Paparella: Volume III: Head and Neck

Section 2: Disorders of the Head and Neck

Part 5: The Larynx, Trachea, and Esophagus

Chapter 28: Acute and Chronic Laryngeal Infections

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Although there are numerous causes of laryngeal infection, the symptoms produced are limited. The most common complaint is hoarseness, but this can be of variable duration and severity. Often the dysphonia can begin as a mild aberration in vocal quality that is intermittent and then becomes more noticeable and of longer duration. Clinically, the rapidity of the progression, as well as associated symptoms, historic features, social and environmental exposures, and concomitant diseases, assist the physician in formulating a diagnostic strategy. The choice of studies and the ultimate need for laryngoscopy and biopsy can then be determined. Operative intervention is not often needed in this group of disorders.

A distinction should be made between acute and chronic (or less acute) processes. This is important in order to arrive at the appropriate diagnosis and correct treatment, especially for diseases that may proceed rapidly to total airway obstruction. Acute laryngeal infection in adults may progress over several hours, but usually several days elapse from the onset of symptoms to presentation to the physician. In the child, this process may be even quicker owing to many factors such as airway and arytenoid cartilage size, degree of mucosal edema, and exudate formed. At any age, pain is common. The odynophagia or odynophonia may be localized to the site of inflammation or may be referred, often to the ear. It should be remembered, however, that not all acute inflammatory conditions need be infectious.

Chronic infections are more indolent, extending over weeks rather than hours or days. Associated symptoms are less dramatic but may be unrelenting. The causes of these infections are multiple, encompassing the gamut of bacterial, fungal, and viral organisms. The inflammatory response elicited stimulates fibrosis, with sometimes permanent alteration in laryngeal function. The noninfectious conditions that simulate chronic infection are myriad and will be discussed later in this chapter.

History

The historic features of laryngeal infection are largely determined by the rapidity of the process. Acute diseases are often preceded by an upper respiratory tract infection or exposure to infected individuals. More frequently, no specific event can be recalled. The rare occurrence of a laryngeal abscess is usually antedated by an event that disrupts the integrity of the laryngeal framework. Radiation therapy with local infection, chondronecrosis, and trauma (either internal or external) are examples of such events. The patency of the upper airway is of utmost concern in all patients with acute infection. Indeed, the airway can be in jeopardy in patients with more chronic disorders if a secondary infection intercedes. The presence of new-onset stridor is an ominous sign and necessitates evaluation of the adequacy of respiration as well as visualization of the laryngeal airway.

The history of prior infections, whether local or systemic is critical. This is particularly true for fungal diseases as well as for the group of granulomatous disorders. Inquiry should be made as to travel to endemic areas of exposure. Laryngeal tuberculosis usually results from prior pulmonary tuberculosis and this must be ascertained. The status of the patient's immune system will need to be evaluated, particularly if the presumed infection is not easily classified. Patients being treated with chemotherapy for diffuse malignancy will have an impaired immune response, and many organisms can be upper airway pathogens in these patients. This is especially true if pneumonitis is also present or if an endotracheal tube has been inserted. Patients with acquired immunodeficiency syndrome (AIDS) are also more susceptible to those infections.

If the cause of the laryngeal inflammation is not readily apparent, a detailed history can help sort out some of the diagnostic possibilities. Smoking and the associated use of alcohol in the 50- to 60-year-old patient (particularly men) raises the concern of malignancy. Passive exposure to smoke as well as chemical irritants in the workplace can produce chronic laryngeal irritation. Prior endotracheal intubation for a surgical procedure or within an intensive care unit setting can induce laryngeal changes, producing voice alteration and occasionally pain.

Symptoms of substernal discomfort, severe pharyngeal fullness or foreign body sensation in the throat upon arising, and frequent eructation raise the concern of reflux esophagitis and secondary laryngeal inflammation. Patients with arthritis of the cricoarytenoid joint will have manifestations of this disease in other joints prior to laryngeal involvement. Rhinoscleroma, polymorphic reticulosis, and Wegener's granulomatosis may all affect the larynx as the first manifestation of these diseases, but upper respiratory tract symptoms within the nose and paranasal sinuses are more common.

Laryngeal edema can be the first finding in true infections or as a manifestation of an allergic response or angioneurotic edema. A family history of similar episodes or swelling involving the skin or gastrointestinal tract suggests the hereditary form of angioneurotic edema.

Physical Examination and Laboratory Evaluation

In all but the most acute situations, an orderly examination of the head and neck structures, including visualization of the larynx and often auscultation of the chest, is mandatory. An otologic examination, looking for inflammation of the auricle (relapsing polychondritis) or a middle ear effusion (in diseases that cause a concomitant nasopharyngitis), can be of diagnostic assistance. Similarly, the nasal respiratory mucosa can be assessed by intranasal examination. Limitations of mandible motion may be a manifestation of arthritis of the temporomandibular joint. Careful palpation of the neck will reveal the presence of enlarged cervical lymph nodes, either inflammatory or neoplastic. The architecture of the skeletal larynx can be evaluated, and the presence of deformity or pain can be assessed.

Mirror or fiberoptic laryngoscopic visualization of the larynx is of paramount importance. If the patency of the airway is in question, as suggested by stridor, tachypnea, and tachycardia, this part of the examination needs to be done in an environment in which the airway can be controlled, such as in the operating room or even after a tracheotomy has

been performed. Assessment of the laryngeal mucosa, the location of any swelling or erythema, and the status of vocal cord motion is essential. A lateral plain neck radiograph can help discern the presence of supraglottic or retropharyngeal swelling, a soft tissue density in the subglottic airway, or the integrity of the vertebral bodies. Computed tomography (CT) scan also play a major role in the evaluation of soft tissue swelling, cartilage destruction, or the degree of cervical adenopathy. Currently, magnetic resonance imaging (MRI) is not as helpful as CT scans in the depiction of laryngeal disorders; however, refinements in the technique may increase the value of this study.

Hematologic tests should not be overlooked. A complete blood count, including a white blood cell count with differential, should be performed when an infection is suspected. Skin tests or cultures from the nose, throat, larynx, or blood may be indicated. Other specific tests, such as determination of immunoglobulin levels, erythrocyte sedimentation rate, rheumatoid factor, and C1 esterase levels, as well as thyroid function studies, should be obtained based on diagnostic considerations.

Direct laryngoscopy may be required for detailed laryngeal inspection, and it may be useful to obtain tissues for biopsy, culture, and smears to identify the presence of organisms. This is not mandatory in every case. The procedures can expose mucosa and underlying tissue to further extension of an infectious process. Therefore, laryngoscopy should be undertaken when noninvasive studies fail to be diagnostic. Once performed, a thorough evaluation of the aerodigestive tract should be accomplished, including bronchoscopy and esophagoscopy when indicated.

Specific Acute and Chronic Laryngeal Infections

Acute Laryngitis

Supraglottitis

Adult supraglottitis is an acute, potentially life-threatening inflammation of the supraglottic structures. In children, the cause is most commonly infection with *Hemophilus influenzae B.* In adults, however, the cause is often undetermined. Many adult cases caused by *H. influenzae* have been reported, but there are numerous cases in which no bacterial organism has been discovered. Case reports have shown various bacteria such as group A streptococcus, *Staphylococcus aureus*, and *Streptococcus pneumoniae* on throat culture, but this has not correlated with blood culture results. A recent prospective study by Shapiro and associates showed no bacterial growth from multiple culture sites in eight adults with supraglottitis. A viral cause has been postulated but not proved. There are no known predisposing factors such as gender or laryngeal anatomic abnormalities, in this disease.

The clinical history is usually a sore throat that progresses in severity to marked odynophagia, often causing drooling. There may be respiratory distress resulting from laryngeal edema.

A fever is sometimes present. Oropharyngeal, hypopharyngeal, and laryngeal examinations reveal marked edema and erythema of the involved structures. The uvula, base of the tongue, epiglottis, aryepiglottic folds, and false vocal cords are all potential sites of

inflammation, and findings in the oropharynx do not preclude involvement of the supraglottis. Epiglottic abscesses have been reported, but they are less common. Cervical adenopathy is frequently present.

Laboratory evaluation should include a white blood cell count, which is often elevated, and cultures of the throat and blood. The most important diagnostic procedure is laryngoscopy, which is performed using either a mirror or a flexible fiberoptic telescope with the patient in a sitting position. If laryngoscopy cannot be performed, a lateral neck radiograph can be obtained; this has been found to correlate reasonably well with findings on laryngoscopic examination. In pediatric patients or in adult patients in respiratory distress, none of the preceding procedures should be done until an airway is established.

Table 1. Viruses Associated With Laryngitis

RNA Viruses	DNA Viruses
Influenza virus	Adenovirus
Parainfluenza virus	Herpesvirus
Rhinovirus	Epstein Barr virus
Myxovirus	Varicella zoster virus
Paramyxovirus	Variola virus.
Coxsackievirus	
Coronavirus	
Respiratory syncytial virus	

The clinical course of supraglottitis is clearly variable. There appear to be two groups of patients: (1) those with rapidly progressive respiratory compromise leading to death if no airway intervention intercedes and (2) those with a much more benign course involving no respiratory compromise and resolution of all signs and symptoms within several days. There have been several retrospective studies attempting to identify the factors that correlate with the severe form of the disease. Two large studies found that patients who presented with rapid onset of symptoms were more likely to require airway intervention. In a study of 56 patients with supraglottitis, Mayo-Smith and co-workers found that those patients with *H. influenzae* bacteremia were more likely to require airway intervention, but this included only five patients, and the numbers were too small to draw any firm conclusions. The relationship between the microbiologic cause and the clinical course requires further study.

Because of the potentially life-threatening nature of the disease, there have been no prospective treatment studies. The standard therapy is to first secure an airway using intubation if necessary. Cultures can then be obtained, and therapy is started with an antibiotic such as cefuroxime, which will treat beta-lactamase-producing *H. influenzae*. Intravenous steroid administration can be used to decrease airway edema. Humidification is also often helpful. The patient is then observed closely in an intensive care-like setting until any possible airway compromise has resolved.

Laryngotracheitis

Laryngotracheitis, or acute laryngitis, is an inflammation of the larynx usually associated with an upper respiratory infection. The cause of the upper respiratory infection is most often viral. Michel and Weinstein provide a good review of which pathogens are commonly involved (Table 1). It is possible for superinfection to develop from bacteria such as group A streptococci, *Staphylococcus aureus,* or *Streptococcus pneumoniae.* Patients with acute laryngitis are more likely than normal individuals to carry *Branhamella catarrhalis* in the nasopharynx, but laryngeal cultures were not taken from the patients studied, so any causal relationship is hypothetical. The clinical course may begin with nasal congestion, rhinorrhea, and sore throat. Hoarseness develops within 1 to 12 days. Unlike the pediatric population in whom the subglottis often becomes affected, with resultant airway narrowing, adults with laryngotracheitis rarely have airway compromise. The course is most often benign with gradual resolution of symptoms. Treatment measures such as humidification and relative voice rest are sometimes helpful. Antibiotics are rarely indicated.

Diphtheria

Corynebacterium diphtheriae are aerobic gram-positive pleomorphic bacilli that produce a toxin causing diphtheria. Immunization has caused a sharp decline in the incidence of the disease, which is now rare. There are occasional outbreaks in inadequately immunized populations, most often in poor residents of urban or rural slums. Only 12 per cent of all cases in the USA are adults aged 20 years or older. Humans are the only hosts, and infection results from contact with upper respiratory tract secretions. Symptoms include fever, cough, and sore throat. The pharynx and larynx may both be affected; there is mucosal erythema and edema with an early exudate. Within 24 to 48 hours of onset, an adherent gray membrane is evident. The edema and membrane may cause airway obstruction. Cervical adenitis is often present. The toxin may cause myocarditis or cranial nerve paralysis.

Diagnosis rests on cultural isolation of the organism with proof of toxinogenicity. Special media such as Loeffler's are used for inoculation.

The disease is treated by administration of the diphtheria antitoxin. Penicillin is used adjunctively. Tracheotomy should be performed if there is airway obstruction. Immunization using the toxic prevents diphtheria.

Chronic Laryngitis

Bacterial

Tuberculosis

Tuberculosis is caused by infection with the tubercle bacillus *Mycobacterium tuberculosis hominis.* In the past, tuberculosis was a common disease of the larynx. With the dramatic decline in the incidence of tuberculosis in the USA, laryngeal involvement is not rare. Levenson and colleagues estimate that there are fewer than 200 new cases per year in the USA. Laryngeal tuberculosis usually results from bronchogenic spread, that is, infected sputum from pulmonary tuberculosis causing direct contamination of the laryngeal mucosa.

In Auerbach's series of 700 autopsies, 37.5 per cent of which showed laryngeal disease, all but two cases were from bronchogenic spread. Hematogenous spread may also be important. Earlier reports usually described the average patient as a male less than 40 years of age, but more recent series show average patient ages of between 50 and 60 years. There continues to be an approximately 2:1 male to female ratio.

As in other chronic laryngeal infections, the most common symptom is hoarseness. In laryngeal tuberculosis, odynophagia is also a frequent and prominent symptom.

Older case reports demonstrated that most patients had radiologic evidence of advanced pulmonary tuberculosis. Levenson and colleagues found this in a recent series of 20 patients. Other authors have found that far fewer patients with laryngeal tuberculosis had concomitant advanced pulmonary tuberculosis. Bull, for example, notes that 4 of his 10 patients had only minimal pulmonary tuberculosis, and only 1 patient had far advanced pulmonary involvement.

The findings on laryngeal examination are varied. There can be diffuse mucosal edema and erythema, solitary or multinodular lesions, ulceration, and sometimes chondritis. Again, the classic description differs from recent reports. Earlier series showed predominantly posterior commissure involvement, whereas more recent studies show no predilection for this site.

Travis and associates note that in their 13 cases, the clinical and pathologic findings depended on the route of infection. Those with bronchogenic spread predominantly had involvement of the true vocal cords, with local edema, granulomas, reactive hyperplasia, ulceration, and epithelioid tubercles. The clinical course after medical therapy involved healing with minimal fibrosis. In those patients with hematogenous spread, the true and false vocal cords, epiglottis, and aryepiglottic folds, tended to be involved, with "paralaryngeal polypoid edema, hyperplasia, subepithelial acid-fast bacilli and minimal ulceration". Clinically these cases progressed to fibrosis and stenosis, and in several of these patients the laryngeal disease was reactivated even after chemotherapy.

Histologic examination shows nodules or tubercles consisting of epithelioid histiocytes with multinucleated giant cells. There may be central caseating necrosis. The diagnosis, however, should not be made solely on histopathologic grounds. Visualization of the organism is required. Tissue culture and smears provide a definitive diagnosis. In any case, direct laryngoscopy and biopsy should be performed to rule out concomitant laryngeal carcinoma. Standard medical therapy consists of a 3-month course of isoniazid, rifampin, and pyrazinamide followed by 9-month or longer course of isoniazid and rifampin. In many cases, this will result in a dramatic clinical response.

Leprosy

Leprosy is caused by infection with *Mycobacterium leprae*, also known as Hansen's bacillus. These acid-fast bacilli have a unique ability to invade nerves. They multiply preferentially in cooler areas of the body. There are three forms of the disease: (1) tuberculoid, which is the least severe; (2) borderline (or dimorphous); and (3) lepromatous, which is the most advanced disseminated form.

Laryngeal involvement is usually a result of nasopharyngeal or oropharyngeal spread. The most frequently affected site is the epiglottis, followed by the aryepiglottic folds and the arytenoid cartilages. Clinical examination reveals either nodular lesions or ulceration. Eventually, cicatricial scarring may result.

Histopathologic examination shows inflammatory edema, chronic inflammation, epithelioid cells, and sometimes foamy histocytes containing the bacillus. There is no laboratory culture medium available for diagnosis.

The treatment of choice is dapsone, which interferes with folic acid synthesis. In lepromatous leprosy, rifampin is given as an adjunctive treatment.

Syphilis

Syphilis is caused by *Treponema pallidum,* a spiral bacterium. There are various stages of the disease: primary, which is manifested by a chancre; secondary, which is characterized by widespread systemic and cutaneous involvement; and tertiary, which is the noninfectious destructive stage causing a high degree of morbidity and mortality. Laryngeal involvement is seen in the secondary and tertiary stages. In the secondary stage, there are erythematous patches or grayish lesions on the mucous membranes. The tertiary stage is characterized by ulcer, granulomatous infiltration, and fibrosis. Cicatricial stenosis can be a sequela of either stage. Laryngeal involvement in congenital syphilis is similar to that seen in secondary syphilis.

The only specific diagnostic test is identification of the bacteria on darkfield examination. Histopathologic examination shows endarteritis and periarteritis with an occasional granulomatous infiltrate and caseation necrosis. Penicillin is the mainstay of treatment.

Rhinoscleroma

Rhinoscleroma is caused by infection from *Klebsiella rhinoscleromatis,* a gram-negative rod also called von Frisch bacillus. Itis endemic in Central America, and South America, souther and central Europe, Egypt, the East Indies and southwestern Asia. The most common part of the body affected is the nose; laryngeal involvement almost always involves extension from the nose and nasopharynx. There are rare reports of isolated subglottic scleroma without nasal involvement. The glottis and subglottic are the most frequently involved laryngeal sites; the disease can then extend into the trachea and bronchi as well.

There are three clinical phases: (1) the catarrhal stage, manifested by exudative discharge and mucosal edema; (2) the granulomatous stage, with granulomatous nodules and infiltrative lesions; and (3) the cicatricial stage, with scarring and stenosis.

Diagnosis is made by growing the organism in culture. This may be difficult, in which case a biopsy specimen must be taken from an area of active disease. Histopathologic examination shows lymphocytes, plasma cells, Russell's bodies (degenerated plasma cells with large, round eosinophilic material), Mikulicz's cells (foamy vacuolated histiocytes), and gram-negative bacilli. Shum and associates recommend immunohistochemistry for specific

identification of the organism in biopsy specimens.

The standard treatment has been streptomycin and tetracycline. Cephalosporins have also been used. In the sclerotic stage, surgery is often required. Relapses are common, and close followup with repeat culture and biopsy are often necessary.

Actinomycosis

Actinomycosis is a granulomatous disease caused by *Actinomyces israelii,* which are anaerobic gram-positive filamentous bacteria. These bacteria are part of the normal oropharyngeal flora, especially in the tonsillar crypts and gingiva. Local mucosa trauma - for example, from dental extraction or caries - may lead to infection with this organism. The disease spreads along connective tissue planes and may present as an inflammatory mass or as nodules with indurated, discolored overlying skin. Breakdown of the skin leads to draining sinus tracts exuding sulfur granules, which are colonies of *Actinomyces* secreting a yellow substance cementing the filaments together.

The cervicofacial area is the most common site of infection. Laryngeal involvement is relatively rare but has been reported. The larynx is affected by spread to paralaryngeal structures from a cervical focus. This can lead to perichondritis of the laryngeal cartilages. Endoscopic examination may show diffuse erythema, purulent exudate, or an exophytic mass.

Diagnosis, which may be difficult, is made by growing the organism in culture using meticulous anaerobic technique. Penicillin is the treatment of choice and should be continued for several weeks after the lesions have healed. With appropriate medical therapy and surgical drainage and debridement, as necessary, complete recovery can be expected.

Fungal

Histoplasmosis

Histoplasmosis is a systemic infection caused by *Histoplasma capsulatum,* a dimorphic fungus. The two forms are the yeast phase, which grows in human tissue, and the mycelial phase, which grows on culture media such as Sabouraud's glucose agar. The mycelia consist of hyphae-bearing spores called conidia. These conidia reside in the soil; their inhalation causes infection in humans. In the USA, the main endemic regions of this organism are the Ohio Valley and the Mississippi Valley. The source of infection is soil contaminated by bat and bird droppings, for example, in chicken houses and caves.

There are several clinical forms of the disease. The initial infection, called the acute pulmonary form, is a mild respiratory illness with cough and chest pain. Hematogenous spread then occurs, and there are mild systemic symptoms such as fever, malaise, headache, and myalgias. Occasionally there may be oral or laryngeal involvement at this stage.

In a small percentage of patients, the disease develops into a severe, potentially fatal, progressive disseminated form with hepatosplenomegaly, lymphadenopathy, and anorexia. Various organ system manifestations include mucocutaneous lesions, meningitis, pericarditis, adrenal insufficiency, and bone marrow involvement. With mucocutaneous disease, lesions

of the tongue and larynx are the most common; these lesions are submucosal masses that may ulcerate in the larynx. The epiglottis, aryepiglottic folds, and the anterior true and false vocal cords are most frequency affected; there may also be true vocal cord fixation. Diagnosis is made by identifying the organism on biopsy specimens or smears. Periodic acid-Schiff or Gomori's methenamine silver strains will show the yeast forms, which are found in macrophages. Tuberculoid granulomas with lymphocytes and foreign body giant cells can also be seen. Skin tests are unreliable; a positive reaction merely indicates past or present exposure to the organism; false-negative results occur because there is a high rate of anergy among patients with active disease. Complement fixation titers are more helpful. Titers greater than 1:16 are suggestive of the disease. Most authors stress, however, that the unequivocal diagnosis of histoplasmosis is made by isolation of the organism in culture.

Choice of therapy for histoplasmosis depends upon the extent of the disease and the status of the host. According to the current recommendation from the National Institute of Allergy and Infectious Diseases Mycosis Study Group, extrapulmonary or disseminated histoplasmosis in patients with non-life-threatening, non-central nervous system disease is oral ketoconazole. Immunocompromised patients and those with central nervous system involvement should be treated with intravenous amphotericin B. Patients with AIDS and histoplasmosis should be treated with amphotericin B.

Blastomycosis

Blastomycosis, also called North American blastomycosis, is caused by the fungus *Blastomyces dermatitidis.* Like the histoplasmosis organism, *B. dermatitidis* has both a yeast and a mycelial form. The disease, which is almost ten times more frequent in males than in females, occurs predominantly in North America, most commonly in the southeastern USA and also in the Mississippi Valley. The environmental source of the organism is presumed to be the soil, but this has never been actually determined. The route of infection is respiratory, with subsequent hematogenous spread to other organs, including skin, bone, and internal genitals.

The patient may have several weeks or months of respiratory symptoms, such as a productive cough, hemoptysis, and pleuritic pain. Laryngeal involvement present with hoarseness. Bennett summarizes the findings on laryngoscopy in progressive stages of the disease: erythema and granular appearance of the mucosa, small abscesses seen as punctate grayish papules sometimes with yellow nodules, mucosal ulcers covered by gray membrane, fibrosis causing vocal cord fixation, and communicating abscesses causing neck fistulas.

A diagnosis of blastomycosis can be made by identifying the organism in culture or on potassium-hydroxide preparations. Histopathologic examination using special fungal strains will also demonstrate the yeast form of the fungus. Granulomas and abscesses may be present. The presence of characteristic pseudoepitheliomatous hyperplasia can be confused with the atypical epithelial hyperplasia seen in squamous cell carcinoma and mistaken diagnosis have been reported.

Historically, the treatment of blastomycosis has been with amphotericin B, but recent multicenter studies have shown that ketoconazole is as effective and much less toxic. The current recommended treatment of non-life-threatening blastomycosis without meningeal

involvement is oral ketoconazole. Amphotericin B is used for therapeutic failures or if intolerance to ketoconazole is present.

Paracoccidioidomycosis

Paracoccidioidomycosis, also known as South American blastomycosis, is a systemic fungal infection caused by *Paracoccidioides brasiliensis.* It is endemic in Latin America. The symptoms of pulmonary disease are fever, productive cough, and dyspnea. Disseminated disease presents with oropharyngeal ulcers and cervical adenopathy. Progressive granulomatous inflammation can involve the larynx and tracheobronchial tree, in which there is a high incidence of stenosis. The close similarity to North American blastomycosis requires that diagnostic differentiation be made by culture. Ketoconazole is the treatment of choice and is curative in most cases.

Coccidiosis

Coccidiosis is caused by the fungus *Coccidioides immitis,* which is endemic in the San Joaquin Valley of California, and in Nevada, Arizona, and Texas, and also in areas of Mexico and Central America and South America. The organism resides in the desert soil; inhalation causes a respiratory infection that can be self-limited or through hematogenous dissemination, can cause infection almost anywhere in the body. Cancellous bone and the meninges are frequently involved. Single or multiple erythematous lesions are found in laryngeal infection.

Intravenous amphotericin B is the most effective therapeutic agent and should be used for disseminated disease. Ketoconazole is not very effective against coccidioidomycosis, but it may have a place for use in patients who are unable to tolerate the side effects of further amphotericin B therapy.

Candidiasis

Candidiasis is a fungal disease caused by various *Candida* species, of which *Candida albicans* and *Candida tropicalis* are the most virulent. *Candida* species are part of the normal flora of the oropharynx, gastrointestinal tract, vagina, and skin.

There is a spectrum of candidiasis, which may include skin infections; noninvasive overgrowth of the oropharyngeal, gastrointestinal tract, and vaginal mucosae; superficial infections of these mucosal areas; and systemic infection involving internal organs. Predisposing factors include immunocompromised hosts and patients on antibacterial therapy. Chronic mucocutaneous candidiasis (CMC) is a specific disorder occurring in patients with defects in cell-mediated immunity, such as thymic aplasia.

Laryngeal involvement can occur in patients with CMC, esophageal candidiasis, or disseminated candidiasis. Esophageal candidiasis causes dysphagia, and laryngeal involvement causes hoarseness. Oral candidiasis is not necessarily present. The laryngeal mucosa is often ulcerated and covered by a thick white-gray exudate. The organism may be seen on biopsy or culture of laryngeal specimens. Therapy is intravenous amphotericin B.

Aspergillosis

There are multiple species of *Aspergillus*, but the most common species causing aspergillosis are *Aspergillus fumigatus* and *Aspergillus flavus*. The spores are ubiquitous in decaying organic matter, and *Aspergillus* can colonize mucosal surfaces. Invasion occurs in immunocompromised hosts.

Otolaryngologic manifestations include sinus invasion with orbital and central nervous system extension. The larynx may be involved as a consequence of sinusitis, lower respiratory disease, or hematogenous spread. A more acute form of the disease has been reported in a leukemic patient with *Aspergillus* epiglottitis.

The organism tends to cause tissue necrosis by invasion of blood vessels. Diagnosis can be made by identifying the organism in the biopsy specimen. Local disease such as sinusitis is treated by excision. Treatment of invasive aspergillosis is with intravenous amphotericin B.

Rhinosporidosis

Rhinosporidosis is caused by the fungus *Rhinosporidium seeberi,* which has never been grown in culture. The disease occurs most frequently in India and Ceylon. It affects mainly the nose and conjunctiva, but laryngeal infection has been reported. Laryngoscopic examination reveals polypoid lesions with submucosal cysts. Biopsy shows thick-walled cysts with sporangia that are filled with spores. Treatment includes surgical excision of the polypoid lesion.

Parasitic

There are no laryngeal parasites that are endemic in the USA, but foreign travel may result in infection with local parasites. Leishmaniasis, syngamosis, and sporotrichosis have all been reported to affect the larynx.

Disorders that May be Confused with Laryngeal Infections

Nonspecific Laryngitis

Both acute and chronic nonspecific laryngeal inflammation are very common disorders. The acute form rarely comes to the attention of the physician and can result from vocal abuse, from exposure to irritating agents such as tobacco smoke or chemicals in the workplace, or after a mild upper respiratory infection in which the larynx becomes secondarily involved. The prevalent complaint is of progressive hoarseness, which is variable in severity and occasionally leads to complete aphonia. Pain or sore throat may occur. Associated symptoms are not invariably found, and respiratory difficulty is uncommon.

The diagnosis of acute nonspecific laryngitis rests on the exclusion of other possible causes of inflammation. Usually this is not difficult. Inspection of the larynx discloses some degree of true vocal cord edema with swelling in any portion of the larynx. Erythema or dilated mucosal vessels are often observed. The mucosa may be thickened, but no exudate or

discrete mucosal lesions are present. Cervical adenopathy is not present.

Treatment of acute nonspecific laryngitis is based on voice rest, humidification, and elimination of the irritating agent. Symptoms usually resolve within days.

Chronic nonspecific laryngitis is based on voice rest, humidification, and elimination of the irritating agent. Symptoms usually resolve within days.

Chronic nonspecific laryngitis is a diffuse mucosal inflammatory process that eventually leads to epithelial hyperplasia. Unlike the acute form, chronic hyperplastic laryngitis does not revert back to a normal state. The causes and symptoms are the same as in the acute form. Often the irritative cause is not apparent, although a strong association exists between chronic laryngitis and infection in other areas of the respiratory tract, particularly the nose, sinuses, and chest. The same pathologic changes of edema, mucosal hyperplasia, keratinization, and fibrosis have been noted in patients who smoke heavily.

The vocal cords in chronic hyperplastic laryngitis are thickened and dull in appearance, with alterations that can be localized or diffuse. Varying degrees of edema and erythema can be found, but this may represent a superimposed acute process. White patches of hyperkeratosis are often noted. The mucosa is often redundant or flabby and may rarely produce some degree of airway obstruction. Such changes may also occur in the supraglottis and subglottis.

Treatment, as in the acute form, consists of voice rest, elimination of the irritating agents, and humidification, particularly in the winter months when dryness can aggravate the inflammation. Voice therapy can be exceptionally beneficial to improve poor vocal habits and strengthen the vocal musculature. Surgery plays a limited role. Laryngoscopy and biopsy may be warranted when areas appear suspicious for malignancy. Redundant mucosa may need to be excised to improve the airway. Kleinsasser advises removal of only one side at a time with a 3- to 4-week interval between procedures to allow adequate healing and restoration of reasonable vocal quality.

Laryngitis Associated with Gastrointestinal Disease

Inflammation of the posterior larynx leading to contact ulceration is not uncommon. Initially described by Chevalier Jackson, the cause was felt to be primarily vocal abuse. The condition is frequently seen in persons who use the voice excessively and loudly and who exhibit a great deal of emotional stress.

Men are affected far more frequently than are women (ratio of 10:1). Hoarseness is the primary symptom. A sense of local irritation or a lump in the throat are frequent associated complaints. On examination, a heaped-up accumulation of granulation tissue is found over the vocal process of the arytenoid cartilage, usually unilaterally. There is a central ulceration, and most often the area is well circumscribed. Occasionally, the opposite arytenoid cartilage may be affected as the problem progresses. Vocal therapy and voice rest have been the treatments of choice; success at total restoration of normal function and appearance has not been great. Because of the poor therapeutic results, other possible causes have been investigated.

Incompetence of the upper gastrointestinal tract with reflux as the cause of laryngitis was first suggested by Cherry and Margulies in 1968. None of the three patients who composed this initial group presented with symptoms of reflux esophagitis, but in questioning, each patient did have typical complaints of this disorder.

Abnormalities in esophageal barium radiographs support the theory of gastroesophagopharyngeal reflux, as shown by the high incidence of hiatal hernia and reflux of barium. The lack of an abnormal x-ray film does not necessarily mean that reflux may not be the cause of the ulceration, since this can be an intermittent finding. Further investigation with esophageal function tests - that is, esophageal manometry including pH monitoring, acid-perfusion, and acid-clearing tests - disclosed dysfunction in 74 per cent of patients with contact ulcers compared with 30 per cent found in the general population. Mucosal irritation is stimulated by gastric contents bathing the posterior larynx. This then stimulates the nonlinguistic responses or recurrent coughing and throat clearing with rapid approximation of the arytenoid cartilages and further mechanical irritation. The cycle thus begun is self-perpetuating until therapy is directed to the gastroesophageal reflux. The usual measures of elevating the head of the bed, administering antacids and acid-reducing medications, and eliminating alcoholic beverages as well as spicy foods and smoking will bring resolution of symptoms and often of the granulomas.

Gastrointestinal reflux not only can induce contact ulcer formation, with associated laryngitis, but also has been shown to potentially induce subglottic stenosis. Inflammatory changes of the upper airway have also been reported with Crohn's disease of the small intestine. The possible mechanisms that could account for the production of upper airway obstruction may be involvement of the cricoarytenoid joint by an arthritic process of direct narrowing of the airway resulting from submucosal edema. In either case, the presence of laryngeal edema or subglottic narrowing can mimic a chronic infection. Specific and correct diagnosis can be arrived at by elucidating a history of gastrointestinal symptoms, which most often are not volunteered by the patient and must be specifically asked for by the examiner.

Inhalational Injury

An acute thermal injury rarely causes laryngeal mucosal damage in isolation. A history of exposure is apparent, as are facial and nasal burns. Indeed, patients with inhalational thermal injuries will also frequently have extensive burns over half of their bodies. Respiratory tract damage may occasionally be found without facial injury; this event is more commonly due to smoke inhalation. In any case, the primary laryngeal response is edema. Mucosal erythema or even soot particles can be detected with fiberoptic endoscopy. Steam injury is more apparent in the subglottis and trachea, whereas other irritants affect the pharynx, supraglottis, and glottis.

Myriad chemicals may produce laryngeal inflammation. The response varies with the substance and the particular patient's sensitivity to such a substance. Some irritants such as acid fumes or petroleum products can be easily discerned by a thorough inquiry; however, more subtle effects can originate in the workplace. Poorly ventilated spaces have led to stagnation, high foreign body particle density, and a sensitivity response called *the closed building syndrome.* Any region of the upper respiratory tract may be involved. Supraglottic or diffuse glottic edema may occasionally necessitate hospitalization. Re-exposure to the

offending environment can induce a recurrence of symptoms.

Laryngeal Carcinoma and Radiation Injury

As with infection, the earliest symptom of laryngeal cancer is hoarseness. The population at risk for epidermoid carcinoma tends to be adults older than 50 years, usually men, with a strong history of cigarette smoking and also of alcohol use. None of these factors would preclude the possibility of infection. Indeed, the presence of erythroplasia, rather than the more usual finding of leukoplakia, in early lesions can mimic an inflammatory process. Larger tumors may become necrotic and secondarily infected, giving the appearance of infection, save for the large tumor bulk. Endoscopy and biopsy can be necessary to differentiate inflammation from neoplasia.

Not all laryngeal cancers will respond positively to radiation therapy. This is particularly true of infiltrating and deeply invasive lesions. Persistent laryngeal edema after a course of radiotherapy should suggest that the cancer has not been eradicated or has recurred or that necrosis of laryngeal cartilage is taking place. Necrosis and persistent carcinoma may coexist. Short treatment times, wide treatment fields, chronic respiratory tract infection, and arteriosclerosis are factors that predispose to radiation necrosis.

Laryngeal edema and voice change are the most common manifestations of radiation injury. Other symptoms of pain, dysphagia, foul odor, and even formation of a fistula suggest infection. If necrotic tissue becomes infected, treatment directed only at the infection is frequently unsuccessful. Laryngectomy may be required to remove not only the necrotic larynx but also the underlying tumor that is often present.

Intubation Granuloma

Any part of the larynx can be injured after endotracheal anesthesia; however, granulomas typically occur in the posterior aspect of the free edge of the vocal cords. The incidence of this complication of intubation is quite low, with various studies noting anywhere from 1 in 100 to 1 in 20.000 procedures. It appears that over the past 20 years, the occurrence of postintubation complications in general have diminished as awareness of potential infection, scarring, and stenosis has increased. This is despite longer periods of intubation in patients of many ages with multiple disorders.

Intubation granulomas appear more commonly in females and are often bilateral. There is no direct correlation with duration of intubation and occurrence of the granuloma. An excessively large tube diameter will predispose to injury and mucosal irritation. Motion, whether of the head, neck or of the endotracheal tube, will aggravate the mucosal injury. The contact region of the tube against the vocal process and medial aspect of the body of the arytenoid cartilage can thereby become damaged with subsequent perichondritis. Secondary infection can easily occur in debilitated patients. The ulceration produced will induce a granuloma, whether sessile or pedunculated, which is visible after extubation.

Symptoms of vocal alteration, such as hoarseness or a breathy voice (caused by inability to addict the vocal cords), are typical. Dyspnea occurs only if the airway is compromised by a large granuloma or if concomitant stenosis is also present. Granulomas

occur in the posterior third of the larynx and are diagnostic when seen in conjunction with a history of endotracheal intubation. This makes confusion with other laryngeal abnormalities uncommon.

Treatment is by excision, often using the laser, and recurrence is infrequent.

Laryngeal Edema

Edema from a wide variety of causes may occur in any region of the larynx. In the earliest stages, it may be difficult to differentiate from infection, although mucosal injection and erythema are found more often in the latter.

Allergic angioedema may result as a response from provocation induced by foods, inhalants, and drugs. The entire respiratory tract or only an isolated portion of the larynx may be affected. A family history of asthma, hay fever, eczema, or edema may be used to differentiate hereditary and nonhereditary types. Aspirin is the most common cause; sensitivities to chicken, bee stings, house dust, cosmetics, and beef have also been reported. Iodine ingestion as well as tetanus antitoxin and vaccines induce the same response. Laryngeal edema may occur after administration of penicillin, either orally or parenterally, and may be delayed for 1 to 4 hours after exposure.

Systemic findings consist of erythema, flushing, urticaria, bronchospasm, and hypotonia. Acute edema from anaphylaxis can lead to respiratory obstruction. Therapy includes the use of epinephrine, antihistamines, corticosteroids, and intravenous fluids.

Hereditary angioneurotic edema is a genetic disease of dominant autosomal inheritance characterized by a deficiency of the enzymatic inhibition of the first component of the complement activating system. Symptoms usually begin in childhood: 50 per cent before age 7 years and 66 per cent before age 13 years. The frequency of attacks diminishes by middle age. Mortality has been reported to vary from 5 to 50 per cent.

Hereditary angioneurotic edema is frequently associated with gastrointestinal symptoms of recurrent abdominal pain, nausea, vomiting, and diarrhea. Painless nonpruritic swelling occurs frequently in the extremities and face and less commonly in the oropharynx. An erythematous, mottling rash, which is not urticarial, is seen in more than 25 per cent of patients. Precipitating factors include trauma, oropharyngeal or dental procedures, emotional upset or anxiety, and menses. Examination of the larynx reveals pale boggy edematous mucosa. Diagnosis is confirmed by laboratory measurement of abnormally low C1 esterase inhibitor. C4 and C2 levels of the complement system will also be depressed.

The acute attack is treated by purified C1 esterase inhibitor and intubation or tracheotomy to protect the airway. Antihistamines, epinephrine, and steroids are not effective. Maintenance of prophylactic measures include the use of the antifibrinolytic aminocaproic acid and tranexamic acid. Androgen derivatives such as methyltestosterone, danazol, or stanozolol have also been used successfully.

Other possible causes of laryngeal edema include increased capillary pressure due to superior vena cava syndrome, internal jugular vein ligation, lowered plasma osmotic pressure

induced by renal failure, impaired lymphatic flow (eg, from thoracic duct ligation), and increased capillary permeability to proteins. The latter results from disorders such as systemic lupus erythematosus, diabetes mellitus, and agranulocytosis, as well as angioedema, either from drug sensitivity or as a hereditary condition. Edema in this group resolves with treatment of the underling disease process.

Endocrine Disturbances

Disturbances of function of many endocrine glands can alter phonation, sometimes by inducing laryngeal edema that can appear to be infectious. The laryngeal alterations are not specific for each disorder but rather must be taken in context with other signs and symptoms.

Acromegaly causes accelerated laryngeal growth and mucosal hyperplasia, lowering the vocal pitch. This is accentuated by involvement of the cricoarytenoid joint.

Thyroid hypofunction (myxedema) will cause vocalis muscle hypertrophy with deepening of the voice. Mucopolysaccharides may be deposited in the subepithelial space and thereby inhibit movement of the vocal cord. This deposition can thicken the vocal cord and may result in diffuse polyposis.

Premenstrual vocal cord edema increases the bulk of the vocal cords, thereby lowering the vocal pitch.

Pemphigus

Pemphigus vulgaris is an uncommon disease that rarely affects the larynx. When it does, its appearance is characteristic. The epiglottis is thickened, and the valeculla is covered with a white fibrinous exudate that is loosely attached to the submucosa. The surrounding mucosa is erythematous, often with ulceration or sloughing of the superficial layers. Blebs, so typically found in cutaneous areas, are rarely seen in the larynx. These findings are often associated with symptoms of local pain and discomfort and may be the first manifestation of a generalized disorder. Involvement of the larynx can precede the skin lesions by months to years.

Diagnosis is based on histologic examination, which discloses intraepithelial acantholysis caused by disruption of intercellular bridges, as well as immunofluorescent antibody studies.

Pemphigus vulgaris should be differentiated from benign mucous membrane pemphigoid, which can also involve the larynx. Pemphigoid produces subepithelial bullae with subsequent scarring, and the disease has a more chronic, indolent course than that of pemphigus.

Sarcoidosis

Sarcoidosis is an idiopathic chronic granulomatous multisystemic disease that involves the larynx in 1 to 5 per cent of cases. The nose and paranasal sinuses are the most frequently affected head and neck sites. The eyes, parotid glands, facial skin, tongue, oral cavity,

pharynx, esophagus, and trachea can also be affected. Cranial neuropathies (eg, of the recurrent laryngeal and facial nerve) have been attributed to sarcoidosis.

Hoarseness, dysphagia, and dyspnea are the most common symptoms of laryngeal sarcoidosis. Progressive airway obstruction can, however, be the first and only manifestation and is caused by either diffuse edema or exophytic masses.

Sarcoid most commonly affects the supraglottic structures with sparing of the true vocal cords. Vocal cord mobility can be impaired by a neuropathy of the recurrent laryngeal nerve. The appearance of the larynx is that of generalized edema. There may be localized areas of nodularity due to superficial granulomas. The supraglottic structures, particularly the epiglottis, are thickened.

Histologic examination of biopsy specimens shows noncaseating granulomas. The biopsy data must be considered together with the clinical findings in order to establish the diagnosis. Other diagnostic possibilities include tuberculosis, syphilis, histoplasmosis, coccidioidomycosis, blastomycosis, and amyloidosis.

Amyloidosis

In contrast to sarcoidosis, the larynx is frequently a focus of amyloid degeneration. This may result from either localized or systemic disease, a primary or idiopathic process, or as a result of other disorders such as multiple myeloma. Amyloidosis in the localized form may also affect the sinuses, nasopharynx, trachea, and bronchi.

Hoarseness and obstruction are the most common laryngeal symptoms, as would be expected from an infiltrating process. The most common location of a discrete nodule is the laryngeal vestibule, followed by the ventricular folds, aryepiglottic folds, and subglottis.

Diagnosis is based on histologic examination of the biopsy material with special amyloid strains of Congo red, which show birefringence under polarized light. Confirmation by electron microscopy may be needed.

Idiopathic Granulomas

There is a group of idiopathic granulomatous diseases that have often confused clinicians and pathologists. Wegener's granulomatosis, idiopathic midline granuloma, and polymorphic reticulosis are included in this group. The latter two diseases may form a continuum, along with true lymphoma, making definite differentiation difficult. All of these disorders have a predilection for the nose, sinuses, and upper airway. The larynx has been involved in cases of each, although less frequently in idiopathic midline granuloma.

In Wegener's granulomatosis, necrotizing granulomas and vasculitis affect the upper and lower respiratory tracts, along with systemic vasculitis and necrotizing glomerulitis. The upper respiratory tract, lungs, or kidneys may be involved alone or in combination, but isolated glomerulitis is nonspecific. The laryngeal appearance is varied, with friable granulomas or ulcerations being preferentially located in the subglottis. Histologic examination reveals necrotizing vasculitis, epithelioid granulomas, giant cells, and fibrinoid necrosis.

Polymorphic reticulosis is more locally aggressive than is Wegener's granulomatosis. Histologically, there is a characteristic lymphoreticular cellular infiltrate with prominent angiocentricity. Vasculitis and epithelioid granulomas are not present.

Differentiation among the idiopathic granulomas is important, since treatment for Wegener's granulomatosis is systemic (cyclophosphamide) as opposed to localized (radiation) for the others. Airway intervention is determined by the degree of compromise regardless of the cause.

Autoimmune Processes

Systemic lupus erythematosus is associated with lesions of mucous membranes in up to 16 per cent of patients and will occasionally involve the larynx. The spectrum of laryngeal manifestations is numerous and includes mucosal ulceration, nodularity, diffuse inflammation with edema, vocal cord hyperplasia, arthritis of the cricoarytenoid joint, vocal cord paralysis, and acute epiglottitis. The occurrence of an acute inflammation can mimic an infection, particularly if airway obstruction is present. Because of these protean features, diagnosis rests on positive immunologic blood tests as well as on histologic examination.

Relapsing polychondritis is thought to be an autoimmune disorder involving cartilaginous structures of the ears, nose, trachea, larynx, ribs, joints, and eustachian tubes. Symptoms are recurrent, with external ear chondritis occurring in three fourths of patients and the larynx and trachea involved at some time in the course of the disease in more than one half of patients.

Hoarseness and laryngeal pain are manifestations of laryngotracheal inflammation. Loss of cartilaginous support can lead to collapse and stenosis with airway compromise. This is aggravated by mucosal edema. Tracheostomy may be necessary in the acute situation.

The findings of pain, erythema, and edema may at first appear to be due to an infection. Diagnosis is based on the occurrence of recurrent inflammation of two or more sites that contain cartilage. Histologic examination reveals only evidence of inflammation, with cartilage atrophy in the later stages.

Arthritis of the Cricoarytenoid Joint

The cricoarytenoid joint, like other synovial joints can become inflamed, leading to symptoms of local pain and hoarseness. Rheumatoid arthritis is the most frequent cause of arthritis of the cricoarytenoid joint. Other causes include gout, mumps, tuberculosis, syphilis, gonorrhea, Tietze's syndrome, and lupus erythematosus. Trauma may also result in arthritis.

Hoarseness is the most common symptom, often associated with odynophonia and odynophagia during an acute episode. A sense of pharyngeal fullness or a sensation of a lump in the throat is also described. Hoarseness may be present in the more chronic phases. Dyspnea and stridor, especially on exertion, result from either unilateral or bilateral arytenoid cartilage fixation.

Inspection of the larynx will reveal marked limitation or complete immobility of the involved vocal cord. During the acute stage, the arytenoid cartilage mucosa will be edematous and erythematous. Palpation of the arytenoid cartilage reveals decreased or no mobility of the cricoarytenoid joint. The laryngoscopic appearance during the acute phase can resemble an abscess formation.

Treatment is directed to the underlying disease. If the airway is compromised, surgical intervention by arytenoidectomy, arytenoidopexy, or tracheotomy may be required.