Ocular Toxoplasmosis

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

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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 toxoplasmosis, 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, toxoplasmosis 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 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 tuberculous.

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 µm in length, with morphologic characteristics consistent with *T gondii*. These crescentic forms of the parasite (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 (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. 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 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 gondii* in tissue. This technique offers the advantage of a thicker section (16 µm); 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 µm) 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 gondii* in tissue. As one example, Holland et al 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).
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crements. Wilder later attributed her
discovery to curiosity over the mor-
phologic characteristics of retinocho-
roidal lesions.7 According to Wil-
liam H. Spencer, MD, an ophthalmic
pathologist who worked closely with
Wilder during many years, she also
attributed her observations to “curi-
osity and persistence” (oral commu-
nication, September 22, 2001). Her
observation was clearly not seren-
dipitous.

Wilder’s description has been
considered a watershed event in the
study of ocular toxoplasmosis, and
her contribution is best under-
stood in context. Although the pro-
fundity of her observation is indis-
putable, Wilder was not working in a
vacuum. During the late 1940s and
early 1950s, there was a growing in-
terest among investigators in the poten-
tial role of T gondii in the patho-
genesis of ocular disease in otherwise
healthy adults. In the first half of the
century, ocular toxoplasmosis was
known only as a disease of new-
borns with congenital infection.8
With the introduction of the Sabin-
Feldman dye test in 1948,9 however,
it became apparent that T gondii infection was widespread among
otherwise healthy adults, a fact that
stimulated great interest in the pos-
sibility of T gondii–associated ocu-
lar disease. For example, Vail et al10
described a series of patients with
chorioretinal lesions who had posi-
tive anti–T gondii antibody tests.
Likewise, Frenkel11 and Rieger12 both
reported high rates of T gondii an-
tibodies or positive skin tests, or
both, in adults with chorioretinal le-
sions. 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 publi-
cation, Rieger12 suggested that T gondii infection might be responsible for
ocular disease. Although he had no
histologic confirmation of this hy-
pothesis, the article includes a draw-
ing of a fundus lesion that is sug-
gestive of what we now consider to
be a typical toxoplasmic retinocho-
roidal lesion. Despite these earlier
publications, it is appropriate to
credit Wilder with finally confirming
the link between T gondii and
ocular disease through her meticu-
losious. In stark contrast to the ear-
tlier work by Guyton and Woods5
cited already, Woods and his col-
leagues13 attributed 29% of their uve-
itis 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 experimen-
tal investigations.”

Wilder also continued her own
studies of ocular toxoplasmosis.
In 1954, she and her colleagues went
on to characterize the original co-
hort 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 in-
fec tion. By their estimate, the ran-
dom chance that a cohort of pa-
ients with retinochoroiditis would
all be seropositive for T gondii in-
f ection was less than 1 in 1000.

Despite her profound discov-
ery, Wilder’s study was limited in the
information it could provide about
ocular toxoplasmosis. As Wilder her-
self admitted, her observations were
consistent with, but did not prove, the
presence of T gondii.3 She lacked the
confirmatory tests, such as immuno-
fluorescent staining or polymerase
chain reaction identification of para-
sitic DNA, that would be required of
a more modern study. She provided
an initial understanding of the histo-
logic characteristics of ocular toxo-
plasmosis 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 dis-
ease, and thus would not be repre-
sentative of the general population,
 nor could it define the full spectrum
of disease. In addition, her article
lacked clinicopathologic correla-
tions that would aid ophthalmolo-
gists 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 immu-
nocompromised host, and ocular
disease in the elderly. During the
several decades after Wilder’s pub-
lcation, it came to be assumed gen-
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ocular toxoplasmic retinochoroiditis is more frequently a manifestation of postnatal infection than heretofore believed.10 Wilder’s study,3 several patients had debilitat-
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ity and pharyngitis, which are hall-
marks of acquired, systemic toxo-
plasmosis.

Questions surrounding the role of immune function in adult pa-
tients with ocular toxoplasmosis were also planted during this time. Rieger,12 for example, had postulated that re-
currences of ocular toxoplasmosis might be related to some kind of com-
promise of the patient’s immunologic defense system, a rather pre-
cious 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 se-
vere, atypical ocular toxoplasmosis among immunocompromised pa-
tients, including those with AIDS3 and those taking immunosuppressive drugs. The description of disease in Wilder’s cases is much more reminis-
cent of findings in these immunocompromised patients than it is of typical recurrent ocular toxoplasmosis in the general population. For ex-
ample, Wilder’s described infection ex-
tending to the sclera; a more recent report described similar findings in a patient with AIDS and toxoplasmic panophthalmitis.20 In Wilder’s ar-
ticle,3 several patients had debilitat-
ging diseases, including diabetes mel-
titus 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, in-
cluding populations that would not be studied in detail for decades to come.

In recent years, several groups21,22 have emphasized that severe, pro-
longed ocular toxoplasmosis can oc-
cur in elderly patients as well, and is more common than heretofore be-
lieved, 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 dis-
 ease substantially. For its tremen-
duous impact on the field of uveitis, we remember Wilder’s seminal ar-
ticle3 on this 50th anniversary of its original publication. In doing so, we also pay tribute to the per-
spicacious Helenor Campbell Wilder Foerster and her unique talents. Duke-Elder24 expressed a senti-
ment that was likely shared by many of her contemporaries. Referring to an opportunity to interact with Mrs Foerster, he wrote, “To visit her, al-
ways enthusiastically looking for something new in her uniquely rich material, was indeed a joy.”

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