Chapter 100: Infections and Manifestations of Systemic Disease of the Larynx

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Infections

As a general rule, infections of the larynx can be divided into those that are acute and those that are chronic. Most significant acute processes occur over a period of less than 7 days, present with airway distress and fever, and are more prevalent and problematic in children than in adults. In contrast, chronic laryngeal infections generally have existed for weeks before presentation; in addition to airway distress, hoarseness and pain may predominate as symptoms, systemic factors may be important, and the infections occur more frequently in adults than in children. Examples of such chronic laryngeal infections include syphilis, tuberculosis, and various fungi.

The history is often the most important tool in the diagnosis. In both acute and chronic infectious processes, one should ascertain (1) the severity and progression of symptoms, especially related to dyspnea, (2) associated regional or systemic signs and symptoms, and (3) precipitating factors. In acute infections, the critical point is the differentiation between run-of-the-mill viral laryngitis and the more serious diseases of croup and epiglottitis. For chronic infections, it is more important to distinguish infection from malignancy, since the two may often appear similar both visually and by history.

Acute infections

Croup or laryngotracheitis

Clinical features. Laryngotracheitis, or croup, can be defined as a subacute viral illness characterized by fever, "barking" cough, and strior. Parainfluenza viruses 1 and 2 and influenza A are the most common causes (Baugh and Gilmore, 1986). It is usually a winter illness and is occasionally epidemic. It most frequently occurs in male infants aged 1 to 3 years and usually lasts 3 to 7 days. Croup may be calle atypical when it occurs in infants less than 1 year old, lasts more than 7 days, or does not respond to appropriate treatment. In atypical cases one must think of other diagnoses, such as a foreign body, subglottic stenosis, or bacterial tracheitis. The term *laryngotracheobronchitis* is sometimes used interchangeably with croup, but some authors prefer the former term to denote a bacterial process, as discusse later.

The crucial factor in laryngotracheitis is the amount of swelling in the subglottic area, which, in infants up to 3 years of age, is the narrowest portion of the upper respiratory tract. Further, since this is the only portion of the upper respiratory tract where a complete cartilaginous ring exists, all edema that occurs here occurs at the expense of the lumen. It is important to remember that stridor at rest does not occur before approximately 80% of the airway is compromise. Since the decrease in cross-sectional area is proportional in a general way to the square of the radius, a small amount of edema at this stage in the illness can result in complete obstruction. That a mucous plug could be fatal at this point is not hard to imagine. An awareness of these facts should emphasize the critical nature of this illness.

Differential diagnosis. The most important differential diagnosis in a child with suspected croup is epiglottitis, which the next section discusses in more detail. In addition, detailed questioning about possible foreign body ingestion should be made. Routine radiographs of the neck and chest are as important in ruling out a foreign body as they are in confirming the diagnosis of croup. Finally, subglottic stenosis may present as recurrent croup. A narrowed subglottic airway, whether it be congenital or acquire, has much less tolerance for the viral edema that accompanies croup, an so minor laryngotracheal infections, which woul pass unnotice in a healthy child, will cause the chil with subglottic stenosis to become striulous. Thus a history of recurrent croup or a history of previous intubation is important to determine.

Spasmodic croup is an ill-defined entity characterized by the acute onset of a barking cough, dyspnea, and stridor. It may be recurrent an also associate with an upper respiratory tract infection but usually is without fever. Spasmodic croup almost always resolves with humidity and reassurance. The history, lack of fever, and radiographic findings help to distinguish it from croup.

Management. Although humidification is often described as a mainstay of treatment in croup, Skolnick (1989) points out in an excellent review article that neither of the two stuies that looked at the effects of humidification on croup found any positive effect. On the other han, the efficacy of inhaled racemic epinephrine is well establishe (Singer and Wilson, 1976; Westley et al, 1978). Further, although most studies of the effects of racemic epinephrine have been performed with the agent being delivered via intermittent positive pressure breathing (IPPB), a recent study by Fogel et al (1982) suggests that delivery via nebulization alone is just as therapeutic.

The use of steroids in the treatment of croup has become less controversial in recent years. A decade ago, Tunnessen and Feinstein (1980) reviewed all studies that had been done up until that time on the efficacy of steroids and concluded that all of the studies had serious methodologic flaws that prevented any definitive conclusions from being mae. Since that time, the evidence that steroids may be helpful in children with croup appears to be mounting. Kairys et al (1989) recently performed a statistical analysis of all nine of the randomized trials of steroid treatment that have appeared in the literature. Their conclusions were that steroids provided significant therapeutic benefit and that the effect appeared to be dose dependent. Similarly, Skolnick (1989), after reviewing all studies comparing steroid versus placebo, found that all of the investigations that used doses of dexamethasone greater than or equal to 0.3 mg/kg reported significant positive effects. Finally, Super et al (1989) recently reported the results of a carefully controlled, prospective, double-blind study that showed significant improvement in stridor and retractions at 12 and 24 hours following a single intravenous injection of dexamethasone (0.6 mg/kg).

When medical management fails, direct airway support via intubation or tracheostomy may be necessary. Indications for such support include rising carbon dioxide levels, a worsening neurologic status, or a decreasing respiratory rate in the face of poor gas exchange. The time-honored procedure is a controlled tracheostomy, preferably performed after an airway is established by endotracheal intubation or rigid bronchoscopy. A recent large series confirms the safety of tracheostomy uner these circumstances, with no mortality in 24 patients with croup (Carter and Benjamin, 1983). Howevr, other large sries successfully using

endotracheal intubation have been reported (Mitchell and Thomas, 1980; Thomspon and Olinsky, 1975). The potential disadvantage of endotracheal intubation is that it could cause further damage in an already edematous subglottic area, especially if the tube is particularly tight fitting. Certainly, the smallest size of tube that allows ventilation should be used. Further, younger infants with smaller subglottic spaces may be at increased risk for complications of endotracheal intubation. With this important reservation, strong support exists for both modalities of airway control, depending on local expertise. The duration of endotracheal intubation is usually 2 to 3 days. Most of these infants presumably will have received a dose of steroid before endotracheal intubation; we recommend that at least one additional dose be given 2 to 4 hours before extubation, with racemic epinephrin used as needed. A tracheotomy tube in the uncomplicated cases can be removed at 5 to 7 days after appropriate evaluation. Despite some reports suggesting the contrary, not all cases are so straightforward; one inevitably will have patients who are difficult to decannulate.

Bacterial tracheitis

Bacterial tracheitis is a serious pediatric pulmonary infection that was initially described by Jones et al (1979). Especially in its early stages, it may be difficult to differentiate from croup, and like the latter, its most common presenting symptom is stridor. Sometimes it may be differentiated from croup on the basis of a higher fever and leukocytosis, but there is certainly an overlap between the two populations. To make diagnosis even more difficult, bacterial tracheitis frequently may develop as a sequela of croup. For exampl, Liston et al (1983) reporte 12 cases of bacterial tracheitis that developed during an outbreak of parainfluenza virus infection. All but on of the patients initially exhibite the clinical features of croup, and six of the seven patints who were cultured for the virus tested positive. Also, of the seven patints with bacterial tracheitis reported by Sofer et al (1983), four were originally admitte with the diagnosis of croup and three with the diagnosis of epiglottitis.

The diagnosis of bacterial tracheitis is made on the basis of thick, purulent tracheal secrtions (Jones et al, 1979). Liston et al (1983) suggested that any child with crouplike symptoms who is not improved after several days of medical management or who develops a high fever or white cell count should undergo bronchoscopy to rule out the presence of such secretions. Their presence obviously indicates a worsening clinical course, and intubation or tracheostomy is often required. Some authors (Liston et al, 1983) recommend tracheostomy over intubation because of the frequency of suctioning that is require, but other series of patients have been successfully managed with intubation alone (Jones et al, 1979).

The most common pathogens isolated are *Staphylococcus aureus* and alpha-hemolytic streptococcus. Cultures should be obtained at the time of laryngoscopy and antibiotic therapy directed accoringly. Although hospitalization is usually prolonged because of the frequent suctioning required, most cases resolve with the appropriate antibiotic treatment. Secondarily acquired pneumonia is the most common complication.

Pediatric supraglottitis

Clinical features. Pediatric epiglottitis, more appropriately termed *supraglottitis*, is an acute infectious process that is usually caused by *Haemophilus influenzae* type B. The disease is much more rare than croup. Although it classically occurs in children age 2 to 4 years, a recent report suggests that the incidence of epiglottitis is increasing among infants less than 2 years (Emmerson et al, 1991). Onset is acute, often over 2 to 6 hours. The child has a high temperature, drools, and sits upright with greater inspiratory than expiratory stridor. A lateral extended soft tissue radiograph is often diagnostic.

The inflammatory process occurs almost exclusively in the supraglottic larynx, with a fiery, cherry-red epiglottis as the most impressive feature. However, aryepiglottic fold false cord involvement also exists. Respiratory obstruction is probably caused by at least two factors: a swollen epiglottis and aryepiglottic fold with supraglottic narrowing, and excessive, thick, tenacious oral and pharyngeal secretions, which accumulate because of odynophagia. Sudden respiratory arrest may be caused by mucouc plugging of the narrowed supraglottic airway, plugging of the supraglottic larynx during inspiratory efforts, or laryngospasm, to which these infants may be particularly susceptible if examine aggressively. The associate odynophagia from the marked inflammatory supraglottic process helps to distinguish this entity from croup.

Although the most important aspect of the illness is supraglottic involvement, the systemic natur is manifested by generalized toxemia, often with positive blood cultures for *H. influenzae* type B (Bottenfield et al, 1980). Presumably the newborn is relatively protected from *H. influenzae* type B infections by the immunity acquired from the mother. This passive immunity to the capsular antigen of *H. influenzae* decreases dy the age of 3 months, howevr, and apparently does not begin to increase from the child's own immune system until 3 to 4 years of age. This lack of antibody production may partly explain the high incidence of *H. influenzae* type B infection in this age group. Interestingly, vaccination in this same age group has not been successful, making the immunologic problem more complex than initially appreciated.

Differential diagnosis. Croup and epiglottitis are usually easily distinguishabl. Remembering the pathophysiology of each condition facilitates one's diagnostic acumen. As already described, the child with epiglottitis classically appears with a 2- to 6-hour history of stridor, sitting upright, and drooling. The child with croup has had a several-days history of prodromal symptoms with worsening stridor and a seal-like (croupy) cough. One should always remember that a foreign body is capable of mimicking either condition, depending on its position in the upper respiratory tract.

Medical management. The cornerstone of epiglottitis management is antibiotics. Although ampicillin has long been thought of as the treatment of choice for *H. influenzae* infections, the rise in ampicillin-resistant strains over the past 15 years has prompted the recommendation that chloramphenicol be added to the treatment regimen of any child with epiglottitis until the sensitivities of the infecting organism can be determined. However, concerns about possible side effects of chloramphenicol (especially bone marrow suppression), as well as the necessity of daily monitoring of chloramphenicol levels, have prompted a

continuing search for an alternative single-drug therapy. Initially, there was some enthusiasm for cefamandole, a second-generation cephalosporin with good activity against both ampicillin-sensitive an ampicillin-resistant *H. influenzae.* However, there was some concern about its poor blood-brain barrier penetration, since the bacteremia stage of *H. influenzae* epiglottitis may occasionally result in *H. influenzae* meningitis (Schloss et al, 1983).

Cefuroxime is now drug of choice for supraglottitis at several large institutions. It has excellent bactericidal activity against virtually all gram-positive bacteria and most gram-negative bacteria, including all strains of *H. influenzae.* In addition, it has adequate CSF pentration an a high margin of safety. Early results with this drug have been excellent (Sendi and Crysdale, 1987). An alternative drug is ceftriaxone, a third-generation cephalosporin with a bactericidal profile similar to that of cefuroxime and even better CSF penetration. Some clinicians prefer ceftriaxone to cefuroxime because of its less-frequent dosing schedule and also because there have been some studies that have shown a slight advantage of ceftriaxone over cefuroxime in the treatment of bacterial meningitis (Lebel et al, 1989).

Airway management. Airway management of a child with suspect epiglottitis begins when the child is first seen in the clinic or emergency department. The first step is to notify the otolaryngologist and anesthesiologist on call. Examination of the child is kept to a minimum and confine to visual inspection and auscultation of the heart and lungs. The child who is stabl may be taken to the radiology department, accompanie by the otolaryngologist or anesthesiologist, for a single soft tissue lateral radiograph. If a portable film can be taken in the emergency department, that is preferable. The child is then taken to the operating room, where mask induction is performe by the anesthesiologist while the otolaryngologist readies the appropriate laryngoscopes and rigid bronchoscopes. Once an appropriate level of anesthesia has been reache, an intravenous line is started and preparations are made for intubation. The larynx is visualize and the diagnosis confirmed. Either nasotracheal or orotracheal intubation is performe, usually with an endotracheal tube one size smaller than would ordinarily be used for the child. The tube is carefully secured and the patient taken to the intensive care unit (ICU). Intubation is usually maintained for 24 to 48 hours. Readiness for extubation is determine by applying positive pressure to the endotracheal tub and listening for the presence of an air leak. After extubation, the child is observed in the ICU for 4 to 6 hours and then may be transferred to a medical floor.

The use of a tracheostomy for airway control should be mentione for historical interest only. Although this was the procedure of choice 20 years ago, several studies comparing tracheostomy to intubation have shown that while the two procedures are similar in terms of low complication rate, tracheostomy results in a significantly increased duration of cannulation and a longer hospitalization (Oh an Motoyama, 1977; Schloss et al, 1983). On the other hand, the risk of accidental decannulation, which has been mentioned as a disadvantage of nasotracheal intubation, has been shown in several large series of patients to be a rare event and easily remedied by reintubation (Crockett et al, 1988; Sendi and Crysdal, 1987).

Adult supraglottitis

Supraglottitis in the adult is, in general, a very different disease from that seen in children. Recent evidence suggests that there appear to be two populations of adult patients: those with a fulminant clinical course, acute respiratory compromise, and blood cultures positive for *H. influenzae* and those with a milder, benign course, no significant respiratory compromise, and no definable pathogen (Mayo-Smith et al, 1986; Mustoe and Strome, 1983). Unfortunately, attempts to identify those patients at risk early in their presentation have proven somewhat difficult. Mayo-Smith et al (1986) noted no difference between patients with epiglottitis who eventually required airway support and those that did not in terms of presenting symptoms (other than airway compromise), temperature, white cell count, or age. The only significant difference was the percentage of patients later positive for *H. influenzae,* which was 56% in the group requiring airway support and only 6% in the group that did not.

Fortunately, however, most adult patients with supraglottitis do not go on to develop the airway compromise typical of an *H. influenza* infection. Of the 56 cases reporte by Mayo-Smith et al, only 14 developed respiratory difficulty, but there were four deaths. However, other studies of patients with adult epiglottitis have reporte an incidence of airway support ranging from 0% to only 8% and no fatalities (Mustoe and Strome, 1983; Shapiro et al, 1988; Fontanarosa et al, 1989).

The diagnosis of supraglottitis in the adult can be made either radiographically or by indirect laryngoscopy. However, since the sensitivity of lateral soft tissue radiographs is not 100% (Fontanarosa et al, 1989), a negative raiograph does *not* rule out the diagnosis. Further, unlike in children, there have been no reporte incidents in adults of indirect laryngoscopy precipitating an airway emergency, so in an adult with suspected epiglottitis, it is preferable for the otolaryngologist to confirm the diagnosis visually. The epiglottis often will not have the bright-cherry-red appearance described in children but rather may be pale, boggy, and edematous. Also, other supraglottic structures, such as the aryepiglottic folds, may be involved to a greater degree than the epiglottis itself.

An epiglottic abcess is a rare complication of supraglottitis that is seen almost exclusively in aults (Heeneman and Ward, 1977). The most common site of involvement is the lingual surface of the epiglottis, and significant airway obstruction may occur as a reslt of the expanding abcess and localized tissue edema. The most commonly isolated pathogens are *Streptococcus* and *Staphylococcus* species.

Recommended management of any ault with supraglottitis is admission to an ICU setting for careful observation and starting appropriate antibiotic an supportive measures. Since results from blood cultures will obviously not be available for at least 24 hors, all patients should be started on coverage for *H. inflenzae,* including ampicillin-resistant strains. A third-generation cephalosporin, such as cefuroxime or ceftriaxone, would be appropriate. Since most patients will not require airway support, prophylactic intubation or tracheostomy is not necessary. However, if an emergency airway is required, most authors recommend intubation, because no problems have been associated with its use and the duration of support needed is usually only 3 to 5 ays,.

Whooping cough

Whooping cough, caused by *Bordetella pertussis*, has been reported with increasing frequency in the USA (Bass and Stephenson, 1987). Originally a disease of chilhood, it is now more commonly seen in infants under 6 months of age and in adults. The reason for the former is that unlike other childhood disease such as measles, mumps, and rubella, there is apparently no passive immunity conferred by the mother to the child in utero, so that newborns are susceptible to pertussis infection until they receive their third immunization shot at 6 months. The number of infected adults is increasing because unlike the natural disease, which confers lifelong immunity, the pertussis vaccine provides a high degree of protection for only 3 years, after which resistance to infection gradually decreases over the next 10 to 15 years.

Unfortunately, the presentation of the disease may also be somewhat atypical in both of these patient populations. Adults may only display a severe and protracted cough, whereas newborns, while usually exhibiting the catarrhal stage and subsequent fever and leukocytosis, may or may not exhibit the episodes of paroxysmal "whooping" cough typical of the disease in children. Treatment is supportive, with frequent suctioning often necessary in infants. Erythromycin, while not changing the clinical course of the disease, has been shown to cause patients to become noninfectious after 1 or 2 days and also has a clear prophylactic effect on individuals who have been exposed to an infected individual but have not yet become symptomatic themselves (Bass, 1986). The recommended dose in both cases is 50 mh/kg/day of the estolate ester form in four divided doses for 14 days.

Other acute infections of larynx

Mumps, measles (rubeola), and chickenpox (varicella) may cause localized laryngeal and tracheal inflammation. Mucous retention cysts of the larynx or even laryngoceles can become acutely infected, causing airway distress from local obstruction. Usually indirect examination leads to the diagnosis, although occasionally computerized axial tomography may be of help, especially with a laryngopyocele.

Conditions that may mimic acute laryngeal infections

In a child, a foreign body should always be considered in the differential diagnosis of acute epiglottitis or croup. In adults, an often overlooked cause of acute hoarseness or stridor is the swelling associated with cricoarytenoid arthritis. This is most commonly seen in patients with rheumatoid arthritis but can also be a manifestation of other connective tissue disorders such as systemic lupus erythematosus and Reiter's syndrome (Leicht et al, 1987). Treatment may include intraarticular injections of corticosteroids as well as systemic corticosteroids or other immunosupportive agents. The swelling may be severe enough to compromise the airway.

Angioneurotic edema may occasionally be considered in the differential diagnosis of acute laryngeal swelling and erythema, but there is usually no associated fever or prodromal symptoms, and this entity is usually accompanied by associated oral, pharyngeal, or neck swelling.

Finally, it is well known that generalized "supraglottitis" may also be associated with radiation therapy. However, it is important to know that various chemotherapeutic agents can exacerbate this reaction months to years after the initial treatment to the larynx with radiation therapy (Wallenborn and Postma, 1984).

Chronic infections

Chronic laryngeal infections often present with a history and symptoms similar to those seen with laryngeal carcinoma. The patient complains of hoarseness, dyspnea, or pain and may report a history of weight loss and tobacco or alcohol abuse. The diagnostic challenge is thus to first rule out the diagnosis of cancer and then establish the correct diagnosis.

Physical examination is often unrewarding. Diffuse laryngeal edema and erythema may be the only pathologic findings, and a noninfectious cause, such as gastroesophageal reflux, must be ruled out. Even if a discrete lesion is visible, it may mimic the appearance of a laryngeal tumor. In the past, this sometimes led to radical surgery being performed for benign disease, such as a total laryngectomy for what turned out to be blastomycosis (Suen et al, 1980). On the other hand, an even more dangerous course of action is for the clinician to suspect a benign process without aggressively searching for a possible carcinoma.

Biopsy is thus the cornerstone of an appropriate workup. In addition to sending tissue for the usual tissue stains, the clinician should also send appropriately prepared specimens for special fungal stains, acid-fast bacillus (AFB) smears, and fungal and AFB cultures. The possibility of sarcoidosis, relapsing polychondritis, and autoimmune disorders should also be considered. If a diagnosis is still not obtained, the patient should be closely observed, and additional biopsies should be done if the symptoms or physical examination changes.

Tuberculosis

Tuberculosis is still one of the most common granulomatous diseases of the larynx. In the past, it commonly developed as a sequela of severe pulmonary tuberculosis, and the areas of the larynx that were in the direct line of mucociliary clearance from the trachea were most commonly involved. These sites included the posterior portion of the true vocal cords, the arytenoid cartilages, and the intraarytenoid space. However, in the past 20 years, this pattern of involvement has changed, and most patients with laryngeal tuberculosis now present without pulmonary symptoms or a history of pulmonary tuberculosis (Bailey and Windle-Taylor, 1981; Levenson et al, 1984; Thaller et al, 1987). Recently, the theory has been advanced that laryngeal involvement is now more commonly caused by hematogenous or lymphatic spread of the organism (Soda et al, 1989).

The most common presenting symptom of laryngeal tuberculosis is hoarseness, with dysphagia or odynophagia out of proportion to the size of the lesion often described. Cough and weight loss have also been noted. Most patients have evidence of pulmonary involvement on chest radiograph. In keeping with the high incidence of hoarseness, the glottis is the most common area of involvement (Thaller et al, 1987; Bailey and Windle-Taylor, 1981), although all areas of the larynx can be involved (Levenson et al, 1984; Soda et al, 1989). A nodular, exophytic lesion or an area of mucosal ulceration, either of which can easily be mistaken for

carcinoma, is often seen.

Diagnosis is usually made by the combination of positive sputum samples, characteristic findings on chest radiograph, and biopsies positive for acid-fast bacilli. Histopathologic examination of biopsied tissue reveals tubercles consisting of a homogenous caseous center (staining red with eosin), a periphery of pale epithelial cells containing one or more giant cells, and an outer zone of lymphocytes. Treatment is essentially medical and consists of the administration of isoniazid and ethambutol. Rifampin, streptomycin, and para-aminosalicylic acid may be useful, depending on sensitivities.

Histoplasmosis

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum,* which exists in a yeast form at body temperature. The mycelial form is found in soil with a high nitrogen content, such as is provided by large amounts of bird or bat feces. Endemic regions include the Ohio and Mississippi River valleys, where 80% to 90% of the population may be infected. Infection is via inhaled spores, which in most cases produce an acute respiratory infection whose only sequela may be small residual calcifications in the lungs and spleen. However, occasionally the disease may develop into a severe, acute cavitary lung form or a more indolent disseminated form. Factors that appear to dispose an individual toward developing one of these more severe manifestations include superinfection with a large number of inhaled organisms, the age of the patient (less than 1 month or elderly), or the presence of immunosuppression or malnutrition.

Laryngeal involvement usually occurs only in those individuals with the chronic dissemination form of the disease. Mucosal ulcers of the upper aerodigestive tract (including the larynx) and hepatosplenomegaly are the two most common manifestations of this stage of the disease. These ulcers may be found on any part of the larynx and may be mistaken for carcinoma (Donegan and Wood, 1984).

The diagnosis of laryngeal histoplasmosis can be somewhat difficult. Histologically, the lesions may show chronic inflammation, granuloma formation, and even pseudoepitheliomatous hyperplasia (Bennett, 1967). However, multiple small calcifications on a chest radiograph are almost pathognomonic, and the intracellular yeast buds may be seen with either periodic acid-Schiff (PAS) or silver stains. There is also a complement fixation test for histoplasmosis that can be useful if high titers are seen (Donegan and Wood, 1984). Treatment is traditionally intravenous amphotericin B, 0.3 to 0.6 mg/kg/day, up to a total dose of 2 to 4 g. However, there is a care report of a patient successfully treated with oral ketoconazole (Fletcher and Prussin, 1990).

Blastomycosis

Blastomycosis is caused by *Blastomyces dermatidis,* a dimorphic fungus that is a natural soil saprophyte and is found throughout the USA. The mode of infection is presumed to be inhaled spores, and the lung is by far the most common site of involvement. Other organ systems are infected secondarily through hematogenous spread. The skin is the most common extrapulmonary site, followed by bone (Dumich and Neel, 1983). Although the larynx is infrequently affected, blastomycosis is important because its appearance can mimic

a neoplastic process such as verrucous or squamous carcinoma (Fig. 100-1). In fact, at least five patients have been documented in the literature as undergoing either surgery or radiation for squamous cell carcinoma of the larynx when later review of their pathologic condition showed blastomycosis (Dumich and Neel, 1983; Ferguson, 1951; Suen et al, 1980).

Patients with laryngeal blastomycosis typically present with hoarseness as their chief complaint (Dumich and Neel, 1983; Mikaelian et al, 19890. Laryngoscopy typically shows scattered granular, exophytic masses, although ulcerative changes have also been noted. The true cords are by far the most commonly inolved site, with extension onto the false cords often seen. Despite a presumed pulmonary route of infection, the chest radiograph of patients with laryngeal blastomycosis is usually normal (Dumich and Neel, 1983; Mikaelian et al, 1989). Diagnosis is by biopsy, with acute and chronic inflammation, microabscesses, and giant cells being seen. However, the most important histologic finding is pseudoepitheliomatous hyperplasia which can occasionally be misread as indicative of a neoplastic process. Fungal stains, such as PAS or Gomori's, will almost invariably show the organism in its yeast form: a double-walled sphere 8 to 15 microm in diameter with single broad-based buds. The standard treatment is intravenous amphotericin B, given daily until a total dose of 25 to 35 mg/kg has been given. However, there is a report of a patient successfully treated with oral ketoconazole (Payne and Koopman, 1984), and results of a recent, prospective randomized trial of this agent for disseminated blastomycosis suggest that this may be a viable outpatient treatment (National Institute of Allergy and Infectious Disease Mycosis Study Group, 1985).

Cryptococcosis

Cryptococcus neoformans is a budding yeast that histologically may be difficult to distinguish from *Blastomyces dermatididis.* It is found in bird droppings and the surrounding soil. Human infection is via inhaled spores, and the resultant pulmonary disease is frequently mild, transitory, and unrecognized. Hematogenous spread may subsequently occur, especially in immunocompromised patients, and the central nervous system is by far the most commonly affected site. Only two cases of laryngeal involvement have been reported, both in immunocompetent individuals (Reese and Colclasure, 1975; Smallman et al, 1989). Both lesions were exophytic and on the true cords. Histology was remarkable for the presence of pseudoepitheliomatous hyperplasia in both cases, as well as large encapsulated budding yeast cells. One patient was treated successfully with amphotericin B, and the other refused treatment and was lost to follow-up.

Coccidioidomycosis

Coccidioidomycosis, also called San Joaquin Valley fever, is a fungal disease endemic to the southwestern USA and norther Mexico. Infection is via inhaled spores, and the lungs are by far the most common site of involvement. Most long-term residents of endemic regions are exposed, usually as children, and persons travelling through these areas may sometimes acquire the disease. Extrapulmonary spread is rare, and only a few cases of laryngeal involvement have been reported (Boyle et al, 1991; Ward et al, 1977). Surprisingly, more than half of these cases have been children (Hajare et al, 1989). The laryngeal lesions may appear as granulation tissue or ulceration and may cause airway compromise. Histology often shows only the presence of granulomas and an inflammatory infiltrate, so the diagnosis must be

made using fungal stains to demonstrate the typical coccidioidal spherules filled with numerous endospheres. Treatment is intravenous amphotericin B.

Actinomycosis

Actinomycosis is an infection caused by any of several species of *Actinomyces,* a gram-positive, filamentous organism that is intermediate between bacteria and fungi. It is a commensal saphrophyte of the normal mouth flora and is commonly found in tonsillar crypts as well as in the gingiva and oral mucosa. It is thought to become a pathogen when some form of trauma allows it to gain access to an anaerobic environment, such as is provided by devitalized tissue, where it rapidly multiplies. The most common site of infection in the head and neck is the oral caviity, but occasional laryngeal infections have been described (Hughes et al, 19840. The presentation in the larynx is similar to that seen elsewhere: localized tissue induration progresses to an abscess, which, if left untreated, will rupture through to the skin to form a draining fistula. Diagnosis is by histopathology or culture and may be difficult. The presence of pathognomonic "sulfur granules" (actually a conglomeration of *Actinomyces* organisms) is variable, and a large number of commensal microorganisms makes identification of individual *Actinomyces* organisms difficult. Culture results are even less likely to make the diagnosis; the organisms are very fastidious, require an anaerobic culture medium, and may take up to 2 weeks to grow. In a study of 181 cases of actinomycosis, Brown (1973) reported that culture results aided the diagnosis only 20% of the time, with the remainder identified via biopsy specimens.

The treatment of choice is penicillin. For deep-seated infection, 10 to 20 million units/day IV for 4 to 6 weeks, followed by oral penicillin, 2 to 4 g/day for several months, is recommended. For early, superficial infections, the oral regimen alone may be sufficient.

Candidiasis

Acute and chronic infection of the larynx caused by *Candida albicans* has become an increasingly severe problem for otolaryngologists. Although most patients present with a mild form of candidiasis that is secondary too either prolonged use of antibiotics or concomitant radiation therapy for a head and neck malignancy, a more serious form can occur in individuals with AIDS or immunosuppressed patients being treated with systemic chemotherapy. The disease almost always spreads to the larynx from the oral cavity and may be concomitant with extensive esophageal involvement. Grossly the lesion may be confused with cancer; microscopically the lesion may show pseudoepitheliomatous hyperplasia or acanthosis (Hicks and Peters, 1982). Both pseudohyphae and yeast forms can be seen on biopsy. Primary laryngeal candidiasis is very rare in the absence of other disease more proximal in the aerodigestive tract. The treatment of choice is nystatin and possibly ketoconazole. In individuals having chronic candidiasis with tissue invasion and systemic involvement, amphotericin B remains the treatment of choice.

Syphilis

Syphilis is an infectious disease caused by the spirochete *Treponema pallidum.* Most cases are acquired through sexual contact, although congenital syphilis has been described. Acquired syphilis may present in a primary, secondary, or tertiary form. The primary presentation is a painless ulcer or chancre at the point of primary contact, usually on the genital, oral, or anal mucosa. It usually heals in a few weeks. Secondary lesions may apppear as the primary lesion is resolving and can present on any cutaneous or mucosal surface, most commonly as widespread erythematous plaques or nodules. The disease then becomes dormant for years to decades, until the gummatous lesions typical of tertiary-stage syphilis appear in almost any tissue of the body. these lesions are composed of granulomatous nodules containing plasma cells, lymphocytes, epithelial cells, and giant cells, with necrotic, avascular centers. Obliterative endarteritis is seen in the blood vessels surrounding and within the nodules. Occasionally a diffuse, rather than nodular, granulomatous reaction is seen.

Involvement of the larynx by syphilis is rare. Secondary syphilis may present as a diffuse laryngeal hyperemia, accompanied by a coalescing, maculopapular rash, usually of the supraglottic region. Tertiary laryngeal syphilis is usually in the form of a diffuse, nodular, gummatous infiltrate. The nodules may ulcerate or coalesce to form larger nodules (McNulty and Fassett, 1981).

Left untreated, syphilis of the larynx may progress to chondritis, fibrosis, and scarring. Treatment consists of high intramuscular doses of penicillin. Patients should subsequently be observed wiith repeat VDRL testing at 6- to 12-month intervals to detect any recurrence of infection.

Hansen's disease (leprosy)

Hansen's disease, or leprosy, is rare in the USA. Even in areas where the disease is relatively common, most individuals who become infected develop a single acute lesion that heals spontaneously. The portal of entry is thought to be the nasal mucosa; thus nasal ulceration with perforation is common. The larynx is the second most frequent site of involvement in the head and neck.

The lepromatous form of Hansen's disease is the most debilitating and is most common in the head and neck. Laryngeal involvement presents initially as erythematous or nodular edema of the supraglottis and progresses secondarily to the glottis (Sandberg and Shum, 1983). In the absence of definitive treatment, the nodules characteristically enlarge, ulcerate, and heal by scar formation. This scarring may occasionally cause laryngeal stenosis and airway obstruction.

Despite the appearance of this lesion, the patient is often pain free. Diagnosis may be made on the basis of history, the presence of other clinical findings, and evaluation of a laryngeal biopsy or nasal smear. Histopathologic examination of tissue specimens reveals edema with a chronic inflammatory infiltrate and the presence of numerous large foam cells. Acid-fast staining can demonstrate an abundance of *Mycobacterium leprae* (Hansen's bacilli) in the foam cells. Treatment consists of the oral administration of either dapsone or dapsone and rifampin, since dapsone-resistant strains of bacilli are being seen with increasing

frequency in endemic areas. Treatment is continued for 1 to 2 years after the organism can no longer be demonstrated on biopsy of affected areas and may require as much as 5 to 10 years of drug therapy.

Differential diagnosis

Chronic infections in the larynx are often difficult to diagnose because physicians fail to suspect diagnoses other than squamous cell carcinoma. When pseudoepitheliomatous hyperplasia is found on microscopic study, one should think of blastomycosis, candidiasis, or histoplasmosis. In addition to bacterial, fungal, and acid-fast infections, other lesions - such as granular cell tumors, relapsing polychondritis, rheumatoid arthritis, Wegener's granulomatosis, and other autoimmune diseases - should be suspected.

Systemic Diseases Affecting Larynx

Sarcoidosis

Sarcoidosis is a chronic granulomatous disease that may involve any organ system. It often presents in young adults and is more common in women and blacks. Its etiology is unknown. Lymph nodes are the most common site of involvement, followed by the lungs, spleen, and liver. Patients usually present with respiratory complaints (cough, shortness of breath, hemoptysis, etc) or have more generalized symptoms such as fever, weight loss, and fatigue. The larynx may be involved in 3% to 5% of patients, usually in the region of the epiglottis (Devine, 1965; Weisman et al, 1980). The initial stages of laryngeal involvement may be relatively benign, the affected mucosa is often described as being covered with one or more white or brown nodules that eventually coalesce to produce a pale, edematous epiglottis, with lesser changes being seen in other supraglottic structures such as the aryepiglottic folds and false cords. It is often stated that the true cords themselves are rarely involved, possibly because of lack of lymphatics, but Bower et al (1980) reported a 24% incidence of glottic involvement in the 40 cases they reviewed. The lesions are rarely painful, and thus hoarseness or partial airway obstruction may be the first sign of laryngeal involvement (Bower et al, 1980).

The microscopic appearance of sarcoidosis resembles that of miliary tubercles and consists of epithelioid cells, macrophages, and giant cells. These giant cells appear larger than those of tuberculosis and contain more nuclei. Inclusion bodies, such as asteroids and Schaumann's bodies, may be a striking feature of the giant cells. Lesions are conspicuous by their absence of caseation and lack of surrounding lymphocytic infiltration.

Treatment usually consists of long-term administration of oral steroids, but some success has recently been reported with intralesional steroid injection (Krespi et al, 1987). This latter may be particularly useful in patients with partial airway obstruction who may otherwise eventually require a tracheostomy. There have also been several case reports of patients whose disease was refractory to steroids and who were treated with low-dose radiotherapy (Fogel et al, 1984).

Wegener's granulomatosis

Wegener's granulomatosis is a syndrome of unknown etiology that is characterized by the triad of necrotizing granulomas of the respiratory system, a necrotizing vasculitis that may affect other organ systems, and glomerulonephritis. Its most common head and neck manifestation is chronic sinusitis and mucosal lesions of the nasopharynx, but occasional cases of laryngeal involvement have been reported. Waxman and Bose (1986) reviewed several large series of patients with Wegener's granulomatosis and reported an 8.5% incidence of laryngeal involvement. This almost always took the form of a smooth, submucosal subglottic mass. Surprisingly, such a mass was the initial manifestation of Wegener's granulomatosis in one quarter of the patients, whereas in the other three quarters it was a late manifestation of their disease. Treatment consisted of either medical therapy (cyclophosphamide or steroids) or surgical excision, with a suggestion that medical treatment may be more successful in the patient with early laryngeal involvement.

Amyloidosis

Amyloidosis is a disease of unknown etiology that is characterized by the extracellular deposition of fibrillar proteins. Clinicallly, it can be divided into two categories: primary amyloidosis, in which there is spontaneous development of amyloid deposits, and secondary amyloidosis, in which the condition is found in conjunction with some other systemic disease such as rheumatoid arthritis or tuberculosis. Primary amyloidosis can be further broken down into localized and generalized forms. In the former, the amyloid deposits are confined to a single organ system or even to a single location in the body, whereas in the latter, as the name implies, the deposits are found to some extent in almost all tissues.

The larynx is rarely involved with amyloid, with approximately 300 cases reported thus far. The most complete review has been that of McAlpine and Fuller (1964), who summarized the 118 cases known at that time. They noted that most cases of laryngeal amyloidosis are of the localized type, in which amyloid deposits are confined to either the larynx alone or to the respiratory system alone. However, since several studies have shown a 15% to 40% incidence of multiple sites of respiratory involvement (McAlpine and Fuller, 1964; Ryan et al, 1977), any person with laryngeal amyloid requires complete endoscopy to rule out synchronous lesions.

Patients with laryngeal amyloid most often present with hoarseness or stridor, since the most common sites of involvement are the vocal cord, ventricle, and false vocal cord. However, any portion of the larynx may be involved. Amyloid deposits have been described as smooth, pinkish gray masses lying under intact epithelium. Under light microscopy, they appear as amorphous, eosinophilic deposits and may show green birefringence under polarization after being stained with Congo red. The diagnosis can be confirmed using electron microscopy, which will show an interlacing mesh of nonbranching fibrils. Treatment of laryngeal amyloidosis is surgical excision. Since mulptiple treatments for recurrent disease are often required, it is important to use techniques that will minimize trauma to the larynx. To this end, several authors have reported good results with the CO_2 laser (Simpson et al, 1984; Talbot, 1990).