Chapter 125: Tracheobronchial and Esophageal Manifestations of Systemic Disease

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A wide gamut of otolaryngeal manifestations may occur as complications of a variety of systemic diseases (Caldarelli et al, 1979; Campbell et al, 1983; Cupps and Fauci, 1981; Kovarsky, 1984; Standefer and Mattox, 1986; Turner et al, 1973; Wiedemann and Matthay, 1989; Wise, 1991). In this context, the otolaryngologist often plays a pivotal role in recognizing the underlying nature of the disorder, defining the extent of upper airway pathology, procuring appropriate biopsy specimens, participating in therapeutic decisions, and managing any complications that may occur. Otolaryngologists are often the first physicians to recognize that otolaryngeal abnormalities are symptomatic of a broader disease and they can mandate a systemic approach to the problem. The diverse pathologic manifestations of primary and systemic diseases affecting the head and neck, oropharynx, nasopharynx, sinuses, and larynx have been addressed elsewhere in this book.

In this chapter, we will discuss specific immunologic and systemic disorders (including collagen vascular diseases, vasculitides, etc) that may involve the upper respiratory tract and esophagus. Although in some cases otolaryngologic features may be common to one or more of these diseases, clinical, radiographic, laboratory, and histopathologic features differ between these conditions. Prognosis and therapy on tracheobronchial and esophageal manifestations that may occur in the context of systemic diseases, but we will also discuss clinical manifestations at additonal sites, review the salient histologic, laboratory, and serologic features, and present a management and therapeutic approach. Some categories of diffuse diseases that have otolaryngologic manifestations are excluded because these topics are discussed in other chapters and other sources. We will discuss fibrosing mediastinitis, a rare, immunologic response to histoplasmosis, mycobacteriosis, or fungal infections, but have specifically excluded other infectious complications including those seen with acquired immunodeficiency syndrome (AIDS), other immunodeficient states, and active tuberculous, fungal, bacterial, or parasitic infections. In addition, metastatic tumors that may present initially in the ear, nose, and throat are not discussed. However, we will briefly review lymphomatoid granulomatosis and nasopharyngeal lymphomas because these disorders have clinical and histopathologic features that are shared by Wegener's granulomatosis and systemic vasculitis. Otolaryngologic manifestations of diabetes and other endocrine disorders are discussed elsewhere, as are neurologic disorders that can lead to laryngeal muscle dysfunction and upper airway obstruction. Finally, the review of congenital diseases presenting as tracheal and esophageal abnormalities is beyond the scope of this chapter.

Upper Airway Obstruction: Assessment by Pulmonary Function Testing

Upper airway obstruction (UAO) is occasionally seen by the otolaryngologist and can be life-threatening. Most commonly, UAO is a result of isolated local pathology, but it may occur with systemic diseases, especially with rheumatoid arthritis, relapsing polychondritis, Wegener's granulomatosis, and amyloidosis. Imaging techniques such as computed tomographic (CT) scanning and direct visualization with laryngoscopy or bronchoscopy may indicate the presence of UAO, but these studies can be negative even when significant functional upper airway obstruction exists. Conversely, infringement of the upper airways can

be seen when no significant functional impairment is present. Therefore, whenever UAO is suspected, functional studies are mandatory to assess the life-threatening potential of lesions in this area.

Simple spirometry and a flow volume loop are sensitive and easily performed studies that can assess the functional integrity of the upper airway (Kryger et al, 1976; Rotman et al, 1975). When UAO is present the abnormal flow volume loop is very reproducible with each patient effort. Often the UAO is obvious by glancing at the configuration of the flow volume loop (Fig. 125-1). Although it is relatively easy to distinguish the flow volume loops of patients with UAO from those of normal patients, it is more difficult to make this distinction if patients have preexisting chronic obstructive pulmonary disease (COPD). The reason is that in COPD expiratory flows are severely depressed (especially at small lung volumes). However, in UAO the limitation of flow at large lung volumes is more severe than that seen in COPD; this serves to differentiate these two conditions. Criteria have been established to distinguish patients with UAO not only from normal subjects but also from patients with COPD: (1) a forced inspiratory flow at 50% of vital capacity (FIF50) equal to or less than 100 L/min; (2) ratio of forced expiratory flow at 50% of the vital capacity (FEF50) to FIF50 greater than or equal to 1; (3) the ratio of forced expiratory volume at 1 second (FEV1) measured in milliliters to the peak expiratory flow rate measured in liters per minute of greater than or equal to 10 mL/L/min; and (4) the ratio of FEV1 to forced expiratory volume in 0.5 seconds of greater than or equal to 1.5 (Rotman et al, 1975). Upper airway obstruction is also characterized by improved flow when a mixture of 80% helium and 20% oxygen is used instead of ambient air for the flow volume loop. Because the upper airway is characterized by turbulent flow, flow rates in UAO can be improved with the administration of the helium-oxygen mixture. This is not the case in patients with asthma or COPD because the site of the obstruction in these diseases is the distal airway where airflow is laminar in nature and therefore unaffected by gas density.

Upper airway obstruction, which can be a manifestation of either supraglottic (extrathoracic) or tracheal (intrathoracic) pathology, can be either fixed or variable. In *fixed* UAO the airway diameter at the site of the lesion is the same during both inspiration and expiration. In this context, both maximal expiratory and inspiratory flow rates are limited equally on a flow volume loop (see Fig. 125-1, A). Thus, the ratio of maximal expiratory flow to maximal inspiratory flow approximates 1. The most common causes of fixed UAO are benign strictures (eg, following prolonged endotracheal intubation) and large goiters. Airway obstruction that is due to intratracheal or supraglottic granulomatous mass lesions or tracheal stenosis in the context of vasculitis, relapsing polychondritis, fibrosing mediastinitis, amyloidosis, or systemic disease may be either fixed (eg, in the context of a permanent stricture or extrinsic compression), truncation of *both* the inspiratory and expiratory limbs of the flow volume loop may be found (see Fig. 125-1, A). More often, however, lesions in the upper airway cause *variable* obstruction to airflow; this reflects changes in airway diameter with changes in phases of respiration. Normally, the trachea (which is *intrathoracic*) is influenced by pleural pressure and dilates with inspiration and narrows with expiration. This difference is exaggerated in the presence of obstructing tracheal masses or inflammatory lesions. Variable intrathoracic obstruction is characterized by limitation in peak expiratory flow, while the inspiratory flow rates are unaffected (see Fig. 125-1, B). Therefore, the peak expiratory flow is much lower than the peak inspiratory flow. In contrast, however, when the site of obstruction is *extrathoracic* (eg, supraglottic lesions), the reverse occurs. With

extrathoracic obstruction, supraglottic portions of the airway will collapse during forced inspiration, which tends to augment the degree of obstruction, and is manifested as a truncation or plateau in inspiratory flow (see Fig. 125-1, C). During expiration, however, the airway dilates because of the positive airway pressure. This decreases the obstruction; thus, expiratory flows are normal in this context. When UAO is variable, the site of obstruction can be determined by whether airflow limitation occurs during inspiration or expiration. To reiterate, when the obstruction is extrathoracic and variable (ie, for lesions above the vocal cords), inspiratory flow is limited and expiratory flow rates are normal. Most commonly, extrathoracic variable obstruction occurs with either unilateral or bilateral vocal cord paralysis, scars, cancer, enlarged lymph nodes, and fat deposits. Indeed the primary pathologic abnormality in patients with the sleep apnea syndrome is increased fat in the postnasal and laryngeal area, which leads to airway obstruction during sleep. When UAO is intrathoracic and variable, expiratory flow rates are reduced and inspiratory are relatively preserved.

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic autoimmune disease characterized primarily by symmetric inflammatory arthritis, but which exhibits protean extraarticular and systemic manifestations. Rheumatoid arthritis is associated with high titers of circulating IgM autoantibodies (rheumatoid factor), which may deposit in tissue, resulting in a vicious cycle of injury and inflammation mediated by leukocytes and a wide array of cytokines. Pathologically, hyperplasia and hypertrophy of synovial lining cells is seen; vascular distension, obstruction, thrombosis, and hemorrhage are regular features. A mixed inflammatory cell infiltrate, comprised predominantly of T lymphocytes and plasma cells, but with scattered polymorphonuclear leukocytes, is characteristic. Palisading histocytes may also be observed, both in articular and extraarticular sites. Varying degrees of fibrosis, tissue destruction, and pannus formation as a result of the chronic inflammatory process may be present. The patient's genetic background clearly plays a role in the generation of an immune response; this disease is far more common in females and an association between rheumatoid arthritis and the histocompatibility marked HLA-DR4 has been documented (Wiedemann and Matthay, 1989). The disease is highly variable in severity and progression and is usually characterized by spontaneous remissions and exacerbations.

Extraarticular manifestations of rheumatoid arthritis occur commonly and may not correlate with the extent or activity of articular disease. Clinical manifestations are protean; cardiac involvement, (pericarditis, rheumatoid nodules in the myocardium or on the heart valves, myocarditis, coronary arteritis), cutaneous vasculitis, subcutaneous nodules, neurologic manifestations (primarily mononeuritis multiplex), and diverse pulmonary manifestations (pleural effusion, pulmonary necrobiotic (rheumatoid) nodules, Caplan's syndrome, pulmonary vasculitis, bronchiolitis obliterans, and chronic interstitial pneumonitis/fibrosis) may occur (Wiedemann and Matthay, 1989; Wise, 1991). Although articular symptoms usually predominate and are the presenting features, occasionally systemic or extraarticular manifestations may precede joint symptomatology. A wide gamut of otolaryngologic complications may occur. The laryngeal structures are most often involved; isolated tracheal or esophageal involvement with rheumatoid arthritis may also occur. Clinical laryngeal involvement has been described in 26% to 53% of patients; even higher prevalence rates (86% in one study) have been noted at autopsy (Broker, 1988; Campbell, 1983). Rheumatoid involvement of the larynx inclues: (1) arthritis of the cricoarytenoid joint, (2) laryngeal

myositis, (3) ischemic atrophy of the recurrent laryngeal nerves, (4) rheumatoid nodules of the vocal cords (Brooker, 1988; Campbell et al, 1983; Kovarsky, 1984; Lawry et al, 1984). The most common patient complaint is hoarseness and a fullness in the throat, often accompanied by dysphagia. Other symptoms include tenderness, edema, and erythema of the throat (Lawry et al, 1984). The presence of cough can be a manifestation of isolated laryngotracheal involvement, but insidious development of pulmonary fibrosis must be excluded with pulmonary function studies and a chest roentgenogram (Wiedemann and Matthay, 1989). The most serious laryngotracheal complication of rheumatoid arthritis is acute UAO, which may present as a life-threatening event (McGeehan et al, 1989). Severe inflammation of the cartilaginous articular surfaces of the cricoarytenoid joint makes it ankylosed and obliterated (Brooker, 1988). Physical examination reveals erythema over the arytenoids occasionally with fixation of the arytenoids and vocal cords. With severe fixation of the laryngeal structures and the vocal cords, respiratory obstruction and stridor may ensue (McGeehan et al, 1989).

The diagnosis can be confirmed with fiberoptic laryngoscopic examination. Pulmonary function testing is critical to document functional compromise and for longitudinal follow-up in confirmed cases. As has been discussed, a flow volume loop is the best test to document UAO (Kruger et al, 1976; Rotman et al, 1975). Depending on the severity of the lesion, either a fixed or a variable pattern of extrathoracic UAO may be seen. In fixed UAO, both the inspiratory and expiratory loop reveal flow limitation. If the obstruction is mild, a variable pattern may be seen in which the expiratory loop is normal but the inspiratory loop shows flow limitation. Tracheostomy to resolve the airway obstruction is advocated in all cases of acute UAO (Campbell et al, 1983; Kovarsky, 1984). Esophageal involvement with rheumatoid arthritis usually indicates direct extension from the laryngeal area. Dysphagia can be caused by inflammation that is limited to the larynx, or may indicate extension to the esophagus. Endoscopic evaluation is necessary to document the extent of involvement. Severe cricoarytenoid arthritis can lead to necrosis of the cervical esophagus. In one reported case, total laryngectomy was necessary to stabilize the situation (Montgomery and Goodman, 1980).

Treatment of tracheal and esophageal manifestations of rheumatoid arthritis is predicated on treatment of the systemic disease. Although nonsteroidal antiinflammatory drugs (NSAIDs) are useful in mild to moderate rheumatoid arthritis, they are inadequate for disease involving the larynx or surrounding structures. Corticosteroids (systemic, local injection, topical) are recommended in this context. Optimal therapy is not clear. Local glucocorticoid injection into the cricoarytenoid area under direct visualization may be of benefit in some cases (Friedman et al, 1982; Habib, 1988). A simpler method of delivering glucocorticoids to the laryngeal area is via inhaled steroid formulations (eg, beclomethasone), which are widely available for the treatment of asthma. These have been beneficial in the therapy of cricoarytenoid arthritis (Kovarsky, 1984). If topical or inhaled steroids provide no relief, high-dose systemic glucocorticoids (eg, prednisone 60 mg/day or equivalent, with a taper) are recommended. In addition, multimodality therapy employing systemic and local/regional corticosteroids may be appropriate for patients with more severe disease. A variety of antiinflammatory, immunosuppressive, and cytotoxic agents (D-penicillamine, gold salts, methotrexate, cyclophosphamide, azathioprine) have been used in rheumatoid arthritis refractory to corticosteroids, salicylates, or NSAIDs, with anecdotal successes. Their role in the treatment of otolaryngeal complications of rheumatoid arthritis, however, has not been specifically addressed.

Relapsing Polychondritis

Relapsing polychondritis is a rare disease (fewer than 500 cases have been reported) characterized by recurrent inflammation and destruction of cartilage of the ears, nose, larynx, trachea, and peripheral joints; cardiovascular manifestations (aortitis, vasculitis, valvular insufficiency, and aneurysms) occur in 30% of cases (McAdam et al, 1976; Moloney, 1978; Wise, 1991). Constitutional symptoms (fever, malaise) may occur. There is no single diagnostic laboratory test that establishes the diagnosis. However, elevations in the Westergren sedimentation rate occur in 80% to 90%, anemia occurs in 50% to 60%, and leukocytosis occurs in 30% to 40% of cases (McAdam et al, 1976; McCaffrey et al, 1978; Michet et al, 1986; Moloney, 1978). It is usually episodic, but typically progresses over months to years. The cause is unknown, but the disease appears to be immune mediated. Relapsing polychondritis has been associated with other connective tissue diseases, including rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and ulcerative colitis, in approximately 10% of cases (Michet et al, 1986; Wise, 1991). Several immunologic aberrations have been described in this disorder, including complement deposition in involved cartilage, circulating antibodies to type II cartilage, and activation of peripheral blood lymphocytes upon exposure to cartilage antigen in vitro (Wise, 1991). Histologically at sites of the disease, the normal collagen is replaced by fibrous tissue; loss of glycosaminoglycans and degeneration of elastin and collagen fibers has been demonstrated (Wise, 1991). A polymorphous inflammatory cell infiltrate is present in the cartilage and fibrous tissue when the disease is active. This inflammatory component provides a rationale for institution of corticosteroid therapy during acute exacerbations of the disease. The disease tends to peak in the fifth decade of life; sex distribution is equal. Auricular involvement occurs in 80% to 90% of cases and is the most common initial feature (McAdam et al, 1976; Moloney, 1978; Wise, 1991). Painful swelling, erythema, and inflammation of the auricular cartilage (which is often bilateral), is characteristic (McAdam et al, 1976; Moloney, 1978). Nasal manifestations occur in 60% to 70% of patients and may be the presenting feature in 10% to 20% of cases (McAdam et al, 1976; McCaffrey et al, 1978, Wise, 1991). Symptoms of laryngotracheal involvement in relapsing polychondritis include hoarseness, choking, laryngeal tenderness, dyspnea, aphonia, wheezing, and stridor. A nonproductive cough or dysphagia may be an early manifestation of laryngotracheal pathology. Inspiratory stridor and dyspnea are signs of impending UAO. Hemoptysis has rarely been described as a presenting feature of relapsing polychondritis. The most serious tracheal complication of relapsing polychondritis is airway obstruction, which is a substantial cause of mortality in these patients. Airway obstruction can occur by three mechanisms (Monsenifar et al, 1982). First, inflammatory swelling of the glottic or subglottic area is the most common cause of UAO in this disorder. Secondarly, encroachment of the glottic or tracheal lumen because of cicatricial contraction may occur late in the course of the disease. Finally, with dissolution of the cartilaginous supporting structure of the trachea, there is dynamic collapse of the airway especially with forced inspiration and expiration. In a patient with known relapsing polychondritis, vigilance should be maintained for any sign of respiratory embarrassment.

These patients should be assessed by combination of methods. Computed tomography is excellent to document the laryngeal and tracheal anatomic structure but oes not assess dynamic UAO. Fiberoptic bronchoscopy permids direct visualization of the laryngeal and trachea area and allows biopsies to be performed. Bronchoscopic appearance of the intrathoracic airway correlated well with pulmonary function testing; however, bronchoscopic

appearance of the extrathoracic airway may be normal during quiet breathing despited impending airway collapse (Krell et al, 1986). Pulmonary function tests, (particularly flow volume loops), are mandatory to assess the likelihood of UAO. A flow volume loop during maximal inspiration and maximal expiration is a sensitive functional guide to dynamic UAO, and is recommended for sequential monitoring in patients with relapsing polychondritis. Normal flow rates during inspiration and expiration virtually exclude significant airway obstruction. Tracheal stenosis with relapsing polychondritis is usually a late manifestation of the disease and reflects diffuse tracheal involvement; however, localized stenosis occurring in the proximal, mid or distal trachea may also occur (see Fig. 125-2) (McAdam et al, 1978; McCaffrey et al, 1978; Michet et al, 1986; Moloney, 1978; Wise, 1991). Laryngeal/tracheal manifestations require tracheotomy more often than patients who develop laryngeal/tracheal disease as a late, end stage complication. Patients with severe laryngeal/tracheal involvement are predisposed to aspiration and recurrent pneumonia because of impaired mucociliary clearance of respiratory secretions from the tracheobronchial tree. Upper airway obstruction has been responsible for 20% to 50% of deaths that are attributed to relapsing polychondritis (McAdam et al, 1976; Michet et al, 1986; Moloney, 1978; Wise, 1991). The other major life-threatening complication of relapsing polychondritis is systemic vasculitis involving major blood vessels (particularly the aorta) leading to aortic insufficiency or aneurysm (Michet et al, 1986). The high incidence of arterial damage observed in this disease supports the theory that relapsing polychondritis is a limited form of systemic vasculitis. Its association with other autoimmune and collagen-vascular diseases also raises the suspicion that relapsing polychondritis may be a subset of a broader disease.

Treatment of relapsing polychondritis involves agents (particularly corticosteroids) that ablate the acute inflammatory process (when present). Because of the episodic nature of the disease, corticosteroids are often preserved for acute flares or clinical exacerbation of disease (McAdam et al, 1976; McCaffrey et al, 1978; Michet et al, 1986; Moloney, 1978). Nonsteroidal antiinflammatory agents may have an adjunctive role, particularly in the management of articular symptoms. However, for more serious symptoms or significant otolaryngologic manifestations, high-dose systemic corticosteroids (eg, prednisone 60 mg/day or equivalent) with subsequent taper, are recommended. Low-dose corticosteroids or alternate-day corticosteroids are often ineffective for this disorder. Immunosuppressive/cytotoxic agents (eg, cyclophosphamide, azathioprine, and 6-mercaptopurine) have been tried, but evidence showing benefit is weak (Kovarsky, 1984; McAdam et al, 1976). Dapsone, an agent that inhibits lysosomal enzymes, has been tried in an attempt to suppress lysosomal enzyme-mediated cartilage degradation; anecdotal successes have been reported, but data affirming its therapeutic efficacy is limited (Kovarsky, 1984). Dapsone should be reserved for patients failing to respond to high-dose glucocorticoids and/or cytotoxic therapy. Surgical management may be required for patients with severe laryngeal or tracheal involvement. However, surgery may be difficult and hazardous in the face of diffuse tracheal pathology. Patients with severe laryngeal swelling may require tracheostomy to relieve UAO. When the trachea is diffusely involved, tracheostomy alone may be insufficient to maintain airway patency. These patients are, therefore, at risk for dying from asphyxation. Tracheal reconstruction is a formidable procedure in this context, and is associated with a high mortality and complication rate. However, this can be considered as a last resort. Alternatively, tracheal stents have been tried as a mechanical method to maintain upper airway patency, particularly while medical therapy is being aggressively pursued. The cumulative experience with tracheal stents is not extensive enough to permit assessment of their long-term effects.

Sjögren's Syndrome

Sjögren's syndrome is a chronic inflammatory disease characterized by keratoconjunctivitis sicca and xerostomia (the sicca complex) (Delavanga et al, 1991; Doig et al, 1971; Fox et al, 1984; Moutsopoulos et al, 1980; Papathanasiou et al, 1986; Silver an Miller, 1990; Weisman and Calcaterra, 1978). Both primary (idiopathic) and secondary forms of the disorder exist. Over 90% of patients with primary Sjögren's syndrome are females; an association with HLA-B8 and HLA-DR3 histocompatibility antigens has been demonstrated. A secondary form of Sjögren's syndrome occurs most often in association with other collagen vascular diseases (Campbell et al, 1983). Secondary Sjögren's syndrome occurs most often in association with rheumatoid arthritis (10%-20% of patients with RA exhibit Sjögren's syndrome), but it can occur in a wide range of autoimmune or connective tissues disorders (Moutsopoulos et al, 1980). Secondary foms may be associated with HLA-DR4, but not HLA-B8 or HLA-DR3 (Moutsopoulos et al, 1980; Papathanasiou et al, 1986; Silver and Miller, 1990; Weisman and Calcaterra, 1978). Histopathologic features include a progressive destruction of salivary and lacrimal glands by lymphocytes and plasma cells, which may lead to fibrosis. This inflammatory/fibrotic process results in decreased production of saliva and tears, leading to dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca) in greater than 80% of cases. Twenty to 50% of cases have enlarged parotid glands (Campbell et al, 1983; Delavanga et al 1991; Doig et al, 1971; Fox et al, 1984; Moutsopoulos et al, 1980; Papathanasiou et al, 1986; Silver and Miller, 1990; Weisman and Calcaterra, 1978). Dryness may extend throughout the otolaryngologic region and may also involve the trachea (xerotrachea) and the lower respiratory tract. Other systemic manifestations of Sjögren's syndrome include dry skin, dry vaginal mucosa, and dryness of the external genitalia. The diffuse lymphocytic infiltration is primarily confined to the exocrine organs, but extraglandular involvement in kidneys, muscles, lungs, or reticuloednothelial system occurs in 20% to 30% of cases (Fox et al, 1984). An increased incidence of lymphoproliferative disorders (including malignant lymphoma) has also been observed (Campbell et al, 1983).

Diagnosis is made by demonstrating reduced amount of tearing (positive Schirmer's test or biomicroscopy), or a decrease in parotid gland flow. Biopsy of minor salivary glands of the lower lip permits histopathologic confirmation. The desiccation that occurs in Sjögren's syndrome can easily extend from the upper respiratory tract to the lower respiratory tract (Wiedemann and Matthay, 1989). Dryness and crusting of the vocal cords and vocal cord nodules may be seen. Tracheal dryness (xerotrachea) and erythema occurs in 20% to 30% of patients and may give rise to dry cough or hoarseness (Moutsopoulos et al, 1980). Dysphagia occurred in 30% of patients with Sjögren's syndrome, hoarseness in 22% according to one study (Doig et al, 1971). Bronchopulmonary involvement occurs in 40% to 70% of patients; in this context, cough, dyspnea, and pleuritic pain are the most common pulmonary symptoms (Delavanga et al, 1991; Wiedemann and Matthay, 1989). Infiltration of the bronchial mucosa with the chronic mononuclear inflammatory cellular infiltrate may result in chronic bronchitis, cough, and thick, tenacious phlegm (Wiedemann and Matthay, 1989). Chronic lymphocytic infiltration of the pulmonary parenchyma may lead to dyspnea, interstitial reticulonodular infiltrates on chest radiograph, and a restrictive ventilatory defect, with a reduced diffusion capacity for carbon monoxide (DLCO) on pulmonary function tests (Papathanasiou et al, 1986). An obstructive defect has been observed in 10% to 15% of patients with Sjögren's syndrome, which may reflect involvement of either small or large airways. Sjögren's syndrome may also involve the esophagus, resulting in dryness of the esophageal mucosa and

dysphagia. Esophageal dysmotility, upper esophageal webs, and esophageal strictures, although rare, have been described (Campbell et al, 1983). Treatment of Sjögren's syndrome is generally symptomatic, with increased vigilance for the development of malignancy. Treatment of associated collagen vascular diseases may ameliorate the symptoms of secondary Sjögren's syndrome. Systemic corticosteroids or immunosuppressive/cytotoxic agents should be reserved for severe systemic Sjögren's syndrome or for serious local complications (Standefer and Mattox, 1986.

Progressive Systemic Sclerosis

Scleroderma or progressive systemic sclerosis (PSS) is an autoimmune disease characterized by the progressive and abnormal deposition of collagen in the skin, small vessels, and organs. Dominant clinical features include Raynaud's phenomenon, sclerodactyly, and esophageal dysfunction, all of which are present in 70% to 90% of cases (Silver and Miller, 1990; Standefer and Mattox, 1986; Weisman and Calcaterra, 1978). High-titer antinuclear antibody can be demonstrated in nearly 100% of cases of PSS. Specific patterns of antinuclear antibody staining (ie, diffuse, centromeric, and nucleolar) may help distinguish between limited and diffuse forms of the disease. For example, a speckled pattern is very characteristic of PSS involving multiple organs (the diffuse variant); by contrast, the anti-centromere pattern has been associated with limited cutaneous scleroderma; antinucleolar patterns may be observed with either diffuse or overlap variants (Campbell et al, 1983; Silver and Miller, 1990; Standefer and Mattox, 1986; Weisman and Calcaterra, 1978). PSS is three to four times more common in females and most often begins between the ages of 30 and 60.

The disease is highly variable both in the extent of its involvement and in the course of its progression. Its salient histopathologic characteristics include excessive deposition of collagen, fibroblastic proliferation, obliteration of small vessels, and secondary hypertensive changes. A marked inflammatory component is usually absent; however, increased T lymphocytes, mononuclear phagocytes, and neutrophils have been demonstrated in skin, muscle, lung and other involved organs in some cases, suggesting that products of inflammatory cells may play a contributory role in the pathogenesis. The mechanism(s) responsible for the exuberant proliferation of collagen are not known, but appear not to involve either immune complexes or complement. Vascular insufficiency caused by obliteration of small arterioles and capillaries (principally as result of excessive collagen deposition) and fibrosis of involved organs may lead to a myriad of clinical manifestations, including systemic hypertension (from involvement of the renal arterioles), pulmonary hypertension (from involvement of pulmonary vessels), and ischemic necrosis of digits, gastrointestinal tract, heart, or other organs (Silver and Miller, 1990; Standefer and Mattox, 1986; Weisman and Calcaterra, 1978). Raynaud's phenomenon occurs in over 80% of cases and is often the earliest manifestation of the disease. Digital ulcerations, pitting, sclerodactyly, skin thickening, telangiectasis, loss of skin folds, and changes in pigmentation reflect loss of the cutaneous capillary bed as well as accumulation of collagen in the skin (Standefer and Mattox, 1986).

Physical findings in the skin of the face, hands, or feet may be a clue to the diagnosis, even in patients presenting with manifestations elsewhere. Head and neck involvement (principally cutaneous and esophageal) occurs in more than 80% of patients with scleroderma and may be the presenting feature ni 30% of patients (Campbell et al, 1983; Silver and Miller,

1990; Weisman and Calcaterra, 1978). Decreased opening of the mouth was noted in 20% of patients with PSS, neck stiffness in 13% in one study (Weisman and Calcaterra, 1978). The cardinal otolaryngologic features of PSS reflect esophageal involvement, which will be discussed later. Clinically evident cardiac manifestations (congestive heart failure, myocarditis, pericarditis) are recognized in only 10% of cases, but cardiac involvement has been demonstrated at necropsy in over 80% of cases (Silver and Miller, 1990; Standefer and Mattox, 1986; Weisman and Calcaterra, 1978). Renal involvement has been the leading cause of mortality in PSS, sometimes caused by renal failure or more commonly by hypertension related to renal arteriopathy. Patients exhibiting multiorgan involvement have a poorer prognosis and are at highest risk for rapid progression of disease. Isolated abnormalities of the trachea or upper airway do not occur. However, laryngeal or tracheal irritation may occur as a result of repetitive esophageal reflux. Lower respiratory tract involvement is a nearly invariable feature. Pulmonary involvement (both interstitial pulmonary fibrosis and pulmonary hypertension) have been demonstrated at necropsy in 80% to 100% of cases (Silver and Miller, 1990). Diffuse interstitial fibrosis complicates PSS in 60% to 80% of cases and is indistinguishable clinically, radiographically, and histologically from idiopathic pulmonary fibrosis except for a higher incidence of pleural involvement (5%-15%) in PSS (Silver and Miller, 1990; Weisman and Calcaterra, 1978). In this context, dyspnea, end-inspiratory bibasilar rales, interstitial/reticulonodular infiltrates on chest radiograps, and decreases in lung volumes and diffusing capacity (DLCO) on pulmonary function tests, are characteristic (Silver and Miller, 1990; Weisman and Calcaterra, 1978). A concomitant obstructive ventilatory defect may reflect peribronchial fibrosis. Initial clinical, radiographic, and physiologic parameters have limited prognostic value because the natural history of interstitial fibrosis complicated by PSS is variable. In most cases, the course is indolent, with inexorable decline in pulmonary function, ultimately resulting in respiratory failure over years. A more fulminant course, characterized by rapid, lethal respiratory failure over weeks to months has been described, but is rare. Five-year mortality from sclerodermatous lung involvement is 30% to 40% (Campbell et al, 1983; Silver and Miller, 1990; Standefer and Mattox, 1986; Weisman and Calcaterra, 1978). At necropsy, histopathology of the lung is dominated by broad bands of collagen, destruction of the alveolar architecture, and pulmonary hypertensive changes; an inflammatory component is usually absent or minimal (Silver and Miller, 1990; Weisman and Calcaterra, 1978). The presence of pulmonary hypertension or a DLCO of less than 40% predicted has been associated with a markedly increased mortality (Silver and Miller, 1990; Wiedemann and Matthay, 1989). Clinically evident pulmonary hypertension (with or without pulmonary fibrosis) occurs in 10% to 40% of cases, reflecting progressive obliteration of the vascular bed, and represents an important cause of mortality. The gastrointestinal tract is almost always involved in PSS; esophageal dysfunction is one of the classic manifestations of this disease. Deposition of fibrous tissue in the submucosa and muscularis of the esophagus, accompanied by smooth muscle atrophy, leads to dysmotility and atonia. Dysphagia, heartburn, and nausea are the most common presenting symptoms of esophageal disease, occurring in more than 50% of the patients (Standefer and Mattox, 1986). The dysphagia has been related to the absence of coordinated peristalsis and the loss of or decrease in esophageal waves. The lower esophageal sphincter is usually incompetent, which leads to recurring reflux. Potential complications stemming from recurring reflux include aspiration pneumonia and esophageal stricture.

Correlations between dysphagia and radiologic abnormalities are imperfect, but radiologic abnormalities (usually of the distal two-thirds of the esophagus) can be

demonstrated in more than 90% of patients with PSS. The classic radiologic finding is failure of the esophagus to empty without the assistance of gravity (Standefer and Mattox, 1986). The distal esophagus is often atonic, with decreased transit time, and dilatation of the proximal end and narrowing of the distal end of the esophagus with rigidity. Decreased peristalsis is relatively specific for clinical scleroderma, with loss of normal mucosal pattern. Dilatations at some level of the esophagus occur in approximately 50% of cases; strictures, in 6% (Standefer and Mattox, 1986). In light of the high prevalence of esophageal involvement in PSS, most experts advise objective assessment of esophageal function to include manometrics or cine-esophagrams in all patients. Small bowel and colon involvement occurs in 10% to 20% of cases of PSS and may manifest as vomiting, abdominal distention, pain, or diarrhea (Campbell et al, 1983; Standefer and Mattox, 1986). Malabsorption secondary to bacterial overgrowth may occur. Paralytic ileus with incomplete obstruction may result from large and small bowel involvement. In summary, the clinical features of PSS are protean and typically involve multiple organs; multiorgan involvement has been associated with an increased mortality. However, a subgroup of patients have pathologic changes that are limited to the skin; these patients have been characterized as the CREST variant (subcutaneous calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia). Patients with CREST variant have a lower incidence of visceral involvement and a less protracted course as compared to patients with diffuse symptomatology.

Unfortunately, no therapy has been shown to influence the course of PSS. Corticosteroids, immunosuppressive/cytotoxic agents, colchicine, cyclosporine, and vasodilators have been tried, but are of unproven efficacy. Therapy with D-penicillamine has been associated with a decrease in the deterioration of pulmonary function in uncontrolled studies, but additional prospective studies are required to determine the role (if any) of D-penicillamine in PSS. Supportive therapy for gastrointestinal disease (antireflux regimens, H2 blockers, antacids, smooth muscle stimulants, etc) may afford symptomatic relief and reduce the incidence of complications. Esophageal dilatation or surgical correction may be considered for patients with severe esophageal strictures or stenosis refractory to medical therapy.

Wegener's Granulomatosis

Wegener's granulomatosis (WG) is a necrotizing granulomatous vasculitis that has a striking affinity for the upper and lower respiratory tracts and may result in tracheal or bronchial stenosis. WG typically affects adults, with a peak incidence in the fourth and fifth decades of life; rare cases have been described in children (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). In the classical form, WG is a systemic disease in which a triad of upper respiratory tract, lower respiratory tract (tracheobronchial tree, lung), and renal involvement is evident, associated with varying degrees of disseminated angiitis (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). However, a limited form of the disease involving only one or two organ systems may occur. Diagnosis such cases may be difficult. The salient histopathologic features include a necrotizing vasculitis involving small vessels (capillaries, arterioles, venules) associated with pronounced geographic necrosis and a mixed inflammatory cell infiltrate. Although well-defined sarcoid-like granulomas are rarely present, scattered multinucleated giand cells or organized collections of histocytes impart a granulomatous character to the lesion (DeRemee, 1991; Fauci et al, 1983). However, the full spectrum of histologic features may not be present on individual biopsy specimens, particularly if superficial mucosal pieces are obtained. In fact, nonspecific inflammatory

changes associated with necrosis are often the most prominent features; such changes should prompt more aggressive histologic and laboratory tests to substantiate the diagnosis.

Pulmonary involvement occurs in 60% to 90% of cases; multiple, nodular mass densities (one quarter of which cavitate) are characteristic, but fleeting alveolar infiltrates, single-mass lesions, atelectasis, pleural effusions, and (rarely) diffuse alveolar hemorrhage may occur (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). Renal involvement occurs in 60% to 85% of cases (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). Abnormalities on urinalysis (proteinuria, microscopic hematuria, red cell casts) usually precede abnormalities in renal function. Clinically overt renal failure is apparent at the time of initial diagnosis in fewer than 20% of cases, but deteriorating renal function may develop within weeks or months of the onset of the renal lesion and is a major cause of death (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). Percutaneous needle biopsy of the kidney can be invaluable in supporting the diagnosis. However, the cardinal features of WG at extrarenal sites (ie, granulomata, necrosis, vasculitis) are rarely observed in renal tissue. Rather, the earliest renal lesion is a segmental glomerulonephritis; with more fulminant disease, a rapidly progressive glomerulonephritis with crescent formation may be evident. These histologic features, although characteristic, are in no way specific for WG. Thus, biopsies of extrarenal sites are usually necessary to substantiate the diagnosis histologically. Cutaneous involvement occurs in 40% to 50% of cases; a myriad of lesions have been described, including ulcerations, papules, nodules, and pustules; biopsy most often demonstrates nonspecific findings of leukocytoclastic vasculitis although the full spectrum of vasculitis, granulomas, and necrosis may be present in some cases (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983).

Central or peripheral nervous system manifestations are present in 20% to 30% of cases and may be devastating (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). Mononeuritis multiplex or polyneuritis are most characteristic but a wide gamut of complications including focal deficits (due to cerebral infarction), vasculitis, hemorrhage, mass lesions, cranial nerve palsies, diabetes insipidus, and paresis (due to spinal cord involvement) have been described (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). Ocular involvement occurs in 20% to 40% of cases and may manifest as superficial conjunctivitis, episcleritis, orbital mass lesions, proptosis, or primary retinal or optic nerve vasculitis (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). Ocular complications may result in permanent visual loss unless aggressively treated, so prompt consultation with an ophthalmologist is essential. A slitlamp examination, radiographs, and tomographic scans of the orbit and sinuses may be necessary to delineate the site and nature of ocular involvement. Constitutional symptoms (fever, malaise, weight loss, fatigue) occur in 15% to 30% of cases (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). Although virtually any organ can be affected, clinically evident cardiac or gastrointestinal tract involvement occurs in fewer than 5% of patients (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983).

Upper respiratory tract involvement (sinuses, ears, orbit, oropharynx, nasopharynx) occurs in more than 85% of cases and often dominates in the early phases of the disorder (Cupps and Fauci, 1981; DeRemee, 1991; Devaney et al, 1990; Fauci et al, 1983; McDonald et al, 1982). Sinus pain or obstructive symptoms occur in more than two thirds of patients at the time of presentation, and abnormalities on sinus radiographs (thickening, clouding, and,

occasionally, bony destruction) can be demonstrated in over 90% of patients (Cupps and Fauci, 1981; DeRemee, 1991; Devaney et al, 1990; Fauci et al, 1983; McDonald et al, 1982). Nasal manifestations occur in 60% to 80% of patients and include persistent rhinorrhea, nasal crusting, pain, epistaxis, congestion, septal perforation, and nasal ulcers (Cupps and Fauci, 1981; DeRemee, 1991; Devaney et al, 1990; Fauci et al, 1983; McDonald et al, 1982). Saddle nose deformity, resulting from destruction of the nasal cartilage, occurs in up to 105 to 15% of cases. In contrast to lethal midline granuloma syndrome, (to be discussed later), WG rarely destroys the palate, alveolar bone, or soft tissues of the face (DeRemee, 1991; Devaney et al, 1990; Fauci et al, 1983; McDonald et al, 1982). Otologic manifestations (otalgia, otitis media, tinnitus, and hearing loss) occur in 25% to 40% of patients (DeRemee, 1991; Devaney et al, 1990; Fauci et al, 1983; McDonald et al, 1982). Hearing loss may reflect vasculitis of the cochlear artery or perforation of the tympanic membrane or destruction of the middle ear from chronic otitis media or mastoiditis. Granulomatous involvement of the oropharynx or larynx may result in hoarseness, sore throat, or inspiratory stridor from upper airway obstruction (DeRemee, 1991; Devaney et al, 1990; Eagelton et al, 1979; Flye et al, 1979; McDonald et al, 1982).

A careful otolaryngoscopic exam is mandatory to look for mucosal ulcerations or granulomatous inflammatory lesions; any suspicious lesions should be biopsied. Unfortunately, histologic confirmation of the diagnosis by superficial biopsy of nasal or oropharyngeal lesions is frequently difficult. In one series of 126 biopsies from nasal or oropharyngeal lesions in 70 patients with WG, the combination of vasculitis, necrosis, and granulomatous inflammation was present in only 16% of specimens (Devaney et al, 1990). Vasculitis and granulomatous inflammation were observed in 21%; vasculitis and necrosis in 23%. The most frequently identified feature was scattered giant cells, which was seen in 42% of biopsies. The yield of diagnostic biopsies varied according to the site. At least one histologic feature (vasculitis, necrosis, granulomatous inflammation) was present in 55% of biopsies from the paranasal sinuses, whereas these features were observed in only 20% and 18% of biopsies from the nose and larynx respectively. Thus, the majority of head and neck biopsies show only nonspecific findings of chronic inflammation and necrosis; in such cases, biopsies of additional sites (or deeper biopsies) may be required to substantiate the diagnosis. Serial sections or deeper cuts of existing pathologic specimens may occasionally be diagnostic.

WG involving the trachea or tracheobronchial tree occurs in 10% to 20% of cases and may give rise to hoarseness, dyspnea, stridor, and progressive airway obstruction (DeRemee, 1991; Devaney et al, 1990; Fauci et al, 1983; McDonald et al, 1982). For reasons that are not clear, over 90% of cases of tracheal stenosis complicating WG have occurred in females even though WG occurs equally in males and females (DeRemee, 1991; Devaney et al, 1990; McDonald et al, 1982). Sinus or nasal symptoms are present concomitantly in more than 80% of cases; tracheal symptoms typically develop months or years after WG has been documented in other sites (DeRemee, 1991; Devaney et al, 1990; McDonald et al, 1982). However, tracheal obstruction/stenosis may be the presenting feature of the disease or the first manifestation of relapse. Thus, aggressive evaluation of hoarseness or unexplained dyspnea in a patient with known or suspected WG is necessary to rule out this complication. Flow loop studies may be helpful, in that truncation of the inspiratory limb (or of both the inspiratory and the expiratory limb) may suggest upper airway obstruction (Kryger et al, 1976; Rotman et al, 1975) (Figs. 125-3, A and B). Soft-tissue films of the neck or AP tomograms of the trachea (or bronchi) may be useful to better delineate the site and extent of stenosis.

We have foun computed tomographic scans to be less helpful unless thin sections are obtained, because the section do not parallel the course of the trachea. Although radiographic techniques are helpful, we believe that direct endoscopic inspection (laryngoscopy, flexible bronchoscopy) is more appropriate to assess the extent of tracheobronchial pathology and mucosal inflammation. Endoscopic and radiographic techniques are complementary and sequential studies may provide reproducible objective parameters to follow the course of the disease. Tracheal involvement is typically limited to the subglottic area; on laryngoscopic examination, a discrete area of reddish, friable circumferential narrowing in the trachea just below the cords and extending for no more than 3 to 5 cm can be appreciated (DeRemee, 1991; Devaney et al, 1990; McDonald et al, 1982). However, more diffuse involvement leading to stenosis or narrowing of the distal trachea or major bronchi from diffuse mucosal edema and granulomatous inflammation may also occur (Fig. 125-4). Reddish, friable mucosa and exuberant granulation tissue may lead to narrowing, obliteration, and stenosis of mainstem or lobar bronchi (Eagelton et al, 1979; Flye et al, 1979). The gross appearance is important to document; biopsies of the involved bronchial mucosa are sometimes helpful, but more commonly demonstrate only nonspecific changes of inflammation and edema.

Owing to the potentially life-threatening nature of tracheobronchial stenosis, aggressive therapy is essential. In most cases, satisfactory results can be achieved with conventional pharmacologic therapy employing cyclophosphamide and corticosteroids. However, for severe or progressive stenosis, urgent tracheostomy may be required because the effects of medical therapy may be delayed for 1 to 3 weeks. For patients with severe tracheal stenosis or bronchostenosis that is refractory to conventional doses of therapy, we have used pulse methylprednisolone (1 g daily for 3 days, followed by a taper) with anecdotal success. Alternative surgical techniques such as tracheal/bronchial dilatation, stents, or tracheal/bronchial reconstruction have been successfully performed on patients with severe tracheal or bronchial stenosis refractory to medial therapy (Eagelton et al, 1979; Fauci et al, 1983; Flye et al, 1979; McDonald et al, 1982). However, in the face of active inflammation, vasculitis, and necrosis, surgical complications and poor healing at anastomotic sites may be problematic; further, progression of the vasculitic lesion has been described following operation. In light of these concerns, we recommend deferring surgery whenever possible until the outcome of medical therapy is known.

Routine laboratory studies are of limited value in the diagnosis of WG but may be helpful in follow-up. Elevations in the Westergren sedimentation rate (ESR) or C-reactive protein (CRP) occur in more than 80% of cases and correlate well with disease activity in most cases (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). Unfortunately, neither of these tests is specific; these tests may also yield elevated rates during intercurrent infections or associated illnesses. Recently, IgG antibodies that react to cytoplasmic components of normal blood neutrophils and monocytes have been identified in sera of patients with active WG, (Cohen et al, 1989; Falk and Jennette, 1988; Jennette and Falk, 1990; Nolle et al, 1989). Circulating antineutrophil cytoplasmic antibodies (ANCA) have been observed in over 90 percent of patients with active generalized WG, but in only 50 to 70 percent of patients with limited, regional disease (Cohen et al, 1989; Falk and Jennete, 1988; Jennette and Falk, 1990; Nolle et al, 1989). Titers of ANCA correlate with activity of disease better than ESR or CRP, and are not influenced by intercurrent infections. However, persistently positive ANCA tests have been reported in 10% to 40% of patients in complete remission (Cohen et al, 1989; Falk and Jennete, 1988; Jennette and Falk, 1990; Nolle et al,

1989), so changes in titer are more valuable in predicting disease activity than a single titer in isolation. The sensitivity and specificity of ANCA has been variable among centers. Perinuclear or nuclear staining patterns may be observed on immunofluorescent studies with connective tissue diseases, idiopathic glomerulonephritis, and other systemic vasculitides distinct from WG (Falk and Jennete, 1988; Jennette and Falk, 1990; Nolle et al, 1989); thus, this pattern is not specific. However, focal granulat intracytoplasmic immunofluorescence has been essociated with specificities exceeding 90% (Cohen et al, 1989; Falk and Jennette, 1988; Jennette and Falk, 1990; Nolle et al, 1989). Although the clinical application of serum ANCA is controversial, we believe that this test is the most promising of the laboratory markers available in the staging of disease activity in WG. Serial titers may be helpful in differentiating relapse from infection in patients with recurrent symptoms, and may guide therapy. Further, a positive ANCA may support the diagnosis of WG in patients exhibiting compatible clinical features but in whom the classical histopathologic features are lacking. We attempt to establish a histologic diagnosis in virtually all cases, but will accept high-titer ANCA as sufficient evidence to initiate therapy in patients with a rapidly progressing course and no easily accessible site to biopsy.

Oral cyclophosphamide (CTX) (1-2 mg/kg/day) in conjunction with corticosteroids is the treatment of choice for WG (Fauci et al, 1983). Remissions have been achieved in 70% to 94% of cases; relapses occur in 20% to 30% of patients as the regimen is tapered or discontinued, but renistitution of therapy is usually efficacious (DeRemee, 1991; Fauci et al, 1983). The dose of CTX may need to be modified to maintain acceptable blood counts (particularly a leukocyte count that is greater than $3000/mm^3$). Although the dosage of corticosteroid needs to be individualized according to the clinical response and presence or absence of side effects, we usually initiate therapy with prednisone 60 to 80 mg/day for 2 to 4 weeks and taper by 10-mg decrements every 1 to 2 weeks for the first 2 months. At that point, we convert to an alternate-day regimen (eg, 60 mg q.o.d.) and thereafter follow a more gradual taper (by 10-mg decrements every 1-3 months). Cyclophosphamide should be continued for a minimum of 1 year after a complete and continuous remission has been achieved because unacceptably high rates of relapse and long-term sequelae have been observed with short-course therapy (4-6 months) (Campbell et al, 1983; Kovarsky, 1984; Standefer and Mattox, 1986). More prolonged therapy may be required for patients exhibiting persistently active or recrudescent disease. Data assessing high-dose intravenous (pulse) CTX for WG is limited. However, in one recent study, pulse CTX plus prednisone induced remissions in 13 of 14 patients with WG, but relapses occurred in 11 patients (79%) (Hoffman et al, 1990). Although pulse CTX may be less toxic than oral CTX, the high relapse rate with pulse CTX argues against its use as primary therapy for WG. Unfortunately, toxicity attributable to CTX (eg, hemorrhagic cystitis, bone marrow suppression, induction of neoplasia, etc) may be substantial. Serious hemorrhagic cystitis complicates oral CTX use ni 3% to 5% of cases and warrants discontinuation of therapy (Cupps and Fauci, 1981; DeRemee, 1991; Fauci et al, 1983). In such cases, we substitute chlorambucil (4-12 mg/day orally) or azathioprine (1-3 mg/kg/day). We prefer chlorambucil when the disease is active because we believe this is more potent in controlling the disease than azathioprine. However, axathioprine is less toxic than chlorambucil and may be used to maintain remissions in patients who have no clinical evidence for active disease (DeRemee, 1991; Fauci et al, 1983).

More recently, trimethoprim/sulfamethoxazole (T/S) has been used with anecdotal success in the treatment of WG (DeRemee, 1988; Israel, 1988). After noticing fortuitous remissions of WG following antimicrobial therapy for concomitant urosepsis, DeRemee (1988) added oral T/S to a previously failing regimen of CTX/prednisone in 31 patients, and observed 26 favorable responses. Late relapses were observed in only 4 patients in this group. More importantly, T/S alone was administered as *initial* therapy for WG in 15 patients with limited disease; in this context, 14 responded, 3 of whom later relapsed. It should be emphasized that this treatment approach was restricted to a highly selective population of patients (usually those with limited disease and representing only 12% of patients with WG seen at the Mayo Clinic). Although controlled prospective studies have not been done, other investigators have also noted favorable responses to T/S (Israel, 1988). The mechanism of action of T/S is not known; antimicrobial, immunosuppressive, or antiinflammatory effects, alone or in combination, may be operative. Several lines of evidence suggest that uncontrolled infection (typically in the upper respiratory tract) may play an important role in the pathogenesis of WG. Chronic sinusitis, otitis, or upper respiratory tract infections often antedate the development of WG; relapses of WG may occur concomitant with intercurrent infections. It is plausible that persistent bacterial (or viral) infections may stimulate antibody formation, leading to the formation of circulating antigen-antibody immune complexes, eliciting an inflammatory response. These data are intriguing, but we are reluctant to recommend T/S as first-line therapy for severe or progressive WG. Additional studies are required to define the role (if any) of T/S in *selected* patients with mild or limited disease or as adjunctive therapy in patients on whom conventional treatment with CTX/prednisone has failed.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LYG) is a rare syndrome first described in 1972. It has clinical, radiographic, and histologic features that overlap with WG, but also display similarities to a malignant lymphoproliferative disorder (Liebow et al, 1972). The initial defining histologic features include an angiocentric, angiodestructive process with extensive necrosis and a polymorphous infiltrate composed of mixed inflammatory cells and foci of atypical (but not frankly malignant) lymphoid cells (Liebow et al, 1972). Occasional multinucleated giant cells or histiocytes imparted a granulomatous character to the lesion, but sarcoidlike granulomas were not a feature. LYG has been grouped with Wegener's granulomatosis and other vasculitides, but the intense inflammatory cellular infiltrate in LYG surrounds but does not destroy vessel walls, distinguishing LYG from a true vasculitis (Katzenstein et al, 1979). In addition, many of the histologic characteristics of LYG (necrosis, small-vessel inflammation) may be observed in lymphoma (Colby and Carrington, 1982; Jaffe and Travis, 1991; Jaffe et al, 1989). Thirty to 50% of patients with LYG in early studies developed lymphoma (Fauci et al, 1982; Katzenstein et al, 1979; Liebow et al, 1972) and foci of LYG and unequivocal malignant lymphoma often coexist in individual patients (Colby and Carrington, 1982). More recent studies employing sophisticated molecular biologic techniques (eg, immunohistochemical stains, monoclonal antibodies, T-cell gene rearrangements) have determined that most lesions characterized as LYG represent a spectrum of lymphoproliferative disorders with a predilection for vascular invasion; most cases have been T-cell lymphomas but polyclonal proliferations may also occur (Jaffe and Travis, 1991; Jaffe et al, 1989).

Clinical manifestations of LYG are protean. In early reports of LYG, pulmonary, constitutional, and central nervous system (CNS) manifestations dominated (Fauci et al, 1982; Katzenstein et al, 1979; Liebow et al, 1972). Lung involvement was nearly invariable and was an important contributory cause of death; chest radiographs typically demonstrated multiple nodular densities or infiltrates (Fauci et al, 1982; Katzenstein et al, 1979; Liebow et al, 1972). Clinically evident renal involvement was notably absent. CNS manifestations (focal mass lesions or vasculitis) occur in 10% to 30% of cases, and may result in devastating sequelae (Katzenstein et al, 1979; Liebow et al, 1972). Cutaneous or subcutaneous lesions have been noted in 30% to 50% of cases; liver, spleen, or lymph node involvement, in 5% to 15% (Fauci et al, 1982; Katzenstein et al, 1979; Liebow et al, 1972). It should be emphasized that in the initial reports of LYG, (which were derived from histopathologic material referred to renowned pulmonary pathologists), upper airway involvement was not emphasized (Katzenstein et al, 1979; Liebow et al, 1972). Subsequently, DeRemee et al (1978) noted that the histologic features of polymorphic reticulosis (PMR), a necrotizing "lymphoma-like" disease with a predilection for the upper respiratory tract, were identical to those observed in LYG. As originally described, PMR referred to destructive, ulcerating lesions involving the upper airway (clinically consistent with lethal midline granuloma) associated with an atypical lymphoid infiltrate invading blood vessels, and extensive parenchymal necrosis (Costa and Delacretaz, 1986; McDonald et al, 1981). Midline malignant reticulosis (MMR) and Stewart's midline granuloma are synonymous with PMR (Costa and Delacretaz, 1986; Crissman et al, 1982; Harrison, 1987; Pickens and Madica, 1989). McDonald et al (1981) reviewed 40 patients with PMR seen at the Mayo Clinic, 28 of whom exhibited upper airway involvement. Ulcerating, destructive lesions of the nose, pharynx, and adjacent paranasal sinuses were the predominant manifestations; extension to the orbit was noted in several patients but (in contrast to WG), none had otologic involvement. Only one had tracheal stenosis. Fifteen had lung involvement, usally in the form of nodular mass densities on chest radiograph; two had mass lesions in the kidney, but non had glomerulonephritis. Skin lesions were present in ten cases; two had brain involvement. Widespread dissemination to liver, spleen, and gastrointestinal tract was noted in some patients. Radiation therapy was highly effective when lesions were confined to the upper airway; in this context, 15 of 20 were alive and well; 4 ied of unrelated causes and one was lost to follow-up. By contrast, all patients with disseminated disease died despite therapy with corticosteroids, cytotoxic drugs, or both. Evolution to malignant lymphoma was noted in four patients. Current concepts suggest that PMR, MMR, and LYG are synonymous terms that represent a spectrum of angiocentric lymphoproliferative disorders, including malignant lymphoma (Chott et al, 1988; Costa and Delacretaz, 1986; Crissman et al, 1982; DeRemee et al, 1978; Harrison, 1987; Ishii et al, 1982; Jaffe and Travis, 1991; Jaffe et al, 1989; McDonald et al, 1981; Pickens et al, 1989; Ratech et al, 1989). No distinctive or consistent laboratory aberrations have been noted in LYG/PMR. Anemia may occur but is rarely severe. The ESR is usually elevated, but does not correlate with the activity or extent of the disease; renal function and urinalysis are normal (Katzenstein et al, 1979; Liebow et al, 1972).

In view of the rarity of these disorders (even large referral centers may see only one or two cases every 2 to 3 years), and the differing terminology used in the literature, the precise incidence of specific organ involvement in LYG is not clear. The striking predilection for involvement of the upper airway noted in published series of PMR probably reflects a selection bias, because many of these patients had been referred to an otolaryngologist for destructive lesions of the upper respiratory tract (DeRemee et al, 1978; McDonald et al,

1981). Similarly, early reports citing a low incidence of upper airway manifestations in LYG were retrospective reviews of cases referred to pulmonary pathologists for histopathologic evaluation (Katzenstein et al, 1979; Liebow et al, 1972). Thus, it is likely that otolaryngeal manifestations may have been overlooked.

Treatment strategies continue to evolve. In an early study, Fauci et al (1982) reported 7 complete and sustained (duration of follow-up exceeded 5 years) remissions among 13 patients with LYG treated with oral cyclophosphamide and prednisone; malignant lymphoma was documented at necropsy in all but one of the fatalities. Although it is plausible that oral CTX/prednisone may have a role in selected cases with limited, early disease and no evidence for malignancy, most investigators have found this form of therapy to be disappointing, particularly once the disease has disseminated (DeRemee et al, 1978; Jaffe and Travis, 1991; Jaffe et al, 1989; Katzenstein et al, 1989; McDonald et al, 1981). In light of the relationship of LYG to malignant lymphoma, an aggressive investigation to include immunologic techniques, monoclonal antibodies, etc, is warranted to rule out malignancy in all cases of LYG. When initial biopsies fail to demonstrate malignancy, additional biopsies of clinically involved sites should be performed. Although optimal therapy is controversial, we believe that aggressive combination chemotherapy for lymphoma is indicated for most cases. Unfortunately, success rates have been low, particularly when the disease has disseminated (DeRemee et al, 1978; Jaffe and Travis, 1991; Jaffe et al, 1989; Katzenstein et al, 1989; McDonald et al, 1981). Radiation therapy may be adequate in cases with limited disease localized to the upper airway (McDonald et al, 1981).

Lethal Midline Granuloma

Lethal midline granuloma (LMG) was originally used to describe a clinical syndrome associated with unremitting, slowly progressive ulceration and erosion of the central face, nose, paranasal sinuses, palate, and deeper structures (Costa and Delacretaz, 1986; Crissman et al, 1982; Harrison, 1987; Pickens and Modica, 1989). The process may be severely mutilating - soft tissue, cartilage, bone, and contiguous structures including the orbit, larynx, and trachea may be destroyed (Costa and Delacretaz, 1986; Crissman et al, 1982; Harrison, 1987; Pickens and Modica, 1989). Systemic involvement is absent, but constitutional symptoms (eg, fever, malaise, weight loss, fatigue) are common. The term *midline granuloma* is confusing because a diverse group of disorders including Wegener's granulomatosis, polymorphic reticulosis/lymphomatoid granulomatosis, lymphoma, and specific bacterial, fungal, mycobacterial, and protozoan infections (leishmaniasis) may cause an identical clinical syndrome (Costa and Delacretaz, 1986; Crissman et al, 1982; Harrison, 1987; Pickens and Modica, 1989). The nomenclature has been further complicated by additional terms (ie, malignant midline granulomatosis, nonhealing midline granuloma of the Stewart type, and midfacial necrotizing lesions) that have been applied to refer to a constellation of disorders with similar clinical features (Costa and Delacretaz, 1986; Crissman et al, 1982; Pickens and Modica, 1989). The early reports of lethal midline granuloma antedated the availability of immunohistochemical and monoclonal antibody techniques that are invaluable in the diagnosis of lymphoproliferative malignancies. With the use of these newer techniques, a specific diagnosis (eg, malignant lymphoma, LYG, monoclonal T- or B-cell proliferations) can usually be made in what historically might have been termed MLG. Thus, this term is usually not seen in more recent medical literature.

Nasopharyngeal Lymphoma

Malignant lymphomas involving the nasopharynx have undoubtedly been categorized in previous publications as lethal midline granuloma, polymorphic reticulosis, and lymphomatoid granulomatosis, because the clinical histopathologic features of these entities overlap extensively (Chott et al, 1988; Costa and Delacretaz, 1986; Crissman et al, 1982; DeRemee et al, 1978; Harrison, 1987; Ishii et al, 1982; Jaffe and Travis, 1991; Jaffe et al, 1989; McDonald et al, 1981; Pickens and Modica, 1989; Ratech et al, 1989). Nasopharyngeal lymphomas are much more prevalent in Japan than in Western countries (Ishii et al, 1982). Nasal obstruction, swelling, epistaxis, pain, or sinusitis are the most common presenting features; extension to the oropharynx and hypopharynx may also occur. The destructive nature of nasal/pharyngeal lymphomas results in extensive necrosis, local inflammation, surface crusting, and ulcer (Chott et al, 1988; Harrison, 1987; Ishii et al, 1982; Ratech et al, 1989).

The diagnosis may be difficult to make because the extensive necrosis and intense inflammatory reaction may obscure the true nature of the process; the demonstration of sheets of neoplastic lymphoid cells establishes the diagnosis (Chott et al, 1988; Harrison, 1987; Ishii et al, 1982; Ratech et al, 1989). Multiple biopsies, including generous sampling of deeper areas, may be necessary to identify the diagnostic neoplastic cell line. When conventional histologic features are not definitive, immunohistochemical and monoclonal antibody techniques may substantiate the diagnosis of malignant lymphoma (Chott et al, 1988; Ishii et al, 1982; Jaffe and Travis, 1991; Jaffe et al, 1989; Ratech et al, 1989). Several investigators have noted the histopathologic similarity of nasopharyngeal lymphoma, lymphomatoid granulomatosis (LYG), and lethal midline granuloma (LMG) syndrome (Chott et al, 1988; Costa and Delacretaz, 1986; Crissman et al, 1982; DeRemee et al, 1978; Harrison, 1987; Ishii et al, 1982; McDonald et al, 1981; Pickens and Modica, 1989; Ratech et al, 1989). Chott et al (1988) described seven patients with ulcerative, destructive lesions of the upper airway and face (clinically consistent with LMG), five of whom had involvement of distant sites. Histologically, a pronounced infiltrate of atypical lymphoid cells surrounding blood vessels, associated with extensive necrosis, was characteristic; three of the patients had previously been diagnosed as LYG, and had failed therapy with CTX and corticosteroids as proposed by Fauci et al (1982). Monoclonal antibody profiles were consistent with T-cell lymphomas in all seven cases. Ishii et al (1982) reported six cases of angiocentric peripheral T-cell lymphomas presenting clinically as midline granuloma; five had pulmonary involvement and all had cutaneous nodules. A prominent histologic feature in these cases was infiltration of vascular walls by neoplastic cells. These clinical, radiographic, and histologic features are indistinguishable from LYG. Ratech et al (1989) noted that 13 of 20 malignant lymphomas arising in the nose, paranasal sinuses, and hard palate exhibited morphologic features consistent with T-cell lymphomas; necrosis and an angiocentric growth pattern were observed in nine and eight cases, respectively. These various studies emphasize the angiocentricity and angiodestructive nature of lymphomas arising in the head and neck, features also observed in LYG. Prognosis for nasopharyngeal lymphoma depends upon the extent of disease at the time of presentation. Aggressive radiation therapy is recommended when the disease is localized, with 5-year survival rates of 30% to 70% (Chott et al, 1988; Harrison, 1987; Ishii et al, 1982; Ratech et al, 1989). Once dissemination has occurred, chemotherapy is advised, but results have generally been poor (Chott et al, 1988; Harrison, 1987; Ishii et al, 1982; Ratech et al, 1989).

Idiopathic Midline Destructive Disease

With aggressive biopsies and the use of ancillary immunologic techniques (eg, immunohistochemical and monoclonal antibody analysis), a specific diagnosis of WG, LYG, or angiocentric lymphoma can usually be made in most cases presenting with "midline granuloma syndrome" (Chott et al, 1988; Costa and Delacretaz, 1986; Crissman et al, 1982; Harrison, 1987; Ishii et al, 1982; Pickens and Modica, 1989; Ratech et al, 1989). However, rare patients exhibit relentlessly progressive, locally destructive, ulcerating lesions that are confined to the midfacial areas and upper airway but lack the histologic features of WG, LYG, or lymphoma after repeated biopsies and meticulous investigation. The term *idiopathic midline destructive disease (IMDD)* is used to refer to this rare subset of patients (Tsokos et al, 1982). By definition, involvement outside the upper respiratory tract does not occur in IMDD. The defining features of this disorder were delineated in a classic paper summarizing 11 patients (Tsokos et al, 1982). Biopsies demonstrated acute and chronic inflammation and necrosis; malignant or atypical cells were invariably absent. Perivascular infiltrates were evident in five cases, but frank vasculitis and fibrinoid necrosis, which are cardinal features of WG, were never observed in IMDD. Granulomata were seen in only 1 of the 11 cases. Pansinusitis and destructive lesions of the nasal septum, palate and facial soft tissues were characteristic; extension to the larynx or trachea occurred in two and one patients respectively (Tsokos et al, 1982). Subglottic stenosis was also described in one patient with IMDD reported by Crissman et al (1982) although this patient also had previously received local radiation therapy. The diagnosis of IMDD is clearly one of exclusion and should only be made when alternative disorders have been reliably excluded after repeated biopsies, serologic studies (including ANCA), and prolonged follow-up to exclude dissemination or evolution into a specific alternative disorder. In one series of 13 cases of "midline granuloma syndrome", IMDD was diagnosed in only one patient; alternative diagnoses were established in the remaining cases (Crissman et al, 1982). Intensive radiation therapy is the treatment of choice for IMDD. High-dose radiotherapy (4000-6000 rads) induced remissions (nine complete; two partial) in all 11 cases reported by Tsokos et al (1982).

Fibrosing Mediastinitis

Fibrosing mediastinitis (also termed *granulomatous, collagenous,* or *sclerosing mediastinitis*) is an extremely rare disorder in which exuberant proliferation of fibrous and connective tissue compresses and encases vital structures within the mediastinum. Mediastinal lymphadenopathy is invariably present, but clinical manifestations of fibrosing mediastinitis are a result of an exaggerated granulomatous and fibrotic response beyond the confines of lymph nodes (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). This fibrotic process may continue to accrue over several years, invading, encasing, and obliterating mediastinal vessels (superior vena cava, pulmonary arteries, and veins), esophagus, trachea, and major bronchi (Dines et al, 1979; Doty et al, 1990; Dunn et al, 1990; Garrett and Roper, 1986; Goodwin et al, 1972; James et al, 1980; Loyd et al, 1988; Rholl et al, 1985; Urschel et al, 1990; Weinstein et al, 1983). Most patients present between ages 20 and 40; the process is usually indolent, and progresses slowly over months or years (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988). In a recent review of 71 patients with fibrosing mediastinitis (21 of whom died), the interval between onset of symptoms and death was 5.9 years (Loyd et al, 1988). Because of the insidious nature and rarity of the process, diagnosis is often delayed. Fibrosing mediastinitis

occurs as a late sequelae of mediastinal adenitis and represents an exaggerated (and aberrant) host response to persistent antigen released from caseous mediastinal or hilar nodes or intrapulmonary foci (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). *Histoplasma capsulatum* has been implicated in 50% to 70% of cases, but occasional cases attributable to *Mycobacterium tuberculosis, Coccidioides immitis, Aspergillus flavus,* and other fungi have been described (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). It is likely that most previously published "idiopathic" cases reflect previous infection with histoplasmosis, because serologic studies for fungi were often not performed (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). The pathogenic mechanisms responsible for the exuberant fibrotic response are not clear; fewer than 1% of patients with histoplasmosis or mycobacteriosis develop fibrosing mediastinitis and even large referral centers see no more than one or two cases every 2 to 3 years (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990).

Clinical features and prognosis differs markedly according to the site, nature, and intensity of the fibrotic/granulomatous pathologic reaction and its relationship to vital structures. The most common lymph node groups involved are in the right paratracheal area, anterior-superior mediastinum, and subcarinal regions (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; James et al, 1980; Loyd et al, 1988; Urschel et al, 1990). Fibrosis related to the right paratracheal lymph node chain may cause obstruction of the superior vena cava (SVC), azygous vein, or right upper lobe bronchus; subcarinal nodal fibrosis can extend posteriorly to involve the esophagus, anteriorly to constrict pulmonary veins (and rarely pericardium) or laterally to the pulmonary arteries, and bronchi; involvement of hilar nodes typically affects pulmonary arteries and bronchi (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). Subcarinal involvement and pulmonary vascular obliteration has been associated with an increased mortality (Dunn et al, 1990; Loyd et al, 1988). Both airways and vessels are involved in approximately 50% of cases of fibrosing mediastinitis; isolated involvement of the airways or vessels occurs in 20% and 30% of cases, respectively (Loyd et al, 1988). Occlusion of pulmonary veins or arteries may lead to congestive heart failure, pulmonary emboli, and pulmonary hypertension (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). Pulmonary arterial involvement is among the most serious complication, as obstruction is usually bilateral and surgical correction is often not feasible (Dunn et al, 1990; Garrett and Roper, 1986; Loyd et al, 1988). Pulmonary venous obstruction has been described in 5% to 18% of cases and usually presents with cough, dyspnea, or hemoptysis (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). Pulmonary hypertension is usually present concomitantly. Narrowing or compression of the trachea occurs in 15% to 30% of cases, usually in association with other regional manifestations; tracheal obstruction may rarely occur as an isolate feature (James et al, 1980). Tracheoesophageal fistulas have also been described (Dunn et al, 1990; Garrett and Roper, 1986; Loyd et al, 1988). Bronchostenosis appears to be among the more common manifestations of fibrosing mediastinitis, although its actual prevalence is not clear. Obstruction of lobar or mainstem bronchi may result in recurrent atelectasis or pneumonitis associated with purulent sputum, cough, wheezing, and fever (Dunn et al, 1990; Garrett and Roper, 1986; Loyd et al, 1988; Urschel et al, 1990). Broncholiths may also occur when the granulomatous process erodes through the bronchial wall, and may result in bronchial obstruction or severe hemoptysis (Garrett and Roper, 1986; Loyd et al, 1988). Cough,

dyspnea, and hemoptysis are the most common symptoms of fibrosing mediastinitis, present in 30% to 40% of cases; SVC syndrome occurred in only 10% of cases in one comprehensive review (Loyd et al, 1988), but higher prevalence rates have been described by others (Doty et al, 1990; Dunn et al, 1990). Dysphagia, resulting from esophageal compression, occurs in 5% to 20% of cases (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). Complete obstruction of the esophagus is rare, however, which probably reflects the mobility and distensibility of this structure. Vocal cord paralysis is rare, but has been described (Loyd et al, 1988).

Physical examination is usually not helpful; neck vein distension, edema and plethora of the upper chest, head and neck, and distended superficial veins may be observed in the context of SVC syndrome. With stenosis or obliteration of pulmonary arteries, an accentuated pulmonic second sound, murmurs of tricuspid or pulmonary insufficiency, or a localized bruit over segments of the pulmonary artery may be heard (Loyd et al, 1988). In this context, echocardiography may demonstrate increased right ventricular size and dilatation of the main pulmonary artery proximal to the pulmonary arterial obstruction (Dunn et al, 1990; Loyd et al, 1988). Chest radiographs typically demonstrate massive widening and enlargement of the mediastinal structures (particularly in the right paratracheal region), reflecting a combination of lymph nodal enlargement and fibrosis (Fig. 125-5, A). Pulmonary parenchymal infiltrates, nodular densities, or atelectasis have been described in 20% to 30% of cases (Dunn et al, 1990; Loyd et al, 1988). Flecks of calcification within the lesion or narrowing of the trachea or bronchi can be appreciated on plain radiographs in some cases, but these features are best observed via computed tomographic (CT) scanning (Fig. 125-5, B) (Weinstein et al, 1983). Computed tomography is superior to standard chest radiographs and should be done to define more accurately the extent of the disease and the relationship of the mass/fibrotic process to specific mediastinal structures (eg, superior vena cava, great vessels, trachea, etc). A well-defined, unilateral mass lesion suggests mediastinal granuloma (an entity that will be discussed shortly), whereas a more diffuse lesion obliterating fat planes and without a discrete mass suggests fibrosing mediastinitis (Loyd et al, 1988; Weinstein et al, 1983). CT is more accurate in defining the extent of airway involvement as compared to standard chest radiographs. In one series, narrowing or stenosis of segments of the trachea or bronchi was detected by CT in five of seven cases, even though tracheobronchial narrowing was noted on chest radiographs in only one case (Weinstein et al, 1983). Magnetic resonance imaging (MRI) is equivalent to CT in evaluating the extent of adenopathy, but CT is superior in demonstrating calcifications and in assessing the patency of the tracheobronchial tree (Rholl et al, 1985). MRI and CT (with contrast) are equivalent in evaluating vascular patency. We believe CT (with contrast) is the radiographic procedure of choice for evaluating the mediastinum; we see little need for MRI in this context. When vascular invasion is suspected, angiography with contrast may demonstrate thrombosis or occlusion of the SVC, great vessels, pulmonary arteries, etc. CT provides a noninvasive means of evaluating the large airways, but we believe that direct endoscopic (bronchoscopic) visualization of the tracheobronchial tree is an important complementary study and provides a better assessment of mucosal edema and airway patency than radiographic techniques.

Mediastinoscopy with appropriate biopsy may be adequate to establish the diagnosis. However, in some cases thoracotomy or median sternotomy may be required to substantiate the diagnosis histologically. At operation, tissue planes are often effaced and obliterated by a dense mass of fibrotic tissue, which invades and destroys normal contiguous structures.

Microscopically, dense bands of mature collagen and proliferating fibroblasts are observed, interspersed with areas of hyalinization; little or no inflammatory response is evident within the zone of fibrosis (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). Less conspicuous areas of granulomatous inflammation (with lymphocytes, plasma cells, and occasional multinucleated giant cells) or a few small foci of caseous necrosis can usually be appreciated (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). Extensive areas of necrosis or vasculitis are not found. Cultures and special stains for fungi and acid fast bacilli (AFB) should be done on all biopsy material. Silver methenamine stains have detected the typical morphology of *H. capsulatum* in 5% to 30% of cases, however, even when a specific infection has been implicated (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). In one study of 38 cases in which a specific etiology was identified, the infection was due to *H. capsulatum* in 26 cases and mycobacteria in 12 (Goodwin et al, 1972). Most other studies have cited a low prevalence of mycobacterial infection. In one recent review, histoplasmosis was implicated in 38 of 68 cases; acid-fast bacteria was implicated in only one patient (Loyd et al, 1988). Urschel et al (1990) implicated histoplasmosis in 12 of 22 cases of fibrosing mediastinitis over a 25-year period; only 1 case was due to mycobacteria. It should be emphasized that serologic testing for histoplasmosis was not performed in most cases termed "idiopathic", and it is likely that a substantial proportion of such cases reflect unrecognized infection caused by *Histoplasma capsulatum.* Serum complement fixation tests for *H. capsulatum* should always be performed because this is the most sensitive means for detecting histoplasmosis; a four-fold rise in titer or a single titer of 1:32 or above is indicative of infection (recent or remote) (Loyd et al, 1988). Skin tests for *H. capsulatum* will alter serologic tests (complement fixation), so they should be deferred until both acute and convalescent titers have been completed. *Coccidioides immitis* is a rare cause of fibrosing mediastinitis; thus, in endemic areas, both serum complement fixation and coccidioidin skin tests should be done. Tuberculin skin testing (PPD) should also be performed, but a positive skin test does not prove a relationship between the granulomatous mediastinitis and tuberculosis.

Unfortunately, the prognosis of fibrosing mediastinitis is poor. Spontaneous resolution does not occur and no pharmacologic treatment has been shown to be effective (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990). The course is usually chronic, with gradual worsening over 3 to 7 years (Dunn et al, 1990; Loyd et al, 1988). Mortality exceeds 30% with most deaths resulting from cor pulmonale, progressive respiratory failure, or complications of surgery (Dunn et al, 1990; Loyd et al, 1988). When a specific infectious agent (such as *H. capsulatum* or *M. tuberculosis*) has been identified, antifungal or antituberculous therapy is recommended, but it is unlikely that these antimicrobial therapies will reverse the fibrotic lesion once it is established. However, Urschel et al (1990) recently reported favorable responses to oral ketoconazole in six of six patients with fibrosing mediastinitis caused by histoplasmosis. In view of the low rate of side effects associated with ketoconazole, we believe that a 6-month trial of this agent is reasonable when histoplasmosis is suspected or confirmed. Amphotericin B has significant toxicity and is not recommended. Corticosteroids or immunosuppressive agents have also been used in an attempt to ablate any inflammatory component and limit the fibrotic response, but data supporting their efficacy is lacking (Dines et al, 1979; Dunn et al, 1990; Goodwin et al, 1972; Loyd et al, 1988; Urschel et al, 1990).

In view of the rarity of fibrosing mediastinitis, little data are available regarding the role of surgery as therapy for this condition. Surgical decompression or resection of involved tissues is difficult and hazardous given the close proximity of the pathologic process to vital structures. The hard consistency of the dense scirrhous mass in fibrosing mediastinitis obliterates tissue planes and is difficult to strip away from the contiguous structures. Enthusiasm for a surgical approach has been dampened by a high rate of surgical complications and lack of firm data supporting efficacy. In one recent review (Loyd et al, 1988), thoracotomy was performed in 44 patients with fibrosing mediastinitis, with 7 operative deaths. No resection was possible in 26 cases (59%). Four of 8 who had pneumonectomy and both patients in whom airway reconstruction was attempted died of operative complications. However, palliation can sometimes be achieved, depending on the nature of the histopathologic response. Superior vena caval bypass or reconstructive procedures have been successful in relieving symptoms in several patients with SVC syndrome, with long-term graft patency (Doty et al, 1990; Dunn et al, 1990; Garrett and Roper, 1986; Loyd et al, 1988; Urschel et al, 1990). It should be emphasized that most cases of SVC obstruction caused by histoplasmosis eventually become asymptomatic as a result of formation of collateral vessels (Dunn et al, 1990; Loyd et al, 1988). Unfortunately, surgery has rarely been helpful when significant pulmonary vascular or airway obstruction exists. Garrett and Roper (1986) noted that pulmonary blood flow could not be restored in 26 previously published cases of pulmonary arterial or venous obstruction caused by fibrosing mediastinitis; however, restoration of pulmonary arterial flow was achieved in 3 patients with pulmonary artery obstruction complicating histoplasmosis when multiple caseous nodes and necrotic debris were surgically removed. This suggests that surgical intervention may have a role when a concomitant inflammatory/caseous component exists. Severe tracheal stenosis complicating fibrosing mediastinitis has resulted in occasional fatalities. Surgical experience in this context is limited, but relief of severe tracheal stenosis or extrinsic tracheal compression has been achieved by partial decortication of the dense fibrous mass in a few cases (Dunn et al, 1990; Garrett and Roper, 1986; James et al, 1980). Surgical options for severe bronchostenosis complicated by hemoptysis or recurrent pneumonia are limited because the hilum is usually rigid and fixed by the dense fibrous tissue. Thus, lobectomy is often not an option, and pneumonectomy may be required (Dunn et al, 1990; Garrett and Roper, 1986; Loyd et al, 1988). Anecdotal successes have been achieved by surgical decompressive procedures for extensive fibrosis affecting the esophagus, pulmonary arteries, and pericardium; repair of tracheoesophageal fistulas has also been successful (Dunn et al, 1990; Garrett and Roper, 1986; Loyd et al, 1988). However, the results of surgery have in general been less than satisfactory and carry a high rate of complications. Thus, resectional/decompressional surgery should be reserved for progressive or life-threatening fibrosis that affects major airways or obliterate great vessels.

Mediastinal Granuloma

The literature may be confusing because some authors have included fibrosing mediastinitis with mediastinal granuloma, a disorder in which extensive granulomatous inflammation (usually in response to *H. capsulatum*) may result in large-mass lesions that compress contiguous structures (Dines et al, 1979; Goodwin et al, 1972; Loyd et al, 1988). Both mediastinal granuloma and fibrosing mediastinitis have both granulomatous and fibrotic elements, but the degree of fibrosis and tendency for invasion of local structures is far more pronounced in fibrosing mediastinitis. Mediastinal granuloma represents a well-demarcated

(often encapsulated) mass of lymph nodes that is often asymptomatic, and has a much better prognosis and response to treatment. Although it has been suggested that fibrosing mediastinitis may represent a late phase of mediastinal granuloma (Dines et al, 1979), most investigators believe that mediastinal granuloma does not progress to mediastinal fibrosis and pathogenic mechanisms of these disorders may differ (Dunn et al, 1990; Loyd et al, 1988).

Mediastinal granuloma is often discovered as a mass lesion on routine chest radiograph, typically in the right paratracheal or hilar regions (Dines et al, 1979; Goodwin et al, 1972; Loyd et al, 1988). Histoplasmosis has been implicated (by skin tests, serologies, or special stains of histopathologic material) in most cases (Dines et al, 1979; Goodwin et al, 1972; Loyd et al, 1988). Surgery has often been performed for diagnostic reasons (eg, to exclude lymphoma) or for relief of specific symptoms (such as dysphagia or SVC syndrome). At surgery, a lobulated mass (3-10 cm in diameter) of coalescent lymph nodes, with areas of caseation, is characteristic (Dines et al, 1979; Goodwin et al, 1972; Loyd et al, 1988). Creamy material can sometimes be expressed from the cystic caseous lesions within the matted nodes; fungal elements (or rarely, mycobacteria) have been detected within these caseous foci in 20% to 30% of cases (Dines et al, 1979; Goodwin et al, 1972; Loyd et al, 1988). Cultures are almost invariably negative, however (Dines et al, 1979; Goodwin et al, 1972; Loyd et al, 1988). Histologically, varying degrees of caseous necrosis, granulomatous inflammation (multinucleated giant cells, epithelioid cells), and fibrous tissue are present; remnants of normal nodal architecture are also evident (Dines et al, 1979; Goodwin et al, 1972; Loyd et al, 1988). A distinct capsule demarcates the granulomatous mass from surrounding structures. The fibrous encapsulated mass may compress or adhere to but does not invade or destroy contiguous structures. Thus, effects on function are usually minimal provided that the capsule is thin (< 5 mm) (Loyd et al, 1988). However, massive enlargement of lymph noes, a thicker capsule, or an exaggerated fibrotic reaction may compress surrounding structures, leading to dysphagia or SVC syndrome but these complications are rarely life-threatening; significant airway compression or pulmonary vascular occlusion is rare (Loyd et el, 1988). In general, the prognosis of mediastinal granuloma is good. Fifty to 75% of patients are asymptomatic or may have a mild cough secondary to tracheal or bronchial irritation (Dines et al, 1979; Goodwin et al, 1972; Loyd et al, 1988). Although most lesions are caused by histoplasmosis, the history of infection is often remote and there is no firm evidence that antifungal therapy is helpful. Surgery is recommended when significant local symptoms are present, but is not necessary in asymptomatic or minimally symptomatic cases. When a capsule is present, surgical resection is usually curative and can be accomplished without major sequelae as the mass can often be easily resected from adjacent structures (Dunn et al, 1990; Loyd et al, 1988).

Sarcoidosis

Sarcoidosis is a poorly understood chronic granulomatous disorder of unknown etiology that may involve virtually any organ system (Neel and McDonald, 1982; Thomas and Hunninghake, 1987). Nonnecrotizing (noncaseating) granulomata at sites of disease are the histologic hallmark of this disorder; T lymphocytes and varying degrees of fibrosis may be seen in the periphery. Vasculitis does not occur. Although the pathogenesis is not clear, an exaggerated cellular immune response may lead to injury, disruption, and destruction of affected organs. The disease is self-limited in two thirds of patients; however, destruction of or injury to vital organs (such as lung, heart, or brain) may lead to serious organ dysfunction

and morbidity. Mortality is low, however, ranging from 2% to 5% (Lynch and Strieter, 1991; Thomas and Hunninghake, 1987). Typically, multiple organs are involved. However, pulmonary manifestations usually predominate; abnormalities on chest radiograph are present in 90% to 95% of cases (Lynch and Strieter, 1991; Thomas and Hunninghake, 1987). Bilateral hilar adenopathy, the classical radiographic feature of sarcoidosis, occurs in 60% to 80% of patients (with or without concomitant pulmonary parenchymal infiltrates), and may be a clue to the diagnosis when patients present with primary otolaryngologic features (Lynch and Strieter, 1991; Thomas and Hunninghake, 1987). In 10% to 20% of cases, pulmonary parenchymal infiltrates are present without apparent lymphadenopathy (Lynch and Strieter, 1991; Neel and McDonald, 1982; Thomas and Hunninghake, 1987). Although the prognosis of pulmonary sarcoidosis is generally excellent (two thirds of cases remit spontaneously), progression of the sarcoid lung lesion may result in significant destruction of lung parenchyma, fibrosis, and progressive respiratory failure. Mortality from end-stage lung disease has been less than 5% in most series. Bronchostenosis may complicate sarcoidosis in up to 5% to 10% of cases, but is rarely severe. However, on occasion, chronic granulomatous infiltration of bronchial submucosa may lead to narrowing of lobar or segmental bronchi, resulting in suppurative complications or postobstructive pneumonitis (Fig. 125-6). A myriad of extrapulmonary features may occur. Involvement of peripheral lymph nodes, skin, and eyes occurs in 20% to 40% of cases. Asymptomatic involvement of liver or spleen occurs in 50% to 70% of cases; symptoms referrable to these organs occur in only 3% to 8% of cases. Symptomatic involvement of heart, central nervous system, muscle, or bone occurs in fewer than 5% of cases.

Although the gamut of manifestations seen in sarcoidosis is beyond the scope of this chapter, otolaryngologic manifestations occur in 20% to 40% of cases of sarcoidosis and the spectrum of lesions that may come under the purview of otolaryngologists is extraordinarily broad (Lynch and Strieter, 1991; Neel and McDonald, 1982; Thomas and Hunninghake, 1987). Lymphadenopathy in the cervical, submental, or submandibular nodal chains occurs in 5% to 10% of cases; patients presenting with lymphadenopathy may be referred to otolaryngologists for diagnostic biopsies. Cutaneous lesions (papules, macules, nodules, erythematous plaques) may be present in the head or neck (primarily nasolabial and periorbital regions) in 5% to 15% of cases (Lynch and Strieter, 1991; Thomas and Hunninghake, 1987). Lupus pernio, a particularly disfiguring lesion characterized by violaceous, infiltrated plaques involving the face is a rare complication of chronic, progressive sarcoidosis involving multiple organs; pulmonary fibrosis, bone cysts, and ocular lesions occur concomitantly in 30% to 50% of cases (Lynch and Strieter, 1991; Thomas and Hunninghake, 1987). Nasopharyngeal symptoms (persistent rhinitis, nasal obstruction, or sinus congestion) occur in 10% to 20% of cases (Lynch and Strieter, 1991; Thomas and Hunninghake, 1987). On physical examination, crusting of the nasal mucosa, septal perforation, nasal mucosal nodules or papules, and polypoid masses may be observed. Involvement of the parotid, salivary, or lacrimal glands occurs in 5% to 10% of patients and may cause swelling, pain, and sicca syndrome (Lynch and Strieter, 1991; Thomas and Hunninghake, 1987). Unilateral or bilateral parotid gland enlargement associated with fever, uveitis, and cranial nerve palsies complicating sarcoidosis was originally described by Heerfordt and has been termed *uveoparotid fever*. Symptomatic laryngeal involvement occurs in less than 1% of patients with sarcoidosis (Chapelon et al, 1990; Neel and McDonald, 1982). Hoarseness is the most common manifestation of laryngeal sarcoid, but dyspnea caused by involvement of the supraglottic structures and resultant UAO may also occur (Chapelon et al, 1990; Neel and

McDonald, 1982). On laryngoscopic examination, the most common finding is diffuse hyperemia and edema of affected regions; nodules or mass lesions have also been described (Neel and McDonald, 1982). Ulceration is rare. Dysphagia may reflect edema and enlargement of the epiglottic structures with secondary mechanical difficulty in swallowing (Neel and McDonald, 1982). The supraglottic structures are characteristically involved, and disease below the glottis has been found in less than 20% of laryngeal sarcoid (Chapelon et al, 1990; Neel and McDonald, 1982). Biopsies of affected areas reveal well-defined noncaseating granuloma and inflammatory or fibrotic changes; necrosis is not a feature.

Systemic corticosteroids have been associated with improvement in over 80% of cases of laryngeal sarcoid (Lynch and Strieter, 1991; Neel and McDonald, 1982; Thomas and Hunninghake, 1987). Intralesional steroids and surgical excision of affected areas may be beneficial in selected cases. Tracheostomy may be require in patients with severe or progressive UAO refractory to medical therapy, although this is exceedingly rare. In view of the excellent results achieved with corticosteroid therapy for laryngeal sarcoid, we recommend corticosteroids (systemic, topical, or intralesion) in favor of more aggressive surgical therapies except in life-threatening cases of upper airway obstruction. Primary involvement of trachea or esophagus occurs in fewer than 1% of cases. A variety of laboratory aberrations may occur in sarcoidosis; hypergammaglobulinemia occurs in 25% of cases; hypercalcemia, in 2% to 5% (Lynch and Strieter, 1991; Thomas and Hunninghake, 1987). Mild elevation in hepatic enzymes occurs in 5% to 15% of cases. These parameters have no significant clinical value, however, because they fail to correlate with disease activity. The single most useful laboratory parameter is serum angiotensin converting enzyme (SACE), which is elevated in 30% to 60% of cases and may correlate with total granuloma burden (and by extrapolation, with activity of the disease) (Lynch and Strieter, 1991; Thomas and Hunninghake, 1987). Serial measurements may thus be helpful in following the course of the disease when objective parameters of disease activity are lacking. SACE may be normal, however, even in the face of active local/regional disease; thus, treatment decisions should not be based solely on SACE levels.

The natural history of sarcoidosis is extraordinarily heterogeneous. Spontaneous remissions occur in nearly two thirds of patients, so treatment should be circumscribed and focused. Corticosteroids are the cornerstone of therapy for sarcoid patients requiring treatment; favorable responses have been achieved with systemic corticosteroids in 50% to 80% of patients and are often dramatic (Lynch and Strieter, 1991; Thomas and Hunninghake, 1987). The long-term impact of therapy is less clear, as relapses may occur as corticosteroids are tapered or discontinued. In view of the high rate of spontaneous remissionms, indications for therapy remain controversial. However, we believe that corticosteroids are indicated for patients exhibiting severe or progressive symptoms or organ dysfunction. Optimal dosage and duration of therapy have not been well defined. However, we usually initiate prednisone in a dose of 40 to 60 mg/day for the first 1 to 4 weeks, with a taper to alternate-day dosing within 6 weeks. In most instances the dose can be reduced by 10-mg decrements every 1 to 2 weeks depending on the clinical severity of the disease and the response, until a dose of 40 mg every other day has been achieved (typically within 2-4 months). At that point, we slow the rate of taper (reducing by 10-mg decrements every 2-3 months) and maintain patients on low-dose alternate-day steroids for a minimum of 1 year in most cases. More prolonged therapy may be required for patients manifesting recrudescent disease. A variety of immunosuppressive/cytotoxic agents including methotrexate, cyclophosphamide, chlorambucil,

azathioprine, and cyclosporine A have been tried and have had anecdotal success. However, owing to their potential toxicity, we have restricted the use of these agents to patients with severe or life-threatening disease refractory to high-dose systemic corticosteroid therapy.

Amyloid

Amyloidosis is a heterogenous group of diseases that is characterized by tissue deposition of an insoluble beta-pleated fibrillar protein (amyloid) in the extracellular matrix (Alroy et al, 1972; Finn and Farmer, 1982; Glenner, 1980; Kyle and Greipp, 1983; Thompson and Citron, 1983). Various biochemical forms of the amyloid protein have been identified, and are classified according to their chemical composition. For example, amyloid AL is derived from immunoglobulin light chains and amyloid AA is derived from amyloid precursor protein A (Glenner, 1980). Amyloidosis is characterized clinically by its association with various clinical syndromes (Glenner, 1980). Primary amyloidosis, the most common variant, can be idiopathic or associated with plasma cell dyscrasias (such as multiple myeloma); this is associated with deposition of the immunoglobulin light chain fragment (amyloid AL). Secondary amyloidosis (amyloid AA) occurs in association with chronic inflammatory disorders such as rheumatoid arthritis, collagen vascular disease, tuberculosis, bronchiectasis, malaria, and other chronic infections (Finn and Farmer, 1982; Glenner, 1980). There is also a group of genetically transmitted amyloid diseases (familiam amyloidosis), many of which appear to be inherited in an autosomal dominant fashion. Deposits of amyloid protein may also occur with advanced age (senile amyloidosis). Amyloid may involve virtually any organ but most common sites of amyloid deposition include the tongue, heart, joints, kidney, gastrointestinal tract, spleen, liver, skin, nervous system, and both upper and lower respiratory tracts (Alroy et al, 1972; Finn and Farmer, 1982; Glenner, 1980; Kyle and Greipp, 1983; Thompson and Citron, 1983).

The diagnosis of amyloidosis (irrespective of clinical subcategory) can be confirmed histologically by demonstrating the characteristic amyloid fibrils in involved tissue(s); amyloid stains pink with hematoxylin-eosin stains but Congo red stains are most useful to detect the protein. A common property of all amyloid compounds is their ability to bind Congo red dye and emit a green fluorescence under polarized light microscopy (Finn and Farmer, 1982; Glenner, 1980). Rectal or gingival biopsies have been positive in more than two thirds of patients with primary amyloidosis; skin biopsies will demonstrate amyloid in up to 50% of cases. Higher yields may be achieved by directed biopsies of clinically involved areas.

Amyloid deposits in the myocardium or pericardium may lead to restrictive cardiomyopathy, conduction disturbances, and congestive heart failure (Glenner, 1980; Kyle and Greipp, 1983). Renal amyloid may result in nephrotic syndrome and varying degrees of renal insufficiency; progressive renal failure is the leading cause of death from primary amyloidosis (Glenner, 1980; Kyle and Greipp, 1983). Amyloid may affect any site in the gastrointestinal tract; hemorrhage, ulcer, obstruction, diarrhea, or malabsorption caused by bowel involvement may occur. Hepatomegaly and splenomegaly are common, but significant hepatic dysfunction is rare. Localized amyloidosis of the esophagus in the absence of involvement elsewhere does not occur. Neurologic involvement is most common in primary and familial forms of amyloidosis; cardinal clinical manifestations include carpal tunnel syndrome and autonomic neuropathy. Both upper (sinuses, nasopharynx, larynx, trachea) and lower respiratory tract (bronchi, lung) infiltration with amyloid may occur (Alroy et al, 1972;

Finn and Farmer, 1982; Glenner, 1980; Kyle and Greipp, 1983; Thompson and Citron, 1983).

It is in this context that the otolaryngologist is in a key position to consider and corroborate the diagnosis. Amyloidosis can cause massive enlargement of the tongue resulting in functional UAO and sleep apnea. The larynx also appears to be a preferred site for deposition of amyloid; the most common area of laryngeal involvement is the vestibule, followed by the false cords, the aryepiglottic folds, and subglottic region (Finn and Farmer, 1982; Thompson and Citron, 1983). Occasionally, laryngeal involvement of amyloidosis can lead to vocal cord fixation and laryngeal stenosis. Tracheal and lower respiratory tract amyloidosis is especially common in patients with primary amyloidosis. Vascular deposits of amyloid in the respiratory tract may also occur with advancing age, but do not usually cause clinical problems in this context. In a review of 157 patients with amyloid localized to the respiratory tract, four major disease patterns were recognized (Thompson and Citron, 1983). The most common pattern involves multifocal plaques within the tracheal and bronchial submucosa; these plaques generally do not extend beyond the airway wall. Symptoms associated with this form of localized amyloidosis include dyspnea, wheezing, stridor, and cough; hemoptysis may result from increased vascular fragility. Occasionaly these amyloid deposits develop calcification and even ossification, earning the designation *tracheobronchopathia osteoplastica* (Alroy et al, 1972). A second form of localized respiratory amyloidosis is the presence of tracheal or bronchial tumorlike masses that are composed of amyloid fibrils. Hilar or mediastinal adenopathy may also occur. A third form of respiratory amyloid includes the presence of one or more discrete pulmonary parenchymal nodules, usually seen as coinlike lesions on chest radiographs. The prognosis for this form of localized amyloid has been excellent. A final form of amyloid presents as diffuse interstitial (alveolar septal) infiltrates on chest radiographs and is associated with dyspnea and a restrictive defect on pulmonary function testing. This manifestation of amyloid may be clinically indistinguishable from idiopathic diffuse interstitial fibrosis and carries a poor prognosis (Thompson and Citron, 1983).

Unfortunately, no pharmacologic treatment has been proven to modify the course of amyloidosis. In secondary forms of amyloidosis, aggressive treatment to the underlying chronic inflammatory or infectious process may delay (and possibly reverse) tissue deposition of amyloid and disease progression (Glenner, 1980; Kyle and Greipp, 1983). Patients with primary amyloidosis caused by multiple myeloma may respond to melphalan/prednisone (used as primary therapy for myeloma) (Glenner, 1980). Similar therapeutic regimens have been tried on patients with other forms of amyloidosis, but are of unproven benefit and may increase morbidity. Colchicine has been used in both primary and secondary forms of amyloidosis, but responses have been inconsistent and this agent is of doubtful efficacy (Glenner, 1980; Kyle and Greipp, 1983). In view of the lack of clearly effective medical therapy, surgical resection of troublesome foci of amyloid may be warranted in selected cases. Surgical or laser resections of symptomatic amyloid deposits involving the larynx, trachea, or bronchi have been performed and have had anecdotal success (Kyle and Greipp, 1983). In rare instances, laryngeal dilatation and tracheostomy have been necessary. No treatment exists for more diffuse amyloid infiltrating the tracheobronchial tree or pulmonary parenchyma.