Chapter 164: Immunologic Mechanisms in Disorders of the Inner Ear

Jeffrey P. Harris

There are myriad causes of sensorineural hearing loss (SNHL), which, despite an exhaustive evaluation, may still defy a precise diagnosis. Often we are faced with concerned and frightened patients who cannot readily fathom our vague explanations for their progressive and inexorable deafness. The recent recognition that a subgroup of these patients may have a treatable form of autoimmune SNHL has lifted the hopes of patients and otolaryngologists - head and neck surgeons alike. Properly identified, patients with autoimmune deafness can be given immunosuppressive therapy with gratifying results. However, many patients with unexplained deafness have been subjected to rather aggressive forms of immunosuppressive therapy in the hopes of restoring their auditory function, even without a firmly established diagnosis of autoimmune disease. This has inevitably led to some doubt as to the existence of this disorder, since these non-autoimmune patients fail to respond to treatment.

This chapter examines the basic mechanisms of immunity, the experimental and clinical evidence that supports an autoimmune etiology for inner ear disease, and an approach to the evaluation and treatment of these disorders when they are established in patients.

Basic Immune Mechanisms

It is clear that over the past 30 years the field of immunobiology has had considerable impact on all areas of clinical medicine. Immunologic principles and techniques have resulted in the development of newer diagnostic and treatment modalities for many disorders that were heretofore considered idiopathic and not amenable to treatment. With this new knowledge has come the need for a continual reassessment of the pathophysiology of all diseases in an attempt to assimilate hypothetical and experimental models into a clinical practicum.

Unfortunately, no area of the body is as difficult to study as the inner ear, locked within the dense otic capsule and unavailable to most of the routine immunobiologic techniques. Whereas the well-established principles of otopathology have greatly advanced our knowledge of the inner ear, application of immunologic techniques to the study of otologic disorders is our new frontier. It is hoped that these studies will bring not only new insight into the etiology of certain ear diseases, but also a better understanding of how the ear functions under diverse circumstances. This chapter examines the experimental and clinical evidence that supports the notion that immunity plays a role in the host defense of the ear, possibly at the cost of its own potential damage.

Systemic Immune System

Much is known about the interplay of immunocompetent cells, antibody, complement, and lymphokines in response to antigen presentation to the body. A detailed description of the immune system is beyond the scope of this chapter; however, in brief, there is a series of interconnected steps that link these processes so that foreign proteins, bacteria, viruses, and malignantly transformed cells can be rendered inactive and cleared from the host. Many of the cells involved in this event are depicted in Fig. 164-1.

1

In normal development, stem cells in the bone marrow differentiate along lymphoid stem cells lines, at which point these cells diverge into either T- or B-destined lymphocytes. T cells are thought to mature via passage through the thymus gland into one of three general classe: (1) helper T cells, (2) suppressor T cells, or (3) cytotoxic T cells. Each of these T-cell subsets has surface antigens that allow the subsets to be distinguished from one another. Functionally, these cells are quite distinct. Helper T cells are though to aid and promote B-cell antibody production. Suppressor T cells help to modulate and down-regulate both antibody production and other immune responses mediated by T cells. Cytotoxic T cells are capable of the direct killing of cells expressing foreign antigens. Collectively, these cells are responsible for lymphokine production, antiviral cytotoxicity, graft-versus-host disease, delayed hypersensitivity responses and graft rejection. B cells derive their characteristics through contact with the fetal liver, now thought to be the equivalent of the bursa of Fabricius.

The first step in the differentiation process is the appearance of mu heavy chains in the cytoplasm. This, in association with a light chain, forms and IgM molecule that ultimately is incorporated into the cell membrane. Concurrently, delta heavy chains may interact with a light chain and form IgD molecules, which similarly become incorporated into the cell membrane. These immunoglobulins serve as recognition units or receptors for their intended antigens. This committed B cell, on encountering its specific antigen, will undergo division and amplification into a plasma cell that secretes IgM molecules or undergoes a heavy-chain switch to one of the other classes of heavy chains, ultimately producing IgM, IgG, IgD, or IgA molecules.

An important step in the activation of the immune response appears to be the role of lymphokines known as interleukins (IL). It is now thought that IL-1 is released from macrophages on antigen processing, which then exerts a stimulatory effect on resting T and B cells. Certain of these T-cell populations (helper cells) then produce IL-2, which serves as a growth factor for antigen-stimulated T cells or antigen-stimulated, activated B cells. Recently many other interleukins have been described (IL-3, IL-6, IL-8) and shown to serve a wide variety of biologic functions, including bone resorption and emeripolsis. These lymphokines therefore are important regulators of T- and B-cell activity after antigen-specific recognition occurs.

Autoimmunity

In the early 1950s Ehrlich proposed an essential element of survival: the concept of unresponsiveness of the immune system to self-determinants (Ehrlich and Morgenroth, 1956). Conversely, when this system breaks down, reactivity against oneself could result in a condition known as "horror autotoxicus" (Ehrlich and Morgenroth, 1956). It is apparent that autoimmune states may result from the reaction of antibodies or cells against self-constituents and that disease states may result either primarily from autoimmunity or secondarily, triggered by some prior injury or tissue damage (Theofilopoulous and Dixon, 1982). Autoimmune disorders are generally considered to be either organ-specific or non-organ-specific diseases. For instance, non-organ-specific would include such disorders as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome, scleroderma, and Goodpasture's syndrome, whereas organ-specific autoimmune diseases includes Hashimoto's thyroiditis, juvenile insulin-dependent diabetes, ulcerative colitis, myasthenia gravis,

pernicious anemia, and Addison's disease. Often patients with one organ-specific disease have coexistent autoantibodies that lead to other autoimmune disorders as well. This is particularly apparent with the autoimmune endocrinpathies where, for example, patients with antithyroid antibodies may have coexistent antiparietal cell antibodies.

There are three primary mechanisms for the development of autoimmune disorders:

1. The presence of autoantibodies against tissue antigens (either natural or modified). In such disorders autoantibodies attach to their specific cell surface antigens, fix complement, and result in tissue damage and organ dysfunction.

2. The deposition of antigen-antibody immune complexes within tissues. The immune complexes are not necessarily directed against these tissues, but because of their blood-filtering capacity they are most often damaged (for example, glomerulus or choroid). Immune complexes can also be deposited into any tissue or fluid spaces throughout the body, and once there they may fix complement, which then results in the liberation of a number of inflammatory mediators. Polymorphonuclear (PMN) leukocytes and monocytes move to these sites, potentiating the injury.

3. The infiltration and destruction of tissue by specific cytotoxic T cells. The activation of these cells may be the result of interleukings released from antigen-activated macrophages and other T cells.

Most recently, the role of genetic factors in the susceptibility and development of autoimmune disease has become recognized. The genes most responsible for autoimmune disease appear to be the major histocompatibility genes and the genes coding for T- and B-cell antigen receptors. The most prevalent HLA-DR alleles associated with autoimmune disease have been found to be DR2, DR3, DR4, and DR5 (Dausset and Contu, 1980; Stastny et al, 1983). The relative HLA-DR allele varies widely; for instance, in Goodpasture's syndrome the association with DR2 has a relative risk of 15, whereas in Graves' disease there is a relative risk of 3 in association with a DR3 allele (Dausset and Contu, 1980).

Experimental Immunology of Inner Ear

The inner ear is an extension of the central nervous system (CNS) and as such should be examined in the same light when considering evidence for the existence of immunologic diseases that affect it.

It is now widely accepted that many degenerative or progressive diseases that affect the CNS are due in great part to the immune reactions taking place in those tissues in contrast to the cytopathic effect of pathogens (Paterson, 1977). An example of this can be seen experimentally in immunosuppressed animals that are relatively unaffected by direct cerebral inoculation of virus until they are immunologically reconstituted and then devel extensive immunopathologic lesions in the brain (Nathanson and Cole, 1970). Such studies have underscorded the importance of the immune system, not only in the prevention of certain diseases, but also in their causation.

Another important aspect of CNS immunity is the presence of the blood-brain barrier. This barrier protects and isolates the brain from the effects of systemic immunity, but only to a certain degree. Early studies by Medawar (1948) demonstrated that the brain, long considered to be immunoprivileged, was only partially so. Although the blood-brain barrier has been shown to prevent the passive transfer of serum antibody into the brain unless a state of increased vascular permeability exists, it appears that primed B cells enter the CNS and become induced to differentiate in situ on antigen exposure. Once stimulated, these cells can locally produce immunoglobulin within the CNS, suggesting that the CNS does come under the "surveillance" of circulating immune cells (Oldstone, 1982).

Finally, classic models of autoallergic disease have been created to study human disorders such as multiple sclerosis and myasthenia gravis through immunization of animals with constituent tissue proteins or enzymes found in the CNS (for example, myelin basic protein, acetylcholinesterase) (Lennon and Carnegie, 1971; Lindstrom et al, 1976a, 1976b; Paterson, 1977). These studies have provided important information regarding the mechanisms of immunopathology in autoimmune disorders that affect the CNS.

The inner ear has proven to have some unique properties that can now be better appreciated when viewed in light of what is understood to operate in the CNS. For instance, immunoglobulin crosses the blood-labyrinthine barrier and is found in perilymph at a level of 1/1000 the concentration found in serum in a manner analogous to the blood-brain barrier (Harris, 1983; Mogi et al, 1982). Further, the inner ear has the property of concentrating immunoglobulins when measured relative to cerebrospinal fluid (CSF) immunoglobulin levels (Harris, 1983; Mogi et al, 1982). This may reflect the water-resorptive properties of the inner ear rather than a specific concentrating mechanism. However, the end result is an immunoglobulin-rich environment that must serve to protect the inner ear from pathogens. The immunoglobulins found in human and animal perilymph appear to be predominantly IgG, with lesser amounts of IgM and IgA identified (Mogi et al, 1982; Palva and Raunio, 1981). An additional piece of information that must be reconciled is that secretory component and IgA have been found in the epithelial cells of the endolymphatic sac (Arnold et al, 1984). This would suggest that the endolymphatic fluid space is a secretory immune site that should be rich in secretory IgA. Up to now, confirmation of this observation is lacking in studies measuring immunoglobulin in endolymph or perilymph (Futaki et al, 1985; Palva and Raunio, 1981). Recently, we have examined the inner ears of mice and rats for the presence of secretory component and IgA in nonimmunized and immunized states. The findings from this study suggest that only under inflammatory conditions do secretory component and IgA become prevalent in the region of the endolymphatic sac (Takahashi and Harris, 1991). A similar observation has been made in other organs (stomach, for example) where secretory component and IgA are usually not found, yet in the presence of inflammation they become detectable in the tissues (Isaacson, 1982). This organ therefore does not seem to represent a classic mucosal immune site.

Because of the close interaction of lymphocytes and macrophages observed within the lumen, the endolymphatic sac has been suggested as the site of host defense within the inner ear (Lim and Silver, 1974; Rask-Andersen and Stahle, 1980). Examination of this site by immunohistochemical techniques revealed that the normal mouse has the full complement of immunocompetent cells including macrophages, PMNs, IgM- and IgG-plasma cells, and T-helper cells (Takahashi and Harris, 1988b).

The next step in assessing the function of such an immune system would be to stimulate the inner ear selectively with antigen and measure the resulting antibody concentrations. In a series of studies, my colleagues and I have challenged the perilymph of naive (primary response) and sensitized (secondary response) animals and observed the antibody levels developing in the perilymph over time. Results of these studies demonstrate that (1) local production of antibody occurs in the inner ear, (2) secondary-response animals develop much higher antibody levels than primary-response animals, and (3) these responses are independent of CSF or serum (Harris, 1983, 1984). Drawing from CNS immunity again, we see a parallel in that primed B cells can reach the inner ear and produce antibody locally; the only questions remaining are where and how does this occur?

Examination of inner ears underoing immune reactions reveals a multitude of inflammatory cells in the scala tympani and within the perisaccular connective tissue and endolymphatic sac lumen (Fig. 164-2). Early on in this response, PMN leukocytes and macrophages predominate; however, over time, lymphocytes (T-helper) and plasma cells become more profuse, with the gradual emergence of a population of T-suppressor cells by 3 weeks, presumably acting to halt the inflammatory response (Takahashi and Harris, 1988a). At the same time that these cells enter the inner ear, interleukin-2 (IL-2) levels markedly increase in the perilymph (Gloddek and Harris, 1989). This parallel rise in cells and interleukins may reflect the chemotactic role of IL-2 and a possible initiating signal for cells to enter the inner ear. Following the onset of an immune response, cells are seen entering the inner ear via the spiral modiolar veins along a bony conduit into the scala tympani (Fig. 164-3) or via the venules surrounding the endolymphatic duct and sac. Whether resident populations of cells are amplified as well or simply involved in antigen processing is not yet known. Comparison of these histopathologic changes with temporal bones from patients with suppurative labyrinthitis shows the same egress of cells from the spiral modiolar vein and the development of a fibro-osseous organization of the scala tympani (Harris et al, 1990). A similar pathologic picture has been seen in a patient with sudden deafness and polyarteritis nodosa, in that the scala tympani was replete with osteoneogenesis and fibromyxoid stromal reaction (Fig. 164-4) that appeared to be the "ghost" of a prior inflammatory response within the cochlea.

To test the central role of the endolymphatic sac in the immunologic reactions observed in the inner ear, experiments were performed in which the endolymphatic sac was surgically ablated before inner ear immune stimulation. In this series of studies, Tomiyama and I found that antibody levels were significantly reduced in the endolymphatic sac-ablated ears and that inflammatory cell infiltrates that customarily accompany such an antigen challenge were markedly diminished (Tomiyama and Harris, 1986, 1987). Subsequent studies blocking the endolymphatic duct and preserving the endolymphatic sac before antigen challenge of the scala tympani confirmed the importance of the endolymphatic sac in the elaboration of the immune response and that this site represents the afferent limb for inner ear immunity (Tomiyama and Harris, 1986, 1987). Thus it seems that the endolymphatic sac provides an immunologic role for the inner ear in addition to its water-resorpitve role, in a manner analogous to that of the gut, which is also known to serve both purposes.

Do these measurable immune responses serve any protective role? In a study involving cytomegalovirus (CMV), a known cause of labyrinthitis and SNHL in humans, animals inoculated with live virus into the inner ear developed progressive deafness and inflammation over an 8-day period (Harris et al, 1984; Woolf et al, 1985). When animals previously exposed to this virus were systemically inoculated with live CMV into the inner ear, they developed rising perilymph antibody levels and were completely protected from hearing loss (Harris et al, 1984; Woolf et al, 1985). This study demonstrated that the cochlea is not a passive organ on exposure to a pathogen and that an immune response can develop to protect and preserve cochlear function. On the other hand, it is well recognized that immune responses can be injurious to organ function if the inciting antigen evokes a sufficiently vigorous response. What evidence is there to suggest that the cochlea may be injured by immunity? Experimentally, Kumagami et al (1976) challenged hyperimmunized guinea pigs with antigen into the stylomastoid foramen as a means of challenging the inner ear and observed changes in action potential (AP) thresholds, as well as evidence of mild endolymphatic hydrops. Woolf and I examined the effect of primary and secondary inner ear immune responses and found that only in secondarily challenged animals did a significant shift in AP thresholds occur, and that this hearing loss developed over time (Woolf and Harris, 1986). This means that the cochlea can withstand antigen exposure primarily, but if prior sensitization has occurred, the result would be significant hearing loss. Further, when virus is injected into the region of the endolymphatic sac, significant hydrops and hearing loss develop in experimental animals (Fig. 164-5) (Fukuda et al, 1988). In animals immune to the virus, endolymphatic sac challenge of the virus is associated with hearing preservation; however, a marked lymphocytic infiltrate occurs in the region of the sac, and the animals develop mild endolymphatic hydrops. This suggests that viruses may indeed cause hydrops if they can reach and replicate within the sac epithelium. Further, in sensitized animals, the reintroduction of a pathogen into the sac results in a vigorous inflammatory event that alters sac function and results in hydrops. Extrapolating from these results, one can begin to understand mechanisms by which the immune response can be protectvie against a pathogen but, in doing so, cause sufficient damage to alter inner ear function.

A clinical example of this can be readily seen from a human temporal bone study of a patient who died with otosyphilis. In this study a lymphocytic infiltrate was seen in the region of the endolymphatic duct and endolymphatic sac with concomitant endolymphatic hydrops (Linthicum and El-Rahman, 1987) (Fig. 164-6). Presumably, the treponemal antigen was the iniciting factor for the accumulation of these cells in a fashion analogous to CMV or antigen in the previously mentioned studies of Fukuda et al (1988) and Tomiyama and Harris (1987). Such a finding explains the persistent symptoms and progressive nature of otosyphilis if chronic antigen stimulation is present in the inner ear.

To underscore the importance of the host response in possibly contributing to inner ear pathology, we attempted to separate the effects of the immune response from the effects of the pathogen itself. To accomplish this, we immunosuppressed animals with cyclophosphamide and inoculated their inner ears with live CMV; we then compared their hearing to a group of normal animals similarly given CMV (Darmstadt et al, 1990). There were two major findings:

1. There was a significant reduction in the inflammatory response within the cochlea following immunosuppressive treatment, and

2. The immunosuppressed animals showed significantly preserved hearing compared to controls. Further, there was a direct correlation between the degree of inflammation and the magnitude of hearing loss. Therefore, contrary to what might be expected with immunosuppression in the face of a virulent pathogen, it is actually the host's response to the invading organism, in this case CMV, which causes the majority of damage rather than the cytopathic effects of the virus itself and if the immune reaction can be blunted, there is a concommitant reduction in pathology. Clinically, this concept has been shown to be important in childhood meningitis, where steroids combined with antibiotics have been shown to dramatically reduce the incidence of sensorineural deafness compared to treatment with antibiotics alone (Lebel et al, 1988).

Experimental Allergic Larbyrinthitis

The concept that the inner ear may also be the target of autoimmune conditions follows from extensive experimental studies conducted on other organ systems. Such animal models have been established for experimental allergic encephalomyelitis (EAE), allergic neuritis, myasthenia gravis, and allergic thyroiditis, to name a few. In 1961 Beickert performed the first study to examine this possibility in relation to the inner ear. Using guinea pigs immunized to inner ear antigen, he was able to demonstrate lesions within the cochlea. In 1963 Terayama and Sasaki immunized guinea pigs with isologous cochlear tissue in Freund's adjuvant and were also able to produce isolated lesions within the cochlea and alterations in Preyer's reflex. Neither study was able to document the development of anticochlear antibodies or the presence of perivascular infiltrates. These observations were essentially ignored at the time because of limited technologic resources that did not allow the researchers to extend their findings as well as a general disregard for autoimmune conditions.

Since that time, Yoo et al (1983b) have reported the development of an animal model with inner ear injury secondary to type II collagen autoimmunity. These animals demonstrated spiral ganglion cell degeneration, atrophy of the organ of Corti, arteritis of the cochlear nerve and stria vascularis, and endolymphatic hydrops with atrophy of the surface epithelium of the endolymphatic duct. In addition, some animals showed otospongiotic changes of the bone of the exteranl meatus and otic capsule (Yoo et al, 1983a). Hearing loss and vestibular dysfunction could be found in some of their animals (Yoo et al, 1983b). These studies suggest that autoimmunity to type II collagen may underlie such disorders as otosclerosis, Meniere's disease, and SNHL associated with relapsing polychondritis. There have been several studies done since that have confirmed these findings (Huang et al, 1986; Ohashi et al, 1989; Soliman, 1990) and several that could not show significant inner ear pathologic findings after the initiation of type II collagen autoimmunity (Harris et al, 1986; Slvsten-Srensen et al, 1988).

Recently I investigated the possible creation of an animal model of autoimmune inner ear dysfunction resulting from exposure to heterologous cochlear tissue (Harris, 1987). Guinea pigs immunized with fresh bovine cochlear antigen in Freund's adjuvant developed significant hearing loss compared with a control group of animals (defined as an increase in eighth cranial nerve (CN VIII) AP threshold that was greater than two standard deviations above the mean for the control ears tested). In the experimental group of animals the presence of anticochlear antibodies was uniformly detected, and 32% of those ears tested (12 of 38) had significant hearing losses. Histologic evidence of immunologic injury was seen as

characterized by spiral ganglion cell degeneration, perivascular infiltration by plasma cells, edema, and hemorrhage. Interestingly, some animals showed unilateral hearing losses, whereas others had bilateral losses of varying degrees. Analysis of their serum by Western blot revealed an antibody against an inner ear antigenic epitope with a molecular weight of 62.000 to 68.000 daltons that was seen in the animals with hearing loss but not in those immunized whose hearing was maintained (Fig. 164-7) (Harris and Sharp, 1990).

This suggests that a specific anticochlear autoantibody was responsible for the hearing loss. Further analysis of this antigen is underway, but preliminary results indicate that it is distinct from type II collagen. Orozco et al (1990) performed similar cross-species immunizations, but in their experiments chick or guinea pig cochlear tissue was injected into mice. They were also able to demonstrate that hearing thresholds increased and that their serum stained the organ of Corti and saccule by immunohistochemistry. Both hydrops and organ of Corti degeneration were seen in the temporal bones of three animals. When this sera was employed in the Western blot assay, we found identical banding in the 62.000 to 68.000 dalton area. Therefore under certain circumstances there may be a specific antigenic epitope that provokes an autoimmune response, ultimately resulting in hearing loss.

The etiology of autoimmunity is unknown, but one theory suggests that the tissues that are involved in this process are of either ectodermal or endodermal origin and are viewed as foreign by the immune system, which is mesodermal. Since the entire membranous labyrinth is of ectodermal origin, this theory would be consistent with the concept that the inner ear is a potential site of an autoimmune process.

Clinical Autoimmune Disease of the Inner Ear

As previously mentioned, autoimmune disease that affects the ear may be either the result of organ-specific disease or the result of a systemic disorder. When examining patients for this disorder, one must attempt to classify such patients into either of these categories.

Veldman et al (1984) reported autoimmune SNHL that resulted from immune complex-induced vasculitis, a defect in PMN leukocytes, and postvaccination serum sickness. Each of these three etiologies is a systemic disorder that causes inner ear dysfunction as a manifestation of the illness. Other reports of immune complex disorders associated with SNHL have surfaced and suggest that steroids may be beneficial in the treatment of these disorders (Kanzaki and Ouchi, 1981).

Polyarteritis nodosa

Polyarteritis nodosa (PAN), a systemic disorder affecting the small- and medium-sized arteries throughout the body, has only rarely been associated with cochlear injury. For example, Malamud and Foster (1941) reviewed 300 cases of PAN and found only two patients with SNHL. Although this is a systemic disorder, hearing loss may be the sole presenting symptom (Bakaar, 1978; Peitersen and Carlsen, 1966; Wolf et al, 1987). Temporal bone histopathologic studies have been reported in PAN. Gussen (1977) found arteritis in the internal auditory artery with widespread cochleovestibular ischemic changes, and osteoneogenesis and fibrous tissue in the basilar turns. Jenkins et al (1981) reported similar pathologic findings, but these findings were restricted to the cochlea.

In a temporal bone study Yanagita et al (1987) reported a case of bilateral deafness associated with nephritis and a B-cell lymphoma. In this patient necrotizing vasculitis was seen in small- and medium-sized arteries throughout the body in association with PAN, and there was complete disappearance of the organ of Corti, atrophy or absence of the stria vascularis, collapse of Reissner's membrane, distortion of the tectorial membrane, and bone formation and fibrosis of the apical turn. Many of these findings have been experimentally produced by the aforementioned immunologic challenges of the cochlea, as well as by sudden interruption of cochlear blood flow (Alford et al, 1965; Kimura and Perlman, 1958). Thus from these temporal bone findings one can conclude that vasculitis is one clearly definable cause of profound hearing loss, and a search for such an etiology should be made in patients with profound unexplained deafness.

Cogan's syndrome

Cogan's syndrome is a disorder of young adults and is characterized by nonsyphilitic interstitial keratosis (IK) and vestibuloauditory dysfunction (Cody and Sones, 1971; Cogan, 1945; Haynes et al, 1980). IK develops suddenly with photophobia, lacrimation, and eye pain and gradually resolves with occasional flares. The vestibuloauditory symptoms are characterized by acute episodes of vertigo, tinnitus, and hearing loss, with the hearing loss progressing to deafness over a 1- to 3-month period. Patients may develop the vestibuloauditory symptoms 1 to 6 months before or after the onset of IK, but it should be noted that these symptoms may precede or follow the eye symptoms by as much as 2 years, in which case the disorder is classified as atypical Cogan's syndrome. Vestibuloauditory symptoms occurring in association with eye disease other than IK, such as episcleritis, uveitis, or conjunctivitis, are also considered atypical Cogan's syndrome. Cogan's syndrome may occasionally be associated with systemic symptoms, which include arthritis, PAN, glomerulonephritis, inflammatory bowel disease, and splenomegaly (Haynes et al, 1980).

The temporal bone findings in this disorder consist of endolymphatic hydrops, plasma cell and lymphocytic infiltration of the spiral ligament (Fisher and Hellstrom, 1961), saccular rupture, osteoneogenesis of the round window, spiral ganglion cell degeneration, and cystic degeneration of the stria vascularis (Wolff et al, 1965). In addition, Zechner (1980) found degeneration of the organ of Corti, as well as fibrosis and osteoneogenesis within the perilymphatic space. In another temporal bone study bilateral cochlear osteoneogenesis and ectopic bone tissue within the vestibular semicircular canals were found in a patient with Cogan's syndrome (Rarey et al, 1986).

Cogan's syndrome is thought to be a hypersensitivity response to one or more infectious agents associated with vasculitis (Cheson et al, 1976). The finding of lymphocyte transformation on exposure of a patient's lymphocytes to corneal antigen, scleroprotein (Brinkman and Broekhuyse, 1978; Char et al, 1975), and inner ear antigen has been reported (Hughes et al, 1983a). This may be evidence that this disorder is organ specific with autoimmunity directed against the eye and ear. It must, however, be remembered that the presence of autoantibodies or sensitized lymphocytes may not be the primary event involved in injury to that tissue. Rather, one may have a non-organ-specific event (that is, immune complex-induced vasculitis) that injures the tissue, releasing antigens to which the immune system then responds.

The responsiveness of this disorder to treatment probably relates to how long the disease has been active before diagnosis. Obviously, if the aforementioned histopathologic features of these "late" cases develop, one should not expect significant improvement with steroid treatment. If, on the other hand, a limited vasculitis results in labyrinthine ischemia, one can predict a beneficial response to treatment.

A condition that has similarities to Cogan's syndrome is the Vogt-Koyanagi-Harada syndrome (VKH). It is characterized by SNHL, dizziness, granulomatous uveitis, depigmentation of the hair and skin around the eyes, loss of eyelashes, and aseptic meningitis. In distinction, CSF abnormalities are uncommonly present in Cogan's syndrome (Wolff et al, 1965). The etiopathogenesis of this condition is thought to involve (1) autoimmunity to the melanocytes and (2) the tissues containing these cells, such as uvea, skin, meninges, and inner ear (Hiraki et al, 1989).

Wegener's granulomatosis

The classic triad of Wegener's granulomatosis consists of (1) necrotizing granulomas with vasculitis of the upper and lower respiratory tracts, (2) systemic vasculitis, and (3) focal necrotizing glomerulitis (Fauci and Wolfe, 1973; McDonald and DeRemee, 1983). McDonald and DeRemee (1983) pointed out that ear manifestations occurred in one fifth of their series of 108 patients and were most often serous otitis media associated with infection or obstruction of the nasopharynx. Although the resultant conductive hearing loss was common, nine patients had sensorineural losses, and five improved with prednisone therapy.

The otologic symptoms of Wegener's granulomatosis have been reported by others, with serous otitis and middle ear involvement being the most common manifestations (Campbell et al, 1983; Kornblut et al, 1982). Recently, Kempf (1989) reported a higher incidence of low to moderate SNHL in 21 of 26 ears examined audiologically.

The etiology of the inner ear disease is unknown. However, if the endolymphatic sac is a mucosal-type immune site, as is found in the upper and lower respiratory tracts and the kidney, perhaps the necrotizing vasculitis would have a predilection for involving the vasculature of the endolymphatic sac as well (Leone et al, 1984).

Since the otologic manifestations may be the sole presenting symptom of these patients, a thorough and repeated search for evidence of the aforementioned classic triad of Wegener's granulomatosis should be performed on patients with unexplained sudden otologic disease. A recently developed test has been described that recognized antibodies to azurophilic granules in neutrophils. This antineutrophil cytoplasmic antibody (ANCA) test is positive in 95% of patients with Wegener's granulomatosis (Schur, 1991).

Behcet syndrome

Behcet's syndrome is a chronic disorder hallmarked by the development of oral and genital mucosal ulcerations and eye lesions. The systemic manifestations may include the skin, joints, vasculature, and CNS (Campbell et al, 1983; O'Duffy et al, 1983). One report described inner ear involvement in this disorder, but because of the small patient sample size, no definitive conclusion could be reached about whether this disorder is associated with

progressive SNHL and disequilibrium or whether the patients had coexistent presbycusis or idiopathic SNHL (one patient) (Brama and Fainaru, 1980).

Relapsing polychondritis

Relapsing polychondritis is a rare disease characterized by recurrent episodes of inflammatory necrosis affecting cartilaginous structures of the ear, nose, upper respiratory tract, and peripheral joints (McAdam et al, 1976). This disease destroys supporting cartilage, resulting commonly in auricular deformity or occasionally saddle nose deformity or tracheal collapse. The auricular inflammation and erythema must be distinguished from bacterial perichondritis and erysipelas. In relapsing polychondritis, erythema spares the lobula but involves the remainder of the pinna equally. Bacterial perichondritis exhibits fluctuations if the entire pinna is involved; erysipelas involves the entire auricle and extends onto the periauricular skin with a well-demarcated irregular margin. The association of vestibuloauditory symptoms helps point toward an immune-mediated rather than an infectious cause. The most life-threatening manifestation is the airway obstruction resulting from loss of cartilaginous support of the trachea. Laboratory abnormalities include increased serum immunoglobulins, and biologically false-positive VDRL (Venereal Disease Research Laboratory) test. The finding of antibodies to cartilage and to type II and IX collagen, as well as the induction of lymphocyte activation on exposure to cartilage, is the basis for this being considered an autoimmune disorder (Ebringer et al, 1981; Rogers et al, 1973). The finding of type II collagen in the tectorial membrane and in the otic capsule provides a rationale for occurrence of an inner ear disorder in the presence of specific autoimmunity directed against collagen (Thalmann et al, 1986; Yoo et al, 1982, 1983a, 1983b).

Antiinflammatory agents have been used with success in reversing the inflammation and SNHL in this disorder.

There are a variety of other rare types of systemic vasculitis, including giant cell arteritis, Takayasu's arteritis, postvaccination vasculitis, and serum sickness in which an occasional incidence of vestibuloauditory dysfunction has been seen (Mair and Elverland, 1977; Rosen, 1949). The basic underlying pathologic condition is vasculitis, with the ultimate consequence being ischemic injury to the inner ear.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystem disease that has protean manifestations (see also Chapter 162). It may have an insidious onset or may be fulminant and rapidly progressive. The malar "butterfly rash" is pathognomonic but present in relatively few patients. Polyarthralgia, arthritis, pleuritis, pericarditis, pneumonitis, myocarditis, endocarditis, nephritis, cranial nerve palsies, meningitis, cerebrovascular accidents, neuritis, scleritis, retinal degeneration secondary to vasculitis, and inflammatory bowel disease (Steinberg et al, 1984; Tan et al, 1982). The otologic manifestations include chronic otitis media with necrotizing vasculitis and progressive SNHL or disequilibrium (McCabe, 1979). The laboratory abnormalities include increased ESR, evidence of circulating immune complexes, and multiple autoantibodies (see discussion of immunoassays). The association of a decreased level of suppressor T cells in patients with SLE is intriguing in light of autoantibody formation, although this does not prove causality, since it may be used by anti-T

cell antibodies also present during the course of the disease.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that mainly affects the joints. This disorder characteristically affects the small joints of the hands and feet and then progressively involves other joints in a symmetric fashion. Extraarticular manifestations include vasculitis, muscle atrophy, subcutaneous nodules, lymphadenopathy, splenomegaly, and leukopenia. Rheumatoid factors (RFs) 19S, 7S IgM, and 7S IgG react against abnormal IgG produced by lymphocytes usually found in the synovia. RF serum titers are present in 75% of patients. RF-IgG complexes within the joint space activate the complement system, resulting in inflammation and tissue injury. This, together with mononuclear cell infiltrates and PMN leukocytes, perpetuates the cycle.

Otologic manifestations of RA have been sporadically reported and include loosening of the transducer mechanism (Moffat et al, 1977) and vestibuloauditory dysfunction (Hughes et al, 1983a; McCabe, 1987). No temporal bone studies have been reported, and the relationship of RA to inner ear dysfunction is not confirmed, since there is no proof that patients with RA have any greater likelihood of developing an isolated ear disorder than does the general population. This holds true for a number of other autoimmune disorders that have been associated with vestibuloauditory dysfunction, including ulcerative colitis, idiopathic thrombocytopenic purpura, polymyositis, and dermatomyositis.

Organ-specific autoimmune inner ear disease

To establish organ-specific autoimmunity, cell-mediated or humoral immunity must be evident against the body's own tissue antigens. In the case of vestibuloauditory autoimmunity, there should be autoantibodies or evidence of cell-mediated immune responses (lymphocyte transformation, lymphokine production, or delayed hypersensitivity) directed against inner ear antigens (cochlea, vestibular, or both).

Since the report by McCabe (1979), attention has focused on the possibility that a new, previously unrecognized form of specific autoimmune SNHL represented a treatable form of deafness. As early as 1958 Lehnhardt speculated that cases of bilateral deafness were caused by anticochlear antibodies; however, no evidence emerged to support this hypothesis (Lehnhardt, 1958). Attempts at creating animal models of autoimmune allergic labyrinthitis failed, as previously discussed (Beickert, 1961; Terayama and Sasaki, 1963). In 1974 Schiff and Brown speculated that amelioration of sudden deafness by ACTH and heparin treatments was evidence of an autoimmune vasculitis etiology. Again, no specific testing was done to confirm this hypothesis or its organ specificity. In McCabe's original series, the bilateral SNHL was asymmetric and progressive over weeks to months and was associated with electronystagmographic (ENG) evidence of vestibulopathy. In addition, a small percentage showed a coexistent facial paralysis (McCabe, 1979).

Although there was initial enthusiasm for lymphocyte migration inhibition assay as a means of demonstrating organ-specific autoimmunity toward inner ear antigens, more recently its specificity and sensitivity have been questioned, and Hughes et al (1986) have promoted lymphocyte transformation as a more sensitive assay. Even in patients having Cogan's

syndrome, however, whose underlying ear dysfunction is clearly autoimmune by nature, the reported stimulation indices have been meager, suggesting that there is still a need for clearer documentation that this is in fact an organ-specific disorder rather than a form of systemic autoimmunity affecting the inner ear as one of its targets. Arnold et al (1985) incubated serum from patients with suspected "autoimmune" SNHL onto sections of nonrelated, healthy human temporal bones and demonstrated positive immunofluorescence labeling in 15 of 21 patients. The five patients who were tested by lymphocyte transformation against inner ear antigen were found to be negative (Arnold et al, 1985).

In a subsequent study 119 serum samples from patients with hearing loss were similarly investigated by immunofluorescence microscopy, and 54% showed labeling against sections of healthy temporal bones. Despite these findings, only 27% of patients treated with prednisolone showed some improvement in hearing (Arnold and Pfaltz, 1987). Other authors have also utilized decalcified temporal bones for immunohistochemistry to demonstrate specific targets of autoimmunity within the inner ear (Gebbers et al, 1987; Soliman, 1988a, 1988b; Soliman and Zanetti, 1988). There still remains a problem in interpreting these results, since antigen degradation occurs with prolonged decalcification and HLA differences between the patients and the cadavers could account for the observed labeling. If the specificity of staining is confirmed, then humoral autoantibodies are implicated in the pathogenesis of this disease. In contrast, cell-mediated immunity is implicated by the studies of Hughes et al (1986) and Berger et al (1989). A number of other studies have looked for the presence of autoantibodies (ANA, anticardiolipin, antismooth muscle, antiendoplasmic reticulum) in a variety of inner ear disorders, and the incidence of one or more of these being positive is surprisingly high (Elies and Plester, 1985; Kempf and Hornig, 1987; Plester and Soliman, 1989; Zanetti et al, 1987). Since many of these tests are nonspecific and are increasingly positive with age in the normal population (for example, ANA), the results of these studies are difficult to interpret. I have examined both cell-mediated and humoral immunity in patients with suspected autoimmune hearing loss, and results to date indicate that the lymphocyte transformation assay is insensitive in 26 patients with a mean stimulation index of 0.77 ± 0.27 compared with 0.8 ± 0.27 in 19 control patients ($p > 0.05$).

In a recent study we employed Western blot analysis in 54 patients with progressive SNHL and found that 19 (35%) showed evidence of a specific anticochlear antibody in their serum (Harris and Sharp, 1990). Of note, the inner ear antigenic epitope, against which their serum reacted, was the same by molecular weight (MW) determination (62.000 to 68.000) as found in the experimental autoimmune SNHL produced in animals. Further, by two-dimensional gel electrophoresis we were able to show that a patient with steroid-responsive autoimmune deafness had autoantibodies that reacted against an inner ear antigen not only with the same MW, but also with the identical isoelectric point as the hearing loss animals. This is compelling evidence that some patients with rapidly progressive SNHL have autoantibodies to a particular antigenic epitope within the inner ear and that this is a true organ-specific autoimmune event. This observation has been confirmed by Moscicki (1990) in 11 patients who demonstrated this antibody on Western blot analysis and whose hearing improved with immunosuppressive therapy. We have extended the original observation to now include 138 patients with rapidly progressive SNHL in whom 46 (33%) were positive by Western blot, and of the positive patients, 29 (63%) were female. This is again in keeping with the female prevalence seen in other autoimmune conditions of the body. Analysis of these positive patients reveals that a spectrum exists from the patient who has deafness and

florid clinical and laboratory evidence of systemic autoimmune disease to the patient who exhibits hearing loss as the only detectable manifestation of autoimmunity (Tables 164-1 and 164-2). Analysis of this inner ear antigen is underway, but preliminary work has shown that it does not represent type II collagen. As stated this is a disease usually found in middle-aged females; however, I have seen several patients in their sixth and seventh decades, as well as seven children to date, with steroid-sensitive progressive deafness.

The pathology of autoimmune SNHL awaits description of a temporal bone from a patient with deafness and no signs of systemic disease. Recently, however, Schuknecht (1991) reported a patient who died with bilateral progressive SNHL and systemic eosinophilia. These temporal bones showed hydrops, mononuclear and plasma cell infiltrates in the scalae, osteoneogenesis in the scala tympani adjacent to the round window membrane, and perivascular infiltrates surrounding the spiral modiolar veins. Of interest was a dense bone formation surrounding the spiral modiolar vein and modiolus that have undergone chronic antigen stimulation (Harris et al, 1990).

Ménière's disease

Ménière's disease is a capricious disorder with a high incidence of bilaterality and a waxing and waning course. These characteristics have led many to wonder if it might also have an autoimmune etiology (Ryan, 1987). It is clear that a number of non-organ-specific autoimmune causes of deafness may have a Ménière's disease-like presentation (that is, Cogan's syndrome, polyarteritis nodosa), and only with the passage of time will the other stigmata of a systemic autoimmune disorder become evident. Hughes et al (1983b) reported 2 to 10 patients with Ménière's disease with a slightly increased stimulation index on lymphocyte transformation assay. I studied 14 nonoperated patients with classic Ménière's disease and failed to find any evidence of significant lymphocyte transformation as compared with 11 controls (stimulation index of 0.95 versus 0.90) (Harris, 1985). There have, however, been reports of elevated circulating immune complexes and other immunologic abnormalities in patients with this disorder. Brookes (1986) reported 54% of patients with Ménière's disease with elevated immune complexes as compared with 2.9% in controls. Morrison and Xenellis (1987) reviewed 671 patients with Ménière's disease and compared them with 689 age- and sex-matched controls. In this study there was a slightly higher incidence of other associated autoimmune disorders (10.3% versus 4%) among the patients with Ménière's disease. Further, there was a highly significant association of the major histocompatibility complex class I HLA allele CW7 and Ménière's disease. The association of this HLA allele has also been reported for autoimmune inner ear disease in general (Bowman and Nelson, 1987).

Yoo et al (1982) reported an elevated type II collagen autoantibody level in patients with Ménière's disease and otosclerosis. Autoimmunity to type II collagen experimentally produced in animals has resulted in widespread inner ear dysfunction (that is, hearing loss, vestibular dysfunction, and endolymphatic hydrops). This form of autoimmunity needs to be considered as an additional feature of autoimmune inner ear disease; however, it is unclear at this time if this represents a primary or secondary autoimmune event.

Treatment

Patients in whom there is clear-cut evidence of autoimmunity and whose deafness and disequilibrium are disabling should be started on an immunosuppressive regimen. The suggested treatment protocols have not been determined by clinical trials but rather by individual preferences. High-dose steroids are generally used, although the recommended dose and duration of treatment vary. Generally, 1 to 2 mg/kg/day (usual dose 60 mg) of prednisone for 4 weeks will provide an initial therapeutic trial. Patients with a beneficial response should continue receiving a high dose for an additional 1 to 2 months and then taper down slowly, first going to alternate-day therapy and, if hearing remains stable, then gradually tapering to 20 mg every other day. The risks of chronic steroid therapy are not trivial and can represent significant morbidity to the patient; therefore they should be throughly discussed. In nonresponsive but desperate cases, cyclophosphamide can then be added at a dose of 2 to 5 mg/kg/day, taken each morning with liberal fluid intake to lessent the risks of urinary bladder toxicity. Peripheral blood should be monitored so that the total leukocyte count does not drop bnelow 3000 cells/mm^3 nor the neutrophil count below 1000 to 15000/mm^3. In a more recent study, McCabe (1989) reported on 66 patients with progressive bilateral deafness who responded to immunosuppression. In his experience, patients more readily improved with cyclophosphamide than with prednisolone. In McCabe's treatment regimens, patients are given an initial trial of high-dose steroids for 3 weeks, and those who respond are then escalated to a cyclophosphamide-prednisolone combination for a 3-month period; the cyclophosphamide is then discontinued, and the prednisolone is slowly tapered. Any drop in hearing is followed by the reinstitution of the full combination of drugs at their original dosage. Administration of cyclophosphamide has been associated with the development of hemorrhagic cystitis and malignancies of the urinary tract; therefore careful monitoring of the patient is indicated during therapy. Chronic administration of alkylating agents has been shown to be leukemogenic, although, of this class of agents, cyclophosphamides has been found to be one of the weakest leukemogens (Kaldor et al, 1990).

In recalcitrant cases in which humoral immune mechanisms appear to be at play (that is, autoantibodies and circulating immune complexes), plasmapheresis can be considered (Luetje, 1989). The frequency and duration of treatment depend on the class of immunoglobulin and its equilibrium characteristics. For example, IgG is widely distributed both intravascularly and extravascularly. Therefore repeated plasmapheresis treatments over a period of time are necessary to reduce the total-body IgG. One can approach reduction to approximately 20% of total-body IgG after eight treatments. A typical protocol would be for daily plasmapheresis for 5 days, then every other day for 2 weeks, and then twioce each week for a total of 10 runs in 1 month. Usually one can assess the benefits of treatment by 1 month. If a beneficial response is seen, maintenance treatment can be done every 10 days or even less often. During plasmapheresis, cyclophosphamide and steroids should be continued in order to maximize the immunosuppressive effect and to prevent the continued production of antibody.

The experience at the National Institutes of Health in treating a variety of autoimmune types of vasculitis including Wegener's granulomatosis and Cogan's syndrome with systemic necrotizing vasculitis has shown that aggressive immunosuppressive therapy should be maintained for 1 year after the disappearance of active disease (Fauci and Wolfe, 1973; Fauci et al, 1978). In general, this proven method for managing potentially life-threatening

autoimmune conditions should serve us well in the management of disabling vestibuloauditory dysfunction.

In the management of hearing loss associated with Cogan's syndrome, it has been recommended that if hearing acuity is poor, a trial of prednisone, 2 mg/kg/day in divided doses, be instituted for 5 to 7 days and, regardless of the response, tapered to 1 mg/kg/day over the next week, and, if after 2 weeks there has been no response, the prednisone should be rapidly tapered and stopped (Haynes et al, 1980). However, a consensus has developed among otolaryngologists treating autoimmune SNHL that some patients will not respond to this short a course of immunosuppression and that cessation of the drug so quickly may result in a serious and perhaps permanent relapse.

Immunoassays

The otolaryngologist - head and neck surgeon is often perplexed by the changing array of immunologic parameters that can be measured in patients suspected of having autoimmune disease. The following tests represent common assays that can be used as specific or nonspecific screening tests in such patients.

Lymphocyte transformation

In 1960 Nowell demonstrated that phytohemagglutinin (PHA), a lecitin from kidney beans, caused the transformation of small lymphocytes into proliferating lymphocytes when cocultured in virto (Nowell, 1960). This observation was then extended to assess lymphocyte responsiveness to antigens or allogeneic cells. The technique involves the isolation of mononuclear cells from whole blood by various purification methods, of which Ficoll-Hypaque is the most widely used. These cells are then placed in culture with nutrient media containing serum, and antigen is then added at various dilutions. The optimal time for proliferative response to develop is from 4.5 to 7 days, at which time tritiated thymidine is added to the wells for a 24-hour period in order to allow for its incorporation into the DNA of the proliferating lymphocytes. Prior sensitization of the lymphocytes to the antigen is required for transformation to occur. A stimulation index is calculated as the ratio of mean counts per minute of the stimulated cultures divided by the mean counts per minute of the nonstimulated cultures (Grieco and Meriney, 1983). It is always important to run an age-matched control in parallel with the experimental subject and a mitogen (for example, PHA) as an additional positive control for assessing the condition of the lymphocytes in culture. The stimulation index is usually greater than 3 for there to be evidence of antigen recognition and greater than 10 in the mitogen-stimulated cultures. Because of the variability of these responses with differing culture conditions, one should take great pains to repeat the testing on individuals with "positive" results.

Lymphokine assays

The basis of lymphokine assays is that various lymphokines are released from lymphocytes following stimulation by antigens, mitogens, surface immunoglobulins, and various membrane receptors. The release of these substances does not necessarily require lymphocyte transformation.

Macrophage migration inhibitory factor

The production of macrophage migration inhibitory factor (MIF) is correlated with the development of delayed hypersensitivity responses on skin testing. In the usual assay, sensitized lymphocytes or normal control lymphocytes are mixed with guinea pig or human monocytes in a capillary tube and incubated in the presence of a specific antigen for 24 hours. The degree of inhibition of migration is determined by dividing the area of migration of the test cells out of the capillary tube by the area of migration of the control cells. Greater than 20% inhibition is considered to constitute a positive MIF response.

Leukocyte migration inhibitory factor

Leukocyte migration inhibitory factor (LMIF) may be produced by either T or B lymphocytes and has a molecular weight of 85.000 daltons. It can be assayed in a fashion analogous to that described above for macrophage MIF.

Serum protein electrophoresis

Serum protein electrophoresis (SPEP) provides an overview of more than 100 serum proteins and in doing so is a good screening test for the presence or absence of normal blood constituents. In addition, the identification of abnormal spikes may indicate gammopathies such as Waldenstrom's macroglobulinemia or multiple myeloma.

Immunoelectrophoresis

Immunoelectrophoresis (IEP) combines electrophoretic separation of serum proteins with immunodiffusion using monospecific antisera. This assay can be used in conjunction with SPEP to determine the presence or absence of normal proteins as well as their relative concentrations. For instance, the absence of serum IgA or alpha1-antitrypsin is readily detectable by this technique.

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR) is a simple means of serially monitoring patients with a diverse range of inflammatory disorders. Its major disadvantages are its nonspecificity and relative insensitivity. The ESR is determined by the serum viscosity; therefore substances such as fibrinogen, acute-phase reactants, and macroglobulins, which are often associated with chronic inflammatory states, have a significant effect on elevating the ESR. Normal values vary somewhat according to age and sex but usually are less than 20 to 25 mm/hr.

Cryoglobulins

A number of systemic diseases are associated with the presence of serum immunoglobulins that have the property of forming precipitates in the cold. Autoimmune, neoplastic, and infectious diseases have been shown to have cryoglobulins at some point in their clinical course, and their presence may play a role in the pathogenesis of some of these disease states. For example, the presence of cryoglobulins is particularly associated with

collagen diseases in which vasculitis is a prominent feature. Cryoglobulins have been found in lupus nephritis, rheumatoid vasculitis, Sjögren's syndrome, and polyarteritis nodosa. They may also be present in occult infections, such as chronic hepatitis B or bacterial endocarditis, or in occult lymphoproliferative disorders. The serial determination of cryoglobulins in a patient's course may be a valuable marker for the activity of the disease and the response to therapy.

Quantitative immunoglobulins

In adults the distribution of quantitative immunoglobulins within the serum is approaximately 85% IgG, 10% to 15% IgA, and 5% to 10% IgM. Serum concentration of immunoglobulins vary widely depending on the immunization status of the individual and the possible presence of certain protein-losing enteropathies or nephropathies. Additional causes of immunoglobulin deficiencies may be secondary to genetic or acquired immunodeficiencies, such as X-linked hypogammaglobulinemia or IgA deficiency. Occasionally, abnormally high levels of a serum immunoglobulin class will reflect the presence of a myeloma. Routine screening of hearing loss patients has not been found to be beneficial to their diagnosis or treatment.

Antinuclear antibody and lupus erythematosus prep

Under most circumstances, tests for autoimmunity will have an overlap region in which normal patients and diseased patients will both show positive responses. This is the case for antinuclear antibody (ANA). Here one must use additional clinical criteria to confirm the suspected diagnosis. There will be patients in whom the ANA is strikingly positive at high dilution, and under these conditions this test will be diagnostic of an autoimmune state. The pattern of fluorescence is variable and may be reported as speckled, nuclear rim, homogenous, or nucleolar staining. These staining characteristics are related to autoantibodies against specific nuclear antigens. An example of this is that the homogenenous staining is caused by antibodies against insoluble DNA histone and may be seen in all collagen vascular diseases, whereas the nucleolar staining is almost uniformly associated with scleroderma. In general, the ANA is positive in 50% of patients with scleroderma and 30% of patients with rheumatoid arthritis; however, up to 7% of normal individuals may have a positive test result, severely limiting its usefulness as a screen for autoimmunity (Grieco and Meriney, 1983).

The lupus erythematosus (LE) prep is a reaction seen in PMN leukocytes from their ingestion of altered nuclear material. This nuclear material has been altered by the action of ANA against DNA histones. This assay is usually performed in the presence of SLE but may only be positive in 20% of patients with SLE at any given time in their course (Grieco and Meriney, 1983). This test is especially useful when one is attempting to differentiate other collagen vascular diseases from SLE.

Anti-DNA antibodies are also measured in patients with collagen vascular diseases, and the specific ANA is classified as native double-stranded DNA (nDNA) or single-stranded DNA (ssDNA). The anti-nDNA is highly associated with SLE, and its presence appears to parallel the activity of the disease and identify those patients at risk for the development of renal disease (Grieco and Meriney, 1983). Anti-ssDNA is less specific and has been found in many types of collagen vascular disease but may be of pathogenic importance, since it has

been eluted from the kidneys of patients with lupus nephritis.

CIQ-binding assay

High values for CIQ binding provide strong evidence for circulating immune complexes of the type that interact with the classic pathway of complement activation (IgG and IgM).

Raji cell assay

The Raji cell assay detects soluble immune complexes in serum and is based on the binding of immune complexes to Raji cells via complement receptors. This assay is unreliable in SLE and other diseases where antilymphocyte antibodies can give false-positive results. *Low* levels of circulating immune complexes by the Raji cell assay are found in about 50% of the normal population.

The following tests are most often helpful in screeing for immune-mediated deafness:

1. ANA

2. Sedimentation rate

3. CIQ binding

4. Raji cell assay

5. Rheumatoid factors

6. Cryoglobulins

7. Urinalysis

8. FTA-ABS.

Summary

Autoimmunity has long been a recognized cause of disorders affecting nearly every organ system in the body. It should come as no surprise therefore that the inner ear would also be the target of such responses. The critical focus of research in the future will be to better recognize autoimmunity as an etiology of vestibuloauditory dysfunction by the development of specific and sensitive laboratory tests and to further identify the possible initiating events and antigenic epitopes responsible for the disease. It is hoped that increased experience with these patients will soon provide a precise and highly efficacious treatment regimen. This will not occur, however, until a prospective controlled study is performed to look at the most effective treatment regimen for this disorder.