FUCHS HETEROCHROMIC CYCLITIS (FHC) IS A CHRONIC, typically unilateral anterior segment uveitis syndrome.1 It is usually painless with limited inflammation characterized by diffuse, scattered, small and medium-sized keratic precipitates with mild anterior chamber flare, minimal anterior chamber cells, and iris atrophy that leads to secondary, acquired heterochromia. Immunohistochemistry of iris biopsies reveals an inflammatory infiltrate consisting mainly of lymphocytes and plasma cells along with few mast cells and eosinophils.1 Unlike other uveitic syndromes, the disease does not respond to corticosteroid therapy. Thus, this disease challenges us both in its pathogenesis and in empiric strategies for treatment. Defining the pathogenesis in this and other uveitis syndromes will direct future approaches to both disease prevention and targeted therapy to limit disease morbidity and the long-term sequelae of ocular inflammation, such as cataract and glaucoma. Quentin and Reiber,2 in an article in this issue of THE JOURNAL, present new evidence that links the rubella virus with FHC, a provocative study that raises additional questions about the pathogenesis of FHC.

Clues about immune pathogenesis in FHC come from analysis of the cellular infiltrate and proteins in the aqueous humor of affected individuals. The cellular infiltrate in the anterior chamber of patients with FHC mainly consists of T lymphocytes. Sampling of the aqueous humor during relative quiescence, at the time of cataract surgery, was performed in an earlier study by Murray and associates.3 Fifteen patients with FHC were sampled for that study, and analysis was performed by RNA extraction followed by reverse transcriptase polymerase chain reaction (RT-PCR). The investigators detected CD3, CD4, and CD8 mRNA, all markers of T lymphocytes, but did not detect CD19, a B-cell marker. The sensitivity of this method was not described, and the negative result for CD19 by RT-PCR does not exclude the presence of B lymphocytes in the anterior chamber. Muhaya and associates4 characterized T cells and cytokines in the aqueous humor removed from 10 patients with FHC during active inflammation. Analysis of the cellular component was performed using flow cytometry, and cytokine analysis was performed by RT-PCR. The cellular infiltrate was largely T lymphocytes (76% of the total cells), which, compared with the peripheral blood, were highly enriched with CD8+ cells (47%). B lymphocytes, as evidenced by CD19 expression, were less than 2% of the total cells. Labalette and coworkers5 collected aqueous and peripheral blood lymphocytes from two patients with active FHC and demonstrated a clonal T-cell receptor repertoire of the infiltrating CD8+ cells.

The clonal nature and predominantly CD8+ T-lymphocyte infiltration are suggestive of a viral pathogenesis in FHC. However, over the past few years there has been increasing interest in other determinants of local cell infiltration, including local expression of specific chemokines and factors that allow local survival or proliferation in sites of immune-mediated disease.6,7 Local cytokine expression also may provide evidence for specific immune functions. However, the studies regarding FHC have produced variable results. One study showed IL-10 and IFN-γ production in nine of 10 samples studied and documented high levels of production in 4 samples.4 Concordantly, IL-12 was observed in most samples at a low level and IL-4 was not detected.4 A different study confirmed the prevalence of IFN-γ and the absence of IL-4 in most patients.3 Curiously, the investigators were unable to detect IL-10 except in 1 sample. IL-10 is a regulatory cytokine, produced by divergent cell types, and the peak production may vary according to the stage of the inflammatory response. These studies point to a Th1-type of immune response in this disease and suggest that the discordant IL-10 results could reflect either sensitivity of detection used by the two groups or differences in the disease activity of patients enrolled in the two studies.

It has been over 40 years since antibodies were observed in the anterior chamber of patients with FHC.8 These antibodies were produced in the eye and defined as the IgG1 class.9 Furthermore, elevation in the inflammatory
production of IgG. Th1 immune responses are also notable for their effective helper function for IgG1 production by cognate B lymphocytes. It is a logical assumption that identification of the antigenic reactivity of the local, intraocular IgG could identify candidates in disease pathogenesis.

In the current study by Quentin and Reiber, aqueous humor samples from patients with FHC, a range of ocular inflammatory conditions and cataract controls were examined for antibody reactivity against known infectious diseases (measles, rubella, varicella zoster, herpes simplex, and toxoplasma) using a commercially available kit. The antibody index was calculated for each antigen and the fraction of specific antibodies determined as a ratio of the specific to total IgG. Surprisingly, 100% (n = 52) of the aqueous humor from patients with FHC had an increased antibody index against rubella. This reactivity is convincingly different from that observed in the cataract control samples. Multiple sclerosis (MS) patients with intraocular inflammation were the only other group with a positive index for rubella. However, the levels of reactivity in MS were less than two thirds of the samples from patients with FHC. Autoimmune diseases of the CNS, including MS, may be associated with the intrathecal presence of antibodies against a range of viruses, and this reactivity may help in disease diagnosis. It is not clear, however, whether this reactivity plays a role in disease pathophysiology. The authors claim that detection of the rubella-associated intraocular antibody reactivity could confirm a clinical diagnosis of suspected FHC. Certainly, this is a provocative idea that requires confirmation by multiple laboratories and with large studies of patients with FHC to be certain that the authors’ observations may be broadly generalized.

Perhaps more intriguing is the authors’ detection, using nested PCR of reverse transcribed aqueous humor RNA, in 18% of tested samples, of the presence of a rubella-specific gene sequence in the aqueous humor. The absence of any positive samples among the cataract controls is reassuring. Although the limit of detection is stated to be highly sensitive, quantitative analysis of the copy numbers in the positive samples would have been desirable; in addition, testing for other rubella-associated sequences could provide further confirmation of the positive results. It would be helpful in these genome-positive patients to understand the status of their prior immunization against rubella as well as any history of active rubella infection. Persistence of genomes in areas of inflammatory diseases is observed in other viral illnesses.

Although anterior chamber sampling is often performed for diagnostic purposes in cases of suspected malignancy or infection, it is not routinely used in the diagnosis of idiopathic inflammatory diseases. The data in this study are interesting and may support a role for rubella in FHC pathogenesis, but confirmatory studies are required. When pathogenic mechanisms are better understood and the nuances of targeted biologic therapies are experimentally confirmed in prospective randomized clinical trials, then routine anterior chamber sampling may become an important part of the diagnostic evaluation for uveitis.

REFERENCES