Ocular Toxoplasmosis

A 50th Anniversary Tribute to the Contributions of Helenor Campbell Wilder Foerster

Gary N. Holland, MD; Kevan G. Lewis, MS; G. Richard O’Connor, MD

In 1952, Helenor Campbell Wilder (later Helenor Campbell Wilder Foerster) confirmed the growing suspicion that *Toxoplasma gondii* was a cause of uveitis in otherwise healthy adults by identifying the presence of parasites in eyes enucleated because of severe intraocular inflammation. Ocular toxoplasmosis was previously known to occur only in newborns with congenital *T gondii* infection. Her report ushered in a new era in the field of uveitis in which toxoplasmic, rather than tuberculosis, was confirmed to be the most common cause of retinochoroiditis. Fifty years later, issues raised in her landmark publication are still being investigated.

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It has been said that the contributions of Helenor Campbell Wilder Foerster (1895-1998) advanced the field of ophthalmic pathology 50 years. Among her most important accomplishments was the confirmation of the presence of *Toxoplasma gondii* in retinal tissue of adult eyes with posterior uveitis. Her observations were described in the article “Toxoplasma Chorioretinitis in Adults,” which was published 50 years ago this month in the ARCHIVES. It is appropriate on this anniversary to revisit that landmark publication and to reflect on the profound impact that it has had on the field of uveitis.

Wilder was the first to recognize *T gondii* histopathologically in necrotic retinochoroidal lesions of adults. She performed her work in an era when tuberculosis was assumed to be the most common cause of granulomatous uveitis. In 1941, for example, Guyton and Woods attributed almost 50% of uveitis cases to tuberculosis. Ironically, many of the specimens in which Wilder visualized *T gondii* had actually been photographed for inclusion in a teaching manual as examples of ocular tuberculosis. The implication of her observations was that a substantial proportion of cases diagnosed previously as ocular tuberculosis were, in fact, toxoplasmic and that *T gondii* should be considered an important cause of uveitis in adults. Within a decade, it was recognized that ocular tuberculosis was in fact rare, while ocular toxoplasmosis became accepted as the most common cause of posterior uveitis.

At the time of her discovery, Wilder was Head of the Ophthalmic Pathology Section of the Armed Forces Institute of Pathology (Washington, DC). In her article (and in an earlier preliminary communication), she presented histologic data from 53 eyes that had been enucleated because of pain and blindness. Patient ages ranged from 14 to 83 years. Retinochoroidal lesions were present in all eyes, but the globes had been enucleated from a diverse group of patients. There had been a history of direct injury to the eye, at various intervals before enucleation, for 13 patients, but in only 3 was the eye penetrated. One patient had diabetes mellitus; 2 had rheumatoid arthritis; 1 had a history of severe tonsil and tooth infections; 1 had a history of gallbladder attacks and heart failure; and 1 had had a sore throat when retinochoroiditis was first noted. A variety of clinical diagnoses had been considered, including neoplasia. Among the 53 cases, 37 were submitted with a prior clinical diagnosis of uveitis; 9 of the 37 were thought to be tuberculosis. Although 3...
of the 53 patients were known to have positive Sabin-Feldman dye tests for anti-\( T \text{ gondii} \) antibodies, with titers of 1:64 or 1:256, diagnoses of ocular toxoplasmosis were apparently not considered.

In many cases, a histopathologic diagnosis had not been made before submission to the Armed Forces Institute of Pathology; 20 were simply identified as having granulomatous retinochoroiditis of undetermined cause. Syphilis was diagnosed in 3 eyes, and the remaining 30 came with a prior histopathologic diagnosis of tuberculosis or possible tuberculosis.

On examination, Wilder found all 53 specimens to have lesions that were granulomatous with central necrosis. Disease was observed in the retina, choroid, and sclera. Within the necrotic areas of retina, she observed organisms, 3 to 5.3 \( \mu \)m in length, with morphologic characteristics consistent with \( T \text{ gondii} \). These crescentic forms of the parasite \( \text{(trophozoites)} \) were found in pairs or rosettes (Figure 1) and were characterized roundly on one end and pointed on the other, with large nuclei displaced toward the blunt end. Spherical forms \( \text{(bradyzoites within tissue cysts)} \) were also found in what Wilder called “pseudocysts.” In another illustration, she showed tissue cysts, which she described as “cystoid structures, possibly pseudocysts with dead organisms” (Figure 2). We now know, of course, that these tissue cysts contain living bradyzoites. Histologic examination of a lymph node biopsy specimen from one patient also showed lesions morphologically similar to the ocular lesions.

In her article, Wilder stated that the method of preparation, using celloidin (rather than paraffin) for embedding of specimens, and oil-immersion light microscopy, were reasons that she was able to observe the organisms, while others had overlooked them for so many years. \(^3\) Pseudocysts could be seen in paraffin-embedded sections, but crescentic forms were observed only by oil-immersion examination of celloidin-embedded sections. At that time, the Armed Forces Institute of Pathology was routinely embedding all specimens in celloidin.

Robert Y. Foos, MD, Emeritus Professor of Pathology at UCLA (Los Angeles, Calif), agrees that oil immersion facilitates the identification of parasites (oral communication, September 2001). As a young ophthalmic pathologist attending the Western Pathology Club (precursor to the Michael Hogan Society) in San Francisco during the early 1960s, he commented that he could not see parasites in a tissue specimen containing \( T \text{ gondii} \) that meeting attendees were examining. An older, distinguished woman sitting next to him suggested that he look through her microscope. That woman was Helenor Campbell Wilder, and through her microscope, which was set up for oil immersion, parasites were clearly visible. Foos also agrees that celloidin embedding is a particularly good technique for identifying \( T \text{ gondii} \) in tissue. This technique offers the advantage of a thicker section (16 \( \mu \)m); the greater amount of tissue allows the observer to focus up and down through a section, providing a better sense of its 3-dimensional aspects than the thinner sections (8 \( \mu \)m) that are cut after paraffin embedding. With thinner sections, unless they are fortuitously sectioned through their long axes, trophozoites will appear as small round or oval figures that may not be recognized as parasites. Nevertheless, many subsequent investigations have shown that celloidin embedding is not necessary for demonstration of \( T \text{ gondii} \) in tissue. As one example, Holland et al\(^6\) later clearly demonstrated both trophozoites and tissue cysts by light microscopy in paraffin-embedded tissue from the eyes of patients with acquired immunodeficiency syndrome (AIDS).
loidalin is not routinely used now because of the excessive time required (up to 6 weeks) for it to harden sufficiently for sections to be cut.

One cannot attribute Wilder’s success to laboratory methodology alone. The reason that she could find *T. gondii* in so many specimens, while others before her could not, has been a subject of discussion for many years. She once told one of us (G.R.O.) that she had been daydreaming about Christmas shopping and other subjects when she recognized the presence of the parasites, but she was being characteristically modest. Everyone who knew her was familiar with the diligence and care with which she evaluated histologic preparations. Wilder later attributed her discovery to curiosity over the morphologic characteristics of retinochoroidal lesions. According to William H. Spencer, MD, an ophthalmic pathologist who worked closely with Wilder during many years, she also attributed her observations to “curiosity and persistence” (oral communication, September 22, 2001). Her observation was clearly not serendipitous.

Wilder’s description has been considered a watershed event in the study of ocular toxoplasmosis, and her contribution is best understood in context. Although the profundity of her observation is indisputable, Wilder was not working in a vacuum. During the late 1940s and early 1950s, there was a growing interest among investigators in the potential role of *T. gondii* in the pathogenesis of ocular disease in otherwise healthy adults. In the first half of the century, ocular toxoplasmosis was known only as a disease of newborns with congenital infection.8 With the introduction of the Sabin-Feldman dye test in 1948, however, it became apparent that *T. gondii* infection was widespread among otherwise healthy adults, a fact that stimulated great interest in the possibility of *T. gondii*-associated ocular disease. For example, Vail et al10 described a series of patients with chorioretinal lesions who had positive anti-*T. gondii* antibody tests. Likewise, Frenkel11 and Rieger12 both reported high rates of *T. gondii* antibodies or positive skin tests, or both, in adults with chorioretinal lesions. These associations did not confirm causation, of course, but did add to the growing suspicion that *T. gondii* plays a role in adult disease. In a 1951 German-language publication, Rieger12 suggested that *T. gondii* infection might be responsible for ocular disease. Although he had no histologic confirmation of this hypothesis, the article includes a drawing of a fundus lesion that is suggestive of what we now consider to be a typical toxoplasmic retinochoroiditis lesion. Despite these earlier publications, it is appropriate to credit Wilder with finally confirming the link between *T. gondii* and ocular disease through her meticulous studies. In an era of scientific questioning, it was Wilder’s observations that confirmed the clinical suspicions and anecdotal data of her contemporaries, illustrating the maxim that “Discovery favors the well-prepared mind.”

The actual conclusions of Wilder’s article were fairly limited in scope. In the summary of her article, she said “Organisms having the morphologic characteristics of *Toxoplasma* have been found in the necrotic retina in granulomatous chorioretinal lesions in 53 eyes of adults.” Also, she went on to say that “the lesions were strikingly uniform and their appearance had in many instances led to a pathologic diagnosis of tuberculosis.” Nevertheless, her contribution dramatically advanced our understanding of ocular toxoplasmosis. In stark contrast to the earlier work by Guyton and Woods5 cited already, Woods and his colleagues13 attributed 29% of their uveitis cases to toxoplasmosis just 2 years after Wilder’s report. In a 1960 publication, Woods14 stated, “The discovery of the parasite by Wilder in the chorioretinal lesions of adults stimulated a great flood of clinical, serologic, histologic, and experimental investigations.”

Wilder also continued her own studies of ocular toxoplasmosis. In 1954, she and her colleagues went on to characterize the original cohort further with serologic testing on additional patients.15 All patients had positive Sabin-Feldman dye tests, and in 87.5% of cases, titers were 1:16 or greater. These additional data strongly supported the hypothesis that the ocular disease found in these patients was caused by *T. gondii* infection. By their estimate, the random chance that a cohort of patients with retinochoroiditis would all be seropositive for *T. gondii* infection was less than 1 in 1000.

Despite her profound discovery, Wilder’s study was limited in the information it could provide about ocular toxoplasmosis. As Wilder herself admitted, her observations were consistent with, but did not prove, the presence of *T. gondii*.3 She lacked the confirmatory tests, such as immunofluorescent staining or polymerase chain reaction identification of parasitic DNA, that would be required of a more modern study. She provided an initial understanding of the histologic characteristics of ocular toxoplasmosis in adult patients, but we have to remember that the cohort she studied was a selected population, consisting exclusively of eyes that had been enucleated because of severe disease, and thus would not be representative of the general population, nor could it define the full spectrum of disease. In addition, her article lacked clinicopathologic correlations that would aid ophthalmologists in diagnosing the disease.

In retrospect, we can look at Wilder’s article and realize that it foreshadowed many of the issues we are studying today, including the role played by postnatally acquired *T. gondii* infections in otherwise healthy adults with ocular disease, ocular toxoplasmosis in the immunocompromised host, and ocular disease in the elderly. During the several decades after Wilder’s publication, it came to be assumed generally that ocular toxoplasmosis in adults represents a late recurrence of congenital disease in nearly all cases.16 A subject that has generated substantial discussion, primarily in the past decade, has been the frequency with which ocular toxoplasmosis can be related to acquired infection.17,18 We know that the prevalence of acquired ocular toxoplasmosis is much higher in certain geographic areas, such as southern Brazil, and in some recent epidemics than traditional teachings would lead us to predict.9 In addition, serologic evidence using new techniques confirms that recurrent
ocular toxoplasmic retinochoroiditis is more frequently a manifestation of postnatal infection than heretofore believed.10 Wilder3 had suggested that at least some of her subjects might have been the victims of acquired toxoplasmosis in adult life. She gave credit for the concept of postnatally acquired T gondii to Rieger.12 In Wilder’s article, clinical information can be found that supports this contention; at least 2 patients had signs and symptoms of acquired infection. For example, they had associated lymphadenopathy and pharyngitis, which are hallmark signs of acquired, systemic toxoplasmosis.

Questions surrounding the role of immune function in adult patients with ocular toxoplasmosis were also planted during this time. Rieger,12 for example, had postulated that recurrences of ocular toxoplasmosis might be related to some kind of compromise of the patient’s immunologic defense system, a rather precocious concept for the early 1950s. The relevance of this concept would not become fully apparent until the era of the AIDS epidemic. In recent years there have been many reports of severe, atypical ocular toxoplasmosis among immunocompromised patients, including those with AIDS and those taking immunosuppressive drugs. The description of disease in Wilder’s cases is much more reminiscent of findings in these immunocompromised patients than it is of typical recurrent ocular toxoplasmosis in the general population. For example, Wilder’s described infection extending to the sclera; a more recent report described similar findings in a patient with AIDS and toxoplasmic panophthalmitis.20 In Wilder’s article,3 several patients had debilitating diseases, including diabetes mellitus and rheumatoid arthritis, that may have compromised host defenses. It is ironic that our understanding of “typical” ocular toxoplasmosis arose out of a relatively atypical series, including populations that would not be studied in detail for decades to come.

In recent years, several groups21,22 have emphasized that severe, prolonged ocular toxoplasmosis can occur in elderly patients as well, and is more common than heretofore believed, in contrast to the concept that evolved after Wilder’s report that ocular toxoplasmosis (at least recurrent disease) has its peak in the second and third decades of life.23 It is interesting to note that in Wilder’s article,3 8 of the cases involved patients whose disease might have occurred after the seventh decade of life.

The impact of Wilder’s discovery demonstrates the potential of a single observation to advance science and the understanding of disease substantially. For its tremendous impact on the field of uveitis, we remember Wilder’s seminal article3 on this 50th anniversary of its original publication. In doing so, we also pay tribute to the periscacious Helenor Campbell Wilder Foerster and her unique talents. Duke-Elder24 expressed a sentiment that was likely shared by many of her contemporaries. Referring to an opportunity to interact with Mrs Foerster, he wrote, “To visit her, always enthusiastically looking for something new in her uniquely rich material, was indeed a joy.”

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Corresponding author and reprints: Gary N. Holland, MD, Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90095-7003 (e-mail: uveitis@sei.ucla.edu).

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