascin, a glycoprotein that may play a structural role and modulate adhesive and migratory functions of cells. Tenascin was expressed at the mRNA level in foci of recent lesions consisting of loose fibrotic buds. Cells in newly formed epithelium were positive for cytokeratin, indicating that they consisted of regenerating type 2 pneumocytes; cells beneath the epithelium were positive for α -smooth muscle actin, and thus apparently myofibroblasts. The authors conclude that tenascin is actively synthesized in early fibrotic lesions of usual interstitial pneumonitis.

To assess the effect of different therapies on survival in patients with usual interstitial pneumonia, Douglas and coworkers (66) analyzed data on 487 patients with a median survival of 3.2 years. Therapies included colchicine (167 patients), prednisone (54 patients), prednisone plus colchicine (71 patients), other therapies (38 patients), and no therapy in 157 patients. Drug or oxygen therapy had no influence on survival. Decreased survival was associated with older age, male gender, lower diffusing capacity, and a history of worsening pulmonary function.

Associated lung cancer. Doubt about the relationship between cryptogenic fibrosing alveolitis, also known as idiopathic pulmonary fibrosis, and lung cancer has arisen because cigarette smoking may also be a risk factor for cryptogenic fibrosing alveolitis. To address this issue, Hubbard and coworkers (67) analyzed data from 890 patients with cryptogenic fibrosing alveolitis and 5,884 control subjects. The incidence of lung cancer was 7.3 times higher in patients with cryptogenic fibrosing alveolitis, and the relationship did not decrease after adjusting for smoking history. The authors conclude that the risk of lung cancer is increased in patients with cryptogenic fibrosing alveolitis, independently of cigarette smoking. This article was accompanied by an editorial commentary by Samet (68).

About 10–13% of patients with idiopathic pulmonary fibrosis die from bronchogenic carcinoma. Carcinogenesis may result from the inactivation of tumor-suppressor genes, and loss of heterogeneity and microsatellite instability is frequently detected in cancers. To investigate genetic alterations at the microsatellite level in sputum cells, Vassilakis and coworkers (69) used 10 polymorphic microsatellite markers in 26 patients with idiopathic pulmonary fibrosis and 26 healthy controls. Half of the patients had genetic alterations. Microsatellite instability was seen in 5 patients, and 10 showed loss of heterogeneity in at least one microsatellite marker. Genetic alterations were not correlated with severity of disease, and they were not seen in the controls. The authors conclude the genetic alterations are frequent in patients with idiopathic pulmonary fibrosis, and may be related to tumorigenesis.

Serum markers. The levels of surfactant protein-A and -D are increased in the serum during an acute exacerbation of idiopathic pulmonary fibrosis. To determine whether the serum concentrations reflect the extent and progression of disease when patients are in a steady state, Takahashi and coworkers (70) followed 52 patients over three years. The concentrations of both surfactant protein-A and -D were correlated with extent of disease on high-resolution computed tomography. The concentration of surfactant protein-D, but not that of -A, was related to annual deterioration in pulmonary function. The concentration of both proteins was higher in patients who died within three years than in those still alive after three years. The authors conclude that the concentration of surfactant protein-D is a good predictor of rate of decline in pulmonary function in patients with sarcoidosis, and that a combination of both surfactant protein-A and -D helps in predicting outcome.

Cellular and molecular mechanisms, in vivo. In idiopathic pulmonary fibrosis, disruption of the epithelial basement membrane associated with fibroblast migration into the alveolar spaces is the key pathogenetic event. To study remodeling in this disorder, Suga and coworkers (71) examined the role of matrix metalloproteases. In 26 patients with usual interstitial pneumonia, expression of matrix metalloprotease-9 (a type IV collagenase preferentially expressed by inflammatory cells including macrophages) predominated in bronchoalveolar fluid and tissue, and its neutrophil-derived activity corresponded with the increase in neutrophils. In eleven patients with non-specific interstitial pneumonia and six patients with bronchiolitis obliterans organizing pneumonia, expression of matrix metalloprotease-2 (a type IV collagenase preferentially secreted by fibroblasts and epithelial cells) predominated, and its activity was correlated with the increase in lymphocytes in bronchoalveolar fluid. The authors conclude that matrix metalloproteases may contribute to pulmonary structural remodeling through type IV collagenase activity.

In patients with various interstitial lung diseases, Lakari and coworkers (72) examined the localization and intensity of two important intracellular antioxidant enzymes. Catalase, but not manganese superoxide dimutase, was constitutively expressed in the healthy lung, especially in type II pneumocytes. In contrast, manganese superoxide dimutase was up-regulated in all of the interstitial lung diseases, whereas catalase was not expressed in any patient. Both enzymes were expressed in the pneumocytes and macrophages in well-preserved areas of the lung in 11 patients with desquamative and in 9 patients with usual interstitial pneumonitis, and in the granulomas of 14 patients with sarcoidosis and 6 patients with extrinsic allergic alveolitis. The authors conclude that the presence of these two antioxidant enzymes in the alveolar regions may protect against the progression of interstitial lung disease.

Dendritic cells, the most potent antigen-presenting cells, play a central role in initiating primary immune responses. To date and coworkers (73) examined the distribution of dendritic cells in 11 patients with diffuse panbronchiolitis, a chronic inflammatory disorder. Marked increases in CD1a⁺, CD1c⁺, and CD83⁺ dendritic cells were seen in the bronchial epithelium and submucosal tissue. The bronchial epithelial cells strongly expressed granulocyte macrophage colony-stimulating factor protein, which plays an important role in the differentiation and function of dendritic cells. The authors conclude that, through their potent antigen-presenting function, increased dendritic cells in the bronchiolar tissue may contribute to the mucosal immune response in patients with diffuse panbronchiolitis.

Cellular and molecular mechanisms, ex vivo. Although angiotensin-converting enzyme is increased in a variety of fibrotic lung diseases, the role of angiotensin peptides on lung fibroblasts has not been previously examined. Marshall and coworkers (74) identified angiotensin type 1, but not type 2, receptors on human lung fibroblasts. Angiotensin II produced a two-fold increase in DNA synthesis, which was inhibited by a specific antagonist to the angiotensin type 1 receptor. Antibodies to transforming growth factor- β produced a 73% decrease in the DNA synthesis induced by angiotensin II; antibodies to platelet-derived growth factor had no effect. The authors conclude that angiotensin II induces the proliferation of human lung fibroblast *in vitro* via activation of the angiotensin type 1 receptor and involving the autocrine action of transforming growth factor- β .

Treatment of fibroproliferative lung disease with anti-inflammatory agents has met with little success. Because thera-

pies that promote fibroblast apoptosis may eliminate excess fibrotic tissue during lung repair, Hadden and Henke (75) examined the effect of three soluble fibronectin peptides on lung fibroblasts. The peptides induced apoptosis of adherent fibroblasts in routine tissue cultures and also of fibroblasts incorporated into a fibrin gel. Apoptosis occurred by disrupting integrin-mediated adhesion to the extracellular matrix. The authors conclude that soluble fibronectin peptides trigger fibroblast apoptosis, and using this approach to eliminate fibroblasts may represent a novel treatment of lung fibrosis.

Animal models. Idiopathic pneumonia syndrome is a highly fatal complication of allogeneic bone marrow transplantation (transplantation between genetically nonidentical members of the same species). In a murine model, Yang and coworkers (76) determined whether the systemic administration of keratinocyte growth factor (a specific mediator of epithelial cell proliferation and differentiation) would upregulate surfactant protein A production during the intense inflammation resulting from allogeneic bone marrow transplantation. On the seventh day after bone marrow transplantation, systemic keratinocyte growth factor increased surfactant A protein and mRNA in allogeneic T cell-recipient irradiated mice. These changes were prevented by cyclophosphamide. The addition of surfactant protein A to alloactivated T cells (T cells from a recipient that become activated against donor antigens) suppressed the production of interleukin-2. The authors conclude that systemic administration of keratinocyte growth factor in recipients of allogeneic T cells upregulates surfactant protein A, and that alloactivated T cells plus cyclophosphamide abolish the protective effect.

Statements and workshops. The diagnosis and treatment of idiopathic pulmonary fibrosis is discussed in an international consensus statement (77).

Pulmonary immunobiology and inflammation in pulmonary diseases are discussed in the summary of a NHLBI workshop by Crapo and coworkers (78).

Progressive Systemic Sclerosis

To develop biomarkers for interstitial lung disease, Takahashi and coworkers (79) measured serum levels of surfactant proteins A and D in 42 patients with progressive systemic sclerosis. The 30 patients with positive CT findings had higher levels of both proteins than did the 12 patients without CT abnormalities. For detecting CT abnormalities, sensitivity was 77% for surfactant protein D and 33% for surfactant protein A; specificity was 100% for surfactant protein D and 83% for surfactant protein A. Six patients had a positive CT scan but a negative chest x-ray, and all but one had elevated surfactant protein-D. The authors conclude that elevations in serum surfactant proteins A and D reflect the presence of interstitial lung disease in patients with progressive systemic sclerosis.

Sarcoidosis

Genetics. In 51 patients who were positive for human leukocyte antigen (HLA)-*DRB1*0301* and *-DRB3*0101* alleles, Grunewald and coworkers (80) examined the relationship between clinical features of sarcoidosis and the degree of accumulation of a segment of the T cell receptor, AV2S3, in bronchoalveolar cells. The number of CD4⁺ T cells containing the receptor segment was higher in the bronchoalveolar fluid of patients who had sarcoidosis for less than two years than in patients with disease of longer duration (30 and 19% of cells). T cells containing AV2S3 were correlated positively with acute onset of disease and with the ratio of CD4⁺ to CD8⁺ cells. The authors conclude that accumulation of cells expressing T-cell receptor AV2S3 is linked with the acute inflamma-

tory response in sarcoidosis, and the associated good prognosis suggests that the cells have a protective role against a presumed sarcoidosis antigen.

Clustering of sarcoidosis suggest the existence of a genetic predisposition, and the major histocompatibility complex (MHC) is thought to be involved. In another granulomatous disease, chronic beryllium disease, the HLA-DPB1 gene has been identified as a major risk factor. Schurmann and coworkers (81) genotyped 122 affected siblings from 55 families for HLA-DPB1 and seven DNA polymorphisms that flank and cover the MHC region on chromosome 6. Multipoint non-parametric linkage analysis showed linkage for the entire MHC region, with a maximum score at the marker locus D6S1666 in the Class III gene cluster. The frequency of HLA-DPB1 alleles on 104 shared chromosomes did not differ from a control group. The authors conclude that genes of the MHC complex are involved in the genetic predisposition to sarcoidosis, but HLA-DPB1 alone does not sufficiently explain the predisposition.

Certain CC chemokines—monocyte chemoattractant protein-1, macrophage inflammatory protein-1 α , and RANTES—have been implicated in the pathogenesis of sarcoidosis. These chemokines are ligands for two receptor molecules, namely CC chemokine receptor (CCR) 5 and CCR2. Genes for these two receptors are characterized by polymorphisms resulting in a nonfunctional surface receptor molecule unable to bind its chemokine ligand. In 66 Czech patients with sarcoidosis and a control sample, Petrek and coworkers (82) analyzed polymorphisms of CCR5 (a 32-bp deletion in the CCR5 gene) and of CCR2 (replacement of valine by isoleucine in the CCR2 gene). The allelic frequency of CCR5 Δ 32 was increased in the patients. In contrast, the CCR2-641 allele was less frequent in the patients, although the difference did not reach significance. The CCR Δ 32 allele was present in 39% of patients requiring glucocorticoids and in only 17% of those not needing treatment. The authors conclude that the polymorphisms of CC chemokine receptors 5 and 2 contribute to susceptibility to sarcoidosis.

Molecular mechanisms. CD13/aminopeptidase N is a metalloprotease located on the outer membrane of a variety of cells. Because aminopeptidase expression is upregulated by type 1 (Th1) helper T lymphocytes and because Th1 response predominates in sarcoidosis, Tani and coworkers (83) examined its significance in bronchoalveolar fluid of 30 patients with sarcoidosis. Activity of CD13/aminopeptidase N was higher in the patients than in controls, and activity was correlated with lymphocyte percentage and the ratio of CD4⁺ to CD8⁺ T lymphocytes. Its concentration was increased in alveolar macrophages of the patients, and it induced *in vitro* chemotactic migration of human lymphocytes. The authors conclude that CD13/aminopeptidase N is expressed in alveolar macrophages in patients with sarcoidosis, and it may have a role in T-lymphocyte involvement in this disorder.

Interleukin-18 induces interferon- γ from type 1 (Th1) helper T cells and enhances the cytotoxicity of natural killer cells and T cells. In 19 patients with pulmonary sarcoidosis, Shigehara and coworkers (84) found that serum levels of interleukin-18 and interferon- γ were elevated and also were correlated with lysozyme activity. In bronchoalveolar fluid, interleukin-18 was elevated but interferon- γ was not. The level of interleukin-18 was correlated with the proportion of lymphocytes in bronchoalveolar fluid and with the level of interleukin-18 in serum. Patients with a positive gallium scan had higher levels of the cytokine. The authors conclude that interleukin-18 induces interferon- γ production in patients with sarcoidosis, and the level in the serum may reflect disease activity.

Histiocytosis X

To determine the accuracy of high-resolution computed tomography in predicting histologic activity in patients with pulmonary Langerhan's cell histiocytosis (also known as histiocytosis X), Soler and coworkers (85) studied 13 patients. The extent of nodular abnormalities on computed tomography was strongly correlated with the density of florid granulomatous lesions on biopsy. The extent of cystic abnormalities on computed tomography was correlated with the density of cavitory lesions, although the latter included inflammatory cavitory granulomas and cicatricial fibrous cysts; most patients with a predominant cystic pattern had small isolated florid granulomas. The authors conclude that high-resolution computed tomography should be interpreted with caution in patients with pulmonary Langerhan's cell histiocytosis.

Diminished exercise capacity in patients with pulmonary histiocytosis X appears to be caused by pulmonary vascular dysfunction, rather than ventilatory limitation. Fartoukh and coworkers (86) found that all of 21 consecutive patients with advanced pulmonary histiocytosis X had severe pulmonary hypertension: mean pulmonary artery pressure 59 mm Hg; cardiac index 2.6 liter per minute per m^2 ; and total pulmonary vascular resistance 25 IU per m^2 . In contrast to 29 patients with COPD and 14 patients with interstitial lung disease, the degree of pulmonary hypertension was not related to the level of pulmonary function. In 12 patients with histiocytosis X, histopathology revealed proliferative vasculopathy involving muscular arteries and veins, with prominent venular involvement. Six patients had biopsies performed after developing pulmonary hypertension, and the vasculopathy had worsened whereas the parenchymal and bronchiolar lesions had not changed. The authors conclude that pulmonary hypertension in patients with pulmonary histiocytosis X may be caused by pulmonary vascular lesions that are independent of the small airway and parenchymal involvement.

Lymphangioleiomyomatosis

Because lymphangioleiomyomatosis (LAM) occurs primarily in women of reproductive age, it is thought that female sex hormones are involved in its pathogenesis. In five untreated women with the disorder, Matsui and coworkers (87) found that estrogen and progesterone receptors were localized mainly in the nuclei of large epithelioid LAM cells (nodules of abnormal proliferating smooth muscle cells). Staining of these receptors was colocalized with that for HMB-45 (an antibody that reacts with a glycoprotein), but not with that for membrane type-1 matrix metalloproteinase. The receptors were not found in five women treated with progesterone and tamoxifen. The authors conclude that progesterone and estrogen receptors are selectively expressed in subpopulations of abnormal smooth muscle cells in lymphangioleiomyomatosis, and that the receptors are downregulated by hormonal therapy.

Aubry and coworkers (88) reported a case of pulmonary lymphangioleiomyomatosis in a man. The patient also had stigmata of tuberous sclerosis complex. Stains showed positive immunoreactivity for hamartin (TSC1) and loss of immunoreactivity for tuberin (TSC2), consistent with a *TSC2* mutation. The authors conclude that this is the first unequivocally documented case of lymphangioleiomyomatosis in a man.

Thoracic lymphangiomas, lymphangiomas, lymphangiectasis, and related disorders were discussed in a state-of-the-art review by Faul and coworkers (89).

Wegener's Granulomatosis

In 19 patients with active Wegener's granulomatosis, Schnabel and coworkers (90) found increased levels of myeloperoxi-

dase, eosinophilic cationic protein, peroxidase activity, and soluble interleukin-2 receptor in bronchoalveolar fluid. Only trace amounts of proteinase 3 were present, and mostly in complexes with α_1 -antitrypsin. In six patients, clinically effective treatment produced a decrease in bronchoalveolar neutrophilia and reversed the elevations in myeloperoxidase and peroxidase activity. The authors conclude that neutrophils contribute to the lung disease of Wegener's granulomatosis.

Bronchiolitis Obliterans Organizing Pneumonia

Cryptogenic organizing pneumonia, also known as idiopathic bronchiolitis obliterans organizing pneumonia (BOOP), is a clinicopathologic syndrome characterized by a spectacular response to glucocorticoid therapy but frequent relapses. To characterize the pattern of relapses, Lazor and coworkers (91) analyzed data in 48 biopsy-proven cases. One or more relapses (mean 2.4) occurred in 27 (58%) patients, at which time 68% were still receiving treatment for the first episode. Compared with 21 patients without a relapse, nine patients experiencing more than three relapses had longer delays between the first symptoms and onset of treatment (22 versus 11 weeks), and had elevations in alkaline phosphatase and γ -glutamyltransferase. Relapses did not adversely affect outcome. The authors conclude that risk of relapse in cryptogenic organizing pneumonia is increased by delays in starting treatment, that mild cholestasis identifies a subgroup at risk of multiple relapses, and that relapses do not affect outcome.

Idiopathic Pulmonary Alveolar Proteinosis

Serological markers, such as surfactant proteins, are found in patients with idiopathic pulmonary alveolar proteinosis, but also occur in patients with other lung diseases. In 24 patients with idiopathic pulmonary alveolar proteinosis from five countries, Kitamura and coworkers (92) detected an autoantibody against granulocyte-macrophage colony-stimulating factor in their sera, and found it to be consistently and specifically present. The investigators also developed a new, convenient latex agglutination test for detecting the autoantibody. Agglutination was positive in 300-fold diluted sera from all 24 patients, but negative in six patients with secondary or congenital pulmonary alveolar proteinosis, in 40 patients with other lung diseases, and in 38 of 40 healthy subjects. The authors conclude that the latex agglutination test for detecting autoantibodies against granulocyte-macrophage colony-stimulating factor is reliable in diagnosing idiopathic pulmonary alveolar proteinosis, with 100% sensitivity and 98% specificity.

Because of emerging evidence that patients with pulmonary alveolar proteinosis lack stimulation by, or responsiveness to, granulocyte-macrophage colony stimulating factor, Kavuru and coworkers (93) gave the factor subcutaneously to four patients during a moderate exacerbation of the disease. After receiving the factor once daily for twelve weeks, three patients showed improvement in symptoms, physiology and x-rays; one patient was removed from the waiting list for lung transplantation. The authors conclude that treatment with granulocyte-macrophage colony-stimulating factor appears to benefit a subset of patients with pulmonary alveolar proteinosis.

It has recently been reported that pulmonary alveolar proteinosis is caused by deficiency of granulocyte-macrophage colony-stimulating factor. Carraway and coworkers (94) found increased levels of the factor in bronchoalveolar fluid and plasma in ten patients, and increased release of the factor from alveolar macrophages; its release after stimulation with lipopolysaccharide was not different than in ten healthy subjects. Release of tumor necrosis factor- α by alveolar macrophages in response to granulocyte-macrophage colony-stimu-

lating factor was decreased in the patients. The authors conclude that granulocyte-macrophage colony-stimulating factor is detectable in patients with pulmonary alveolar proteinosis, and that the response of alveolar macrophages to stimulation with the factor is decreased in some patients.

Pulmonary Drug Toxicity

Bhalla and coworkers (95) followed the pulmonary function of 150 consecutive patients receiving chemotherapy for breast cancer. Three cycles of standard induction chemotherapy (cyclophosphamide, doxorubicin, 5-fluorouracil) produced a 13% decrease in diffusing capacity, accompanied by increases in interleukin-6, interleukin-8, neutrophils and lymphocytes in bronchoalveolar fluid. When induction chemotherapy was followed by standard-dose chemotherapy (cyclophosphamide, cisplatin, bischloroethylnitrosourea [BCNU]), diffusing capacity fell to 81%. When induction was followed by high-dose chemotherapy, combined with autologous bone marrow transplantation (the patient's own stem cells) and peripheral blood progenitor cell support, diffusing capacity fell to 55%. Over the subsequent two years, prednisone produced a gradual improvement in diffusing capacity. The authors conclude that induction chemotherapy produces asymptomatic pulmonary inflammation and dysfunction, which primes the lungs for more severe injury during subsequent chemotherapy.

Hypersensitivity Pneumonitis

Because acute episodes of farmer's lung are characterized by an influx of neutrophils causing oxidative stress, Behr and coworkers (96) assessed whether antioxidant defenses are altered. In 15 patients with farmer's lung, exposure to hay for one hour caused a 31% decrease in vital capacity, 17% decrease in diffusing capacity, and 14% fall in PO₂. In the bronchoalveolar fluid at six hours, neutrophils were three times higher than in healthy controls, and total and reduced glutathione were decreased to one-quarter of the control values. The authors conclude that the intrapulmonary levels of glutathione, quantitatively the most important antioxidant of the lung, are decreased in patients with farmer's lung.

In inflammatory disorders, leukocyte rolling is mediated by the interaction of E-selectin and P-selectin (both of these adhesion molecules are expressed on endothelium) with their ligand, sialyl-Lewis^x (SLe^x). Pan and coworkers (97) determined whether blocking this interaction might suppress the infiltration of T-helper (Th1) lymphocytes into the lungs of mice with hypersensitivity pneumonitis. In lungs sensitized with *Saccharopolyspora rectivirgula*, the agent causing farmer's lung, antigen exposure induced marked perivascular and peribronchial infiltration with lymphocytes and granuloma formation. The pathologic changes were suppressed by SLe^x ganglioside analogues. The authors conclude that the molecular interaction between E- and P-selectin with their ligand, sialyl-Lewis^x, mediates the recruitment of lymphocytes into the parenchyma in a murine model of hypersensitivity pneumonitis.

Neutrophils secrete many molecules that may contribute to the development of hypersensitivity pneumonitis, such as the matrix metalloproteinases, collagenase-2 and gelatinase B. In 15 patients with hypersensitivity pneumonitis, Pardo and coworkers (98) found that lung samples contained variable quantities of neutrophils (0.7 to 4.8%) and the degree of lung neutrophilia was correlated with the extent of fibrosis ($r = 0.60$). Tissue neutrophils showed intense staining for collagenase-2 and gelatinase B. The authors conclude that persistent traffic of neutrophils loaded with gelatinase B and collagenase-2 may contribute to the injury in hypersensitivity pneumonitis.

Summer-type hypersensitivity pneumonitis is a common form of hypersensitivity pneumonitis in Japan. In 22 patients with this disorder, Miyagawa and coworkers (99) isolated strains of *Candida albida*, but never of *Trichosporon cutaneum*, in the home. In cultures of bronchoalveolar cells, antibodies to *Cryptococcus neoformans* and *Trichosporon cutaneum* were found in all patients. Most of the antibodies were absorbed by *Candida albida*. The authors conclude that *Candida albida* may be the etiologic agent in most cases of summer-type hypersensitivity pneumonitis.

Rodent Model of Bleomycin Fibrosis

Bleomycin-induced lung fibrosis results in changes in tissue mechanics secondary to alterations in the extracellular matrix. To determine how changes in mechanics and the matrix evolve over time, Ebihara and coworkers (100) studied parenchymal strips from rats with bleomycin-induced lung fibrosis. Oscillatory resistance and elastance were increased, peaking at 14 days after bleomycin; hysteresis was decreased, reaching a nadir at 7 days. Biglycin, a small proteoglycan, was increased at all times; fibromodulin, another proteoglycan, and elastic fibers were increased at 14 and 28 days. Collagen was increased only at 28 days. The authors conclude that the changes in tissue mechanics were maximal before the increase in collagen content, and that proteoglycans may play a critical role in determining changes in lung tissue behavior.

Proteoglycans are core proteins involved in the assembly of the extracellular matrix in situations of development and repair. Venkatesan and coworkers (101) investigated whether expression of proteoglycans is altered in bleomycin-induced pulmonary fibrosis in rats. Lung samples at 7 and 14 days after administration of bleomycin revealed prominent inflammation and abundant proteinaceous material, and fibrosis had occurred by 28 days. At 7 and 14 days, versican, a large proteoglycan, was present, as was biglycan and fibromodulin. The authors conclude that changes in all subclasses of proteoglycans occur during the development of bleomycin-induced pulmonary fibrosis.

In acute lung injury and chronic fibrosis produced by bleomycin in rats, Sato and coworkers (102) investigated the role of endothelial intercellular adhesion molecule-1 in leukocyte kinetics. During the initial phase of acute lung injury, expression of the adhesion molecule was enhanced in the venules and a second upregulation occurred during the early phase of fibrosis; a sustained increase occurred in the capillaries during both phases and little change occurred in the arterioles at any time. Although leukocytes did not firmly adhere to the walls of the arterioles and venules, rolling leukocytes were increased in the venules and were correlated with the transitional changes in intercellular adhesion molecule-1. The authors conclude that intercellular adhesion molecule-1 plays a role in recruitment of leukocytes to the microvasculature in both the acute injury and the chronic fibrosis resulting from bleomycin.

Because of the potential role of oxidants in causing pulmonary fibrosis, Tamagawa and coworkers (103) studied the effect of an antioxidant, lecithinized superoxidase dimutase, on pulmonary fibrosis in mice resulting from bleomycin. A low dose of the antioxidant attenuated the severity of the fibrosis, and suppressed the increases in lymphocyte and neutrophil counts, and the expression of messenger RNA for interleukin-1 β and platelet-derived growth factor- α . The authors conclude that the antioxidant, lecithinized superoxide dimutase, inhibits the development of pulmonary fibrosis in bleomycin-treated mice.

Because reactive oxygen species play an important role in pulmonary fibrosis, Hagiwara and coworkers (104) deter-

mined whether *N*-acetylcysteine, an antioxidant, would attenuate the fibrosis induced by bleomycin in mice. *N*-Acetylcysteine attenuated the cellular infiltrate and the fibrotic change, and repressed the levels of macrophage inflammatory protein-2, cytokine-induced neutrophil chemoattractant, macrophage inflammatory protein-1 α , and lipid hydroperoxide. The authors conclude that aerosolized *N*-acetylcysteine ameliorated the acute pulmonary inflammation induced by bleomycin and attenuated the subsequent pulmonary fibrosis.

The critical transcription factor, nuclear factor- κ B, is actively involved in pulmonary fibrosis caused by bleomycin. In mice injected with bleomycin, Zhang and coworkers (105) examined the therapeutic benefit of antisense oligonucleotides to the p65 subunit of nuclear factor- κ B. Control mice died within nine days of receiving 300 mg per kg of bleomycin. Intravenous administration of the antisense oligonucleotide before and after bleomycin increased survival to 40%. Treated mice had less weight loss, improved lung hydroxyproline, and less histologic damage. Large amounts of antisense oligonucleotides were found within blood monocytes and alveolar macrophages. The antisense oligonucleotides inhibited nuclear factor- κ B in the macrophages. The authors conclude that antisense oligonucleotides are incorporated into activated alveolar macrophages and ameliorate the lung injury from bleomycin in rats and improve survival.

Fas is a cell-surface receptor whose binding with Fas ligand mediates apoptosis. To determine the role of this interaction in the development of bleomycin-induced pulmonary fibrosis, Aoshiba and coworkers (106) studied mice deficient in Fas and mice deficient in Fas ligand. The development of cellular infiltrates, fibrosis, and apoptosis in the bronchiolar and alveolar epithelium following bleomycin instillation was similar in Fas-deficient mice, Fas-ligand-deficient mice, and wild-type mice. The authors conclude that bleomycin-induced pulmonary fibrosis does not require an interaction of Fas with Fas ligand, and Fas-independent pathways mediate that epithelial cell apoptosis after bleomycin exposure.

To determine whether hepatocyte growth factor might have therapeutic potential for pulmonary fibrosis, Dohi and coworkers (107) examined its effect on the repair of lung injury caused by bleomycin. In normal mice, intratracheal administration of hepatocyte growth factor led to proliferation of bronchial and alveolar epithelial cells. In mice subjected to lung injury from bleomycin, it attenuated collagen accumulation. Hepatocyte growth factor enhanced surface plasmin generation, expression of urokinase activity, and cell migration in *in vitro* studies with pulmonary epithelial cells. The authors conclude that hepatocyte growth factor has potent effects on epithelial cells, which may prove beneficial in the management of pulmonary fibrosis.

OCCUPATIONAL LUNG DISEASE

In 563 patients with nonasbestos pneumoconiosis, Katabami and coworkers (108) determined the incidence of diffuse interstitial fibrosis by computed tomography. Of 563 patients, 55 (10%) had diffuse interstitial fibrosis. Lung cancer occurred in 53% of patients with interstitial fibrosis and in 15% of patients without fibrosis. Squamous cell carcinomas were peripheral in type in all patients with interstitial fibrosis and in 72% of patients without fibrosis; histology revealed dysplasia in peripheral bronchioli in 69% of patients with fibrosis and in 30% of patients without fibrosis. The authors conclude that patients with pneumoconiosis and diffuse interstitial fibrosis have an increased incidence of lung cancer, especially of peripheral-type squamous cell carcinoma.

To assess alterations in oxidant and inflammatory mediators in coal miners, Vallyathan and coworkers (109) did bronchoalveolar lavage in 20 control subjects and 23 underground coal miners. The subjects were nonsmokers, and only two miners had moderate changes (category 2) on chest x-ray. The miners with x-ray changes had increased levels of antioxidant enzymes (catalase 19 fold, glutathione peroxidase 22 fold, and superoxide dismutase 6 fold), interleukin-1, interleukin-6, tumor necrosis factor- α , fibronectin, and α_1 -antitrypsin. The up-regulation of antioxidant defenses and cytokines was not evident in the miners with clear x-rays. The authors conclude that development of coal workers' pneumoconiosis is associated with oxidant stress and upregulation of cytokines.

Patients with asbestos exposure may complain of chest pain that cannot be easily explained. To determine whether abnormalities on chest x-ray are associated with chest pain, Mukherjee and coworkers (110) studied 1,280 subjects with prior exposure to asbestos. Some chest pain was reported by 43% on a questionnaire. On logistic regression models, chest pain was associated with both benign pleural disease and diffuse parenchymal disease on chest x-ray. On further stratification, anginal pain was associated with both radiological abnormalities, and nonanginal pain was associated with parenchymal disease. The authors conclude that chest pain is associated with parenchymal or pleural abnormalities on chest x-ray in subjects exposed to asbestos.

An important step in the development of silicosis is the injury of alveolar macrophages by inhaled crystalline silicon dioxide. Wisniowski and coworkers (111) examined whether vitronectin, an adhesive protein that is a natural constituent of the lung, would offer protection against silica exposure. In rats exposed to silica, vitronectin was increased in their bronchoalveolar fluid. Vitronectin decreased injury to alveolar macrophages, the production of free radicals, and the respiratory burst in alveolar macrophages resulting from silica. The authors conclude that vitronectin may protect alveolar macrophages during initial exposure to silica.

Hamada and coworkers (112) investigated the role of mast cells and their fibrogenic growth factors in silicosis. The volume density of mast cells was increased in silicotic lung and most mast cells contained basic fibroblast growth factor. The volume density of collagen/reticulin fibers was increased and correlated with the growth factor. In large nodules, mast cells containing the growth factor were found only in the periphery of the nodule. The authors conclude that the production of basic fibroblast growth factor by mast cells may contribute to lung injury in silicosis.

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