

16. Immunologic lung disease

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This review summarizes the recent advances regarding pathogenesis, diagnosis, and treatment of immunological diseases of the lung. Rather than attempt a comprehensive analysis, we have focused on selected diseases that are of particular relevance to the practicing physician, and the material has been organized according to the dominant immunologic mechanisms underlying the disease. Because of the redundancy that characterizes the mammalian immune repertoire, this system of classification inevitably produces overlap but facilitates acquisition of what is otherwise a disparate collection of facts. The principal lung immunologic mechanisms are most broadly classified as innate or adaptive immune processes. Innate immunity includes neutrophils and complement that are important in diseases, such as pneumonia and the acute respiratory distress syndrome. Adaptive immunity involves T and B cells capable of recognizing discrete antigens. T_H1 - and T_H2 -dependent adaptive immune responses underlie some of the most common and important of lung diseases, including tuberculosis and asthma, respectively. Other important immunopathologic processes include granulomatous inflammation that characterizes sarcoidosis and Churg-Strauss vasculitis, and autoimmunity, which is characteristic of antiglomerular basement membrane disease and others. (*J Allergy Clin Immunol* 2003;111:S613-23.)

Key words: Lung, inflammation, T_H1 cell, T_H2 cell, interleukin, IFN- γ interferon, granuloma, pneumonia, vasculitis, eosinophil, autoimmune

The pathogenesis of most lung diseases involves, either primarily or secondarily, immune or inflammatory mechanisms. The specific causes of immune-mediated lung disease are many and include infectious, noninfectious, and idiopathic agents that complicate systematic organization of these syndromes. In contrast, the inflammatory mechanisms that underlie disease induced by many different agents are broadly similar, providing a more rational system for disease classification. The full range of human immune responses is limited, and specific responses typically use redundant elements. In this way, the same immune response may efficiently counter many different agents, but distinct elements within the same immune repertoire will, in a manner dependent on the etiologic agent, actually determine disease resolution or progression.

In this chapter, we consider the causes of lung disease based on the major types of pulmonary immune responses. We emphasize five principal types of lung immunologic responses and discuss selected clinical examples of

Abbreviations used:

ACE: Angiotensin converting enzyme
ANCA: Anti-neutrophil cytoplasmic antibody
ARDS: Acute respiratory distress syndrome
BAL: Bronchoalveolar lavage
COPD: Chronic obstructive pulmonary disease
IFN: Interferon
IL: Interleukin
 T_H : T helper
TLR: Toll-like receptor
TNF: Tumor necrosis factor
TRALI: Transfusion-related acute lung injury

each (Table I). Innate inflammatory mechanisms, which underlie many types of community-acquired pneumonia and the acute respiratory distress syndrome (ARDS), include complement- and/or neutrophil-dependent processes without significant involvement of adaptive immune cells (T and B cells). Most other lung inflammatory disorders involve T cells as the principal immunologic determinants of disease, including T_H1 cells that secrete interleukin (IL)-2 and interferon (IFN)- γ , and T helper (T_H2) cells that secrete IL-4, IL-5, IL-13, and other cytokines. Granulomatous inflammatory mechanisms may be either T_H1 - and T_H2 -biased, but are sufficiently distinct pathologically and physiologically to warrant their separate classification. All the preceding entities involve either infectious (eg, tuberculosis, community-acquired pneumonia) or noninfectious (eg, hypersensitivity pneumonitis, berylliosis) agents acquired through environmental contact. In contrast, endogenous antigens underlie the autoimmune syndromes, although environmental influences are likely important here as well.

INNATE INFLAMMATORY MECHANISMS Community-acquired pneumonia

Pneumonia refers to primary infection inducing typical symptoms (eg, fever, productive cough, pleuritic chest pain) or signs (eg, pulmonary rales, consolidation) referable to the lung. Community-acquired pneumonia is seen exclusively in persons contracting illness from a non-hospital environment and usually involves common bacterial pathogens such as *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, or *Haemophilus influenzae*, and some viruses. Despite a careful search, a specific etiologic agent is never cultured in most cases of community-acquired pneumonia; however, retrospective serologic testing against specific organisms can increase the diagnostic yield.

Despite the availability of potent, broad-spectrum antimicrobial agents, pneumonia remains a significant economic burden and a leading cause of morbidity and

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0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.124

TABLE I. Immunopathologic classification of lung inflammatory disorders

Innate inflammatory mechanisms	
	-Community-acquired pneumonia
	-ARDS
	-TRALI
	-Ischemia/reperfusion acute lung injury
T _H 1-related inflammatory mechanisms	
	-Hypersensitivity pneumonitis
	-COPD
T _H 2-related inflammatory mechanisms	
	-Asthma
	-Pulmonary eosinophilia syndromes
Granulomatous inflammatory mechanisms	
T _H 1-related	
	-Tuberculosis
	-Berylliosis
	-Sarcoidosis
T _H 2-related	
	-Churg-Strauss vasculitis
Autoimmune mechanisms	
	-Wegener's granulomatosis
	-Antiglomerular basement membrane disease

mortality. Pneumonia from all causes is the seventh leading cause of death in the United States and community-acquired pneumonia carries a 10% mortality for persons aged 65 or older.¹ Advanced age and lung comorbidities, such as emphysema, are important determinants of death and disability from pneumonia.

Neutrophils, complement, and macrophages have long been thought to protect the airways from microbial colonization and invasion, but recent studies have emphasized the importance of several new families of lung defense proteins. β -Defensins are small, cationic peptides produced by lung epithelia of humans and mice and, at least in vitro, have direct bactericidal properties. Defensins also chemoattract dendritic and T cells to sites of inflammation and may thus activate adaptive immunity against a variety of lung pathogens.² Another group of interesting innate immune molecules is the toll-like receptor (TLR) family, which includes 10 human homologues. TLR2, 3, 4, 5, 6, and 9 are receptors for unique viral or bacterial-derived molecules and, like defensins, promote both innate and adaptive immune responses. Specific mutations in the TLR4 gene may predispose people to develop septic shock with gram-negative microorganisms, suggesting that TLR4 is important for protective immunity against this group of pathogens.³ Antibiotics will remain the mainstays of antimicrobial therapy in pneumonia, but newer therapies based on endogenous defensins and TLRs are being developed.

Acute respiratory distress syndrome

ARDS remains a challenging and mysterious affliction, striking persons with a variety of critical illnesses, but most often those with sepsis. Difficulty breathing, tachypnea, and cough are usually accompanied by severe hypoxemia, and chest roentgenograms typically reveal pulmonary alveolar consolidation. ARDS affects more than the lung; dys-

function in multiple organs, such as the liver, kidneys, and brain, and mortality, estimated at approximately 35%, is usually the result of failure of organs other than the lung. Mortality resulting from ARDS has declined over the past 20 years, but it remains perhaps the most common single cause of death in the medical intensive care unit.

ARDS is the end result of an uncontrolled systemic inflammatory response initiated by a wide variety of insults. Increased circulating surfactant proteins and von Willebrand factor⁴ normally bound to vascular endothelium, are found in bronchoalveolar lavage (BAL) and sera of affected patients, indicating disruption of both airway epithelium and vascular endothelium. However, the hallmark of ARDS, which accounts for the major signs and symptoms of disease, is the filling of the alveolar spaces with pulmonary edema fluid, and is presumably the consequence of an abnormally permeable lung vascular endothelium. Diffuse, homogeneous airspace consolidation seen on standard chest roentgenograms is usually more patchy if seen on computed tomograms of the chest, reflecting both alveolar filling and collapse, the latter thought to result from a defect in surfactant production.

Significant strides in unraveling the immunopathologic basis of ARDS have recently been made. The inflammatory cell most often implicated in ARDS is the neutrophil, and neutrophil-specific chemokines, especially IL-8, are strongly upregulated in BAL from affected patients. Transforming growth factor alpha, migration inhibition factor, IL-2, and IL-6 are also present in airway fluid from ARDS patients, and the proinflammatory transcription factor NF- κ B is strongly activated in alveolar macrophages. Further, inhibition of IL-8 reduces the incidence of ARDS in experimental models.⁵ Despite these findings, a detailed understanding of the pathophysiology of ARDS is lacking. Neutropenic patients also develop ARDS, suggesting the existence of other important mechanisms for disease; at least some of the inflammation is actually the result of mechanical ventilation itself.⁶

Recent clinical trials have focused on the potential beneficial effects of anti-inflammatory interventions and limiting lung injury induced by mechanical ventilation. An earlier study of corticosteroid therapy given in the early phase of ARDS was unsuccessful, but a more recent analysis of intravenous methylprednisolone given later in disease, during a period of presumed scarring and fibrosis, found significant benefit regarding survival and earlier weaning from the mechanical ventilator.⁷ Infectious complications were common in this small trial, however, and the beneficial effects require confirmation in a larger, prospective study. Partial liquid ventilation with the perfluorocarbon chemical perflubron likely also attenuates inflammation, while simultaneously improving oxygenation.⁸ These effects may result in reduced ventilation time and earlier discontinuation of the mechanical ventilator, but side effects of perflubron therapy, including transient hypoxemia, bradycardia, pneumothorax, and mucus plugging are worrisome. Much more experience with this innovative therapy is required before it can be recommended in ARDS management.

Perhaps the most important advancement in ARDS therapy has been the discovery that modification of traditional mechanical ventilation protocols substantially improves clinical outcomes. High-frequency oscillation ventilation and airway pressure release ventilation improve oxygenation and may reduce both time on the mechanical ventilator and days in the intensive care unit, but are understudied with respect to overall survival.⁹ However, a large, randomized, controlled study recently confirmed that patients receiving conventional volume-based mechanical ventilation using small tidal volumes (6 ml/kg) and optimal peak end expiratory pressures had 23% greater survival, irrespective of the underlying clinical condition, compared with patients receiving larger tidal volumes.¹⁰ Consequently, volume ventilation that uses smaller tidal volumes in conjunction with optimized end expiratory pressures is now the preferred ventilatory modality in ARDS.

Adjunctive therapies in ARDS have been shown to improve some clinically relevant endpoints. Such treatments include the use of nitrous oxide, prostaglandins E1 and I2, surfactant,¹¹ and a diet low in carbohydrates and high in antioxidants and fish oil.¹² However, none of these therapies has been shown to improve survival, and their place in routine management consequently remains uncertain.

Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is an important variant of ARDS seen in the setting of transfusion of any blood-derived product. Patients develop typical signs and symptoms of early ARDS within minutes of transfusion and often require mechanical ventilation. TRALI carries a 6% mortality and an incidence of approximately 0.2% per patient transfused, but the syndrome is probably underdiagnosed. The pathogenesis of TRALI is linked to transfusion of anti granulocyte antibodies and perhaps other substances, including bioactive lipids¹³ that result in sequestration of neutrophils and monocytes in capillary beds. Subsequent activation of granulocytes and complement results in endothelial injury.¹⁴ Recurrent episodes of TRALI may be observed and are particularly likely with blood products derived from multiparous donors.¹⁵ In addition to supportive therapy (no specific therapy has yet been defined), consideration should be given to avoiding blood products derived from multiparous donors in patients with previous episodes of TRALI and who remain transfusion dependent.

ISCHEMIA/REPERFUSION LUNG INJURY

ARDS-like acute lung injury is also seen in the setting of vascular reperfusion of ischemic tissues. The syndrome is associated with ischemia of especially the intestines and lung,¹⁶ and may also be seen complicating vascular surgery involving prolonged arterial occlusion. The pathogenesis is thought to be related to activation of complement and neutrophils with subsequent damage to the vascular endothelium, resulting in hydrostatic fluid

extravasation. As with ARDS, treatment is largely supportive, but preliminary data suggest that the syndrome may be preventable with the use of agents that inhibit selectin-mediated neutrophil adherence to the endothelium.¹⁷

T_H1-RELATED INFLAMMATORY MECHANISMS

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis results from repeated inhalational exposure to antigens derived from thermophilic *Actinomyces*, a variety of fungal pathogens, most commonly *Cryptococcus* and *Trichosporon*, and bird dander and feathers. Patients typically present with cough and shortness of breath and usually reversible interstitial pulmonary infiltrates. Unless patients are removed from the offending antigen, permanent lung destruction and respiratory compromise are inevitable. T_H1-like cells bearing a restricted alpha/beta antigen receptor repertoire and producing IFN- γ have been described from hypersensitivity pneumonitis patients,¹⁸ and it is believed that delayed-type hypersensitivity reactions are important in the pathogenesis. In addition to antigen removal, treatment typically includes use of systemic corticosteroids.

Chronic obstructive pulmonary disease

The pathological hallmarks of chronic obstructive pulmonary disease (COPD) are inflammation of the peripheral airways (Fig 1, A), resulting in prolonged expiratory airflow and loss of elastic recoil caused by the destruction of lung parenchyma, collectively referred to as emphysema.¹⁹ When severe, COPD can greatly increase the work of breathing while simultaneously reducing efficiency of the cardiovascular system from loss of pulmonary vasculature. The end-stage result of these processes is debilitating shortness of breath and congestive heart failure. Because these signs and symptoms are somewhat nonspecific, diagnosis can be difficult and hinges on finding reduced airflow (typically assessed by the FEV1 recorded through spirometry), together with reduced lung diffusing capacity of carbon monoxide (DL_{CO}), an index of the efficiency of lung gas exchange. Emphysematous enlargement of the lung, as assessed by either computed tomography or conventional chest roentgenograms, can support the diagnosis.

COPD is currently the fourth leading cause of death in the United States, the 12th most prevalent disease worldwide, and is projected to rise to the fifth in the next 2 decades.²⁰ Tobacco smoking is clearly the most important etiologic factor in COPD worldwide, but other inhaled irritants and genetic factors, especially alpha-1-antitrypsin deficiency, are important in some patient subsets. Early pathogenetic studies reported a marked increase in the number of neutrophils and macrophages in the airways of humans and animals exposed to cigarette smoke, and several hypotheses propose that COPD and emphysema are mediated through cigarette smoke-induced activa-

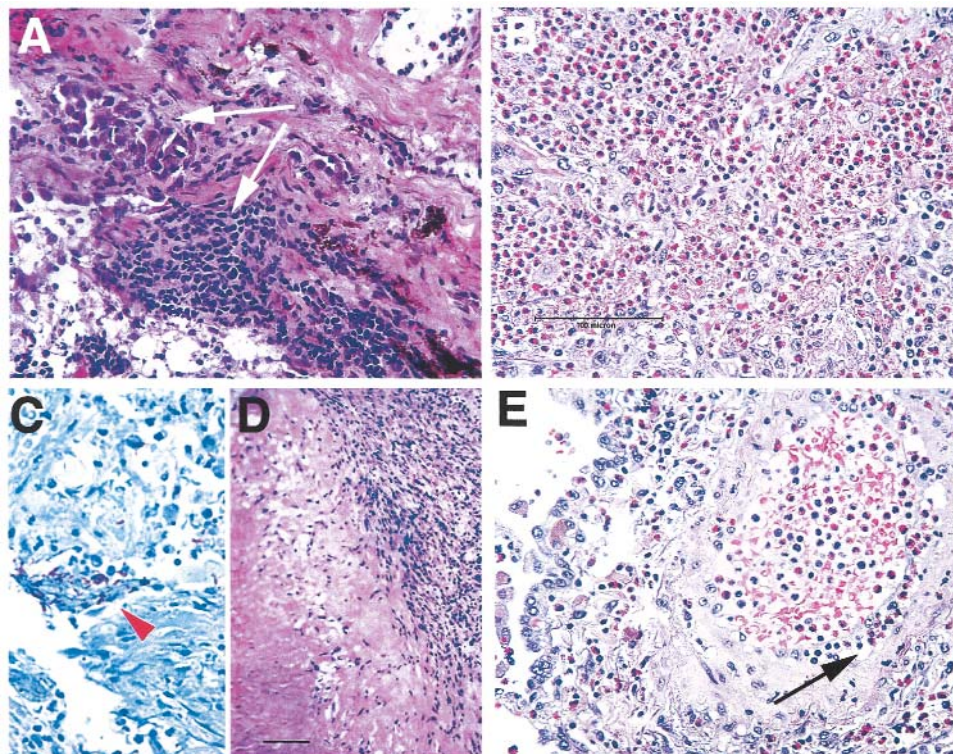


FIG 1. Histopathologic appearance of selected immunologic lung diseases. Pronounced inflammation that includes mononuclear (*upper arrow*) and neutrophilic (*lower arrow*) infiltrates is apparent in the lung of a patient with end-stage COPD (**A**). Sheets of eosinophils (red granular cytoplasm) are seen in another patient with acute idiopathic eosinophilic pneumonia (**B**). Pulmonary tuberculosis is marked by the presence in infected tissues of the causative organism, *Mycobacterium tuberculosis*, as revealed by acid-fast (Kinyoun) staining (**C**, *arrowhead*). *M tuberculosis* is most readily detected at the site of caseating granulomas (**D**), which are marked by circumscribed areas of necrosis (*far left*) surrounded by palisading histiocytes. In contrast, Churg-Strauss vasculitis, another granulomatous pulmonary syndrome, is marked by inflammatory invasion of vascular walls (*arrow*) and abundant eosinophils (**E**). Relative size is indicated by the 100- μ m bars in **B** and **E**. All sections except **C** stained with hematoxylin and eosin. (Photomicrographs courtesy of Dr. Linda Green, Houston Veterans Affairs Medical Center).

tion of these cells (Fig 1, A). According to the protease-antiprotease theory of COPD pathogenesis, activated macrophages and neutrophils release matrix-degrading enzymes (matrix metallo-, serine, and cysteine proteases) that cause the lung parenchymal destruction that underlies emphysema.²¹ In support of this hypothesis, experimental models have shown a correlation between recruitment of macrophages and neutrophils to the airways and the dose of inhaled cigarette smoke, and administration of proteases with elastolytic activity can alone induce emphysema.²² More recently, a role for T cells in the pathogenesis of COPD has been proposed, especially T_H1 cells,²³ although neutrophils and macrophages should not be discounted as the ultimate mediators of disease, because of their unique ability to synthesize and secrete a large number of extracellular matrix-degrading molecules.²²

Treatment of COPD is limited to the use of bronchodilators and managing tobacco addiction, with lung transplantation and alpha-1-antitrypsin replacement therapy reserved for highly selected patients. More recently, the results of several clinical trials investigating anti-inflammatory therapy on COPD outcome have been published. These trials, based on the consistent observation of

lung inflammation in COPD patients, have shown no effect on the exaggerated rate of decline in lung function after treatment with inhaled corticosteroids.²⁴ Thus, once an exaggerated decline in lung function is initiated in susceptible individuals, treatment with anti-inflammatory agents plays little, if any, role in slowing the decline. However, systemic treatment with corticosteroids may provide modest improvement in patients admitted to the hospital with acute COPD exacerbations,²⁵ and current recommendations from the American Thoracic Society include the use of inhaled corticosteroids in patients with moderate to severe COPD.²⁰

T_H2 -RELATED INFLAMMATORY MECHANISMS

Asthma

Asthma is one of the most common and debilitating lung diseases in the industrialized world and is strongly linked to the presence of lung T_H2 cells and other atopic phenomena. This important respiratory illness is discussed fully in Chapter 6.

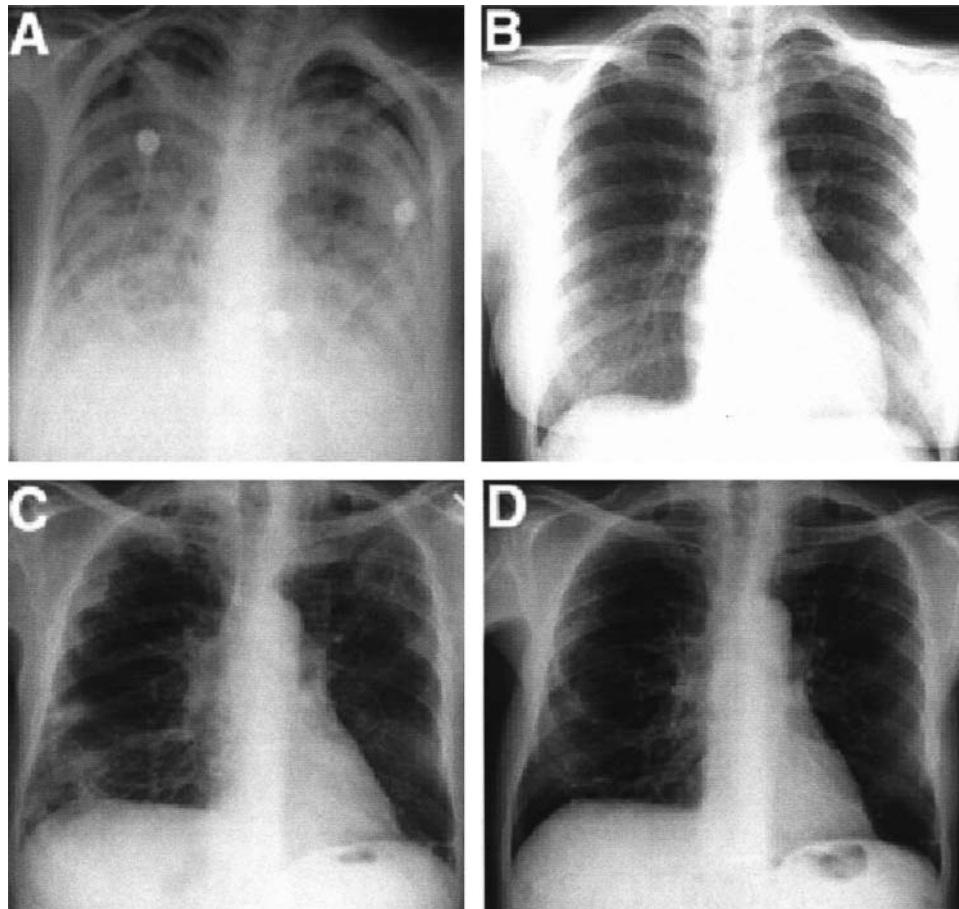


FIG 2. Radiologic appearance of selected immunologic diseases of the lung. **A**, Severe example of idiopathic acute eosinophilic pneumonia demonstrating diffuse bilateral alveolar infiltrates and pleural effusions that resolved 7 days after initiation of corticosteroid therapy (**B**). **C**, Untreated Churg-Strauss syndrome showing patchy, bilateral interstitial and alveolar infiltrates. Corticosteroid therapy again produced dramatic improvement in these lesions (**D**). (**C-D**, courtesy of Dr. Remzi Bag, Baylor College of Medicine).

Pulmonary eosinophilia syndromes

These diverse lung diseases (Table II) are popularly grouped according to the increased presence of tissue or BAL eosinophils (>20% of all inflammatory cells). It is unclear whether the eosinophil actually contributes to disease, but the marked dependence of eosinophils on the cytokine IL-5 and T helper-type 2 (T_H2) cells for their development and recruitment suggests a common immunopathologic basis for many of the syndromes. The diseases underlying many of the eosinophilic syndromes are discussed elsewhere in this chapter or in this series; the idiopathic syndromes and allergic bronchopulmonary mycosis are discussed below.

Idiopathic eosinophilic pneumonia

Patients with the acute form of this rapidly progressive syndrome present with cough, fever, dyspnea, pleuritic chest pain, and diffuse myalgias. Hypoxemia is common and may rapidly progress to complete respiratory failure requiring mechanical ventilation. Chest roentgenograms typically reveal diffuse, migratory, bilateral alveolar or inter-

stitial opacities; pleural effusions are invariably present at some point in the course of disease (Fig 2, A).²⁶ The chronic form of idiopathic eosinophilic pneumonia is similar to the acute variety, but patients have a more prolonged course, are more atopic, and predominantly female. The chest roentgeno-gram in chronic idiopathic eosinophilic pneumonia often shows peripheral alveolar and interstitial opacities and pleural effusions; parenchymal scarring is a possible late sequela.²⁷ In addition to eosinophils, which are present in the BAL and lung parenchyma (Fig 1, B), the BAL of patients with idiopathic eosinophilic pneumonia contains lymphocytes, IgA, IL-5, and eosinophil-specific chemokines.²⁸ Further, rare patients having idiopathic eosinophilic pneumonia in association with cutaneous T-cell lymphomas exhibit a predominant T_H2 cytokine profile.²⁹

The treatment of idiopathic eosinophilic pneumonia is with oral or intravenous glucocorticosteroids together with supportive therapy, as needed. Correctly diagnosed patients will all respond, usually with a complete remission. Relapses are common, only with the chronic form of disease, but are readily managed with repeated courses of steroids.³⁰

TABLE II. Pulmonary eosinophilia syndromes**Primary or idiopathic:**

Idiopathic acute eosinophilic pneumonia
 Idiopathic chronic eosinophilic pneumonia
 Hypereosinophilic syndrome
 Churg-Strauss syndrome

Secondary reactions to:

Inhaled antigens (asthma, hypersensitivity pneumonitis)
 Fungal hypersensitivity (allergic bronchopulmonary mycosis)
 Drugs or toxins
 Primary lung infections
 Neoplasms
 Collagen vascular disease
 Sarcoidosis

Hypereosinophilic syndrome

In contrast to the relatively benign course of idiopathic eosinophilic pneumonia, hypereosinophilic syndrome is an often fatal malignant or premalignant condition involving T_H2 -like T cells that infiltrate and disrupt many organs, but especially the lungs, skin, peripheral nerves, and myocardium. Eosinophilia is presumably the result of the dysregulated production of IL-5. Steroids are occasionally helpful, but IFN- α and bone marrow transplantation have also been used successfully.³¹

Allergic bronchopulmonary mycosis

Other than asthma, allergic bronchopulmonary mycosis is probably the most common cause of lung eosinophilia in temperate climates and is associated with a variety of fungi, but particularly *Aspergillus fumigatus*, that are capable of colonizing the epithelial surface of the lung. The exact incidence and prevalence of allergic bronchopulmonary mycosis is unknown, but recent clinical studies suggest that the syndrome is underdiagnosed.³²

In addition to asthma, which is almost invariably associated with allergic bronchopulmonary mycosis, diagnostic criteria also include precipitins and positive skin prick test to *Aspergillus* species, blood eosinophilia, and chest roentgenograms showing recurrent and often variable parenchymal infiltrates. Minor diagnostic criteria include elevated total serum IgE levels, sputum cultures positive for *Aspergillus*, bronchial casts in sputum, and bronchiectasis.

Allergic bronchopulmonary mycosis is increasingly recognized as a complication of cystic fibrosis and may be difficult to diagnose in this setting. Patients with specific IgE and skin prick tests, together with precipitating antibodies to the suspected organism, are more likely to have a diagnosis of allergic bronchopulmonary mycosis.³³ For the majority of cystic fibrosis patients with superimposed allergic lung disease caused by *A. fumigatus*, positive skin prick tests for two recombinant antigens, Asp f 4 and Asp f 6, reliably distinguish sensitized patients from those with true disease.³⁴ Bronchoscopy with lung biopsy is being increasingly recognized as a useful adjunctive diagnostic aid in especially difficult cases.³⁵

Despite its infectious etiology, treatment of allergic bronchopulmonary mycosis has traditionally relied on

the use of systemic corticosteroids. However, a recent clinical trial demonstrated that addition of the antifungal agent itraconazole to glucocorticosteroids safely provides additional clinical benefit in patients infected with *A. fumigatus*.³² This combined therapeutic approach, which may also reduce the incidence of invasive fungal disease complicating glucocorticosteroid monotherapy, should be applied to all patients with allergic bronchopulmonary mycosis.

GRANULOMATOUS INFLAMMATORY MECHANISMS

Granulomas are distinct immunologic units not unique to the lung, but characteristic of some of the most important and interesting of lung diseases. Most granulomas consist of organized collections of T and B cells surrounded by histiocytes (macrophages with indistinct cell boundaries) and, if caused by an infectious etiology, large, multinucleated giant cells present usually at the granuloma center (Fig 1, D). A typical granuloma is 0.5 to 1.5 mm in diameter and is held together by a loose connective tissue stroma. Granulomas form either in response to persistent antigen exposure or from the presence of undigestible particulate antigen, but the molecular control of granuloma formation and persistence remain largely unknown.

Whether found in the lung or elsewhere, granulomatous diseases of all types share many common features. Once an antigen is inhaled, it undergoes phagocytosis by resident alveolar macrophages, leading to their activation. Once activated, macrophages secrete a variety of molecules that promote granuloma formation, immunity, or both, including angiotensin-converting enzyme (ACE), 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), osteopontin, and tumor necrosis factor (TNF)- α .

Other than a marker for the presence of granulomatous disease and its activity, ACE lacks disease specificity and has limited diagnostic and therapeutic utility. Similarly, high serum levels of $1,25(OH)_2D_3$ are a common feature of granulomatous diseases and are believed to induce the hypercalcemia common to them. IFN- γ , likely the product of T_H1 cells, is perhaps the most important stimulus for $1,25(OH)_2D_3$ synthesis by macrophages.³⁶ In addition to its function in calcium metabolism, $1,25(OH)_2D_3$ likely plays a complex role in immunity through its dual roles in augmenting macrophage antimicrobial activity, but simultaneously inhibiting T_H1 -specific responses.

Osteopontin is a multifunctional glycoprotein secreted by many granuloma cells that is implicated in regulation of chemotaxis, T-cell development, and cell adhesion—all essential elements to granuloma formation. Based largely on work with mice, osteopontin is emerging as a major stimulus for T_H1 cell development.³⁷ The cytokine TNF- α is also critical to granuloma development and plays an important role in containment of the prototypical granuloma-inducing infectious agent, *Mycobacterium tuberculosis*, the agent of tuberculosis. Increased susceptibility to tuberculosis³⁸ and other intracellular,

TABLE III. Features of pulmonary granulomatous diseases

Granulomatous lung disease	Radiographic appearance	Principal antigens
Sarcoidosis	Variable	Unknown*
Tuberculosis	Lobar (primary); Upper lobes (reactivation)	Secreted antigen 85A/B, SL-I, glycolipids, DAT, PPD
Fungi (including bronchocentric granulomatosis)	Lobar; ill-defined infiltrates; "air crescent": invasive aspergillosis	Many
Hypersensitivity pneumonitis	Interstitial reticulonodular	Fungi, bacteria, animal proteins, Au, isocyanate
Berylliosis (other metals include Al, Ni, Zr, Ti)	Radiographically similar to sarcoidosis	Soluble Be†

*Proposed antigens have included occult bacterial and mycobacterial infections, mycobacterial superantigen, and hard metals.

†Mandatory occupational exposure limit < 2.0 *g/m³; however, threshold limit for disease is unknown—cases reported at < 2 *g/m³.

granuloma-inducing organisms has been noted in patients receiving the TNF- α inhibitor, infliximab. Recognition of such heightened susceptibility, especially to tuberculosis, has led to a recent consensus statement for screening and prophylaxis of patients at risk for or with previously active tuberculosis before initiation of anti-TNF therapy.³⁹ Together, these findings indicate that the granuloma is required to control certain infectious pathogens, and that the importance of TNF- α in infection control lies in its requisite role in granuloma formation.

Several important diseases involving infectious and non infectious etiologies are remarkable for the prominence of lung granulomas (Table III). These include the T_H1-dominated diseases tuberculosis, sarcoidosis, and berylliosis, and the T_H2-dominated vasculitic entity, Churg-Strauss syndrome.

Tuberculosis

Caused by the intracellular pathogen *M tuberculosis*, human tuberculosis is an ancient and extremely common scourge. Primary tuberculosis is often silent, but symptomatic disease usually presents as a febrile and often painful pneumonic process (pleurisy) involving the lower lung lobes, frequently complicated by sterile pleural effusions or tuberculous empyema. Without treatment, most normal patients will eventually recover spontaneously from primary tuberculosis, entering a period of quiescent, or latent, disease, only to develop reactivation disease later in life, especially after immunosuppressive procedures, infections, malignancies, or drug trials. In contrast to primary disease, reactivation tuberculosis typically involves the upper lung lobes. Without treatment, patients may progress along one of three clinical routes, including spontaneous resolution, progressive fibrocavitary lung disease with extensive local tissue destruction, and widespread dissemination of infection to virtually any organ. Since the advent of pasteurization of milk and milk products, primary gastrointestinal tuberculosis is no longer common. Regardless of the presentation, tuberculosis is diagnosed by identification of the organism from sputum or infected tissue (Fig 1, C), or by PCR-based amplification of *M tuberculosis* DNA.

Mortality from tuberculosis in the United States and Europe has dropped remarkably, from 500/100,000 in early 19th century England to the current United States

mortality rate of <1/100,000. In striking contrast, the estimated annual incidence rates of tuberculosis are rising in sub-Saharan Africa and elsewhere.⁴⁰ Worldwide, smear-positive disease prevalence in 2000 was estimated at greater than 6 million cases, and as many as one third of the world's population may have latent infection.

After inhalation of an infective dose of *M tuberculosis* (possibly as few as 1 to 5 bacilli), the organism is phagocytosed by resident alveolar cells, after which a period of latency occurs that may last for many years. Studies of close contacts of persons with tuberculosis have been most useful in studying early responses after exposure. Enzyme-linked immunocell spot assays of BAL fluid samples from household contacts of patients with active sputum smear-positive and culture-positive tuberculosis have shown higher frequencies of IFN- γ producing cells with specificity to *M tuberculosis*-secreted antigen 85.⁴¹ However, study of human immune responses in the period immediately after infection is obviously difficult, and because of the asymptomatic nature of latent infection, progress in understanding this important disease period is lacking. Latency traditionally has been thought to arise in the setting of a host hypoxic response. The granuloma (Fig 1, D) itself may provide a suitably anaerobic environment, although *M tuberculosis* DNA, presumably from latent organisms, has been identified from grossly normal tissue. Virulence of mycobacteria is associated with resistance to nitric oxide and 1,25(OH)₂D₃, two important factors in the host's immune response. Important mycobacterial-specific genes, especially sigma factors that underlie disease virulence, are now being defined.⁴²

The importance of CD4⁺ T cells in the host's antituberculous response is most clearly illustrated in AIDS patients with marked depletion of this T-cell subset. Low CD4⁺ T-cell levels in peripheral blood have been correlated with impairment of delayed-type hypersensitivity responses and increases in smear-positive pulmonary and extrapulmonary disease. At any stage of illness, a T_H1-predominant pattern of cytokine production (ie, IFN- γ) is associated with curative responses as opposed to noncuring, fibrocavitary disease marked by a predominant T_H2 phenotype.⁴³

Multidrug chemotherapy with isoniazid and rifampin-based regimens, given under direct observation (directly observed therapy) where possible, is the mainstay of modern pulmonary tuberculosis treatment.

Current clinical trials are focused on discovering drug schedules that maximize compliance without compromising efficacy. One means for accomplishing this may be to reduce the frequency of drug dosing, a promising strategy to use newer drugs, such as rifapentine, with longer serum half-lives.

Sarcoidosis

Sarcoidosis is a disease of unknown etiology characterized by the presence of multiple noncaseating granulomas resulting in multiple organ dysfunction, but especially involving the lung. The high prevalence of hilar lymphadenopathy and asymptomatic disease in the African-American population clearly suggests a genetic basis, and numerous HLA haplotype associations have been identified. Although clinically of little utility in defining disease progression or severity of disease, the following radiographic disease classification is widely used among clinicians: stage 0: no apparent disease; stage 1: hilar lymphadenopathy; stage 2: hilar lymphadenopathy and parenchymal interstitial abnormalities; stage 3: lung parenchymal interstitial abnormalities; stage 4: fibrocavitary disease. Pulmonary function testing usually shows restriction, but sarcoidosis is one of a handful of lung diseases that can have mixed obstructive and restrictive physiology.

Histologically, sarcoidosis is characterized by the presence of perilymphatic, noncaseating granulomas with an abundant rim of perigranulomatous lymphocytes. The perigranulomatous lymphocyte population contains both CD4⁺ and CD8⁺ T lymphocytes, and intracellular cytokine staining profiles demonstrate a T_H1 (IFN- γ) predominant cytokine pattern.⁴⁴ Diagnosis of sarcoidosis is made based on finding this characteristic pathology in lung, or perhaps other tissues, in the absence of known granuloma-inducing agents. Despite occasional claims of an infectious or occupational etiology to sarcoidosis (tuberculosis and berylliosis, respectively), careful studies consistently reveal a substantial population of patients with no identifiable trigger. Oral corticosteroids are typically given for symptomatic disease, but probably do not improve long-term outcome.⁴⁵ The importance of TNF- α in granuloma formation provides additional therapeutic insight. Infliximab, a modified anti-human TNF- α antibody, has been used successfully as a treatment for refractory sarcoidosis, but serious side effects might preclude its widespread use.

Berylliosis

Berylliosis is clinically identical to sarcoidosis, but results from environmental exposure to beryllium, often in an occupational setting. The Occupational Safety and Health Administration mandates a workplace permissible exposure limit <2 mg/m³ per 8-hour time-weighted average, lower level exposures have been reported to result in symptomatic disease, resulting in proposals to reduce exposure limits (see http://www.osha.gov/dts/hib/hib_data/hib19990902.html). Like sarcoidosis, berylliosis is associated with a broad spectrum of lung abnormalities,

ranging from patchy radiographic opacities to diffuse interstitial lung disease.

Clustering of cases of hypersensitivity pneumonitis and berylliosis within patients bearing certain MHC and TNF- α polymorphisms suggests a common pathogenetic link between these distinct lung diseases. Treatment of berylliosis centers on removal of the patient from the offending metal. Corticosteroids are commonly used as adjunctive therapy, but randomized efficacy studies have been inconclusive, and their use remains controversial.

Churg-Strauss syndrome

Churg-Strauss syndrome, a necrotizing vasculitis with autoimmune features, is characterized by airway obstruction, eosinophilia, and the presence of circulating antineutrophil cytoplasmic antibodies (p-ANCA).⁴⁶ The most common organs involved are lungs, skin, and nervous system, and the diagnosis often is established from a combination of clinical findings, including abnormal chest roentgenograms (Fig 2, C), positive serologic tests for p-ANCA, and characteristic pathology (Fig 1, E). Because Churg-Strauss syndrome is exclusively found in patients with a history of asthma and allergies, and the prominent pathologic feature is necrotizing vascular and tissue granulomas, the term "allergic granulomatosis and angiitis" is used synonymously.

The significance of p-ANCA in Churg-Strauss syndrome pathogenesis is unclear, but binding of these autoantibodies to endothelial cells in small to medium-size vessels may initiate vascular inflammation that may progress to vasculitis.⁴⁷ Cytokine production patterns of T-cell lines cloned from patients with Churg-Strauss syndrome indicate the presence of both T_H1 and T_H2 cells, although T_H2 cells appear to predominate.⁴⁸

Churg-Strauss syndrome has been reported in patients taking a variety of pharmaceuticals, including leukotriene receptor modifiers, corticosteroids, and macrolide antibiotics, although the precise role of these medications in disease remains controversial.^{49,50} Treatment of Churg-Strauss syndrome is based on reinstituting systemic corticosteroids and discontinuing possible offending medications, which leads to disease resolution in the majority of patients. Resistance to corticosteroids is usually overcome by addition of cyclophosphamide or other immunosuppressants.

AUTOIMMUNE LUNG DISEASE

Several of the autoimmune systemic vasculitides and rheumatologic disorders (reviewed in Chapters 14 and 15) affect the lung at some point during their course, often causing serious physiologic impairment. Autoimmune diseases that affect the lung can be divided into those that feature vasculitis and those that spare inflammation of the blood vessels (Table IV).⁵¹ This classification remains useful; however, new insights suggest that the same syndromes may be functionally categorized according to immunopathologic criteria. For example, whereas Churg-Strauss vasculitis, discussed above, is

predominantly associated with local T_H2 cytokine production, another granulomatous pulmonary syndrome, Wegener's granulomatosis, is marked by the presence of T_H1-like cells.⁵² Other autoimmune lung syndromes such as antglomerular basement membrane disease (Goodpasture's syndrome) are predominantly antibody-mediated with no defined T-cell phenotype.

Wegener's granulomatosis

The lesions of Wegener's granulomatosis are characterized by the presence of necrotizing vasculitis, microabscess formation, and granulomatous inflammation composed of neutrophils and T_H1-like cells producing IFN- γ .⁵¹ These lesions frequently induce symptoms referable to the upper and lower respiratory tracts and kidneys (the classic triad), but other organs such as the eye and skin are also frequently involved.⁵³ ANCA is present in the sera of the majority of patients with Wegener's granulomatosis.^{54,55} A perinuclear pattern of autoantibody staining (p-ANCA) is based on reactivity to myeloperoxidase, nuclear antigens, elastin, and/or lactoferrin, but, with the exception of myeloperoxidase, their detection is not specific for vasculitis.⁵⁶ A cytoplasmic pattern of autoantibody staining (c-ANCA) is specific for lysosomal proteinase 3 and is more strongly associated with vasculitis. In the absence of classic organ involvement in c-ANCA-positive patients, the diagnosis of Wegener's granulomatosis is established by tissue biopsy.

The etiology of Wegener's granulomatosis is unknown, but autoantibodies directed against neutrophil granule proteins and activated T_H1-like cells are strongly associated with active disease. A model has been suggested, whereby in susceptible individuals, environmental antigen(s) trigger excessive IL-12 release from monocytes that facilitates outgrowth of T_H1 cells, which in turn orchestrate subsequent inflammation, tissue breakdown, and antibody responses to proteins released from disrupted cells.⁵⁷ A recent clinical study determined survival, organ damage, and predictors of these outcomes in a population-based, longitudinal cohort study of patients with Wegener's granulomatosis. Treatment with cyclosporin A and corticosteroids led to a 10-year survival rate of 75% in patients with Wegener's granulomatosis, but did not prevent severe organ damage. Furthermore, the presence of baseline organ dysfunction and prolonged therapy with more than 20 mg/day of prednisone were markers of poor outcome.⁵⁸

Goodpasture's syndrome

Goodpasture's syndrome (antglomerular basement membrane disease) involves diffuse pulmonary hemorrhage, glomerulonephritis, or both, often presenting simultaneously, in association with circulating antglomerular basement membrane antibodies.⁵⁹ Goodpasture's syndrome has an incidence of 0.5 cases/million Europeans per year and affects primarily white males.⁵⁹ The characteristic anti-glomerular basement membrane autoantibodies bind to an endogenous antigen, the 235 amino acid carboxy-terminal noncollagenous domain of

TABLE IV. Autoimmune/rheumatologic diseases of the lung

With vasculitis	Without vasculitis
Wegener's granulomatosis	Goodpasture's disease
Churg-Strauss syndrome	Systemic lupus erythematosus
Lymphocytic vasculitis	Rheumatoid lung disease
Sjögren's disease	Systemic sclerosis (Scleroderma)
Polymyositis/dermatomyositis	Ankylosing spondylitis
Microscopic polyangiitis	
Polyarteritis nodosa	
Behçet's disease	

type IV collagen, normally present in alveolar and glomerular basement membranes.⁶⁰ Why this molecule becomes the target of autoimmune attack is not understood, but the human class II major histocompatibility antigen DR15, which is strongly associated with Goodpasture's syndrome, has the unique capacity to bind many peptide sequences within the non-collagenous domain of type IV collagen.⁶⁰ Thus, formation of antglomerular basement membrane antibodies may, in part, reflect loss of tolerance to certain basement membrane antigens and the aberrant presentation of specific basement membrane peptides to the immune system.

The autoreactive antibodies in Goodpasture's syndrome are the likely cause of disease, as they selectively bind and destroy the basement membranes of the lungs and kidneys, typically resulting in glomerulonephritis and alveolar hemorrhage. When severe, alveolar hemorrhage can result in exsanguination or, more commonly, asphyxiation, and is the leading cause of death in Goodpasture's syndrome.⁵⁹

The diagnosis of Goodpasture's syndrome rests on detection of circulating anti-glomerular basement membrane antibodies in patients with an appropriate clinical presentation.⁶¹ Removal of the offending autoantibodies by plasmapheresis and inhibition of further antibody production through immunosuppression are the mainstays of therapy. Based on clinical experience, Ball et al suggest immediate initiation of plasma exchange therapy (4-L exchanges of plasma every other day) and systemic steroids (2 mg/kg methylprednisolone intravenously every 8 hours) in patients who present with pulmonary or renal hemorrhage.⁵⁹ Once the presence of antglomerular basement membrane antibodies is established, cyclophosphamide is started (2 mg/kg) and further adjusted to keep the white blood cell count above 5,000/mm³ for a total of 6 months. Overall, despite early aggressive treatment, the prognosis of patients with Goodpasture's syndrome depends on the degree of renal involvement, with less than 50% crescents on renal biopsy predicting a favorable response to treatment.⁵⁹

SUMMARY

The immunologic lung diseases represent the largest and most important group of lung disorders. Over the last 5 years, much has been learned regarding the

immunopathogenesis of many of these syndromes, especially ARDS, granulomatous lung disease, and COPD, and improved therapies are being developed based on these findings. It seems reasonable to predict that equivalent strides will be made in the ensuing half-decade and that, as our understanding of the immune mechanisms that underlie pulmonary disease becomes progressively refined, therapeutic advances will accelerate.

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