Biological and Clinical Aspects of Autoimmune Inner Ear Disease

ANDREW J. GRIFFITH, B.S.

Medical Student and Graduate Student in the Departments of Internal Medicine and Molecular Biophysics and Biochemistry, Yale University School of Medicine, New Haven, Connecticut

Received October 28, 1991

The clinical presentation, diagnosis, and management of autoimmune inner ear disease are reviewed. Recent studies indicating an autoimmune etiology and pathogenesis are discussed, along with a comparative analysis of several promising new animal models. Further studies to define the natural history, pathogenesis, and diagnosis of the disease are suggested.

INTRODUCTION

Autoimmune inner ear disease was first proposed as a distinct entity by McCabe in 1979 [1]. He described a series of 18 patients with sensorineural hearing loss and hypothesized that this hearing loss was caused by an autoimmune process involving the inner ear. His hypothesis was based on diagnostic studies and treatment experience with the 18 patients, whose clinical patterns were not congruent with known disease entities and appeared to merit their own category. All of these patients responded to chronic cortisone and cyclophosphamide therapy, and thus McCabe emphasized the importance of recognizing this condition, since it is one of the few forms of sensorineural deafness for which there is a treatment [1].

CLINICAL PRESENTATION

Auditory Signs and Symptoms

The typical patient is most commonly middle-aged and female, although patients of all ages and both sexes have been described [1–5], including children as young as eight years [5]. The patient usually presents with bilateral, asymmetric, progressive hearing loss over a course of days to months. Some patients with a long history of deafness in one ear may present with recent unilateral hearing loss in the functioning ear. Although as many as 21 percent of patients initially present with unilateral hearing loss, it has been proposed that this condition may be the result of early detection of disease which would eventually progress to bilateral loss [5]. Symptoms may fluctuate, but the more common natural history of the disease appears to be steady progression of hearing loss [1,5]. Hearing loss may occur at any frequency, and therefore the audiogram may be flat, downsloping, or upsloping. Localizing tests

17

Abbreviations: ELISA: enzyme-linked immunosorbent assay   FTA: fluorescent treponemal antibody   kDa: kilodalton(s)

Address reprint requests to: Andrew J. Griffith, B.S., Section of Rheumatology, Dept. of Internal Medicine, Yale University School of Medicine, 609 LCI, P.O. Box 3333, New Haven, CT 06510-8056

Copyright © 1992 by The Yale Journal of Biology and Medicine, Inc.
All rights of reproduction in any form reserved.
demonstrate the hearing loss to be sensorineural. Speech discrimination is usually decreased but may be normal in some cases [1,6].

**Vestibular Signs and Symptoms**

In addition to auditory symptoms, these patients may also present with vestibular complaints. Most, but not all, patients will experience true vertigo, light-headedness, or ataxia [1,5–7]. Vestibular testing in these patients usually reveals bilateral reduced or absent caloric responses, with reductions in caloric response paralleling the hearing loss [6,7]. At present it is unclear whether patients may present with isolated vestibular symptoms in the absence of auditory findings since sensorineural hearing loss was required for establishment of the diagnosis in previous studies [1,5,6]. Prospective studies of patients presenting with vestibular symptoms alone should determine if autoimmune inner ear disease can affect the vestibular system without auditory system involvement.

**Additional Otologic Symptoms**

In addition to hearing loss and vestibular symptoms, tinnitus and aural pressure are also frequent complaints [1,5]. A retrospective study of Hughes et al. [5] found that approximately one-half of patients experienced aural pressure and one-third had tinnitus, and thus these symptoms are common in this disorder. The association of these symptoms with hearing loss and dizziness in autoimmune inner ear disease may mimic the presentation of Meniere's disease [5,8]. In fact, it is not clear that these two diseases represent different clinical entities, except that corticosteroid therapy is effective in the former condition but not in the latter.

**Neurologic Symptoms**

Facial palsies have been described in two patients [1,4], and in both cases the facial paralysis occurred on the same side(s) as the sensorineural hearing loss. It is unclear if facial nerve palsy is a manifestation of the inner ear disease itself, since in one of the two cases it was part of a concomitant inflammatory polyneuropathy [4]. In either case, cranial nerve VII palsy is uncommon but can occur in association with this disorder.

**Association with Other Autoimmune Disorders**

Patients with autoimmune inner ear disease will frequently have or subsequently develop other diseases thought to be autoimmune in origin. These other diseases include Cogan's syndrome, chronic ulcerative colitis, rheumatoid arthritis, polyarteritis nodosa, carotidynia, temporal arteritis, systemic lupus erythematosus, Hashimoto's thyroiditis, polymyositis, juvenile rheumatoid arthritis, and systemic vasculitis [1,5,9–12]. Hughes et al. [5] retrospectively studied 52 patients with autoimmune inner ear disease and demonstrated that 29 percent of them had one of these other immune diseases, and thus co-occurrence with these other diseases is relatively common.

**PATHOPHYSIOLOGY**

**Evidence for Immune-Mediated Tissue Injury**

Several lines of evidence indicate that the etiology of autoimmune inner ear disease is immune-mediated. First, sera from these patients frequently contain
circulating immune complexes, suggesting that inner ear injury may occur via an immune complex-mediated (Type III) hypersensitivity reaction [2–4]. This type of reaction can be initiated by the formation of immune complexes in autoimmune disease or persistent infection (see [13] for review). Second, there is a nearly universal response of the disease to systemic corticosteroid and cytotoxic therapy [1,2,4,6,12,14]. These therapies are known to be effective in other diseases of inflammatory or autoimmune origin, and their efficacy in treating autoimmune inner ear disease suggests that the pathogenesis of this disease is also immune-mediated. Third, temporal bone pathology in one specimen from a patient revealed vasculitis, “ghosts” of blood vessels, and granulomatous tissue, all of which indicate immune injury [1]. Examination of more specimens is required, however, before it can be concluded that this is a uniform finding indicative of immune injury to the inner ear. Fourth, the frequent association of this disease with other known or suspected autoimmune diseases indicates that it is an autoimmune process itself or it is a result of these other systemic autoimmune processes [5,15]. In summary, the current facts suggest that tissue injury is mediated by immune mechanisms.

Despite these observations, autoimmune inner ear disease may be a misnomer, since there is no definitive evidence implicating autoimmunity in this disease. At least some tissue injury may be attributed to the deposition of circulating immune complexes in inner ear tissue, resulting in local inflammation and tissue damage, but it should be noted that immune-mediated tissue injury may occur via a combination of different mechanisms (see [13] for review). Immediate (Type I) or delayed (Type IV) hypersensitivity could also potentially cause inner ear tissue injury similar to that which is observed in autoimmune inner ear disease, although there is currently no evidence to suggest this process. In contrast, there is substantial evidence that inner ear injury is at least partially mediated by an antibody-dependent cytotoxicity (Type II hypersensitivity) mechanism. In Type II hypersensitivity, antibodies bind to antigen(s) present on cells, leading to phagocytosis, killer cell activity, or complement-mediated lysis. Elucidation of the inner ear antigenic targets of such antibodies would provide compelling evidence for Type II-mediated inner ear injury, and would definitively establish autoimmune inner ear disease as a bona fide primary autoimmune process.

**Evidence for an Autoimmune Etiology**

Laboratory studies of peripheral blood lymphocytes and antibodies from patients with this disorder have provided the most convincing argument that the disease has an autoimmune etiology. In contrast to routine screening tests, assays of antigen-specific immune responses to pooled inner ear antigen preparations have provided the best evidence for an autoimmune process in this disease.

Earlier investigations used the enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence to detect humoral immunity to inner ear antigens [6,8,10,16–18]. The ELISA is a solid-phase assay for the measurement of serum levels of antibodies against crude inner ear antigen preparations, whereas indirect immunofluorescence detects the direct binding of serum antibodies to thin sections of bovine or guinea pig cochlear tissue. Only some of the studies detected antibodies to inner ear antigens [16–18], although the discrepancies most likely arise from differences in experimental technique.

These findings were extended by a recent study of Harris and Sharp, who used two-dimensional gel electrophoresis and immunoblot analyses to define, at the
molecular level, the autoantigen(s) recognized by anti-inner ear antibodies [19]. They found that 19 of 54 sera from patients with autoimmune inner ear disease selectively bound an antigen (or antigens) migrating as a single or double band at 68,000 molecular weight. Whereas only one of 14 normal human sera bound this antigen, sera from four of five control patients with ulcerative colitis recognized this antigen (or antigens). Of note is the fact that patients with ulcerative colitis have been shown to be predisposed toward developing sensorineural hearing loss [9,11]. It is therefore unclear if the presence of this antibody (or antibodies) is specific for patients with inner ear disease or if it is found nonspecifically in autoimmune or inflammatory disorders. It will be interesting to determine if the 68 kilodalton (kDa) antigen (or antigens) is unique to the inner ear or if it is ubiquitous among different tissues, since the former finding would imply a specific (Type II) autoimmune process directed against the inner ear.

The concept of humoral autoimmune response directed against inner ear antigens is further supported by a series of studies which demonstrated that the inner ear has the anatomic components to mount an immune response [20,21]. It has been shown that the endolymphatic sac provides an immunologic role for the inner ear in a manner similar to that of gut-associated lymphoid tissue [22-24]. Thus the inner ear is not an immunologically privileged organ and appears to have the potential to generate a primary autoimmune process.

Several investigations have also demonstrated cellular immune responses to inner ear antigens, further supporting a role for autoimmunity in disease pathogenesis [1,25]. These studies employed the lymphocyte migration inhibition assay and the lymphocyte transformation test, both of which measure the response of the patient’s lymphocytes to pooled inner ear antigen preparations [26]. These preparations are crude extracts of inner ear membranes from people without autoimmune inner ear disease. The lymphocyte transformation test measures the difference in proliferation of the patient’s lymphocytes in the presence and absence of these antigens. The measured difference in proliferation is compared to that of lymphocytes from normal human control subjects. The lymphocyte migration inhibition assay is an analogous assay, measuring lymphocyte migration in the presence or absence of inner ear antigens. A significant difference between the responses of the patient and normal control lymphocytes is considered a positive response in either assay [26].

Several studies have now shown that lymphocytes from patients with autoimmune inner ear disease respond positively in these assays using inner ear membrane preparations [1,5,6,8,10,25], indicating the existence of an inner ear antigen-specific cellular immune response in these patients. Not all patients, however, will have positive lymphocyte transformation tests or migration inhibition assays, and some patients without autoimmune inner ear disease will respond positively in these assays [1,25]. Thus these assays are not completely specific nor sensitive for autoimmune inner ear disease, and a cellular autoimmune response may not be a uniform feature in these patients. Alternatively, the limited sensitivity and specificity of the assay may be a reflection of the assay itself, and not of the actual immune response itself. Indeed, other groups have been unable to demonstrate a significant cellular immune response using such assays [12,16]. Further studies with more purified antigen preparations might increase the sensitivity and specificity of these assays, providing more uniform and reliable results.

Despite the evidence demonstrating cellular and humoral autoimmune responses directed against inner ear tissue, there are still basic questions regarding the
relationship of the immune lesion to disease manifestations in these patients. The frequent association of the disease with other autoimmune diseases is especially interesting, as it may indicate a possible common denominator between them. For example, some individuals may be genetically predisposed to develop autoimmunity, and such individuals who develop autoimmune inner ear disease might be prone toward developing autoimmunity against other tissues as well. Alternatively, autoimmune inner ear disease may be a final common pathway for inner ear disease in a host of different immune-mediated disorders. For instance, if inner ear injury is caused by circulating immune complexes, any systemic inflammatory or infectious disorder which produces circulating immune complexes could potentially result in inner ear tissue injury. Therefore it is possible that autoimmune inner ear disease does not truly represent a distinct disease entity, but rather is a syndrome with multiple different etiologies. Finally, it is unknown whether the observed immune response actually causes tissue injury or if it is merely an epiphenomenon. The initial inner ear injury may not be immune-mediated, and the observed anti-inner ear immunity is a response to the injury but not its cause. In summary, further investigations are required to define the immune lesion (or lesions) and its relationship to inner ear damage and disease manifestations.

Animal Models of Disease

Because of the difficulties encountered using human subjects to study the disease, several investigators have created animal models for autoimmune inner ear disease. The most promising models involve the immunization of rodents with inner ear antigens, and have yielded somewhat conflicting results.

For example, Yoo et al. [27] immunized rats with native bovine type II collagen, a major structural protein of the inner ear [28-30], and induced sensorineural hearing loss in these animals. The immunized animals had high levels of antibodies to native type II collagen, and affected animals had histopathologic changes consisting of cochlear nerve degeneration and perineurial vasculitis [27]. A subsequent study further characterized the temporal bone lesions in this model. These lesions consisted of mild atrophy of the organ of Corti and spiral ganglion degeneration, vestibular dysfunction with vacuolar degeneration of the cristae ampullares, otospongiosis-like lesions in the tympanic annules, cochlear vasculitis, and eustachian tube disease [31]. Of note is the fact that both cellular and humoral immune responses to type II collagen were demonstrated in this study. Moreover, a subsequent study demonstrated that antibodies to type II collagen were present in the inner ear perilymph [32]; however, comparison of the described histopathologic changes to those which occur in human disease is difficult, owing to the lack of human temporal bone pathology specimens.

Harris performed similar experiments in which he studied the effects of type II collagen autoimmunity in the well-established Wistar-Furth rat model of type II collagen autoimmune arthritis [33]. No hearing loss was found in the immunized animals, except for four animals that had spontaneous, purulent otitis media. All immunized animals showed very significant serum and perilymph antibody titers to type II collagen. No morphological abnormalities of the external, middle, or inner ears could be identified, however, in contrast to Yoo's observation that type II collagen autoimmunity results in ear disease [27,31].

In order to characterize further the role of antibodies to type II collagen in inner ear disease, Cruz et al. used guinea pigs to compare cochlear alterations produced by
induction of anti-type II collagen antibodies with alterations produced by passive transfer of anticochlear antibodies [34]. They found loss of nuclei in the spiral ganglia in both experimental groups, but significant changes in the brainstem auditory evoked response were not present. They concluded that antibodies to type II collagen may play an important role in human autoimmune sensorineural hearing loss, but other cochlear antigens may be important [34].

Harris investigated the role of other cochlear antigens by immunizing guinea pigs with fresh bovine cochlear antigens, which produced a significant hearing loss compared to a control group of animals [35]. The presence of anticochlear antibodies was uniformly detected in the experimental group of animals, and 32 percent of those ears tested had significant hearing losses. Histologic examination revealed spiral ganglion cell degeneration, perivascular infiltration by plasma cells, edema, and hemorrhage. Some animals showed unilateral hearing losses, whereas others had bilateral losses of varying extent. Western blot analyses demonstrated an antibody that was present in the hearing loss animals, but not in those immunized, in which hearing was maintained. Although the particular autoantigen (or autoantigens) was not identified, the results suggest that a specific anticochlear autoantibody was responsible for the hearing loss [35]. Subsequent work has indicated that the immunodominant autoantigen is not type II collagen [36], supporting the results of Harris's previous study [33] and that of Cruz et al. [34].

Soliman has constructed a similar model, in which guinea pigs are immunized with a crude inner ear antigen preparation [37]. These animals develop sensorineural hearing losses and specific anti-inner ear antibodies whose immunofluorescence patterns are similar to those of sera of human patients. In addition, these animals have inner ear histopathologic changes which closely resemble those discussed above [35].

The discrepancies between the studies of Harris et al. [33] and those of Yoo et al. [27,31] may arise from differences in the animal strains used and quantitative or qualitative differences in the immune response and its subsequent effects on tissue injury. Moreover, the animal models may represent somewhat different disease entities, as Yoo's type II collagen autoimmunity model appears to approximate Meniere's disease more closely [38-40]. Furthermore, Yoo et al. have demonstrated increased levels of antibodies to type II collagen in the sera of patients with otosclerosis and Meniere's disease [41], indicating that this model more closely approximates these latter two conditions than it does autoimmune inner ear disease itself. Taken together, all of these studies show that cochlear antigens are important in the autoimmune response and disease pathogenesis of these animals. The role of type II collagen in inner ear disease is presently unclear, but definition of the cochlear autoantigen(s) and histopathologic changes in human disease should clarify this issue. Such studies should also identify which animal models most closely approximate the human disease, and the extent to which results obtained with the animal models can be extrapolated to human disease.

**DIAGNOSIS**

There are no uniform criteria for the diagnosis of autoimmune inner ear disease. Obtaining inner ear tissue biopsies is not feasible in human patients, and, as a result, the diagnosis is not made histopathologically. The clinical picture, laboratory studies, and response to treatment are currently the cornerstones of diagnosis. The individ-
ual diagnostic criteria are each nonspecific and can be met in a number of other disorders, but together they can be used to identify autoimmune inner ear disease with a moderate degree of success.

**Clinical Diagnosis**

As described above, the disease is a progressive, bilateral, asymmetric, sensorineural hearing loss. Although sensorineural origin and asymmetry are the only features which appear to be uniformly present among all patients, the onset and time course of disease are especially useful in diagnosis. Specifically, its progression over days to months serves to distinguish it from several other diagnostic possibilities. For example, chronic progressive deafness of adolescence, presbycusis, or recessive progressive hereditary deafness all follow a slower time course [1]. In addition, recessive progressive hereditary deafness can be distinguished on the basis of a positive family history, whereas autoimmune inner ear disease does not appear to have a hereditary component.

Additional findings such as vestibular symptoms, aural pressure, and tinnitus are frequently present but are neither sensitive nor specific for the disease [7]. Therefore they have limited utility in establishing the diagnosis.

The clinical history is also essential for ruling out other causes of sensorineural hearing loss such as noise-induced hearing loss, luetic hearing loss, head trauma, perilymphatic leak, or drug toxicity. Laboratory studies should include fluorescent treponemal antibody (FTA) testing to rule out luetic hearing loss, if it is indicated by the clinical history. Radiologic studies may be required to evaluate the possibility of a tumor causing the hearing loss. The clinical diagnosis of autoimmune inner ear disease thus remains a diagnosis of exclusion rather than of positive findings.

Patients presenting with autoimmune inner ear disease may frequently be identified by the presence of concomitant autoimmune diseases such as systemic lupus erythematosus, Cogan’s syndrome, and others [1,5,10,12]. The co-occurrence of these with inner ear disease is not diagnostic for autoimmune inner ear disease, but should prompt the clinician to proceed with an immunological laboratory workup.

Finally, autoimmune inner ear disease can mimic Meniere’s disease in its clinical presentation [6,8]. Such patients should undergo evaluation for autoimmune inner ear disease, including immunological laboratory testing, since treatments for the two conditions are different. Patients who have failed conventional therapy for Meniere’s disease should probably be started on a trial of corticosteroids, regardless of the results of immunological tests [15].

The diagnosis of autoimmune inner ear disease cannot be made on clinical grounds alone, since the disease is heterogeneous in its presentation and its features are nonspecific. The clinical findings are neither sensitive nor specific for detection of this disease and should serve only to identify those patients who do not fit neatly into other disease categories and thus merit further evaluation. This evaluation relies on immunological laboratory studies, with the goal of empirically identifying patients who will benefit from systemic corticosteroid therapy.

**Laboratory Diagnostic Evaluation**

None of the laboratory evaluations for autoimmune inner ear disease is 100 percent sensitive or specific, but they are generally useful prognostic indicators for response to corticosteroid therapy [15,25]. Laboratory tests for the identification of
TABLE 1
Clinical Analyses for Autoimmunity
(adapted from [3])

| Serum IgM, IgG, IgA |
|---------------------|
| Rheumatoid factors |
| Autoantibodies      |
| Antinuclear antibodies |
| Antiperinuclear antibodies |
| Smooth muscle autoantibody |
| Anti-thyroglobulin antibody |
| Circulating immune complexes |
| Complexes containing IgG, IgM, IgA |
| Complement system   |
| CH50, C3, C4, Clq   |
| Microbiology        |
| Epstein-Barr virus  |
| Cytomegalovirus     |
| Hepatitis B virus   |
| Toxoplasmosis       |
| Syphilis            |
| Rickettsiae         |

the disease can be classified as either antigen-specific or antigen-nonspecific tests of immune function. Antigen-nonspecific tests include the erythrocyte sedimentation rate, serum immunoglobulin levels, rheumatoid factor, autoantibodies, circulating immune complexes, and complement levels. Veldman suggests the laboratory studies outlined in Table 1 to evaluate the presence of autoimmunity [3,15]. At least some of these tests will usually be abnormal in autoimmune inner ear disease, and their availability to most clinicians makes them useful for routine screening [15].

In contrast, antigen-specific tests such as the lymphocyte transformation test, the migration inhibition assay, and indirect immunofluorescence and Western blot analyses of cochlear antigens are available only in a limited number of research laboratories. These tests appear to be useful in identifying those patients who will respond to steroid therapy. Although their sensitivity and specificity are high, these are not 100 percent [17,25]. Hughes et al. reported that 79 percent of patients with positive lymphocyte transformation test results responded to corticosteroid therapy [25]. Positive results in these assays in the context of the appropriate clinical picture thus predict a beneficial response to corticosteroid treatment, and such treatment should be instituted in these patients. In patients with negative test results who otherwise appear to fit the clinical picture of autoimmune inner ear disease, the decision to start steroid therapy is more difficult, given the lack of quantitative objective data. Some patients with negative laboratory test results will, however, respond to corticosteroid therapy [12,17], and, given the possible deleterious outcome, a trial of corticosteroids is warranted in such patients [1,25].

Response to Corticosteroid Therapy

A positive response to corticosteroid therapy is the third criterion for the diagnosis of autoimmune inner ear disease. It consists of a test of treatment with either corticosteroids [6] or corticosteroids and cyclophosphamide [1,42]. A reversal or
stabilization of the hearing loss with corticosteroid treatment confirms the presumptive diagnosis.

MANAGEMENT

Treatment guidelines for autoimmune inner ear disease remain controversial; however, current therapeutic regimens include systemic corticosteroids, cytotoxic agents such as cyclophosphamide, and plasmapheresis. The former two therapies are suppressors of immune function, and the rationale for their use is that tissue injury is immune-mediated and immunosuppression should thus decrease tissue damage. Similarly, the rationale for plasmapheresis is that removal of circulating acute-phase immune complexes might decrease inner ear tissue injury. This therapy is based on the assumption that at least some tissue injury is caused by immune complex deposition.

Systemic Corticosteroid Therapy

At present, many but not all patients respond to short-term, high-dose corticosteroids followed by maintenance doses over several months. Patients should be followed both clinically and audiometrically to assess the effect of therapy. Hughes et al. recommend a trial of prednisone at 1 mg/kg/day by mouth for one month if steroids are not contraindicated [5]. They believe this dosage and duration are adequate for a trial of therapy, and maintenance therapy of 10 mg orally every other day can be continued for many months if required to maintain hearing. These authors stress that corticosteroid treatment, even at maintenance levels, should not be discontinued prematurely if the patient fails to show an initial dramatic response. In addition, treatment delayed up to several months still can help some patients to recover useful hearing. Finally, a dramatic initial response is not always maintained even if the immune process is inactive [5]. Hughes treats such patients with second-course, high-dose corticosteroids, but offers cytotoxic drugs to them and to those patients who fail to respond initially to corticosteroids. Their initial experience with this regimen was improved hearing in four patients, stabilized hearing in four patients, and decreased hearing in one patient [6]. All except one patient regained normal or near-normal hearing levels or levels amenable to a hearing aid [6]. Similar results have been reported by Moscicki et al., who found that patients frequently required a second course of high-dose corticosteroids for adequate remission of disease [12]. Several other groups have also found that corticosteroid therapy is effective in reversing, or at least stabilizing, hearing loss [2,14].

Concurrent Cytotoxic and Systemic Corticosteroid Therapy

McCabe has emphasized that the mainstay of therapy is cyclophosphamide, not corticosteroids [42]. He contends that corticosteroids alone are not adequate treatment, or even a test for treatment, because many patients who actually have the disease will be missed and their hearing will irrevocably be lost. Patients who progress to total deafness gain no benefit from treatment once reaching that point. On the other hand, patients who have severe loss improve to moderate loss, moderate losses improve to a mild loss, and mild losses improve to normal hearing. He stresses that the most important gain in patients with severe loss is improvement in discrimination scores, enabling them to be rehabilitated with hearing aids (e.g., improvements of 40 percent to 50 percent in discrimination).
McCabe's test of treatment is the administration of cyclophosphamide, 2 mg/kg by mouth every 12 hours, and prednisolone, 30 mg by mouth every other day, for three weeks [42]. If there is any significant improvement in speech discrimination or pure tone audiometry, full treatment is commenced. Full treatment consists of continuation of the same drugs and levels for three months, at which time the cyclophosphamide is stopped and the prednisolone continued for two weeks. If the hearing is at least stabilized, prednisolone is tapered over two weeks, but if hearing drops before or after the prednisolone has been tapered, full treatment is reinstituted for an additional three months. The same procedure is then repeated if necessary. Some patients require treatment for as many as eight such cycles (two years) but no longer than that [42].

The cyclophosphamide is safe when given at the 2 mg/kg dose if the patient's white blood count is monitored carefully. The count should be taken weekly, and if it drops below 5,000 cells per cubic mm, the drug should be stopped until it goes back above 5,000. This condition rarely happens because of the concomitant prednisolone, which promotes a leukocytosis. McCabe sees this leukocytosis as the chief role of prednisolone in treatment, not its immunosuppressant activity [42].

It is not clear what the optimal treatment protocol is for patients with autoimmune inner ear disease. McCabe's approach probably treats more patients successfully than would be possible with the use of steroids alone, but quantitative data have not yet been published to support this concept. Cyclophosphamide therapy is, however, more toxic than corticosteroid treatment. Rigorous comparison of the treatment modalities is currently impossible, though, since detailed treatment regimens and results have not been published. Prospective studies are needed to provide rational guidelines for the treatment of these patients.

**Plasmapheresis**

This therapy has theoretical benefits but practical limitations. Treatment results with plasmapheresis are largely anecdotal, and its utility is unclear due to the lack of controlled prospective studies. In one uncontrolled study, six of eight patients receiving plasmapheresis therapy had improved auditory function [43]. Moreover, three of the patients no longer required immunosuppressant medication to maintain their hearing. Plasmapheresis is expensive, however, with one month of outpatient treatments costing approximately $5,000. Insurance coverage of this treatment for autoimmune inner ear disease is not guaranteed and is an important consideration when deciding whether to start treatment. Hughes et al. thus feel that the primary indication for plasmapheresis is progressive autoimmune hearing loss which has not responded to sequential or concurrent cytotoxic drug therapy [6]. In summary, plasmapheresis remains an expensive experimental therapy of unknown benefit, and controlled studies are required to determine its role in treating autoimmune inner ear disease.

**PROBLEMS AND FUTURE DIRECTIONS**

Much remains to be learned about the natural history of autoimmune inner ear disease, as well as its incidence and prevalence. This situation exists largely because the methods currently used to define and diagnose the disease are inadequate. Past studies have been largely retrospective, and there is a great need for controlled prospective investigations to define more accurately the patient population and the
clinical manifestations of the disease. Current and future studies should also include: 
(1) The examination of human temporal bone specimens in order to elucidate the etiology and histopathogenesis of inner ear tissue injury: such studies would also aid in the interpretation of animal models, where histopathologic data are easily obtained but cannot yet be extrapolated to the human disease process until similar data are also available for human patients. (2) Definition of the inner ear autoantigens recognized by antibodies in the sera of human patients: this finding would establish the disorder as having an autoimmune component, and the purified autoantigens could be used to improve the sensitivity and specificity of laboratory tests currently used to identify the disease. (3) Prospective trials to compare the treatment results of corticosteroid, cytotoxic, and plasmapheresis therapies: not only would such trials aid clinicians in treatment decisions, but they would also be useful in identifying patients, since response to immunosuppressive therapy is currently a diagnostic criterion. These studies should thus improve our understanding and treatment of autoimmune inner ear disease, as well as provide new insight into the basic biology and immunology of the inner ear.

ACKNOWLEDGEMENTS

I thank Dr. Steven Rauch, of the Massachusetts Eye and Ear Infirmary and Harvard Medical School, and Dr. John Kveton, of the Section of Otolaryngology at Yale University School of Medicine, for helpful discussions and advice. I also thank Drs. Peter Blier and Janine Evans, of the Section of Rheumatology at Yale University School of Medicine, and Dr. Kveton for critical reading of the manuscript.

REFERENCES

1. McCabe BF: Autoimmune sensorineural hearing loss. Ann Otol Rhinol Laryngol 88:585–589, 1979
2. Kanzaki J, Ouchi T: Steroid-responsive bilateral sensorineural hearing loss and immune complexes. Arch Otorhinolaryngol 230:5–9, 1981
3. Veldman JE, Roord JJ, O'Connor AF, Shea JJ: Autoimmunity and inner ear disorders: An immune-complex mediated sensorineural hearing loss. Laryngoscope 94:501–507, 1984
4. Veldman JE: Cochlear and retrocochlear immune-mediated inner ear disorders. Ann Otol Rhinol Laryngol 95:535–540, 1986
5. Hughes GB, Barna BP, Kinney SE, Calabrese LH, Nalepa NJ: Clinical diagnosis of immune inner ear disease. Laryngoscope 98:251–253, 1988
6. Hughes GB, Kinney SE, Barna BP, Calabrese LH: Practical versus theoretical management of autoimmune inner ear disease. Laryngoscope 94:758–766, 1984
7. Hughes GB, Kinney SE, Hamid MA, Barna BP, Calabrese LH: Autoimmune vestibular dysfunction: Preliminary report. Laryngoscope 95:893–897, 1985
8. Hughes GB, Kinney SE, Barna BP, Calabrese LH: Autoimmune reactivity in Meniere's disease: A preliminary report. Laryngoscope 93:410–417, 1983
9. Summers RW, Harker L: Ulcerative colitis and sensorineural hearing loss: Is there a relationship? J Clin Gastroenterol 4:251–252, 1982
10. Hughes GB, Kinney SE, Barna BP, Tomsak RL, Calabrese LH: Autoimmune reactivity in Cogan's syndrome: A preliminary report. Otolaryngol Head Neck Surg 91:24–32, 1983
11. Weber RS, Jenkins HA, Coker MD: Sensorineural hearing loss associated with ulcerative colitis. Arch Otolaryngol 110:810–812, 1984
12. Moscicki RA, Ramadan H, Castro OJ, Nadol JB,Bloch KJ: Corticosteroid response and immunologic studies in idiopathic progressive sensorineural hearing loss. J Allergy Clin Immunol 81:217, 1988
13. Roitt I, Brostoff J, Male D (ed): Immunology, 2nd edition. New York, Gower Medical Publishing, 1989
14. Wilson WR, Byl FM, Laird N: The efficacy of steroids in the treatment of idiopathic sudden hearing loss. Arch Otolaryngol 106:772–776, 1980
15. Veldman JE: Immunology of hearing: Experiments of nature. Am J Otology 10:183–187, 1989
16. Arnold W, Pfaltz R, Altermatt H-J: Evidence of serum antibodies against inner ear tissues in the blood of patients with certain sensorineural hearing disorders. Acta Otolaryngol (Stockholm) 99:437–444, 1985
17. Arnold W, Pfaltz R: Critical evaluation of the immunofluorescence microscopic test for identification of serum antibodies against human inner ear tissue. Acta Otorhinolaryngol (Stockholm) 103:373–378, 1987
18. Soliman AM: The use of immunofluorescence in the non-decalcified frozen guinea pig cochlea to detect autoantibodies in inner ear disorders. Arch Otolaryngol 244:241–245, 1987
19. Harris JP, Sharp PA: Inner ear autoantibodies in patients with rapidly progressive sensorineural hearing loss. Laryngoscope 100:516–524, 1990
20. Lim D, Silver P: The endolymphatic duct system. A light and electron microscopic investigation. In Proceedings of Barany Society Meeting. Edited by J Pulec. Los Angeles, CA, 1974
21. Rask-Andersen H, Stahle J: Immunodefence of the inner ear? Acta Otolaryngol 89:283–294, 1980
22. Harris JP: Immunology of the inner ear: Evidence of local antibody production. Ann Otol Rhinol Laryngol 93:157–162, 1984
23. Tomiyama S, Harris JP: The endolymphatic sac: Its importance in inner ear immune responses. Laryngoscope 96:685–691, 1986
24. Tomiyama S, Harris JP: The role of the endolymphatic sac in inner ear immunity. Acta Otolaryngol (Stockholm) 103:183–188, 1987
25. Hughes GB, Barna BP, Kinney SE, Calabrese LH, Nalepa NL: Predictive value of laboratory tests in “autoimmune” inner ear disease: Preliminary report. Laryngoscope 96:502–505, 1986
26. McCabe BF, McCormick KJ: Tests for autoimmune disease in otology. Am J Otology 5:447–449, 1984
27. Yoo TJ, Tomoda K, Stuart JM, Cremer MA, Townes AS, Kang AH: Type II collagen-induced autoimmune sensorineural hearing loss and vestibular dysfunction in rats. Ann Otol Rhinol Laryngol 92:267–271, 1983
28. Yoo TJ, Tomoda K: Type II collagen distribution in rodents. Laryngoscope 98:1255–1260, 1988
29. Ishibe T, Choe IS, Yoo TJ: Type II collagen distribution in the ear of the developing chick embryo. Laryngoscope 99:547–553, 1989
30. Ishibe T, Cremer MA, Yoo TJ: Type II collagen distribution in the ear of the guinea pig fetus. Ann Otol Rhinol Laryngol 98:648–654, 1989
31. Yoo TJ, Floyd RA, Sudo N, Ishibe T, Takeda T, Tomoda K, Yazawa Y, Stuart J, Choe IS, Ha SC: Factors influencing collagen-induced autoimmune ear disease. Am J Otolaryngol 6:209–216, 1985
32. Yoo TJ, Yazawa Y, Floyd R, Tomoda K: Antibody activity in perilymph from rats with type II collagen-induced autoimmune inner ear disease. Ann Otol Rhinol Laryngol 93 (Supplement 113):1–2, 1984
33. Harris JP, Woolf NK, Ryan AF: A reexamination of experimental type II collagen autoimmunity: Middle and inner ear morphology and function. Ann Otol Rhinol Laryngol 95:176–180, 1986
34. Cruz OL, Miniti A, Cossermelli W, Oliveira RM: Autoimmune sensorineural hearing loss: A preliminary experimental study. Am J Otology 11:342–346, 1990
35. Harris JP: Experimental autoimmune sensorineural hearing loss. Laryngoscope 97:63–76, 1987
36. Harris JP: Autoimmunity of the inner ear. Am J Otology 10:193–195, 1989
37. Soliman AM: Experimental autoimmune inner ear disease. Laryngoscope 99:188–193, 1989
38. Yoo TJ, Yazawa Y, Tomoda K, Floyd R: Type II collagen-induced autoimmune endolymphatic hydrops in guinea pig. Science 222:65–67, 1983
39. Yoo TJ, Tomoda K, Hernandez AD: Type II collagen-induced autoimmune inner ear lesions in guinea pigs. Ann Otol Rhinol Laryngol 93 (Supplement 113):3–5, 1984
40. Yoo TJ: Etiopathogenesis of Meniere's disease: A hypothesis. Ann Otol Rhinol Laryngol 93 (Supplement 113):6–12, 1984
41. Yoo TJ, Stuart JM, Kang AH, Townes AS, Tomoda K, Dixit S: Type II collagen autoimmunity in otosclerosis and Meniere's disease. Science 217:1153–1155, 1982
42. McCabe BF: Autoimmune inner ear disease: Therapy. Am J Otology 10:196–197, 1989
43. Luetje CM: Theoretical and practical implications for plasmapheresis in autoimmune inner ear disease. Laryngoscope 99:1137–1146, 1989