

Chapter 87: Infections

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Granulomatous Infection

Granulomatous infection is a serious worldwide problem. It is important to identify a granulomatous infection because for the most part it is amenable to treatment, and without proper intervention considerable morbidity may result. These infections often involve mucous membranes of the oral cavity and cervical lymph nodes. The otolaryngologist - head and neck surgeon may be the first to evaluate the patient; another common situation is that the physician receives a pathology report indicating granuloma on a biopsy specimen and then must establish a specific diagnosis. This chapter is intended to aid the approach to granulomatous infections from both of these viewpoints. Important clinical aspects of diagnosis and treatment of these infections are highlighted. For a more exhaustive review of the microbiology, the reader is referred to standard reference texts.

Histopathologic aspects of granuloma formation

Granuloma is derived from the Latin word *granulum*, which means a small particle of grain. Certain infections and noninfectious agents are capable of evoking a distinctive histologic pattern of chronic inflammation, termed *granulomatous inflammation*. The microscopic hallmark is the granuloma, which is a 0.5 to 2 mm collection of modified macrophages called *epithelioid cells*; this is usually surrounded by a rim of lymphocytes. The epithelioid cells may coalesce and fuse to form a Langhans' or foreign-body type of giant cell. Further histologic description of the central necrosis associated with some granulomas has been utilized by pathologists; however, because there is interpretative overlap and clinical inconsistency, terms such as *caseous*, *gummatous*, *liquefaction*, and so forth are not pathognomonic for a specific etiology.

It is currently well accepted that granuloma formation is initiated by the migration of monocytes and macrophages into an area of inflammatory or immunologic reactivity. However, the precise factors that initiate the formation of a granuloma are not known with certainty. It appears that one common theme in the formation of a granuloma is the inability to dispose of portions of the phagocytized material, which in some way signals the macrophage to transform into the epithelioid cells. This correlates with the clinical chronicity of most granulomatous infections, such as tuberculosis. It also appears that T-lymphocyte neoplasms can release mediators that stimulate monocytes and macrophages to accumulate and to undergo granulomatous transformation; this may account for the granulomas in selected clusters of cancer cells.

It is important to emphasize that the granuloma is a histologic hallmark of a variety of infectious and noninfectious processes. It is not specific or any one etiology but has a rather predictable host response to a variety of known agents. The following segments of this chapter deal with granulomatous infections, with a descriptive emphasis on aspects of interest to the otolaryngologist - head and neck surgeon.

Anthrax

Anthrax is caused by a gram-positive rod, *Bacillus anthracis*. The skin may become infected as a result of either direct contact with animals infected with anthrax or contact with the anthrax spores that contaminate certain materials, such as goat hair or hides. The cutaneous form accounts for more than 95% of cases. The initial skin lesion begins as a small papule and progresses into a necrotic ulcer with significant surrounding edema. The lesion is painless, and regional lymphadenopathy may be present. *B. anthracis* spores may be inhaled and cause hemorrhagic mediastinitis, or they may be ingested and cause gastrointestinal anthrax; of interest to the otolaryngologist, they may be absorbed by the pharyngeal mucous membranes from contaminated food and lead to local edema and adenopathy.

Care should be observed in the handling of tissue materials to prevent direct cutaneous inoculations at the time of examination or surgery. The organism is usually readily visible on a Gram's stain of material scraped from the ulcer and can be cultured. Penicillin G is the treatment of choice in a dosage regimen of 10 million units every 4 to 6 hours until the surrounding edema subsides. Oral penicillin therapy may then be instituted until the total duration of therapy (10 to 12 days) is completed. In the penicillin-allergic patient, erythromycin or tetracycline may be substituted. The diagnosis should be suspected in anyone with the aforementioned findings and a history of exposure to potentially contaminated material.

Cat-scratch disease

The etiologic agent of cat-scratch disease remains unknown; however, a small, pleomorphic, rod-shaped bacillus was observed within the microabscesses of infected lymph nodes (Wear, 1983). Although the putative organism has been stained and visualized, it has not been cultured.

In 1988 a group of acquired immunodeficiency syndrome (AIDS) patients was reported to have bacillary angiomatosis, an infection characterized by angiomatous lesions of the skin and viscera (Knobler, 1988). A bacterium was identified in these lesions that had similar characteristics to the cat-scratch disease bacillus. Patients responded to antibiotic treatment, most notably erythromycin. Current research is underway to determine if these separately identified bacilli are the same organism.

The mode of transmission of cat-scratch disease is presumably by direct contact from a cat scratch, bite, or lick. In the majority of patients a history of exposure to a cat can be obtained, and a primary inoculation site can be found. The involved cat is generally not ill.

A classic feature of cat-scratch disease is regional lymphadenitis. Associated with this is a primary lesion, which may be a papule, vesicle, or pustule. Proximal lymphadenitis usually appears within 2 weeks after inoculation. The lymph nodes may be tender, but there is no fixation. If suppuration does not occur by 6 weeks, it usually will not occur after that time. The lymphadenopathy usually resolves within 3 months. Involved nodes may include the submental, submandibular, cervical, occipital, and supraclavicular lymphatic channels. Cervical nodes may be equally affected in the anterior or posterior triangles of the neck. Enlarged nodes within the salivary glands may cause symptoms of obstruction and local

inflammation. Concomitant constitutional symptoms include low-grade fever, generalized headache, malaise, myalgias, and anorexia. Other less common manifestations of cat-scratch disease include the ocular glandular syndrome of Perinaud, encephalitis, osteomyelitis, pneumonia, hepatomegaly, splenomegaly, thrombocytopenic purpura, and skin lesions, including erythema nodosum, erythema multiforme, and erythema annulare.

The diagnosis of cat-scratch disease should be considered in anyone presenting with cervical lymphadenopathy. Of primary importance is the history of exposure to a cat along with the presence of a primary lesion. A biopsied lymph node may show a typical picture of multiple necrotic granulomas with microabscesses. The lymph nodes should be stained with Warthin-Starry silver impregnation stain for visualization of the organism. A positive skin test may be helpful in establishing the diagnosis; however, no material is commercially available. The antigen must be developed locally from the material that is aspirated from infected lymph nodes. This is usually not readily available, and the skin test also has the problems of concentration standardization. It is my experience that attempting to utilize the skin test is impractical. The diagnosis is usually established without the need for skin testing. It is important in this situation to obtain a lymph node biopsy for histologic interpretation and appropriate culture and smears to exclude other granulomatous processes.

The management of cat-scratch disease is supportive. Analgesics may be used, along with local therapy (warm compresses). Antibiotics and steroids appear to be of no benefit, except erythromycin, which may be helpful for selected patients with prominent or lingering symptoms. There is no evidence that cat-scratch disease is transmitted from human to human, so the patient does not require any particular isolation, nor should the suspected cat be isolated, since it is usually well and appears to be infectious for only a limited time. If suppuration of nodes occurs, needle aspiration may be indicated to relieve pain. Formal incision and drainage may result in sinus tract inflammation and are not encouraged.

Toxoplasmosis

Toxoplasmosis is a protozoan disease caused by *Toxoplasmosis gondii*. The organism causes infection in a wide variety of different animals. Humans are infected by ingestion of the tissue cysts contained in meats and other food products. Toxoplasmosis can cause severe, life-threatening illness in immunodeficient patients, ocular toxoplasmosis with chorioretinitis, and fetal wasting via a congenital infection acquired by mother during gestation. The reason this infection is of interest to the otolaryngologist is that acute infection is of interest to the otolaryngologist is that acute infection may occur in the normal host manifested by cervical lymphadenopathy and associated symptoms of low-grade fever, malaise, and sore throat. Skin rash and hepatosplenomegaly may also exist.

Specific serologic tests are available, and atypical lymphocytes may be visualized on the peripheral blood smear. With the appropriate clinical setting, the peripheral blood smear is usually enough to establish the diagnosis. Biopsied lymph nodes may show granuloma formation; however, this is not typical. The histopathologic changes typically reveal a reactive follicular hyperplasia with clustered epithelioid histocytes and focal distension of sinuses with monocytoïd cells.

Toxoplasmosis usually is diagnosed as heterophil-negative infectious mononucleosis syndrome. The clinical course is benign and self-limiting, and specific antimicrobial therapy is usually not necessary for the immunocompetent host who develops acute toxoplasmosis.

Actinomycosis

Actinomycosis is a chronic suppurative infection characterized by multiple draining sinuses. Although it is often confused with a fungus, the actinomycete is actually a bacterium with microaerophilic and anaerobic requirements for growth. *Actinomyces* species are endogenous oral saprophytes and thus cause cervical facial infections, which generally follow some sort of dental manipulation or trauma.

Cervical facial actinomycosis usually appears as a painless, slowly enlarging, typically bluish induration at the lower border of the mandible. It is not unusual for fistulization to occur. A second mode of presentation is more representative of an acute pyogenic infection, also occurring at the angle of the mandible or other area of the neck. The physician should nevertheless realize that clinical infection can occur anywhere in the head and neck, including the salivary glands, paranasal sinuses, eye, ear, and face. Cervical fluid actinomycosis can spread without regard to fascial tissue planes. Lymph node involvement is unusual unless involved directly with the infection. Osteomyelitis of the jaw is the most common local complication. On examination, a palpable mass and draining sinuses usually exist. A characteristic purplish coloring of the overlying skin may be seen, and trismus may exist.

The definitive diagnosis of actinomycosis is made bacteriologically. A curettage technique is used to obtain specimens from deep in the sinus tract area. Simple swabbing of the sinus tract may result in contamination from surface organisms. The laboratory should be informed that actinomycosis is suspected, so that the appropriate anaerobic culture technique is utilized. It is also important to obtain material for microscopic examination, since typical sulfur granules may be demonstrated. These sulfur granules are distinctive and represent a mycelial mass that is cemented and mineralized by calcium phosphate. When the sulfur granule is given Gram's stain, gram-positive branching filaments are observed.

In a highly suspicious case, even if cultures are sterile and smears unremarkable, therapy is indicated if other causes are excluded. The drug of choice is penicillin G given intravenously in a dosage of 10 to 20 million units/day for 4 to 6 weeks and followed by oral penicillin, 2 to 4 g/day for an additional 6 to 12 months, depending on the response to therapy. Cervical facial infection has a good prognosis if it is treated early and appropriately. The patient allergic to penicillin can be given tetracycline. Cervical facial actinomycosis is often misdiagnosed initially and has been termed "a masquerader in the head and neck". It is important that the physician be familiar with the varied presentations of cervical facial actinomycosis and suspect it in anyone with chronic draining sinuses or an acute pyogenic neck mass.

Brucellosis

Brucellosis is caused by bacteria of the genus *Brucella*. The infection is transmitted to humans from sheep, reindeer, swine, cattle, and goats. Brucellosis is uncommon in the USA. It principally involves farmers and veterinarians.

The organisms gain entry through the skin, conjunctiva, or oral pharynx, enter the blood stream, and then localize in tissues, evoking a granulomatous reaction. The incubation period is usually 1 to 3 weeks. It is usually an acute febrile illness characterized by headache, fever, chills, and myalgias. Physical findings include lymphadenopathy and hepatosplenomegaly. Complications that may be seen include large-joint arthritis, spondylitis, meningitis, and very rarely endocarditis or pneumonitis.

Since cervical lymphadenopathy is common, the physician may be confronted with a patient who has brucellosis and should consider this diagnosis in anyone who has occupational exposure to potentially infected animals or who has ingested unpasteurized milk. The definitive diagnosis depends on an elevated brucella antibody titer. Blood cultures may also be positive, as may be cerebral spinal fluid and urine cultures. Many patients recover with simple rest and symptomatic care over several weeks; however, an earlier cure is seen with tetracycline therapy.

Tularemia

Tularemia is caused by a gram-negative pleomorphic rod, *Franciscella tularensis*. The natural reservoir appears to involve rabbits and ticks. After inoculation of the organism from a tick bite or via direct contact - for example, through direct hand contact with the tissue of an infected animal - a skin ulcer forms. Regional lymph nodes are involved and show typical granulomatous changes.

Of particular interest to the otolaryngologist is the ulceroglandular, glandular, or oculoglandular presentation of tularemia. In the ulceroglandular presentation, which is the most common, a primary lesion exists, along with tender regional lymphadenopathy. The glandular presentation is similar except that there is no primary skin lesion. The oculoglandular presentation results from entry via the conjunctival sac. Photophobia and decreased visual acuity may exist with cervical and preauricular lymphadenopathy. Also of interest is the oropharyngeal form of tularemia. Previously, it was thought to be primarily a pediatric problem, but in a 1986 report the majority of patients were older than 15 years of age (Luotonen et al, 1986). Patients with oropharyngeal tularemia may have exudative pharyngitis and cervical lymphadenopathy. The peripheral leukocyte differential count may show atypical lymphocytes, and the diagnosis may be confused with infectious mononucleosis.

It is important to consider the possibility of tularemia in anyone presenting with the appropriate exposure history along with fever and lymphadenopathy. The diagnosis may be confirmed by a serum agglutination test. Streptomycin is the drug of choice for treatment.

Treponemal infections of head and neck

The most common and serious treponemal disease in the head and neck region of interest to the otolaryngologist is syphilis, caused by *Treponema pallidum*. *T. pallidum* cannot be cultivated in vitro, and thus diagnosis of syphilis is based on clinical grounds, serologic testing, and direct observation of the organism from a primary lesion. A number of non-pathogenic treponemes can be found in the oral cavity, which may make microscopic examination difficult for the inexperienced observer reviewing a dark-field preparation from

an oral lesion.

Syphilis is usually acquired by sexual contact. It can be spread by kissing or touching a person who has active lesions on the lips or oral cavity. Accidental direct inoculation can occur when handling infected material, and syphilis of the fingers is sometimes seen in medical personnel. Currently a disproportionate number of cases are being reported in homosexual men. After establishing the diagnosis of syphilis, it is important to locate all sexual contacts of the infected patient. It is not unusual to find several other people at risk and in fact incubating syphilis; they should receive epidemiologic treatment.

After *T. pallidum* penetrates the intact mucous membranes, it enters the lymphatics and bloodstream and disseminates throughout the body. Virtually any organ in the body can be invaded. The organisms divide every 30 hours. Clinical lesions appear when a concentration of 10^7 organisms per gram of tissue is reached. The incubation period is directly proportionate with the size of the inoculum.

Syphilis is best understood clinically if divided into various stages: incubating, primary, secondary, latent, and late. The incubation period is usually around 3 weeks but may range from 30 to 90 days. The primary stage refers to the development of the primary chancre lesion, which occurs at the site of initial inoculation. The secondary stage is evidenced 2 to 12 weeks after contact. At this point mucocutaneous manifestations occur. After the secondary stage subsides, the latent period, in which the patient is relatively asymptomatic, begins. During this period the manifestations of secondary syphilis may occur for up to 4 years after initial contact. After this arbitrary time period, late syphilis begins. This is the point at which arteritis of the aorta or central nervous system may occur, with resultant cardiovascular or central nervous system syphilis. Gummas may involve any organ but most commonly the skin, liver, bone, and spleen.

The physician who sees any oral ulcerations should suspect primary syphilis. Usually the ulcer is painless. It may occur on the upper or lower lip, tonsil, tongue, or even - rarely - the larynx. The intraoral lesions usually have a grayish depressed area with some surrounding induration. Painless regional cervical lymphadenopathy may occur at this time. The spirochete can be visualized from scrapings of the chancre area. Pathologically the lymph nodes may have granulomas but are usually characterized by reactive hyperplasia.

The secondary stage of syphilis is the most clinically florid stage of this infection. Oral mucosal lesions are usually seen as white papules or macules. The physician may see other manifestations, including loss of eyelashes, localized alopecia, acute rhinitis, laryngitis, otitis media, and pharyngitis, as well as cutaneous eruptions of the external ear. Regional lymphadenopathy may also occur. The patient may have vague constitutional symptoms, such as malaise and low-grade fever.

A variety of other organ systems may also be infected during the secondary stage. There may be central nervous system involvement with meningitis, renal involvement, gastrointestinal involvement, and musculoskeletal involvement.

The differential diagnosis of secondary syphilis is such that it has been called the great imitator. As a patient enters the latent stage of syphilis, symptoms may resolve. However, mucocutaneous relapses are common manifestations during the latent period. At this point approximately one third of the patients undergo spontaneous and apparent complete remission. One third of the patients have latent disease, and one third develop symptomatic late syphilis. Of those who develop symptomatic late syphilis, one third develop cardiovascular disease, one third develop central nervous system disease, and one third develop gummatous-type lesions.

For the physician the clinical presentation of tertiary syphilis may involve a saddle deformity of the nose with nasoseptal or hard-palate perforation. The syphilitic gumma appears to affect the maxilla more frequently than the mandible, and the gummatous lesion of the tongue may be confused with a carcinoma. Laryngeal involvement presents as a diffuse nodular gummatous infiltrate; perichondritis may occur secondary to ulceration. The temporal bone may be involved with osteomyelitis. Other signs that the physician may see involve cranial nerve injury with resultant vocal cord paralysis, hearing loss, vertigo, or dysphagia.

Finally, syphilis may be passed in utero to the fetus. The clinical signs of congenital syphilis include frontal bossing, short maxilla, saddle nose, protruding mandible, high palatal arch, Hutchinson's incisors, and mulberry molars. Nerve deafness has been reported, and - except in the unusual cases in which middle ear ossicles are involved, with resultant conductive hearing deficit - syphilis causes central neural hearing deficits. There may be a 25% to 38% hearing loss associated with congenital syphilis. The incidence of hearing loss in patients with acquired syphilis is not known.

The diagnosis of syphilis is straightforward. The primary chancre and secondary skin and mucous membrane lesions are usually teeming with spirochetes. They can be seen with appropriate dark field microscopy. In addition, serologic testing has proved useful. Most cases of primary, secondary, and tertiary syphilis have a positive reagin test. In primary and secondary syphilis it is not unusual to have a high titer that returns to normal with successful therapy. In the untreated case the reagin test may eventually revert to low titer or even become negative. A specific antitreponemal antibody test, such as the FTA-ABS or MHA-TP test, helps to confirm the diagnosis. Since there are many causes of a false-positive reagin test, it is imperative that any abnormal serology test be confirmed with an antitreponemal antibody test. If done appropriately, this specific antitreponemal antibody test has few false-positive readings.

The recommended treatment regimen for syphilis of less than 1 year's duration is 2.4 million units of benzathine penicillin G by intramuscular injection; for syphilis of greater than 1 year's duration, 7.2 million units should be given in a regimen of 2.4 million units by intramuscular injection weekly for 3 consecutive weeks; and for neurosyphilis, 4 million units of aqueous penicillin G should be given intravenously every 4 hours for 10 days followed by benzathine penicillin as noted above for syphilis of greater than 1 year's duration. All patients with possible syphilitic hearing loss should be treated for a prolonged period and, unless it is contraindicated, should also receive prednisone, 30 to 60 mg per day.

The physician should be familiar with the Jarisch-Herxheimer reaction. This consists of the abrupt onset of fever, chills, myalgia, headache, tachycardia, vasodilation with flushing, and subsequent mild hypotension after penicillin injection. It is common in secondary syphilis

but can occur in any of the stages. It is usually transient and lasts for only 12 to 24 hours. It is thought to be correlated with release of an endotoxic type of material from the spirochetes in response to penicillin. Patients should be warned of this before treatment so they do not think that they are having an allergic reaction. It should be treated with antiinflammatory drugs such as aspirin, fluids, and rest.

Granuloma inguinale

The infectious agent is *Calymmatobacterium granulomatis*, a gram-negative bacteria. The precise mode of transmission is not known, but it is thought that sexual transmission may play a role. The infection usually presents with an indurated nodule that subsequently forms an exuberant, granulomatous, heaped-up type of ulcer. The lesion may continue to enlarge by satellite lesions, which are painless; and the genitalia are involved in 90% of cases. The most common nongenital site of infection is the oral cavity. A cicatricial type of lesion is most characteristic of the oral manifestations of the infection. Scar formation and contracture result and may be extensive. Diagnosis may be established by scraping the ulcer and observing the causative organism in large histiocytic cells. Tetracycline, ampicillin, and trimethoprim sulamethoxazole have been shown to be effective. The patient responds to treatment with resolution of symptoms and shrinking of lesions within the first several days. Treatment should be continued until the lesions have completely healed. Because of the possible sexual transmission of this disease, an epidemiologic investigation of sexual contacts should be undertaken, and they should be treated too.

Hansen's disease

Although relatively uncommon in the USA, Hansen's disease (leprosy) is one of the major unconquered infectious diseases in the world. It has been estimated that more than 12 million patients may be affected worldwide. The number of reported cases in the USA is increasing primarily as a result of increased immigration. The majority of patients diagnosed with leprosy in the USA have immigrated from Mexico, Puerto Rico, Vietnam, China, India, the Phillipines, or Samoa. The physician should be familiar with the clinical manifestations of this infection; leprosy has classic manifestations in the head and neck.

The causative organism is *Mycobacterium leprae*. When stained by the Ziehl-Neelsen method it is an acid-fast bacillus. It is generally accepted that human-to-human spread is the primary source of infection. The precise mode of transmission is not clear; however, it is known that the nasal discharge of infected patients may contain 10^8 acid-fast organisms per milliliter. It has also been observed that the organism may remain viable in dried nasal secretions for several days. This suggests that infections may well be acquired via the respiratory tract from inhalation of organisms. Other potential sources of infection are breast milk, biting insects, and direct skin-to-skin contact.

Clinically leprosy is best understood by classification based on immunologic, bacteriologic, clinical, and histopathologic findings that appear to correlate with host resistance. On this basis a spectrum of disease activity ranging from full tuberculoid to borderline tuberculoid to borderline lepromatous to full lepromatous has been created. Lesions may be erythematous macules, papules, nodules, or plaques. The area may be anesthetic. The physician may see several varied manifestations of this infection.

Four stages of lepromatous leprosy of the nose have been established, ranging from mucous membrane edema to eventual perforation. The findings consist of atrophy of the anterior nasal bone and alveolar maxillary process with collapse of the nose. The oral lesions may include nodules, ulceration, and scarring. Periodontoclasia as well as macrocheilia may occur. Recurrent ulceration on the lips with scarring may give rise to a fish-mouth deformity. Ulceration and fibrosis of the vocal cords may occur and result in hoarseness, pain, and possibly even airway obstruction eventually. Facial nerve paralysis may occur, as may auditory nerve involvement. Ear deformities are seen in a substantial number of patients and manifest as nodules or ulcerations. Eyebrow and eyelash loss is noted, and a variety of different eye changes may occur, including keratitis and iridocyclitis. Neck adenopathy may be seen.

A biopsy of the skin reveals a spectrum of granulomatous changes, and the organism may be seen within infected lymph nodes.

The physician should be alert to the possibility of leprosy when assessing any patient with a dermatologic, neurologic, or any multisystem complaint who is not native to the USA or western Europe. There are no known blood tests that are diagnostic for leprosy. The most definitive way to establish a diagnosis is to obtain a biopsy of either a lymph node or more preferably a skin lesion. The specimen should be stained specifically for *M. leprae*.

The treatment of leprosy depends on which state of the disease the patient is in. Dapsone, rifampin, chlofazamine, and ethionamide have been used with success. Treatment may be required for a period of several years.

Granulomatous Fungal Infections in Otolaryngology

Most systemic invasive fungal infections evoke a granulomatous tissue reaction. The associated clinical course may be indolent or rapidly progressive. In this section the classic systemic fungal processes commonly seen in otolaryngology practice are discussed.

Candida species

There are several species of candidal organisms, of which *Candida albicans* is probably the most important for humans. *Candida* species are normal commensals and are commonly found on diseased skin, in the gastrointestinal tract, in the female genital tract, and often in the urine of patients with indwelling bladder catheters. For this normal human commensal to become a significant pathogen, there must be some disruption of normal host defense mechanisms. This may be from altered lymphocyte or reticuloendothelial cell function or from deficiency of humoral factors and complement. Other predisposing factors that are important include administration of antimicrobial agents that allow candidal overgrowth and disruption of the normal integumentary system such as occurs with hyperalimentation or other intravascular catheters.

Serious *Candida* infection can afflict almost any organ. The central nervous system, lungs, cardiac valves, kidneys, muscles, joints, intraabdominal organs, and eyes have all been sites of infection. The otolaryngologist most commonly sees involvement with oral thrush. The lesion is characterized by creamy white patches on the tongue and other oral mucosal

surfaces. Oral thrush has been characterized into four different types by Lehner: (1) acute atrophic candidiasis, thought to be a sequela of acute pseudomembranous candidiasis; (2) chronic atrophic candidiasis, a chronic inflammatory reaction under dental plates; (3) angular cheilitis, an inflammatory reaction at the corners of the mouth; and (4) *C. leukoplakia*, which is a firm white plaque involving the cheek, lips, and tongue and which may have a protracted course.

Oral thrush is a nuisance type of problem for most patients, but it may herald a serious underlying problem, such as AIDS or chronic mucocutaneous candidiasis. If there is persistence of infection, relapse, or failure to respond as anticipated, then a search for an immune defect should be undertaken. *C. folliculitis* may involve the head and neck. Infection of the ear, laryngeal infection, and nasal ulcers caused by *Candida* have also been reported.

Chronic mucocutaneous candidiasis is an infection of the skin, mucous membranes, hair, and nails that often has a protracted course. One of the major problems is disfiguring lesions of the face, scalp, and hands. The underlying process appears to be a defective T cell lymphocyte response to *Candida* organisms. The initial manifestation of this disease is usually oral thrush or nail infection. It usually presents in infancy, but the onset may be after 30 years of age, and endocrinopathies, such as hypoparathyroidism and Addison's disease, may subsequently occur.

The treatment of *Candida* infections depends on the site of involvement and whether or not it is a systematic process. Topical antifungal agents are usually successful for oral thrush. Serious candidal infections should be treated with systemic amphotericin B. In certain circumstances, oral 5-flucytosine or ketoconazole may be required in addition to amphotericin B.

Aspergillus species

Aspergillus is a ubiquitous mold. There are several different species; however, *Aspergillus fumigatus* is generally the most important. *Aspergillus* infections are usually acquired by inhalation. A variety of different sites have been infected, including bone, lungs, and brain. The physician may see a fungus ball in a chronically obstructed paranasal sinus. The maxillary sinus is the most common site. Drainage procedures are usually curative in this situation. Occasionally invasive sinusitis may occur, and the patient may show signs of an enlarging mass. Radiographically there may be opacification of the sinus with bony destruction. The patient may have nasal obstruction, proptosis, and pain. As mentioned previously, surgical extirpation of the fungus ball is often curative. In invasive disease, intravenous amphotericin B is also required.

Mucormycosis

Mucormycosis generally refers to a variety of different fungal agents that clinically can cause infection in the lung, gastrointestinal tract, or skin or that can be disseminated. Of particular interest is the well-known rhinocerebral form of mucormycosis. This disease classically appears in a patient with uncontrolled diabetes and acidosis. It has been seen in patients who are on immunosuppressive therapy or have underlying malignancy. The fungus apparently invades through the palate or the mucous membranes of the nose or paranasal

sinuses and then proceeds by direct invasion to involve contiguous structures. Black necrotic lesions may be found on the hard palate of the nasal mucous membrane. The course is usually fulminant, and there is associated headache and symptoms of orbital vein congestion (such as eye irritation, swelling, and lacrimation), and patients may be semicomatose. Findings of cavernous sinus thrombosis may also exist. When such a situation appears, diagnosis and therapy are urgent concerns. Appropriate radiographs should be obtained to delineate the extent of anatomic involvement. Computerized tomography has been shown to be a useful modality in this setting. Appropriate material must be immediately stained and cultured. In the appropriate setting empiric antifungal therapy should be instituted. Bacterial agents have also been implicated, so empiric antibiotic therapy is also indicated until the results of cultures and smears are available.

Cryptococcus neoformans

Cryptococcus neoformans is an encapsulated fungus that reproduces by budding. The most common site of infection is the central nervous system. The lungs may also be infected and on rare occasions other areas as well, such as the heart, liver, and kidneys. Bone lesions may also commonly be seen. Skin lesions may exist in as many as 10% of patients and may commonly appear as painless lesions on the face and scalp. The lesions may appear as small papules, pustules, or soft subcutaneous masses; they may even present with the more typical granulomatous appearance - a large ulcer with slightly undermined edges. There usually is no lymphadenopathy and no oral mucosal lesions. Treatment of cryptococcal disease requires amphotericin B and 5-flucytosine.

Systemic granulomatous fungal infections

Of the deep systemic mycoses, histoplasmosis, blastomycosis, and paracoccidioidomycosis are the three major infections generally affecting the mucous membranes of the head and neck. They all have a common airborne spread of infection, a disseminated form of infection, and similar differential diagnosis.

Histoplasmosis

Histoplasmosis is caused by the fungus *Histoplasma capsulatum*. In a skin testing survey, it appears that the major endemic area is in the central USA. Therefore otolaryngologists are most likely to encounter the disease in the Midwest, particularly in the Ohio and Mississippi river valleys. The organism is acquired via inhalation into the lungs. Acute or chronic pulmonary infection may result. A rare and generally more serious condition, disseminated histoplasmosis, may occur in patients who are immunosuppressed - such as infants and individuals who may have other forms of altered immunity.

It is not uncommon in disseminated histoplasmosis to have oral mucosal lesions. Heaped-up ulcers involving the tongue, buccal mucosa, and larynx may be seen, or plaque-like lesions may appear with subsequent central ulceration. The patient may complain of sore throat, hoarseness, or dysphagia. Systemic symptoms suggestive of disseminated illness include fever, fatigue, and weight loss. The lesions seen in the oral cavity may resemble carcinoma, tuberculosis, or syphilis. Since the oral mucosal lesions may be the initial manifestation or an early manifestation of dissemination, it is important for the physician to

consider this possibility. For accurate diagnosis a biopsy of the lesion must be done for fungus culture and stain. Serologic antibody testing may be helpful but often is not diagnostic. The histoplasmin skin test is of no value in this situation. Treatment of disseminated infection requires amphotericin B.

Blastomycosi

Blastomycosis is caused by *Blastomyces dermatitidis*. Infection caused by this fungus is similar to histoplasmosis, in that it causes an acute and chronic pulmonary infection and also a disseminated form. Oral pharyngeal manifestations are much less common with blastomycosis than with histoplasmosis. The organism is inhaled into the lung and then may disseminate or cause local disease. The usual inflammatory lesion in the lung is characterized by granuloma formation with epithelioid giant cells. This histopathologic picture might not be seen in extrapulmonary sites. As an example, with cutaneous lesions a pseudoepitheliomatous hyperplasia with microabscess formation may be seen that mimics squamous cell carcinoma of the skin. This response may also be seen when the mucosal surfaces of the oral pharynx or mouth are involved.

The thyroid gland and larynx have been implicated on rare occasions as sites of blastomycotic infection. Skin lesions are the most common occurrence after pulmonary manifestations. The lesions usually appear as verrucous lesions that begin as papules or pustules and then become crusted. They may have a gray or violaceous hue to them. The lesions may be mistaken for squamous cell carcinomas. A second type of lesion is more ulcerative, with only slightly raised lesions and a bed of red granulation tissue. Both types of lesions may be seen in the same patient. Similar lesions may occur on the mucous membrane of the nose, mouth, or larynx. If lesion occurs on the face, there usually is no regional lymphadenopathy.

A diagnosis is made by obtaining appropriate specimens for fungal smear and cultures. A serologic antibody test is available and may be helpful in establishing the diagnosis. The presence of a skin lesion implies disseminated blastomycosis and requires systemic antifungal therapy, usually with amphotericin B.

Paracoccidioides brasiliensis

Paracoccidioides brasiliensis is a dimorphic fungus and a major cause of systemic mycosis in Latin America. It is notable that paracoccidioidomycosis has a relatively restricted geographic distribution, extending from Mexico to Argentina. Although cases have been reported in North America, Europe, and Asia, the afflicted patients had previously been residents in the endemic area. Clinically the majority of patients infected with *P. brasiliensis* have an oral mucosal lesion. The lesion may appear as infiltrated or ulcerated areas within the mouth, lips, gums, tongue, or palate or may involve the nose or larynx. They have a granulomatous appearance with some surrounding edema. Ulcerated lesions may have a mulberry-like appearance. Lesions of the skin are also very common and tend to occur around the mouth. They are usually ulcerated and warty appearing, with infiltration into the subcutaneous tissue. Cervical adenopathy is also commonly seen.

This diagnosis should be considered in anyone from an endemic area. Smears and cultures should be taken from lesions. Treatment with a sulfonamide or with amphotericin B or imidazole compounds is indicated.

Tuberculosis and nontuberculous mycobacterial infections

A *Mycobacterium tuberculosis* infection is generally transmitted via inhalation of airborne droplets' nuclei. In the lung a granulomatous reaction occurs, and in most instances this results in tissue hypersensitivity and lesion containment. On occasion the infection may proliferate and go on to cause disseminated tuberculosis from this primary event. The organisms disseminate to various parts of the body; they may lay dormant there for many years but can reactivate at any time in the patient's life.

A much less common method of acquiring *M. tuberculosis* is via direct contact. An example of this is direct skin infection from contamination of an abrasion that might occur during a pathologist's or surgeon's examination of infected tissue.

The nontuberculous mycobacteria and "atypical" mycobacteria are similar to the *M. tuberculosis* organism; however, they are generally less virulent and infect only individuals with some sort of altered immunity. They are generally not susceptible to the usual antituberculous drugs and may be transmitted more commonly via direct cutaneous inoculation; overall they are much more common causes of head and neck infection.

Members of the atypical mycobacterial group have been classified according to their pigmentation and their ability to grow in light or dark laboratory conditions. Probably the most common infection caused by atypical mycobacteria is a corneal ulcer. Its usual mode of transmission is by direct inoculation into the eye via contaminated foreign material. Cervical lymphadenitis is also commonly caused by atypical mycobacteria.

In dealing with an infection caused by an atypical mycobacterium, the physician should be certain to request an appropriate acid-fast smear and culture from several biopsy specimens. In addition, if an atypical mycobacterium is identified, susceptibility testing is necessary because these organisms are often resistant to commonly used antituberculous drugs. Finally the patient should be screened for possible involvement of other organ systems, particularly the lungs.

M. tuberculosis infection of the head and neck is relatively rare. Neck involvement often occurs simultaneously with pulmonary disease. For this reason if a head and neck lesion is suspected of being tuberculous, it is mandatory that a chest radiograph be taken. Skin testing may also be helpful. The skin test with purified protein derivative should be applied with other routine skin antigens, such as mumps, *Candida*, and saline control. This allows for the detection of possible allergy. It is important that the personnel applying the skin test understand the appropriate application and interpretation of any results.

Ocular tuberculosis can occur in the form of uveitis, scleritis, conjunctivitis, or keratitis.

The parotid gland may be involved in one of two syndromes: one is an acute glandular enlargement, and the second is a more chronic asymptomatic lesion. Tuberculosis of the oral cavity may coexist with active pulmonary disease. It is thought to represent self-inoculation from infected sputum. Normal saliva has an inhibitory effect on mycobacteria, so that usually there is a predisposing factor that somehow damages the intact mucosa. This may take the form of poor dental hygiene, trauma, or leukoplakia. The tongue is the most common site of infection in this instance. Tooth sockets, the floor of the mouth, the lips, and the buccal mucosa also can be involved. The lesions may be single or multiple and may be painful. They can take the form of nodules, fissures, plaques, or vesicles. There may be regional lymphadenopathy. Involvement of the pharynx is very rare.

Tuberculosis may present as a chronic ulcer. The patient complains of a chronic sore throat, and a spread via the eustachian tube may result in otitis media. Primary involvement of cervical lymph nodes or lymphadenitis may also be seen with *M. tuberculosis* but is more commonly seen with the atypical mycobacteria. Patients have slow, progressive enlargement of lymph nodes and may have fever, local pain, or malaise. These symptoms do not invariably exist. The anterior nodes are most commonly involved.

Laryngeal tuberculosis at one time was very common. It was thought that the main mode of acquisition was via bronchogenic spread. Laryngeal lesions usually show edema and granulomatous ulcerations. The most common site of involvement is the membranous true vocal cord, usually where multiple lesions are seen. Patients may complain of cough, hoarseness, or a weakened voice and may have some painful swelling or pain, which may radiate to the ear. Tuberculous thyroiditis is uncommon but has been demonstrated in disseminated infections.

The diagnosis and management of tuberculous and non-tuberculous infections in the head and neck regions are essentially the same as for pulmonary lesions. It is important that the organism be identified. Susceptibility testing should be performed to ensure that the organisms are sensitive to the usual drug regimens recommended. Drug treatment has changed in the last several years, so that a shorter course of chemotherapy is usually successful. A regimen of drugs such as isoniazid and rifampin is usually successful if given for 12 months for an *M. tuberculosis* infection. Atypical mycobacterial infections may require longer treatment and involve multiple drug regimens. Surgery has a role in diagnosis but may also be needed for the management of lymphadenitis, extensive lesions, or (for example) salivary glands that are unresponsive to medical therapy.

Acquired Immunodeficiency Syndrome

AIDS has become a worldwide pandemic. Mortality from AIDS is greater than for toxic shock syndrome or Legionnaires' disease, two recently described infectious epidemics. It is estimated that currently in the USA 750,000 people are HIV infected, and of these 300,000 have AIDS. Worldwide it is estimated that at least 6 million people are infected with the AIDS virus. Heterosexual transmission is increasing at an alarming rate. This section highlights areas of interest and concern to the otolaryngologist and describes some of the more prominent head and neck manifestations.

In 1981 AIDS as a clinical entity first was reported in a clustering of gay male patients with Kaposi's sarcoma and another group with *Pneumocystis carinii* pneumonia. Soon thereafter, nongay intravenous drug users were reported with similar diagnoses. Then in 1982 AIDS was diagnosed in hemophiliacs who had received pooled factor VIII products. This epidemiologic data suggested a transmissible infectious agent. In 1983 and 1984 groups working independently identified a virus isolated from AIDS patients to which almost all patients mounted an antibody response. In 1987 it was decided to call this virus human immunodeficiency virus (HIV). It is classified as a retrovirus and is lymphotropic. Once it infects helper lymphocyte cells (CD4), it ultimately kills them. This results in a profound immunodeficiency for the host, with consequent vulnerability to a variety of opportunistic infections. For approximately 1 to 10 years after infection, the patient may appear well but be capable of parenterally transmitting the virus to others; for example, by sexual contact or by shared contaminated needles. Eventually, patients usually develop lymphadenopathy and the CD4 count is depleted to such an extent that various tumors or opportunistic infections appear that cause the primary mortality in these patients.

There are a variety of manifestations of HIV infection that the otolaryngologist may see. Oral candidiasis is a common infection, occurring in the majority of patients at some point in their illness. It mostly presents as thrush, or removable white plaques. Erythematous candidiasis presents as a blotch area of localized erythema. Angular cheilitis with fissures may also be seen. Diagnosis is made by culture or potassium hydroxide smears, demonstrating yeast and hyphal elements. Treatment modalities include oral nystatin or clotrimazole troches. Oral antifungal systemic agents, such as ketoconazole and fluconazole, are sometimes preferred, because they are taken as a once or twice daily regimen, but these drugs are more expensive.

Hairy leukoplakia is an Epstein-Barr virus - induced, abnormal proliferation of squamous epithelial cells. It is a nonmalignant proliferation of squamous epithelial cells. It is a nonmalignant process but has proved predictive of worsening immune function in the HIV-infected patient. It is usually located on the lateral tongue borders. Occasionally, however, it can be seen on the labial or buccal mucosal surface. It is white, and the surface may acquire hairlike projections. It is usually asymptomatic except for cosmetic complaints and a "cottony" dry sensation experienced by some patients. No specific treatment is available, but there are sporadic reports of success with acyclovir, tretinoin, and zidovudine.

Herpes simplex virus can cause ulcerative stomatitis and painful ulcerations, and on occasion varicella zoster and cytomegalovirus can be cultured in association with oral ulcerations. Human papillomaviruses have been reported to cause intraoral warts.

HIV-infected patients may suffer from severe gingivitis, periodontitis, or necrotizing stomatitis. There have been isolated, rare reports of patients with *Histoplasma capsulatum* or *Mycobacterium avium-intracellulare* oral mass lesions and ulcers. In all probability a variety of other infectious agents and causes will manifest with oral lesions, so the otolaryngologist would be well advised to culture and prepare a biopsy specimen of any unusual-appearing lesion in a patient known or suspected to have HIV infection.

Salivary gland enlargement may be seen in association with HIV infection. The etiology is not clear, but is reminiscent of that seen in Sjögren's disease. Patients may have xerostomia or localized discomfort.

I have recently seen an AIDS patient with headache and invasive sinusitis caused by blastomycosis. No intranasal lesions were apparent. Extrapulmonary *Pneumocystis carinii* has been reported from otitis external drainage.

Neck adenopathy may exist, associated with either fungal, mycobacterial, protozoal, or viral infection. Since the adenopathy may represent infection or tumor in this setting, the otolaryngologist often is in the situation of performing a lymph node biopsy.

Infectious agents have been observed on smears and have been cultured from lymph nodes, so in addition to histologic screening for cancer and Kaposi's sarcoma, appropriate cultures and stains for acid-fast, fungal, aerobic, and anaerobic organisms should be requested. When a biopsy is done, the lymph nodes of many patients do not show evidence of tumor or infection but reveal a spectrum of histologic subtypes (Domingo and Chinn, 1983; Guarda et al, 1983; Joachim et al, 1984; Reichert et al, 1983), ranging from follicular hyperplasia to a partial lymphoid depletion with loss of pericortical lymphocytes and poorly defined follicular mantles with variable hyalinization of germinal centers. Multinucleated giant cells may be seen. At the end of the spectrum is lymphoid depletion (burnout) of both B- and T-cell areas. In the absence of infection or obvious cancer, these patients may manifest nonspecific symptoms such as cough, weight loss, diarrhea, fever, and malaise.

It appears that the incidence of squamous cell carcinoma of the tongue is increased in AIDS patients (Lozada et al, 1983). In addition, the intraoral site has been identified as an extranodal presentation of non-Hodgkin's lymphoma in homosexual men (Ziegler et al, 1984). Finally, Kaposi's sarcoma has been the most commonly reported tumor associated with AIDS (Kriegel and Friedman-Kien, 1985). It is much more aggressive than the form previously reported in the USA, which primarily affected elderly individuals. Kaposi's sarcoma may appear with neck adenopathy and may be observed in the oral cavity. The lesions are usually deep blue, brown, or purplish and can appear on either the gingiva or the hard palate.

Diagnosis of HIV infection can be suspected clinically by the appearance of the opportunistic infection, persistent lymphadenopathy, or wasting syndrome, but infection is best confirmed by identifying the presence of HIV antibody. The most commonly used technique is the enzyme-linked immunosorbent assay (ELISA) with a confirmatory antibody test using the Western blot technique. As with any test, there are occasional false-positive and false-negative results. Recently, a new technique called polymerase chain reaction (PCR) has identified HIV DNA sequences that can provide a more accurate diagnosis than ELISA antibody detection.

There is no cure for HIV infection, but antiretroviral therapy with zidovudine (AZT) and di-deoxyinosine (ddI) has slowed the progression of illness. A variety of new agents have been utilized in treating the opportunistic infections that occur. Since treatment is available and the prognosis has improved, it is important to correctly diagnose infected patients at an early stage in their illness.

The risk of acquiring HIV infection during surgery depends on several factors, such as inoculum size, duration of exposure, and type of incident. From available information it appears that if a needle stick injury occurs involving an HIV patient, the risk of transmitting infection to the health care worker is approximately 1 in 300 to 1 in 400. Occupational acquisition has clearly been reported, and even though the risk may appear relatively small, universal precautions and barrier protection, as recommended by the Centers for Disease Control (CDC), should be routinely observed for all patients in the ear, nose, and throat (ENT) surgical setting.

It is of historical interest that the issue of the HIV-infected surgeon has focused on the ENT specialty, in that a primary legal precedent was established in New Jersey in the case of an HIV-infected ENT surgeon (*Behringer v. Medical Center*). The only documented case of transmission of HIV from a health care worker to a patient involved an HIV-infected Florida dentist, presumably because of break in technique or problems with contamination of equipment while working in the oral cavity. The ENT surgeon should be familiar with the CDC guidelines on exposure-prone, invasive procedures and, if the surgeon is infected with HIV, should be familiar with local and state health rules and regulations regarding notification of hospitals, colleagues, and patients. Since the risk of transmitting the HIV infection to a patient in the health care setting is so remote, understandably, there has been vigorous debate about the need to disclose a surgeon's HIV status or the need to modify surgical practice. Public policy interests and legal requirements may more definitively dictate in the future the responsibilities of the HIV-infected surgeon.

Needle-Associated Cellulitis in Drug Addicts

Problems that are both medical (Becker, 1979; Hussey and Katz, 1950; Litt and Schonberg, 1975) and surgical (Geelhoed, 1976; Geelhoed and Joseph, 1974; Pollard, 1973) and that are associated with illicit parenteral drug use have been extensively catalogued in the literature; however, little in the way of head and neck involvement has been reported. Otolaryngologists are familiar with the necrosis of the nasal mucosa that results from the chronic inhaling ("snorting") of heroin or cocaine and the rosette signs of cigarette burns along the neck and clavicular area caused by smoking addicts "nodding off" after IV injections. An assortment of unusual problems associated with the injection of drugs into the neck region has been described. With the increase in illicit drug trafficking and IV abuse, these complications will become more clinically apparent.

The antecubital vein is the preferred site for self-administration of intravascular drugs for most addicts, since it is usually easily accessible. However, it eventually becomes sclerotic after repeated use. Addicts then may utilize other peripheral distal extremity veins, with the "puffy hand" syndrome resulting from venous and lymphatic obstruction (Geelhoed, 1976); they may even use the femoral vein, with potential disastrous complications (Pace et al, 1984). As all these veins are sclerosed, addicts may utilize the internal jugular vein approach. The most commonly utilized site is at the inferolateral aspect of the sternocleidomastoid muscle immediately above the clavicular area. The area is referred to as "the pocket show" (Lewis et al, 1980) to the internal jugular vein. To inject into the internal jugular vein, the addict uses a mirror, performs a Valsalva maneuver to view the external jugular vein, and then injects deep to the protruding external jugular vein toward the suprasternal notch (Bell et al, 1983; Merhar et al, 1981). Alternately the addict may go and have a street "specialist"

inject into this area.

Several different complications have been reported when addicts have utilized this internal jugular vein approach, including pneumothorax (Bell et al, 1983), mycotic aneurysm of the subclavian artery (Ho and Rassekh, 1978), internal jugular vein thrombosis (Merhar et al, 1981), hoarseness or high-pitched voice from direct needle injury to the recurrent laryngeal or vagus nerve or from the local irritative effects of the substance injected, and paralysis thought to be secondary to particulate embolization (Lewis et al, 1980).

Since skin and soft tissue infections account for the most common infections in drug addicts, it is not unexpected that the first published report of a complication of illicit internal jugular vein injection involved a carotid triangle abscess (Sanders, 1976). Since then several cases of neck cellulitis and cervical abscess have appeared (Lewis et al, 1980; Merhar et al, 1981; Zemplyni and Colman, 1984). Physical findings include an inflammatory soft tissue neck mass and trismus with neck extension or head rotation. Computerized tomography may identify small gas bubbles indicative of an abscess and may also identify venous thrombosis (Merhar et al, 1981). Ultrasonography of the neck may not always be feasible because of the local tenderness.

Drug addicts often share drug paraphernalia and do not sterilize the equipment between times of use. It is not uncommon for drug addicts to take prophylactic antibiotics in an attempt to prevent infections (Novick and Ness, 1984). These factors account for some relatively unusual organisms being cultured from skin and soft tissue infections. Organisms such as *Serratia marescens*, *Pseudomonas aeruginosa*, *Eikenella corrodens*, and methicillin-resistant staphylococcal species may be found. To date, the most common isolates associated with neck injection have been *Staphylococcus aureus* and streptococcal organisms.

If one is faced with a neck abscess in a drug addict, it is important to ascertain the precise bacteriologic etiology. Material must be obtained from the abscess for aerobic and anaerobic cultures. Gram's stain and blood cultures should also be obtained. Pending final cultures and interpretation of the Gram's stain, a reasonable treatment regimen might include an aminoglycoside plus an antistaphylococcal agent such as nafcillin. If a pure culture of a gram-negative organisms such as *Pseudomonas aeruginosa* is obtained, then combination therapy with an aminoglycoside plus an anti-pseudomonal penicillin is indicated.

Appropriate drainage of abscesses must be performed in a timely manner. Any patient with a potentially infected neck mass or with scars or needle tracks in the neck region and with peripheral sclerosis of the veins should be suspected of having a potential complication of internal jugular vein injection. In addition to managing the acute problem, the physician should be aware of the other potential associated complications.