Dear Colleagues,

We would like to welcome you in the name of the Board of Trustees and the Therapeutic Workshop of the Lyme Borreliosis Foundation.

The purpose of the Congress - in line with the Foundation's guiding principles- is to:

Recall the knowledge about Lyme borreliosis from the past centuries, and to merge it with the latest clinical experience and the learning from most recent experiments.

To seek an answer to the contradiction: why is it that the spirochete is sensitive to several antibiotics, but it is still able to escape from antibiotic treatment and the defence mechanism of the body. To find an answer: how can we still achieve complete healing.

To share the way of evaluating the laboratory findings, the classic and modern ways for (differential) diagnostics

To inform attendants about the most recent methods of therapy, therapeutic schemes.

The indirect objective of the congress is to call attention to the fact that Lyme borreliosis can only be defeated via a multi-disciplinal effort, with the help of consultation among several specialists.

This disease is endemic in Hungary, it affects a significant part of the population, and thus the diagnosis and therapy has to be organized accordingly

We need to change the current diagnostic and therapeutic (prescription) practice (point 32 of the 3rd attachment to the NM decree 37/1997.XII.5.), which blocks the way to successful healing (College of Dermatology).

We do hope that the presentations in the congress will help to coordinate the efforts for successful healing.

With best wishes,

Budapest, May 13., 2000.

Professzor Dr.Fehér János
President of the Board

Dr. Bózsik Béla Pál
Secretary for the Board

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Professzor Dr. János Fehér
President of the Board, Lyme Borreliosis Foundation, H, EU

Secretary for Congress:
Dr. Béla P Bózsik
Secretary of the Board, Lyme Borreliosis Foundation, H, EU

Scientific Comitte for the Congress:
Colleagues for the Therapeutic Board, Lyme Borreliosis Foundation, H, EU

Professzor Dr. János Fehér
President of the Therapeutic Board
Dr.Timmer Margit
Secretary of the Therapeutic Board
Dr. Béla P.Bózsik
Dr. Klára Esztó
Dr. Éva Csoma
Dr. Andrea Hollósy
Dr. Anna Pornói
Dr. Márta Schleer

The International Scientific Congress
of The Lyme Borreliosis Foundation
CONGRESS VENUE

The **Tea Salon** of Danubius **Hotel Gellért**

Official languages: English
and Hungarian (with interpretation)
Registration fee: 40 USD After March 25, 2000

Services included in the full registration fee:
- entry to the lectures
- interpretation
- entry to the exhibit
- scientific material of the Congress
- congress bag
- three free coffee breaks

Danube room lunch tickets (3500 HUF) can be ordered at the Congress Office

Congress Office hours (in the lobby of the Tea Salon)
May 12, 2000 from 7 AM to 4 PM
May 13, 2000 from 8 AM to 1 PM

Certificates of Attendance will be issued at the Congress Office. Here you can also subscribe to a publication that will contain the full text of the lectures. This will probably be published as a supplement to one of the Hungarian periodicals. The estimated price is 2000 HUF. Copies of the movie made by the Lyme Borreliosis Foundation, which will be playing continuously throughout the congress, will also be available here for 1500 HUF, and you can also subscribe to the educational multimedia CD-ROM (estimated price between 5000 and 10000 HUF).

Exhibits

There is going to be an exhibition of instruments and methods used in the prevention, diagnosis and treatment of Lyme borreliosis. It is going to be held in the Gobelin Room and on the gallery.

Information

If you need any information, please contact the MOTESZ Travel Agency:

Tel.: (36-1) 312-3807 Fax: (36-1) 302-5610

PLANNED SCIENTIFIC PROGRAM

Chairmen: Prof.Dr.Feher, President, Board of the Foundation

Friday, May 12, 2000

8.30 Inaugural speech about the Anniversary

I. The Roots — How The Community Helped The Patients in the Past

- the Christian Helpfulness,
  prof.Dr.József Török,historian for Curch,Pázmány Péter Catholic Univ. Bp.,H –15'
- in the New World,
  Karen Vanderhoof-Forschner Lyme Disease Foundation, Conneticut,USA, Founder –15'
- in Hungary, during and after the communist era,
  Dr. Béla Bodnár, Assistant for Political Changing, first legal adviser of the LBF –15'
- the past ten years of the LBF
  Dr.Bózsik, Béla Paul, secretary, Board, Lyme Borreliosis Foundation, Founder –15'

II. About The Vector Of Lyme Borreliosis

- Ecology of the agent of Lyme disease,
  Sam Telford, III[rd] Harvard Med.Univ.,MA,USA –15'
- the diseases spread by ticks and their differential diagnosis
  prof.Dr.Mikola István, President, Hungarian Society for Zoonoses –20'
- ways of prevention; bio-pesticides in the eradication of ticks
  Dr.Bratek Zoltán,mycologist, Eötvös Loránd University,Budapest,H –10'

III. The Epidemiology Of Lyme Borreliosis – Theory vs. Practice

- the epidemiology of Lyme Borreliosis in (Central) Europe
  prof.Dr.Gerold Stanek, Hygiene Institute, University of Vienna

IV. About The Causative Agent

- its discovery and biological properties
  Guy Baranton,Pasteure Inst.Paris,F –25'
- its sensitivity to antibiotics
  Uwe Neubert, Dept.Dermatology, Univ.Münich,D –15'
- alternative forms of the Lyme Disease Spirochete – Borrelia burgdorferi
  Claude Garon, CDC,Rocky Mountains Laboratorium,Mo,USA –20'
- its effects on the host: Lymphocytic tropism by *Borrelia burgdorferi.*
  D.Dorward,CDC,Rocky Mountains Laboratorium,Mo,USA –20'
- Public Health benefits of a Lyme disease vaccine.
  Sam Telford, III[rd] Harvard Med.Univ.,MA,USA –15'
- Bioengineering a Vaccine with a broad range of Specificity for Lyme boreliosis
  Benjamin J.Luft, Univ.Hospital Health Science Ctr. Stony Brook,NY,USA –15'

V. Lyme Borreliosis

- Immunology
  Prof.Dr.Péter Gergely, Clin.Dermatology, Semmelweis Med.Univ.,Bp.,H –20'
- Pathology, *Dr. Judith Miklóssy, Dept.Neuropathology,Univ.Lausanne,CH*–20'
- a new hypothesis for the pathogenesis of Lyme Borreliosis
  Dr. Béla Paul Bózsik, secretary, Board, Lyme Borreliosis Foundation, Founder –10'

VI. The Diagnosis Of Lyme Borreliosis

- about laboratory tests and how they should be interpreted
  prof.Dr.Gerold Stanek, Hygiene Institute, University of Vienna –20'
- interpreting CSF tests; about antibodies in CSF and the blood-brain barrier
  Dr. Christine Bencsik, Dept.Neurology,Szentgyörgyi.A.Med.Univ, Szeged –15'
- the Dual-Dur® reagent and classic dark-field microscopy
  Dr. Béla Paul Bózsik, secretary, Board, Lyme Borreliosis Foundation, Founder–15'

VII. The Clinical Picture

- the similarities and the differences of spirochetoses focused on Syphilis and Lyme Borreliosis *prof.Dr. László Török,Chief,Dept.Derm, County Hosp.Kecskemét,H* –15'
- Unusual cases of Lyme Borreliosis.
  prof.Dr.Elisabeth Aberer, Clinics for Dermatology, University of Graz, AT –15'
- differential diagnosis based on our experience
  Dr. Zoltán Horváth, Chief, Erzsébet Hospital, Sopron,H –15'

VIII. Estimation of the cost-benefit effect of Lyme borreliosis to the Society

- the costs to the society of treating LB depending on the quality of care
  Karen Vanderhoof-Forschner Lyme Disease Foundation, Conneticut,USA, Founder–20'
- the zoonoses in Hungary from the aspect of the occupational hygiene
  Dr.Nagy Attila, health advisory –15'
- the zoonoses in the aspect from insurance medicine
  Dr. Kéri Julianna, consultant – Dr.Horváth Imre leader health officer, Hungária Insurance Co. –15'

SATURDAY, MAY 12, 2000

IX. Therapy

- the art of Medicine and the GCP in the consideration of the bylaw
  Dr. Béla Bodnár, Assistant for Political Changing, first legal adviser of the Foundation–15'
- treatment of Lyme Disease: a North American Perspective
  Benjamin J.Luft, Univ.Hospital Health Science Ctr. Stony Brook,NY,USA –30'
- home-infusion: outpatient care – one-day hospital treatment
  David W.Kazarian, President, Am Soc of Consultant Pharmacologist,Fl –15'
- cardiological aspects: the gate to the infection of the entire body
  Dr. Kornélia Keszler, Cardiologist, Connecticut, USA –15'

X. The Experience Of The Members Of The Therapy Workgroup Of The Lyme Borreliosis Foundation

- the combined antibiotic therapy in experiments and in the literature
  Dr. Béla Paul Bózsik, secretary, Board, Lyme Borreliosis Foundation,–15'
- dermatology: the key to diagnosis and therapy
  Dr.Clara Esztó, Chief Dermatologist, Hospital for Sports
- Lyme Borreliosis in the practice of family practitioners
  Dr.Martha Schleer, internist, family doctor in the capital
- rheumatology: pitfalls and new perspectives in Lyme Borreliosis

Dr.Anna Pornói, internist, rheumatologist,Jávorszky County Hospital,Vác,H –15'

- the two faces of neuroborreliosis:

** neurology *Dr.Andrea Hollosy, neurologist* –15'
** psychopathology *Dr.Clara Őry, psychiatrist* –15'

- Lyme Borreliosis oculi
  Dr.Eva Csoma–Dr.Gabriella Burka,opthalmologists St.John Municipal Hospital,Bp,H
- our experience with a ten-year follow-up of Lyme Borreliosis patients
  Dr.Margit Timmer–Dr. Ildikó Vincze, Dermatologists,Outpatient Dermatology,
  St.Rokus County Hospital,Budapest,H –15'

XI. Therapeutical Guidelines Of The Members Of The Therapy Workgroup Of The Lyme Borreliosis Foundation – Closing Speech –15'

A CHRISTIAN HELPFULNESS

Professzor Dr. Török József
Pázmány Péter Hittudományi Egyetem, Budapest, Magyarország

Christianity took the teachings of Jesus Christ very seriously, including the healing and the tending to of the sick. This many times included the looking after of the poor and broken hearted. After the Christian persecutions, the parameters of the institutions broadened, first of all amongst the religious orders. In their rules there were separate chapters dealing with the tending of the sick, which stressed the fact that they must pay special attention to them. Outside of medicine, they have the right to nutrients which helped them in the in their physical strengthening. The religious orders, being near hot springs not only aided their own sick, but those who lived in the surrounding area.

The main turning point occurred after the first Christian Campaigns when in **1099** the Christian knights occupied Jerusalem. Around he already functioning hospital and the chapel of St. John, a community formed of who's duties were to tend to the sick and give shelter to the pilgrims. Gérard de Martigues was the first leader of this community and in 1113 attained approval from the pope. The community, which tended to the sick, quickly became an order of knights, and within their rules, they precisely and to exhaustion gave orders on how to tend to the sick.

Along with the healing of the physical body, they at the same time connected this with the healing of the soul. This was a marker for the **Merciful Order** founded in the 16th century.

There was a separate order of knights, which tended to the lepers in Europe of the middle ages.

In the new age, first of all the female orders undertook to the tending of the sick and within these orders the physical-spiritual healing as one unit ruled as the basic christian principle, which is prevalent in today's christain society.

TEN YEARS OF THE LYME BORRELIOSIS FOUNDATION

Béla P. Bózsik, M.D.
Lyme Borreliosis Foundation, Budapest, Hungary

I proposed the terminus technicus for the name of the disease in 1984-85. I initiated to set up a Foundation in Hungary in 1990. The Lyme Borreliosis Foundation was officially registered in 1991, with a mission to support the research and therapy of Lyme Disease, and to inform patients and doctors about it.

The logo of the Foundation represents winning the fight against the evil serpent the winner will tread on it without being harmed.

The activities of the Foundation can be summarized as follows:

- Supporting the scientific work in the Laboratory for Serology of the former National Institute of Hygiene: building a computer network and develop soft-ware for processing the data,
- Helping to inform patients and easing the work of doctors via information booklets,
- Producing a video film and a computer game to share the information with the wider public and mass media: the cut down version of the video and the demo version of the game will demonstrate the work of the Foundation.
- The therapeutic workshop of the Foundation gives professional advice about the prevention, diagnosis and therapy of Lyme borreliosis.
- Supporting the research for new diagnostic methods and therapies.
- Organizing international scientific cooperation, as a part of this, the foundation organized this international scientific Congress in Hungary, at the tenth anniversary of the Lyme Borreliosis Foundation.
- Helping to change the Hungarian regulations for the benefit of the patients. One fact that should be emphasize the importance of the disease: as a result of the work by social organizations and scientists, state Connecticut has just passed a law that allows a three month therapy in the case of Lyme borreliosis. This should lead us to change the current Hungarian therapy and prescription regulations.

ECOLOGY OF LYME DISEASE

Sam R. Telford III, D.Sc. Dept. of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts USA.

The various related spirochetes comprising Borrelia burgdor-feri *sensu lato are maintained in a* ***Holarctic distribution*** *by ticks of the Ixodes persulcatus species complex.*

The adult stage of these "deer" ticks seem to require a medium sized to larger mammal for the reproductive (definitive) host. Immature ticks (larvae and nymphs) will also feed on large mammals, but may also infest smaller mammals, birds, and reptiles. Although there is utility in conceptualising ***the main hosts*** *for the tick life cycle as deer for adult ticks, and the ecologically dominant muroid rodent for immature ticks, such relationships vary spatially and temporally. Similarly, although dogma suggests that the main reservoir hosts for Lyme disease spirochetes are the locally ecologically dominant mouse (in northeastern U.S.,* Peromyscus mice*; in Eurasia* Clethrionomys voles *and* Apodemus mice*), again, these* ***associations may vary in time and space.***

Nevertheless, over the scale of evolutionary time, ***Lyme disease spirochetes*** and the other zoonotic microbes associated with "deer" ticks (babesiae, ehrlichiae, and tickborne encephalitis viruses) ***appear to be well adapted to*** *rodents, suggesting that for ecological and epidemiological investigations of new foci, such animals should be considered the main reservoir until proven otherwise.*

*Variations on the primary theme –****local adaptation****– will always be present in a given focus of transmission, but the relative importance of such variation needs to be described.*

Examples of discrepancy within the published literature regarding the "importance" of various species as reservoir hosts for Lyme disease spirochetes may accordingly be explained by such local adaptation.

DISEASES TRANSMITTED BY TICKS AND THE DIFFERENTIAL DIAGNOSIS THEREOF

István Mikola, MD, General Director
Chairman of the Hungarian Zoonosis Society

About half of the identified 200-220 types of zoonosis of different etiology fall under the category of **cyclozoonosis**, where pathogens (bacterium, virus protozoon) are transmitted by some vector (ticks, mosquitoes, bloodsucking flies, louses, fleas, and other hymenoptera) from infected individuals (animal or human) to susceptible ones.

In Hungary, ticks are the primary vectors. According to recent studies, Ixodes ricinus, Dermacentor marginatus, D. pictus, D. reticulates, Haemophysalis concina, and H. punctata are the most common species.

All tick species are **real or biological vectors** meaning that pathogens are able to reproduce in their digestive canal and organs, while eggs separating from the ovaries transmit the pathogens to offsprings of various forms of development (larva, nymph, and imago) contributing not only to the **horizontal**, but also to the **vertical** spreading of the disease.

Vectors play a double role. Firstly, **their body gives shelter** from outside factors, which may be destructive for pathogens such as dehydration, UV radiation, pH changes, antibiosis, thus ensuring prolonged survival of pathogens. Secondly, they provide **optimal conditions for reproduction** for different pathogens. By the beginning of the invasive period (spring, early fall), an invasive dose of a great germ count of 10^6-10^9 will be developed in their body, which they may transmit through bloodsucking within their area of vagility.

Among cyclozoonosis cases in Hungary, I would like to present our experience regarding the epidemic nature, clinicopathology, treatment, and prevention of

- tick encephalitis,
- Lyme-disease,
- Q-fever, and
- tularaemia.

The **prevention** of cyclozoonoses is a complex task requiring a well-coordinated and extensive professional cooperation. In order to **prevent the overpopulation** of small rodents (mice, voles, shrews, moles, hedgehogs) and other wild animals (forest mammals and birds) constituting the primary bio-ecological systems as well as of the vector fauna living close together with such animals, nature-friendly agro-techniques, rational plant protection, and continuous water management are a must. In addition, **rodents and ticks shall be exterminated**. With repellent agents, **vectors shall be kept away** from both animals and humans as well as **exterminated** on the body surface of animals by applying acaricides. The most important daily task, however, is to **remove ticks immediately** after hiking or other outdoor activities. The above tasks are not medical issues, although they are a precondition of successful prevention. Medical enlightenment, clarification of the origin of suspicious pathographies, precise pathognomy, well-timed immunization, and, if required, a targeted therapy are, however, the responsibility of specialists and the patent's fate is subject to their proficiency.

METHOD OF PREVENTION: THE USE OF BIOPESTICIDES FOR TICK CONTROL

Dr.Bratek Zoltán, mycologist, Eötvös Loránd University, Budapest,Hungary

The most common diseases of insects are caused by viruses and fungi. The use of viruses is very problematic due to difficulties of their artificial production. Products based upon entomopathogenic fungi as new pest control agents have recently become commercially available. In favorable weather conditions, natural epizootics of entomopathogen fungi can significantly reduce insect populations. Conidia of entomogenous fungi germinate on the surface of insect cuticle and infect their insect hosts rather by active penetration of the insect cuticle than via the host's digestive tract. Most entomopathogenic fungi convert to a yeast-like phase in the haemolymph. Penetration of host tissues will disrupt host physiology and cause death of insects.

Relatively few papers have been published in the field of the biology of entomogenous fungi in ticks. Moreover, neither the distribution of tick species, nor the limits of their populations are discovered in Hungary. In addition to taxonomical problems, difficulties in collecting ticks due to their hiding behavior also make our work more complicated.

We collected ticks from natural tick populations in the Carpathian Basin to isolate many new strains of entomopathogenic fungi. As a result, we managed to isolate strains of Paecylomyces species many times. Some strains of Beauveria bassiana, Pandora neoaphidis and Fusarium spp. were also isolated. Scopulariopsis brevicaulis was frequently detected in dead ticks. This species seems to be a saprobiont without any role in fungal pathogenesis in ticks. Frequent occurrences of certain yeast species were found. Mycosis of tick eggs caused by Fusarium was not rare. Based on comparisons of isolated fungal strains, differentiations on tick populations were made.

Under optimal conditions, artificial infection leads to almost total mortality in 11 days. Re-isolation from sporodochium of Paecylomyces species formed on dead ticks were successful confirming that the Paecylomyces strains used are primary pathogens. Further studies are required on using detergents and adjuvants, which allow spore germination at suboptimal relative humidity and cause effective dispersion of hydrophobic spores.

To ensure the widespread use of mycoinsecticides against ticks, inexpensive and efficient methods of their use in the field must be developed.

EPIDEMIOLOGY OF LYME BORRELIOSIS IN EUROPE

Gerold Stanek, MD
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National Reference Centre for Borrelia
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Globally, Lyme borreliosis is the most frequent tick-borne bacterial disease. Only hard ticks of the genus Ixodes are known to transmit *Borrelia burgdorferi* sensu lato to humans. At least three genospecies cause disease in humans, *B. afzelii*, *B. burgdorferi* senus stricto, and *B. garinii*.

In central Europe the transmission of borrelia occurs already **after a tick attachment period of less than 6 hours in up to 18 % of cases**; the average attachment period is 24 hours in the majority of cases. It is evidence based that the way of tick removal (eg. by ointment, twisting, nail polish) does not increase the risk of infection. Tick-bites occur most frequently on Saturday and Sunday (about 43 % of all). This underlines that Lyme borreliosis is predominantly an infection of leisure. The location of the tick-bite on the body depends on the contact with the ground. In children more than 75 % of the bites are seen on head and neck; in adults most bites occur on the lower extremities, inguinal and gluteal region and lower abdomen. In army recruits who were exposed to the ground during combat training, tick-bites were predominantly seen on the upper extremities (ca 40 %).

Results of a population based study in Bavaria show that 16 % of the entire population experience a tick-bite per year. The rate of developing Lyme borreliosis after tick-bite was found to be 3 % on average.

By seroconversion (serum antibodies in a second sample two to four weeks after an initial negative sample after tick-bite) **about 20 % were found infected without clinical manifestation.**

The annual incidence rate of Lyme borreliosis is highest in countries of central Europe such as Slovenia, Austria and Southern Germany. Recent data reveal that **the incidence amounts to 0.7 %** on average in these countries.
The number of patients treated for Lyme borreliosis per year in Austria was found to be 11 per practitioner. If one considers this figure as accurate (based on the clinical diagnosis of Lyme borreliosis) **the incidence rate would further increase to 1.5 %.**
However, the uncertainty in establishing reliable data of the incidence of Lyme borreliosis is due to the difficulties to prove even the specificity of early manifestations. The specific diagnosis could only be assessed by culture of the agent from skin or body fluid. Usually, this is not the routine procedure and it is known that serology can not assist in this stage of the disease. Further, there are clinical features which are still poorly defined. Then, it is still a matter of controversy whether borrelia can be cleared completely from the body by antibiotic therapy.
At present, **in 18 countries of Europe reporting of Lyme borreliosis is mandatory**. However, reporting of Lyme borreliosis alone would not guarantee that more reliable data will be obtained. The drawbacks in establishing incidence and prevalence data are mostly due to missing facilities for long-term observation of patients.

DISTINCT LEVELS OF GENETIC DIVERSITY ARE ASSOCIATED TO DIFFERENT ASPECTS OF PATHOGENICITY OF *BORRELIA BURGDORFERI SENSU LATO*.

Guy Baranton and Daniele Postic Institut Pasteur Paris FRANCE

Initially described as a single species, *Borrelia burgdorferi sensu lato* is now considered as a complex of a dozen species. Several of these species are sympatric, however their respective associated ecological niches, remain unclear. Probably, the host spectrum of a given species plays a major role, i.e. birds for *B. garinii* (*B.g.*) and *B. valaisiana* in contrast to rodents for *B. afzelii* (*B.a.*).

Among the up to now 12 described species, only 3 are clearly pathogenic for humans : *Borrelia burgdorferi* sensu stricto (*B.b.*s.s.), *B.g.* and *B.a.*. Usually, the chronic evolutive forms of the disease are mutually exclusive. It has been shown by both direct (PCR and isolation) and indirect (serology) methods that each of the 3 pathogenic species is preferentially associated with a given clinical presentation :

- *Borrelia burgdorferi* sensu stricto: **arthritis**,
- *Borrelia garinii*: **neurological disease**,
- *Borrelia afzelii*: **cutaneous syndroms**.

However, the situation is complicated by the **frequent association of 2 or more species, both in ticks and in hosts.** Nevertheless, there is a clear correlation between the geographical distribution of the *Borrelia* species and the local predominance of a given clinical presentation.

Recently, a huge diversity of sequences of the *ospC* gene, has been documented. More than twenty highly distinct genotypes are recorded in each of the 3 main species. A hypothesis is that *B.b.*s.l. developed a kind of repertoire of OspC different epitopes to escape the host immune response. This decreases the risk for a previously infected tick by transtadial way to be cured when feeding upon an immune host.

Unexpectedly, the *ospC* sequences of strains isolated from human skin (Erythema migrans) represent only a fraction of the possible genotypes. Moreover, sequences from *Borrelia* isolated from chronic Lyme disease, are associated with a further reduced fraction of the *ospC* genotypes.

In conclusion, the preferential organotropism of the bacterium appears to be in part driven by its taxonomy, although the duration and severity of the disease appears to be under the control of a single gene: *ospC*.

BORRELIA BURGDORFERI SENSU LATO – ITS SENSITIVITY TO ANTIBIOTICS

Professor Dr. UweNeubert, Clinic for Dermatology, University of Munich, Germany

Since the discovery and cultivation of the etiologic agent of Lyme disease in the early eighties, it became possible to examine its sensitivity to antibiotics by in vitro and in vivo studies. In the meantime several investigations using different compilations of borrelial strains ranging between 1 and 30 tick and human isolates have been performed. Generally, the results of these studies confirmed clinical experience in the antibiotic therapy of Lyme borreliosis. However, the efficacy of penicillin, over decades the antibiotic preferred by European dermatologists in treating Erythema migrans and Acrodermatitis Chronica Atrophicans patients was initially somewhat underestimated due to inadequate test methods. With the macrolides, especially with erythromycin and roxithromycin, discrepancies between excellent efficiency in vitro and insufficient therapeutic results in vivo became evident. In the contrary, most betalactam antibiotics, e.g. the aminopenicillins and the newer cephalosporins proved to be effective in vitro and in vivo. With the tetracyclines, high concentrations are needed to achieve borreliacidal efficacy. However, comparing and assessing the results of the in vitro studies concerning the inhibitory and borreliacidal activities of antimicrobial agents one has to consider that up to the questionable suitability of BSK media for susceptibility testing, the size of inocula, the appropriate time of incubation considering the stability of antibiotics and the basic definitions of inhibitory and killing activity towards *Borrelia burgdorferi*.

Apart from these technical problems the total number of borrelial isolates hitherto examined in vitro is quite low. Considering the remarkable genetic variability of *Borrelia burgdorferi* sensu lato individual deviations in antibiotic susceptibilities may be far greater than generally believed. Apart from other strategies of *Borrelia*

burgdorferi to escape the attacks of immune systems and antibiotics like binding to and invading eucaryotic cells or changing morphologically into cystic persisters and individual though relative resistance to certain antibiotics should be taken into account as one of the possible reasons for unexpected treatment failures.

In own experiments comparing the antibiotic sensitivities of 24 *Borrelia burgdorferi* sensu stricto, *Borrelia afzelii,* and *Borrelia garinii* isolates we found several significant differences in minimal inhibitory and bactericidal concentrations of antibiotics between the three species.

Furthermore as routinely established in long-term treatments of chronic infections by slow-growing microorganisms like mycobacteria and already realized in first pilot trials, also combinations of antiborrelial agents should be included in prospective studies with a view to synergistic effects and the prevention of resistant germs.

ALTERNATIVE FORMS OF THE LYME DISEASE SPIROCHETE – *BORRELIA BURGDORFERI*

Claude F. Garon, Ph.D. Chief, Rocky Mountain Laboratories Microscopy Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana, 59840 USA.

Lyme disease is a multi-system disorder claiming increasing medical interest worldwide. The causative agent is a highly motile, helical microorganism measuring approximately 15 μm long and 0.2 μm wide and is classified as a member of the genus *Borrelia*. An outer sheath completely surrounds the protoplasmic cylinder. Between this protoplasmic cylinder and the outer sheath are wound the periplasmic flagella. While this description accurately describes both laboratory cultured *Borrelia* and clinical samples derived from Lyme disease patients, careful microscopy often reveals the presence of other structural forms which appear to be associated with borrelial growth.

These structures are of special interest and questions arise as to the role, if any, of these detectable bioproducts in the pathogenesis of Lyme disease. We have shown that naturally elaborated, outer membrane **blebs** are frequently seen both attached to spirochetes and free in growth media. These **are produced in enormous numbers** in *Borrelia burgdorferi* cultures and in other gram negative microorganisms as well. Using both scanning (SEM) and transmission electron microscopy (TEM), we demonstrated the presence of intact borrelial DNA molecules within these structures. Subsequently, using a capture/detection method, we were able to find evidence of these structures in infected ticks, animals and humans and, importantly, this material was shown to possess a potent, non-specific, mitogenic activity for murine B-cells.

While biologically significant concentrations of several eukaryotic cell inhibitors showed little effect on the growth of *Borrelia burgdorferi* when added to BSK-II cultures, PPMP, a sphingolipid analogue, showed immediate and profound inhibitory effects when monitored by dark-field microscopy, TEM, field emission SEM and by optical density measurements.

PPMP(*dl-threo*-1-phenyl-2-palmitoylamino-3-morpholino-1-propanol) is known to inhibit the synthesis of sphingomyelin in chinese hamster ovary cells, to inhibit the synthesis of glucosylceramides in a large variety of mammalian cells, and to affect the tubovesicular membrane network of malaria infected erythrocytes. No direct effect on prokaryotic cells has been demonstrated. However, PPMP concentrations as low as 225 micromolar produced detectable effects on growth of *Borrelia burgdorferi*. Ultrastructural examination of these cultures by both SEM and TEM revealed a striking conversion of the worm-like, spirochetal form to a spherical morphology. Intermediate forms were readily detectable and the effect appeared to be both dose and time dependent. While **spheroplasting** *of spirochetes and many other bacteria* have been reported *following antibiotic treatment*, *this is the first description of such a morphological alteration using a specific lipid analogue.*

Backscattered electron detection following staining with the cancer drug, Cisplatin, has revealed DNA lining the inner surface of the outer membrane of the borrelial spheroplasts. Experiments are underway to further characterize the DNA, protein and lipid profiles of purified spheroplasts and, using the single cell isolation capability of the Cell Robotics Laser Workstation, to test for viability.

We would argue that *Borrelia burgdorferi* appears to produce a variety of alternative forms during growth, some of which possess potent biological effects. Therefore, the possibility that structures other than the viable, intact, spirochete might contribute to the persistence and/or pathogenesis of Lyme disease should be more carefully evaluated.

LYMPHOCYTIC TROPISM BY *BORRELIA BURGDORFERI.*

David W. Dorward, NIH/Rocky Mountain Laboratories, Hamilton, Montana, USA.

Lymphocytic involvement in dermatological, neurological, and musculo-skeletal pathology of Lyme borreliosis is well documented. Inflammatory lymphocytic infiltrations commonly occur at foci of symptoms exhibited by patients. During the last decade numerous studies have shown that spirochetes and spirochetal bioproducts including extracellular membrane vesicles and prominent membrane lipoproteins such as OspA, OspB, and OspC induce lymphocytic proliferation, polyclonal immunoglobulin secretion, and inflammatory cytokine production. Furthermore, several clinical studies have suggested links between prolonged infections with *B. burgdorferi* and development of primary cutaneous B cell, and possibly other lymphomas.

In order to investigate the role of spirochete-lymphocyte interactions in Lyme borreliosis, our laboratory has developed synchronized (in vitro), and murine (in vivo) model systems. For in vitro analyses, spirochetes and cultured or purified primary human or mouse lymphocytes are cooled to 4 degrees C, and mixed. Under these conditions attachment of spirochetes to susceptible lymphocytes occurs, but cell penetration is inhibited. After 1 hr, the mixtures are warmed to 37 degrees C, enabling progression of semi-synchronous bacterial-host cell interactions and resulting cytopathic events. Such in vitro work has shown that *B. burgdorferi* can target, invade, and kill both cultured and purified primary human B and T cells. Phenotypic segregation of susceptible and resistant populations of host cells, and of lymphotropic and non-lymphotropic *B. burgdorferi* indicated that both spirochetal and host-cell factors mediate the interactions. Fluorescent and electron microscopy showed that invasion and subsequent emergence from the lymphocytes could cause envelopment of spirochetes in one or more layer(s) of lymphocytic membrane. The enveloping membranes displayed lymphocytic antigens and effectively masked prominent spirochetal surface antigens. In the presence of susceptible lymphocytes, up to 30 percent of lymphotropically enriched spirochetes exhibited such

membrane envelopes. *Following removal of B and T cells by filtration, lymphocytic membrane envelopes persisted for approxi-mately one spirochetal generation.*

Although such processes have not been demonstrated in human patients, recent studies provided evidence of spirochetal-lymphocyte associations in experimentally infected mice. A population of *B. burgdorferi* strain Sh-2-82, enriched by affinity for L3T4 (CD4+), Lyt-2 (CD8+), and B220 (CD45+) mouse lymphocytes, was injected intradermally into young mice. At intervals ranging from 1 hr to 21 days, blood and spleens were recovered from infected and sham-infected mice. Lymphocytes were purified from the specimens using immunomagnetic beads. The beads and immobilized lymphocytes were placed into BSK-H medium and allowed to incubate for 10-21 days. Preparations of circulating and splenic lymphocytes from all animals injected with spirochetes produced cultures of *B. burgdorferi* at 2 and 3 days post-challenge. Recovery of spirochetal cultures was transient, with no cultures recovered at 6 or 7 days, and one culture recovered at 21 days post–challenge. No cultures were obtained from animals that were injected with medium lacking spirochetes, or from immuno-magnetic beads incubated with spirochetes alone. Immunoblot analysis showed that by day 4 all experimentally infected animals exhibited humoral responses to infection.

These results indicate that ***B. burgdorferi*** **is lymphotropic in vitro and in vivo**. In the mouse experiments, the association between the spirochetes and lymphocytes withstood density gradient centrifugation and several buffer and media washes, suggesting a direct and physically stabile interaction. Whether the processes of attachment, invasion, emergence, and the acquisition of lymphocytic membrane envelopes observed in vitro also occur in vivo remains to be determined. However, these findings suggest that **interactions with lymphocytes may represent a previously unrecognized niche**, possibly contributing to spirochetal colonization and dissemination in mammals, and to pathogenic consequences of Lyme borreliosis.

UTILITY OF LYME DISEASE VACCINES

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Although the etiology of Lyme disease was described no more than 20 years ago, knowledge has rapidly accumulated to the point that a first generation vaccine against infection and disease is now commercially available for human use in the United States.

A unique mode of action is apparent in *that circulating antibody stimulated by administration of Borrelia burgdorferi sensu stricto recombinant outer surface protein A (rOspA) is ingested during the bloodmeal taken by the infecting tick, and this serves to attenuate or destroy spirochetes before they are transmitted to the vaccinated host.*

Local variation in the antigenic structure of OspA, however, seems to argue against the use of this vaccine in sites where other members of *Borrelia burgdorferi* sensu lato are present (such as most sites in Eurasia).

Public health considerations provide both arguments for and against the need for or deployment of a Lyme disease vaccine.

- Lyme disease is usually easily treated with oral antibiotics when detected during the acute phase. However,
- sequelae may be severe for a small proportion of the population who become infected. In addition,
- the burden of Lyme disease in certain American communities is similar to that of gonorrhea in urban ("inner city") centers, and it is the most common arthropod-transmitted infection in much of the Holarctic.

Accordingly, public health considerations suggest that reducing incidence is generally meritorious, and even imperfect first generation vaccines may provide benefit to certain communities.

Much speculation has accompanied the development and testing of the current American rOspA vaccine inasmuch as this protein may activate plasminogen, or molecularly mimic LFA-1, suggesting the possibility of longterm adverse health implications for those who are vaccinated.

However, the vaccine dose and site of administration reduce the likelihood of plasmin-related pathology. Similarly, the potential for autoimmune complications of vaccination seems small at the level of populations inasmuch as no such pathology has been recorded for the thousands of subjects of the Phase II and Phase III testing.

BIOENGINEERING A VACCINE WITH A BROAD RANGE OF SPECIFICITY FOR LYME BORRELIOSIS

Professor Dr. Benjamin J. Luft

The overall efficacy of a recombinant vaccine depends upon:

1. *the selection of one or more immunoprotective target(s); and*
2. *the frequency of genetic variation which can alter the antigenicity of the immunoprotective epitopes of the target proteins.*

Careful delineation of protective epitopes on target antigens is essential for the development of vaccine candidates as well as to under-standing the limitations of such vaccines.

Structural models of these targets have provided us with critical information about conformation and specific residue surface accessibility for defining protective epitopes, and co-crystal structures with Fab fragments of protective antibodies further delineated critical antigen surfaces.
Population genetics provided vital information on the heterogeneity of these proteins.
Detailed epitope mapping provided the information needed for the bioengineering of chimeric antigens needed to expand the specificity of a candidate vaccine.
This approach provides a rational strategy for the selection, testing and design of recombinant Borrelia surface proteins as vaccine candidates for the prevention of Lyme borreliosis by merg-ing structural and molecular approaches.

We have used such an approach to develop a vaccine for Lyme borreliosis which has a broad range of specificity against ***all three genospecies*** *of Borrelia burgdorferi sensu lato which cause Lyme borreliosis.*
These chimeric proteins do not contain putative autoreactive epitopes.
This may represent an important advance in the prevention of Lyme borreliosis.

IMMUNOLOGY OF LYME BORRELIOSIS

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Lyme disease is caused by infection with the spirochete Borrelia burgdorferi (and related species). Some infected patients – without medical intervention – clear the spirochetes, while others mount an insufficient immune response allowing reinfection or chronic disease, resulting in joint, neurologic, cardiac and skin inflammatory symptoms. In most cases without therapy, spirochetes persist in the tissues for a long period.

The humoral immunity (i.e. antibodies) is essential in Lyme disease. In SCID mice, lacking B and T cells, T cell transfer cannot protect animals from infections while transfer of splenocytes (B and T cells) does. IgM antibodies can usually be detected 3-4 weeks after infection, IgG antibodies appear usually after 6 weeks. However, in some cases of chronic infection, there are no detectable antibodies. IgG antibodies may persist for years even after successful eradication of spirochetes. Antibodies are directed against a number of Borrelia antigens. Some of them can be used for serological diagnosis. Antibodies against outer surface protein (Osp) A and B exert a direct cytocidal effect on spirochetes. It is of special interest that an IgG1 antibody (termed CB2) against OspB, can cause lysis of the outer membrane of the spirochete without complement, the mechanism of which is unknown. These antibodies can prevent infection but unable to clear parasites. This effect is of great interest, for the vaccination strategies are based on these antibodies.

T cell response against Borrelia antigens (in particular against OspA) can be detected usually in the chronic phase of the disease. It is disputed, whether strong T cell response is associated with autoimmune phenomena (see below), or not.

The lack of effective immune response results in the presence of spirochetes in the tissues. We do not exactly know why parasites can escape host defenses. There are many, though incomplete

explanations for this phenomenon: a) hiding in privileged sites, b) antigenic variation, and c) intracellular localization. The exact reasons for persistence remain to be elucidated.

Autoimmunity, like in other chronic infections, as a consequence of antigenic persistence and molecular mimicry (cross-reactivity) may lead to the activation of autoreactive cell clones resulting in a sui generis autoimmune disease. Autoimmunity is suspected both in neuroborreliosis and in chronic Lyme arthritis. The etiopathogenesis of such cases of chronic Lyme arthritis resembles to that seen in reactive arthritis.

In most cases, Lyme arthritis can be treated successfully with antibiotic therapy. About 10% of patients are resistant to therapy, and the clinical features in these patients resemble to that seen in rheumatoid arthritis. No traces of spirochetes can be detected in the synovial samples of 90% of such patients. This indicates that synovitis may persist in some patients with Lyme arthritis after the apparent eradication of parasites from the joints.

The role of molecular mimicry in autoimmunity in Lyme disease has been suspected for a long time.

1. OspA and human leukocyte function-associated antigen (LFA-1, or CD11a/CD18, or integrin $\alpha_1\beta_2$) share homologous peptide sequence which may serve as autoantigen. Indeed, synovial T cells from patients with chronic Lyme arthritis react with this peptide or with intact LFA-1, while other patients fail to do so.

2. A cross reactivity between human heat shock protein (hsp) 60 and Borrelia antigens was also found (n.b. a cross reactivity between Mycobacterial hsp 65 and human hsp 60 family has long been observed in rheumatoid arthritis).

It has been supposed that patients with appropriate **genetic background** after priming with Borrelia infection can develop a chronic autoimmune arthritis. While HLA B27 (an MHC class I antigen) has something to do with the development of reactive arthritis, in chronic Lyme arthritis the role of HLA class II antigens is suspected. It has been supposed that HLA DR4 positive individuals are more prone to develop such cronic Lyme arthritis.

SOME HISTOLOGICAL ASPECTS OF NEUROBORRELIOSIS

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Using silver techniques, the number of spirochetes in the infected tissues was reported to be very low[1]. When immunohistochemistry or polymerase chain reaction (PCR) is used, the antigenic and genetic variability of the spirochetes may render their detection difficult. Using PCR the outer membrane protein genes OspA and OspB of Borrelia burgdorferi have been detected in the tick vector, but not so far in synovial fluids or tissues of patients with Lyme disease[2].
Here, some difficulties related to the histopathological diagnosis of neuroborreliosis are discussed. Some histopathological data of neurosyphilis are reviewed and some recent observations derived from our laboratory are presented with respect to the neuropathological diagnosis of Lyme disease.

Striking similarity between neurosyphilis and neuroborreliosis

The striking similarity of the clinical but also of the pathological manifestations of neurosyphilis and neuroborreliosis was reported by several authors[3]. The pathogenic role of Treponema pallidum was clearly established in several chronic neurological disorders. It is therefore understandable that current research focus on the putative role of Borrelia burgdorferi in several chronic neurologic and neuropsychiatric disorders. Even the occurrence of dementia associated with cortical atrophy and microgliosis, known to occur in late stages of neurosyphilis, was reported in the tertiary stage of neuroborreliosis[1].
Spirochetes may invade the parenchyma of several organs, including the brain without the challenge of lymphoplasmocytic inflammatory

reaction[1,4]. As early as in 1907, Benda[5] discovered massive conglomerations of spirochetes without inflammatory reaction in the organs in cases of a congenital syphilis. In 1906, Sträussler[6] described peculiar multiple "miliary areas of necrosis" in the cerebral cortex in a case of dementia paralytica and Gruetter[7], Hauptmann[8], Herschmann[9] and Schob[10] demonstrated "balls of spirochetes" as the cause of these necroses. Noguchi and Moore[11] published their work in 1913, establishing that Treponema pallidum is the causative agent of general paresis. Jahnel[12] described the dissemination of the micro-organisms scattered through the cerebral cortex in the form of circumscribed colonies, or thick masses collected around cortical blood vessels. Dieterle[13] reported black argyrophilic patches of spirochetes in the brain and noticed that in many instances they dotted the entire convolutional arch. Pacheco e Silva[14] noticed that the proliferation of spirochetes in the form of colonies in the cerebral cortex was particularly associated with the atrophic form of general paralysis which corresponds to the progressive stationary paralysis. All the authors agree that the accumulation of spirochetal colonies is confined to the gray matter, particularly to the cortex, and that their presence in the white matter is rare.
Steiner[15] pointed out that in artificial mediums, cultured spirochetal colonies show a striking resemblance to the appearance of the spirochetal conglomerations in congenital syphilis and dementia paralytica. Microscopically, theses colonies showed yellowish centers from which strands of shiny black spirochetes radiated peripherally. The occurrence of amyloid deposition in syphilis including in the tertiary stages of neurosyphilisis is well known. Similar colonies of spirochetes were observed in the cerebral cortex of three patients with chronic neuroborreliosis[16]

Polymorph and/or degenerative form of spirochetes

The characteristic spiral and helical shape of the spirochetes is known to be sensitive to changes in unfavorable physico-chemical environment. With respect to Treponema pallidum, Warthin and

Olsen (1930)[17] reported the almost constant association of granular silver staining forms with perfectly preserved spirochetes in the lesions of latent syphilis. They have pointed out that the degenerative forms may be present, even when the typical spirochetes may be apparently absent. So-called granular form of spirochetes were described by Pacheco e Silva[14] in the cortex of general paretic cases. In joints of patients with Lyme arthritis spirochetes and globular antigen deposits were also seen in and around blood vessels in areas of lymphocytic infiltration[18]. Degenerating spirochetes are recognized by the presence of spherical granules on one or both ends of the individual organism, by deformed spirals, by ring or loop formation, by parts fused together or even by isolated granules[15].
Histochemical, immunohistochemical and ultrastructural investigations, using transmission electron microscopy and atomic force microscopy was performed in our laboratory in order to analyze polymorphism of Borrelia burgdorferi in different culture conditions or when co-cultured with mammalian cells. Our results revealed obvious morphological changes, indicating, that like reported in syphilis, degenerative or atypical forms of Borrelia burgdorferi may be present in infected tissues, even in the absence of typical regularly coiled spirochetes. Therefore, to consider the presence of these polymorph, degenerating spirochetes in the histopathological diagnosis of Lyme disease is important.

Natural and synthetic bacterial components, by their biological activities, may induce chronic inflammation and amyloid deposition in mammals.

Not only the natural but also the synthetic bacterial components (e.g. bacterial peptidoglycan) are inflammatory cytokine inducers, activate complement of the classic pathway, affect vascular permeability, generate nitric oxide and induce apoptosis and proteoglycan synthesis. Bacterial cell walls are highly resistant to degradation by mammalian enzymes, and thus may provide a

persisting inflammatory stimulus[19,20]. Persisiting bacterial remnant may well be a factor triggering cascade of events which would resulting in chronic inflammation and amyloid deposition.

I would like to join Fallon and Nields[1] to stress that "The lessons painfully learned in syphilis apply here: delays in diagnosis and treatment can result in a treatable, acute illness becoming a chronic one with, in some cases, with devastating consequences."

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A NEW HYPOTHESIS OF PATHOGENESIS

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Lyme borreliosis is known to be a chronic progressive disease of the whole body. The causative agent is present in unusually low numbers. Host immune responses are oscillating and disproportionate with periods of hyperactivity as well as apparent inadequacy. What follows is a tentative explanation for all this, based on the data I have collected in thirteen years.

Authors apparently agree that – except for the initial period of hematogenous spread – Borrelia burgdorferi sensu lato cannot be detected in the circulation regardless of the technique employed. My experience is not consistent with this finding. During the course of Lyme borreliosis, I was able to detect Borrelia burgdorferi sensu lato with dark-field microscopy of most native blood samples concentrated 1000 times. My results were confirmed by the studies of Wormser et al. and are also supported by theoretical considerations. During the development of Lyme borreliosis, more and more organs are known to become affected, which indicates that repeated spreading may occur (in addition to being a sign of changing pathogenicity). Moreover, during patient follow-up, late-stage autoimmunity-related symptoms were always alleviated by antibiotics, which also suggests that the pathogens are still present in advanced disease. Disease progression may even be stopped by a combination of yet another antibiotic cure and attempts at restoring the immune system. After such treatment, the patients only needed medications to relieve the symptoms of permanent pathological changes.

Detailed patient history and follow-up revealed that there is no connection between the emergence of symptoms and the detectability of the causative agent. This is probably best explained by the unique properties of this pathogen rather than individual differences.

Borrelia burgdorferi is well-adapted to its hosts. Genetic polymorphism plays an important role in this process. Cross-reactivity between Borreliae and certain host tissue antigens is one sign of adaptation; this is why the Lyme borreliosis spirochete is not

detected early in the disease. Thus, Lyme borreliosis begins as a chronic infection. Chronicity is also explained by the fact that the causative agent inhibits the immune response in many ways. This is why inflammatory infiltrates are minimal, if present; MHC class II antigens and IgM to IgG conversion are inhibited. The latter explains the persistence of IgM. With time, Borreliae managed to acquire phagocyte-membrane envelopes to protect themselves while, at the same time, they can misdirect host immune responses by producing leukocyte factors that cause systemic inflammation. Intact Borreliae can repeatedly produce leukocyte factors, which is why a low number of pathogens can induce a disproportionate systemic reaction. These events, however, do not seem to occur often enough to explain all of the features of the pathogenesis of Lyme borreliosis.

Borreliae, including Borrelia burgdorferi sensu lato are known to be capable of a process called shedding both in vitro and in vivo. This process is documented in a native sample in the figure attached. The inserts are the pictures of immunofluorescent staining with monoclonal antibodies from Professor Barbour; they prove that the spirochetes in the pictures are Borrelia burgdorferi sensu lato and suggest that, besides peripheral shedding, another (central) type of shedding also exists, which involves the flagellar antigens„D".

The spheroid bodies shed are 0.5 micrometer wide, have no cell wall but may even contain DNA beside the surface antigens of Borrelia burgdorferi (Osp-A, B and D), antibodies and complement. Enzymes may accompany these in the outer polysaccharide envelope. The spheroid bodies (blebs) shed are the type of immune complexes that experimental evidence proved to be the most effective inducers of immune response against the components of the blebs. This is why, theoretically, several different antibodies and autoantibodies are expected to develop in Lyme borreliosis. Sigal also considers these immune complex blebs to be a factor of pathogenesis. The in vitro blastogenesis and IgM production induced by the blebs proves their antigenic properties, which is also reaffirmed by fact that a diagnostic technique is based on them.

The development and shedding of blebs (which move along the surface of the pathogen) in native samples can be provoked with

penicillin; their movement and the process of shedding is inhibited by doxycyline. This suggests that intracellular structural proteins and cell metabolism are affected. During the examination of native samples, I saw several instances of shedding and also had a chance to see the "naked" spirochetes after the shedding.

Based on my own observations, several case reports and the literature I reviewed, I contend that there are three main stages in the pathogenesis of Lyme borreliosis:

I. The spirochetal stage: the pathologic process is limited to the surface of Borrelia burgdorferi. The few immune complexes formed are neutralized by the host or complement activation. No specific antibodies can be detected and there are no symptoms, but the process has begun.
II. The infectious stage: the targeted organs become affected. The immune response is mounted; there are signs of moderate autoimmune reactions.
III. Autoagressive stage: Pathologic processes seem to be autonomous (independent of the causative agent). In fact, Borrelia burgdorferi sensu lato still plays a role, which is suggested by the effectiveness of antibiotics.

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DIAGNOSIS OF LYME BORRELIOSIS: PROTOCOL FOR THE PRACTICE

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Agents of disease

Borrelia, bacteria of the family Spirochaetaceae.
B. burgdorferi sensu lato (s.l.), 10 species, 3 borrelia species are currently considered human pathogens: **B. afzelii**, **B. burgdorferi** sensu stricto (s.s.), **B. garinii**

Endemic areas

Northern hemisphere
(North-, Central- and Eastern Europe, Asian parts of Russia, China, Japan)
Geographic distribution of borrelia species:

Europe:	**B. afzelii**, **B. burgdorferi** s.s., **B. garinii**
Asia:	**B. afzelii**, **B. garinii**
USA:	**B. burgdorferi** s.s.

Transmission

By bite of hard ticks of the genus Ixodes:

I. ricinus	(Europe),
I. persulcatus	(European Russia and Asia),
I. scapularis	(USA east and central north) and
I. pacificus	(USA west);

In endemic areas up to 50 % of ticks are infected

Notice: Only about 60% of patients remember the tick bite

CLINIC

~20 % inapparent

Stage 1: Erythema (chronicum) migrans (in ca. 60 % only manifestation), Borrelia Lymphocytoma (rare manifestation), unspecific symptoms including stiff neck and shoulder pain (rare accompanying symptoms)

Stage 2 (ca 20%): Neuroborreliosis (radiculoneuritis, meningoradiculitis, cranial nerve paresis, meningitis, meningoencephalitis, radiculomyelitis, encephalitis, encephalo-myelitis), arthritis (intermittend), myositis, carditis, ophthalmitis (rare), hepatitis (very rare)

Stage 3:

chronic arthritis, acrodermatitis chronica atrophicans, chronic neuroborreliosis (very rare; meningoencephalitis, radiculomyelitis, encephalitis, encephalomyelitis)

CRITERIA FOR THE DIAGNOSIS

(according to: European Union concerted action on risk assessment in Lyme borreliosis: clinical case definitions for Lyme borreliosis. Wien Klin Wochenschr 108 (1996) 741-747)

Erythema (chronicum) migrans (EM)

Expanding red or bluish red patch usually located around the tick-bite site (≥ 5 cm in diameter), frequently central clearing, border clearly distinct and more intensely coloured but not markedly elevated, only rarely multiple erythemas

Results of laboratory tests NOT essential for the diagnosis of EM !

Culture or detection of B. burgdorferi s.l. nucleic acid in skin biopsies establishes – of course - the specific diagnosis

Borrelia Lymphocytoma (LB, rare)

Painless bluish-red knots or plaques, localised usually on ear lobe, ear helix, nipple or scrotum (more frequently seen in children, especially ear).

Supportive is a (mostly) concomitantly existing or previous EM**.**

Compulsory: increasing titre of IgG antibodies to B. burgdorferi s.l. or IgG seroconversion.

Supporting and for differential diagnosis: histological detection of a B-cell-pseudolymphoma.

Culture or detection of B. burgdorferi s.l. nucleic acid in skin biopsies establishes – of course - the specific diagnosis

Acrodermatitis chronica atrophicans (ACA)

consult expert in dermatology

Long lasting red or bluish-red skin disorder, usually on the extensor side of the extremities. Originally doughy skin swelling which will atrophy later. Possible skin induration over bony prominences.

Compulsory: Serology; high concentration of specific IgG-antibodies in serum.

Histological appearance and culture or detection of B. burgdorferi s.l. nucleic acid in skin biopsies establishes – of course - the specific diagnosis

NERVOUS SYSTEM INFECTION NEUROBORRELIOSIS

consult expert in neurology

Early Neuroborreliosis

Painful meningo-radiculoneuritis with or without facial palsy or other cranial neuritis (Garin-Bujadoux-Bannwarth syndrome). In children mostly meningitis, isolated unilateral sometimes bilateral facial palsy, other cranial neuritis. Supportive**:** previous or simultaneous EM.

Compulsory: Lymphocytic pleocytosis in CSF **and** intrathecally produced specific antibodies (send in CSF and blood) **or** culture and/or demonstration of specific nucleic acid sequences from CSF.

! Shortly after onset of symptoms demonstration of intrathecal antibodies may not yet be possible. In a disease of only a few days duration or in children with isolated facial palsy CSF pleocytosis may be lacking **!**

Chronic Neuroborreliosis (very rare)

Long lasting encephalitis, encephalomyelitis, meningo-encephalitis, radiculo-myelitis.

Compyulsory: Detection intrathecally produced specific antibodies **and** lymphocytic pleocytosis in CSF **and** antibodies to B. burgdorferi s.l. in serum.

LYME CARDITIS

consult expert in cardiology/rhythmology

Unexpected, acut onset of AV-Block II-III, rhythm disturbances, sometimes myocarditis or pancarditis**. Supportive:** Previous or simultaneously existing EM.

Compulsory: Serology; detection of increasing titre of IgG serum antibodies to B. burgdorferi s.l. or IgG seroconversion.
Culture or detection of B. burgdorferi s.l. nucleic acid sequences in endomyocardial biopsies establishes – of course - the specific diagnosis.

LYME ARTHRITIS

consult expert in rheumatology

Acute onset of arthritis (objective joint swelling) of one or a few large joints, mostly the knee. Short and intermittent attacks and sometimes change to chronic arthritis and history of another manifestation of Lyme borreliosis during the previous year.
Compulsory: Serology; high concentration of specific IgG antibodies in serum.
detection of B. burgdorferi s.l. nucleic acid sequences in synovial fluid and/or synovial membrane sample establishes – of course - the specific diagnosis (culture is not recommended as the success rate is below 0.1%).

LABORATORY DIAGNOSIS

Serology

"Two Test Procedure" is current standard

Numerous commercially available products are available. Results obtained with those are not necessarily the same, neither quantitatively nor qualitatively !

Thus, results from different laboratories must not be compared with each other.

Rule: Change of antibody concentration in body fluids (blood, CSF) can only be determined if samples taken at various time points are tested simultaneously with the same system.

First Test

ELISA IgG (and IgM), with whole cell antigen or recombinant antigens,
Immunofluorescence assay with whole organisms , or
Hemagglutination assay with whole cell antigen

Second Test

Immunoblot (Western blot) IgG with whole cell antigen or recombinant antigens.

The Western blot result displays the reactivity of antibodies in body fluids with distinct borrelia protein antigens that were electr-ophoretically separated before. Because of the reactivity pattern one can decide whether the reaction is specific or unspecific.

Culture = growth of borrelia in artificial media

Culture of borrelia from skin, cerebrospinal fluid, blood, biopsy of muscle and endomyocardium, synovial fluid, and synovial membrane

Sample must be collected before onset of antimicrobial chemotherapy !

Culture and Identification of borrelia in reference laboratories.

Nucleic acid amplification techniques (NAT)

Borrelia nucleic acid ca be detected in various samples after the onset of antimicrobial chemotherapy.

Appropriate samples are: skin, synovial fluid, synovial membrane. NATs with cerebrospinal fluid, blood, biopsy of muscle and endomyocardium are restricted to certain diagnostic problems.

NATs should only be performed in experienced reference laboratories.

INTERPRETATION OF SEROLOGICAL RESULTS ("BORRELIA SEROLOGY", SERUM ANTIBODIES)

!! Never without knowledge of the patient and her/his disease !!

!! Positive borrelia serology alone is NO indication for antibiotic treatment !!

ANTIBODIES IN SERUM

IgM and IgG positive:	Without clinical manifestation no indication for treatment → control in 1 - 2 months
IgM and IgG negative:	Frequent result in patients with Erythema migrans; treatment compulsory despite lacking humoral immune response to the clinically clearly identified borrelia infection. Later serological examinations may also be negative or may become positive. The latter result does not show treatment failure .

IgM positive, IgG negative: Without clinical manifestation no treatment; control in 1-2 months; same result shows a problem of the IgM sensitivity of the test system used
→ reference laboratory.

IgM negative, IgG positive: Without clinical manifestation mere indication of previous infection, possibly incomplete immunity.
Control in 2-4 months

PROPHYLAXIS

Immunoprophylaxis

Recombinant OspA Vaccine (LYMErix™ SKB): ONLY for the USA, as only
B. burgorferi s.s. OspA serotyp 1 used, further 7 European serovars not included.

Rekombinant polyvalent OspC Vaccine (BAXTER Hyland Immuno):
Developed for Europe and Eurasia; currently in clinical trials.

Chemoprophylaxis after tick-bite

Is NOT recommended

DIAGNOSTIC PROCEDURES OF CEREBROSPINAL FLUID IN NEUROBORRELIOSIS.

Krisztina Bencsik
Department of Neurology, Albert Szent-Györgyi Medical and Pharmaceutical Center, University of Szeged, Szeged, Hungary

The American Academy of Neurology determined the indication of lumbar puncture in 1993. Based on the guidelines the examination of cerebrospinal fluid (CSF) necessary in inflammatory-, demyelinisation diseases and the subarachnoidal hemorrhage if the CT scan is negative. To diagnose neuroborreliosis as an inflammatory disease the CSF analysis is a basic requirement. The presence of the inflammation must be certified and the pathogen has to be determined if possible. In Bannwarth syndrome the CSF show aseptic encephalitis with characteristic increase of mononuclear cells (100-500 cell/μl). As a verification of the humoral immune response the Link-index is increased in the quantitative analysis of the CSF proteins and oligoclonal bands (OGB) can be visualized by the qualitative analysis.
The pathogen can not determine directly from the CSF. The most widely used diagnostic tests prove the presence of antibodies against Borrelia Burgdorferi.
To set up the diagnosis of neuroborreliosis the whole clinical picture have to be evaluated with the patient's history, the clinical symptoms and the results of CSF tests.

DualDur® REAGENT AND A CLASSIC MICROSCOPIC METHOD

Dr.Bózsik Béla Pál
Lyme Borreliosis Foundation Budapest, Hungary

The examination of Lyme borreliosis, as it was called in 1985 "*Lyme disease and related disorders"* was off to a head start , when the results from the **liofilezett savók** arrived from CDC. However, it was stopped just as fast as it started. The laboratory of serology at the leading institute of Hungary had to ask free examinations from Professor Stanek in Vienna between 1985-1988. The travel agency Budapest *Tourist* offered to transport the collected sera deep-freezed into Vienna.

In this way I had a special opportunity to compare the serological findings with the actual symptoms. It soon became clear to me that during the pathogenesis of Lyme borreliosis it is not only in the first 4-6 weeks that the production of antibodies is missing; it is not only after the initial antibiotic treatment that the immune reaction is decapitalised: the production of antibodies may change or even cease again and again during the evolution of the disease due to several factors. It became more and more evident that **Lyme borreliosis seronegativa** causes several patients to suffer. To prove and to cure this was my most important task from that point. – I also needed to objectively decide whether the treatment was effective and I had to be able to define the time-frame of the treatment. I started the investigations in May 1986.

The direct investigation of the causative agent - then called Lyme-Spirochete – was almost impossible because of the very low number of bacteria even in the active phases of the disease.

On the other hand, it was well known that *van Leeuwenhoek* described already in *1683* the characteristic shape of Spirochetes. We also know from the experiments by *Fodor between 1885-87* that the blood of healthy patients does not contain microbes. The causal relations of the disease are described in *Koch's postulates from 1891: „The suspected causative agent should be present in the body of ill patients, while it should be absent in healthy patients"*. The classic diagnosis of Lues, the well known *Spirochetosis*, is done via **dark field microscopy since 1905** according to Schaudinn and Hoffman**.** The laboratory diagnosis of borrelioses is primarily based on verifying the

spirochetes in blood.– *Borrelia burgdorferi* sensu lato is verified from native blood (because it is not easy to dye), other Borreliae are dyed.

Pseudospirochetes have also been known for a long time, since 1913 – they look very similar. Aberer and Duray showed various shapes of borreliae in cultures of *Borrelia burgdorferi* sensu lato in 1991. It is also well known that these bacteria have a different morphological picture in blood. Knowing all these problems, the only solution seemed to be to examine native blood, after the formation of myeloid figures and pseudo-spirochetes has been blocked, without harming the vital functions of spirochetes.

DualDur® reagent is a modified culture medium that delivers the above requirements. When examining the sample, a relatively large volume, 7 ml of whole blood we do the following steps: first the cellular bodies are deposited via a slow centrifuge, then the supernatant is centrifuged at 12 000 g so that the sample is concentrated a thousand times; the supernatant is poured off, the resulting pellet is then re-suspended. We take 2-3µl of the re-suspended pellet on a slide and we examine it under a dark-field microscope. Magnifications of 40-60 times with a dry lens can give a sharp picture through an iris. This can be observed with an eye-piece of 15 times magnification.

The pictures from the microscope were recorded through a personal computer. We were able to take motion pictures of the spirochetes while they were multiplying, shedding, moving – to prove their existence. We could identify that these pictures were those of *Borrelia burgdorferi* sensu lato, via immunoflurescent investigations with monoclonal antibodies donated by Professor (anti-OspA, antiflagellin). In the 7ml of whole blood taken directly into 3 ml **DualDur®** there were no artificial products, the membranes of cellular bodies were hardened. The spirochetes from *Borrelia burgdorferi* sensu lato cultures could move freely in **DualDur®**.

The reliability of the diagnostic method was verified through the serological investigations of seropositive patients, run in parallel. Clinical doctors also verified these results during the 3-5 years of follow-up treatment of the patients. This examination can be used to form a diagnosis in the most questionable cases, in **Lyme borreliosis seronegativa**, or to prove the effectiveness of a treatment.

SIMILARITIES AND DIFFERENCES IN DIFFERENT TYPES OF SPIROCHETOSES, ESPECIALLY IN SYPHILIS AND LYME BORRELIOSIS

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Hungary

Syphilis and Lyme borreliosis are systemic infectious diseases with primary manifestations affecting the skin, myocardium, as well as the locomotors and the nervous systems. Other organs however, might be also involved.

These interdisciplinary diseases can mimic a wide variety of clinical syndromes in all fields of medicine.

Apart from the above-mentioned features, the stages and the chronic course of the diseases, their proneness to chronic course and relapses, occurrence of latent periods, spontaneous recovery, specific aspects related to pregnancy and blood transfusion, as well as the principles of therapy and the problems related to recovery, all exhibit striking **similarities**.

The **differences** are rather revealed in the clinical picture of different stages: syphilis has more heterogeneous and polymorph symptoms, with atrophy and sclerosis that develop in the later stages of the disease. As a rule, extracutaneous manifestations affecting the locomotors and the nervous system occur only in Lyme borreliosis and are hot found any more in syphilis. The involvement of other organs, i.e. the incidence of cardiovascular and neural symptoms, also differs in these clinical entities. Lack of the subjective complaints is very typical of syphilitic patients.

Nevertheless, many questions related to these forms of Spiroche--toses still remain unanswered and will be a source of many surprises to medical professionals.

UNUSUAL CASES OF LYME BORRELIOSIS

Elisabeth Aberer,
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Lyme borreliosis (LB) is an infection which can affect many organ systems and causes stage-specific changes. The skin lesions of the first stage of disease are most typically expressed as erythema migrans (EM). Signs for dissemination are multiple EM and extracutaneous symptoms such as headache, myalgia, arthralgia, fatigue which are most often observed in European patients. In the second stage of disease, the skin, the neurologic system and the joints can be affected. Borrelia lymphocytoma arises most often at the ear lobes in children, at the mamillary region in adults. The neurologic symptoms comprise meningitis in children, facial palsy or other cranial neuritis and painful meningo-radiculoneuritis in adults. Symptoms in the musculoskeletal system involve one or a few joints mostly the knee presenting as arthritis. Muscles can be just painful or even show myositis. In some patients recurrent headache or arthralgias with or without fatigue are present. In the chronic stage of LB the skin is affected as acrodermatitis chronica atrophicans. Single cases of chronic neuroborreliosis have been reported. The musculoskeletal symptoms are similar to the symptoms in the second stage but rather persistent.

The European Concerted Action on Lyme Borreliosis (EUCALB) has defined **criteria** which are necessary for the diagnosis of the different manifestations of LB. Besides typical clinical findings stage-specific laboratory data are necessary for confirmation of the diagnosis. The best proof for a *B.burgdorferi* infection is the culture of the microorganism or the detection of specific *B.burgdorferi* DNA from skin, joint fluid and tissue, blood or CSF. Serological methods can support the diagnosis but with regard to the high seropositivity rate of healthy individuals are often difficult to interpret.

In well defined symptoms of LB **unusual skin manifestations** arise as concomitant symptoms and probably can be **associated with LB.**

Dermatoses that arise **with** acrodermatitis chronica atrophicans(**ACA**) are

- *Morphea (circumscribed scleroderma)*
- *Lichen sclerosus et atrophicus*
- *Anetoderma*

with erythema migrans

- *Persistent erythema migrans with meningoradiculoneuritis in HIV-positives*
- *Papular lymphocytoma in a slowly regressing EM-lesion*
- *Myositis concomitant with culture proven EM*

The spectrum of diseases associated with a borrelia infection has enlarged e.g. culture–proven ocular involvement, chorea as a sign for neuroborreliosis with intrathecal antibody synthesis.

When talking about unusual cases of Lyme borreliosis only those cases can be considered where a borrelia infection has been proven by culture or PCR- methods.

In the following diseases *B.burgdorferi* has been cultivated

- *Morphea*
- *Livid erythemas with myopathia*
- *Dermatomyositis (from skin and muscle)*
- *Granuloma annulare*
- *Annular erythema*
- *Relapsing febrile nodular panniculitis*
- *Snapping finger*

Borrelia DNA has been detected in skin biopsies and/or in the urine of

- *Morphea*
- *Lichen sclerosus et atrophicus*
- *Granuloma anulare*
- *Lymphocytic infiltration*
- *Malignant B-cell lymphoma*

In summarizing our own unusual culture proven cases we can add

- *Infiltrative borrelia lymphocytoma of the skin*
- *Psoriasis vulgaris in erythema migrans lesions*
- *Circumscribed scleroderma combined with Churg-Strauss granulomas*
- *Reversible monoclonal hyperimmunoglobulinemia after erythema migrans*

Several other unusual cases of LB have been reported **in the literature** such as Shulman syndrome, Raynaud syndrome, persistant pityriasis rosea, sarcoidosis, granulomatous thrombophlebitis and others. However, further laboratory investigations are necessary in these conditions to prove a borrelia infection in these diseases.

An important point to emphasize is that the different pathological changes seen in LB, such as arthritis or skin sclerosis represent reaction patterns that can also be induced by other microorganisms or trigger factors. It is well known that arthritis arises after infection with chlamydia, streptococci and other microorganims. Morphea has also been observed after vaccination or trauma. It was shown that infection by *B.burgdorferi* can also induce morphea which does not mean that all cases of morphea are caused by borrelia. In the United States *B.burgdorferi* sensu stricto is the only genospecies. Morphea - cases in the US have not been observed in association with a *B. burgdorferi* infection. Only *B.afzelii* and *B.garinii* have been linked with morphea. Since borrelia show the potency for persistence and since they even can be cultured from normal appearing skin, the relevance of findings must be discussed in any suspected case. Moreover, it is also suspec-ted that borrelia survive in the skin for decades without symptoms. The development of ACA has been observed several times after trauma. Whereas EM can be caused by all *B.burgdorferi sensu lato* species, in ACA mostly *B.afzelii,* and in lymphocytoma *B.garinii* and *B.afzelii* has been identified.

In unusual cases, typing of the *B.burgdorferi* genospecies has yet to be performed.

From our own studies it was obvious that *B.afzelii* has the potency to cause sclerotic skin lesions, myositis and B-cell proliferation.

THE CLINICAL PRACTICE OF LYME BORRELIOSIS

THE DIFFERENTIAL DIAGNOSIS OF CLINICAL PICTURES WITH RESPECT TO CASES OF LYME BORRELIOSIS

Dr. Zoltán Horváth chief physician, Head of ward:
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Hungary

Correct diagnosis and differential diagnosis of a disease are important issues in clinical and psychical respect both for the physician and the patient. While there are many patients who almost recover when getting to know the diagnosis, there are also many who become ill in that case.

However, most people are made sick by the lack of diagnosis.

The statements and concepts above can typically relate to patients suffering from Lyme disease.

Besides AIDS the infectious disease called *'great imitator'*, which is of bacterial origin and transmitted by ticks, is at the centre of attention all over the world. *Zoonosis classified as a chronic system disease* occurs everywhere in the world, it is very common in Europe and is an **endemic disease in Hungary**. We could hardly find a medical field which is not related to this systemic disease, which is famous for its variety of symptoms.

Our knowledge related to every aspect of the clinical picture has expanded, the clinical spectrum has widened and now we could state that in its clinical respect *Lyme disease is one of the most significant 'border-line clinical pictures'*. **Lyme disease may not be excluded when diagnosing multi-systemic chronic systemic diseases.**

It seems practical to conclude that the clinical pictures including limitation of motion in the case of hundreds of patients appearing at the consultations of rheumatism specialists, syndromes imitating cardiac infarction, cases classified as sclerosis multiplex, the increased number of patients in need of psychological and psychiatric treatment, disorders of the nervous system, ophthalmologic and pulmonary

diseases, and those of ear-nose-throat may be traced back to one common origin, which once might have been triggered by a borrelia infection.

Unfortunately it is one *of the most frequently misdiagnosed diseases* even in the USA. Also in our country there are cases that are not properly diagnosed, not properly identified or not identified at all. 'Great imitator' might copy numerous clinical pictures of various aetiologies. Apart from its early manifestation on the skin *(Erythema migrans)* it is not easily diagnosable even after collating clinical practice and serological results. This is where the most important message of the current presentation derives from, namely, that Lyme disease as an possibility must not be excluded in relation to almost all clinical pictures. If excluded it leads to not identifying and properly treating a curable disease.

At the same time, in the event of a false positive diagnosis, we are faced with the dilemma of a *'overdiagnosed clinical picture'*. Furthermore we must not disregard the side-effect or the cost of a sustained and unnecessary antibiotic treatment. The importance of diagnosis and differential diagnosis is further emphasised by the fact that spontaneous recovery has not been confirmed yet while the existence of chronic inflammation is proven right from the start. Associated autoimmune phenomena and the fact of reinfection is undoubtedly known and acknowledged. Nowadays it is almost obligatory and pursuant to our meeting becomes statable that every colleague should be acquainted with the survey and differential diagnosis of the data in the history of a clinical picture and with the principles of the therapy. The differential diagnostic approach is the most difficult one in relation to this disease. It is especially evident when observing cases that are diagnosed late. Due to the widening of diagnosis and differential diagnosis practice treating Lyme disease has also entered a new era. Thus, instead of simplified approaches, the therapeutic practice of this important endemic disease is based on more extensive knowledge and wider experience in a more modern way and on considerations prompted by common sense. The main target set by the **'Therapeutic association'** created between the

patient and medical 'TEAMS' (physician, trained workers) treating and nursing patients and realising tasks related to the disease in practice is to get patients understand that success is never ensured by the diagnosis and treatment even if done with the best intentions. *This was our policy when in Hungary we were the first to organise a* **Lyme Club** *in Sopron, which is still the only one in existence.*

The protocol of the epidemiological, diagnostical, differential diagnostical treatment and after-treatment of Lyme disease forms a dialectical unity. In certain cases diagnosis is extremely easy, in the majority of cases, however, the problem of realising a reliable differential diagnostic approach, separation and therapeutic strategy is still unsolved.

As part of our presentation we are going to inform you about practice in Sopron in connection with patients suffering from Lyme disease. Instead of describing the clinical picture from several aspects we are going to concentrate on the following ones:

1. Questions related to anamnesis, which has vital importance in respect of daily practical diagnostic work.
2. Recently approved staging to facilitate diagnosis.
3. Differential diagnostical tasks related to manifestations of the system of organs, touching on a number of diagnoses to differentiate. Linked to this the interpretation of serological results, besides the clinical picture, facilitate confirmation or exclusion.

We are going to deal with major changes, recommended and approved therapeutic principles with regard to therapy.
Finally we are intending to publish the conclusions that can be reached by us and with our mediation perhaps by every colleague.

During the diagnosis and differential diagnosis of chronic, multi-systemic diseases it has become indispensable to consider Lyme disease by now.

CONCLUSIONS

1. SOPRON AND ITS ENVIRONMENT IS AN ENDEMIC TERRITORY IN RESPECT OF THE HIGH INCIDENCE RATE OF INFECTED TICKS.
2. THE STAGING OF THE DISEASE MAY ONLY HAVE DIDACTIC SIGNIFICANCE.
3. DIAGNOSIS IS TO BE BASED ON CLINICAL SYMPTOMS AND THE CLINICAL SPECTRUM SHOULD BE LEARNT AS COMPREHENSIVELY AS POSSIBLE.
4. THE CLASSIFICATION, FORM AND RATE OF INCIDENCE OF OUR JOINT-CASES CORRESPOND TO DATA PUBLISHED IN PROFESSIONAL LITERATURE.
5. SEROLOGIC RESULTS IN THEMSELVES ARE NOT DECISIVE AND OFTEN NOT INFORMATIVE EITHER (FALSE-POSITIVE-FALSE NEGATIVE)
6. NEW EXAMINATION METHODS ARE NEEDED TO CONFIRM THE DIAGNOSIS AND TO SHOW THE PERSISTENCE OF LIVE PATHOGENS IN THE SYSTEM OF ORGANS.
7. THIS DISEASE HAS A RELATIVELY GOOD PROGNOSIS AND IS RESPONSIVE TO TREATMENT. EARLY DIAGNOSIS IS IMPORTANT, THERE ARE CASES THAT ARE RESISTANT TO THERAPY – EVEN DEATHS HAVE BEEN REPORTED.
8. THE LENGTH OF ANTIBIOTIC TREATMENT APPLIED CURRENTLY DOES NOT SEEM SUFFICIENT. COMBINED TREATMENT COULD BE A SOLUTION IN THE FUTURE.
9. IT WOULD BE USEFUL TO CREATE STANDARDIZED PRINCIPLES OF TREATING FREQUENT FORMS OF DISEASES AFFECTING JOINTS.
10. WE ARE JUST HANGING BEHIND THE DISEASE, ONLY EFFICIENT PREVENTIVE METHODS COULD BRING ANY PROGRESS.

THE SIGNIFICANCE OF ZOONOSES IN HUNGARY WITH RESPECT TO LABOR ISSUES

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National Public Health and Medical Officer's Service, Budapest

Besides other living creatures, mankind is a the prominent designer, user, developer, and sometimes passive object of both living and lifeless environment – the so-called macro-ecological system. In the interconnecting system of living organisms (plants, animals, and humans), the diverse variety of pathogenic microorganisms (bacteria, viruses, fungi, external and internal parasites) are the **sources of infectious diseases** in a wider sense of the word. Several (200-220) species are known, which under natural circumstances are able to establish, reproduce, and cause infection or disease due to their genetically determined characteristics not only in animals, but also in humans. They are the **zoonotic pathogens, and the diseases caused by them are the zoonoses**. As a common element of such diseases, their causative agent can without difficulty spread from one individual to the other of susceptible species.

Infection is usually transmitted from animal to human, however, in the case of numerous important zoonoses, it may be the other way around.

Zoonoses are infectious diseases spread all over the world with various numbers of cases per year, different economical damages and significance regarding public health depending on certain fundamental climatic, geographic, and macroecologic factors (countries of continental, Mediterranean, and tropic climates), the economical and social development of a given country, and last but not least, the epidemiological competence of veterinarian and medical services as well as their capacities to

be used in daily routine. Situations greatly vary across developing and developed countries.

The classification of zoonoses according to their epidemiological characteristics has already been adopted in Hungary, too. In many cases, such classification may also refer to the origin of the infection and the pathogen's method of spreading. Therefore, we can differentiate between ortozoonoses, cyclozoonoses, metazoonoses, geozoonoses, and saprozoonoses.

Zoonotic pathogens may spread in many different ways. Sometimes the same microorganism would infect in several ways making not only clarification of etiology, but also prevention very difficult.

Wild animals, rodents in forests and fields, small burrowing mammals, wild birds as well as vectors living in their bio-ecological system (ticks, bloodsucking arthropods, insects) play a major role in transmitting pathogens. Such animals may infect humans directly or through domesticated animals.

Due to the epidemiological situation, the number of zoonotic cases as well as their identified types are lagging far behind the actual incidents of such diseases in Hungary. The reasons for such disagreement are:

- Insufficient harmonization of the effective relevant regulations (Act No. XCI of 1995 on Veterinary Medicine and order No. 41/1997 (V.28.) FM on its execution) with order No. 18/1998 (VI.3.) NM as well as with EU regulations on the prevention of zoonosis (guidelines No. 92/117/EEC, orders No. 95/1 (January 1, 1995) and 97/22 (April 22, 1997)).

- Inadequate frequency of use, performance, and laboratory capacity of etiological diagnosis.
- Inefficient cooperation of public health and veterinary administration and institutions, delayed or no information service.
- Loosening discipline in the field of epidemiology-related work.

In addition to a well-coordinated collaboration between experts of different sectors, an effective approach to zoonoses also requires the determined adjustment and active involvement of all members of society.

INSURANCE MEDICAL ASPECTS OF ZOONOSES

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Hungária Biztosító, Budapest, Hungary

Zoonoses can be considered as insurance events when their occurrences appear in form of insurance-accident.

In view of insurance medicine the insurance-accident is such an injury of a person which injury happens independently from the victim, occurs suddenly and by an outside influence and it causes physical damage of the human body, or it can cause impairment, deterioration of the health status, or death.

These kinds of the insurance-accidents or accident-complications are mainly the infectious diseases, which occur directly there are indirect causes of the diseases (which never have been occurred without the influence of the accidents).

Among the zoonoses the following diseases can be considered as insurance-accidents: food poisonings caused directly by foodstuffs or foods of animal origin, illness caused by bites of animals or insects like the illness or tick-borne encephalitis but the Lyme disease, too.

The authors give detailed information on the accident-like zoonoses listed according to the ICL 10, which can be accepted as insurance-accidents.

TREATMENT OF LYME DISEASE: A NORTH AMERICAN PERSPECTIVE

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Treatment of Lyme disease is based on the recognition of the stage of infection and an understanding of the pharmacodynamics and pharmacokinetics of antimicrobial agents vis a vis the pathogen. Below is a summary of the current state of the art of treatment of Lyme disease surmised from studies performed in the United States.

EARLY LYME DISEASE:

1. **Randomized, prospective, double-blinded clinical studies have demonstrated** that doxycycline (100mg twice daily), amoxicillin (500mg three times daily) and cefuroxime axetil (500mg twice daily) are all effective for the treatment of early localized or disseminated Lyme disease in the absence of neurologic involvement. A **three week course** of therapy is generally recommended although shorter courses may be adequate, particularly for localized disease. *Doxycycline has the additional advantage of activity against the agent of human granulocytic ehrlichiosis (HGE) which may co infect patients with early Lyme disease.* Therapy with cefuroxime axetil is equally effective to doxycycline for the treatment of erythema migrans and is recommended as an alternative treatment because of cost. For children, doxycycline, 100mg twice daily (not to be used for children under 9 years of age), amoxicillin 50mg/kg/day divided three times per day (maximum of 500mg/dose), or cefuroxime axetil, 30-40 mg/kg/day twice daily (maximum 500mg/dose), for 21 days is recommended.

2. Oral doxycycline has been shown to be equally effective to ceftriaxone for the treatment of acute disseminated Lyme disease in the absence of central nervous system (CNS) involvement.

3. Oral regimens should be selected only after a careful clinical evaluation has failed to reveal any evidence of CNS involvement.

4. Acute CNS Lyme disease manifested by meningitis or radioculopathy responds to intravenous (IV) ceftriaxone 2mg daily for 14 to 28 days. Penicillin in a dose of 24 millon units daily IV is a satisfactory alternative as is cefotaxime 2g IV three times daily. For children, ceftriaxone, 50-60mg/kg/day in a single dose (maximum 2g) for 14-28 days administered IV or IM, or penicillin G, 200,000-400,000 units/kg,day (maximum 20 million units/day) divided q 4h administered 14-21 days is recommended.

5. Macrolide antibiotics are not presently recommended as first line therapy for early Lyme disease.

RECOMMENDATIONS FOR LATE LYME DISEASE:

LYME ARTHRITIS

Lyme arthritis may usually be treated successfully with either oral or IV antibiotic therapy. In a large multicenter trial, Lyme arthritis was often treated successfully with IV ceftriaxone, 2g per day for 2 or 4 weeks. In a smaller randomized trial, oral doxycycline, 100mg twice daily, or amoxicillin, 500mg four times daily, in each instance for 30 days, was also effective in most patients; courses of oral therapy of shorter duration have not been studied systematically. Oral therapy is easier to administer; it is associated with fewer side effects and is considerably less expensive Its advantage is that such patients may still develop chronic neuroborreliosis which seems to require IV therapy for successful treatment. Further controlled trials are needed to compare oral with IV therapy. For children, treatment of Lyme arthritis is the same as for erythema migrans except treatment is for 30 days.

TREATMENT-RESISTANT LYME ARTHRITIS

In patients who have persistent joint swelling after recommended courses of antibiotic therapy, it is perhaps reasonable to treat once again with a 4-week course of oral antibiotics or with a 2- or 4-week course of IV ceftriaxone. If patients have persistent arthritis despite two months of oral therapy or one month of IV therapy, treatment is recommended with anti-inflammatory agents. Intra-articular steroids, nonsteroidal anti-inflammatory agents, including hydroxychloroquine, may be of some benefit. If persistent joint swelling is quite painful or if it limits function, arthroscopic synovectomy may reduce the period of joint swelling. For children, if symptoms fail to resolve after 2 months or there is a recurrence, treatment is the same as for neurologic disease.

CHRONIC NEUROBORRELIOSIS

For patients with chronic neurologic abnormalities, which some-times occur with episodes of arthritis, treatment is recommended with IV ceftriaxone, 2g once a day for 2 to 4 weeks. Based on anecdotal evidence, alternative medications may include IV cefotaxime 2g every 8 hours, IV sodium penicillin G 5 million U every 6 hours or high dose oral doxycycline. The response to treatment is usually slow and may be incomplete. However, unless relapse is shown by objective measures, retreatment is not indicated. For children, treatment with ceftriaxone, 50-60 mg/kg/day in a single dose (maximum 2g) for 14-28 days administered IV or IM, or penicillin G, 200,000 400,000 units/kg/day (maximum 20 million units/day) divided q 4h administered 14-21 days is recommended.

LYME DISEASE:
HOMECARE – INFUSION SERVICES

David W. Kazarian President, American Society of Clinical Pharmacologists and Infuserve America Saint-Petersburg Florida USA

This lecture discusses the technologies, which make home care possible, the treatment of Lyme and the products used in the home environment.

Treatment regiments will be discussed, as well as the products that make delivery of the regimens possible at home. The safeguards and products, which protect the patient as well as the hands on nursing and pharmaceutical care, which occurs in the home, will be reviewed.

Delivery systems, pumps, elastomeric delivery devices, syringe pumps will be reviewed as well as central access devices which insure the IV line is kept open will be demonstrated.

Pharmaceutical care plans will be reviewed as well as physician, nurse, pharmacist communication and computer intervention as well as electronic imaging. Communication is the key to successful home treatment, and methods, which facilitate that communication, such as Internet e-mail, voice mail, and fax communication will be reviewed.

A brief history of Homecare in America will be presented, how it started and where it's gone over the past decade.

THE ROLE OF THALLIUM STRESS TESTING IN LYME DISEASE

Kornélia Keszler Connecticut,USA

The spirochetes transmitted by ticks to humans cause Lyme Borreliosis. The patients can present with various clinical symptoms: dermatological, neurological, cardiac rhematological, psychiatric and ocular.

The most readily recognized feature of cardiac involvement has been the various degrees of heart blocks on the ECG tracings. This usually responds to antibiotic therapy. Common and predominant cardiac complaints are chest pains, mild to moderate exertional dyspnea, and palpitations.

The diagnosis of myocardial involvement by Borrelia Burgdorferi (Bb) has been very limited in the absence of a high degree atrioventricular (AV) block.

Three cases of Lyme Borreliosis are reported here where distinct image pattern has been observed on Thallium stress testing in these patients. The patients **had various transient arrhythmias without high degree heart blocks**. All three patients live in endemic areas, all three patients had tick bites, erythema migrans (EM) rash, and positive serology for Lyme Disease.

Thallium imaging of the myocardium can be helpful in identifying patients with cardiac involvement with *Borrelia burgdorferi sensu lato* who were symptomatic but their resting ECG were normal.

DERMATOLOGY. KEY TO THE RECOGNITION AND TREATMENT OF LYME BORRELIOSIS

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In Hungary, Lyme borreliosis is the most frequent disease caused and spread by ticks. If not recognised upon its first symptom located on the skin, this illness will affect the whole organism and become a chronic disease. About sixty percent of the patients suffering from Lyme borreliosis first and foremost turn to a dermatologist with their complaints and only a few consult a specialist of another medical department. Complete recovery from the illness highly depends on early established diagnosis and consistent treatment

It is a fact confirmed by literature that a low percent of patients are not cured despite the usually adequate early antibiotic treatment, although there are no more visible symptoms on the skin, moreover, in some cases – as in the case of lues – the illness vanishes serologically, that is, the patients prove to be seronegative.

At that stage of illness, the patient has new symptoms (e.g. arthralgia, neuritis, myalgia etc.), but solely the anamnestic data and those skin symptoms first observed by the dermatologist point to the disease affecting the entire organism As regards the actual symptoms, other physicians (e.g. rheumatologists, neurologists) are from the diagnostic point of view at a disadvantage as against the dermatologists, as they can only come to the correct diagnosis by making special efforts (tissue culture, punction-analysis, biopsy, special laboratory test methods, etc.), requiring considerable time and money.

In the case of certain patients suffering from Lyme borreliosis, we can observe dermatological features, which deviate from the typical forms of erythema migrans (e.g. morphea-like plaques, lichen sclerosus et atrophicus, multiplex erythema migrans).

The recognition of their connection with the anamnesis and other possibly associated symptoms, though not of dermatological character, but indicative of Lyme disease, as well as the verification of the supposed persistence of Lyme borreliosis is likewise the task of the dermatologist.

Because of the above facts as well as due to its supreme importance, the author advocates that – as in the case of syphilis, although somewhat differently due to the peculiar nature of that illness – the dermatological medical attendance should not only comprise the treatment, but also the continued care of the patients with skin features indicative of Lyme borreliosis.

To stress the importance of care, some cases with complicated diagnosis and treatment will now be demonstrated. According to the symptoms, the care of patients should be undertaken in close co-operation with specialists qualified in other medical fields.

In addition to the recovery of patients, the importance of care would also be justified by its "cost-benefit" factors. Moreover, the epidemiological, public health, labor-sanitarian, and legal aspects of the disease are also of great importance as the Borrelia infectedness of ticks is significant in Hungary.

LYME BORRELIOSIS IN THE PRACTICE OF A FAMILY PRACTITIONER

Márta Schleer, M.D. Internal Specialist, Family Practitioner

Family practitioners play a key role in the prevention, diagnosis, and treatment of Lyme borreliosis. Such role is ensured by their special, confidence-based relationship to their patients. Family practitioners are therefore entitled to equally apply conventional knowledge and up-to-date procedures in their decisions of individual responsibility in the interest of their patients.

I have been working as a family practitioner in the same district for 27 years. Besides my activity as a family practitioner, I have been actively looking for patients suffering in Lyme borreliosis in my district as well as in my personal environment since 1987.

I have managed to identify Lyme borreliosis in 29 cases. Five of them came from another district, while seven patients suspected that they were suffering from Lyme borreliosis and, after hearing my specialization, deliberately chose me to be their family practitioner. **So, in my average-sized Budapest district of 1500 people, I have detect-ed 17 cases of Lyme borreliosis that is 1.13 per cent of the adult population**.

In all cases, diagnosis was based upon a detailed anamnesis, a comprehensive physical check-up, and a thorough examination to confirm or exclude other illnesses.

Due to possible lapse of memory, repeated documentation of the anamnesis was necessary in several cases. If patents could not remember the tick bite, I still made a note of the possibility.

Simultaneously with the general check-up, I also requested special laboratory tests for Lyme borreliosis.

Two patients showed ECM symptoms, while in another six cases, there was a retrospective diagnosis of ECM. Both proven re-infections were accompanied by ECM. In my practice, **ECM was only found in 27.6%** of all cases.

I have met the following complaints and symptoms among my patients: arthralgia, arthritis (especially at knee and small joints), myalgia, myasthenia, muscle spasm, headache, lack of initiative,

dysmnesia, imbalance, deterioration of vision, papillitis, pain, and numbness indicating impairment of cerebral nerves II, V, VII; radiculopathia and other symptoms of peripheroneural impairment, rhythm disturbances, pericardial fremitus, feeling of collapse, severe night sweat, subfebrilis, moderate anaemia, slightly increased ESR. I often found "unjustified" dysuria despite negative urological diagnosis. Some patients reported soft or deformed nails.

In patients with Lyme borreliosis, symptoms formed various groups. Even in monosymptomatic cases, symptoms indicating the illness of the entire organism have soon developed.The course of the disease often proved to be fluctuating: a spontaneous remission was usually followed by a relapse in every two or three weeks.

I always established the diagnosis of Lyme borreliosis after **consultation** with specialists of the affected fields.

After confirmation of Lyme borreliosis, I informed the patient of the nature of the disease and the planned method of therapy**. I executed a personalized treatment** after learning the antibiotics previously applied – for another illness, too (after antibiotics anamnesis). In cases of chronic or relapsing Lyme borreliosis unsuccessfully treated with monotherapy, I applied a combined antibiotic treatment.

As a family practitioner, I had the opportunity to closely monitor the course of the disease. I controlled the condition of patients with regular physical and laboratory tests. I did not notice significant side effects. After-care is currently taking place with the following results:

- **Healed** 24/29 (**82.8%**), *6 of them beyond five years, 2 of them beyond three years.*
- **Not healed** 5/29 (**17.2%**), *chronic cases, repeated treatment is under way.*

I present the case history of a **family practitioner** patient. The doctor have **suffered** from a disease of unknown origin **for 12 years**. Her problems and symptoms did not match any of the then known clinical pictures, therefore, her colleagues explained her condition with exhaustio, hysteria, and menopause despite the fact that they have noticed organic disorders at several examinations. The diagnosis of Lyme borreliosis turned out to be a relief for her. Despite her 12-year-long illness, her antibiotic treatment resulted in the anticipated healing. She has been complaint-free and working for 11 years.

THE TWO FACES OF NEUROBORRELIOSIS: ORGANIC NEUROLOGICAL DISORDERS OF CHILDREN AND ADOLESCENTS

Andrea Hollósy, MD

PSYCHOPATHOLOGICAL CONCOMITANT SYMPTOMS

Klára Őry, MD

Examinations took place at a neurological clinic for children and adolescents by applying neuropsychological methods according to official international classification and by using the appropriate scales.

We have studied 10 patients aged 7-17 between 1991 and 1997 with follow-up in three and five years. From 1992, 20 subjects aged 15-45 have participated in the psychological tests.

Neurological problems and symptoms included headache, vomiting, nausea, visual disturbances, facial palsy, motor disorders, hemiparesis, limb pain, paraesthesia, and convulsions.

Clinical examinations involved routine neurological tests.

Serology was performed at the formerly Nathional Institute of Hygiene as well as at other diagnostic stations in doubtful cases. Occasionally, pathogens were directly analyzed, too.

In each case, therapy involved a long lasting, combined antibiotic treatment, possibly prolonged, supplemented by vitamins and roborants as well as physiotherapy.

One patient got better, although failed to attend the control. The other patients attend regular controls and all maintain a good quality of life.

Neuropsychological tests covered both mental and emotional functions. Among mental functions, declining

performance, while among emotional ones, oppression and various phobias were noticeable.

Patients had dysthymia and dysphoria. In 13 cases, "depressio sine depressionem" was revealed, but several so-called panic disorders were also found.

***Conclusions*:** both the diagnosis and the differential diagnosis of neuroborreliosis require careful consideration; seronegativity found at the first examination may not exclude clinical picture justifying further examinations. Combined therapy must be followed by long lasting care.

The examination of mental functions and emotional status is unconditionally recommended, because upon the onset of the disease both practitioner and patient first focus on somatic symptoms. Psychic deficits may, however, prevail from the beginning, even if patient failed to reveal this fact. Relaxation and supportive psychotherapy introduced may be supplemented by cognitive and behavior therapy, if needed. All these therapies are also important for somatic treatment.

LYME BORRELIOSIS OCULI

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Eighteen patients were treated with Lyme borreliosis complications between 1990-1997.

Diverse manifestations of the disease were observed: *Pars planitis, Iridocyclitis, Neuritis retrobulbaris, Vasculitis, Chorioretinitis, Myositis orbitalis, Nervus abducens paresis, Nervus facialis paresis, Haemorrhagia corporis vitrei, Hyperaemia papillae and Pseudotumor cerebri.*

The half of the patients has mentioned tick-bite. Thirty per cent of the patients had typical skin manifestation and four patients were treated because of the joint complains. The time interval between the tick-bite and the clinical signs reached one month up to years.

At all of the patients, **the diagnosis** was supported by different exams (dental, rhynological, urological, rheumatological) due to aspecific symptoms and accomplished by laboratory and serological tests.

In patients treated with *Neuritis retrobulbaris, Pseudo-tumor cerebri and Myositis orbitalis CT scan and MR* were performed.

Before **the treatment**, anamnesis and positive serolo-gical tests were obligatory.

At the beginning, penicillin treatment was started and recurrent manifestation ceftriaxon was given 2 gm b.i.d. for 4 weeks.

We have found good results in patients treated with doxycycline if the antibiotic treatment started in the early period of the disease.

In certain cases, the lack of successful treatment was attributed to the intracellular propagation of the bacteria and weak penetration of the antibiotics through the cell membrane.

That is even more difficult to treat if the bacteria penetrated through the blood-brain barrier.

At least one-month antibiotic treatment is mandatory due to multiplication cycle of the bacteria.

In summary: The proper diagnosis of Borrelia infection proved to be rather difficult due the diverse symptoms, the complicated, expensive laboratory tests, and the lack of the uniform way of medical thinking.

Because of the increasing number of tick/bite, in cases of ophthalmologic disease due to undetected infectious foci Lyme disease should be supposed. All efforts should be done to make a proper diagnosis and successful treatment.

FOLLOW-UP STUDY OF LYME BORRELIOSIS

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Authors reviewed clinical data and therapy regimen of patients admitted to the Department between 1989-1997 with diagnosis of Lyme borreliosis. Based on the experience of 1272 treated cases of chronic and disseminated Lyme disease they conclude that the generally prescribed **antibiotic monotherapy** *regimen failed to reach complete recovery in most of the cases. It seems that similar to other spirochetal infections* **after** ***a*** *shorter or longer* **period of temporal remission the symptoms reappeared.**

In these patients, the authors introduced individually planned **combined antibiotic therapy** based on the guidelines available in the literature. This approach improved clinical symptoms significantly in some severe, therapy-resistant cases. The remission seems to be maintained during the 3-5 years of the follow-up study.

These findings raise the question whether *the traditional antibiotic therapy of Lyme borreliosis should have reconsidered in terms of length of treatment and/or the appropriate choice of antibiotic agents.*