Paparella: Volume II: Otology and Neuro-Otology

Section 3: Diseases of the Ear

Part 4: Inner Ear

Chapter 39: Granulomatous Disorders and Related Conditions of the Ear and Temporal Bone

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Granulomatous disorders of the ear and temporal bone comprise a heterogeneous family of diseases linked by a common morphological denominator - the granuloma. Although the term *granulomatous inflammation* frequently calls to mind a select group of diseases (eg, tuberculous and fungal infections), the demonstration of a granulomatous inflammatory process introduces a broad group of diagnostic possibilities. Furthermore, under certain circumstances, diseases typically associated with granulomatous inflammation may present in an unusual fashion. The immunocompromised patient suffering from an opportunistic infection, for example, may be incapable of mounting a fully developed granulomatous inflammatory response. Accordingly, adequate evaluation of the patient with granulomatous disease may require a considerable number of ancillary studies, in addition to routine clinical and histological evaluation. As in all diagnostic endeavors, an atmosphere of effective communication between the primary physician, laboratory consultant, and radiologist is of critical importance in this regard. In this review, consideration is given to some of the basic aspects of granuloma formation in humans, followed by a discussion of the significant granulomatous disorders affecting the ear and temporal bone. For convenience, the latter discussion is divided into infectious disorders, noninfectious inflammatory processes, and selected miscellaneous conditions of controversial origin.

General Aspects of Granuloma Formation

Investigations conducted over the past two decades have added considerably to our understanding of the granulomatous inflammatory process in humans. Comprehensive reviews of much of this work are available in the literature and will not be repeated in detail here; nevertheless, for purposes of this discussion, some of the more salient aspects of the biology of granuloma formation will be presented in brief. *Granulomatous inflammation* may be defined as a special variant of chronic inflammation, characterized histologically by an organized aggregate of mature mononuclear phagocytes. It should be distinguished from other forms of chronic inflammation lacking these closely apposed collections of mononuclear phagocytes, and from *granulation tissue,* best regarded as a repair response. The central figure, then, in the development of granulomatous inflammation is the mononuclear phagocyte (monocyte) and its derivatives - the tissue macrophages, the epithelioid cell, and multinucleated giant cells.

The initial event in granulomatous inflammation, as with other forms of inflammation, is *tissue injury* associated with the presence of a foreign material. Insoluble or poorly digestible substances associated with only minimal tissue injury, in particular, seem especially liable to provoke a granulomatous response in humans. In the typical sequence of granuloma

formation, an initial acute (neutrophilic) inflammatory response is followed by an influx of monocytes at the site of tissue injury. Although the factors responsible for this monocytic influx remain poorly understood, it is clear that certain microorganisms, complement components, and lymphocyte-derived chemotactic factors play a role in this directed migration. At the site of inflammation, these immature monocytes gradually increase in size to assume the morphologic characteristics of mature tissue macrophages and so-called *epithelioid cells.* These changes seen on light microscopy are associated with the development of increased content of certain hydrolytic enzymes, and complex changes at the level of the cell membrane. In addition to chemotactically directed migration, local proliferation of monocytes at the site of the developing granuloma contributes further to the inflammatory cell population. As the tissue phagocytes continue to mature, local cell adhesion increases, contributing to the compact, organized appearance of the granuloma that is evident at the light microscopic level. Fusion of neighboring monocytes, possibly mediated by gamma interferon and other lymphokines, results in the formation of *giant cells,* another feature of the classic granuloma.

Granulomas are divided by some investigators into high-turnover and low-turnover variants, depending on whether the agent inciting granuloma formation is toxic or inert, respectively. Mycobacteria or fungi, for example, exert a toxic effect on tissue macrophages, and are associated with a comparatively high rate of local cell turnover. Those phagocytes responding to more inert substances, such as carbon and lipid debris, are associated with low-turnover kinetics.

Once formed, the granuloma may be accompanied by a number of other changes, including necrosis and infiltration by other types of inflammatory cells. The nature and intensity of these auxiliary changes vary considerably, depending on factors such as the type of primary tissue insult and the host's immune response. Although delayed hypersensitivity, or cell-mediated immunity to the irritating stimulus, is not a prerequisite to granuloma formation in all cases, an intact immune response may significantly modify the *intensity* of the granulomatous response. The immunocompromised patient, accordingly, may be incapable of developing a mature, classic granuloma in the presence of certain opportunistic pathogens.

The ultimate fate of the granuloma is determined by the fate of the priary injurious agent. Should the provoking agent persist in an essentially unaltered form, the granuloma will tend to persist in the tissues. Alternatively, should the inciting agent be partially or completely degraded, the granuloma may resolve. As in the case of granuloma formation, resolution of the granuloma may be influenced by host factors, including the integrity of the host immune response.

With this basic review of granuloma formation and resolution in mind, consideration will now be given to those conditions associated with development of granulomas and related lesions in the ear and temporal bone, as outlined in Table 1. In some instances (eg, tuberculosis) the nature of the primary injurious agent is reasonably well understood; in yet other conditions, such as Wegener's granulomatosis, the primary stimulus to granuloma formation remains obscure.

Table 1. Granulomatous Diseases and Related Conditions of the Ear and Temporal Bone

I. Infectious Diseases
- A. Bacterial infections
  1. Tuberculosis
  2. Syphilis
  3. Hansen's disease
  4. Miscellaneous
- B. Fungal infections
  1. External otomycosis
  2. Fungal infections of the middle ear, inner ear, and supporting structures
     a. Cryptococcosis
     b. Mucormycosis
     c. Aspergillosis
     d. Miscellaneous

II. Noninfectious Granulomas and Related Conditions
- A. Foreign body granulomas
  1. Reactions to implants
  2. Poststapedectomy granulomas
  3. Cholesterol granuloma
- B. Wegener's granulomatosis
- C. Polyarteritis nodosa
- D. Sarcoidosis

III. Miscellaneous Disorders
- A. Histiocytosis X
- B. Xanthoma of the temporal bone
- C. Inflammatory polyps.

Infectious Granulomas

Bacterial Infection

Bacterial infections are among the most common disoders affecting the temporal bone. The majority of bacterial infections of the ear occur in association with an upper respiratory infection. Of the many bacteria capable of producing ear infections, those responsible for most cases of otitis *(Streptococcus pneumoniae* and *Haemophilus influenzae)* are associated with an acute inflammatory response, dominated morphologically by a neutrophilic inflammatory infiltrate. A smaller number of organisms produce a predominantly granulomatous inflammatory reaction. These infections, which differ from the usual bacterial infections of the temporal bone by virtue of their epidemiology, symptomatology, and treatment, as well as their morphologic manifestations, are discussed in following paragraphs.

Mycobacterial Infections of the Ear and Temporal Bone
(excluding Hansen's disease)

Tuberculosis is often regarded as the prototype of the granulomatous disorders. Virtually any organ system in the body may be the site of tuberculous infection, and the

temporal bone is no exception in this regard. Descriptions of tuberculous infection of the ear first appeared in the middle decades of the 19th century, antedating by nearly 30 years Robert Koch's discovery of the tubercle bacillus in 1882. In the early decades of the 20th century, commensurate with the high prevalence of tuberculosis in the general population, tuberculous otitis media and mastoiditis were recognized as a significant health problem, especially in the pediatric population. A 1915 review by Turner and Fraser, for example, implicated tuberculosis in 2.8 per cent of cases of otitis media in children under the age of 15; among patients less than 1 year of age, tuberculous infection was responsible for a staggering 50 per cent of cases of suppurative otitis media. The high prevalence of infection in younger age groups was due, at least in part, to the widespread contamination of milk by *Mycobacterium bovis* in the early decades of this century.

With the advent of improved public hygiene and the development of effective antituberculous therapy over the ensuing decades, the prevalence of tuberculosis declined significantly in western countries. Mycobacterial infections of the temporal bone remain, nevertheless, an important diagnostic and therapeutic challenge, particularly in areas with a high prevalence of pulmonary tuberculosis. Prompt diagnosis may be difficult, owing not only to the declining incidence of the disease, but also to the comparatively nonspecific signs and symptoms that often accompany the infection.

Etiology and Pathogenesis

The majority of instances of mycobacterial infection involving the temporal bone are due to *M. tuberculosis. M. bovis* infection, although formerly a significant problem in western countries, is decidedly less frequent, owing to improved public sanitation and the routine pasteurization of milk. On rare occasions the so-called "atypical" mycobacteria are capable of producing otomastoiditis. *M. fortuitum* has been implicated in at least two cases of mastoiditis in recent years, following otologic surgery and the administration of steroids. Primary infection of the temporal bone due to *M. avium* has been reported in at least one case in the absence of antecedent surgical manipulation or steroid therapy. Distinction between the various mycobacterial species requires culture of the organism, supplemented by appropriate biochemical studies. Accurate identification of the offending organism is of some importance, inasmuch as the various mycobacterial species vary considerably in their susceptibility to available antimicrobial agents.

The pathogenesis of tuberculous otomastoiditis is variable. In many instances, tubercule bacilli apparently gain access to the otic structures via *hematogenous dissemination* from a distant site. In some cases, the primary site of infection (eg, lung) may be readily apparent, whereas in others the distant focus of infection may be obscure. *Lymphatic channels* may provide an additional route of infection. Lymphatic dissemination has been implicated, for example, in those cases of tuberculous mastoiditis complicating cervical tuberculous lymphadenitis. Foci of pharyngeal tuberculosis, similarly, may gain access to the temporal bone via lymphatic tributaries. Finally, *direct extension* of infection to the middle and inner ear via the eustachian tube or external auditory canal has been implicated in some cases of tuberculous otitis. The spread of tubercule bacilli via the eustachian tube may account for the comparatively high prevalence in the past of tuberculous ear infections in infants fed unpasteurized mild. Infection of the ear via the external auditory canal has been implicated

in those rare cases of mycobacterial infection by saprophytic species (eg, *M. fortuitum* and *M. avium).*

Morphology

Mycobacterial infection of the temporal bone may begin in the marrow space of the temporal bone, within the tympanic membrane, or within the mucosa of the middle ear and mastoid air cells. The presence of mycobacteria provokes an initial neutrophilic inflammatory response, rapidly succeeded by an influx of immature mononuclear phagocytes. The poorly digestible liposaccharide coat of the mycobacteria provides a stimulus to granuloma formation, characterized by maturation of the accumulated histiocytes into mature tissue macrophages, epithelioid cells, and giant cells. Lymphocytes, granulation tissue, and varying amounts of mature fibrous tissue may be encountered as the granuloma matures. As delayed hypersensitivity toward the organism develops, multiple foci of cheeselike, or caseous, necrosis develop. Within the tympanic membrane, coalescence of the foci produces multiple perforations; within the middle ear, erosion of the ossicular chain and fallopian canal may occur, with resultant conductive hearing loss and injury to cranial nerve VII.

The granulomatous inflammatory process may extent ultimately into the labyrinth of the temporal bone via the round and oval windows. Contiguous extension to the mastoid process, with obliteration of the mastoid air spaces by necrotic debris and proliferating granulation tissue, may occur as the disease progresses. Destruction of normal osseous structures results in the formation of multiple bony sequestra, some of which may be extruded through draining sinus tracts or membranous perforations. In neglected cases, extension of the granulomatous inflammatory process into the overlying skin and regional lymph nodes may produce persistent fistulae, often in the postauricular region. Medial extension of the inflammatory process into the cranial vault is infrequently encountered, perhaps due to the comparative resistance to infection of the dura mater.

In the later stages of the disease, some evidence of a repair reaction in the form of fibrosis is usually encountered, especially at the periphery of caseous foci. In the presence of extensive necrosis, however, histologic evidence of a repair reaction may be minimal.

Accurate diagnosis of mycobacterial infection in material submitted for pathologic examination requires the demonstration of acid-fast bacilli, using either special stains (vide infra) or in vitro isolation of the organism, inasmuch as other infectious processes may mimic the changes encountered in tuberculosis. Identification of the organism may require examination of multiple tissue sections.

Clinical Manifestations

Tuberculous otitis, although classically a disease of children or young adults, may affect any age group. In a minority of patients, the disease may present as an acute otitis. In the majority of cases, however, the clinical manifestations are those of a chronic, insidious inflammatory process. Early symptoms include a sensation of fullness in the ear, often associated with the gradual onset of painless drainage from the ear. Despite the tissue destruction that may accompany tuberculous otitis, pain is minimal or absent in the majority

of patients in most series. Paralysis of the facial nerve is encountered in approximately 30 to 45 per cent of patients.

Hearing loss presents an important and serious problem in tuberculous otitis. Hearing loss tends to occur early in the course of the disease and is characteristically of greater severity than would be expected based on the clinical extent of the disease. The hearing loss often antedates other symptoms and may be the conductive, sensorineural, or mixed type. Physical examination of the ear in the early stages reveals a hyperemic, thickened tympanic membrane, containing a variable number of yellowish tubercules. Retraction of the membrane is usually absent. As the disease progresses, the upper portion of the tympanic membrane may swell, and the short process of the malleus may become eroded or otherwise obscured. Perforations are commonly encountered within the tympanic membrane, ranging from pinpoint defects to large perforations involving the majority of the membrane. The mucosa of the middle ear is hyperemic and may contain pale granulations. Granulation tissue may be present in sufficient quantity to produce a polypoid mass within the adjacent external auditory canal. Fixation or erosion of the ossicles and the appearance of a caseous auricular discharge are features of long-standing infection. Periauricular and cervical lymphadenopathy are evident in approximately 50 per cent of patients with otic tuberculous infection.

Radiographic studies of the mastoid area reveal evidence of increased soft tissue density in the region of the mastoid antrum in some patients. Bony destruction may be difficult to define; radiographic evidence of sclerosis is uncommon.

Diagnosis

Prompt diagnosis is of paramount importance in cases of suspected tuberculous otitis. The onset of significant hearing loss in a patient with a past history of tuberculosis may be the first clue to the presence of tuberculous otitis; a history of prior tuberculous infection is absent in more than 50 per cent of patients, however. Any persistent aural discharge warrants appropriate microbiologic evaluation. Smears of the aural discharge stained by the Ziehl-Neelsen technique reveal the presence of acid-fast bacilli in up to 20 per cent of cases of tuberculous otitis. Cultures of the external auditory canal are reported to be positive in from 5 to 35 per cent of cases. It must be emphasized that fluid or other tissue submitted to the laboratory in cases of suspected mycobacterial infection should be clearly identified as such, so that materialmay be stained appropriately and cultured on an appropriate medium (eg, Lowenstein-Jensen agar or a comparable solid medium). Physical examination of the nose, pharynx, and lungs may uncover coexistent foci of tuberculous infection. Culture of nasal secretions, the pharynx, sputum, urine, and occasionally gastric washings increase the likelihood of isolating a pathogenic mycobacterial species.

Radiographic examination of the chest, including apical lordotic views, is of value in the evaluation of cases of suspected tuberculosis. Normal chest x-rays have been reported in up to 50 per cent of patients with tuberculous otitis, however; a normal chest radiograph, accordingly, does not preclude a diagnosis of tuberculous otomastoiditis. Finally, the tuberculin skin test may be of additional diagnostic value in suspected tuberculosis cases. The intradermal injection of intermediate-strenght purified protein derivative (PPD) will elicit a standard reaction within 48 to 72 hours in the majority of patients suffering from tuberculous infection. Approximately 20 per cent of patients with clinical evidence of tuberculosis,

however, will fail to react to intermediate-strength PPD injections. In such cases, an injection of second-strength purified PPD may evoke a positive reaction. Inasmuch as the tuberculin test may be positive in patients with *healed* tuberculosis as well as in those with active mycobacterial infection, the positive reaction should be confirmed by appropriate clinical and pathologic examination of infected tissues.

Treamtent and Prophylaxis

Antituberculous chemotherapy remains the mainstay of treatment in mycobacterial infections of the ear and mastoid. A combination of two or three antituberculous agents, including isoniazid, rifampin, ethambutol, ethionamide, streptomycin, and pyrazinamide, is recommended. Four-drug combinations have been utilized in the treatment of rare cases of otomastoiditis caused by atypical mycobacteria (eg, *M. avium* and *M. fortuitum*). With coexistent tuberculous infection involving the pharynx or cervical nodes, surgical removal of diseased tissue may expedite response to drug therapy. Local treatment of the ear in early cases includes removal of accumulated auricular discharge.

In more advanced cases, surgical intervention may be indicated. Subperiosteal abscess, persistent postauricular fistulae, evidence of intracranial extension of the infection, and the presence of cholesteatoma generally mandate surgical intervention. Evidence of cranial nerve VII paralysis or labyrinthitis may indicate the need for surgery, although instances of response of facial palsy and labyrinthitis to chemotherapy have been noted. When surgery is required, the techniques are comparable to those utilized in surgical treatment of chronic suppurative otomastoiditis of any cause.

The prevention of tuberculous infection of the ear is accomplished at several levels. Appropriate public health policies, including pasteurization of milk, remain a major factor in the prevention of aural tuberculosis. Improper nose blowing, iserting foreign bodies in the ear canal, and unnecessary instrumentation may all contribute to the development of tuberculous otitis as well as nontuberculous infections of the ear. The eradication of concomitant foci of active tuberculosis elsewhere in the body is imperative in the treatment of secondary ear infections. Close contacts of infectious cases, especially contacts in the pediatric population, may benefit from chemoprophylaxis with isoniazid.

Treponemal Infections of the Ear and Temporal Bone

Although the origins of the disease are obscure, syphilis has been recognized as a significant health problem since the closing decades of the 15th century. During the latter part of the 15th century and the early decades of the 16th century, the "Great Pox" - a particularly virulent form of syphilis - ravaged much of the population of Europe. Thereafter, the disorder continued to manifest itself in a more subdued form, spread primarily via prostitution and the movements of armies over the European continent. Despite the introduction of effective antimicrobial therapy for syphilis, the infection remains a significant health problem in many countries, including the USA. The 35.241 cases of primary and secondary syphilis reported in the USA in 1987 represent a national incidence of 14.6 cases per 100.000 population, a significant increase over the 9.4 / 100.000 incidence rate reported in 1977. A 500 per cent increase in the incidence of congenital syphilis was reported in New York City between 1986

and 1988, representing the largest increase since the introduction of penicillin for the routine treatment of syphilis in pregnant women in the early 1950s.

Syphilis, one of medicine's "great imitators", is a disease of widely variable symptomatology. Although otologic symptoms may be masked by other clinical features of infection, in some instances, involvement of the ear may be the sole or dominant clinical manifestation of syphilis. The clinical manifestations of aural syphilis, furthermore, may mimic those of other ear diseases. Because of the specificity and effectiveness of antimicrobial therapy in the treatment of early cases, and the comparatively poor response of late acquired or congenital syphilis to medical therapy, prompt recognition of otic syphilis is of importance in the optimal management of the disease.

Etiology and Pathogenesis

Syphilis is caused by *Treponema pallidum,* a thin, filamentous spirochete of the Treponemataceae family. The organism averages 6 to 10 microns in length and less than 0.2 micron in diameter, and contains from 6 to 14 spirals. Because of its small size, the organism cannot be visualized at the level of the light microscope with ordinary bacterial (eg, Gram) stains. Identification of the organism requires darkfield microscopy of fresh tissue, fluorescent antibody techniques, or the use of various silver impregnation techniques on fixed tissue sections. *T. pallidum* cannot be grown in vitro, in contrast to nonpathogenic treponemes, and is destroyed by hearing or prolonged refrigeration. Due to our current inability to cultivate pathogenic treponemas in vitro, the confirmation of treponemal infection rests with serologic studies, clinical evaluation, and the morphologic identification of the organism.

Morphology

The temporal bone and other otic structures may be involved in virtually any stage of either congenital or acquired syphilis. Treponemes apparently gain access to the ear and temporal bone via hematogenous dissemination from a regional or distant primary site. In the case of acquired syphilis, common primary sites in the head and neck region include the lip, oral mucosa, and tonsillar area. At comparable stages, the lesions of congenital and acquired syphilis in the ear are morphologically indistinguishable. That is, the histologic manifestations of early congenital syphilis are comparable to those seen in the secondary stage of acquired infection; changes in late congenital disease bear a resemblance to those seen in the tertiary stages of acquired disease. The earliest histologic changes related to treponemal infection are characterized by a mononuclear inflammatory infiltrate, occasionally dominated by plasma cells, with an accompanying obliterative endarteritis. In some instances, the early inflammatory response gives way to a nonspecific, chronic productive inflammatory response, dominated by dense fibrosis. Such changes are common in the periosteal region in the case of osseous infection. Local ischemia secondary to obliterative endarteritis likely contributes to the fibrous tissue response in such cases. In other instances, the later histologic changes are characterized by the development of so-called gummata. The *gumma* is a focus of granulomatous inflammation, characterized by a central area of coagulation necrosis, surrounded by a well-vascularized zone of epithelioid histiocytes, lymphocytes, and occasional giant cells. A peripheralzone of proliferating fibroblasts and a lymphoplasmacytic inflammatory infiltrate is common. As the lesion matures, the density of the peripheral fibrocollageouns border characteristically increases.

Treponemal organisms can be demonstrated morphologically during both the acute and chronic phases of syphilis. Treponemes are present in large numbers in the ears of infants succumbing to overwhelming early congenital syphilis. Although treponemes characteristically decrease in number as the disease becomes more chronic, the organisms have been demonstrated within the temporal bones of patients suffering from the effects of late congenital syphilis.

The distribution of lesions within the ear in cases of established syphilis is variable. In the inner ear, the histologic picture is often dominated by inflammation of the otic capsule, with or without gumma formation. Secondary resorption of the otic capsule is common and is often accompanied by some degree of endolymphatic hydrops. Within the cochlea, atrophy of the organ of Corti, stria vascularis, and spiral ganglia are frequently encountered. Vestibular changes, including degeneration of the maculae of the utricle and saccule, as well as atrophy of the cristae of the semicircular canals, may be present. Progressive degeneration of the cochlear and vestibular end organs results, in turn, in atrophy of the cochlear and vestibular branches of the eight cranial nerve. Productive periostitis with associated periosteal new bone formation may produce irregularity of the inner margins of the bony labyrinth. In severe cases, the lumina of the labyrinth are obliterated by new bone formation. These latter changes tend to involve the vestibule and semicircular canals to a greater degree than the cochlear system.

Within the middle ear, some degree of submucosal fibrosis is common. Deformities of the middle ear ossicles, notably the crura and footplate of the stapes, may be encountered, as well as fusion of the incudomalleal and incudostapedial joints. Fusion of the head of the malleus with the lateral wall of the attic has also been described in long-standing cases. Perforation of the tympanic membrane complicated by secondary cholesteatoma may produce additional middle ear changes.

Lesions of the external ear may develop during any stage of syphilis, although primary cutaneous lesions are admittedly rare. In secondary syphilis, the wide range of lesions seen in other cutaneous sites may involve the skin of the auricle and external auditory canal. In later stages, gummata may produce distortion of the external ear. Gummatous osteitis in this site may culminate in erosion of the bony portion of the external auditory canal, with the formation of bony sequestra and mucosal ulceration.

Clinical Manifestations

The clinical manifestations of otic syphilis vary with the stage of the disease, as well as the distribution of lesions within the ear. For purposes of discussion, it is reasonable to divide otic syphilis into congenital and acquired forms.

Congenital Syphilis

Congenital syphilis remains a significant public health problem in the USA, despite the development of effective antimicrobial therapy. The persistence of congenital syphilis in this country, estimated to occur in approximately 0.05 per cent of live-born children, is due at least in part to the increased incidence of primary and secondary syphilis in women of childbearing years. The fetus may acquire syphilis in utero at any stage of pregnancy,

including the first trimester. A significant number of cases of syphilis that are acquired in utero terminate in stillbirth. Among live-born infants suffering from congenital syphilis, two major presentations are recognized: *early* congenital syphilis in children under the age of two, and *late* congenital syphilis.

The manifestations of early congenital syphilis are protean, and include pemphigoid cutaneous eruptions, coryza, hepatosplenomegaly, respiratory distress, nephrosis, hematologic abnormalities, enterocolitis, choreoretinitis, and meningitis. Involvement of the ear is not, in general, a prominent feature of early congenital syphilis.

The manifestations of late congenital syphilis differ considerably from the early form of the disease. Hutchinson's classical triad of tooth deformities, interstitial keratitis, and cranial nerve VIII deafness, while uncommon, is virtually pathognomonic for the late for of the disease. Skeletal changes include frontal bossing, high palatal arch, saddle nose deformity, saber tibia, and clavicular deformity. Other manifestations include linear cutaneous scars (rhagades), mental retardation, hydrocephalus, convulsions, paresis, and uveitis. In contrast to early congenital syphilis, otic involvement may be a striking feature of the late congenital form of the disease. The frequency of otic disease in cases of congenital syphilis in reported series ranges from approximately 25 per cent to 38 per cent. Gummata of the external ear and adjacent tissue may produce conspicuous local deformities. Deafness may occur at any time during the course of the disease. In those cases occurring early in childhood, the deafness is characteristically of sudden onset, bilaterally symmetrical, and profound. Vestibular symptoms are often absent. Among those cases occurring in adolescence or adulthood, the symptoms may begin abruptly or gradually, are often asymmetrical, and fluctuate. Hearing loss is characteristically of the sensorineural type secondary to labyrinthine involvement, with the most striking deficit in the lower frequencies; poor speech discrimination and loudness recruitment are typical. A conductive auditory deficit may occur in those cases complicated by middle ear disease. Vestibular symptoms, including vertigo, nausea, and gait disorders, may also be encountered. Approximately one-fourth of patients exhibit a combination of vertigo, hearing loss, and tinnitus, prompting a diagnosis of endolymphatic hydrops. A positive fistula test may be elicited in the absence of a tympanic membrane perforation (Hennebert's sign). CLinical manifestations may mimic those of Ménière's disease, although bilateral involvement and onset of symptoms in childhood favor a diagnosis of congenital syphilis.

Acquired Syphilis

Acquired syphilis, like the congenital form, remains a significant public health problem in the USA. Involvement of the ear may occur at any stage of acquired syphilis. Variable mucocutaneous eruptions, including condylomata lata, may be observed in the auricle and external auditory canal during the secondary phase of the disease; gummata of the auricle may complicate the tertiary phase.

Involvement of the inner ear may be encountered in both early and late acquired syphilis. Patients with acute syphilitis meningitis may develop bilateral profound sensorineural deafness as a result of extension of infection of the vestibulococchlear nerve. Inner ear involvement is well documented in cases of late acquired syphilis. Approximately 20 per cent of patients with latent syphilis, and up to 70 per cent of those with neurosyphilis, manifest

some evidence of cranial nerve VIII impairment. Symptoms and signs, including sensorineural deafness accompanied by vestibular dysfunction, are similar to those observed in late congenital syphilis. Otosyphilis has been recently recognized as an important complication of human immunodeficiency virus (HIV) infection; manifestations appear to be similar to those found in acquired otosyphilis in general but may develop at a more rapid rate than in HIV-negative individuals.

Diagnosis

Because pathogenic treponemes cannot be cultured in vitro, the diagnosis of syphilis rests on the morphologic demonstration of the organism, or on serologic tests for syphilis. Examination of exudative cutaneous lesions by darkfield microscopy permits the identification of treponemes in early congenital syphilis, as well as in primary and secondary stages of postnatally acquired infection. Multiple examinations by an experienced observer may be necessary to demonstrate the organism. *T. pallidum* may also be demonstrated in tissue sections using a variety of silver impregnation techniques (eg, Dieterle, Warthin-Starry). Such impregnation techniques do not distinguish between pathogenic and nonpathogenic organisms, however; in addition, special care must be taken to avoid interpreting artifacts as organisms. Finally, immunofluorescence techniques using primary antibodies directed against *T. pallidum* have been used to demonstrate organisms in tissue sections. Using such techniques, organisms morphologically compatible with *T. pallidum* have been demonstrated in the inner ear of patients with late syphilis, even following the administration of therapeutic doses of penicillin. The persistence of such organisms has been proposed by some authors to explain the comparatively poor response of chronic ear disease to antimicrobial therapy.

Serological tests for syphilis remain the standard in the diagnosis of syphilis beyond the primary stage. Two general types of tests are available for the serologic diagnosis of syphilis. The first group, designated *reagin tests*, measures the antibody response to a lipoidal antigen that arises during the course of treponemal infection. The nontreponemal group of antibodies contains both IgG and IgM; titers vary to some degree with the stage of the disease. The most common reagin tests employed in the clinical laboratory are the VDRL (Venereal Disease Research Laboratory) and RPR (Rapid Plasma Reagin). Reagin tests are typically reactive in cases of early congenital and secondary acquired syphilis. In later stages of the disease, the serum reagin tests may become nonreactive even without therapy. In cases of neurosyphilis, for example, such tests are nonreactive in up to 50 per cent of cases. Following therapy, non-treponemal antibody tests typically become nonreactive within one year of treatment. Finally, it should be noted that a positive reagin test is not specific for syphilis. Up to 40 per cent of all positive reagin tests are classified as false positives. False positive results may be encountered during certain acute nontreponemal infections, following immunization, and in the presence of certain chronic disorders, including drug addition, autoimmune disease, and hyperglobulinemia of any type. The prevalence of false-positive tests increases, in addition, with age.

The second major group of serologic tests for syphilis measures the antibody response to specific treponemal antigens. The two most important serological tests of this type are the fluorescent treponemal antibody absorption test (FTA-Abs) and the microhemagglutionation assay for treponema pallidum (MHA-TP). Antibody titers to specific treponemal antigens are positive in 100 per cent of cases of secondary syphilis. Antibody to specific treponemal

antigens generally persists even in late disease, although serum titers may decline in chronic cases.

Treatment

The treatment of choice of syphilis in all stages is penicillin G. In cases of penicillin hypersensitivity, other antibiotics, including tetracyclines, erythromycin, and the cephalosporins, have been used successfully in the treatment of syphilis. Early acquired syphilis is generally treated using intramuscular benzathine penicillin G. A second dose of benzathine penicillin G administered intramuscularly is recommended by some authorities 1 week after the initial dose. *Very* early syphilis is successfully treated by the same regimen used in the treatment of concomitantly acquired gonorrhoea. Pregnant patients with early syphilis are treated with the same regimen as nonpregnant patients. Hospitalization of pregnant patients during therapy has been recommended by some authors, because of the risk of Jarisch-Herxheimer reaction. Documented adequate therapy of the pregnant mother minimizes the risk of congenital syphilis in the neonate. However, if adequate maternal therapy can not be documented, the infant should be treated for presumed early congenital syphilis.

The treatment of congenital syphilis has been outlined by the Centers of Disease Control (CDC). All infants, regardless of maternal therapy, should be examined carefully at birth and at frequent intervals thereafter until nontreponemal serologic tests for syphilis are negative. Symptomatic infants, or asymptomatic infants with abnormal cerebrospinal fluid, are treated with aqueous crystalline penicillin G, or aqueous procaine penicillin G, for a minimum of 10 days. Asymptomatic infants with normal cerebrospinal fluid are treated with benzathine penicillin G in a single dose.

The treatment of otic syphilis in the early stages is the same as that employed for early syphilis in general. Treatment for late otic syphilis is controversial and not entirely satisfactory. Patients with sensorineural hearing deficits secondary to late syphilis have generally been treated with benzathine penicillin G over an approximately 3-week period. Corticosteroids (eg, prednisone) have been employed concurrently, with appropriate tapering at the end of treatment. Reported responses to regimens employing a combination of antibiotics and corticosteroids have been variable; in general, however, the prognosis for syphilitic deafness in late congenital or acquired disease is poor.

Miscellaneous Bacterial Infections

A variety of bacteria in addition to the mycobacterial and treponemal species discussed above are capable of eliciting a granulomatous inflammatory response. In many of these, aural manifestations may occur concomitantly with other, more striking clinical manifestations.

Hansen's Disease

Hansen's disease, or leprosy, is a chronic granulomatous disease caused by *Mycobacterium leprae*. The infection, documented since antiquity, represents a significant health problem worldwide. It is less common in the USA, although endemic cases have been reported, notably in Florida, Texas, Louisiana, and Southern California. The disorder is

probably spread via direct contact through the skin or mucous membranes of the nose and oral cavity.

Morphology

The lesions of leprosy develop following an incubation period generally ranging from 3 to 5 years. The lesions of leprosy vary in character, depending principally on the immune status of the host, but exhibit a predilection for the cooler areas of the body. Pathologically and clinically, leprosy may be classified into two major forms - *tuberculoid* and *lepromatous* - depending upon the host's immune response. In patients with well-developed cellular immunity, the lesions assume the tuberculoid form, characterized by a granulomatous inflammatory response with well-developed epithelioid cells, giant cells, and lymphocytes. Bacilli are generally few in number. At the other end of the spectrum, patients with a minimal degree of cellular immunity to *M. leprae* develop a tissue reaction characterized by loosely arrayed, often foamy histiocytes containing innumerable acid-fast bacilli. Bacilli may also be demonstrated within nerve sheaths, endothelial cells, and even the epithelial cells of hair follicles. Intermediate degrees of host immunity are associated with histologic alterations that represent a spectrum between the lepromatous and tuberculoid forms: namely, borderline tuberculoid, borderline, and borderline lepromatous patterns. In all forms of leprosy, including intermediate patterns, the inflammatory reaction tends to involve the dermis and superficial nerve trunks. The exuberant histiocytic response in lepromatous leprosy typically spares the epidermis; in contrast, epidermal invasion is common in the tuberculoid variant of the disease. A necrotizing obliterative vasculitis may be encountered in some variants of lepromatous leprosy, especially in patients of Mexican origin (Lucio phenomenon).

Clinical Manifestations

Clinically, a variety of macular or infiltrative mucocutaneous lesions may be encountered in leprosy. In the lepromatous form, lesions tend to be poorly defined; extensive, confluent mucocutaneous involvement is common. Loss of the eyebrows, especially laterally, has been cited as a useful diagnostic feature in lepromatous leprosy. The lesions of tuberculoid leprosy tend to be better-defined, elevated lesions with flat, hypopigmented centers. Neural involvement, manifested by impaired cutaneous sensation, as well as occasional autonomic and motor deficits, may be encountered as the disease progresses.

Virtually any area of the head and neck may be involved in leprosy. *Ear deformities*, present in up to three-fourths of patients with leprosy, are typically limited to the external ear and are associated with diffuse infiltration, discrete nodules, or ulceration. Later, cartilaginous destruction may contribute to further auricular deformity.

Diagnosis

The diagnosis of leprosy rests on the demonstration of acid-fast bacilli, either in tissue biopsies or smears of tissue fluids. A modified acid-fast stain such as the Fite stain, which employs a gentler decolorizing step than the standard Ziehl-Neelsen stain, reliably demonstrates the organism. Although the organism may be grown in vivo in the foot pads ofmice and certain hamsters, the organism cannot be cultured in vitro. Skin tests, such as the

Mitsuda lepromin test, yield a significant number of false positive results and are not recommended as a primary diagnostic maneuver.

Treatment

The drug of choice for leprosy is diaminodiphenylsulfone (dapsone). The drug is administered orally for a prolonged period; in cases of lepromatous leprosy, life-long therapy may be necessary.

Other Bacterial Infections

Other bacteria may rarely be associated with a granulomatous inflammatory response, especially in cases of osteomyelitis. *Salmonella* and *Brucella* species, in particular, may elicit a well-developed granulomatous reaction indistinguishable from tuberculous or fungal infections. Adequate bacteriologic cultures, supplemented with serologic studies, are required for accurate identification of the offending organism. Specific otic manifestations referable to these rare forms of osteomyelitis are not well defined.

Histologic changes in the ear comparable to those noted in rhinoscleroma, a chronic granulomatous inflammatory process due to infection with *Klebsiella rhinoscleromatis,* have been reported in two patients. In one of these patients, otic inflammation occurred concomitantly with more typical nasal mucosal disease. In the second patient, however, inflammation of the middle ear, mastoid, and external auditory canal occurred in the absence of obvious upper respiratory involvement.

Mycotic Infections

The fungi are a heterogeneous and ubiquitous group of organisms which generally exist as saprophytes in soil, dust, and various forms of decaying organic matter. Under most circumstances, fungi are organisms of low virulence, and enjoy a comparatively peaceful coexistence with the human species. In recent years, however, the prevalence of serious fungal infections has increased dramatically because of the increasing use of broad-spectrum antibiotics, corticosteroids, and cytotoxic chemotherapy, as well as the acquired immune deficiency syndrome (AIDS) epidemic. Increasing numbers of cases of fungal infections involving the middle ear and inner ear, in addition to other more common sites, have been reported among immunocompromised patients.

Fungi may infect virtually any portion of the ear and supporting structures. The clinical presentation, therapy, and population at risk for such infections vary with the site of involvement. For purposes of discussion, it is convenient to divide fungal otitis into those infections involving the external ear, and those involving the middle ear, inner ear, and temporal bone.

Mycotic Infections of the External Ear

Fungi have been recognized as a significant cause of external otitis for decades. Fungi may be the primary pathogen in cases of external otitis or, alternatively, may be part of a mixed infection in this location. Although many fungi have been implicated in cases of

external otitis, *Aspergillus* species are the most common isolates, accounting for approximately 70 per cent of cases of external otitis in one series, followed in frequency by *Candida* species.

Etiology and Pathogenesis

The prevalence of fungal otitis externa is greater in areas of high humidity than in those where the humidity is low. Humid conditions presumably allow fungi, which exist as normal saprophytes within the external auditory canal, to proliferate. Alterations in cerumen in an atmosphere of high humidity presumably diminish local resistance to the organisms. In this context, it should be mentioned that a diagnosis of fungal otitis externa requires clinical evidence of *inflammation* of the external ear; by virtue of their normal residence in the external auditory canal, the simple isolation of fungal organisms from this site by the microbiology laboratory is of limited significance.

Clinical Manifestations

The clinical manifestations of fungal otitis externa include a sense of diffuse "irritation" involving the external canal in the majority of patients. Pain, tinnitus, pruritus, aural discharge, and hearing loss may be encountered in 30 to 50 per cent of patients. Examination of the external ear may reveal soft debris or even a frank mycelial plug occluding the external auditory canal. A variable degree of meatal stenosis has been noted in approximately one-third of patients. Manipulation of the auricle tends to exaggerate the local pain in most patients. The skin of the external auditory canal is often excoriated and friable. Ulceration of the epidermis of the tympanic membrane, as well as perforation of that structure, may be seen in a minority of patients.

Diagnosis

Microscopic examination of aural swabs stained with lactophenol blue following potassium hydroxide digestion of the specimen permits presumptive identification of fungal pathogens in most patients with fungal otomycosis. Biopsies of the external auditory canal stained by either the Gomori methenamine silver (GMS) or periodic acid-Schiff (PAS) method also readily demonstrate the organism. Biopsies, in addition, have the advantage of demonstrating actual tissue invasion by the suspected pathogen. *Aspergillus* species are presumptively identified by the presence of uniform, dichotomously branching septate hyphae with terminal conidiophores (fruiting bodies). *Candida* species are characterized morphologically by the presence of budding yeast forms and pseudohyphae. Other fungal genera, including *Penicillium, Cladosporium,* and *Rhizopus,* may be encountered and presumptively identified in biopsy material. Final identification of most fungi, however, rests with in vitro culture and characterization of the organism.

The optimal recovery of organisms for culture requires cooperation between the examining physician and the clinical laboratory. If transportation of the specimen is delayed, the material obtained for culture via biopsy or swab should be refrigerated at 4°C to prevent bacterial overgrowth. Material obtained for culture should be plated on an appropriate culture medium and incubated for a minimum of 30 days. The media employed for the isolation and

identification of fungi fall into two major categories: nonselective and selective. *Nonselective media,* such as Sabouraud's dextrose agar, permit the growth of most fungi, and are useful in the evaluation of suspected external otomycosis. *Selective media* are designed to inhibit the growth of potential bacterial and fungal contaminates via the presence of one or several antibiotics (cycloheximide, penicillin, streptomycin, or chloramphenicol). Because a significant number of cases of external otitis are caused by rapidly growing saprophytes, such selective media may actually inhibit the growth of the organism responsible for the infection.

Treatment

The treatment of most cases of external otomyocis is local. Cleansing and drying of the external auditory canal, coupled with the application of topical antimicrobial agents, results in symptomatic improvement in most patients. Topical nystatin produces fairly prompt improvement in most patients suffering from external otomycosis due to *Candida* organisms.

Mycotic Infections of the Middle Ear, Inner Ear, and Supporting Structures

In contrast to external otomycosis, in which infection can arise in the absence of broad-spectrum antibiotics or immunosuppression, mycotic infections of the middle ear, inner ear, and adjacent structures are primarily a problem of the immunocompromised population. Infection can involve the inner ear and adjacent structures via either *contiguous spread* from the meninges, nasopharynx, or middle ear cavity or by the *hematogenous* route. Of the potential routes of infection, contiguous spread probably accounts for the majority of mycotic infections of the inner ear. Although virtually any fungus is capable of producing both local and systemic infection in the immunocompromised host, the mycoses of greatest importance in the inner ear include cryptococcoss, the mucormycoeses, aspergillosis, and candidosis. All of these organisms are capable of producing a classical granulomatous inflammatory response, although the histologic changes vary from case to case, depending on the specific infectious agent, as well as the status of the host's immune system. *Cryptococcus neoformans,* in particular, may be associated with minimal inflammatory responses in the setting of overwhelming infection. Some organisms, notably *Aspergillus* species and the agents responsible for mucorymycosis, have a special tendency to invade blood vessels. This vascular invasion, with associated arterial and venous thrombosis, is responsible for the extensive tissue necrosis that may be seen in these infections.

The various pathogens implicated in internal otomycosis, their histopathologic features, clinical manifestations, and treatment are discussed in the following paragraphs.

Cryptococcosis

Cryptococcosis is a mycotic infection caused by the yeast *C. neoformans.* The organism is distributed worldwide, and is characteristically recovered in the debris around pigeon roosts. Within the host, and in most tissue culture media, *C. neoformans* grows as spherical, generally encapsulated yeast forms occurring singly and in pairs. In almost all instances, cryptococcal infection begins in the lungs. In patients with adequate host defenses, the infections remains localized and may resolve without symptoms. In patients with primary or secondary immunodeficiency disorders, however, the organism may disseminate to virtually

any organ. The central nervous system is an especially vulnerable site. Central nervous system cryptococcosis probably represents the most common serious form of cryptococcal infection; the infection may present as a localized mass (cryptococcoma) or, more commonly, as a diffuse meningitis. Signs and symptoms referable to the central nervous system are protean, and include evidence of increased intracranial pressure, altered mental status, ocular disorders, seizures, and motor deficits. The cerebrospinal fluid (CSF) changes in most cases include a lymphocytic pleocytosis, although neutrophils may occasionally predominate. CSF protein is elevated, and CSF glucose is reduced in approximately one-half of patients. Definitive diagnosis is accomplished by the demonstration of cryptococcal polysaccharides (cryptococcal antigen) within the CSF, by the demonstration of organisms within the CSF utilizing India ink preparations, and by culture.

Most cases of otic cryptococcosis probably occur secondary to meningeal disease. An estimated 27 per cent of patients with central nervous system cryptococcosis manifest some evidence of hearing loss, generally in the form of a sensorineural deficit.

Morphology

Histologic examination of the temporal bone in fatal cases of otic cryptococcosis reveals infiltration of the nerve trunks in the internal auditory canal by organisms; similar changes may affect the cochlear and vestibular end organs. Severe atrophy of the spiral ganglion cells and cochlear nerve fibers occurs, although the hair-cell population within the organ of Corti may be spared. Involvement of the facial nerve within the fallopian canal has been reported. In tissue sections, the organism appears as a budding yeast form ranging from 5 to 10 microns in diameter. The organisms may be visible in routine hematoxylin and eosin preparations, but are best demonstrated using some modification of the methanimine silver or periodic acid-Schiff stains. Mucicarmine stains accentuate the organism's polysaccharide-rich capsule in many cases. The intensity of the host response varies considerably. In some cases, overwhelming numbers of organisms are encountered without a significant tissue reaction. At the other extreme, well-formed granulomas, complete with epithelioid histiocytes and giant cells, may be present. Intermediate tissue reactions, characterized by more loosely arrayed histiocytes, plasma cells, and lymphocytes may also occur.

Diagnosis. The diagnosis of cryptococcosis is accomplished by the identification of yeast forms in tissue biopsies or body fluids, by the demonstrating of cryptococcal polysaccharide antigen within body fluids, and by isolation of the organism from normally sterile body fluids. The presence of cryptococcal antigen is effectively demonstrated in the laboratory using the latex agglutination technique on CSF, blood, or urine. Approximately 95 per cent of those patients with cryptococcal meningitis and nearly one-third of patients with other forms of cryptococcal infection will develop a positive CSF latex agglutination test. The organism grows well in vitro as 37°C on nonselective media such as Sabouraud's dextrose agar. Those selective media containing cycloheximide may inhibit the growth of some pathogenic strains of *C. neoformans.* The use of non-selective media, accordingly, is recommended for samples obtained from normally sterile body sites, such as CSF. Samples obtained from potentially contaminated body sites, such as sputum, should be plated on selective media.

Treatment. Effective treatment of cryptococcosis, as for most systemic mycoses, requires the prolonged administration of parenteral amphotericin B.

Mucormycosis

Mucormycosis is an opportunistic fungal infection caused by a species of the genera *Rhizopus, Mucor,* and *Absidia.* Mucormycosis is typically an acute, rapidly progressive infection, often associated with poorly controlled diabetes mellitus. The disease is not restricted to this population, however, and may complicate the course of patients debilitated by malnutrition, immunosuppressive therapy, lymphoproliferative disorders, or burn injury. The organisms are widely distributed in decaying organic matter, and proliferate rapidly in the presence of any carbohydrate-containing substances; this rapid growth on carbohydrate-rich materials provides a plausible explanation for the special susceptibility of patients with poorly controlled diabetes to mucormycosis. The organism gains access to the susceptible host through several routes, including the sinonasal tract, gastrointestinal tract, and skin. The resultant clinical manifestations depend on the degree of host debility as well as the portal of entry.

Morphology

Regardless of the site of origin, however, the histologic changes encountered are similar. In tissue, the fungi responsible for mucormycosis are characterized by broad, nonseptate, haphazardly branching hyphae, that are reasonably well demonstrated in hematoxylin and eosin, PAS- or GMS-stained sections. The organisms exhibit a special predilection for blood vessel invasion, which is associated, in turn, with local thrombosis and ischemic necrosis. The host inflammatory response varies from case to case, and from area to area within the same patient. In some instances, host reaction is minimal or absent. In other cases, the invading hyphae are associated with a well-developed neutrophilic inflammatory response. Less frequently, the organisms provoke a granulomatous inflammatory response, especially in chronic lesions.

Clinical Manifestations. As noted previously, the clinical manifestations of mucormycosis depend on the portal of entry as well as on the ability of the host to respond to the infection. Involvement of the ear and temporal bone by mucormycosis generally occurs in the context of rhinocerebral infection; the portal of entry in such cases is presumably the sinonasal tract. Rhinocerebral disease characteristically presents as a fulminant infection involving the sinonasal tract, eyes, and central nervous system. Early sinonasal involvement is heralded by a thick nasal discharge associated with necrosis of the mucosa of the lateral nasal wall and septum. Sinusitis with radiographic opacification of one or several sinuses, palatal necrosis and ulceration, and palsies of multiple cranial nerves indicate invasion of contiguous structures. Orbital cellulitis, with ophthalmoplegia and proptosis, is a harbinger of central nervous system invasion. Widespread necrosis of bone and soft tissue is a feature of advancing disease, related to the angioinvasive characteristics of the organism noted previously.

Otic Involvement. Involvement of the ear in cases of rhinocerebral mucormycosis occurs as a consequence of direct extension of the infection via the eustachian tube or the meninges, or by hematogenous spread. Auditory deficits of both the sensorineural and

conductive type may occur, depending on the site of infection within the ear. Facial palsy may complicate spread of infection to the fallopian canal. Histologic examination of the temporal bone and adjacent structures in fatal cases of otic mucormycosis reveals the characteristic broad, nonseptate, branching hyphae within the temporal bone, middle ear cavity, and adjacent soft tissues. Infiltration of the wall of the eustachian tube and tensor tympani muscle by fungi may be seen in those cases that follow spread by infection from a nasopharyngeal focus. Invading hyphal forms, accompanied by extensive necrosis, may be encountered within the cochlear and vestibular apparatus. Infiltration of various neural structures, including the cochlear and vestibular branches of the cranial nerve VIII, the facial nerve, and the trigeminal nerve, may be prominent. Those cases of otic mucormycosis arising secondary to meningeal involvement are associated with similar changes involving the cranial nerve VIII as it courses through the internal auditory canal.

Treatment and Prognosis. In most instances, otic involvement represents only a minor component of acute, rapidly progressive rhinocerebral infection. Therapy includes parenteral amphotericin B and surgical debridement of infected tissue. In the case of poorly controlled diabetes mellitus, optimum control of the patient's underlying metabolic disorder is essential. The prognosis of rhinocerebral mucormycosis is poor, owing to the rapidly progressive nature of the infection and the underlying debilitated state of most patients. Although past series report an overall mortality in the range of 90 per cent, aggressive therapy has resulted in local control of disease in some patients. In at least one report, rare cases of chronic mucormycosis in the rhinocerebral area have responded satisfactorily to surgical debridement.

Miscellaneous Mycotic Infections

Other fungi, in addition to *C. neoformans* and the genera responsible for mucormycosis, may infect the temporal bone. *Aspergillus* species, although more commonly associated with external otomycosis, may infect the inner ear in debilitated patients. In one reported case, the organism gained access to the temporal bone via the internal auditory canal, presumably from a meningeal focus. Like the agents of mucormycosis, *Aspergillus* species invade the tissue as hyphal forms and exhibit a similar penchant for blood vessel invasion. The organisms are best demonstrated using silver impregnation (eg, GMS) or PAS stains. They can be distinguished from the general responsible for mucormycosis by virtue of their septation, more uniform diameter, and regular, dichotomous branching. Occasionally, deposits of birefringent calcium oxalate crystals in the tissue may provide a clue to the presence of *Aspergillus* organisms. Conidiophores are rarely encountered in foci of invasive disease. Definitive identification of species is accomplished through in vitro culture on Sabouraud's agar or a comparable medium. Amphotericin B, with or without surgical debridement, is utilized in the treatment of invasive disease.

Candida species and *Histoplasma capsulatum* may also produce middle ear and inner ear infection in debilitated hosts; these organisms generally gain access to the temporal bone and adjacent structures via hematogenous dissemination. In addition, *Candida* infection of the inner ear, likely representing contiguous spread from a focus of middle ear infection, has been reported. parenteral amphotericin B has been used successfully in the treatment of disseminated infection caused by these yeast forms.

Noninfectious Granulomas

In addition to various infectious agents discussed in the preceding paragraphs, a variety of noninfectious processes are capable of eliciting a granulomatous inflammatory response. In some instances, as in the case of foreign body granulomatus reaction to surgical implants, poststapedectomy granuloma, or cholesterol granuloma, the stimulus to granuloma formation is reasonably well defined. In other instances, notably sarcoidosis and Wegener's granulomatosis, the etiology of the inflammatory process is incompletely understood.

Foreign Body Granulomas

As noted in the introductory paragraphs, the appearance of any poorly digestible substance within the host tissues may provoke a granulomatous inflammatory reaction. Foreign material may enter the ear accidentally, of course, as in the case of trauma. In other instances, foreign bodies may be deliberately introduced into the ear, as in the case of ossicular chain replacements or the cochlear implants. The nature of the host reaction in such cases is dependent in large measure on the nature of the graft. Changes in ossicular and cortical bone autografts are characterized by progressive substitution of the grafted bone with vitalized bone with no significant inflammatory response. Cartilaginous autografts, similarly, elicit little inflammatory response, although an incidental loss of matrix rigidity has been noted. In contrast, porous, high-density polyethylene grafts provoke a rather vigorous foreign body granulomatous reaction. Although the long-term effect of such changes on the high-density polyethylene graft material has been debated, it has been suggested that such changes have a deleterious effect on graft survival and, ultimately, on sound transmission.

Poststapedectomy Granulomas

A special example of foreign body granulomatous reaction within the ear is the poststapedectomy granuloma. Stapedectomy, followed by the implantation of grafts or prostheses, has been associated with the development of an exuberant granulomatous reaction in the region of the oval window, associated with a major sensorineural hearing deficit. Symptoms characteristically develop within 2 to 6 weeks following stapedectomy and are characterized by sensorineural hearing loss, with a moderate elevation in bone conduction threshold and a severe reduction in speech discrimination scores. Hearing loss, although gradually progressive in the majority of patients, may occur abruptly in an occasional patient. Variable degrees of dizziness, unsteadiness, and tinnitus have been reported.

Physical examination reveals a soft, vascular mass, generally extending from the oval window to the tympanic membrane. Intravestibular extension may also occur. Although the inflammatory mass within the tympanic cavity characteristically produces some degree of distortion of the tympanic membrane, the latter structure may be normal.

Histologically, the poststapedectomy granuloma is characterized by fibroblastic and capillary proliferation, mononuclear inflammatory cell infiltration, and occasional foreign body giant cells. Polarizable foreign material is demonstrable in some patients, typically in minute quantities. In the case of fat-wire implants, fat necrosis is common and may serve as the primary stimulus to granuloma formation. In later stages, dense fibrosis may dominate the light microscopic picture, with a greatly diminished inflammatory cell population.

Accurate diagnosis of the poststapedectomy granuloma, followed by complete surgical removal, may prevent permanent sensorineural hearing loss.

Cholesterol Granuloma

Before leaving the topic of foreign body granulomatous reaction, the cholesterol granuloma, a special variant of foreign body granulomatous reaction, should be mentioned. The cholesterol granuloma represents a host reaction to cholesterol crystals. Although described in several body sites, it is the normally aerated bony cavities - notably the paranasal sinuses, tympanic cavity, and mastoid air-cells - that are especially likely to harbor the cholesterol granuloma. Involvement of the petrous apex of the temporal bone represents a less common but well-documented site. Recognition of the entity in the ear, and its distinction from cholesteatoma, is of importance in planning appropriate therapy.

Etiology and Pathogenesis

The origin of cholesterol granuloma in humans has been the subject of considerable debate. Recurrent hemorrhage, followed by degradation of erythrocytes and the deposition of cholesterol crystals, likely plays at least some role in the development of the lesion, as is evidenced by the ability of purified cholesterol crystals in the middle ear cavity to produce a granulomatous inflammatory response. The presence of blood in the middle ear space in the absence of ventilatory obstruction is probably not, by itself, sufficient to produce cholesterol granuloma, however, as is evidenced by the comparative rarity of the condition following such events as mastoid or middle ear surgery. Impairment of normal ventilation and/or drainage of naturally pneumatized structures probably also play an important role in the pathogenesis of cholesterol granuloma.

In experimental systems, obstruction of the foramen pneumaticum of the chick humerus results in the formation of intramedullary cholesterol granulomata. Such mechanical obstruction, by creating an effective vacuum within a normally aerated structure, presumably predisposes to recurrent minute hemorrhages within the cavity and the accumulation of seromucinous fluid. Recurrent hemorrhage and subsequent breakdown of blood products provide a nidus for subsequent foreign body reaction in the form of cholesterol crystals.

Virtually any mass lesion within the middle ear cavity may produce mechanical obstruction to ventilation and subsequent cholesterol granulomas. Cholesteatoma, for example, by virtue of its ability to obstruct the antrum of the middle ear, may be associated with cholesterol granuloma. It is important that cholesteatoma be distinguished from cholesterol granuloma occurring in the *absence* of cholesteatoma, inasmuch as the therapy for the two lesions differs significantly.

Morphology

Cholesterol granuloma involving the middle ear space generally arises ni a fluid-filled middle ear. In some instances, the fluid within the middle ear space is of a clear, serous, or seromucinous character; in other instances, sufficient numbers of extravasated erythrocytes are present to impart a tenacious, reddish-brown appearance to the fluid. The latter cases are characteristically associated with the poorly movable, bluish-black tympanic membrane

(idiopathic hemotympanum). On gross examination, the actual cholesterol granuloma typically comprises brown to yellow-brown viscous material, which may compress adjacent structures. Bone erosion is characteristically absent unless cholesteatoma is present. In the case of those lesions arising within the petrous apex of the temporal bone, the cholesterol granuloma presents as a sharply demarcated, expansile lesion that may produce considerable deformity of the internal auditory canal. Associated dysfunction of cranial nerve VII and VIII may occur, owing to local pressure. The lesion is fairly easily defined in this site using computed tomography (CT), in which case it appears as a sharply marginated, rounded mass that is isodense with the adjacent cerebral parenchyma. Magnetic resonance imaging (MRI) may be of further value in defining the extent of the cholesterol granuloma in some instances

Microscopically, the appearance of cholesterol granuloma is identical in all sites. Major components in the cholesterol granuloma include cholesterol clefts, hemosidering, degenerating erythrocytes, fibrosis, capillary proliferation, and a variable giant cell inflammatory response.

Treatment

Most cases of cholesterol granuloma are treated by drainage and evacuation of the lesion. Removal of any obstructing mass lesion in a normally pneumatized structure such as the middle ear cavity is of importance in the prevention of recurrences. In the cases of cholesterol granuloma involving the petrous apex, placement of a Silastic drain into the mastoid cavity following drainage and evacuation of the cholesterol granuloma has been advocated. Both translabyrinthine and retrolabyrinthine, as well as transsphenoidal and transclival, approaches have been used in petrous apex lesions, depending on the preoperative auditory status of the patient.

Regional and Systemic Granulomatous Disorders and Vasculitides

Wegener's Granulomatosis

Wegener's granulomatosis, first defined as a clinical entity by Wegener in 1936, is a multisystem disorder of unknown etiology, characterized by necrotizing granulomatous vasculitis involving the upper and lower respiratory tracts and by renal insufficiency. Once regarded as a rapidly progressive disease with a uniformly fatal outcome, the introduction of effective chemotherapy has dramatically altered the course and prognosis of Wegener's granulomatosis in many patients. Although the disorder is most familiar to physicians involved in the care of patients with head and neck diseases as a progressive, destructive lesion involving the nose and paranasal sinuses, otic involvement is a well-documented phenomenon in Wegener's granulomatosis. Indeed, in a minority of patients, otologic symptoms may be the first clue to the presence of the disorder.

Etiology

The etiology of Wegener's granulomatosis remains unknown. Current evidence suggests that Wegener's granulomatosis represents a florid hypersensitivity reaction, perhaps in response to an antigen that gains access to the host via the respiratory tract. Certainly the pathologic changes encountered in Wegener's granulomatosis at the light microscopic and

ultrastructural levels share some features with those diseases in which the host immune response plays a significant role (eg, the allergic granulomatosis of Churg and Strauss).

Morphology

Morphologically, the lesions of Wegener's granulomatosis in extrarenal sites are characterized by necrotizing granulomatous inflammation and vasculitis. These may be encountered in a variety of sites but are typically most prominent in the respiratory tract. The necrosis is of a peculiar type, described by some authors as having a "gritty" character. At the light microscopic level, these irregular foci of necrosis are characterized by obliteration of cell detail and abundant karyorrhectic debris, an appearance similar to the caseous necrosis encountered in mycobacterial and fungal infections. At the periphery of the necrotic foci, granulation tissue, fibrosis, and scattered multinucleate giant cells are characteristic. Eosinophils may be present, although their numbers are typically few. Stains for specific infectious agents, always a reasonable procedure in the setting of a granulomatous inflammatory process, are unrevealing. The necrotizing granulomatous inflammation is most prominent in soft tissue, although bony and cartilaginous structures may also be involved. Superinfection by bacteria, especially *Staphylococcus aureus*, is associated with a prominent acute inflammatory exudate.

Frank *vasculitis* may occur in any organ but is best demonstrated in open biopsies of involved pulmonary parenchyma. Its presence in the upper respiratory tract, in contrast, may be difficult to demonstrate. The vasculitis involves both arterial and venous channels of medium to small caliber and is characterized in its early stages by fibrinoid necrosis of the vessel wall with disruption of the elastic lamellae; recent thrombi are common in areas of active vasculitis. In more quiescent lesions, the vessel wall is distorted by a variable degree of intimal and medial fibrosis, with persistent disruption of the internal elastic lamella in arterial channels. Elastic tissue stains may be of value in delineating these changes. The vessel lumina may be partially or completely obliterated by organizing thrombi.

The most common *renal* lesion encountered in Wegener's granulomatosis is a focal, segmental, necrotizing glomerulonephritis. In more severe instances of glomerular injury, a pattern of crescentic glomerulonephritis may be encountered, associated clinically with evidence of rapidly progressive renal insufficiency. Other changes, including nonspecific chronic interstitial nephritis, diffuse glomerulonephritis, and glomerulosclerosis, may be present. Vasculitis is extremely uncommon in renal biopsy material, although postmortem studies have reported a fairly high frequency of active or quiescent vasculitis in this site. Frank granulomatous inflammation is almost never encountered in the kidney; many examples of purported granulomas in this site probably represent altered glomeruli rather than true granulomas.

Clinical Manifestations

Clinically, the disease is one of adulthood, with a mean age of presentation in the fifth decade in most series; a modest male predominance has been noted. Over 90 per cent of patients develop signs and symptoms referable to the nose and paranasal sinuses, including persistent rhinorrhea, sinus pain, mucosal crusting, and ulceration. Frank destruction of bony and cartilaginous structures in this site may occur, leading to collapse of the nasal bridge and

the characteristic saddle nose deformity. Midfacial destruction is characteristically less pronounced than that seen in midline malignant reticulosis, a primary lymphoproliferative disorder often confused with Wegener's granulomatosis. Superinfection with bacteria, especially *Staph. aureus*, may occur at any time and must be distinguished from exacerbation of the underlying Wegener's granulomatosis.

Laryngeal involvement, especially subglottic inflammation and stenosis, occurs in the minority of patients. Signs and symptoms referable to the lower respiratoy tract include a chronic persistent cough, intermittent hemoptysis, and ill-defined chest discomfort. Pleuritic chest pain may occur. Radiographic examination of the chest reveals randomly distributed infiltrates and nodular densities, generally bilateral, and frequently cavitary. Occasionally, pulmonary infiltrates may be of a transient character.

Renal involvement is well documented in Wegener's granulomatosis and, prior to the development of effective chemotherapy, remained the single most important cause of death. Renal involvement may vary from subclinical disease to renal failure. Urinary findings are nonspecific and include the presence of perturea, hematurea, and erythrocyte casts secondary to glomerular injury. Proteinuria may reach the nephrotic range in a minority of patients.

Involvement of the skin, manifested by changes including papulo-vesicular eruptions, subcutaneous nodules, and frank ulceration, may be seen in up to one-half of patients. Ocular involvement, similarly, is seen in about one-half of patients and includes conjunctivitis, corneal ulcerations, scleromalacia, proptosis, and retinal artery thrombosis. Other organ systems potentially affected include the central and peripheral nervous systems, heart, and joints.

Otic involvement occurs in up to 40 per cent of patients with Wegener's granulomatosis and, in a minority of patients, may be the presenting complaint. The most common form of otic involvement takes the form of serous otitis media, secondary to eustachian tube dysfunction. Superinfection with bacteria, especially *Staph. aureus* or *Pseudomonas aeruginosa*, may result in the involvement of a suppurative otitis media. Direct involvement of the ear has been reported but must be regarded as exceedingly rare. Granulomata involving the tympanic membrane, and granulomatous inflammation in the retrolabyrinthine portion of the temporal bone and mastoid, have been encountered.

Diagnosis

The diagnosis of Wegener's granulomatosis should be suspected in any patient with clinical evidence of an inflammatory process in the upper respiratory tract or ear that fails to respond to conventional therapy, especially in the presence of coexistent lower respiratoy tract and/or renal disease. Regrettably, there is no single diagnostic test for Wegener's granulomatosis. Biopsy of involved areas demonstrating necrotizing granulomatous inflammation may be the first clue to the disease. Because such changes may be mimicked by other processes requiring substantially different therapy (eg, tuberculosis, fungal disease, treponemal infections, and neoplasms), routine histology should be supplemented by appropriate special stains, cultures, and serologic studies. Laboratory studies, including the erythrocyte sedimentation rate, while nonspecific, may provide a valuable supplement to physical examination in assessing the course of the disease.

Treatment

Wegener's granulomatosis is treated effectively in the majority of cases using cyclophosphamide in daily doses, coupled with prednisone for acute exacerbations. As noted previously, when dealing with an apparent acute exacerbation, bacterial superinfection must be excluded by appropriate clinical and laboratory means.

Polyarteritis Nodosa

Polyarteritis nodosa is a necrotizing vasculitis involving predominantly small to medium-sized arteries. Although not a granulomatous disorder in the strictest sense, its occasional confusion with Wegener's granulomatosis, coupled with its ability to produce ear disease, warrants its inclusion in this brief discussion.

Etiology and Epidemiology

Polyarteritis nodosa is a distinctly uncommon disease, with an incidence of 1 per 100.000 population in most series. Persons of virtually any age may be afflicted, although the disease most commonly strikes those in the middle adult years, with a mean age of onset of 45 years. Males appear to develop the disease more often than females, with a male to female ratio of approximately 2:1. Since its initial description ni 1866 by Kussmaul and Maier, the etiology of polyarteritis nodosa and related vasculitides has been the subject of considerable speculation. Some evidence suggests that the majority of vasculitides are associated with the deposition of immune complexes in blood vessel walls, followed by local activation of complement, and secondary vascular injury. Although the evidence linking a given antigen to the development of vasculitis is often circumstantial, the presence of hepatitis B surface antigenemia in up to 50 per cent of patients with polyarteritis nodosa lends support to an immunopathogenic mechanism.

Morphology

Pathologically, polyarteritis nodosa is characterized by segmental, transmural necrotizing inflammation of small to medium-sized muscular arteries. Branch points, in particular, seem especially vulnerable to vascular injury. In the early stages, the inflammation is characterized by transmural fibrinoid necrosis of the vessel wall with disruption of the elastic lamellae, thrombosis, and aneurysm formation. A polymorphous inflammatory infiltrate dominated by neutrophils accompanies the necrosis; giant cells are characteristically absent. In the later stages, segmental fibrosis of the media and intima, accompanied by minimal occlusion or aneurysmal dilatation, may be seen. Virtually any vessel may be involved by the disease, although the arteries of the kidney, heart, liver, gastrointestinal tract, peripheral nerves, mesentery, testes, and skeletal muscle are most commonly affected.

Clinical Manifestations

The clinical manifestations of polyarteritis nodosa are directly related to the local ischemia and/or hemorrhage that follows vascular injury. The signs and symptoms of the disease are of a protean nature, as might be anticipated from the widespread distribution of vascular injury. Constitutional symptoms, including fever, weight loss, and fatigue,

characteristically accompany signs and symptoms of specific organ dysfunction. Renal involvement, present in up to three-fourths of patients, may result in proteinuria, hematuria, renal insufficiency, and hypertension. Abdominal pain is frequent, secondary to localized or diffuse involvement of mesenteric and/or celiac tributaries. Cardiac involvement, manifested by myocardial infarction, congestive heart failure, or cardiac arrhythmias, is a major source of morbidity and mortality. Cutaneous lesions secondary to local vasculitis include ischemic ulcers, purpura, and gangrene. Arthralgias, peripheral neuropathy, muscle pain, testicular pain and swelling, and retinal hemorrhage may occur at any time during the course of the disease.

Otic Involvement. Involvement of the *ear* and *temporal bone* complicates the course in a minority of patients; in exceptional cases, hearing loss may be the initial manifestation of polyarteritis nodosa. Auditory deficits characteristically assume the form of a mixed conductive and sensorineural process, secondary to involvement of the mucosa of the middle ear and the bony labyrinth, respectively. In some instances, serous otitis media may herald the development of significant hearing loss. In such cases, it has been suggested that viral antigenemia attendant to an infectious otitis may serve as the initiating event in the subsequent evolution of polyarteritis nodosa.

Diagnosis

The diagnosis of polyarteritis nodosa may be difficult due to the variable and often baffling symptoms that accompany the disease. Evidence of specific organ dysfunction, such as peripheral neuropathy or renal insufficiency, in a patient with the constitutional symptoms noted previously should suggest the diagnosis. Hepatitis B surface antigen, although demonstrable in the serum of up to 50% of patients with polyarteritis nodosa, is much less common in patients with otic disease. Arteriography may demonstrate the presence of segmental narrowing and aneurysms of visceral arteries, and is of value in evaluating those sites not readily accessible to biopsy. Finally, biopsy of clinically involved tissues, including skin, muscle, testes, kidney, and peripheral nerve, is helpful in documenting the presence of active or healed vasculitis.

Treatment and Prognosis

The prognosis of untreated polyarteritis nodosa is dismal. Aggressive treatment of the disease with corticosteroids has resulted in an improvement in the 5-year survival rate to approximately 50 to 60 per cent. More recently, plasmapheresis and the use of cytotoxic agents have been advocated in the therapy of rapidly progressive disease.

Cogan's Syndrome

Cogan's syndrome is a condition characterized by nonsyphilitic interstitial keratosis associated with auditory and vestibular dysfunction. The syndrome may be associated with more widespread manifestations of polyarteritis nodosa and is regarded by some writers as a variant of the latter disease. A cell-mediated, autoimmune origin has been proposed for the auditory and vestibular manifestations of the disorder. Cogan's syndrome is typically a disease of young adults and is associated with the abrupt onset of vertigo, tinnitus, nausea, and sensorineural deafness. Both unilateral and bilateral auditory involvement may occur. Corneal inflammation, accompanied by blurred vision, increased lacrimation, and late corneal

vascularization characterize the ocular changes. Morphologic changes including necrotizing vasculitis, endolymphatic hydrops, and cochlear neuronal degeneration have been described. Vascular alterations are indistinguishable from those noted in typical polyarteritis nodosa. Like polyarteritis nodosa, the disease requires aggressive therapy with corticosteroids.

Sarcoidosis

Etiology and Epidemiology. Sarcoidosis is a chronic, multisystem granulomatous inflammatory disease of unknown etiology with a special predilection for the monocyte system and lungs. Since its description in 1899 by Boeck, the etiology of sarcoidosis has been debated. A remarkable number of potential causes, including *Mycobacterium tuberculosis,* atypical mycobacteria, viruses, mineral dusts, and pollens, have been implicated from time to time; despite these efforts, a single causative agent remains to be elucidated. The distribution of sarcoidosis is worldwide, with particularly high prevalence rates in northern Europe, the USA, and Australia. In the USA, a higher incidence in the black and Puerto Rican populations has been noted. The disease may affect any age group, with a peak incidence between the ages of 20 and 40.

Morphology. Morphologically, sarcoidosis is characterized by compact noncaseating granulomas, composed of mature epithelioid cells and giant cells of the foreign body or Langhans' type. Laminated Schaumann bodies and collagenous "asteroid" bodies may be encountered within the cytoplasm of the giant cells; while once thought to be relatively specific for sarcoidosis, similar inclusions may be encountered in a variety of infectious and noninfectious granulomatous processes. Occasional foci of necrosis may be present; polarizable material is typically absent. Although virtually any organ may be involved by sarcoidosis, the lungs, regional lymph nodes, spleen, and liver emerge as some of the more common sites of involvement. Perivascular lymphocytic infiltration, associated with demyelination and axonal degeneration of cranial nerves VII and VIII, has been noted in temporal bone sections from one patient with auditory and vestibular dysfunction secondary to sarcoidosis.

Clinical Manifestations. The potential clinical manifestations of sarcoidosis are numerous, as might be anticipated from the wide spectrum of organ involvement. In general, signs and symptoms referable to the lower respiratory tract, ranging from asymptomatic hilar lymphadenopathy to progressive respiratory failure and cor pulmonale, dominate the clinical picture. Generalized lymphadenopathy, splenic enlargement, hepatic dysfunction, cutaneous eruptions, and ocular impairment may be encountered. Involvement of the nervous system occurs in approximately 10 per cent of patients with sarcoidosis; in patients with coexistent inflammation of the uveal tract and parotid glands (Heerfordt's syndrome), the incidence of nervous system involvement is significantly higher.

Otic Involvement. Hearing impairment secondary to sarcoidosis is uncommon but well documented. The pathogenesis of hearing impairment in sarcoidosis remains to be clearly established. Direct granulomatous inflammation of the temporal bone or cranial nerve VIII, compression of cranial nerve VIII due to meningeal sarcoidosis, and direct infiltration of the brain stem have all been proposed as potential mechanisms of hearing loss. Reported cases of deafness in sarcoidosis are of the sensorineural or mixed type; no convincing cases of pure conductive deafness have been documented. The auditory deficit may be unilateral or bilateral

and of variable severity. No diagnostic audiometric pattern has been recognized. Coexistent ocular inflammation and dysfunction of cranial nerve VII have been described in 80 per cent and 40 per cent of cases, respectively, involving cranial nerve VIII. Up to 20 per cent manifest some degree of parotid swelling.

Diagnosis. The diagnosis of sarcoidosis rests on both clinical findings and the demonstration of noncaseating granulomas. Cultures and special stains to rule out infectious agents are always in order, inasmuch as the granulomas of sarcoidosis may be mimicked by infectious processes, and vice versa. Serum levels of angiotensin-converting enzyme, derived from the cytoplasm of epithelioid cells, are reportedly elevated in from 50 to 80 per cent of patients with active sarcoidosis and have been reported to be a useful monitor of disease activity. The test is not absolutely specific for sarcoidosis, however, and may be negative in patients with clinically evident disease. Nonspecific laboratory alterations include an elevated erythrocyte sedimentation rate, hypergammaglobulinemia, hypercalcemia and hypercalciuria, and elevated hepatic enzymes.

Treatment. The treatment of sarcoidosis varies with the extent of disease activity. Some patients with localized sarcoidosis, especially those cases associated with erythema nodosum and arthritis, undergo spontaneous remission. In contrast, patients with progressive disease involving the respiratory tract, central nervous system, or heart benefit from the administration of corticosteroids. Long-term therapy may be required in some instances. Patients with chronic, progressive disease must be carefully followed, even after an apparently successful course of corticosteroid therapy, because of a significant percentage of relapses in that population.

Miscellaneous Granulomatous Disorders

Histiocytosis X

The term *histocytosis X* traditionally embraces three imperfectly separated forms of histiocytic proliferation, designated eosinophilic granuloma of bone, Hand-Schüller-Christian disease, and Letterer-Siwe disease. Forty years after its recognition, the nature of this proliferation remains unsettled, with some evidence favoring a reactive process, and other evidence favoring a neoplastic process. Despite uncertainty about the fundamental nature of histiocytosis X and because of the central role of the histiocyte in the proliferation, this group of diseases is often in conjunction with more traditional granulomatous disorders.

Pathogenesis

Compelling evidence has emerged from recent investigations to suggest that the histiocyte, as defined by light microscopy, comprises at least two functionally and immunologically distinct cell populations. One population, presumably derived from the bone marrow and related to the circulating blood monocyte, gives rise to the majority of tissue phagocytes. This group of cells elaborates certain proteolytic enzymes, including alpha-1-antitrypsin and alpha-1-antichymotrypsin; an antigenic marker, the S-100 protein, is absent from these cells. The traditional granuloma, as discussed in the preceding sections of this chapter, represents a localized collection of these marrow-derived elements.

A second histiocytic population apparently develops independently of the traditional monocyte-macrophage system. These cells appear in the thymic medulla early in gestation, and in their differenitated state populate the T-cell-dependent areas of lymph nodes and spleen. Members of this cell population also include the Langerhans' cells of the normal dermis. In contrast to the monocyte-derived histiocytes, these T-zone histiocytes lack alpha-1-antitrypsin and alpha-1-antichymotrypsin and express the S-100 protein and CD-1 antigen. Although their function remains incompletely defined, these cells almost certainly play a role in antigen processing. The majority of the lesions included under the traditional umbrella of histocytes X represent proliferations of these T-zone histiocytes.

Clinical Manifestations

The members of the histiocytes X family - eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease - define a spectrum of clinical disease ranging from a solitary, frequently asymptomatic lesion of bone or viscera to a fulminant, rapidly progressive disease involving multiple organ systems.

Solitary Eosinophilic Granuloma. This is a disease of children and young adults. Although visceral lesions may be encountered, the skeletal system is the most frequent site of involvement; the skull, long tubular bones of the extremities, ribs, pelvis, and vertebral bodies are favored sites. The usual osseous lesions are characterized radiographically by a well-defined area of radiolucency; periosteal reaction usually is inconspicuous. Temporal bone involvement is common, and is frequently accompanied by otic manifestations (vide infra).

Hand-Schüller-Christian Disease. Also designated chronic disseminated histiocytosis and multifocal eosinophilic granuloma, this form of histocytosis X tends to involve a slightly younger age group than does solitary eosinophilic granuloma. It occupies a position intermediate between the comparatively indolent solitary eosinophilic granuloma and the more aggressive Letterer-Siwe disease. Chronic debility rather than death is typical. The lesions of Hand-Schüller-Christian disease may involve a variety of skeletal and extraskeletal sites, with signs and symptoms referable to the location of the lesions. Involvement of the hypothalamic-pituitary axis, orbital areas and skull is associated with the pathognomonic triad of diabetes insipidus, exophthalmus, and radiolucent skeletal defects. This traditional triad of Hand-Schüller-Christian disease occurs in less than 10 per cent of patients with chronic disseminated disease, however. As in the case of solitary eosinophilic granuloma, involvement of the ear and temporal bone, discussed below, is well recognized. Involvement of the base of the skull, in particular, is much more common in multifocal eosinophilic granuloma than in the solitary form of the disease.

Leterrer-Siwe Disease. The proper classification of Letterer-Siwe disease remains controversial. The disease characteristically presents in the first year of life, and is associated with widespread, massive organ infiltration by proliferating histiocytes and an acute or subacute, progressive course. In contrast to solitary and multifocal eosinophilic granuloma, the infiltrates in Letterer-Siwe disease are of a more diffuse character. Soft tissue, cutaneous, and visceral infiltration tends to overshadow osseous involvement. The microscopic features of the disease, discussed briefly below, differ somewhat from those associated with solitary or multifocal eosinophilic granuloma, and have led some authors to classify Letterer-Siwe disease as a variant of malignant histiocytosis.

Morphology

Morphologically, eosinophilic granuloma is a localized, soft, yellow-to-tan lesion that may contain foci of necrosis. At the light microscopic level, the lesions of histiocytosis X are characterized by sheets of polygonal histiocytes containing abundant eosinophilic cytoplasm with indistinct cell borders. The nuclei are irregular, with deep grooves or folds and solitary small nucleoli; they differ from the typical reniform nuclei of reactive macrophages. Mitotic figures are infrequent in the low-grade lesions. Inflammatory cells, including eosinophils, lymphocytes, and occasional plasma cells, are present in variable numbers. Multinucleated giant cells, vacuolated histiocytes, and areas of fibrosis and hemosiderin deposition may be encountered, especially in those lesions of long duration or those subjected to previous trauma. Foci of necrosis are common.

In the more aggressive lesions (Letterer-Siwe disease) the cell infiltrates are more monomorphous, consistingalmost entirely of abnormal histiocytes; inflammatory cells are few, and giant cells and secondary changes are absent. A mild degree of cytologic atypia may be encountered in the proliferating histiocytes, but a significant degree of nuclear atypia should suggest a diagnosis of malignant histiocytosis rather than Letterer-Siwe disease.

Ultrastructural examination accentuates the deep nuclear folds evident at the light microscopic level that typify the Langerhans' cell. The proliferating histiocytes possess abundant cell processes and contain, in addition to the usual cytoplasmic organelles, a characteristic pentalaminar structure comprising two parallel unit membranes enclosing a striated, electron-dense core. These curious structures, variably designated Langerhans' or Bierbeck granules, are continuous with both the cisternae of the endoplasmic reticulum and the external cell membrane. A possible role in antigen processing and presentation has been proposed for these organelles. The characteristic granules are demonstrated with ease in most cases of solitary or multifocal eosinophilic granuloma. They may be sparse or absent in biopsy material from patients with Letterer-Siwe disease.

Otic Involvement

Aural manifestations may be encountered in any of the forms of histiocytosis X, an association recognized since one of the earliest descriptions of the disease by Schüller in 1915. One comprehensive series noted involvement of the ear or temporal bone in 15 per cent of affected patients. Radiographic examination of the temporal bone discloses an even higher incidence of temporal bone involvement if asymptomatic patients are included in the survey. In a smaller percentage of patients, otologic signs and symptoms may be the first or dominant feature of the disease. Among patients with otic involvement, otitis media and otorrhea are among the most common manifestations. In contrast to more common causes of suppurative otitis media, the tympanic membrane is characteristically intact, a potentially important diagnostic sign.

Postauricular swelling, with anterior displacement of the external ear, is seen in up to 30 per cent of patients. Massive destruction of the mastoid process may be encountered, simulating cholesteatoma, infectious mastoiditis, or metastatic neoplasm. Extension of the infiltrate into the posterior portion of the bony external auditory canal may result in displacement of the mucosa of the canal. Further extension of the process into the external

canal may simulate bacterial otitis externa, or may present as an isolated aural polyp. It is important for the pathologist examining such lesions to be aware of the possibility of histocytosis X, in order to distinguish the changes in the curetted or biopsied material from nonspecific chronic inflammation.

Although any of the contiguous soft tissue or osseous structures may be involved by the disease, definite infiltration of the otic capsule is uncommon. Auditory deficits are variable, and may be of the conductive or sensorineural type; vertigo is uncommon. Among patients with histiocytes X involving the temporal bone, bilateral disease is encountered in approximately 30%.

Diagnosis

The diagnosis of histiocytosis X requires a high index of suspicion based on clinical grounds, supplemented by biopsy of involved tissues. In cases with widespread osseous lesions and/or evidence of visceral involvement, the diagnosis may be suspected fairly early. In patients with localized disease, however, infectious otomastoiditis or cholesteatoma may be suspected. The demonstration of proliferating Langerhans-type histiocytes admixed with a variable number of the eosinophils and other inflammatory cells, in an appropriate clinical context, establishes the diagnosis of histiocytosis X.

Treatment

The prognosis and treatment of histiocytosis X depend on the stage of the disease. Solitary asymptomatic skeletal lesions are associated with a high incidence of spontaneous resolution. Persistent local disease may be treated successfully by curettage or by low dose radiotherapy. For more extensive visceral lesions, especially the rapidly progressive forms, single or multi-agent chemotherapy may be of benefit.

Xanthoma of the Temporal Bone Associated With Hyperlipoproteinemia

Xanthogranulomas, or lipid rich granulomas, may be encountered in many sites. Most commonly, these are local phenomena arising either in response to local injury accompanied by hemorrhage or in the absence of a definable stimulus. Less commonly, xanthogranulomas may be a manifestation of an abnormality in lipoprotein metabolism. At least one instance of xanthogranuloma formation associated with type V hyperlipidemia has been reported, associated with unilateral sensorineural deafness. Histologic examination of the lesion in this case revealed soft tissue deposits of cholesterol associated with a foreign body granulomatous reaction. Whether the sensorineural auditory deficit in this case arose as a direct consequence of the xanthogranuloma or, alternatively, arose secondary to coexistent vascular disease, was not determined.

Benign Aural Polyps

Benign aural polyps represent a tissue response to chronic injury. Clinically, such polyps must be distinguished from neoplastic proliferations in the same area, eg, jugulotympanic paragangliomas, lesions that differ substantially in prognosis and treatment from the non-neoplastic proliferations known as benign aural polyps. The traditional

granuloma, as defined in preceding sections, is not an essential part of the benign aural polyp. Nevertheless, many of the granulomatous disorders discussed above may be associated secondarily with aural polyps. For this reason, these lesions are discussed in conjunction with the more traditional granulomatous diseases of the ear and temporal bone.

Benign aural polyps have been designated by a large number of ptentially confusing terms. Names such as mucous polyp, myxomatous polyp, fibromyxomatous polyp, granulation polyp, connective tissue polyp, and fibroangioma reflect the wide variety of connective tissue alterations encountered in these non-neoplastic proliferations. Aural polyps characteristically arise in the context of chronic otic inflammation and may occur in several sites, including the mucosa of the middle ear, the eustachian tube, and the external auditory canal. In a sense, the aural polyp may be regarded as a local exaggeration of inflammatory changes involving the adjacent mucosal surface. As a corollary to this, histologic examination of the polyp may provide insight into changes in the aural mucosa less accessible to clinical examination and biopsy.

The gross appearance of aural polyps ranges from punctate, reddened mucosal elevations to polypoid masses sufficient to obstruct the lumen of the eustachian tube or external auditory canal. The composition of the polyp varies with the duration of the lesion, but as a rule is dominated by connective tissue. Many aural polyps consist predominantly of granulation tissue (ie, proliferating fibroblasts) and thin-walled reactive vascular channels embedded in a loose, edematous connective tissue matrix. In deference to the abundant granulation tissue, lesions of this type are often designated *granulation polyps.* Histologic examination of such polyps may reveal evidence of recent and remote hemorrhage, attesting to the delicate nature of the reactive vessels that make up the polyp.

Most aural polyps are invested, at least in part, by epithelial cells derived from the overlying native mucosal surface. The epithelium may be of the keratinizing or nonkeratinizing stratified squamous variety, cuboidal, or columnar; mixtures of the various epithelial types are common. Ciliated columnar epithelium, complete with goblet cells, may be encountered in middle ear polyps arising in the context of chronic otitis media.

On occasion, deep invaginations of the surface epithelium into the subjacent stroma of the polyp may be encountered. If mucous-secreting epithelium is present, these inclusions may become dilated and cystlike and, in histologic section, may simulate gland formation. Such polyps have been designated *mucous membrane polyps* but do not differ in pathogenesis or behavior from those aural polyps lacking a prominent epithelial component.

Inflammatory cells are not an intrinsic part of the granulation polyp, although a variable number of macorphages, plasma cells, and lymphocytes are frequent companions of the proliferating fibrovascular tissue. An acute suppurative process superimposed on chronic otitis media, however, may produce significant acute inflammatory changes in the aural polyp. These polyps, occasionally designated *acutely exacerbated granulation polyps,* contain an intense, neutrophilic inflammatory infiltrate, most pronounced in the superficial portions of the polyp. The presence of such acute inflammatory changes in an aural polyp may indicate the emergence of an acute inflammatory process in the adjacent mucosa requiring surgical intervention.

As the connective tissue of the aural polyp matures, the fibrocollagenous matrix assumes a denser quality than that encountered in the typical granulation polyp. Such polyps have been designated *connective tissue polyps*, to distinguish them from the younger granulation polyps. Aural polyps containing mature connective tissue may contain prominent vessels, causing some to be designated as "angiomatous" or "fibroangiomas". While descriptive, such designations tend to obscure the fundamental relationship between these more mature aural polyps and those accompanied by more typical granulation tissue.

Certain middle ear problems, especially those rising in the vicinity of the eustachian tube, may contain abundant lymphoid tissue within the stroma, complete with reactive follicular centers. The descriptive term *lymphatic polyp* has been applied to these lesions. The abundant lymphoid tissue in such polyps is a reflection of the well developed lymphatic parenchyma that normally resides in this portion of the ear. Columnar epithelium, including goblet cells, represents the most common epithelium in aural polyps arising in this site. As in the case of the so-called mucous membrane polyp described previously, invaginations of the columnar surface epithelium may produce prominent, mucinous cysts that simulate gland formation in histologic sections of the polyp.

Histologic examination of the aural polyp may provide information about the condition of the mucous membrane of the adjacent middle ear. Significant acute inflammatory changes in an aural polyp correlate with evidence of acute exacerbation of chronic otitis media and, as noted above, may indicate the need for surgical intervention. Finally, the benign aural polyps described above may be associated with a wide range of other specific processes, including neoplasms, cholesteatoma, tuberculosis, or histiocytosis X; more recently, extrapulmonary *Pneumocystis carinii* infection occurring in AIDS has been added to the ever-expanding list of disorders associated with such polyps. Careful clinical and histologic examination of the aural polyp in such cases may provide important diagnostic, therapeutic, and prognostic information.

Summary

A variety of processes, both infectious and noninfectious, may be associated with the development of granulomas in the human ear and temporal bone. Optimal therapy is based, in all cases, on accurate diagnosis. Thorough clinical evaluation, coupled with an atmosphere of cooperation between the primary physician, laboratory consultant, radiologist, and other ancillary personnel, continues to serve as the foundation for the management of this diverse group of diseases.