Lyme borreliosis

- a historic review and perspective -

or

The pre-Lyme history of Lyme borreliosis in Europe: important observations, knowledge and thoughts about an etiologic factor ……..

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The puzzle of Borreliosis, AKA Lyme disease

TICK EM LABC ACA

Spirochete Granule Cyst L-form

Borrelia burgdorferi sensu lato

Multi-system symptoms

Positive effect of antibiotic treatment

Relapse after antibiotic treatment

Antiquity of *Borrelia burgdorferi*
DNA in saved ticks and skin of mice

1884 Europe:

Lancet 1995 Nov 18; 346(8986): 1367. Antiquity of the Lyme-disease spirochaete in Europe [letter]. Matuschka et al.
In **1884-88** Ixodes ticks attached to a fox are collected and preserved in Austria. Two of them are later found to be infected with B. burgdorferi.

1894 USA:

J Infect Dis 1994 Oct; 170(4): 1027-32. Detection of Borrelia burgdorferi DNA in museum specimens of Peromyscus leucopus. Marshall et al.
In **1894** a researcher from a Massachusetts museum collects and preserves white-footed mice. DNA from B. burgdorferi (ospA) was later detected in ear skin samples from 2 mice from Dennis, Massachusetts.

EM
tick saliva contain a thermolabile inflammatory agent

1936 Dermatol Wochenschr 1936;102:125-131. [Zur Ätiologie des Erythema chronicum migrans] **Askani** presents two cases of EM. He review the literature on tick studies, lots of references.
From observations made on inoculation of tick-saliva, it seems that tick saliva contain a thermolabile inflammatory agent (toxin?).
He also mentions several - already at that time - known tick-transmitted infections:

1. **Spirillose** des Menschen = **Febris recurrens** (*S. duttoni*) - *Ornithodorus moubata*
2. Europäische **rekurrens** (*S. Obermeieri*) - *Ornithodorus moubata*
3. **Spirillose** der Rinder und Pferde - *Boophilus decoloratus*
4. **Spirillose** der Gänse und Hühner - *Argas miniatus*
5. Texasfieber (vielleicht identisch mit 3) - *Boophilus annulatus*
6. Texasfieber mit Blutharn (hemoglobinuria) - *Boophilus annulatus* und *Boophilus decoloratus*
7. Hämoglobinurie der Rinder (6 und 7 sind zwei verschiedene Piroplasmosen) - *Ixodes ricinus*
8. Ostafrikanisches Küstenfieber - Nur das Rind und nur durch *Ixodes* infizierbar
9. Südeuropäische Piroplasmose (Schaf in Rumänien) - *Rhipicephalus bursa*
10. Hydrämie in Italien (maligne Gelbsucht der Hunde) - *Ixodes ricinus*
11. Exanthematische Zechenfieber der Menschen in Südfrankreich (Regendanz) - *Rhipicephalus sanguineus*

Acrodermatitis Chronica Atrophicans (ACA)

1883 Arch Dermatol Syph 1883; 10:553-556. [Ein Fall von diffuser **idiopatischer Haut-Atrophie**].

Buchwald describes the atrohic stage of ACA (apparently the first description ever?)

1902 Arch Dermatol Syph 1902; 61:57-76 + 255-300. [Über acrodermatitis chronica atrophicans].

On the basis of 12 of their own and 14 other cases published by others, including a thorough review of literature and evaluation of the histologic changes in different stages, **Herxheimer and Hartmann** proposes a new name ”**Acrodermatitis Chronica Atrophicans**” (ACA) for a skin condition that is characterized by:

- it usually starts peripherally on the extremities (acro-)
- it starts with an inflammatory stage (dermatitis)
- it has a year-long course (chronica)
- the atrophic end-stage look like ”zerknittertes Cigarettenpapier” (atrophicans)
- other important observations noted by these authors was:
  A prominent blue-red discolouring is another hallmark.
  Not an inherited condition. **No obvious etiology found, although the authors mention that from the disease progression, it could be an infection, they could not find any evidence of this on microscopy. No beneficial effect of any known therapy incl. Arsenicals.**
  All stages of the disease may be represented in the same patient in diffferent skin areas. There may be dysestesia (burning or cold), but it is rarely accompagnied by other symptoms, and only a few patients displayed possible systemic manifestations.
  No previous Erythema migrans, and no previous tickbites or insect-stings noted.

ACA expanded:
tumorlike infiltrations and joint symptoms

1910 Arch Dermatol Syph 1910; 105:145-168. [Über strangförmige Neubildungen bei acrodermatitis chronica atrophicans]. **Herxheimer and Schmidt** expands the description of ACA to include tumor-like string-formed mononuclear infiltrations with some fibrosis in 2 ACA cases and doing an extensive review of the literature, comparing the histologic changes described withn their own findings:

"In der Kutis findet wir ein äusserst dichtes Infiltrat, dessen Elemente teils in dichten Nestern, teils regellos angeordnet sind. Das Infiltrat besteht aus mononukleären, kleineren und grösseren Lymphocyten, ferner aus Spindelzellen, Mastzellen und äusserst spärlichen Plasmazellen. Die Kerne der Lymphozyten sind vorwiegend rund, an verschiedenen Stellen etwas ausgezogen, birnförmig." …. "Mitosen konnten vereinzelt beobachtet werden." …

1921 Arch Dermatol Syph 1921; 134:478-487. [Zur Kenntnis der acrodermatitis chronica atrophicans]. **Jessner** reports a case story where the disease began with a pain in her left elbow, so painful that it made her unable to work, about half a year before typical ACA infiltrations in the same arm developed. This is apparently the first noted clear association of arthritis/arthralgia with ACA - although a patient described by Herxheimer et al in 1902 (case XI) was descibed to have pain in her feet before ACA, it is not clear whether the pain was located in the joints ?:

"Vor 2 Jahren zeigte sich die Hautaffection am rechten Arm. Schon vor Ausbruch der Hautkrankheit habe sie haüfig Schmerzen in den Füssen nach dem Gehen empfunden, auch seien diesselben haüfig angeschwollen gewesen."

ACA expanded:
sensory disturbances, lymphocytomas, heart problems

1924 Dermatol Wochenschr 1924;79:1169-1177. [Bericht über 66 Fälle von Acrodermatitis chronica atrophicans]. **Jessner and Loewenstamm** (p. 1174) describe arthritis and sensory disturbances:

Arthritische Veränderungen

"Wenngleich arthritische Veränderungen im Sinne der Arthritis deformans bei älteren Menschen nicht gerade selten sind, möchten wir doch hervorheben, dass wir sie bei unseren Pat. zu häufig gefunden haben, als der Akroderm. gelegen waren 1). …. Wir sahen sie bei 9 Pat. von denen 2 erst 37 Jahre alt waren. Es handelte sich um mehr oder weniger hochgradige Verdickungen, höcherige Konfiguation der betreffenden Gelenke; in 2 Fällen waren diese bereits unbeweglich. Bei Akroderm. beider Unterarme bestand bei einer Frau eine Arthritis deformans der rechten Schulter und des linken Handgelenks, bei einer anderen nur des linken schultergelenks. Nur in einem der Fälle war der Unterschenkel, dessen Zehenphalangen stark deformiert waren, sklerodermatisch verändert."

Beschwerden und Sensibilitätsstörungen

"Von Beschwerden, die bei der Akroderm. beobachtet wurden, seien erwähnt: Juchen, Raubheits- Kälte, Hitze- und Schwächegefühl, Brennen, Stechen, "dumpfe" Schmerzen. Von unseren Patienten klagten 22 [1/3] über derartige oder ähnliche, mehr oder weniger lästige Sensationen. Dagegen konnten wir Störungen der Sensibilität nur 3mal nachweisen."

1929 Dermatol Wochenschr 1929;88:293-301. [Über miliare lymphocytome der Haut]. **Mulzer and Keining** describe a case with ACA development over 20 years, later she develop multiple small lymphocytomas without follicles. The patient also had heart problems, short breath on exercise, dizziness and rheumatic problems that had increased over the last years.

ACA expanded:
preceded by rash (EM ?), compare histology with lues …

1925 Arch Dermatol Syph 1925;149:142-175. [Über Dermatitis atrophicans und ihre pseudo-sklerodermatischen Formen] **Ehrmann and Falkstein** describe more stories and microscopical changes in several cases of ACA. A very illustrative case is descibed, who was seen several times between 1903-1924, during which time the development of all the typical ACA skin changes in different areas of the skin: Most remarkable is the following first remark given on that patient: 7. A.L. …. "Vor 22 Jahren zuerst ein roter Fleck [EM?] am rechten Unterschenkel mit Jucken, 1 Jahr später Schmerzen im linken Oberschenkel, nach weiterem Jahr Anscwellung und Rötung beider Unterschenkel mit Jucken. Abwechselnd Besserung und erneute Schwellung."

The authors argue for the disease process being an Infektion showing microscopic similarities with lues (syphilis):

Es ist unwahrscheinlich, dass ein Toxin -… - in der Blutbahn kreist und als gelöste Substanz gerade nur an bestimmten Stellen in schädigender und - ... - in fortlaufend schädigender Menge und Konzentration durch Jahre und Jahrzehnte hindurch abgelagert werde und Infiltrate mache, die die elastischen Fasern auslösche." ….. "Es bliebe nun unter der Annahme, dass es sich um ein lebendes Virus handelt, übrig, die Wege zu beschreiben, die uns durch die histologischen Befunde gewisen werden. Bei den oberflächlichen Formen, die sich an die primären Herde anschliessen, fanden wir wie andere Autoren die Lymphbahnen erweitert, einseitig oder zirkulär von aus dem die Lymphbanen umgebenden Blutcapillaren stammenden Infiltrat umgeben und hie un da sogar von Lymphocyten erfüllt. **Es ist ein Verhältnis von Gewebe und Infiltrat, das lebhaft an primäre Lues erinnert**, an Bilder aus der Umgebung der Initialsklerose; nur ist das Infiltrat nicht immer so dicht wie bei der Lues, aber hier wie dort durch die grosse Menge der Plasmazellen ausgezeichnet. Man muss sich mithin vorstellen, dass der supponierte Erreger durch die Bindegewebsspalten in das Lymphgefässsystem gelangt und von dort aus auf die in den umgebenden Blutcapillaren befindlich Lymphocyten chemotaktisch einwirkt und sie und die unter dem Einfluss der Erreger gebildeten Plasmazellen zur Auswanderung ins Gewebe bringt. Ähnlich, wie bei der Lues, folgt das Infiltrat auch den perivenösen Lymphräumen." …

"Mithin haben wir folgende Wege des Virus histologish nachgewiesen:

1. Fortschreiten längs des oberflächlichen Gefässnetzes in der papillaren und subpapillaren Schicht.
2. Auf dem Wege des tiefen Lymphgefässnetzes zwischen den Balken der Cutis propria bei den sklerosierenden Formen, auch perivenös.
3. Die perivenösen Lymphräume und Lymphgefässe der tiefen Cutisschicht und der oberen Subcutis bei den strangförmigen Formen.
4. Fortschreiten sowohl in den tiefen, als in den oberflächlichen Schichten, bald mit gleicher Geschwindigkeit, bald ungleich schnell oder auch Festgehaltensein des Virus längs eines venösen Gefässes and gewissen Punkten (Fibrombildung).
5. Die Blutbahn. Somit steht nichts mehr im Wege, um das Krankeitsbild der Dermatitis atrophicans als meist lokale, fortschreitende Infektion mit gelegentlicher Dissemination, wie sie bei allen lokalen Infektionen vorkommt, aufzufassen.

ACA treatment
penicillin works

1946 Nord Med 1946;32:2783. [Penicillinbehandling vid dermatitis atrophicans Herxheimer] **Nanna Svarts** describes very positive effect of penicillin on 2 patients with ACA and elevated ESR, the reason for trying antibiotic treatment, plus in a pt. with uncharacteristic chronic dermatitis.

Translation from Swedish of the authors last remarks:

"The effect of penicillin in these cases of chronic dermatitis of several years duration [5-6 y] is remarkable. The explanation for the good effect must be that an ongoing infection is cause of the dermatitis. This relationship is of great theoretic as well as practical importance"

1949 Acta Derm Venereol Suppl (Stockh) 1949;29:572-621. The penicillin treatment of acrodermatitis chronica atrophicans (Herxheimer). **Thyresson** reports on good effect of penicillin treatment for 10-14 days of 57 patients with ACA; 10 cases had a duration over 20 years; 3 patients were WR positive. 7 were cured, 28 improved and 5 showed slight improvement, best results were obtained in cases of shorter duration but even cases doomed incrurable i.e. in late atrophy stage improved; two cases became symptomfree despite 10-20 years history; inflammation and nodules disappeared and sensory disturbances and pain improved. Improvement continued over months after treatment, but a few patients were retreated due to recurrence, this resulting in a further marked improvement.

"Hence it would be expedient in certain cases to repeat the penicillin treatment". …. "It has been pointed out in the foregoing that an elevated sedimentation rate is quite common in acrodermatitis atrophicans chronica, and that the sedimentation rate, though falling, in most cases, in connection with penicillin treatment, nevertheless does not usually reach normal values after treatment. This fact possibly implies that penicillin in these cases is not capable of definitively checking the infectious process."

ACA expanded
treatment eliciting Jarisch-Herxheimer reaction, bone marrow inflammation

1951 Hautarzt 1951;2:6-14. [Die Behandlung der Akrodermatits chronica atrophicans Herxheimer mit penicllin]. **Götz & Ludwig** describe 16 cases of ACA treated with penicillin. Nine were retreated, one even 3 times. Authors discuss against an infectious aetiology, argues for that effect of penicillin is due to a sympatholytic activity of penicillin. Case 10 experienced fever during injections:
"Während der Injektionen kommt es zu einem vorübergehenden Temperaturanstieg bis 38.8oC".

1952 Arch Dermatol Syph 1952;195:164-170. [Sternalmarkfunde und ihre Beziehungen zur Blutsenkungsgeschwindigkeit bei acrodermatitis chronica atrophicans]. **Hauser** describes inflammatory changes in the bone marrow of 25 ACA patients.
"Eine mehr oder minder deutliche Vermehrung der plasmacellulären und auch lymphoiden Retikulumzellen, entweder uín einer diffusen Durchsetzung des Markes oder in herdförmiger Anhäufung konnten wir bei 13 von 25 Patienten feststellen. Ein gehäuftes Vorkommen von Mastzellen fiel weiterhin hier und dort in den Markausstrichen bei 8 Kranken auf, zum Teil bis 4 Mastzellen im Blichfeld. Eine mehr oder weniger stark ausgeprägte Eosinophilie des Konocenmarkes war bei 18 von den 25 Untersuchten feststellbar."…
"Dagegen wiesen 3 Kranke mit normaler oder nur gering erhöhter Senkung (von 5,15,17 mm in der ersten Stunde) neber einer geringenEosinophilie oder normaler Eosinophilenzahl keine Vermehrung lymphoider oder plasmazellulärer Retikulumzellen im Knochenmark auf."

1955 Arch Dermatol Syph 1955;199:350-393. [Zur Kenntnis der akrodermatitis chronica atrophicans] **Hauser** discuss the relationship among ACA, EM, and lymphocytomas, chronic inflammatory changes in regional lymph nodes and in the bone marrow, serum-globulin changes that influences the sedimentation reaction. He describes 52 cases (followed with histology), in which he notes the female overweight of about 60-80% (also found in several literature studies) and the typical age-distribution: ACA may being in all ages including children below 10 years old, but it usually begins in the 4-5th decade of life. He also notes that some patients develop bone-deforming arthritis and osteoporosis. He concludes that all these findings must be related and that ACA is a systemic disease. He also suggests a correlation between ACA cases and the distribution of sheep (Ixodes) ticks, i.e. he notes the rural residency of most patients, very few cases arising in cities, and that the world destribution of ACA follows the distribution of the Ixodes tick (maps). He notes the effect of antibiotics (penicillin, aureomycin, streptomycin) clearly points to a systemic infection, with main changes in the skin, yet multiple serologic and histologic studies are unsuccesful in finding the etiologic agent (lots of references).

ACA statistics
- review of 840 cases ...

1955 Arch Klin Exp Dermatol 1959;208:516-527. [Beitrag zur Symptomatologie der akrodermatitis chronica atrophicans (Pick-Herxheimer)]. **Donnerman et Heite** review 840 previously published and own cases of ACA and does statistic calculations on age-distribution, and rates the occurrence of the different changes and localisations of fibroid nodules, dermato-sclerosis, macular atrophy (anetodermie) and ulcerations and they conclude that the co-occurence of dermatosclerosis and ulceration is significant, while fibroid nodules and ulceration does not occur together.
The age-distribution of the erythematous changes follows a bell-formed normal distribution curve with its center about 35 years of age, while the patients with fibrinoid nodules lies 5 years later. The type of changes also depends on the skin localisation, fibroid nodules occor more often on the arms, while dermatosclerosis on the legs.

Erythema (chronicum) migrans
(EM / ECM)

1910 Arch Dermatol Syph 1910; 101:404. **Afzelius A.** Sitzung vom 28. Oktober 1909: ”Afzelius erwähnt ein von Ixodes reduvius wahrscheinlich hervorgerufenes Erythema migrans bei einer älteren Frau (the first case described, seen in 1908)”

1910 Arch Dermatol Syph 1910; 105:423-430. [Erythema annulare, entstanden durch Insektenstiche] **Balban** describes 3 cases of ”erysepeloid Rosenbach” or erythema migrans-like skin changes, which **developed at the site of an insect-sting**, in case one there was visible stingmark, and case 2 & 3 told about the sting. Size of rash up to 14 cm.

1913 Arch Dermato Syph (Berl) 1913; 118: 349-56. [Über eine seltene Erythemform (Erythema Chronicum Migrans)]. **Lipschütz** describes a long-lasting rash that he names erythema chronica migrans. He claims to be the first but was not.

1920 Acta Dermatol Venereol (Stockh) 1920; 1:422-427. **Strandberg** describe ECM plus lymphocytoma (a migrating erythema on the chest**,** probably caused by a tick bite, where **a** blue-red skin tumor also developed in the middle of the erythema at the nipple - alsom mentioned under LABC)

1921 Acta Dermatol Venereol 1921; 2:120-25. Erythema chronicum migrans. **Afzelius** describe the characteristics of ECM:

"Das klinische Bild des Erythema chr. migrans ist sehr characteristisch. Die Krankheit beginnt mit einer (und zwar immer nur ein einziger), ziemlich kleinen plaque von runder Form. Diese verbreitet sich peripherisch, dadurch dass ihre Ränder eineb schmalen, 1/2-2 cm breiten, roten Ring bilden, der sich allmählich erweitert, während das Centrum nach und nach abblasst, und zuletzt eine ganz normale Hautfarbe, zuweilen auch einen schwach cyanotischen Ton annimt. Weder der wandernde rote Ring, noch de verblassende Hautfläche zeigen die geringste Abschuppung oder Exudation; höchstens ist der Ring leicht prominent. Keine oder sehr unbedeutende subjektive Symptome. Je weiter der Ring peripher fortschreitet, umso blasser und weniger deutlich wird er, bis er zuletzt, nach einigen Wochen, oder meistens nach einigen Monaten. Ganz verschwindet. Bei kürzerer Dauer behält er seine runde Form, bei längerer nimmt er eine unregelmässigere Gestalt an, und einzelne Teile des Ringes verschwinden zuweilen vor den anderen. Die Dauer des Erythems wechselt innerhalb weiteren Grenzen, von ein paar Wochen … bis zu einem Jahr und darüber.”

EM expanded:
multiple EMs, meningitis and encephalitis, hallucination

1923 Arch Dermatol Syph 1923;143:365-374. [Weitere Beitrag zur Kenntnis des erythema chronica migrans]. **Lipschütz** describe a case with more than one ECM, the rings floating together (picture). Review the literature and discuss possible etiology:
"Vielleicht handelt es sich um eine spezifische, durch den Stich eines Holzbock (tick) vermittelte Hautinfektion, und in weiteren Untersuchungen wäre daher der mikroskopisch-bakteriologischen Erforschung des Darmkanales bzw. Speichelsekretes des Holzhocks Aufmerksameit zu schenken, nachdem auch bei anderen ungleich wichtigeren Infektions-krankheiten die Bedeutung der durch Insektenstiche vermittelten Keimübertragungen demonstriert worden ist (z. B. Rikettsien bei Fleckfieber usw.)"

1930 Acta Dermatol Venereol (Stockh) 1930;11:315-321. Erythema chronicum migrans Afzelii. **Hellerström** describe a patient with typical ECM (actually two 'melting' together), which later develop chronic lymphocytic meningitis and encephalitis, with periodically relapsing hallucinations and disorientation.
This is apparently the first time psychiatric manifestations of the disease is noted, but it is not the first time that ECM and meningitis occur together.
Hellerstöm obviously had not read Garin and Bujadoux 1922, Paralysie par les ticques, when he wrote: "Nach der Literatur zu urteilen ist eine chronische Meningitis zusammen mit einem Erythema chronicum migrans früher nicht beobachtet worden".

EM expanded
meningo-encephalitis, paresis, radicular pain

1922 J Med Lyon 1922;71:765-767. [Paralysie par les Tiques]. **Garin and Bujadoux** reports a case of an extremely painful meningo-radiculitis that developed 3 weeks after a known tickbite (I. hexagonus) on his left buttock, which was followed by an enlarging rash at the site of bite, accompagnied by irradiating pain in left ichiadicus area and later belt-formed lower thoracic pain and also irradiating pain in the right arm extending down to the elbow. After suffering very much from this painful condition for 2 1/2 month the patient developed paresis of his right deltoid muscle, and the muscle atrophied. Then sign of meningitis developed: positive Kernig and sign of inflammation in cerebro-spinal fluid (meningitis), with incread albumin and 75 WBCs. No microbes were visible in CSF.
Wasserman reation was slightly positive, but the patient had no sign of syphilis. Most remarkable was also the very **positive effect of treatment with novarsenobenzol (arsenic),** that quickly relieved most of the patients pain. The authors note that the Wassermann reaction is sometimes positive in other tick-borne diseases like Rocky Mountain Spotted fever and relapsing fever (!), and discuss a possible etiology being an infective agent and they report some very interesting observations made by HAWDEN, in Columbia.

1941 **Bannwarth** - see next slide - though he did not recognize any previous tickbite nor erythema migrans in his patients, he describes thoroughly what we today recognize as the typical borrelial meningo-radicutitis and has some interesting theories about 'rheumatism / allergy' ….

1947 Nord. Med. 35:1754-?, 1947. Polyradiculitis efter Skovflaatbid. **Dalsgaard-Nielsen & Kierkegaard** describe a woman age 35, who developed - 3 weeks after a tickbite - ECM, and leucocytic meningitis with a benign course, and radicular pain. The meningitis commenced after 11 weeks and was initially accompagnied by a slight rise in temperature.

1948 Acta Dermato Venereologica 1948;28(3): 295-324. Spirochetes in Aetiologically Obscure diseases. **Lennhoff develops a special staining technique for spirochetes** and finds this type of pathogen in several skin diseases including EM, but others (ex. Hård) later have difficulty and is unsuccesful in reproducing his stain and findings.

EM with meningitis
arguments for a spirochetal infection

1950 Southern Medical Journal 1950;43:330-334. Erythema chronicum migrans Afzelius with meningitis. At a meeting in Cincinatti Nov. 14-17, 1949 **Hellerström** discuss the etiology and pathogenesis of erythema chronicum migrans Afzelius with meningitis (own case and review).

”the present writer feels inclined towards interpreting erythema migrans, with or without meningitis, as due to an infective agent (a spirochete?) with allergizing (and immunizing?) behaviour, the organism being transmitted by ticks and, possibly, other insects.”..

”**Concerning the etiology of erythema chronicum migrans the following facts should be pointed out:**

1. The condition follows upon the bite of certain species of *Ixodes* (possibly also *Culex*, occasionally)
2. In one and the same subject, a bite may sometimes cause one or several eruptions, while this or similar effect is not produced on other occasions.
3. Considering the large number of persons exposed to tick bites, erythema migrans is a rare result of the bite.
4. In cases presenting two or more migrating erythemas, there is some doubt as to whether the sites of the separate erythematous circles always strictly correspond to the position of the tick bite or bites.
5. Regional lymphoglandular enlargement has occasionally been noted.
6. Intracutaneus tests with extract prepared from *Ixodes* species afford evidence tending to show that the area enclosed by the actual erythematous circle and its immediate vicinity differ in their allergic behaviour (Hellerström, Dalsgaard-Nielsen and Kirkegaard).
7. In a proportion of instances, the eruption is associated with monocytic or leucocytic meningitis, radiculitis and, occasionally encephalitis with bulbar symptoms (Hellerström, Gelbjerg-Hansen, Dalsgaard-Nielsen, Kirkegaard, et alii)
8. In material taken from the eruption spirochetoid bodies have been demonstrated (C. Lennhoff).
9. As to the eruption, it is further known that injections of ”iodobismitol” or arsphenamine will cause its temporary (few injections) or definite (more injections) subsidence (C. Lennhoff, E. Hollström)
10. Both the eruption and the meningitis will readily yield to penicillin (E. Hollström, Leczinsky), but not to sulfonamides.
11. Both the eruption and the meningitis may subside spontaneusly and are practically without exception mild in character.
12. The following negative results deserve attention: a) negative transmission tests in normal subjects with extracts prepared from the affected skin (Preininger, Hollström); b) failure of cultures with the affected skin and spinal fluid; c) it was not possible to demonstrate antibodies to various bacteria in the serum of patients and the Wassermann test was negative; d) no antibodies such as occur in cases of various virus diseases (eastern and western equine encephalo-myelitis, St. Loius encephalitis, choriomeningitis) could be demonstrated in the blood (Dalsgaard-Nielsen and Kirkegaard); and e) the toxoplasmosis reaction was negative with blood serum (Hellerström).

EM treatment
bismuth, neoarsphenamin, mapharside and penicillin works

1951 Acta Derm Venereol Suppl (Stockh) 1951;31:235-243. Successful treatment of erythema migrans Afzelius. **Hollström**. An account is given of sixteen cases of erythema chronicum migrans Afzelius treated with bismuth, neoarsphenamine, mapharside, and penicillin, either separate or in various combinations. In 14 cases (two patients defaulted) the therapeutical action upon the erythema was unmistakable and sometimes very rapid. If the dosage was insufficient, or if there were long intervals between the injections, the erythema was apt to pale down only partly or disappear temporarily. Penicillin appeared somewhat superior to the other drugs used, entailing a highly gratifying curative effect in a case with frank meningitis. The aetiology is discussed of the condition, special attention being given to the conclusions possibly to be drawn from the good therapeutical results.

"An efficacious method of treating erythema chronicum migrans has not been known formerly, nor was it considered strictly necessary to treat that condition as causing but mild discomfort. Since, however, erythema migrans has been shown in a proportion of instances to involve the central and peripheral nervous system (Hellerström, 1930; Bode, 1933; Bing, 1945; Gelbjerg-Hansen, 1945; Sälde, 1946; Dalsgaard-Nielsen and Kierkegaard, 1947; Leczinsky, 1949), at the present moment the question of successful treatment is of current interest even from the practical point of view. On the other hand, the aetiology of the condition being obscure, apart from the established fact that in the major proportion of instances the eruption follows upon a tick bite, it has hitherto not been possible to attack the causal factor. **Using the spirochaetal stain envolved by him, Lennhoff has succeeded in demonstrating organisms resembling spirochaetes in biopsy specimens taken from the erythematous lesions.** With a view to the possibility of the spirochaetes demonstrated being the causal factor, according to Lennhoff's directions groups of erythema migrans cases have been treated with spirochaeticides at the St. Göran's Hospital, Karolinska Sjukhuset, and Stockholm South Hospital. The series comprises 16 patients with typical erythema chronicum migrans."

"Of particular interest is the action of penicillin on the neuro-meningeal symptoms sometimes associated with erythema migrans." … "The therapeutical results achieved with penicillin indicate that erythema migrans is infectious in nature, and the effects of all the drugs used in treatment, in particular the bismuth salts and neoarsphenamine, tend to suggest a spirochaetae as the causative organism. Definite evidence is still lacking in this respect, but the therapeutical results in conjunction with Lennhoff's findings of spirochaetes in histological sections prepared from lesions of erythema migrans and with the demonstrated presence of spirochaetes in ticks, render probable that a spirochaete is the infective agent."

EM treatment
penicillin

1958 Acta Dermatol Venereol (Stockh) 1958;38:285-289. Penicillin treatment of erythema chronicum migrans Afzelius. **Hollström** reviews 77 of his own cases of EM-patients, seen in the years 1948-1957, 62 were women (80.5%) and 15 men, with ECM who was treated with penicillin. Relapses occurred if given too low doses (under 600.000 U in 3%). Average age was 43 years. Preceding tick-bite was observed by 27.3%, other insects stings: 11.7%. Erythema occurred between 14 days and 4 months after the bite/sting, and disapperared within two weeks after begin of treatment in 89.2 %. There was considerable variation in incidence over the years, from zero cases in the very warm and dry summer of 1955, up to 30 cases the following year. Everything - especially the beneficial effect of penicillin - points to an infectious etiology, but his transfer-experiments to healthy subjects are unsuccesful.

"Possibly a special disposition towards the disease is a necessary condition for its development."
"Prior to the terapeutic trial with spirocheticides including penicillin there was no efficient treatment: the erythema spread over the entire body surface with central clearing. The whole integument having been affected, immunity was generally thought to exist. As EM is rapidly cured by penicillin, yhe formation of antibodies will probably be interrupted, analogously to what is the case in penicillin treatment of scarlet fever. It is thus to be expected that a patient suffering from EM abd having been treated with penicillin may develop the disease afresh. Such a case is actually included in my material. The patient was a woman who in 1952 presented typical EM following insect bite. She was cured after treatment with 600.000 units penicillin. In 1957 she had the same disease again, although witout a history of insect bite. Also at that time 600.000 units penicillin produced cure within 1 week."

1962 Syph 1962;89:247-260. [L'erythema chronicum migrans]. **Dégos, Tourraine et Aroute** report 6 of 7 patients with typical ECM reacting positive on Girouds microagglutinations-test for **rickettsia**, either two received no treatment, one was treated with local steroid alone, others with local steroid in combination with either terramycin or rovamycin; 1 patient was retreated due to relapse of skin change, two other patients were seen again about a year later due to fever, but was not retreated with antibiotics.

This may be the first report of possible co-infection with rickettsial agents also transmitted by ticks?

Multiple ECMs
caused by mosquitobite

1966 Acta Derm Venereol (Stockh) 1966; 46:473-476. Erythema chronicum migrans (Afzelli) associated with mosquito bite. **Hård** reports unsucces in demonstrating spirochetes a la Lennhoff and not being able to transfer the disease via ticks fed on EM. Reports a female case, with latent syphilis, who was never exposed to ticks, since she lived way north of the tick-border in Sweden, who developed multiple ECM after mosquitobites in 1959; no general symptoms. Lesion subsided on 600.000 units penicillin x 2. She was well during 1960, but in 1961 she presented with the same history and lesions as before, 600.000 units penicillin for four days. Same story again in 1962 seen by the author who took picture of multiple EMs of varying size; typical ECM histology.

"The available literature contains no report of a case with so many lesions on so many occasions."

EM and arthritis in USA

1970 Arch Dermatol 1970 Jul;102(1):104-5. Erythema chronicum migrans. **Scrimenti**, associate clinical professor in the Department of Dermatology at the Medical College of Wisconsin, and an expert on LD skin infection, reports the first instance of an EM rash known to be acquired in the United States. The patient was a physician who had been grouse hunting in Wisconsin and had removed small, engorged ticks from his body. In his report, Scrimenti describes the accompanying neurologic and arthritic symptoms and discusses the use of penicillin as treatment.
(source: Karen V. Forschner: Everything You Need To Know About Lyme disease)

1976 JAMA 1976 Aug 16;236(7):859-60, 236(21): 2392. Erythema chronicum migrans in the United States. **Mast et Burrows describe** 4 (+6) cases of erythema chronicum migrans occurred within a one-month period in southeastern Connecticut. The syndrome may include advancing erythematous rash stemming from an apparent insect bite, hyperesthesias, myalgias, malaise, fever, lymphadenopathy, and, rarely, meningitis. Treatment with penicillin, the tetracycline, or, in our experience, erythromycin usually results in prompt resolution.
Two of the latter 6 patient developed monoarthritis with effusion, both RF positive. ”One patient was systemically ill with fever, myalgia and malaise. He experienced complete relief of symptoms and resolution of the effusion within 48 hours of beginning the penicillin regimen. The other patient with arthritis was less symptomatic, and the symptoms and effusion gradually rersolved over three weeks under expectant observation.” … ”We continue to believe that ECM is a unigue erythema caused by an infectious, nonbacterial, but antibiotic-sensitive agent probably transmitted by an arthropod vector. The arthritis appears as a delayed event.”
In a comment to above article (on the same page), Hazard, Leland and Mathewson reports two more cases of ECM with myalgia, diagnosed in Hyannis, who later were reported to have developed arthritis.

1977 Arthritis Rheum 1977 Jan-Feb; 20(1): 7-17. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three connecticut communities. **Steere AC et al.** An epidemic form of arthritis has been occurring in eastern Connecticut at least since 1972 …. To date the typical patient has had three recurrences, but 16 patients have had none. A median of 4 weeks (range: 1-24) before the onset of arthritis, 13 patients (25%) noted an erythematous papule that developed into an expanding, red, annular lesion … Neither cultures of synovium and synovial fluid nor serologic tests were positive for agents known to cause arthritis. **"Lyme arthritis" is thought to be a previously unrecognized clinical entity, the epidemiology of which suggests transmission by an arthropod vector.**

Meningo-radiculitis (Bannwarth)
rheumatic / allergic reaction to latent or reactivated infection ?

1941 Arch Psychiat Nervenkr 1941;113:284-376. [Chronische lymphocytäre meningitis, entzündliche polyneuritis und rheumatismus]. **Bannwarth** describes - in a 92 pages long essay - 15 patients who suddenly developed signs of chronic meningo-radikulitis, who - despite not displaying overt symptoms of meningitis at any time - had from a few to over 3000 white cells in their spinal fluid persisting over many months, and usually also increased spinal protein. ESR normal or only slightly increased. Hematological status either normal or slight lymphocytosis with normal or slightly increased WBC. Rarely elevated temperature and in these cases only subfebrilia. Many had had sign of 'rheumatism" before. Symptoms are often wandering, waxing and waning. Parestesias were often described as burning, stabbing, hypersensitive to touch pains. None had signs or tests positive for lues. Ten had throrough bacteriologic testing, all but one streptococci infected were negative.

Bannwarth argues that this syndrome must be a "rheumatic / allergic disease" based on previous or latent reactivated infection. Although he does not link tickbite or rashes, this article is a must read; a few citations:

"Ich darf zunächst einmal mit besonderem Nachdruck betonen, dass sich nach den Vorgeschichten und nach den klinischen und serologischen Befunden bei **keinem Kranken Hinweise auf eine luische Grundlage der Nervenleiden** ergeben haben. **Dieser Punkt muss besonders hervorgehoben werden, da die Krankheiten bei oberflächlicher Betrachtung gerade mit der chronischen luischen Meningitis noch am meisten Ähnlichkeit haben**." ….

"**Dagegen bleibt bei den mehr chronisch verlaufende rheumatischen Leiden auch der Primärinfekt meistens im Latenzstadium der Entzündung. Aber auch er kann vom Arzt bei einer wirklich gründlichen Untersuchung fast immer gefunden werden**"

"Es ist weiter wesentlich, dass der Begriff "Rheumatismus" durchaus nicht an eine Miterkrankung der Gelenke gebunden ist.." ….

"Der "Rheumatismus" ist sehr oft **ein ausgesprochen chronische Leiden**. **Es ergeben sich hier wie auch in anderer Beziehung gewisse Übereinstimmungen mit der Syphilis und der Tuberkulose. Auch sie sind chronische Krankheiten, die zwar latent werden können, im allgemeinen aber sehr zur rezidivierenden Manifestation neigen.** Mag der "Rheumatismus" auch oft als eine akute Erkrankung imponieren, so beweist doch meistens schon die genaue Befragung der Kranken, dass dem akuten Leiden bloss ein Aufflammern sehr chronischer Vorgänge zugrunde liegt. **Das wissen um den chronisch rezidivierenden und exacerbierenden Verlauf des "Rheumatismus" gehört zu den grundlegenden Erkenntnissen seiner Erforschung.** Gleichgültig ist dabei, ob die Schübe einen hoch akuten, einen heimlich schleichenden oder einen sehr chronischen Eindruck machen (nach Veil). Für die von Fall zu Fall wechselnde lokalisation der rheumatiscen Entzündung an den Gelenken, Muskeln, Gefässen, Eingeweiden, oder am Nervensystem usw. sind, ähnlich wie bei der Syphilis und Tuberkulose, Gesetzmässigkeiten massgebend, deren verwichelte Verhältnisse wir heute noch nicht durchschauen."

Lymph-Adenosis Benigna Cutis (LABC)
central follicle, histologic similarity to ACA
effect of penicillin

1911 Frankf Z Pathol 1911;6:352-359. [Zur Frage der Follikel und Keimzentrenbildung in der Haut]. **Burckhardt** describe the histology of a lymphocytoma with a central paler follicle, located in an area of a raspberry-red skin tumor of a few weeks duration. Outside the follicle, the histology is like described above, and the author concludes that it is a local chronic inflammation, not a general lymphadenopathy, nor a hematological disease.

1920 Acta Dermatol Venereol (Stockh) 1920; 1:422-427. **Strandberg** describes a 4-year old girl with an unusual form of slowly migrating erythema on the chest**,** probably caused by a tick bite, where **a** blue-red skin tumor also developed in the middle of the erythema at the nipple; the tumor was not examined histologically, but it was most probably a lymphocytoma, and this the first time a lymphocytoma is being associated with tick bite.

1921 Arch Dermatol Syph 1921;130:425-435. [Über gutartige lymphocytäre Neubildungen der Scrotalhaut des Kindes] **Kaufmann-Wolf M** describe 2 boys - age 4 and 10 - display several up to 5 mm tumors in scrotal skin, that on histologic examination is lymphadenomas with central follicles. (Pictures of scrotum, microphotograph of follicles).

1950 Dermatologica 1950;100:270-273. [Die penicillinbehandlung der Lymphocytome] **Bianchi** describe 6 cases of typical lymphocytoma (Lymphadenosis cutis benigna), who were treated with daily injections of penicillin of 300,000 to 600,000 units, and thereby cured. This fact argues in favour of an infectious aetiology of this disease.

The trial penicillin therapy was based on the histologic similarities between the inflammatory stage of ACA and LABC = lymphocytic and plasmacellular infiltration - and after penicillin had showed good effect on ACA.

Transmissibility
the tick - transfer experiments ACA

1913 Parasitology, vol. VI, 1913, p. 283-297. **Hadwen** describe ”Tick paralysis” in sheep and man following bites of Dermacentor venustus - referenced by Garin and Bujadoux in ’Paralysie par les Ticques”. According to them, **Hadwen** had found that:

- It was possible to infect lambs and pheasants with ”tick paralysis” via a tickbite. The illness showed about 6-7 days after the bite.
- It was not possible to reproduce the illness via injection of blood from a sick person into an animal.
- The pathologic agent itself was not found.

1955 Hautarzt 1955;5:491-504. [Die Acrodermatitis chronica atrophicans Herxheimer als Infektionskrankheit]. **Götz** - after having conducted animal experiments without success of tranferring ACA, thus believing that ACA is NOT an infection, and because an effective treatment now exists = penicillin - decides to carry out tranfer experiment of ACA skin to 4 physicians including himself.
For the first time in history transfer of ACA-skin to healthy subjects is succesful, both from an ACA-patient to subjects A & B, and again passage from A to C, resulting in the following symptoms: hyperestesia, joint problems, an expanding erythema that looks like EM, lymphadenitis and also small lymphocytoma-like nodes in the skin.
Götz notes that the disease is disseminated throughout the body, much like syphilis.
These experiments proves that ACA is an infection, but thorough bacteriologic and virologic examination, especially focusing on spirochetes gave no result, and animal-inoculation also with negative result.
One subject developed symptoms after inoculation, then went to Italy i.e. warm weather 35oC, and experienced improvement in her symptoms, but the symptoms recurred when returning to a colder climate! Götz combines this observation with previous observations: a thermolabile agent in tick saliva, ACA often cold-induced, ACRO-acrodermatitis and lack of success in inoculation-experiment on animals with warmer body temperature - and argues that the pathogen probably prefers a lower skin temperature.

Transmissibility
transfer experiments

1955 Klin Wochenschr 1955;33:185-186. [Tierexperimentielle Untersuchungen zur Ätiologie der acrodermatitis chronica atrophicans Herxheimer]. **Lohel** injected blood from patients with different dermatoses; the mice were sacrificed after 14 days and tested for pallida-reaction (Pallida-antigen, Promonta-Hamburg). 58,95% of the ACA injected mice reacted positive in pallida-reaction, while mice inoculated with blood from patients with other dermatosis were below 2% positive.
These results indicate an infectious etiology to ACA and point to a spirochete. Most remarkable is that the infection could be tranferred by blood.

1955 Hautarzt 1955;6:494-496. [Experimentelle Übertragung des erythema chronicum migrans von Mensch zu Mensch]. **Binder, Doepfmer and Hornstein** transplant biopsies from the perifery of ECM from a patient to their own arms and further in serial passage from D. to the others and a forth subject. Typical EM lesions developed in al 7 transplanted areas within 1-3 weeks, and were expanding over months, without being accompagnied by other symptoms or abnormal bloodtests. This experiment proves the infectious nature of ECM; search for the causative agent was, however, unsuccesful.

1956 Hautarzt 1956, 6:249-252. [Die Acrodermatitis chronica atrophicans Herxheimer als Infektionskrankheit]. **Götz H**. Follow-up to the 1955 ACA-skin-implant experiment on previous slide.
Further observation (A 277 days (penicillin), B. 312 days, C 250 days) show that the skin changes were reduced somewhat but not gone after many months. Histologic examination 9-10 months after the transplant showed what the authors interpret as abortive ACA inflammatory stage with begin of atrophy, while subject B, who had a preexisting tendency to cold hands and cyanosis, also developed early symptoms of ACA on a hand. Subject A had to be treated with penicillin due to another reason, which led to prompt healing of the skin changes and sensitivity. Authors find that subjectively increased bone-sensitivity is common in ACA patients, and this sign may be used to discriminate from other conditions with skin discoloration. These findings support ACA being a transferable chronic infection, that responds well to antibiotic treatment.

Transmissibility
transfer experiments

1957-1958 Hautarzt 1957;8:197-211, 1958; 9:153-165, 1958; 9:263-269 - 1958;9: 311-315. [Die lymphadenosis benigna cutis als übertragbare infektionskrankheit. ….] **Paschoud** proves the infectious etiology of LABC by repeated transfer, in 3 passages, of the skin changes to 10 human subjects (ear lobe and back). If the transplant is injected into deeper layers of skin or loose skin, a large lymphocytoma tend to develop more often, while a more superficial injection or in areas of more tight skin like the back, it may results in a central necrosis as often seen in tickbíte, and an over many months centrifugally spreading typical EM (histology verified), sometimes small miliary lymphocytomas may be found as residues in areas passed by a wandering EM (”Streulymphocytome”); he notes the change from LABC to ECM and vice versa during the long run.

The author also notes that the spread of the EM happens in steps with pauses of 5-7 days where the lesion stays about the same size, giving the impression of healing, but then suddenly the rash increasing further 1-2 cm in size within a day (I think this observation may be explained from our present knowledge on the spirochetal life-cycle - the cyst form?).

The author discuss the histologic similarities to ACA (lymphocytic and plasma-cellular infiltration and loss of elastic fibers) and describe the timely very variable course of the disease, documented by photos and repeated histologic examination. He proves the beneficial effect of penicillin, rovamycin and Röntgen irradiation (and describes relapses, and the need for retreatment) and he describes the histologic involution and the residual changes after treatment. More important - he finds that transfer of the LABC skin change is not possible until after a certain maturation of the original skin change (8-10 weeks), which may explain the many previous unsuccesful transfer attempt.

The result all speaks for an infectious etiology, however, a very thorough search does not reveal a possible agent.

The granule form of the spirochetes
- old works on a spirochetal etiology of the *relapsing fever borreliae*

For references, some old articles OCR'ed and a pictorial on the alternate form of spirochetes, see
http://groups.yahoo.com/group/LymeRICK/files/Spirochetes/

1911 British Medical Journal April 1, 1911: 752. **Balfour** describe the 'infective granule' in spirochaetosis of Sudanese Fowls.

1914 Compt Rend Acad Sci, clviii, pp 1815-1817, 1914. 'Les Spirilles de la fievre recurrente sont-ils virulent aux phases successives de leur evolution chez le pou? Demonstration de leur virulence á un stade invisible.' **Nicolle and Blanc** describe transmission of louseborne relapsing fever at a time when NO spirochetes were visible in the blood.

1915 Annals Trop Med and Parasitol, ix, pp 391-412. **Fantham** describes differences in morphology of the spirochaetes in bronchial spirochetosis, including development of a 'granule form' that can later develop into new smaller spirochaetes. Lots of comparable pictures made by help of a camera lucida, shows that the granule size is a bit smaller than diplococci (pneumococci).

1914-15 Compt Rend Acad Sci 1914, clviii, pp 1926-1928 'Des periodes de latence du Spirille chez le malade atteint de fievre recurrente.'
Compt Rend Acad Sci 1915, clix, pp 119-122 'De la periode de latence du spirille chez le Pou infecté de fievre recurrente.'
Sergent and Foley: write they have previously found (1908) that material from crushed lice, that had been feed blood meal on a recurrent fever sick and filtered, was still infectious despite the fact that no spirochetes could be seen in the inoculation material. In these works the authors examine lice for spirochetes from the first day and up to 14-16 days after the infectious blood meal; they find that during the first mean 8 days after the infectious meal, spirochetes can not be visualized, but thereafter a growing number of spirochetes reappear.
They conclude that the infectious agent of louseborne relapsing fever must be in a very small form that is equally infectious and that the infectious agent changes to this form during the apyretic periods between relapses and that this period in man is of a mean of 8 days duration.

The granule form of the spirochetes
- newer observations on the cyst form of *B. burgdorferi*

1988 Ann N Y Acad Sci 1988:468-70. Concurrent neocortical borreliosis and Alzheimer's disease. Demonstration of a Spirochetal Cyst Form. **MacDonald**. … progressive dementia / Alzheimer's disease was based on clinical criteria. The brain was removed at autopsy, frozen (unfixed) ….. The author received the frozen brain and utilized methods previously described' for in vitro culture, cytologic, immunohisto-chemical, and silver impregnation studies. Argyrophilic plaques and neurofibrillary tangles were found in the frontal lobe and hippocampal formation in sufficient number to establish the neuropathologic diagnosis of Alzheimer's disease (FIG. 1A). Spirochetes were visualized in imprint preparations of freshly thawed frontal lobe cortex with monoclonal antibody H5332, which specifically binds to the outer surface membrane of Borrelia burgdorferi (FIG. 2). Borrelia spirochetes were recovered from cultures of freshly thawed cerebral cortex and hippocampus in Barbour-Stoenner-Kelly medium. **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 using the monoclonal antibody H9724, which binds to class-specific axial filament proteins of Borrelia spirochetes**.

1996 Am J Dermatopathol 1996 Dec; 18(6): 571-9. Heterogeneity of Borrelia burgdorferi in the skin. **Aberer et al**. "The reliability of various in vitro techniques to identify Borrelia burgdorferi infection is still unsatisfactory. Using a high-power resolution videomicroscope and staining with the borrelia genus-specific monoclonal flagellar antibody H9724, we identified borrelial structures in skin biopsies of erythema chronicum migrans (from which borrelia later was cultured), of acrodermatitis chronica atrophicans, and of morphea. In addition to typical borreliae, we noted stained structures of varying shapes identical to borreliae found in a "borrelia-injected skin" model; identical to agar-embedded borreliae; and identical to cultured borreliae following exposure to hyperimmune sera and/or antibiotics. We conclude that the H9724-reactive structures represent various forms of B. burgdorferi rather than staining artifacts. These "atypical" forms of B. burgdorferi may represent in vivo morphologic variants of this bacterium."

1997-99 Infection 1997 Jul-Aug; 25(4): 240-6. May-Jun;26(3):144-50. APMIS 1998 Dec;106(12):1131-41. **Brorson's** demonstrate transversion of cystic forms of Borrelia burgdorferi to normal, mobile spirochetes. "The cysts observed in our study seem to resemble the spheroplast-L-forms observed by other researchers …. The biological activity of the cystic forms was confirmed by the step by step development to normal mobile spirochetes in BSK-H medium, and also indicated by the presence or RNA in 5-week-old cysts …. The creation of as many as five spirochetes from each cyst may explain why the generation time was shorter for production of mobile spirochetes from cysts compared to that for normal mobile spirochetes cultivated conventionally. … It seems as though normal mobile spirochetes are developed from the dense core structures or the cyst by being "fed" with core substances as the "infant-spirochete" protrudes from the cyst. T… Old cystic forms of B. burgdorferi require prolonged cultivation to convert to normal mobile spirochetes (4 weeks as opposed to 9 days for young cysts). Similar cystic forms may occur in the human organism … and they may explain the long periods or latency, resistance to antibiotics, negative serological results, and low PCR sensitivity. For these reasons it is important to examine the antigens of the envelope of the cysts.

The granule form of the spirochetes
- newer observations on the cyst form of *B. burgdorferi*

2000 Microbiology 2000 Jan;146 (Pt 1):119-27. Serum-starvation-induced changes in protein synthesis and morphology of Borrelia burgdorferi. **Alban et al.** confirms Brorsons findings that B. burgdorferi under unfavourable conditions form cysts that are able to revert to spirochetal for, when introduced to a more suitable medium.

"Usually, 30-50% of cells incubated in BSK-II-S formed cyst-like structures over 2-4 weeks. …. One hour after the onset of serum-starvation, cells lost normal motility at one or both poles and began twisting into knots. Within 24h, cells starved of serum were completely non-motile ans 30-40% had begun to encyst. After 48h incubation in RPMI, ~90% of serum-starved cells had formed cysts (Fig.1). In contrast, control cells ... remained motile and no cysts were observed."

2001 APMIS 2001 May;109(5):383-8. **Conversion of Borrelia garinii cystic forms to motile spirochetes in vivo**. **Gruntar et al.**

Cystic forms (also called spheroplasts or starvation forms) and their ability to reconvert into normal motile spirochetes have already been demonstrated in the Borrelia burgdorferi sensu lato complex. The aim of this study was to determine whether motile B. garinii could develop from cystic forms, not only in vitro but also in vivo, in cyst-inoculated mice. The cysts prepared in distilled water were able to reconvert into normal motile spirochetes at any time during in vitro experiments, lasting one month, even after freeze-thawing of the cysts. Motile spirochetes were successfully isolated from 2 out of 15 mice inoculated intraperitoneally with cystic forms, showing the infectivity of the cysts. The demonstrated capacity of the cysts to reconvert into motile spirochetes in vivo and their surprising resistance to adverse environmental conditions should lead to further studies on the role and function of these forms in Lyme disease.