

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

Marie Kroun, MD
Denmark

kroun@ulmar.dk
http://LymeRICK.net

1

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

2

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

1884 Europe:
Lancet 1895 Nov 18; 346(8986): 1367. Antiquity of the Lyme-disease spirochaete in Europe [letter]. Matuschka et al.
In 1884-85 **ludovici** 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.

3

EM
tick saliva contain a thermolabile inflammatory agent

1936 Dermatol Wochenschr 1936;102:125-131. [Zur Ätiologie des Erythema chronicum migrans] **Askanl** 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. Spirochäse des Menschen = *Fabris recurrens* (*S. duttoni*) - *Ornithodoros moubate*
2. Europäische rekurrens (*S. Obermeieri*) - *Ornithodoros moubate*
3. Spirochäse der Rinder und Pferde - *Boophilus decoloratus*
4. Spirochäse der Gänse und Hühner - *Argas minatus*
5. Texasfieber (vielleicht identisch mit 3) - *Boophilus annulatus*
6. Texasfieber mit Blutharn (hemoglobinuria) - *Boophilus annulatus* und *Boophilus decoloratus*
7. Häufiggelenkurie der Rinder (6 und 7 sind zwei verschiedene Piropilamosen) - *Ixodes ricinus*
8. Ostafrikanisches Küstenfieber - Nur das Rind und nur durch **ludovici** infizierbar
9. Südeuropäische Piropilamose (Schlaf in Rumänien) - *Rhipicephalus bursa*
10. Hyalämie in Italien (maligne Gelsucht der Hunde) - *Ixodes ricinus*
11. Exanthematische Zeckenfieber der Menschen in Südafrika (Regenzanz) - *Rhipicephalus sanguineus*

4

Acrodermatitis Chronica Atrophicans (ACA)

1883 Arch Dermatol Syph 1883; 10:553-556. [Ein Fall von diffuser idiopathischer Haut-Atrophie].
Buchwald describes the atrophic 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 (chronic)
- the atrophic end-stage look like "zerfrittertes 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. Anesthetics.**
All stages of the disease may be represented in the same patient in different skin areas. There may be dysesthesia (burning or cold), but it is rarely accompanied by other symptoms, and only a few patients displayed possible systemic manifestations.
No previous Erythema migrans, and no previous licks or insect sting noted.

5

ACA expanded:
tumorlike infiltrations and joint symptoms

1910 Arch Dermatol Syph 1910; 105:145-168. [Über strangförmige Neubildungen bei acrodermatitis chronica atrophicans]. **Herxheimer and Schmitt** 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 within their own findings:
"In der Kute findet wir ein **ausserst dichtes Infiltrat**, dessen Elemente teils in dichten Nestern, teils regellos angeordnet sind. Das Infiltrat besteht aus mononukleären, kleineren und grosseren Lymphocyten, ferner aus Spindelzellen, Mastzellen und ausserst spärlichen Plasmazellen. Die Kerne der Lymphocyten sind vorwiegend rund, an verschiedenen Stellen etwas ausgezogen, birnförmig." ... "Mögen können vereinzelt beobachtet werden." ...

1921 Arch Dermatol Syph 1921; 134:478-487. [Zur Kenntnis der acrodermatitis chronica atrophicans]. **Jesener** 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 described 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 Hautaffektion am rechten Arm. Schon vor Ausbruch der Hautkrankheit habe sie häufig Schmerzen in den Füssen nach dem Gehen empfunden, auch seien dieselben häufig angeschwollen gewesen."

6

ACA expanded: sensory disturbances, lymphocytomas, heart problems

1924 Dermatol Wochenschr 1924;70:1169-1177. [Bericht über 66 Fälle von Acrodermatitis chronica atrophicans]. **Jesser and Loewenstamm** (p. 1174) describe arthritis and sensory disturbances:
Arthritische Veränderungen
"Wenigstens 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 Verkrümmungen, nacheinander Kollagenation 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: Jucken, Raubheits-Kälte, Hitze- und Schwächegefühl, Brennen, Stechen, "dumpf" Schmezen. 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 Lymphocytoide der Haut]. **Müller and Kainig** describe a case with ACA development over 20 years, later she develop 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;140:142-175. [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 described, 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: This remarkable is the following first remark given on that patient: 7. A.L. ... "Vor 22 Jahren kommt ein roter Fleck (EM?) im rechten Unterschenkel mit Jucken. 3 Jahre später Schmerzen im linken Oberschenkel, nach weiteren Jahr Anschwellung und Rötung beider Unterschenkel mit Jucken. **Ausgedehnter Blasenrauh (und enorme Schwelung)**. **The authors argue for the disease process being an infection, however microscopically similar to lues (syphilis).**
Es ist unverständlich, dass ein Fleck ... in der Bluthirn-häut und als gelblich Substanz gerade nur an bestimmten Stellen in schubartigen und ... in fortwährend schubartigen Menge und Konzentration durch Jahre und Jahrzehnte hindurch abgelaufen wurde und infolge machte, die die makroskopisch gesehenen wässrigen ... Sie bilden nun unter der Annahme, dass es sich um ein Miliäres Virus handelt, die Wege zu beschreiben, die es durch die histologische Befunde gehen werden. Bei der charakteristischen Form, die sich in der primären Herd ausbreitet, findet man die andere Äußerung des Organismus wieder, nämlich die Art der Ausbreitung der Lymphocyten-empfindlichen Blutgefäße, abnormen Inhalt umgeben und hat es die Folge von Lymphocyten erfüllt. Es ist ein Verhältnis von Gewebe und Infekt, das selbst mit primäre Lues übereinstimmt, aber die Umgruppierung der Infektstoffe, nur ist das Infekt nicht immer so dicht wie bei der Lues, aber hier wie dort durch die grosse Menge der Plasmazellen begleitet. Aber muss sich nicht erklären, dass der suppurative Erythel durch die Bindungsgefäße in das Lymphgefäßsystem gelangt und von dort aus auf die im umliegenden Blutgefäß befindlichen Lymphocyten charakteristisch verweilt und so und so unter dem Einfluss der Energie gelähmter Plasmazellen zur Auswanderung im Gewebe bringt. Ähnlich, wie bei der Lues, folgt das Infekt auch den peripheren Lymphbahnen."
"Mitin haben wir folgende Wege des Virus histologisch nachgewiesen:
1. Fortschreiten längs des oberflächlichen Cutisnetzes in der papillären und subpapillären Schicht.
2. Auf dem Wege des feinen Lymphgefäßnetzes zwischen den Balken der Cutis propria bei den sklerodermatischen Formen, auch peripher.
3. Die peripheren Lymphbahnen und Lymphgefäße der feinen Cutis und der oberen Subcutis bei den atrophischen Formen.
4. Fortschreiten sowohl in den feinen, als in den oberflächlichen Schichten, bei mit gleicher Geschwindigkeit, bald eigentlich schief oder auch Postulieren des Virus längs eines verengten Gefäßes und gewissen Fortsetzungen (Fortschreitungen).
5. Die Substanz. Somit läuft nichts mehr im Wege, um das Krankheitsbild der Dermatitis atrophicans als meist lokale, fortwährende Infektion mit gelegentlicher Dissemination, wie sie bei allen lokalen Infektionen vorkommt, aufzufassen."

ACA treatment penicillin works

1946 Nord Med 1946;32:2783. [Penicillinbehandlung vid dermatitis atrophicans Herxheimer] **Nanna Svartz** 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.
Transition from Swedisch to the authors last remarks.
"The effect of penicillin in these cases of chronic dermatitis of several years duration (5-6 yrs) is remarkable. The explanation for the good effect must be that an ongoing infectious 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). **Tyrnesson** 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 deemed incurable i.e. in late atrophy stage improved; 2 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 definitely checking the infectious process."

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

1951 Hautarzt 1951;2:6-14. [Die Behandlung der Akrodermatitis chronica atrophicans Herxheimer mit Penicillin] **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 sympathetic activity of the patient. **Case 10 experienced fever during injections:**
"Während der Injektionen kommt es zu einem vorübergehenden Temperaturanstieg bis 38,6°C."
1952 Arch Dermatol Syph 1952;195:164-170. [Sternalmarkfunde und ihre Beziehungen zur Blutsenkungsgeschwindigkeit bei acrodermatitis chronica atrophicans]. **Hausser** describes inflammatory changes in the bone marrow of 25 ACA patients.
"Eine mehr oder minder deutliche Vermehrung der plasmacellulären und auch lymphoiden Retikulocysten, entweder in einer diffusen Durchsetzung des Markes oder in heftiger Anhäufung konnten wir bei 13 von 25 Patienten feststellen. Ein gehaltloses Vorkommen von Mastzellen bei weitaus aller und dort in den Makroausstrichen bei 8 Kranken auf, zum Teil bis 4 Mastzellen im Blutsfeld. Eine mehr oder weniger stark ausgeprägt eosinophile des Knochenmarkes nur bei 13 von den 25 Untersuchten feststellbar."
"Dagegen wiesen 3 Kranke ein normales oder nur gering erhöhtes Senkung (von 5,15, 17 mm in der ersten Stunde) neben einer geringgradigen oder normalen Eosinophilie keine Vermehrung lymphoide oder plasmacellulärer Retikulocysten im Knochenmark auf."
1955 Arch Dermatol Syph 1955;199:350-393. [Zur Kenntnis der akrodermatitis chronica atrophicans] **Hausser** discuss the relationship among ACA, ESR and lymphocytoma chronic inflammatory changes in regional lymph nodes and in the bone marrow, serum-globulin changes and influence the sedimentation reaction. He describes 52 cases followed with histology, in which he notes the female overweigh of about 60-80% (also found in several literature studies) and the typical age-distribution. ACA may begin in all ages including children below 10 years old, but it usually begins in the 40-50s because of it, he also notes that some patients develop bone-destroying 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 tick (Ixodes ricinus), i.e. the rural residency of most patients, very few cases arising in cities, and that the world distribution of ACA follows the distribution of the Ixodes tick (respo). He notes the effect of antibiotic (penicillin, aureomycin, streptomycin) clearly points to a systemic infection, with main changes in the skin, yet multiple serologic and histologic studies are unsuccessful 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 al** 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-occurrence of dermato-sclerosis and ulceration is significant, while fibroid nodules and ulceration does not occur together. The age-distribution of the erythematous changes follows a bell-form normal distribution curve with its center about 35 years of age, while the patients with fibroid nodules lies 5 years later. The type of changes also depends on the skin localisation, fibroid nodules occur more often on the arms, while dermato-sclerosis on the legs.

Erythema (chronicum) migrans (EM / ECM)

1910 Arch Dermatol Syph 1910; 101:404. **Azrelus A.** Sitzung vom 28. Oktober 1909: "Azrelus erwähnt ein von **Loedes redivuus** wahrscheinlich hervorgerufenes **Erythema migrans** bei einer älteren Frau (the first case described, seen in 1909)"
1910 Arch Dermatol Syph 1910; 105:423-430. [Erythema annulans, entstanden durch Insektenstiche] **Balban** describes 3 cases of "erysipeloid Rose" or erythema migrans-like skin changes, which developed at the site of an insect-sting, in case one there was visible stigmata, and case 2 & 3 told about the sting. Size of rash up to 14 cm.
1913 Arch Dermatol Syph (Berl) 1913; 118: 349-56. [Über eine seltene Erythemform (Erythema Chronicum Migrans)]. **Lipschütz** describes a long-lasting rash that he names erythema **chronicum migrans**. He claims to be the first but was not.
1920 Acta Dermatol Venereol (Stockh) 1920; 2:142-147. **Strandberg** describe **ECM plus lymphocytoma** (a migrating erythema on the chest, probably caused by a tick bite, when a skin and skin tumor also developed in the middle of the erythema on the right - also mentioned under LABC)
1921 Acta Dermatol Venereol 1921; 2:120-25. Erythema chronicum migrans. **Azrelus** describe the characteristics of ECM:
"Das klinische Bild des Erythema chr. migrans ist sehr charakteristisch. Die Krankheit beginnt mit einer oder zwei rötlichen, seltener blasseren papulösen Form. Diese verbreitern sich peripherisch, dadurch dass ihre Ränder etwas schmalen, 1/2-2 cm breiten, roten Ring bilden, der sich allmählich erweitert, während das Centrum nach und nach abblässert, und zuletzt eine ganz normale Hautfarbe, zwecks auch einen schwach opaleszenten Ton annimmt. Wodurch die weissen rote Ring, noch die verbleibende Hautfläche zeigen die geringste Abschuppung oder Exfoliation. Hochstens ist der Ring nicht prominent. Keine oder sehr unbedeutende subjektive Symptome. Je weiter der Ring peripher fortschreitet, umso besser und weniger deutlich wird er, bis er zuletzt, nach einigen Wochen, oder meistens nach einigen Monaten, ganz verschwindet. Bei kürzerer Dauer beobachtet er eine runde Form, bei längerer nimmt er eine unregelmässige Gestalt an, und einzelne Teile des Ringes verschwinden zuweilen vor den anderen. Die Dauer des Erythema wechselt innerhalb weiten 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 Darmkanals bzw. Speicheldrüsen des Holzbocks Aufmerksamkeits zu schenken, nachdem auch bei anderen ungleich wichtigeren Infektionskrankheiten die Bedeutung der durch Insektenische vermittelten Keimübertragungen demonstriert worden ist (z. B. Rickettsien bei Fleckfieber usw.)."

1930 Acta Dermatol Venereol (Stockh) 1930;11:315-321. Erythema chronicum migrans Afzelli. **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**. **Hellerström** obviously had not read **Garin and Bujadoux 1922**, Paralyse par les tiques, when he wrote. "Nach der Literatur zu urteilen ist eine chronische Meningitis zusammen mit einem Erythema chronicum migrans früher nicht beobachtet worden".

13

EM expanded meningo-encephalitis, paresis, radicular pain

1922 J Med Lyon 1922;71:765-767. [Paralyse par les Tiques]. **Garin and Bujadoux** reports a case of an **extremely painful meningo-radicitis** that developed 3 weeks after a **known tick bite** (I. hexagonus) on his left buttock, which was followed by an **erysipelatous rash at the site of bite**, accompanied by irradiating pain in left thoracic area and later well-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 2-12 months the patient developed **paresis of his right distal muscle**, and the muscle atrophied. Then sign of meningitis developed: **positive Kernig and sign of inflammation in cerebro-spinal fluid (meningitis)**, with increased albumin and 75 WBCs. No microbes were visible in CSF.
Wasserman reaction was slightly positive, but the patient had no sign of syphilis. Most remarkable was also the very **positive effect of treatment with neovarsinobenzol (arsenic)**, that quickly relieved most of the patients pain. The authors note that the **Wasserman** 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 **Banwarth** - see next slide - though he did not recognize any previous tick bite nor erythema migrans in his patients, he describes thoroughly what we today recognize as the typical borrelial meningo-radicitis and has some interesting theories about "the causation" a theory.

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

1948 Acta Dermatol Venereologica 1948;28(3): 295-324. Spirochetes in Antellogically Obscure diseases. **Lennhoff** develops a special staining technique for spirochetes and finds this type of pathogen in several ill diseases including EM, but others (see next) later have difficulty and is unsuccessful in reproducing his stain and findings.

14

EM with meningitis arguments for a spirochetal infection

1950 Southern Medical Journal 1950;43:330-334. Erythema chronicum migrans Afzelli with meningitis. At a meeting in Cincinnati Nov. 14-17, 1949 **Hellerström** discusses the etiology and pathogenesis of erythema chronicum migrans Afzelli 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 tick may sometimes cause one or several eruptions, while that of 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 intraspinal meningitis has occasionally been noted.
 6. Immucineous tests with extract prepared from Ixodes species afford evidence tending to show that the acids excreted by the adult erythematous circle and its immediate vicinity differ in their allergic behaviour (Hellerström, Dalsgaard-Nielsen and Kierkegaard).
 7. In a proportion of instances, the eruption is associated with menocytic or leucocytic meningitis, radiculitis and, occasionally encephalitis with tubular symptoms (Hellerström, Gøtzberg-Hansen, Dalsgaard-Nielsen, Kierkegaard, et al).
 8. As to the eruption, it is further known that injections of 'iodosinonil' or arphenamine will cause its temporary (few injections) or definite (more injections) subsidence (C. Lennhoff).
 9. In material taken from the eruption spirochetal bodies have been demonstrated (C. Lennhoff).
 10. Both the eruption and the meningitis will readily yield to penicillin (E. Hellerström, Lennhoff), but not to sulfamerazine.
 11. Both the eruption and the meningitis may subside spontaneously 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 (Pharogee, Høiby); 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 Wasserman test was negative; d) no antibodies such as occur in cases of various viral diseases (eastern and western equine encephalomyelitis, St. Louis encephalitis, chikungungu) could be demonstrated in the blood (Dalsgaard-Nielsen and Kierkegaard); and e) the seroprecipitation reaction was negative with blood serum (Hellerström).

15

EM treatment bismuth, neorsphenamin, mapharside and penicillin works

1951 Acta Derm Venereol Suppl (Stockh) 1951;31:225-243. Successful treatment of erythema migrans Afzelli. **Hollström**. An account is given of sixteen cases of erythema chronicum migrans Afzelli treated with **bismuth, neorsphenamin, mapharside, and penicillin**, either separately or in various combinations. In 14 cases (two patients defaulted) the therapeutic 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 therapeutic 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, 1936; Bode, 1933; Bing, 1945; Gøtzberg-Hansen, 1945; Salbe, 1946; Dalsgaard-Nielsen and Kierkegaard, 1947; Luncké, 1948), 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. In the spirochetal diseases, however, the spirochetes are considered as the organisms resembling spirochetes in biopsy specimens taken from the erythematous lesions. With a view to the possibility of the spirochetes demonstrated being the causal factor, according to Lennhoff's directions groups of erythema migrans cases have been treated with spirocheticides 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-meningitis symptoms sometimes associated with erythema migrans. ... The therapeutic results achieved with penicillin indicate that erythema migrans is infectious in nature, and the effects of the drug used in treatment, in particular the bismuth salts and neorsphenamine, tend to suggest a spirochetal as the causative organism. Definite evidence is also lacking in this respect, but the therapeutic results in comparison with Lennhoff's findings of spirochetes in histological sections prepared from lesions of erythema migrans and with the demonstrated presence of spirochetes in ticks, render probable that a spirochete is the infective agent."

16

EM treatment penicillin

1958 Acta Dermatol Venereol (Stockh) 1958;38:285-289. Penicillin treatment of erythema chronicum migrans Afzelli. **Hollström** reviews 77 of his own cases of EM patients, seen in the years 1948-1957. 62 were women (80.7%) and 15 men, with ECM who was treated with penicillin. Eruption 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 biting, and disappeared 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 unsuccessful.
 "It is a special disposition towards the disease is a necessary condition for its development."
 "Prior to the therapeutic 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, the 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 and 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 without a history of insect bite. Also at that time 600,000 units penicillin produced cure within 1 week."

1962 Syph 1962;89:247-260. [Erythema chronicum migrans]. **Déjeu, Touraine et Arcaute** 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?

17

Multiple ECMs caused by mosquito bite

1966 Acta Derm Venereol (Stockh) 1966; 46:473-476. Erythema chronicum migrans (Afzelli) associated with mosquito bite. **Hård** reports unsuccess in demonstrating spirochetes in a 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 mosquito bites 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 1961, 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."

18

EM and arthritis in USA

1970 Arch Dermatol 1970 Jul;102(1):104-5. Erythema chronicum migrans. **Sordani**, 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, **Sordani** describes the accompanying neurologic and arthritic symptoms and discusses the use of penicillin as treatment. (source: Karen V. Foschtner: Everything You Need To Know About Lyme Disease)

1976 JAMA 1976 Aug 16;236(7):859-60, 236(12): 2992. Erythema chronicum migrans in the United States. **Most of Burrows describe** 4 (H) 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, hyperostheias, 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 resolved over three weeks under expectant observation. "We continue to believe that ECM is a unique erythema caused by an infectious, rickettsial, but antibiotic-sensitive agent probably transmitted by an arthropod vector. The arthritides 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 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 Psychiatr Nerven 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-radiculitis, 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 subfebrile. Many had had sign of 'rheumatism' before. Symptoms are often wandering, waxing and waning. Paresthesias were often described as burning, stinging, hypersensitive to touch pains. None had signs or tests positive for lues. Test had through 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:**
 "In der zweiten Gruppe mit besondereh Nachdruck betonen, dass sich nach den Vorgeschichten und nach den klinischen und serologischen Befunden bei keinem Kranken Hinweise auf eine luesische Genese der Nervenleiden ergaben haben. Dieser Punkt muss besonders hervorgehoben werden, da die Krankheben bei oberflächlicher Betrachtung gerade mit der chronischen luesischen Meningitis noch am meisten Ähnlichkeit haben."
 "Dagegen bleibt bei den mehr chronisch verlaufende rheumatischen Leiden auch der Primärrhekt meistens im Laborstadium der Entzündung. Aber auch es kann vom Arzt bei einer wirklich gründlichen Untersuchung fast immer gefunden werden"
 "Es ist weiter wesentlich, dass der Begriff "Rheumatismus" durchaus nicht eine Erkrankung der Gelenke gebunden ist."
 "Der "Rheumatismus" ist sehr oft ein ausgesprochen chronische Leiden. Es ergaben sich hier wie auch in anderer Beziehung gewisse Übereinstimmungen mit der Syphilis und der Tuberkulose. Auch wie sind chronisch wiederkehrende, die zwar latent werden können, im allgemeinen aber sehr zur wiederkehrenden Manifestation neigen. Mag der "Rheumatismus" auch als eine akute Erkrankung angesehen werden, so besteht doch ein Zusammenhang mit dem chronischen Verlauf. Die meisten bis am Aufkommen sehr charakteristischer Vorgänge zugrunde liegt. Das wissen um den chronisch verlaufenden und wiederkehrenden Charakter der Erkrankung ist ein wichtiger Bestandteil der Erkenntnis seiner Erkrankung. Gleichgültig ist dabei, ob die Zeichen einen hoch akuten, einen chronischen oder ein intermittierenden Verlauf nehmen. Für die von Fall zu Fall wechselnde Lokalisation der rheumatischen Erkrankung an den Gelenken, Muskeln, Gefäßen, Ergüssen, oder am Nervensystem usw. und ähnlich wie bei der Syphilis und Tuberkulose, Gesetzmäßigkeiten massgebend, deren verwechselte Verhältnisse wir heute noch nicht durchzusehen."

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

1911 Frankl Z Pathol 1911;6:352-359. [Zur Frage der Follikul und Keimzentrenbildung in der Haut]. **Burckhardt** describe the histology of a lymphocytoma with a central pale 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 Venerol (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 Haut des Kindes]. **Kaufmann-Holm** 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]. **Banich** 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 "Paralyse par les Tiquees". 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 Henzheimer als Infektionskrankheit]. **Götz** - after having conducted animal experiments without success of transferring ACA, thus believing that ACA is NOT an infection, and because an effective treatment now exists = penicillin - decides to carry out transfer experiment of ACA skin to 4 physicians including himself. For the first time in history transfer of ACA skin to healthy subjects is successful, both from an ACA-patient to subjects A & B, and again passage from A to C, resulting in the following symptoms: hyperaesthesia, joint problems, an expanding erythema that looks like EM, lymphadenitis and also small lymphocytoma-like spots 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 through 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 35°C, and experienced improvement in her symptoms, but the symptoms returned 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. [Tierexperimentelle Untersuchungen zur Ätiologie der acrodermatitis chronica atrophicans Henzheimer]. **Lohel** injected blood from patients with different dermatoses; the mice were sacrificed after 14 days and tested for patella-reaction (Pattella-antigen, Pirozetta-Henriberg). 56.50% of the ACA injected mice reacted positive in patella-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 transferred by blood.

1955 Hautarzt 1955;6:494-496. [Experimentelle Übertragung des erythema chronicum migrans vom Mensch zu Mensch]. **Binder, Dopfner and Hornstein** transplant biopsies from the pteryly of ACA 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 all 7-13 weeks, and were expanding over months, without being accompanied by other symptoms or abnormal bloodtests. This experiment proves the infectious nature of ECM; search for the causative agent was, however, unsuccessful.

1956 Hautarzt 1956; 6:249-252. [Die Acrodermatitis chronica atrophicans Henzheimer als Infektionskrankheit]. **Götz H.** Follow-up to the 1955 ACA-skin-inflant experiment on previous slide. Further observation (A 27 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 preceding 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 lues-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 result in a central necrosis as often seen in tickbite, and an over many months centrifugally spreading typical EM (histology verified), sometimes small milary lymphocytomas may be found as residues in areas passed by a wandering EM ("Streu-lymphocytome"). 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, novomyon 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 (6-10 weeks), which may explain the many previous unsuccessful transfer attempt. The result all speaks for an infectious etiology, however, a very thorough search does not reveal a possible agent.

