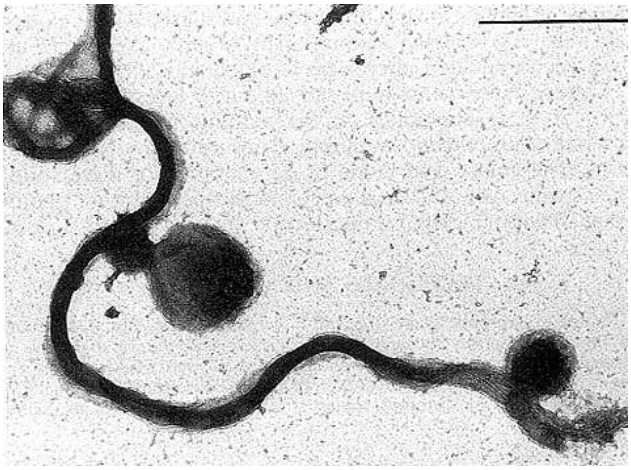
Lyme Disease

Survival in Adverse Conditions

The Strategy of Morphological Variation in Borrelia burgdorferi & Other Spirochetes

1900-2001



Granule formation in B. burgdorferi after 24 h incubation with ceftriaxone.
Kersten A; Poitschek C; Rauch S; Aberer E. 1995.

"It must also be borne in mind that coccoid bodies may be present when spirochaetes as such cannot be detected."

—Fantham HB. 1916.

December, 2001

This relatively large Borrelia [Borrelia burgdorferi] is not readily detectable in blood smears or thick drops of Lyme disease patients and susceptible host animals, yet engorgement on infected hosts results in up to 100% infected ticks....

RML [NIH's Rocky Mountain Lab] scientists Dave Dorward and Claude Garon using silver staining, transmission and scanning electron microscopy investigated the nature of naturally elaborated membrane blebs on the surface of cultured B. burgdorferi or free in the medium, and found both linear and circular DNA... These most recent findings [of RML researchers and others] do confirm the development of membrane-derived cysts, blebs, spherules, vesicles and the potential transformation to motile, helical spirochetes... as a "survival mechanism" of spirochetes to overcome or escape unfavorable conditions.

Willy Burgdorfer, discoverer of Borrelia burgdorferi.
Keynote Address - The Complexity of Vector-borne Spirochetes.
12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders. 1999.

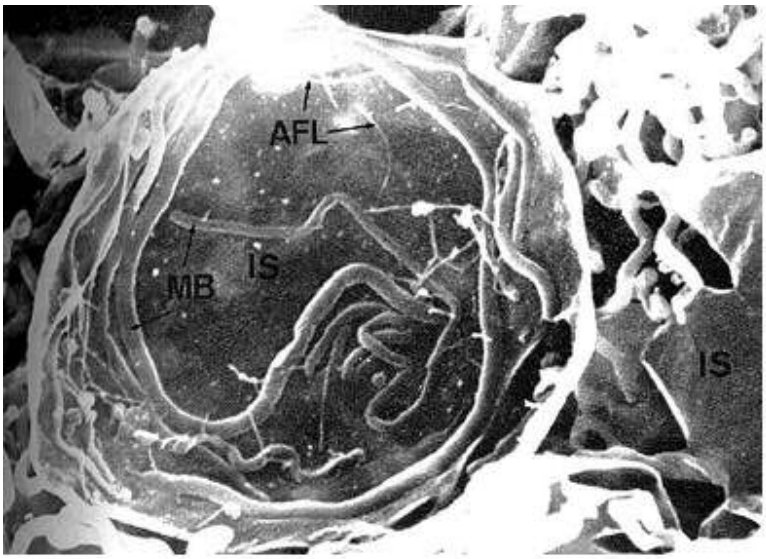
Contents

Observations of Alternate Morphological Forms of Spirochetes: A Selection of Photographs and Quotations

"The number of particular forms depends on the conditions of existence. Under favourable conditions elongated forms predominate, and under unfavourable conditions the rounded forms."
—Ovcinnikov NM; Delectorsku VV. 1966.

CYSTS—PROTECTIVE FUNCTION

"Under stressful conditions, the treponeme 'packs' itself into a compact roll and becomes covered with a transparent mucoid capsule, which resists the penetration of drugs and antibodies. The organisms may persist in this form for a prolonged period without any reaction from the host. The encysted treponemes and the host coexist more or less peacefully, but under propitious circumstances the cysts may be transformed again into the usual spiral, which damages the cells of the host and elicits a response."
—Ovcinnikov NM; Delectorsku VV. 1971.



Treponema macrodentium cyst, showing spirochetes coiled inside.
Umemoto T; Namikawa I; Yoshii Z; Konishi H. 1982.

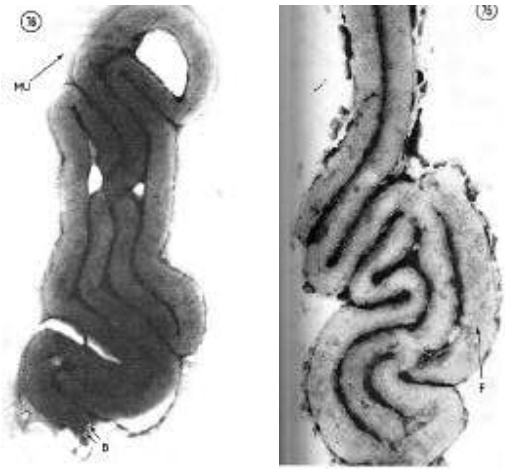
"If the stress is not lethal, accessory envelopes are formed and the treponemes become well encapsulated and may survive new stresses many times stronger than the initial one."
—Ovcinnikov NM; Delectorsku VV. 1971.

"The addition of tetracycline inhibits cyst formation, demonstrating that cyst formation [in B. burgdorferi] requires protein synthesis and that cysts are not merely degenerative forms." [(a)]
"The cyst forms seem resistant to conventional antibiotics. Note the enormous concentration of tetracycline needed to inhibit cysts, much greater than that achievable in humans." [(b)]
—[(a)]Alban PS; Johnson PW; Nelson DR. 2000.
—[(b)]Alban PS; Nelson DR. 1999.

B. burgdorferi cyst forms.
Alban PS; Johnson PW; Nelson DR. 2000.

"This phenomenon, combined with the ability of the cysts [of B. burgdorferi] to reconvert to normal, mobile spirochetes, may explain a reactivation of the disease after an illusory cure..."
—Brorson O; Brorson SH. 1999.

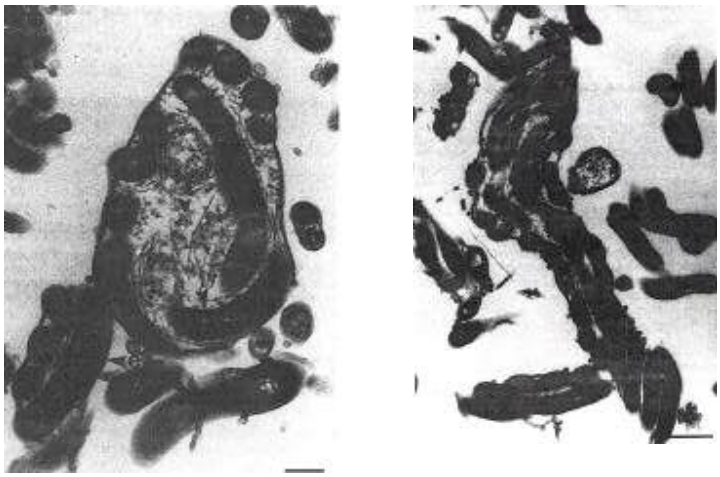
B. burgdorferi after exposure to penicillin concentration of 0.125 mg/l. Coiled up spirochete forming a spherical structure (spheroplast).
Schaller M; Neubert U. 1994



T. pallidum packed into a cyst surrounded by a mucous-like membrane (left & right photos).
Ovcinnikov NM; Delectorskij VV. 1968.

CYSTS—PROTECTIVE FUNCTION (cont'd)

"We conclude that such cysts... [serve to] by-pass adverse circumstances and to ensure the propagation of the organism. ...This agrees with what usually happens in protozoa in nature; ...the majority of cysts in protozoa are a means of protecting their contents against unfavorable conditions but some of them are designed rather to ensure a long period of rest. Later, depending on conditions when the harmful exposure is past, protective cysts become multiplication cysts. They are not merely protective but also serve for reproduction."
—Al-Qudah AA; Mostratos A; Quesnesl LB. 1983.

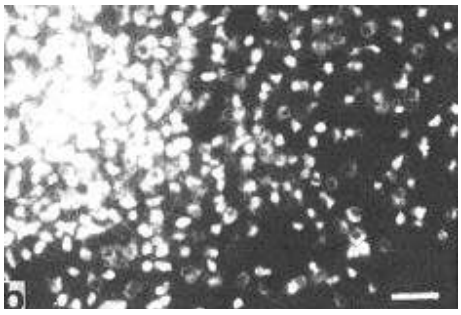


B. burgorferi. Left: A cystic structure with spirochetes inside. Right: A beginning cyst containing four spirochetes.
Brorson O; Brorson SH. 1998.

"Low biological activity [of cysts in distilled water] was demonstrated ...suggesting a torpor state. When BSK-H medium with serum was added to cystic forms only, they seemed to wake from this torpor state, and once again become metabolically active...

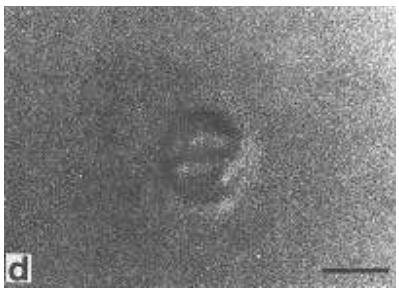
The effectiveness of antibiotics requires active metabolism by the bacteria, and therefore it is likely that cystic forms of B. burgdorferi may be resistant to antibiotic treatment. ...In vivo these encysted forms may explain why Borrelia infection can be temporarily dormant, why a reactivation of the disease may occur when the conditions suit B. burgdorferi, and why the infection may relapse after treatment with antibiotics."
—Brorson O; Brorson SH. 1997.

"Borrelial cystic forms could therefore be responsible for the frequent failures of antibiotic therapy and for the commonly reported relapses of Lyme disease."
—Gruntar I; Malovrh T; Murgia R; Cinco M. 2001.



B. burgdorferi cysts from distilled water. Presence of RNA demonstrated by staining.
—Brorson O; Brorson SH. 1998.

"Some cysts contain round lamellar structures or formations filled with a granular mass. We suggest that this mass is a store of nutrient material."
—Ovcinnikov NM, Delektorskij VV. 1969.

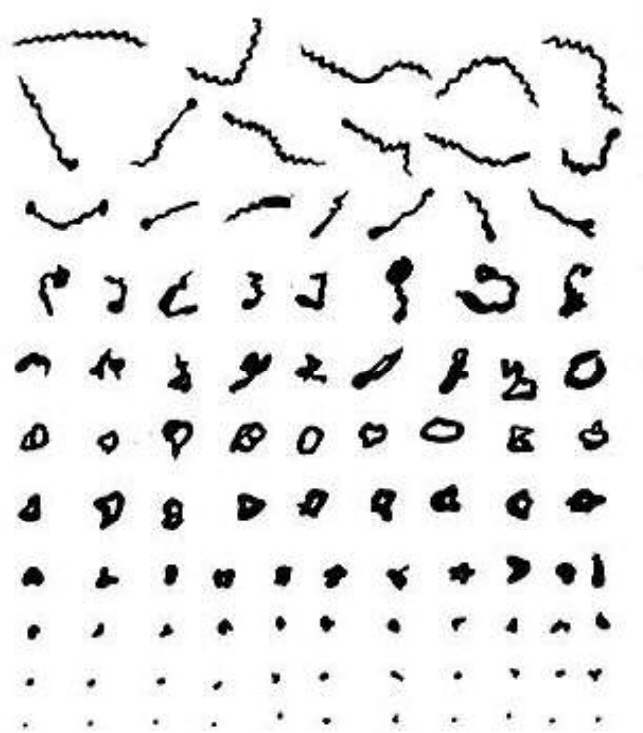


B. burgdorferi cyst from distilled water. Coiled spirochetal structure inside cyst.
Brorson O; Brorson SH. 1998.

"An unexpected observation was the identification of cystic forms of the Borrelia spirochete in dark-field preparations of cultured hippocampus, and in imprints of hippocampus... A cystic form of the Borrelia spirochete would explain the ability of the microbe to persist in the host during a prolonged period of asymptomatic clinical latency, which spans the period between primary infection and the expression of tertiary manifestations of neuroborreliosis."
—MacDonald AB. 1988.

TRANSFORMATION OF SPIROCHETES TO CYSTIC AND GRANULAR FORMS

"Another aspect [of spirochetal infections]... is the apparent continuation of the disease process after the organisms are no longer detectable. ...Why is it so difficult to culture or even visualize spirochetes in the synovium and synovial fluid of patients with Lyme arthritis of long duration? What is tertiary syphilis in the absence of Treponema pallidum?"
—Benach JL; Coleman JL. [Coyle PK, ed.]. 1993.



"A definite cycle of transformation is apparent. ...The first stage is apparently the development of a knob, usually at one or both ends, but occasionally in the middle of the organism; the ends then bend together, forming a horse-shoe loop, this in turn becomes an irregular circle, which contracts into a solid irregular granule, finally becoming a single, small, rounded granule. ...A submicroscopic form following the minute granule is inferred, but we are not ready to offer positive demonstration of it at the present moment."
—Warthin AS: Olson RE. 1930.

Treponema pallida: transformation to granules in aortic focal lesions.
Warthin AS; Olson RE. 1930.

"Manouelian regarded these forms as representing a transmutation series from the typical spirochete form to a minute corpuscle which can pass through a filter. These atypical granules are much more numerous than the typical spirochetes, and are very abundant where the latter are rare or cannot be demonstrated at all. He regards the presence of these granules as confirmatory of the syphilitic nature of a late lesion, even in the absence of typical spirochetes."

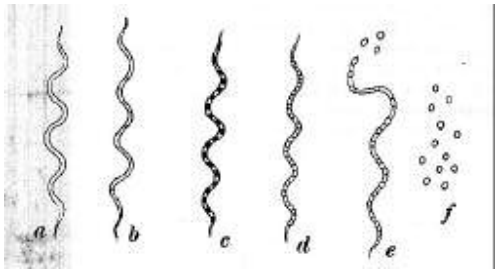
"Levaditi confirmed the work and conclusions of Manouelian. He describes the stages leading from the spirochete to the granules, the ultimate granules being from 0.1 to 0.3 microns in diameter. He believes that these findings might explain late syphilis without spirochetes, paresis without spirochetes, and finally malignant syphilis. The resistant forms are not sensitive to the chemicals that kill the vegetative (spirochete types)."
—Warthin AS; Olsen RE. 1931.

B. burgdorferi. Conversion of a spirochete to a cystic form within an interval of 15 min.
Brorson O; Brorson SH. 1998.

TRANSFORMATION OF SPIROCHETES TO CYSTIC AND GRANULAR FORMS (cont'd)

"...the existence of the causative agent of syphilis in a nonspirochetal form has long been hypothesized to explain the latency of syphilis and the infectivity of tissues devoid of demonstrable treponemes."
—Al-Qudah AA; Mostratos A; Quesnel LB. 1983.

"Lyme disease is clinically and histologically characterized by inflammatory reactions that are out of proportion to the few numbers of spirochetes at lesion sites..."
—Nordstrand A; Barbour AG; Bergström S. 2000.



Hindle E. 1912.

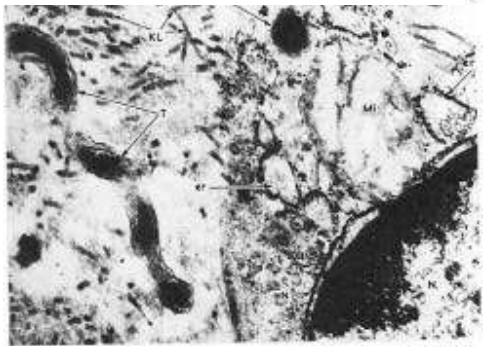
"By means of examination with the dark-ground illumination, I have frequently observed the breaking up of the spirochaete into a number of coccoid forms (? spores), in the manner described by Balfour (1911) for this species, and also by Bosanquet (1911) for S. anodontae. I can entirely confirm Balfour's description of this interesting process, which takes place at the crisis of the disease or after drug treatment. ...The spirochaete gradually assumes the appearance of a chain of beads contained within the transparent cell-wall."
—Hindle E. 1912.

"Groups of coccoid bodies still retaining the outline of the spirochaete from which they originated are of fairly frequent occurence."
—Fantham HB; Cantab MA. 1916.

"The organism may appear as a chain of granules which outline a complete spirochaete."
—Ewing J. 1907.

Granular dissolution of B. burgdorferi in medium after adverse conditions.
Aberer E; Kersten A; Klade H; Poitschek C. 1996.

"...the Western blots displayed consistent differences between the protein antigens recognized in vegetative cells and cysts. ...By forming cysts, it is also conceivable that B. burgdorferi cells evade detection by the immune system."
—Alban PS; Johnson PW; Nelson DR. 2000.



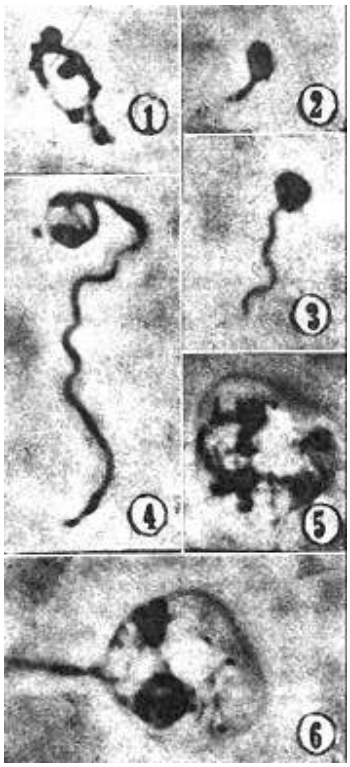
T. pallidum in a rabbit.
Ovcinnikov NM; Delektorskij VV. 1971.

"We found that cysts which are produced by inoculating B. burgdorferi in CSF at 37°C can be PCR negative using conventional DNA extraction and OspA primers (unpublished observation). This is either because the cyst wall inhibits the entrance to the genome or because the genomes of spirochetes have been changed. ...PCR detection of B. burgdorferi spirochetes often may given false-negative results [19]."
—Brorson O; Brorson SH; Henriksen TH; Skogen PR; Schoyen R. 2001.

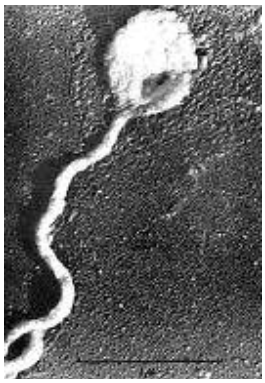
"Very interesting are the studies by Hoyer and King who demonstrated the loss of a portion of the chromosomal DNA in an L-form of Enterococcus."
—Mursic VP; Wanner G; Reinhardt S; Wilske B; Busch U; Marget W. 1996.

INTERMEDIATE STAGES IN THE CONVERSION TO CYSTIC FORMS: END KNOB

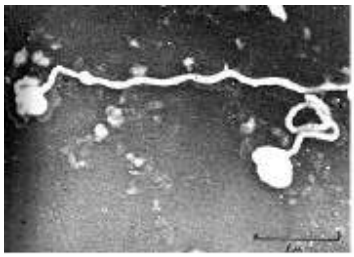
"...in many specimens a curious knoblike structure was seen at the end of many organisms. Their almost uniform shape and density suggest that these are not extraneous particles of the preparation but a part of the organism itself."
—Wile UJ; Picard RG; Kearny EB. 1942.



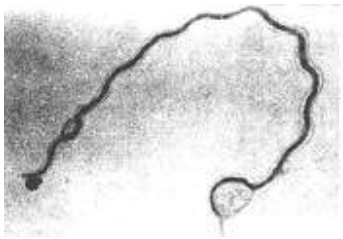
Species unknown (above).
Delameter ED. 1950.



Leptospira.
Czekalowki JW; Eaves G. 1954.

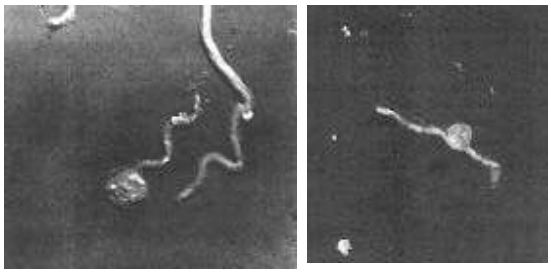


Leptospira.
Czekalowki JW; Eaves G. 1954.



T. pallidum.
Wile UJ; Picard RG; Kearny EB. 1942.

In vivo T. pallidum— in aqeous humor of eye.
Smith JL; Israel CW. 1967.



Borrelia vincentti.
Hampp EG; Scott DB; Wyckoff RWG. 1948.

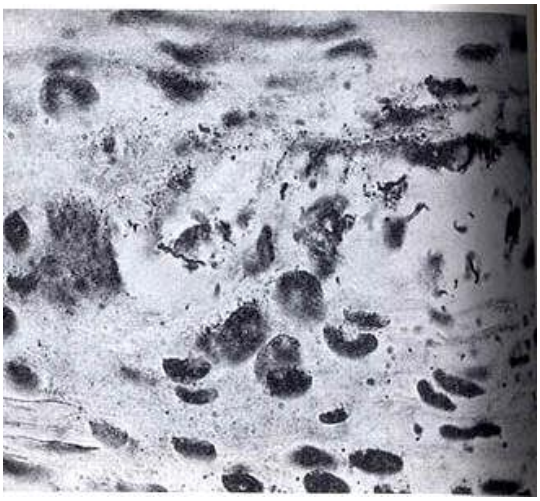
Borrelia burgdorferi.
Brorson O; Brorson SH. 1999.

"Irregularly spheroidal, dense bodies... are often found attached to the spirochetal cell, frequently near the end; such a dense body may be in close apposition to the outside of the spirochetal cell-wall or may be connected to it by a short stalk."
—Mudd S; Polevitsky K; Anderson TF. 1943.

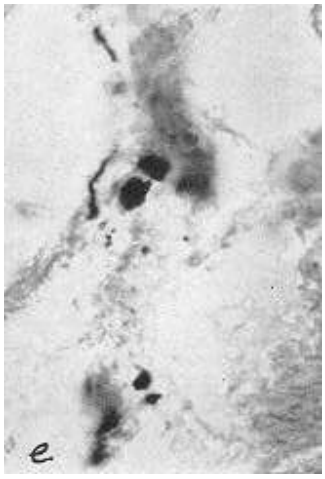
INTERMEDIATE STAGES IN THE CONVERSION TO CYSTIC FORMS: END KNOB (cont'd)

"It is not uncommon to find a spirochaeta with a bulbous extremity at one or both ends, or even in the centre..."
—McDonagh JER. 1912.

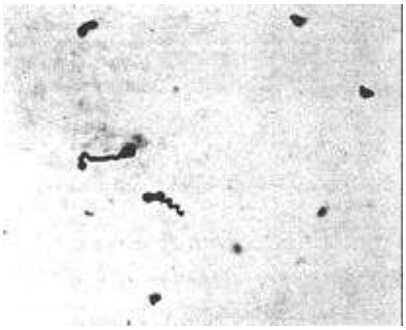
B. burgdorferi. Skin biopsy specimen revealing terminal granule.
Aberer E; Kersten A; Klade H; et al. 1996.



Species not identified.
Lennhoff C. 1948.

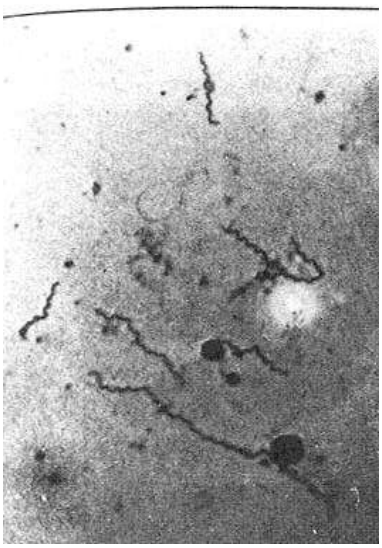


2 photos above:
Species unknown. In brain autopsy.
Steiner G. 1952.



Treponema pallida in aortic focal lesion.
Warthin AS; Olson RE. 1930.

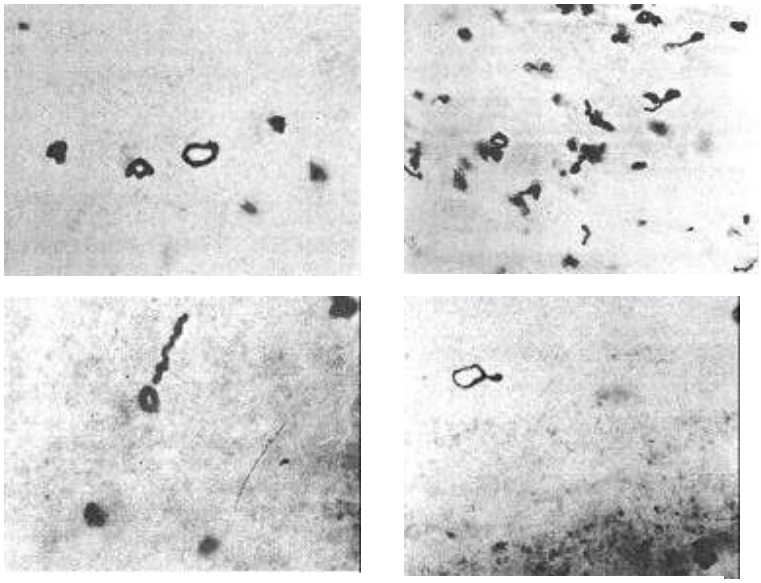
"It was calculated that the formation of spherical bodies may reduce their surface by up to 75% as compared to the single form. Thus, the reaction surface for antibodies or other compounds produced by the host is considerably diminished."
—Wolf V; Wecke J. 1994.



Treponema pallida.
Noguchi H. 1911.

INTERMEDIATE STAGES IN THE CONVERSION TO CYSTIC FORMS: LOOP FORMATIONS

"In the phagocytes the spirochetes were often found coiled into a loop, or circle, or horse-shoe form, which apparently gradually contracts until it forms a round granule still taking the silver impregnation."
—Warthin AS; Olson RE. 1930.

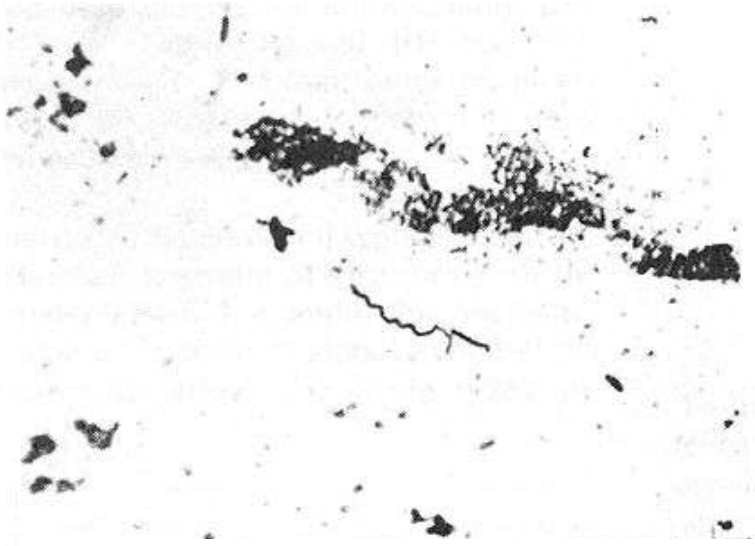


"There are all intermediate stages between well preserved regularly coiled spirochetes and granular bodies."
—Steiner G. 1952.

Treponema pallidum. Contracting loop forms and granular forms in aortic focal lesion.
Warthin AS; Olson RE. 1930.

"We found spiral organisms in the lymph nodes and the cerebrospinal fluid of rabbits and of treated patients, which do not always show the typical morphological appearance of T. pallida as seen in a chancre or in an acute orchitis.

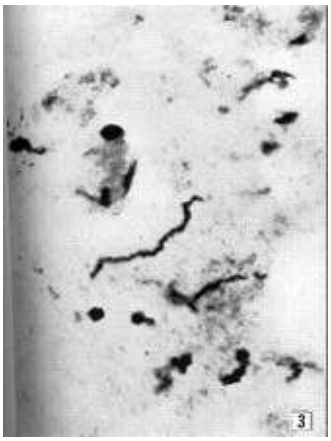
These organisms are the same as those seen in late untreated experimental syphilis and are called T. pallida by numerous authors whose scattered publications do not seem to have attracted much attention."
—Collart P. et al. 1964.

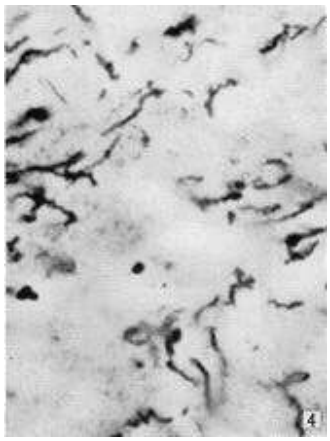


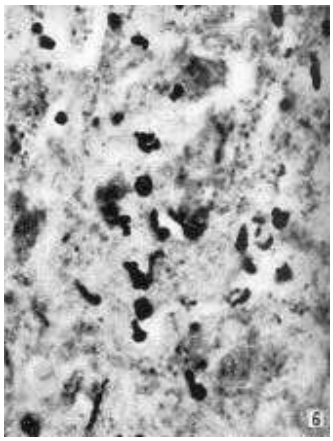
A tabetic treated with 40 mega units penicillin.
Collart P; Borel LJ; Durel P. 1964.

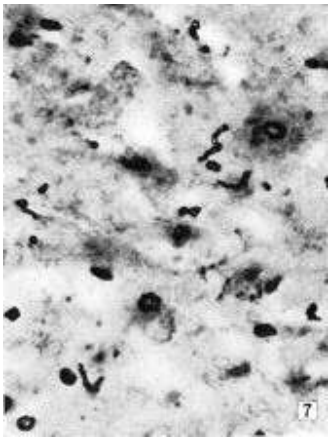
INTERMEDIATE STAGES IN THE CONVERSION TO CYSTIC FORMS: LOOP FORMATIONS (cont'd)

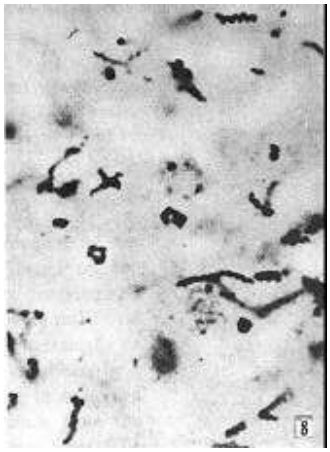
"...filamentous forms, short forms, irregular forms, thick long forms, circular forms, forms with terminal ovoid body, free ovoid bodies, incomplete serrated circular forms, comma forms, intracellular circular smooth and serrated forms, extracellular granular circular forms, and granular forms" were found in an active syphiloma of a rabbit.
—Campbell RE; Rosahn PD. 1950.











All five photographs: Loops and other formations in active syphiloma of a rabbit.
Campbell RE; Rosahn PD. 1950.

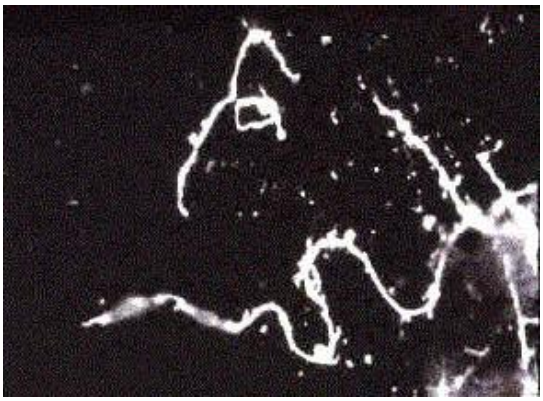
"It is therefore feasible that in spirochetes an antigenic as well as a morphological transformation occur at the same time."
—Klieneberger-Nobel E. 1951.

"The antigenic variation in B. burgdorferi may occur inside the cyst while the microbe is protected against external stress."
—Brorson O; Brorson S. 1998.

"It seems likely that the spirochetes should be considered as a separate group of micro-organisms distinct from the bacteria and also distinct from the protozoa."
—Delamater ED; Haanes M; Wiggall RH; Pillsbury DM. 1951.

SPORE-LIKE, MINUTE GRANULES

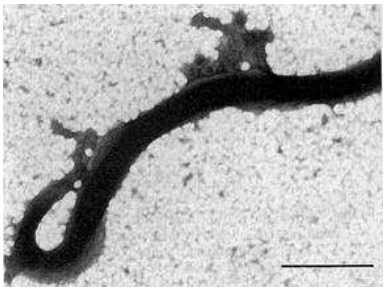
"...the spirochaetes undergo an astonishing change. They discharge from their periplastic sheaths spherical granules, and it is apparently these granules which enter the red cells, develop in them and complete a cycle of schizogony...In process of time the spirochaete loses its activity, becomes difficult to see, and eventually all that is left of it is the limp and lifeless... [that the granules] do not appear to take on the Romanowsky stain may explain why they have not previously been noticed... I have found these granules to be resistant forms and their presence in countless numbers in the tissues might explain part of the mechanism of relapse and the difficulty of curing completely some of the more chronic spirochaetal infections, as, for example, syphilis and yaws."
—Balfour A. 1911.



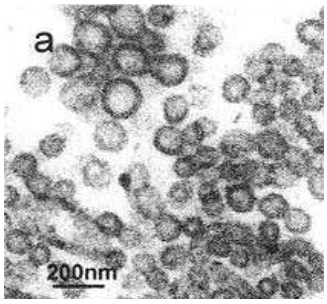
Borrelia burgdorferi, "Granule shedding."
Burgdorfer W. 1999.

"...huge amounts of liposome-like blebs are shed [by Borrelia burgdorferi]... Bb-blebs can penetrate through the cell membrane into the cytoplasm, accumulate in the cytosol and enter the nucleus. Bb-blebs abrogate the T-cell stimulatory capacity of dendritic cells."
—Filgueira L; Beermann C; Groscurth P. 2000.

"The formation of tiny refractile granules is also well documented for many species of all genera in the Spirochaetae. Whether these are pathogenic per se remains at this date a controversial point. There is little doubt that even for T. pallidum these granules are infective. "
—Mattman LH. 1993.



B. burgdorferi. Shedding of membrane blebs.
Kersten A; Poitschek C; Rauch S; Aberer E. 1995.



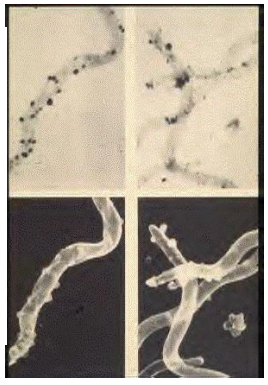
B. burgdorferi. Blebs in dermis.
Beerman C. et al. 2000.

"This form [small granules] is apparently resistant and latent and becomes infective when it regenerates spirochetes."
—Klieneberger-Nobel E. 1951.

"The breakdown into granules is especially pronounced under the action of penicillin and immune sera."
—Ovcinnikov NM; Delectorsku VV. 1971.

B. burgdorferi.
Left:
Membrane blebs.
Burgdorfer W. 1999.

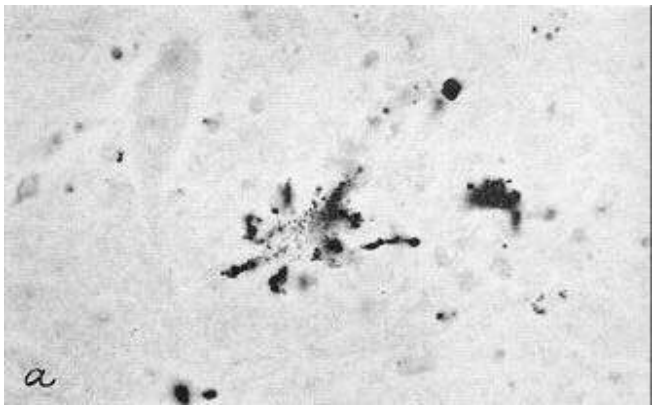
Right:
After exposure to penicillin.
Schaller M;
Neubert U. 1994.



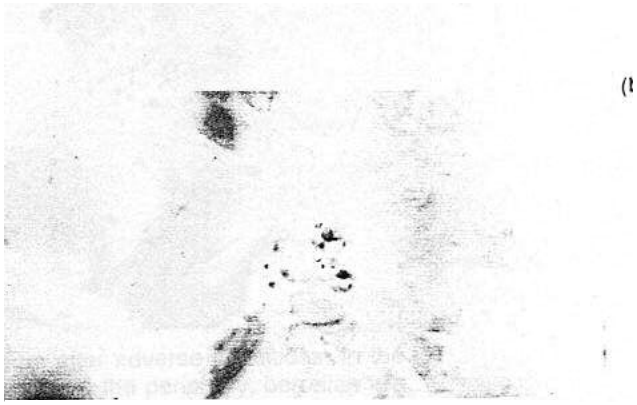
"...scientists Dave Dorward and Claude Garon [of NIH's Rocky Mountain Labs] investigated the nature of naturally elaborated membrane blebs on the surface of cultured B. burgdorferi or free in the medium, and found both linear and circular DNA..."
—W. Burgdorfer. 1999.

AGGREGATIONS OF MINUTE GRANULES

"Granular bodies in general may represent 1) involutional forms (a) with possibility of redevelopment into typical spirochetal forms, (b) representing beginning disintegration and final death of the spirochetes, (c) possibility of (a) and (b), that is redevelopment into spirochetal forms as well as irreversible disintegration; 2) specific evolutional forms in the life-cycle of the spirochete. At present no decision between 1) or 2) is possible."
—Steiner G. 1954.

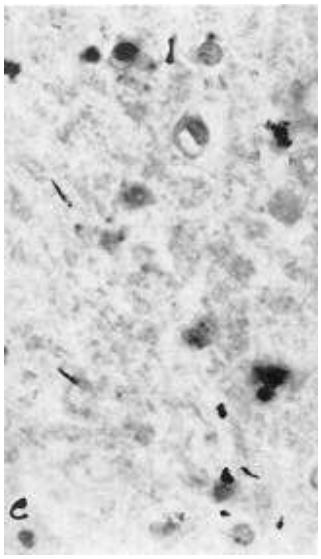


Granular bodies in human brain autopsy. Steiner G. 1952.



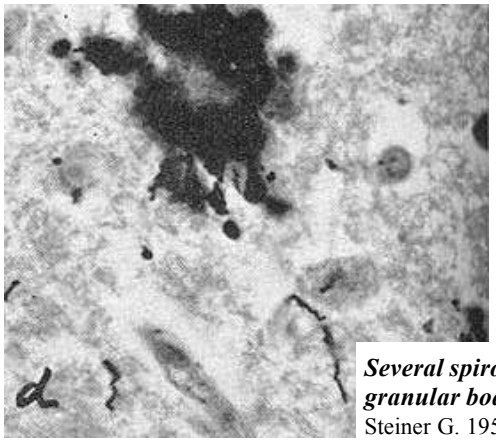
B. burgdorferi. Small granules in skin (ACA).
Aberer E; Kersten A; Klade H et al. 1996.

"Assuming for a moment that the vital theory is correct it seems certain that they [granule clumps] are therefore capable of multiplication in the granular form, and probable that their development into spirillar shape is an exceptional occurrence brought about by influences not as yet fully determined."
—Leishman WB. 1920.

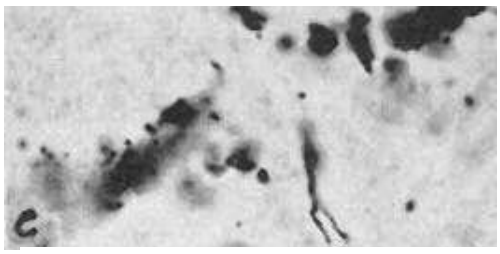


Extracellular granular bodies and other variant spirochetal forms.
Steiner G. 1952.

Granular bodies seen at one end of spirochete.
Steiner G. 1952.



Several spirochetes; granular bodies.
Steiner G. 1952.

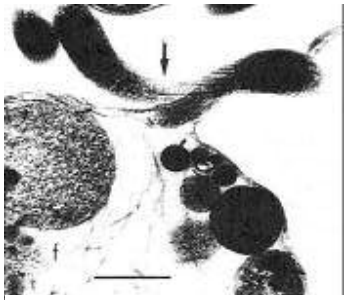


Entwined (Y-form) spirochetes and granular bodies.
Steiner G. 1952.

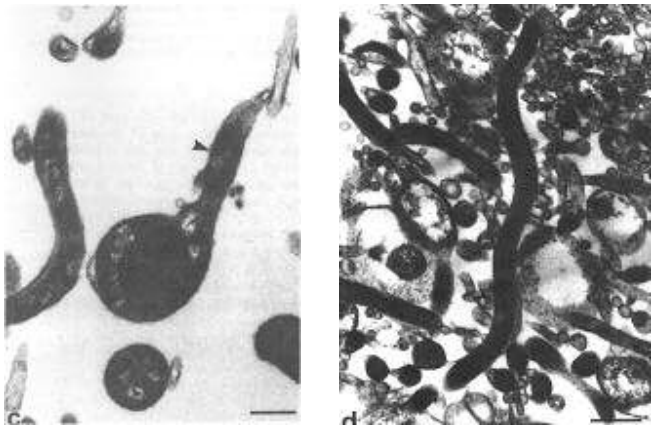
"There seems to exist an alternation between the actual spirochetal phase and a granular phase which, it is assumed, may represent the regenerative or L phase. This latter phase is at the same time resistant and responsible for the periods of latency. It is able to reproduce young spirochetes which may in various ways differ from the preceding generation. The existing information indicates that the spirochetal L phase consists of particles which are almost submicroscopic." —Klieneberger-Nobel E. 1951.

SPIROCHETES DEVELOPING FROM CYSTS

"...it seems likely from these observations that there are two means of vegetative reproduction, consisting of (1) transverse division... and (2) the production of gemmae or buds which eventuate into unispirochetal cysts..., within each of which single spirochetes develop and differentiate, and from which they subsequently emerge."
—Delamater ED; Wiggall RH; Haanes M. 1950.



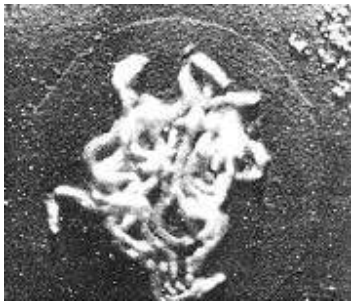
Intestinal spirochete—release from a cyst.
Gebbers JO; Marder HP. 1989.



B. burgdorferi. Left: Spirochete developing from core-like cyst. Right: A normal mobile spirochete which has been converted from a cyst is seen among some cystic structures.
Brorson O; Brorson SH. 1998.

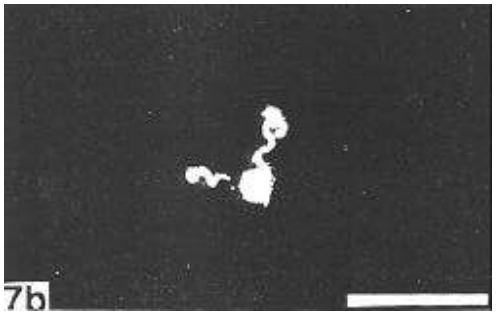
"Interesting conclusions can be drawn from the results of [our] cyst inoculation experiments on mice: B. garinii cystic forms maintain their capability to reconvert into normal spirochetes not only in vitro but also in vivo and can therefore be considered infective, at least in BALB/c mice."
—Gruntar I; Malovrh T; Murgia R; Cinco M. 2001.

"...an alternate type of reproduction from these bodies is a sprouting filament which may become the spirochete. ...The spirochetal cysts differ from bacterial L-bodies in usually forming only a few spirochetae rather than the numerous parent forms which may pack a reverting L-body of most species. Secondly, a sprouting cyst usually thrusts out a spirochetal form rather than the infinite varieties of rhizoid growth which can emerge from an L-body of most bacteria."
—Mattman LH. 1993.

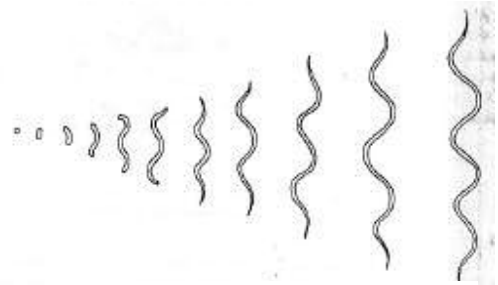


B. vincentii spirochetes within cyst.
Hampp EG; Scott DB; Wyckoff R. 1948.

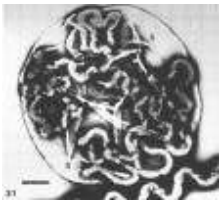
T. pallidum. Multi-spirochetal cyst showing developing spirochetes and attached gemmae.
DeLamater et al. 1951.



B. burgdorferi. Developing spirochetes seen protruding from a cyst.
Brorson O; Brorson SH. 1999.



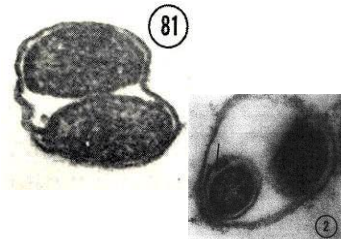
Development of spirochetes from coccoid bodies.
Hindle E. 1912.



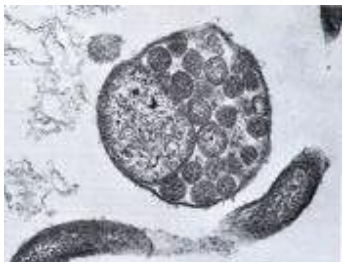
Leptospira.
Spirochetes within cyst.
Ritchie AE. 1976.

CYSTS—REPRODUCTIVE FUNCTION

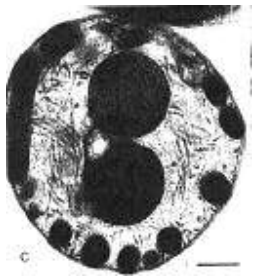
"In vitro findings suggest that spirochetes may develop in cysts, contrary to the traditional view that transverse fission is their main mode of reproduction."
—Gebbers JO; Marder HP. 1989.



(Left) Cyst containing treponemes.
Ovcinnikov NM; Delectorskij VV. 1968.
(Right) Borrelia vincentii.
Bladen HA; Hampp EG. 1964.

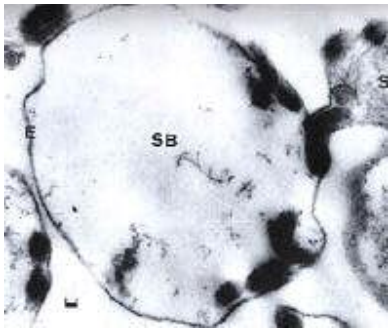


B. burgdorferi. Round gemma containing protoplasmic cylinder and several small granules.
Barbour AG; Hayes SF. 1986.

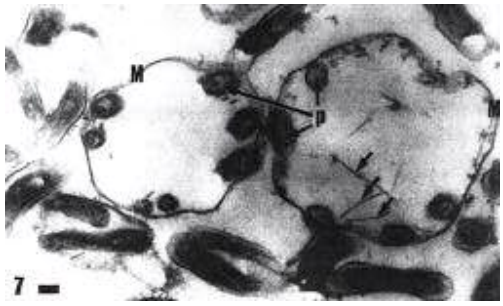


Intestinal spirochete—protoplasmic cylinders.
Gebbers JO; Marder HP. 1989.

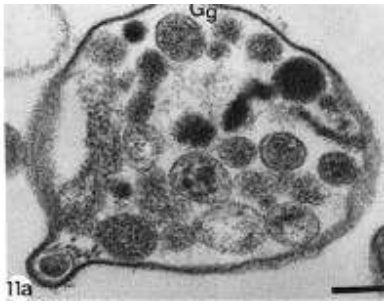
"According to Levaditi the granular form represents the pre-spirochetal phase of the syphilitic agent. The granules are able to retransform themselves into young spirochetes and then into the long, spiral form. The granular form persists in the tissues during periods of latency and withstands specific treatment. ... Levaditi's conception would be in agreement with the fact that spirochetes are not found in certain diseased tissues, that they are not demonstrated in nerve fibres from cases of paralysis of the insane and of tabes and that latent stages of the disease resist chemotherapeutic treatment."
—Klieneberger-Nobel E. 1951.



Oral spirochete—each end forming a spherical body.
Umemoto T; Namikawa I. 1980.



T. microdentium—granules within cysts.
Listgarten MA et al. 1963.



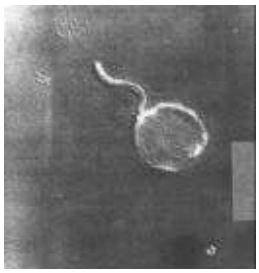
B. burgdorferi.
Gemma containing granules.
Hayes SF; Burgdorfer W. 1993.

"The occurrence of these cysts may clarify why attempts to cultivate B. burgdorferi may be unsuccessful despite the presence of infection. (The cystic forms will be especially difficult to discover when cultivated from blood, since thrombocytes have a similar size and shape.)"
—Brorson O; Brorson SH. 1997.

"As the granules disappear after a fresh piece of brain tissue has been in running water for twenty-four hours, it is to be assumed that the substance of the granules, stainable with silver, is not stable. Nor can granules be demonstrated when pieces of brain tissue have been kept in alcohol, solutions of formaldehyde or osmic acid."
—Hassin GB; Diamond IB. 1939, describing findings by Kon Y. 1933.

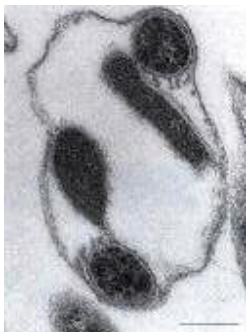
CYSTS—REPRODUCTIVE FUNCTION (cont'd)

"Treponemal cysts change into small segments (granule-spores) with two-layered envelopes, and these later develop into the usual spiral form of treponeme."
—Ovcinnikov NM; Delectorsku VV. 1968.

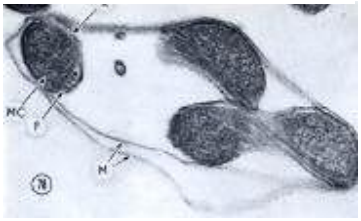


Borrelia vincentti.
Hampp EG; Scott DB; Wyckoff RWG. 1948.

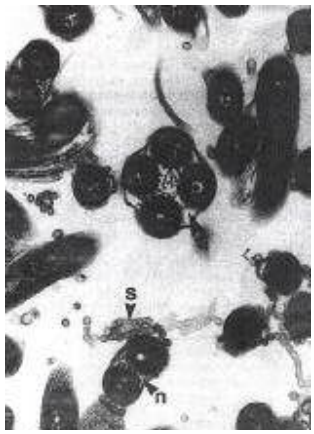
"It is not rare to find a round body connected with one or two young pallida as though the latter were just sprouting from the former."
—Noguchi H. 1911.



B. burgdorferi. Spherical body revealing intracellular, coiled spirochetal parts.
Kersten A: Poitschek C; Rauch S; Aberer D. 1995.

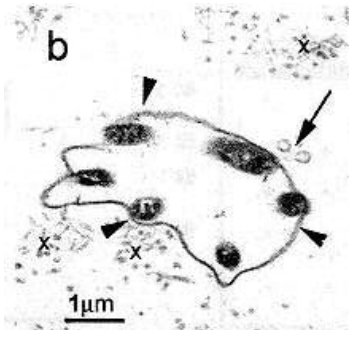


Cyst containing treponemes.
Ovcinnikov NM; Delectorskij VV. 1968.

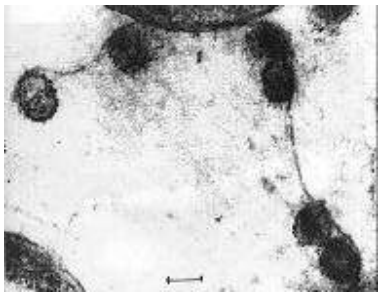


Borrelia burgdorferi: fission within cyst.
Brorson O; Brorson SH. 1997.

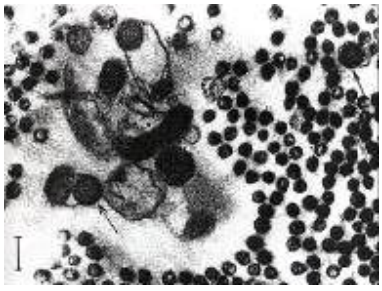
"The observation of transverse fission of spirochetes inside the cysts indicates a more complex regeneration of B. burgdorferi than assumed earlier, and may give the bacteria quantitative advantages when they finally escape from the encysted forms."
—Brorson O; Brorson SH. 1997.



B. burgdorferi shedding blebs (arrow) in the dermis.
Beerman C. et al. 2000.



B. burgdorferi. Cyst-like material.
Hulinska D; Bartak P. et al. 1994.

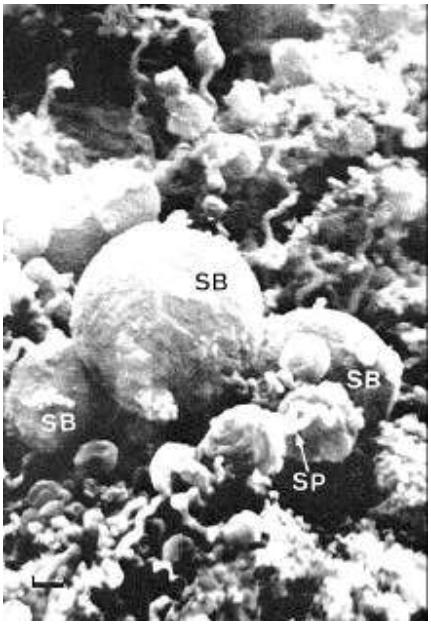


B. burgdorferi.
Alban PS; Nelson DR. 2000.

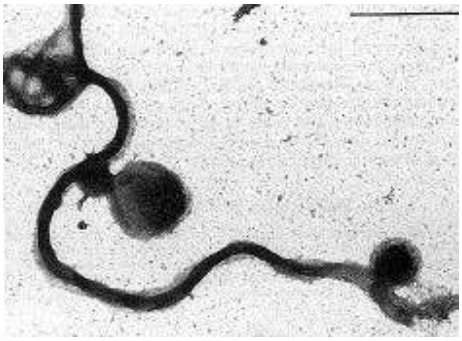
"Cortisone can sometimes reactivate latent syphilis in rabbits. Two rabbits out of twelve which had been treated and then given cortisone presented the classical lesions of late syphilis. These observations appear to be evidence of persistence of the vitality of the T. pallida."
—Collart P; Borel L; Durel P. 1964.

VARIANT MODE OF REPRODUCTION: BUDDING

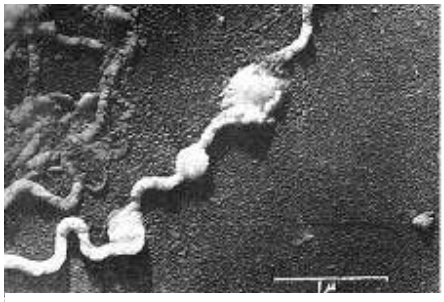
"Dr. Meirowsky observed the aggregation of apparent chromatin granules into small globules, or expansion which might assume a lateral or end-on position to the spirochaetal body. Extrusion of these followed, and the buds thus formed remained attached by a fine pedicle or stalk at the point of extrusion.... spirochaetal buds have the property of dividing."
—Meirowsky E. (Abstract by Dr. H.C. Semon). 1914.



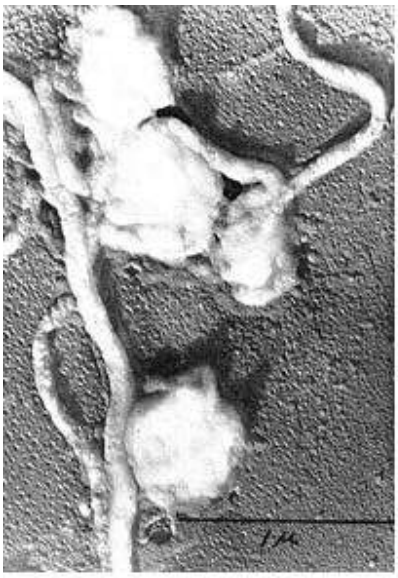
Spherical bodies along oral spirochete, formed in a sucrose-containing broth.
Umemoto T; Namikawa I. 1980.



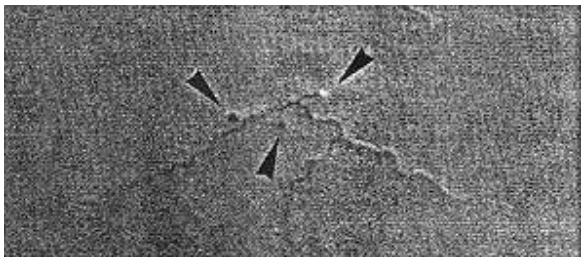
Borrelia burgdorferi granules, after 24 h incubation with ceftriaxone.
Kersten A; Poitschek C; Rauch S; Aberer E. 1995.



Leptospira icterohaemorrhagiae. Multiple formation of granules in different positions of the leptospiral body.
Czekalowski JW; Eaves G. 1954.



Leptospira Czekalowski. A small clump of granules with the associated leptospiral bodies.
Czekalowski JW; Eaves G. 1954.

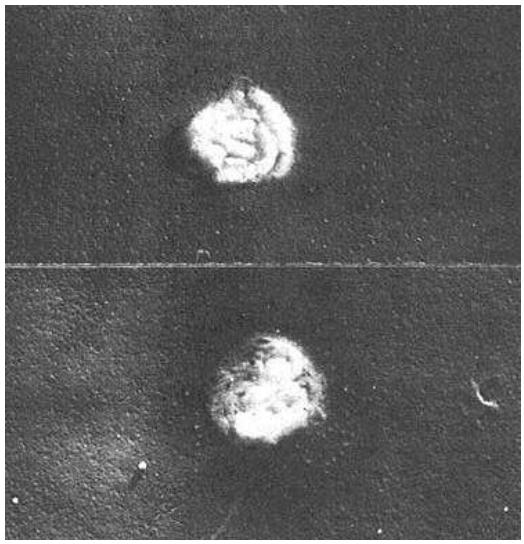


B. burgdorferi in skin biopsy. Granules connected to borrelia spirochetes by a fine stalk.
Aberer E; Kersten A; Klade H; et al. 1996.

"Other spirochaetes... show the curious appearance of a lateral or, more rarely, a terminal protrusion or "bud". This lateral bud was described by me in my earlier papers and has also been observed by many others, both in connection with Spirochaeta duttoni and other spirochaetes."
—Leishman WB. 1918.

BUDDING—FREE GRANULES

"It [Spirochaeta Duttoni] may possibly multiply also by a process in which the fragmented chromatin of an encysted parasite is extruded in granules, each of which may subsequently develop into a new spirochaeta."
—Dutton JL. 1907.

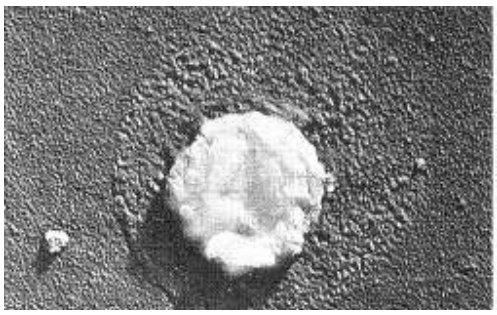


(Top) Borrelia vincentii. (Bottom) Treponema pallidum.
Hampp EG; Scott D; Wyckoff RWG. 1948.

"Typical free granules, the end products of granule "shedding" ...consist for the most part of what appear to be short sections of spirochetes closely packed together."
—Hampp EG; Scott D; Wyckoff RWG. 1948.

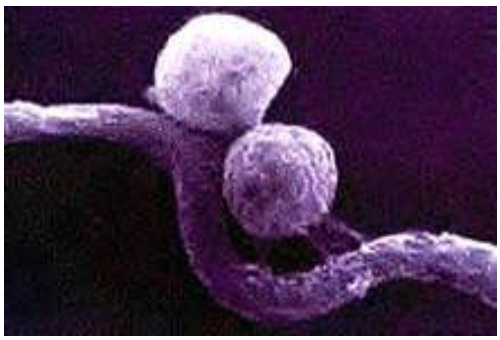
"We also find free spheroid or ovoid bodies containing a denser granule in their interiors, which develop into a commalike body. This commalike body is liberated as such and eventually grows and spirals into a typical treponeme." —Coutts WE; Coutts WR. 1953.

"Steiner was able to observe within some silver cells fragments of spirochetes... Silver cells [represent] the advanced stage of a spirochetal infection."
—Hassin GB; Diamond IB. 1939,
describing findings by Steiner G. 1931.



Leptospira: free granule with central mass consisting of leptospiral fragments.
Czekalowski JW; Eaves G. 1954.

B. burgdorferi. Gemma-like bodies among collagen fibers in ECM.
Aberer E; Kersten A; Klade H; Poitschek C. 1996.

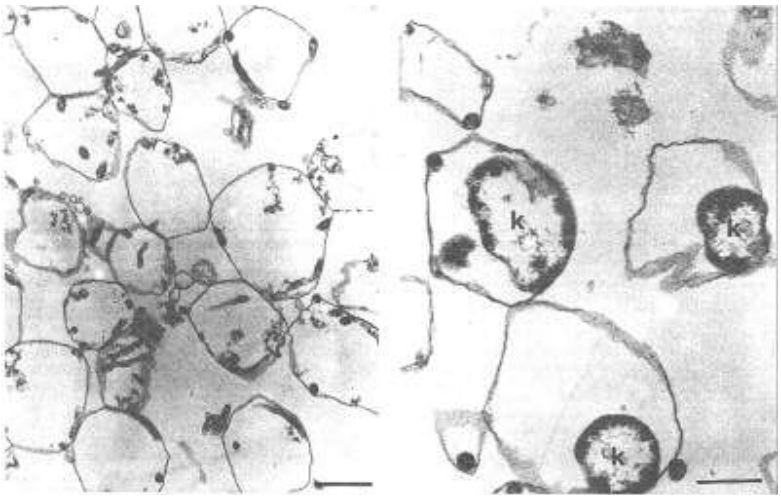


Borrelia burgdorferi.
Mursic VP; Wanner G; Reinhardt S. et al. 1996.

"Not all spirochetes have knobs though they appear able to develop them in any part of their length. From this knob, or granule, as it is frequently called, another spirochete may develop. In this way the spirochete multiplies in the culture tube. Multiplication by granule formation may take place in the body sometimes, for instance in condylomata and in the grey matter of the brain in general paresis. Moisture appears to favor this method of development. That the adult male phase is capable of developing in this way, has led many to think that it is the only way in which it can multiply. These observers forget, however, that a culture tube is a very different thing from the human body."
—McDonagh JER. 1924.

CYSTS—IN SPINAL FLUID

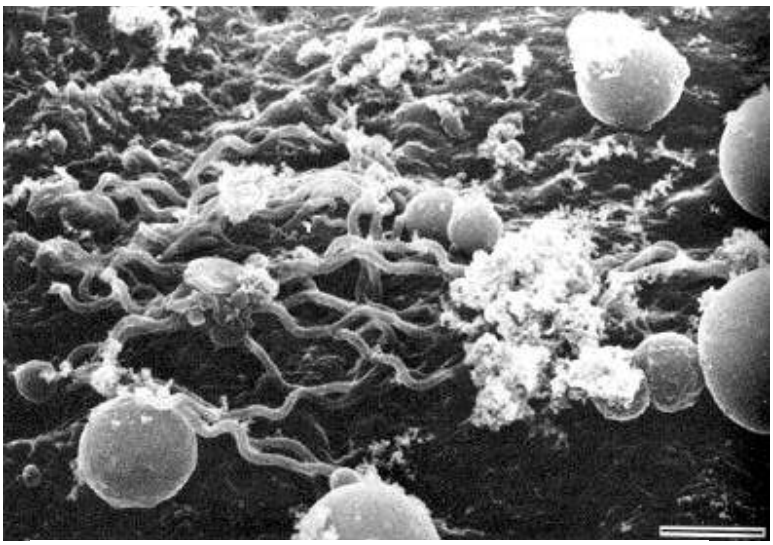
"The conversion to cystic forms may explain why cultivation of spinal fluid often gives negative results with respect to B. burgdorferi... It is not known whether cystic forms of B. burgdorferi can be detected by PCR, but if we assume that cysts cannot be detected by PCR, this may explain why PCR on spinal fluid is negative even when the patient has the diagnosis of neuroborreliosis."
—Brorson O; Brorson SH. 1998.



Borrelia burgdorferi. Cystic forms after 24 h incubation in spinal fluid. Left: relatively empty cysts, in spinal fluid of low protein concentration. Right: core structures in many of the cysts, in spinal fluid with high concentration of protein.
Brorson O; Brorson SH. 1998.

The formation of cysts was somewhat different depending on the concentration of protein in the spinal fluid. ...Slower conversion was observed in spinal fluid with a higher concentration… The biological activity of the cysts was manifested by their ability to reconvert to normal, mobile spirochetes. ...According to our estimates, about 50% of the cysts reconverted… The cysts observed in our study seem to resemble the spheroplast L-forms observed by other researchers which appear to have defects in their cell wall manifested by resistance towards B-lactam antibiotics."
—Brorson O; Brorson SH. 1998.

CYSTS—IN TICKS

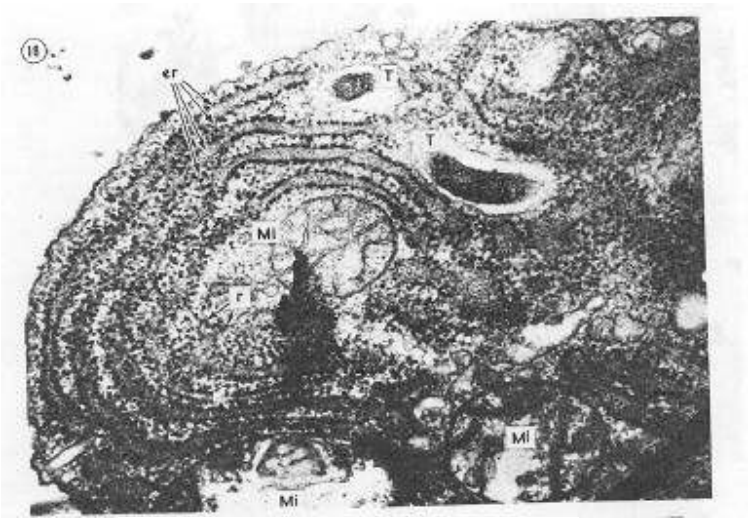


Borrelia burgdorferi associated with the epithelium of the midgut of a tick.
Barbour AG; Hayes SF. 1986.

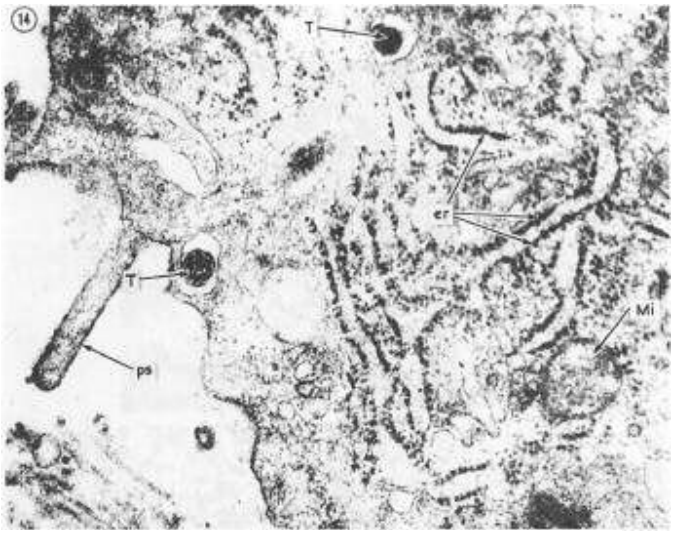
"The spirochetes… bore their way into the cells, and after becoming more or less coiled up, often producing cyst-like forms, segment into a number of "coccoid bodies." These intracellular coccoid bodies multiply by transverse fission, especially in the cells of the Malpighian tubules and the ovary. ... When the crystals escape from the Malpighian tubule the intracellular coccoid bodies may also become free and thus the Malpighian secretion is continually infected… The development of intracellular coccoid forms into normal spirochetes and also into fusiform bacilli has been repeatedly observed in the tick. If an Argus be kept at a temperature of 37°C., after about five days the spirochaetes appear…"
—Hindle E. 1912.

INTRACELLULAR CYSTS AND SPIROCHETES

"The presence of borreliae in macrophages and keratinocytes, as shown in our studies and also in Berger's silver staining studies, supports the hitherto unproven concept that borreliae may survive intracellularly."
—Aberer E; Kersten A; Klade H; Poitschek C; Jurecka W. 1996.

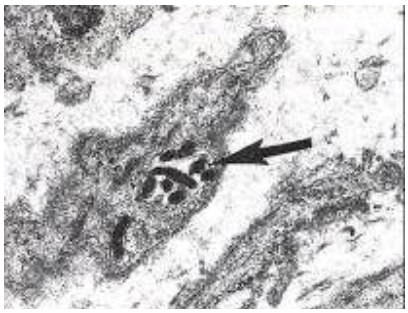


T. pallidum (T) inside plasma cell.
Ovcinnikov NM; Delektorskij VV. 1971.

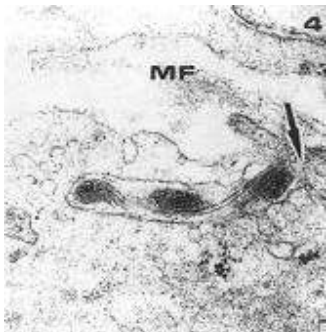


Intact T. pallidum (T) inside a cell, in ultrathin section of material from the site of a chancre.
Ovcinnikov NM; Delektorskij VV. 1971.

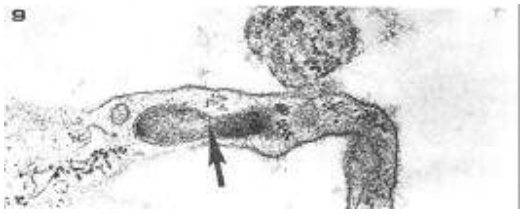
"Human foreskin fibroblasts protected B. burgdorferi from the lethal action of a 2-day exposure to ceftriaxone at 1 microgram/mL, 10-20 x MBC. In the absence of fibroblasts, the organisms did not survive. ...An intracellular site of survival would provide protection, since many of the antibiotics are much less concentrated in the cells than in extracellular spaces. ...Possibly fibroblasts and keratinocytes are the initial sites of this intracellular survival. This is especially relevant in that the first contact between the spirochete and the host in Lyme disease occurs in the skin."
—Georgilis K; Peacocke M; Klempner MS. 1992.



T. pallidum. Intracellular cyst.
Lauderdale V; Goldman JN. 1972.



T. pallidum.
Within a vacuole inside the cell cytoplasm.
Lauderdale V; Goldman JN. 1972.

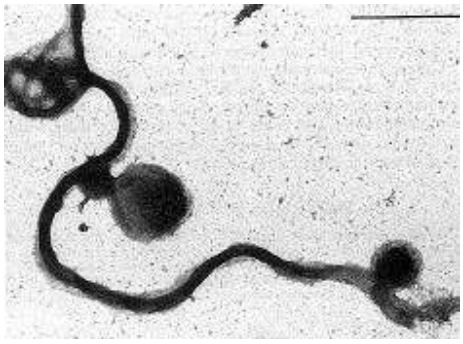


T. pallidum. Inside a fibroblast.
Lauderdale V; Goldman JN. 1972.

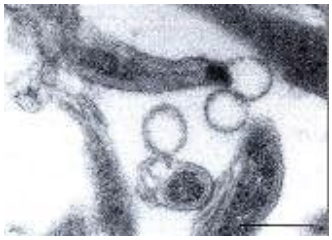
T. pallidum. Inside a Leydig cell.
Lauderdale V; Goldman JN. 1972.

MORPHOLOGICAL CHANGES AFTER CHEMOTHERAPY

"Penicillin treatment, if given late in the disease, of whatever dosage and duration, is unable to destroy all the treponemes which have been present in the organism for a long time. ...Is the persistence of T. pallida after treatment unique to this species? Probably not; and what we call cure, in a clinical sense, probably does not correspond to total bacteriological destruction. ...The condition of bacteriological quiescence is perhaps what we call clinical cure… As the infection ages, less typical organisms are found…"
—Collart P; Borel L; Curel P. 1964.



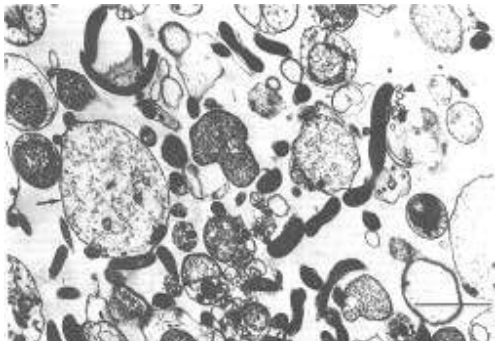
Borrelia burgdorferi granules, after 24 h incubation with ceftriaxone.
Kersten A; Poitschek C; Rauch S; Aberer E. 1995.



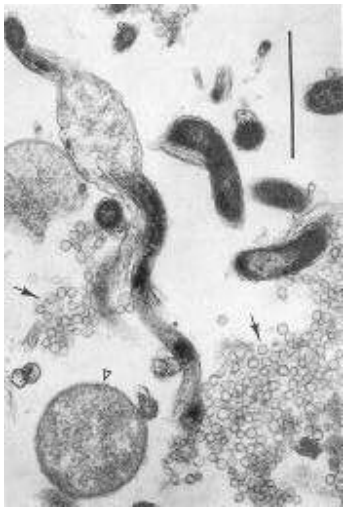
B. burgdorferi. Two blebs at end of a borrelia organism induced by penicillin after 24 h of incubation.
Kersten A; Poitschek C; Rauch S; Aberer E. 1995.

B. burgdorferi, after 2 h of incubation with Mab H6831.
Sadziene A; Jonsson M; Bergstrom S; Bright RK; Kennedy RC; Barbour AG. 1994.

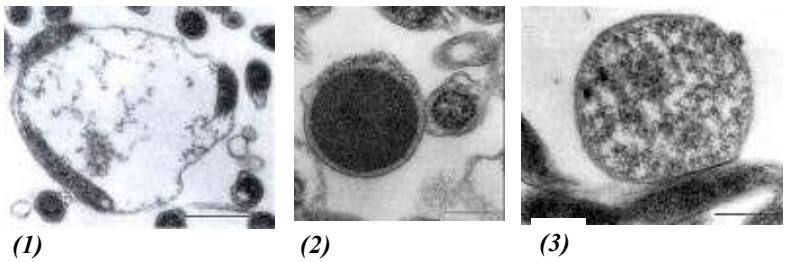
"A prominent electron microscopic finding was the abundance of small membranous blebs or vesicles in the penicillin-treated culture. ...A possible consequence of penicillin-induced membrane vesicle formation is the Jarisch-Herxheimer reaction... A release of numerous blebs containing such material conceivably could precipitate the Jarisch-Herxheimer reaction."
—Barbour AG; Todd WJ; Stoenner HG. 1982.



B. burgdorferi. After treatment with 2 µg vancomycin per ml (twice the MIC) for 24 h.
Kazragis RJ; Dever LL; Jorgensen JH; Barbour AG. 1993.



B. hermsii after penicillin exposure. Ovoid and spherical structures, blebs.
Barbour AG; Todd WJ; et al. 1982.

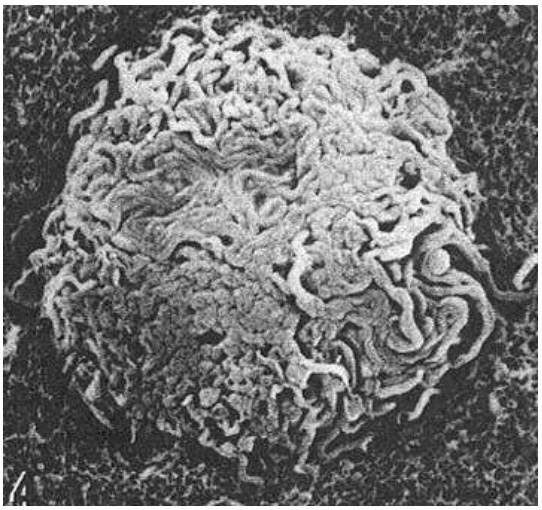


(1) ***(2)*** ***(3)***

B. burgdorferi cystic structures formed after exposure to antibiotics.
(1) After 24 h exposure to ceftriaxone—formation of vesicles.
(2) After 96 h exposure to doxycycline—developing spherical body.
(3) After 24 h exposure to penicillin—vesicle adhering to outer surface of spirochete.
Kersten A; Poitschek C; Rauch S; Aberer D. 1995.

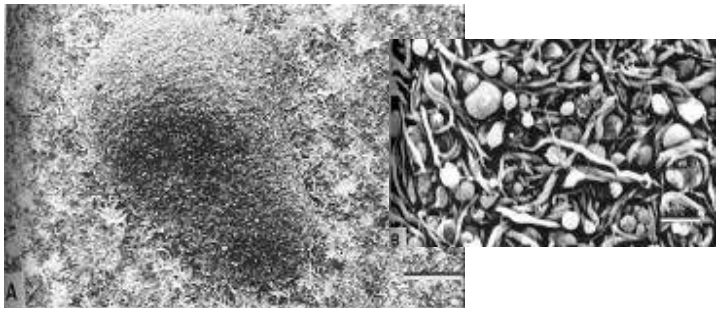
COLONY FORMATION/REPRODUCTION

"Morphologically these ball-like masses are round or oval accumulations, made up of spirochetes closely packed together. ...I believe such conglomerations represent centers of spirochetal reproduction... [They] are seen only in recent stages of active syphilis... They are never found in chronic syphilis... From these centers a diffuse penetration of spirochetes into the neighboring tissue takes place."
—Steiner G. 1940.



Human oral treponeme colony.
Umemoto T; Namikawa I; Yamamoto M. 1984.

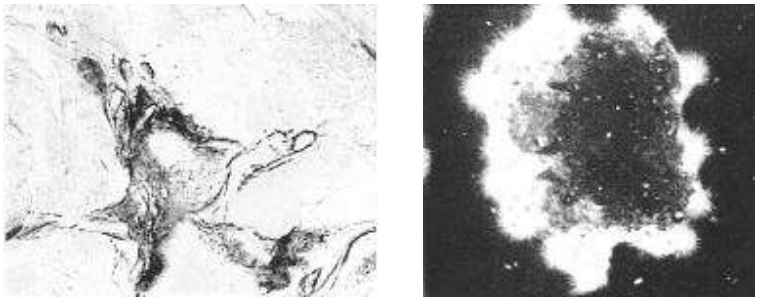
Borrelia duttoni.
Steiner G. 1940.



Borrelia burgdorferi colony.
Left: high-level view. Right: detail view, with cystic structures evident.
Kurtti TJ; Munderloh UG; Johnson RC; Ahlstrand GG. 1987.

"The morphological forms of borreliae seen in biopsies were correlated with clinical findings. Seropositive patients showed clumped and agglutinated borreliae in tissue, whereas seronegative patients exhibited borreliae colony formation...

Borrelia may escape immune surveillance by colony formation and masking within collagen, resulting in seronegativity."
—Aberer E; Kersten A. et al. 1996.

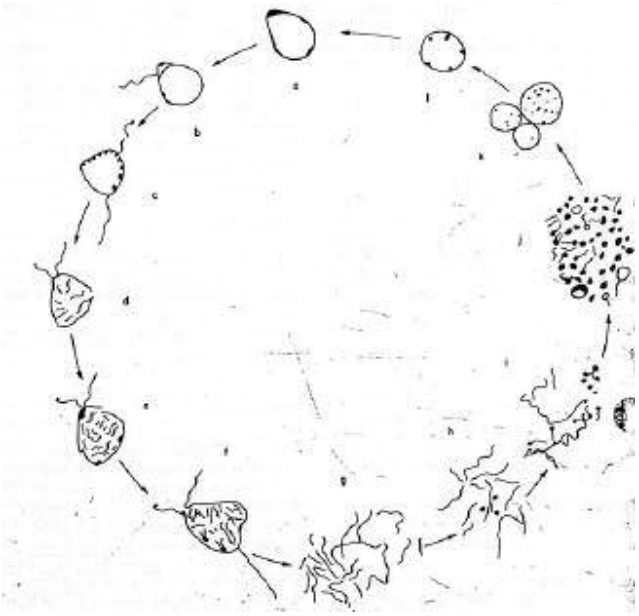


(Left) In vivo B. burgdorferi "colony" — in the collagen of an erythema chronicum migrans biopsy.
(Right) B. burgdorferi colony formed in BSK-medium after exposure to adverse conditions.
Aberer E; Kersten A. et al. 1996.

ATTEMPTS AT LIFE CYCLE INTERPRETATIONS OF VARIANT FORMS

"So firm has been the belief in the spirochaeta pallida, that that organism is taken for granted as being the sole agent of everything syphilitic. Now let us, for a moment, ask ourselves two questions: 1. Why is the incubation period of syphilis so long? 2. Why do not one or two injections of salvarsan cure every case? If syphilis is conveyed by the passage of spirochaetae from one person to another, ought not the initial lesion to begin to show itself two or three days after intercourse, as is more or less the rule with bacterial infections--viz., ulcus molle, gonorrhoea, diphtheria, &c.?

The diseases which have a long incubation period are nearly all due to protozoa; the incubation period is long because the infective organism has to go through a cycle of changes before it can give rise to symptoms. Since the spirochaeta is a protozoon--as assumption which one may safely make, owing to its rapid destruction under salvarsan--is it not possible that it is only one of the phases in the life cycle of the syphilitic parasite?

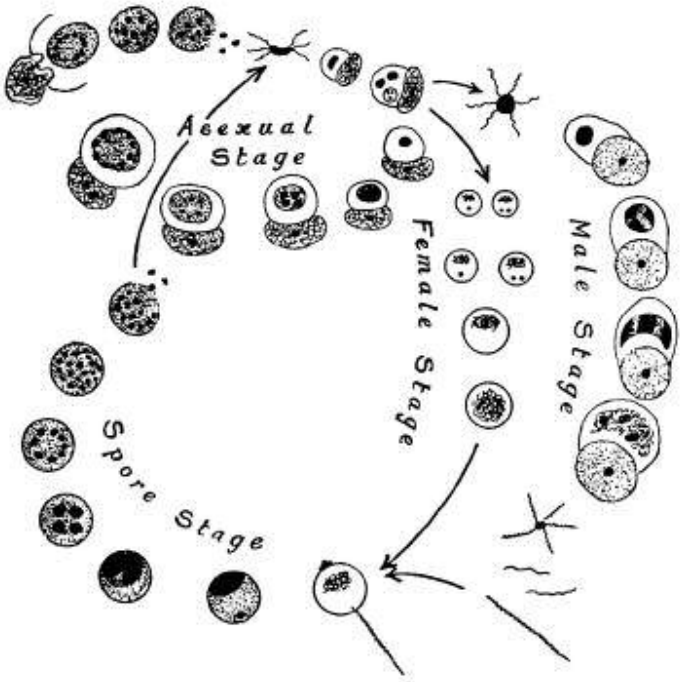


The Reiter treponeme: a proposed life cycle.
Al-Qudah AA; Mostratos A; Quesnel LB. 1983.

The action salvarsan has on spirochaetae in general is phenomenal. No spirochaetae are found in films made from the blood or discharge from a chancre after 48 hours following a single injection. ...In spite of this recurrences occur again and again. ...

Another little point! All are agreed that it is fearfully difficult -- is it possible at all? – to find the spirochaeta pallida in a gumma. In the tertiary stage of syphilis, then, the number of spirochaetae must be considerably less than in the secondary; but which stage of the disease is the harder to cure?"
—McDonagh JER. 1912.

"In most specimens the female gametocytes and zygotes are to be found in greatest abundance; it seems that neither salvarsan nor mercury has any influence upon them..."
—McDonagh JER. 1913.



T. pallidum.
McDonagh JER. 1913.

LIFE CYCLE INTERPRETATIONS (cont'd)

Development inside a tick

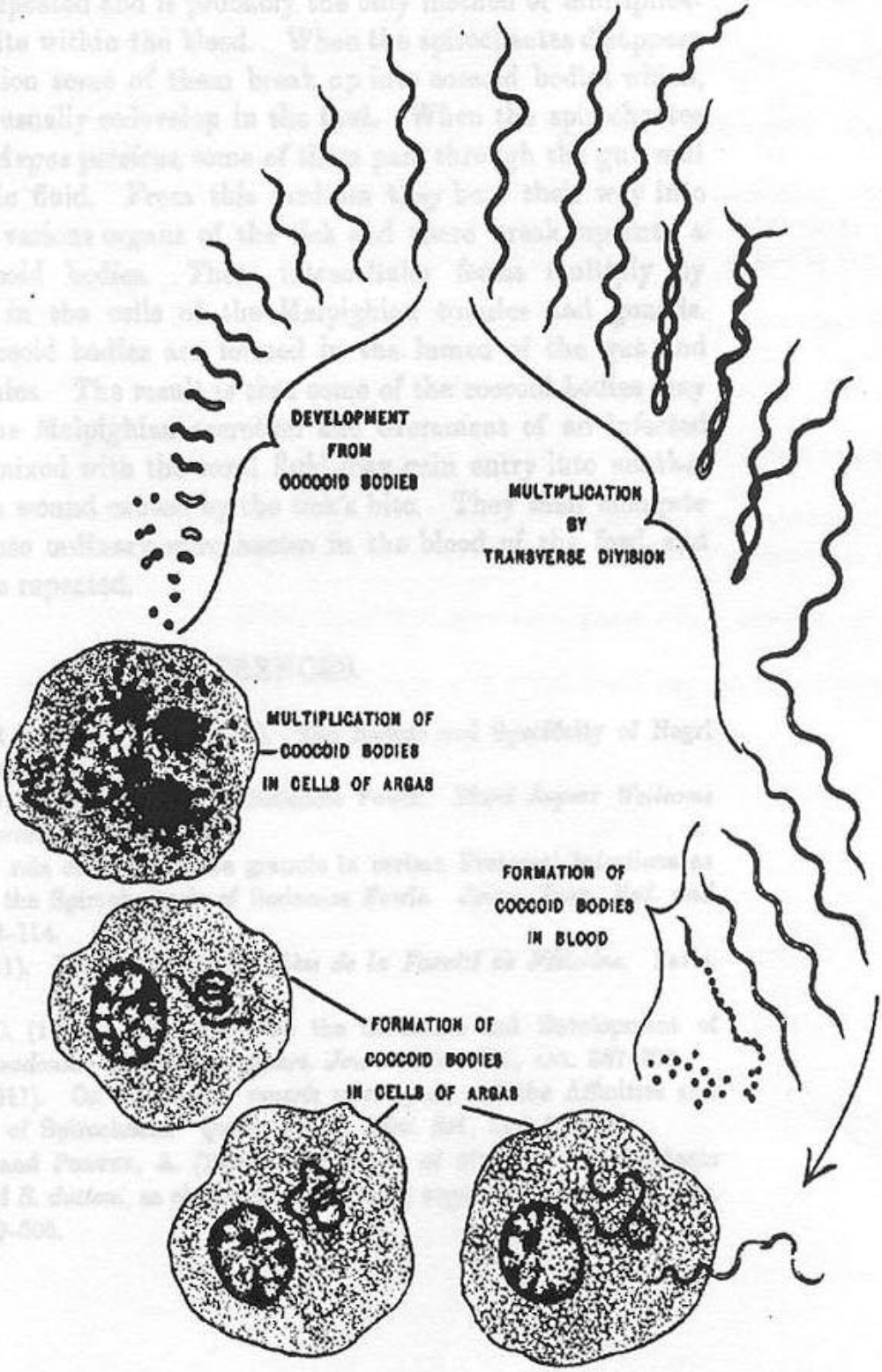


Diagram *A*. The life-cycle of *Spirochaeta gallinarum* (diagrammatic).

Hindle E. 1912.

"After swimming about for some time in this form, the spirochaete appears to rupture at one end and the coccoid bodies escape into the surrounding medium, leaving an empty sheath behind them. In some cases the whole cell-wall seems to disintegrate before the coccoid bodies escape, but the final result is the same, viz. the liberation of a varying number of minute round or ovoid bodies. ...although in some respects they resemble the spores of bacteria--especially the Disporea--in their formation, yet the fact that they stain deeply and also multiply... at once differentiates them from true spores. ...

In order to develop into spirochaetes it is necessary for them to escape from the cell into a fluid medium..."

—Hindle E. 1912.

REFERENCES

1. Aberer E; Kersten A; Klade H; Poitschek C; Jurecka W.
Heterogeneity of Borrelia burgdorferi in the skin.
American Journal of Dermatopathology, 18(6):571-9. 1996.

2. Alban PS; Johnson PW; Nelson DR.
Serum-starvation-induced changes in protein synthesis and morphology of Borrelia burgdorferi.
Microbiology, Jan;146 (Pt 1):119-27. 2000.

3. Alban PS; Nelson DR.
Serum starvation-induced cyst formation in Borrelia burgdorferi under defined conditions.
Presented at the 1999 International Conference on Lyme disease in Munich, Germany.

4. Al-Qudah AA; Mostratos A; Quesnel LB.
A proposed life cycle for the Reiter treponeme.
Journal of Applied Bacteriology, 55:417-428. 1983.

5. Balfour A.
The infective granule in certain protozoal infections, as illustrated by the spirochaetosis of Sudanese fowl.
British Medical Journal, 1:752. 1911.

6. Barbour AG; Hayes SF.
Biology of Borrelia species.
Microbiol Rev, 50:381-400. 1986.

7. Barbour AG; Todd WJ; Stoenner HG.
Action of penicillin on Borrelia hermsii.
Antimicrobial Agents & Chemotherapy, 21:823-9. 1982.

8. Beermann C; Wunderli-Allenspach H; Groscurth P; Filgueira L.
Lipoproteins from Borrelia burgdorferi applied in liposomes and presented by dendritic cells induce CD8(+) T-lymphocytes in vitro.
Cell Immunology, May 1;201(2):124-131. 2000.

9. Benach JL; Coleman JL.
Overview of spirochetal infections.
In "Lyme Disease," ed. P. Coyle, M.D. St. Louis; Mosby-Year Book, Inc. 1993.

10. Bladen HA; Hampp EG.
Ultrastructure of Treponema microdentium and Borrelia vincentii.
Journal of Bacteriology, 87:1180-1191. 1964.

11. Brorson O; Brorson SH; Henriksen TH; Skogen PR; Schoyen R.
Association between multiple sclerosis and cystic structures in cerebrospinal fluid.
Infection,29(6):315-319. 2001.

12. Brorson O; Brorson S.
An in vitro study of the susceptibility of mobile and cystic forms of Borrelia burgdorferi to metronidazole.
APMIS, 107(6):566-576. 1999.

13. Brorson O; Brorson S.
A rapid method for generating cystic forms of Borrelia burgdorferi, and their reversal to mobile spirochetes.
APMIS, 106(12):1131-1141. 1998.

14. Brorson O; Brorson S.
In vitro conversion of Borrelia burgdorferi to cystic forms in spinal fluid, and transformation to mobile spirochetes by incubation in BSK-H medium.
Infection, 26(3):144-50. 1998.

15. Brorson O; Brorson SH.
Transformation of cystic forms of Borrelia burgdorferi to normal mobile spirochetes.
Infection, 25:240-6. 1997.

16. Burgdorfer W. *[Discoverer of Borrelia burgdorferi]*
Keynote Address - The Complexity of Vector-borne Spirochetes.
12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders.
New York City, April 9-10, 1999.
Full text available online at: www.medscape.com/medscape/cno/1999/lyme/Story.cfm? story_id=534.

17. Campbell RE; Rosahn PD.
The morphology and staining characteristics of Treponema pallidum. Review of the literature and description of a new technique for staining the organisms in tissues.
Yale Journal of Biology and Medicine, 22:527-543. 1950.

18. Collart P; Borel L; Durel P.
Significance of spiral organisms found after treatment in late human and experimental syphilis.
British Journal of Venereal Diseases, 40:81-89. 1964.

19. Coutts WE; Coutts WR.
Treponema pallidum buds, granules and cysts as found in human syphilitic chancres and seen in fixed unstained smears under darkground illumination.
American Journal of Syphilis, 37:29-36. 1953.

20. Czekalowki JW; Eaves G.
Formation of granular structures by Leptospirae as revealed by the electron microscope.
Journal of Bacteriology, 67:619-627. 1954.

21. Delamater ED; Haanes M; Wiggall RH; Pillsbury DM.
Studies on the life cycle of spirochetes. VIII. Summary and comparison of observations on various organisms.
J Invest Dermatol, 16:231-256. 1951.

22. Delamater ED; Newcomer VD; Haanes M; Wiggall RH.
Studies on the life cycles of spirochaetes: I. The use of phase contrast microscopy.
American Journal of Syphilis, 34:122-125. 1950.

23. Dutton JS; Todd JL.
A note on the morphology of Spirochaeta Duttoni.
Lancet, 2:1523. 1907.

24. Ewing J.
Note on involution forms of Spirochaete pallida in gummata.
Proceedings of the New York Path. Soc., n.s. 7:166-171. 1907-8.

25. Fantham HB; Cantab MA.
Spirochaetes and their granule phase.
British Medical Journal, 1:409-411. 1916.

26. Filgueira L; Beermann C; Groscurth P.
Liposome-like vesicles from Borrelia burgdorferi modulate the function of human dendritic cells.
J Invest Dermatol, 114(1):23. 2000.

27. Gebbers JO; Marder HP.
Unusual in vitro formation of cyst-like structures associated with human intestinal spirochaetosis.
Eur J Clin Microbiol Infect Dis, 8:302-306. 1989.

28. Gruntar I; Malovrh T; Murgia R; Cinco M.
Conversion of Borrelia garinii cystic forms to motile spirochetes in vivo.
APMIS, 109(5):383-8. 2001.

29. Hampp EG; Scott D; Wyckoff RWG.
Morphologic characteristics of certain cultured strains of oral spirochetes and Treponema pallidum as revealed by the electron microscope.
Journal of Bacteriology, 56:755-769. 1948.

30. Hampp EG; Scott D; Wyckoff RWG.
Morphologic characteristics of certain cultured strains of oral spirochetes and Treponema pallidum as revealed by the electron microscope.
Journal of Bacteriology, 56:755-769. 1948.

31. Hassin GB; Diamond IB.
Silver cells and spirochete-like formations in MS and other diseases of the central nervous system.
Archives of Neurology & Psychiatry, 41:471-483. 1939.

32. Hayes SF; Burgdorfer W.
Ultrastructure of Borrelia burgdorferi.
In "Aspects of Lyme borreliosis," ed. K. Weber, W. Burgdorfer. Berlin; Springer-Verlag. 1993.

33. Hindle E.
On the life-cycle of spirochaeta gallinarum.
Parasitology, Vol IV, pp. 463-477. 1912.

34. Hulinska D; Bartak P; Hercogova J; Hancil J; Basta J; Schramlova J.
Electron microscopy of Langerhans cells and Borrelia burgdorferi in Lyme disease patients.
Zbl Bakt, 280:348-349. 1994.

35. Kazragis RJ; Dever LL; Jorgensen JH; Barbour AG.
In vivo activities of ceftriaxone and vancomycin against Borrelia spp. in the mouse brain and other sites.
Antimicrobial Agents & Chemotherapy, Nov;40(11):2632-6. 1996.

36. Kersten A; Poitschek C; Rauch S; Aberer E.
Effects of penicillin, ceftriaxone, and doxycycline on the morphology of Borrelia burgdorferi.
Antimicrobial Agents & Chemotherapy, 39(5):1127-33. 1995.

37. Klieneberger-Nobel E.
The filterable forms of bacteria.
Bacteriol Rev, 15:77-103. 1951.

38. Kon Y.
Über die Silberreaktion der Zellen.
Jena, Gustav Fischer. 1933.

39. Kurtti TJ; Munderloh UG; Johnson RC; Ahlstrand GG.
Colony formation and morphology in Borrelia burgdorferi.
Journal of Clinical Microbiology, 25:2054-2058. 1987.

40. Lauderdale V; Goldman JN.
Serial ultrathin sectioning demonstrating the intracellularity of T. pallidum.
British Journal of Venereal Diseases, 48:87. 1972.

41. Leishman WB.
The Horace Dobell lecture on an experimental investigation of Spirochaeta duttoni, the parasite of tick fever.
Lancet, 2:1237-1244. 1920.

42. Leishman WB.
A note on the "granule clumps" found in Ornithodorus moubata and their relation to the spirochaetes of African relapsing fever (tick fever).
Annales de l'Institut Pasteur, 32:49-59. 1918.

43. Lennhoff C.
Spirochaetes in aetiologically obscure diseases.
Acta Dermato-Venereologica, Vol 28 Fasc 3:295-324. 1948.

44. Listgarten MA; Loesche WJ; Socransky SS.
Morphology of Treponema microdentium as revealed by electron microscopy of ultrathin sections.
Journal of Bacteriology, 85:932-939. 1963.

45. MacDonald AB.
Concurrent neocortical borreliosis and Alzheimer's disease: Demonstration of a spirochetal cyst form.
Annals of the New York Academy of Sciences, 539:468-470. 1988.

46. Mattman LH.
Cell wall deficient forms: stealth pathogens.
CRC Press, Inc., Boca Raton, Fla., 2nd ed. 1993.

47. McDonagh JER.
The life cycle of the organism of syphilis.
Lancet, 2:1011. 1912.

48. McDonagh JER.
The complete life history of the organism of syphilis.
British Medical Journal of Dermatology & Syphilis, 25:1-14. 1913.

49. McDonagh JER.
The nature of disease.
Heinemann, London. 1924.

50. Meirowsky E. (Abstract by Dr. H. C. Semon)
On the biological position of the Spirochaeta pallida and its development.
British Journal of Dermatology, 26:185. 1914.

51. Mudd S; Polevitsky K; Anderson TF.
Bacterial morphology as shown by the electron microscope; V. Treponema pallidum, Treponema macrodentium and Treponema microdentium.
Journal of Bacteriology, 46:15-24. 1943.

52. Mursic VP; Wanner G; Reinhardt S; Wilske B; Busch U; Marget W.
Formation and cultivation of Borrelia burgdorferi spheroplast L-form variants.
Infection, 24(3):218-26. 1996.

53. Noguchi H.
A method for the pure cultivation of pathogenic Treponema pallidum.
Journal of Experimental Medicine, XIV:99-112. 1911.

54. Ovcinnikov NM; Delectorsku VV.
Current concepts of the morphology and biology of Treponema pallidum based on electron microscopy.
British Journal of Venereal Diseases, 47:315-328. 1971.

55. Ovcinnikov NM; Delectorsku VV.
Further studies of the morphology of Treponema pallidum under the electron microscope.
British Journal of Venereal Diseases, Jun;45(2):87-116. 1969.

56. Ovcinnikov NM; Delectorsku VV.
Further study of ultrathin sections of Treponema pallidum under the electron microscope.
British Journal of Venereal Diseases, 44:1-34. 1968.

57. Ovcinnikov NM; Delectorsku VV.
Morphology of Treponema pallidum.
British Journal of Venereal Diseases, 35:223-229. 1966.

58. Ritchie AE.
Morphology of leptospires.
The Biology of Parasitic Spirochetes, Johnson RC, ed. NY Academy Press, pp. 19-37. 1976.

59. Sadziene A; Jonsson M; Bergstrom S; Bright RK; Kennedy RC; Barbour AG.
A bactericidal antibody to Borrelia burgdorferi is directed against a variable region of the OspB protein.
Infection & Immunity, 62(5):2037-2045. 1994.

60. Schaller M; Neubert U.
Ultrastructure of Borrelia burgdorferi after exposure to benzylpenicillin.
Infection, 22(6):401-406. 1994.

61. Smith JL; Israel CW.
The presence of spirochetes in late seronegative syphilis.
JAMA, 199(13):980-984. 1967.

62. Smith JL; Israel CW.
Spirochetes in the aqueous humor in seronegative ocular syphilis. Persistence after penicillin therapy.
Archives of Ophthalmology, 44:474-477, April. 1967.

63. Steiner G.
Morphology of spirochaeta myelophthora in multiple sclerosis.
Journal of Neuropathology, 13:221-29. 1954.

64. Steiner G.
Acute plaques in multiple sclerosis, their pathogenic significance and the role of spirochaetes as etiological factor.
Journal of Neuropathology, 11:343-72. 1952.

65. Steiner G.
Morphologic appearances of spirochetal reproduction in tissues.
Archives of Pathology: 189-199. 1940.

66. Steiner G.
Krankheitserreger und Gewebsbefund bei multipler Sklerose: Vergleichend-histologisch-parasitologische Untersuchungen bei multipler Sklerose und anderen Spirochatosen.
Ergebn. d. Hyg., Bakt., Immunitatsforsch. u. exper. Therap., 12:269-464. 1931.

67. Umemoto T; Namikawa I; Yoshii Z; Konishi H.
An internal view of the spherical body of Treponema macrodentium as revealed by scanning electron microscopy.
Microbiology & Immunology, 26(3):191-198. 1982.

68. Umemoto T; Namikawa, I; Yamamoto M.
Colonial morphology of treponemes observed by electron microscopy.
Microbiology & Immunology, 28:11-22. 1984.

69. Umemoto T; Namikawa I.
Electron microscopy of the spherical bodies of oral spirochetes in vitro.
Microbiology & Immunology, 24:321-334. 1980.

70. Warthin AS; Olsen RE.
The apparent sequence of spirochetes and granular forms in syphilitic buboes.
American Journal of Syphilis, 15:145. 1931.

71. Warthin AS; Olson RE.
The granular transformation of Spirochaeta pallida in aortic focal lesions.
American Journal of Syphilis, 14:433-437. 1930.

72. Wile UJ; Picard RG; Kearny EB.
The morphology of spirochaeta pallida in the electron microscope.
JAMA, 199:880-881. 1942.

73. Wolf V; Wecke J.
Formation of multiple treponemes.
Zbl Bakt, 280:297-303. 1994.