



# The Continuing Ophthalmic Challenge of *Bartonella henselae*

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**Purpose:** To better understand the history and epidemiology of *Bartonella henselae* infections of the eye and adnexa, and their relationship to cat scratch disease (CSD). We also assess *B. henselae* infection as a public health threat.

**Methods:** We reviewed the available literature concerning *B. henselae* infections of the eye and CSD, and attempted calculation of the incidence and prevalence of both *B. henselae* eye infections and CSD from the database of the Rochester Epidemiology Project.

**Results:** It took nearly a century of determined effort to reveal that Henri Parinaud's oculoglandular syndrome (POGS) (1889) and Leber's stellate retinitis (1916) were the result of *B. henselae* infection and are subtypes of CSD. These ocular infections remain of clinical, epidemiologic, and public health concern to ophthalmologists with many unanswered questions. Their incidence and prevalence have yet to be accurately determined. Our attempt to achieve this through the Rochester Epidemiology Project database suggests a major obstacle is inconsistent with nonunanimous diagnostic terminology and coding.

**Conclusions:** Modern serologic testing and molecular diagnostic techniques offer ophthalmologists the opportunity to make *B. henselae* infection of the eyes an area of "precision medicine." For this to happen, greater awareness and teaching about this disease, updated terminology, and a greater clinical and research effort are required. *Ophthalmology Science* 2021;1:100048 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Cat scratch disease (CSD) begins with inoculation of the bacterium, typically through a bite or scratch from an infected animal. The first sign is usually an erythematous pustule or papule at the site of inoculation 3 to 5 days after exposure.<sup>1</sup> This localized infection often spreads to the draining lymph nodes, typically within 1 to 2 weeks.<sup>1</sup> Fever, fatigue, anorexia, and malaise usually ensue; this represents the extent of the disease in 75% of patients.<sup>1,2</sup> Rarely, the organism may spread to virtually any organ, with manifestations ranging from granulomatous hepatitis and splenic abscesses<sup>3</sup> to encephalopathy<sup>1</sup> and osteomyelitis.<sup>1</sup>

Ocular manifestations include oculoglandular syndrome, which is represented by preauricular lymphadenopathy and conjunctival granulomas that typically are restricted to the palpebral conjunctiva.<sup>1</sup> The most common posterior segment manifestation of CSD is focal chorioretinitis.<sup>2</sup> Neuroretinitis is relatively common, characterized by optic nerve head edema and the deposition of exudates in a stellate configuration around the fovea. Serous retinal detachments, vitritis, and vaso-occlusive episodes have also been observed.<sup>2</sup> Most patients have good visual recovery, although some may have permanent vision loss.<sup>4</sup>

## Parinaud's First Report of Parinaud's Oculoglandular Syndrome

Henri Parinaud (1844–1905) was a notable figure (Fig 1) in early ophthalmology and neurology. He reported in 1889: "In the space of four years, between 1877 and 1881, [I]... saw three cases of an eye condition that I believe has not been reported. It is an eminently infectious form of conjunctivitis, which constantly causes the suppuration of lymph nodes and which appears to be transmitted to humans by animals."<sup>5,6</sup> All 3 patients, he observed, lived in a part of Paris where animal markets and butcher shops were common, and where anthrax was prevalent.

During this time, Louis Pasteur (1822–1895) (Fig 2) and Robert Koch (1843–1910) (Fig 3) were laying the foundations of medical bacteriology. Koch, in fact, had only recently succeeded in isolating pure cultures of the anthrax bacilli by growing them in the aqueous humor of the ox's eye.<sup>7</sup> Few laboratories existed that could culture pathogens or identify them by microscopy. Parinaud left the discovery of the etiology of Parinaud's oculoglandular syndrome (POGS) for future generations.

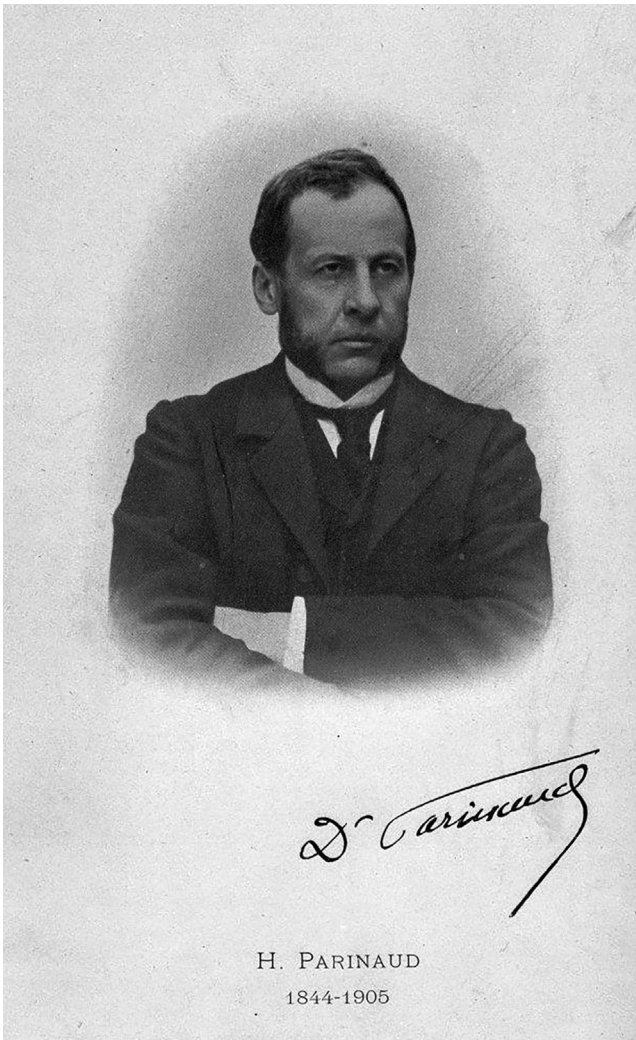


Figure 1. Portrait of Henri Parinaud in *Annales d'oculistique*, Doin (Paris), 1905, p. 320. Public Domain via Wikimedia Commons.

It was not until 1985 that *Bartonella* spores were identified in POGS<sup>8</sup> and the bacterium linked to the ocular manifestations in an effort that has been called “one of the triumphs of microbiology.”<sup>9</sup> More recent concerns have been expressed that the *Bartonella henselae* group of eye and systemic diseases may be “an under-appreciated public health problem.”<sup>10</sup>

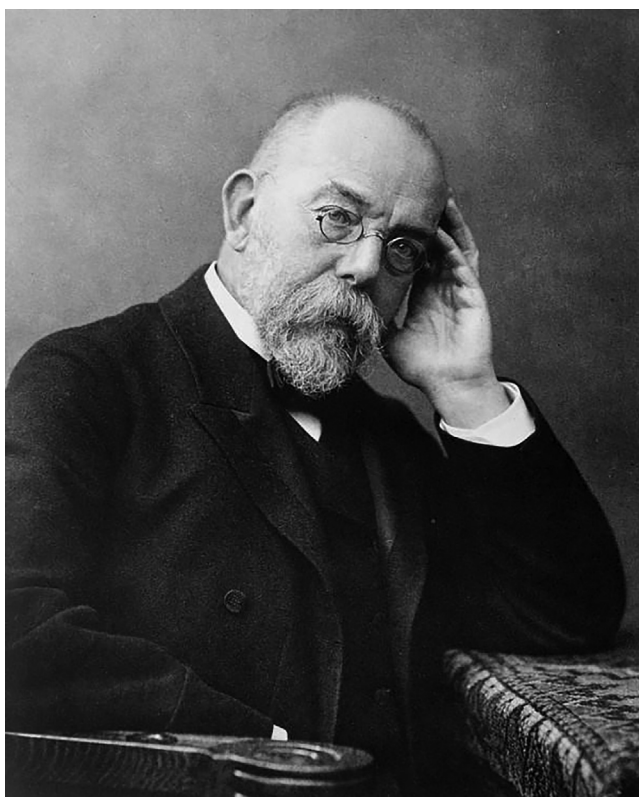
### Verhoeff identifies Leptothrix in Parinaud's Oculoglandular Syndrome

Frederick Herman Verhoeff, a recent graduate of the new Johns Hopkins Medical School, arrived in 1900 as the pathologist at the Massachusetts Eye and Ear Infirmary and learned about Parinaud's 1889 description of the syndrome that now bears his name from a medical doctoral thesis published in 1890.<sup>11</sup> Verhoeff (Fig 4) had developed a



Figure 2. Studio portrait of Louis Pasteur, restored. Before 1895. Copied from Portraits from the Dibner Library of the History of Science and Technology (reworked). Public Domain.

modification of the Gram stain for bacteria along with culture techniques. Verhoeff and George S. Derby applied these to tissue from a patient with POGS under their care and reported their findings in 1904.<sup>12</sup> They noted an additional 10 cases in the literature as well as several cases from Ernst Fuchs,<sup>13</sup> who was as yet unacquainted with the observations of Parinaud. Verhoeff concluded the infection was “a non-pyogenic suppuration...not due to any of the known organisms.” In subsequent articles published in 1905,<sup>14</sup> 1913,<sup>15</sup> and 1918,<sup>16</sup> Verhoeff's series increased to 12 cases, which he believed were distinct from tuberculosis and other granulomatous infections, “...each presenting the same characteristic histologic picture.” He believed he had identified in each case non-branching filamentous organisms which “may for the present be classed as leptothrix.” Verhoeff noted that St. Bernheimer, an ophthalmologist in Vienna “fully confirmed my findings in a report in 1906.”<sup>17</sup> Jonas S. Friedenwald (Fig 5), Verhoeff's counterpart in eye pathology at Johns Hopkins, in 1929 reported: “...in the center [of the inflammatory nodules] the strands of a filamentous organism can be demonstrated by proper staining technique. The organism, a leptothrix has been cultivated

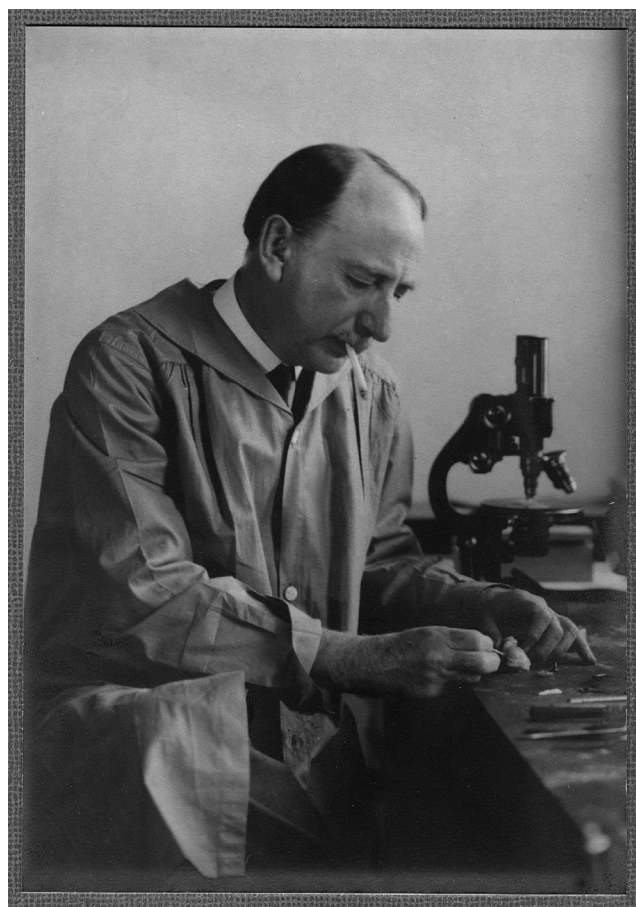


**Figure 3.** Robert Koch 1843-1910, photogravure after a photo by Wilhelm Fechner around 1900, Public Domain.

on Sabouraud's medium and is infectious. Its normal distribution in nature is unknown."<sup>18</sup>

At the time of Verhoeff's death in 1968, David Cogan (Fig 6), in his laudatory obituary notice, listed first among Verhoeff's contributions "the descriptions of leptotrichosis conjunctivae" in POGS.<sup>19</sup> With the development of more modern serology and polymerase chain reaction techniques for diagnosis in the 1970s and 1980s, Verhoeff's microorganism proved not to be the major etiologic factor in POGS.

But an initiative of another sort, in which Verhoeff and Friedenwald played a significant role in establishing, was to lead to the identification of *Bartonella henselae* as the true cause: namely, the founding of the Registry of Ophthalmic Pathology at the Armed Forces Institute of Pathology (AFIP) in 1921.<sup>20,21</sup> Through the joint action of the American Academy of Ophthalmology and Otolaryngology and the Army Medical Museum, a central laboratory was established at the museum (the forerunner of the AFIP) to which the nation's ophthalmologists and pathologists could send ocular tissues for sectioning and evaluation. Both Verhoeff and Friedenwald served as civilian pathology consultants. The Registry of Ophthalmic Pathology stimulated the formation of other units by specialty societies until there were more than 30 registries.<sup>21</sup> Parinaud's oculoglandular syndrome and cat scratch fever were among the medical problems studied.



**Figure 4.** Frederick Herman Verhoeff 1874–1968. Date unknown. Photo ID: MIS 05-7066-1. Image courtesy of the Otis Historical Archives, National Museum of Health and Medicine.

### The Recognition of Cat Scratch Disease and Its Relation to Parinaud's Oculoglandular Syndrome

In 1931, 50 years after Parinaud's article, Dr. Robert Debré (1882–1976) (Fig 7) and his colleague Georges Semelaigne (1892-1984) examined a 10-year-old boy at the University of Paris with suppurating epitrochlear adenitis associated with numerous cat scratches. Unable to definitively establish a feline origin for the infection, they nevertheless called it "cat scratch disease." Debré suspected tuberculosis, tularemia, pasteurellosis, and infectious mononucleosis as possible etiologies, but was unable to establish convincing proof.<sup>9</sup>

Dr. Lee Foshay, a microbiologist at the University of Cincinnati, was also studying "cat fever," which he suspected was a form of tularemia. He and Debré met in 1947, after which each produced a similar antigen from the pus of affected patients for use as a diagnostic skin test, which was described in Debré's 1950 publication.<sup>9,22</sup>

Soon, a growing number of clinical reports appeared that defined the catalogue of manifestations and subtypes of CSD. Of particular importance were Greer and Keefer's first



Figure 5. Dr. Jonas S. Friedenwald. Courtesy of Dr. Peter J. McDonnell, Chairman of the Wilmer Eye Institute, Johns Hopkins Medicine.

report of CSD in the United States in 1951<sup>23</sup> and Dr. Hugh A. Carithers' 1967 study of 1200 CSD patients, 99% of whom had had cat contact and a positive skin test for CSD.<sup>1,24,25</sup> These studies firmly established that POGS was the form CSD took when the inoculation site was near the eye.

Another “atypical” subtype of CSD of particular concern to ophthalmologists was the so-called neurological form, which manifests with central nervous system involvement.<sup>26</sup> This occurs in approximately 5% of patients with CSD and can include retinal inflammation, optic nerve inflammation, macular hard exudates, vascular occlusions, and angiomas. Originally described by Leber (Fig 8) in 1916 as “stellate maculopathy,”<sup>27,28</sup> its association with the etiologic agent of cat scratch fever was suggested by Gass et al (Fig 9) in 1984.<sup>29</sup>

### Identification of *Bartonella henselae* as the Etiologic Agent for Cat Scratch Disease and Parinaud’s Oculoglandular Syndrome

In the 1970s, the AFIP began a concerted effort to identify the etiologic agent for POGS and CSD. In 1983 Wear et al<sup>30</sup> demonstrated a small gram-negative motile coccobacillus in an infected lymph node specimen by a Warthin-Starry and Brown Hopp Gram stain; it is not known whether the patient had oculoglandular syndrome. In 1984, Margileth found identical organisms in biopsy material taken from CSD inoculation papules.<sup>31</sup>

In 1985, Donald J. Wear, Lorenz E. Zimmerman, and others found the same bacilli in the conjunctiva of patients with Parinaud’s syndrome and concluded that the “cat

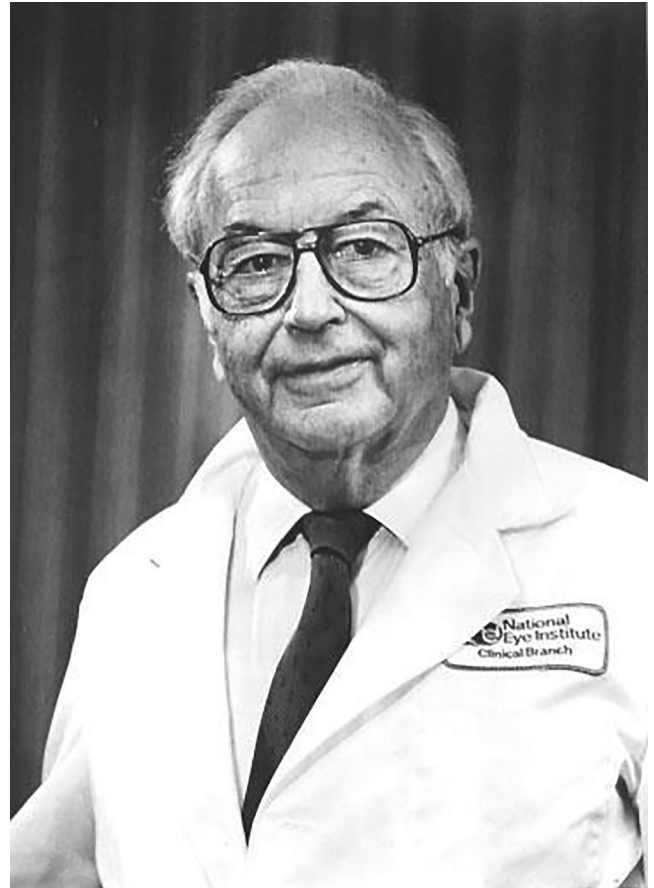


Figure 6. David G. Cogan, MD. Image courtesy of the Cogan Collection, National Eye Institute/National Institutes of Health.

scratch disease bacillus” was a major cause of POGS<sup>8</sup> (Figs 10 and 11). Just before this, in the third edition of *Ophthalmic Pathology*, Zimmerman and William Spencer had written that infections like tuberculosis and tularemia “may cause ipsilateral enlargement of the preauricular lymph nodes—a nonspecific condition known as ‘Parinaud’s oculoglandular syndrome.’”<sup>32</sup>

Also in 1985, Diane M. Hensel, a technologist working with tissue from an HIV-infected patient, discovered the *henselae* spores of *Bartonella*.<sup>33</sup> The species name *Henselae* was officially proposed as a tribute to Diane M. Hensel in 1992.<sup>34</sup> The first successful isolation and culture of the “cat scratch disease bacilli” was accomplished by English et al<sup>35</sup> in 1988. Sequences of the 16S bacterial RNA from bacteria in POGS and CSD were shown to be consistent with *Bartonella henselae*. English et al<sup>35</sup> also reported that their studies of isolated bacteria fulfilled Koch’s postulates.

By 1985, polymerase chain reaction, enzyme-linked immunosorbent assays and immunofluorescence assays had been introduced and used in the diagnosis of POGS and CSD, confirming *B. henselae* to be the essential cause of these diseases. Parinaud’s oculoglandular syndrome in turn has come to be accepted as a subtype of CSD.



Figure 7. Robert Debré, Public Domain via Wikipedia commons.

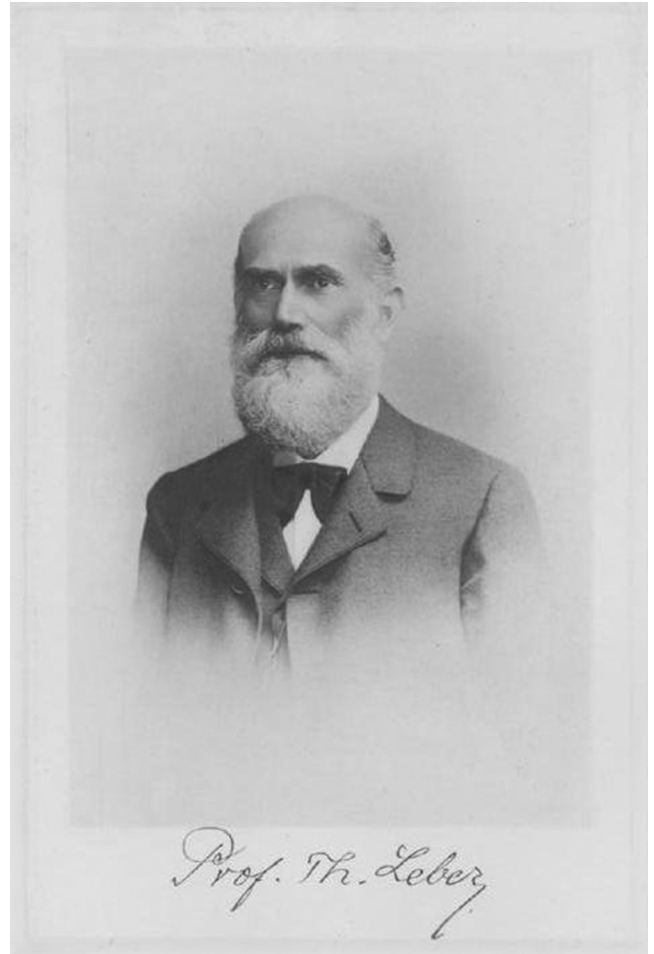


Figure 8. Theodor Leber (1840–1917). F. Langbein & Co., Public Domain.

### Is *Bartonella henselae* an Underappreciated Public Health Problem?

According to the Centers for Disease Control and Prevention, CSD, which includes POGS as a subtype, causes a substantial burden of disease nationwide and disproportionately affects children.<sup>36</sup> This study, which is based on a review of the 2005–2013 National Health Insurance databases, estimated that 5% to 7% of patients with CSD had POGS. This report, as well as others,<sup>37</sup> stresses the lack of published data and factors contributing to a probable under-reporting of cases.<sup>38</sup> That number was suspected to be artificially low because CSD is usually self-limited or patients are often not worked up for *B. henselae*.<sup>37</sup> It estimates that, based on the data collected of CSD patients aged less than 65 years in the United States, approximately 12 500 patients are diagnosed with CSD annually. No published data were found regarding the incidence of neuroretinitis, focal retino-choroiditis, or other ocular complications due to *B. henselae*. It is assumed that the course may be more severe in immunocompromised patients. The total direct medical costs for CSD (as of 2013) are estimated to be approximately \$10 million annually.<sup>38</sup>

### Attempted Calculation of Incidence and Prevalence of POGS from the Rochester Epidemiology Project Database

We attempted to calculate the incidence and prevalence of POGS in Olmsted County, Minnesota, residents by interrogating the Rochester Epidemiology Project database, a resource that has been applied to hundreds of diseases for more than half a century.<sup>39</sup> The largest obstacle proved to be the inconsistent, nonunanimous diagnostic coding for POGS throughout the years and across the different health record systems in use in Olmsted County. An initial query using the diagnostic codes POGS or cat scratch disease yielded a combined total of 782 unique patients between 1990 and 2019. However, the search identified no patients with both diagnoses. A search for patients with a diagnostic code of *Bartonella* over the same time period found 9 unique patients. Two of those patients also had a CSD diagnosis code, but none had a POGS code. Searching for patients with one of the diagnostic codes above as well as a billing code for an ophthalmic examination found 457 unique patients. It was not possible to identify by diagnostic



Figure 9. J. Donald M. Gass, MD. Image courtesy of the Director, Truhlsen-Marmor Museum of the Eye & The Stanley M. Truhlsen, MD, Director of Ophthalmic Heritage.

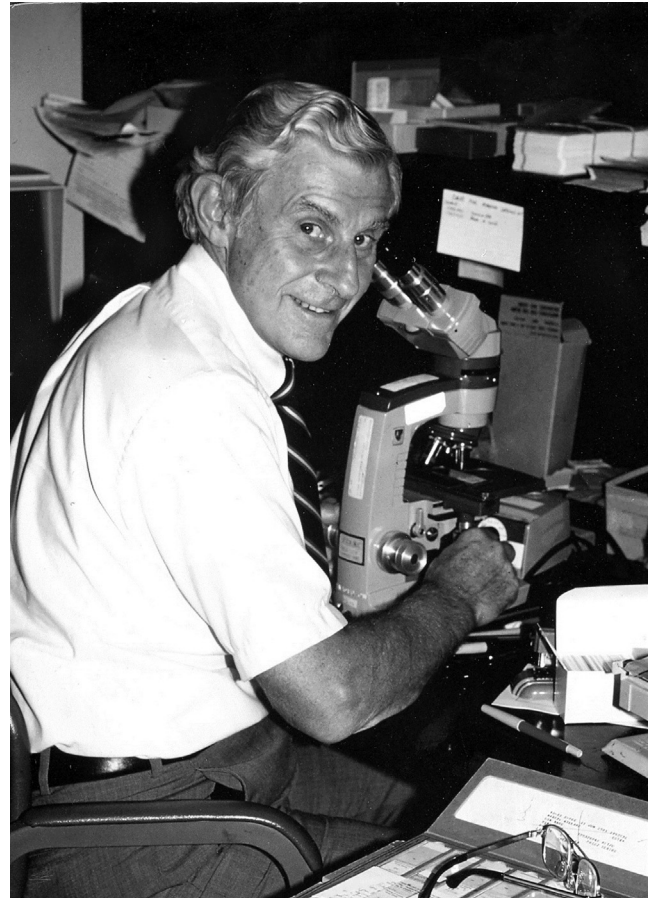


Figure 11. Lorenz E. Zimmerman, MD, at work at the Armed Forces Institute of Pathology. Courtesy of Dr. Mary Louise Zimmerman Collins.

codes or billing records if the time of the ophthalmic exam matched the time of the diagnosis.

Next, we searched for all patients who had undergone laboratory testing for Bartonella between 1998 and 2019. Of 529 patients, only 8 had a positive result. Although 348 of the 529 patients had undergone an ophthalmic examination at some point during their life, it was not possible to identify by diagnostic codes or billing records if any of these patients

had been seen for an eye exam around the time of their laboratory testing.

### Historical Considerations Regarding Bartonella as a Public Health Problem

Although *B. henselae* is a rather recent discovery, the genus has affected humans for millennia; RNA from *Bartonella quintana* has been detected in a 4000-year-old mummified body from a cave in southern France<sup>40</sup> and in a 1000-year-old body in the Andes of Peru,<sup>41</sup> as well as in the preserved 600-year-old body of a cat.<sup>40</sup> Two acute diseases of public health significance are caused by *Bartonella* species. A *Bartonella bacilliformis* epidemic killed an estimated 10 000 workers during construction of the La Oroya–Lima railway in Peru between 1878 and 1903.<sup>42,43</sup> Now known as Carrion’s disease, this infection remains endemic in Peru. Trench fever, most commonly seen today in underhoused and homeless populations, is due to *B. quintana* transmitted through body lice. The name is based on its occurrence among combatants in 20th century trench warfare; up to one-third of British soldiers were infected during World War I.<sup>43</sup>



Figure 10. “Welcome to the AFIP” website image. Information presented on AFIP is considered public information and may be distributed or copied.

*Bartonella* bacteria have mammalian reservoirs in which they cause chronic, asymptomatic bacteremia,<sup>44</sup> and the vectors for most of these are ectoparasites, including fleas, lice, and ticks. The CDC<sup>45</sup> has reported that 40% of domestic and adopted shelter cats have evidence of *B. henselae* bacteremia. The cats, which usually show no signs of illness, are commonly infected through flea bites. *Bartonella henselae* can be detected in the erythrocytes of bacteremic animals for months or longer.<sup>46</sup> The cats themselves transmit the bacteria to humans through scratches and licking.<sup>47</sup> People can become infected simply by rubbing their eyes after contact with a cat.<sup>38,46</sup>

With regard to infected cats having a *B. henselae* septiemia and being asymptomatic, it is interesting to note that in 1878, at the same time that Parinaud was collecting the initial patients with POGS, Robert Koch was formulating his postulates and wrote: “I have on many occasions, examined normal blood and normal tissues that insure such organisms are not overlooked, and I have never in a single instance found bacteria. I therefore conclude that bacteria do not occur in the blood or tissues of healthy animals or humans.”<sup>47,48</sup>

The mechanism of action of *B. henselae* once it enters the human body is apparently unique. The bacterium can directly “inject” proteins into the endothelial cells that inhibit apoptosis (programmed cell death).<sup>49</sup> Tsukamoto et al<sup>50</sup> reported that *B. henselae* also secretes a bioactive substance that promotes angiogenesis, even when not in contact with endothelial cells; this is the first report of a VEGF growth factor protein produced by bacteria.

Study of the molecular genetics and genetic diversity of *B. henselae* is progressing, but slowly. Sixteen genotypes have been identified within 75 *B. henselae* human strains studied with multispacer typing.<sup>51</sup> However, studies incorporating more diverse geographic origins and clinical features are needed to improve our understanding of *B. henselae* population dynamics.

## Conclusions

The World Health Organization estimates that 61% of all human diseases are zoonotic.<sup>52</sup> When Henri Parinaud observed his initial series of POGS patients in 1889, he shrewdly suspected a single disease of animal origin. It then took half a century to determine that most cases were a subset of cat scratch disease and a full century to discover the etiology. Ophthalmologists, the American Academy of Ophthalmology, and the Armed Forces Institute of Pathology’s Registry of Ophthalmic Pathology all played a significant role in determining *Bartonella henselae* to be its major cause. *Bartonella henselae* has several features that have led to speculation about its potential as a public health threat. Our lack of knowledge about several aspects of this bacterium *B. henselae* is a marked vulnerability. In regard to its epidemiology, its true incidence and prevalence are approximations or assumptions. The disease is self-limited at present and responds to some available antibiotics but is capable of

undergoing mutations to make it more virulent. We need to monitor the disease, be aware of its geographic diversity, and better understand its pathobiology.<sup>53,54</sup>

The ophthalmic community must be proactive, starting with clinical recognition. Residency programs can familiarize residents with the disease’s clinical aspects and the laboratory test needed to make the diagnosis. The American Board of Ophthalmology can promote such awareness through its initial and continuing certification assessments. The American Academy of Ophthalmology, through its IRIS<sup>®</sup> Registry, can bolster the data on incidence and prevalence, and the National Eye Institute can encourage more detailed knowledge of the molecular genetics of *B. henselae* and the pathogenesis of the diseases. The CDC can provide more up-to-date statistics on its occurrence including its morbidity in childhood and in patients over 65 years. The global “Stop Spillover” virus-hunting effort might include *Bartonella* bacteria among those diseases it tracks.<sup>54</sup>

Since 1985, essentially all cases of POGS reported in the literature refer to patients shown by serology or molecular testing to have *B. henselae* infections. In the future, this eponym should refer only to cases fitting Parinaud’s original clinical description that are caused by *B. henselae* and are a subset of cat scratch disease. We suggest discontinuing the use of the term “Parinaud’s oculoglandular syndrome” and replacing it with “Parinaud’s oculoglandular disease.”

Currently, International Classification of Diseases 10<sup>th</sup> Edition (ICD-10) codes describing *Bartonella* infections include Systemic Bartonellosis (ICD-10: A44.0); Cutaneous and Mucocutaneous Bartonellosis (ICD-10: A44.1); Other Forms of Bartonellosis (ICD-10: A44.8); Bartonellosis, Unspecified (ICD-10: A44.9); and the umbrella code Bartonellosis (ICD-10: A44).<sup>55</sup> There also exists a code that is shared between the terms Parinaud’s Conjunctivitis and Parinaud’s Oculoglandular Syndrome (ICD-10: H10.89).<sup>56</sup>

The creation of additional ophthalmology-specific codes would increase diagnostic precision and facilitate consistent reporting of these conditions. We propose the creation of the following new ICD-10 codes: “Intraocular Bartonellosis,” “Conjunctival and Orbital Bartonellosis,” and “Ocular Bartonellosis.” The Intraocular Bartonellosis code should be assigned only when evidence of chorioretinitis, neuroretinitis, vitritis, or other intraocular findings have been confirmed. Conjunctival and Orbital Bartonellosis would capture the findings of the traditional term Parinaud’s Oculoglandular Syndrome. Ocular Bartonellosis could serve as an umbrella diagnosis. Such diagnoses should be assigned only when laboratory-confirmed *Bartonella* infection has been established in the presence of the respective clinical findings or when the history and systemic symptoms strongly suggest *Bartonella* as the causative agent. These diagnostic codes should only be assigned when other diagnoses with similar possible presentations have been excluded or are highly unlikely. Using more precise terminology should help to determine the true incidence and prevalence of a disease that almost certainly is more common than generally assumed.

## Footnotes and Disclosures

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Abbreviations and Acronyms:

**AFIP** = Armed Forces Institute of Pathology; **CSD** = cat scratch disease;

**ICD-10** = International Classification of Diseases 10<sup>th</sup> Edition;

**POGS** = Parinaud's oculoglandular syndrome.

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*Bartonella henselae*, cat scratch disease, precision medicine, serologic testing, Parinaud's oculoglandular syndrome.

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