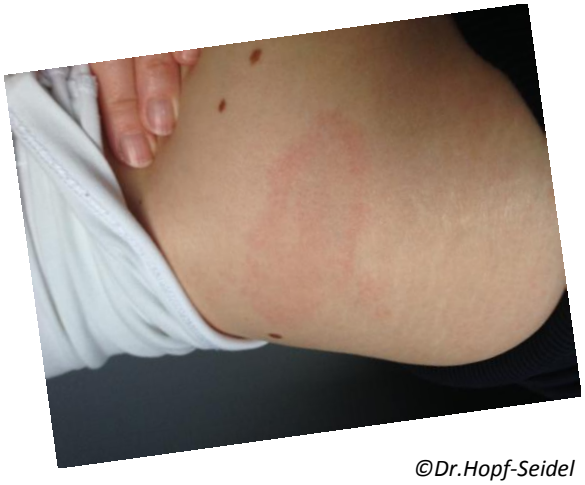
From a tick bite to (chronic) Lyme Disease (LD) or chronic Lyme Borreliosis



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The life cycle of ticks and the bacteria Borrelia as well as symptoms and treatment recommendations for Lyme Disease and some of its chronification factors.

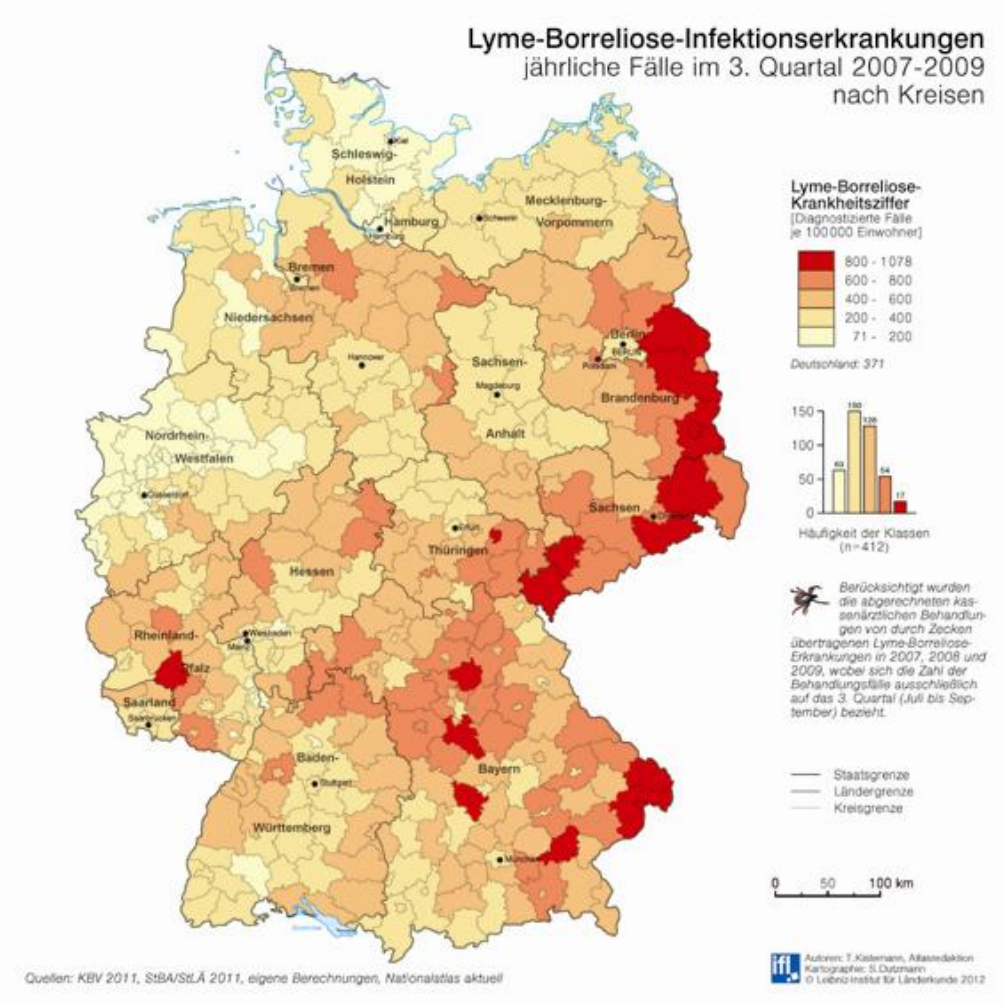
by Dr. Petra Hopf-Seidel (revised in December 2016)

English version by Karin van der Ent and the author; edited by Jacques Amelard

Every year at spring time numerous articles appear in the media about the dangers of tick bites. The number of patients with (chronic) Lyme Disease (LD) or Lyme Borreliosis is rising steadily because of a lack of early detection and due to inadequate treatment of this tick-borne disease. However, articles about illnesses caused by ticks usually do not differentiate clearly enough between all of the types of germs ticks can carry. So far 30 different co-infections, besides the Borrelia genospecies, have been found in ticks. In general, the emphasis of media reports is usually placed on warning the readers about FSME (**F**rüh**s**ommer-**M**eningo-**E**ncephalitis) i.e. **T**ick-**b**orne **e**ncephalitis (TBE), against which vaccination is available. The pharmaceutical industry even describes this vaccination as a "tick vaccination" which can imply a false sense of protection against all tick related diseases. What is usually not clearly mentioned is the fact that TBE is a tick borne viral infection and is relatively rare in comparison to LD or Lyme Borreliosis, which is a bacterial infection caused by the spirochete Borrelia burgdorferi s.l. ("s.l." is from the Latin expression "sensu lato", which means "in a broader sense").

In Germany TBE infections are rare in comparison to the annual rate of new infections of LD. For the past 10 years laboratories have reported never more than 550 TBE infections per year (in 2015 there were only 220 cases), whereas the median number of new and chronic-persistent LD-cases (all equally identified by code "A 69.2" specified by the 10th version of the **I**nternational statistical **C**lassification of **D**iseases and related health problems (ICD-10)) is increasing steadily. Borrelia infections and

their treatment have to be reported by the doctors to the Krankenkassen (German governmental health insurers). For the years 2007 to 2009 approximately 303,000 cases of LD were reported annually. Statistically, the figures at the third quarter of the year usually represent about half of the new LD infections for the year. Therefore the annual number of patients newly infected with Borrelia in the years 2007-2009 was around 600,000. In 2012, the number of patients who received treatment, for both new and chronic Borrelia infections, was one million (Source: Kistemann, Thomas (2012): Regionale Verbreitung der Lyme-Borreliose. In: Nationalatlas aktuell 6 (04.2012), Leipzig: Leibniz-Institut für Länderkunde).



http://aktuell.nationalatlas.de/

Other estimates for Germany, based on various scientific studies and statistics of regional departments of health, indicated that in 2008 about 2.5% of the German population, or about two million Germans required treatment for newly-acquired and chronic LD. In 2009 there was an incidence of 1.5% of the population of recently-contracted Lyme Borreliosis in highly endemic regions like Baden-Württem-berg (for details see www.praxis-berghoff.de. Texte/Häufigkeit der Lyme-Borreliose in der BRD. Stand 2011, revised 7/14).

The steadily increasing number of patients with LD is a cause for concern not only to German authorities but also to authorities of all European countries, especially Eastern Europe. United States authorities are concerned, too. In 2008, the World Health Organization (WHO) declared Lyme disease the fastest spreading infectious disease - faster than tuberculosis and malaria – and therefore de-

clared it as a “world epidemic”. In the USA, the **C**enters for **D**isease **C**ontrol and Prevention (CDC) red-flagged Lyme disease in October 2008 as an “emerging epidemic”. The number of newly-infected patients annually has increased in the USA since 1982 nearly 25-fold. Some data suggest it may actually be over 440 000 LD cases each year and by 2012 the number of U.S. counties with a high incidence of Lyme disease had risen to 182 (between 1993 and 1997 only 43 U.S. counties had a high incidence of LD).

The exact number of newly- infected LD patients in Germany is uncertain mainly due to the lack of mandatory reporting of Borrelia infections, in contrast to mandatory reporting requirements for TBE by all German laboratories. Furthermore it would be difficult to find conclusive reporting criteria for new Borrelia infections because only about 40% - 50% of all the infected develop a bull’s eye rash or a lymphocytoma, both of which are sure and typical early signs of infection. There is also great variation in early symptoms from patient to patient (see **Early Symptoms** page 11).

Please note that additional pathogens carried by hard ticks such as Rickettsia, Ehrlichia/Anaplasma, Chlamydia, Babesia, Bartonella and Mycoplasma and their clinical symptoms are not covered in any detail in this article. Their many and varied symptoms only add to the difficulties in recognizing a Borrelia infection correctly and in time.

The many chronic but wrongly diagnosed and therefore falsely treated LD patients show that the general public today does not have enough information about the different stages of Lyme disease nor, unfortunately, do enough doctors. This is one of the reasons for this article: I wish to share my experience over the last thirteen years treating patients who came to me with the chronic form of LD because of a failure to detect and treat their early and later chronic clinical symptoms.

I wish to emphasize that this article deals exclusively with (chronic) Lyme disease in Germany caused by the genospecies Borrelia burgdorferi s.l., which is transmitted by the hard tick Ixodes ricinus. But as the life cycles of Borrelia and their carriers as well as the resulting clinical symptoms are the same all over the world, this article could help to broaden the general knowledge about Lyme disease. Other insects like mosquitos, mites, horseflies and fleas are considered carriers as well because Borrelia DNA has also been found in them. However, to my knowledge, scientifically-backed studies establishing these insects as directly infecting carriers have so far not been undertaken.

In addition to transmission by ticks or other carriers, there is evidence of intrauterine transmission of Borrelia spirochetes by infected mothers to their fetus, as well as transmission of Borrelia in their permanent forms (so-called round bodies which are persister forms like granula, “cysts” and/or biofilms) through blood transfusions and organ transplants. There are some recent studies about sexual transmission of LD from male to female (see articles in the Appendix) and a very recent one (publ. 11/15 at the Norvect conference in Oslo by Alan Mac Donald, MD) proves histologically the presence of Borrelia in the testicles of a long-time LD patient. The documented and published case of George W. Bush and his wife Laura (who contracted LD from her newly infected husband through sexual transmission) has also confirmed that spirochetes of the genospecies Borrelia can be transmitted sexually. This is similar to an Infection with spirochetes of the genus Treponema pallidum, which are already long acknowledged and well documented as the cause of the sexually transmitted disease (STD) syphilis. Borrelia species have been found in human semen and vaginal fluids. They have also been found in breast milk but it is still unclear whether this could lead to an (active) infection of the breast-fed baby, to a permanent silent infection or to an infection at all.

In this article, I address the life cycle and behavior of the tick as well as aspects of the spirochete of the genospecies Borrelia and its various life forms during its existence. I present the possible clinical consequences for the human host after a sting by an infected tick (not a bite because a tick has no mouth at all, only a sting, scientifically called a hypostome). Emphasis is given to the early clinical signs at the onset of the disease, after infection has taken place, to facilitate its early recognition and to prevent chronic stages of Lyme Borreliosis. In this way, hopefully, more light can be shed on this "chameleon" disease, so-called because of its many changing symptoms. This article also describes the most frequent clinical symptoms of chronic Lyme disease. How chronic LD can affect quality of life can be understood by looking at the numerous mentally and physically debilitating symptoms (see Symptoms of chronic Lyme Disease page 17 ff).

Furthermore, I will outline a few of the many known causes that may lead to chronic systemic inflammation associated with chronic persistent Lyme Disease. I will review the established, officially-recommended testing methods for Borrelia infections: antibodies and the Western-/Immunoblot. I will also cover several in Germany newly available methods of identifying an infection caused by these spirochetes. I will describe various antibiotic treatments in conjunction with other effective therapy ways to reduce the symptoms not only of Lyme Disease but of other multisystemic inflammation of different origins as well. As we know today, the underlying reason why LD patients feel so unwell is due to a chronic multisystemic inflammation (so-called silent inflammation) which can be diagnosed by some well-defined laboratory tests.

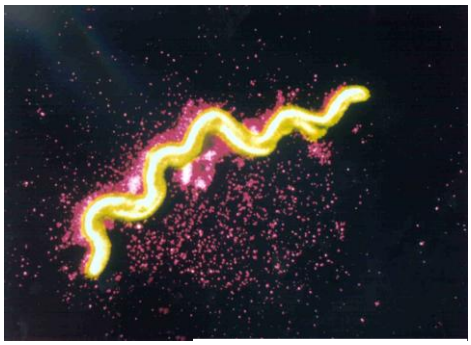
Because physicians often find it very difficult to identify and treat an infection years after the initial infection has taken place, many chronic persistent Lyme Borreliosis patients remain untreated or are treated insufficiently, causing the number of chronic cases to steadily increase.

At the end of this article I list in the Appendix the addresses of laboratories that provide the described tests for Borrelia DNA in ticks and humans as well as many other helpful laboratory values.

I. How does Lyme disease or Lyme Borreliosis develop?

Borrelia are corkscrew-shaped bacteria belonging to the spirochete family just like the spirochete *Treponema pallidum* which causes syphilis. Borrelia as well as Treponema pallidum can set off a multitude of symptoms due to multisystem inflammation if the ensuing infection is not recognized and treated early enough.

Punctures of the skin are painless due to a local anesthetic in the saliva of the tick. The blood of a mammalian host - be it animal or human - is sucked up through the stinger (hypostome). The warmth of the sucked-in blood of the host changes the adhesive protein OspA to OspC produced by the spirochete in the midgut of the tick, in Europe mainly the hard tick *Ixodes ricinus*. This change enables the spirochete Borrelia to detach from the intestinal lining of the tick and to become mobile. Only then are the Borrelia bacteria able to migrate from the midgut via the hemolymph of the tick to the salivary glands and thus from there Borrelia can be transmitted via the saliva to the host. One single tick can carry a bacterial load from a few hundred up to several million Borrelia spirochetes. (This staggering number has been detected by the Polymerase-chain-reaction (PCR) technique described below.)



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A corkscrew spirochete

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Close-up photo of the stinger (hypostome) and two front legs of a tick

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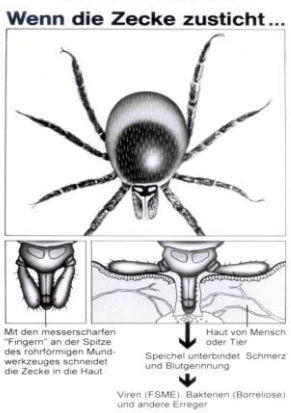
Close-up photo of the stinger of a tick



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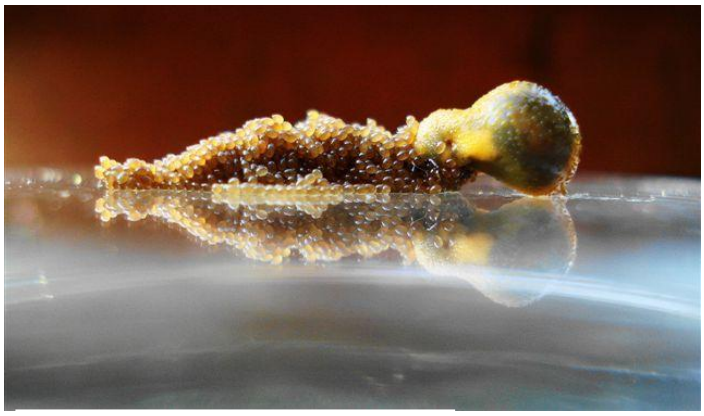

Birth of a few thousand new ticks

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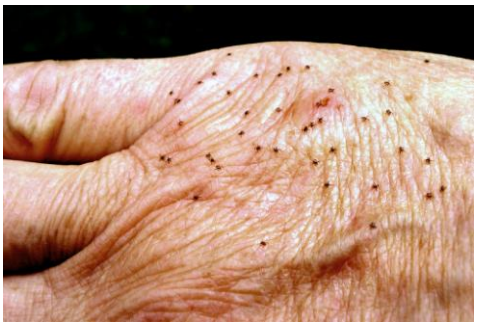
Small mammals like shrews or other ground-and-shrub-frequenting animals, as well as deer, are for the genospecies Borrelia primarily only intermediate hosts. Humans are usually so-called dead-end hosts but may also be intermediate hosts, when they transmit the Borrelia spirochetes sexually or from mother to fetus as described above. Certain warm-blooded vertebrates such as some farm animals (goats, cows, rabbits) and deer do not become sick themselves with Lyme Disease and are even able to rid ticks of their Borrelia germs. But others, like dogs and horses, fall quite ill after being in-

fected with Borrelia. Why this is the case is not yet well understood, but it is the subject of very interesting ongoing scientific research by Prof. Matuschka and Dr. D. Richter, Charité Berlin.

II. The life cycle of a tick

The life cycle of a tick begins with an egg which soon becomes a larva with six legs.

Tick's larvae hatch from thousands of eggs while the adult female dies



A hand full of larvae

In the photograph above an adult female tick has just given birth to a few thousand eggs and some of them have already transformed into larvae and are able to roam. The first meal of a larva is usually taken from small rodents or birds by stinging mostly their delicate skin around the eyes or ears. This blood meal transforms the larva to an asexual nymph, the youth in the tick's life cycle. It now has eight legs and requires another blood meal to further transform itself. At this stage it is the most dangerous form of a tick for humans because it accounts for 75% of human infections with Borrelia. Nymphs may now also choose medium-sized mammalian hosts as their stinger is already capable of penetrating thicker skin. The third and last blood meal in a tick's life is only necessary for the adult red-backed female to enable her to lay her few thousand eggs. The all black male adult tick, however, does not need any further blood meal because it dies immediately after mating.

Mating time for a couple of ticks

Ticks have no head, i.e. no eyes, no ears, no mouth or teeth, so they can't see, hear or bite. But they sense an approaching animal or human host through a different sensory organ, the so-called Haller's organ. This organ is located inside each of their two front legs. It reacts to CO_2, exhaled by the potential host, or to ground vibrations caused by a passing animal or human. When the potential host comes close enough the tick climbs onto it in no time at all and crawls along the skin searching for

the right spot to attach. Then the tick fixes itself into the skin of their new host by burrowing their barbed stinger (Hypostome) into it. After a while they become tightly anchored into the host's skin with the aid of their saliva which acts like a fast-acting glue; they cannot be pulled out easily any longer.

Ticks can lie in wait for days and weeks without eating anything. They wait with their front legs elevated ready to cling to a new host. This lurking stance of ticks always indicates that they are hungry and are ready for their next necessary meal of fresh blood.

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Lurking hungry tick

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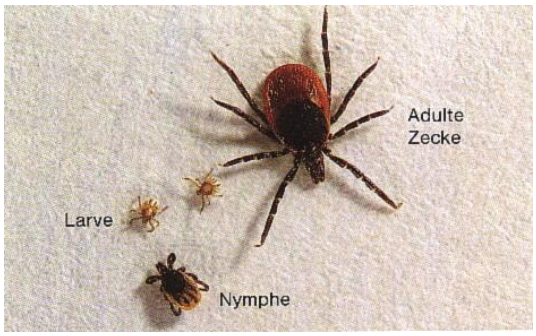
Haller`s organ in the front legs

Most people are bitten by the nymph tick, the eight-legged, still asexual "teenager" of the tick family. Nymphs are responsible for 75% of human infections, while the adult female tick only accounts for 25%. The time span between the attachment of a tick and infection with genospecies Borrelia varies from approximately four to six hours to up to more than 24 hours depending on several factors. For example, if Borrelia germs are already present in the salivary glands of the tick at the time of attachment, then only a short attachment time is necessary for an infection to take place. Earlier studies show that this is the case in about 20% of ticks (for further details see: www.dr-hopf-seidel.de /Artikel/ Beiträge zur Infektionswahrscheinlichkeit im Verhältnis zur Zeckensaugzeit).



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The life cycle of a female tick

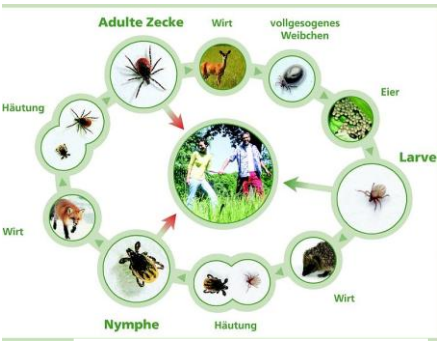

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Diagram of the life cycle of a tick

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A female tick firmly engorged

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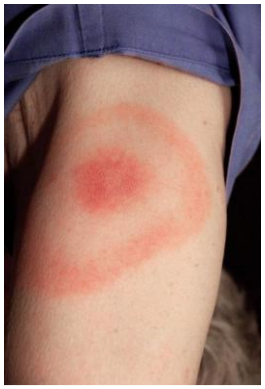
Hungry and lurking, waiting for a host

After the tick has sucked up the warm blood of its host it starts to vomit it back (regurgitate).This results that the content of its saliva and it's mid-gut, which contains lots of Borrelia, being spit back into the host through the channeled puncture made by its hypostome. Only the host's red blood cells are retained in the tick's body to feed it for the rest of its life. As soon as the Borrelia spirochetes have entered the host they start to actively move around with their rubber-band like "propellers" called endoflagellas, which are fixed lengthwise within their bodies. Through these cork- screw like movements they enter blood vessels, go deeper into the surrounding tissue, muscles and tendons and, because of their antigenic properties, cause a localized immune reaction in the host: the wandering erythematous rash referred to medically as the Erythema migrans (EM). This red or purple skin reaction around the sting area increases in size day by day after its initial appearance. This process can begin immediately after the tick's sting or can even develop many weeks after, but it mostly occurs within the first week after the tick has attached itself. The skin reaction is normally painless and does not go into the deeper layers of the skin, but itchiness, burning sensations, blisters or even pain can still occur as the EM progresses. The inner circle of the rash often becomes somewhat lighter so that it resembles a bull's eye, hence its name: "bull's eye rash". There are many forms and shapes of an EM. Sometimes it mimics a growing fungal infection with a pronounced outer ring so, erroneously, an antifungal local treatment is given or it is mistaken for an allergic reaction against insects and therefore an anti-allergic drug or cortisone cream is wrongly prescribed. EM's have so many different shapes and so many varied forms of skin reactions that it is not always easy to recognize them correctly. Furthermore, it is important to know that, statistically speaking, only 40%-50% of all infected patients will develop an **EM**, which is a **sure sign** of an early Borrelia infection. Thus half of all those infected by Borrelia may stay undiagnosed and untreated, and therefore can become chronically ill. The so-called **lymphocytoma**, which mainly develops in children but not exclusively so, is also **a sure sign of an early LD infection**. Predominantly, a lymphocytoma will be seen on very soft tissue like the ear lobes, cheeks, nipples or scrotum. It can look like a swelling after an insect bite but it doesn't itch and doesn't go away within a day.

Examples of different manifestations of EM and of Lymphocytoma



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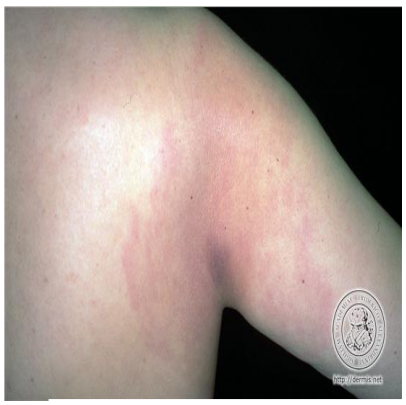
Classical bull's eye rash



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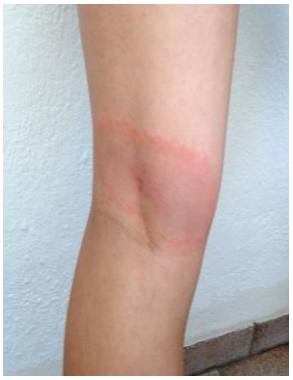
Erythema migrans around the armpit



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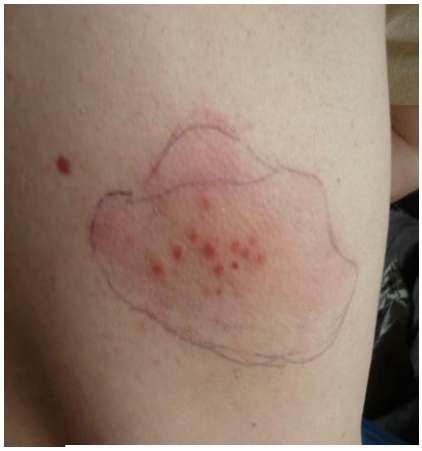
EM in the back of the knee



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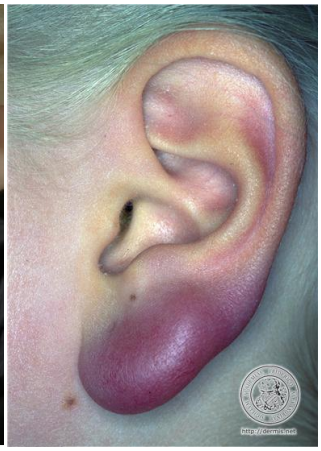
Blisters in a three day old EM



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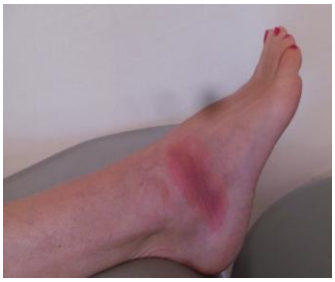
Lymphocytoma of the earlobe



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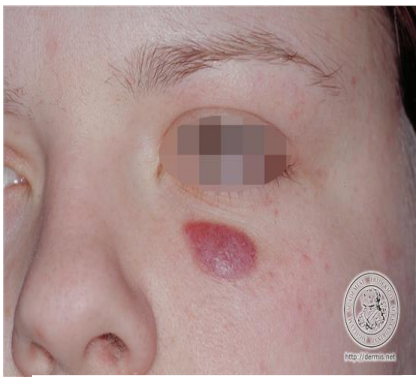
Fresh EM four days after infection



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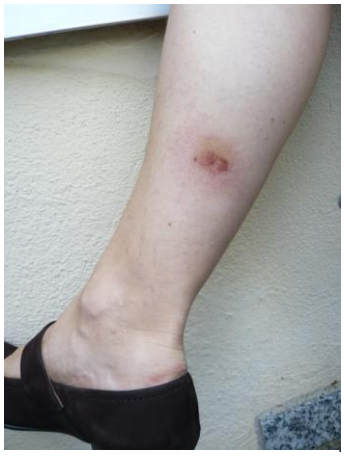
Lymphocytoma of the cheek



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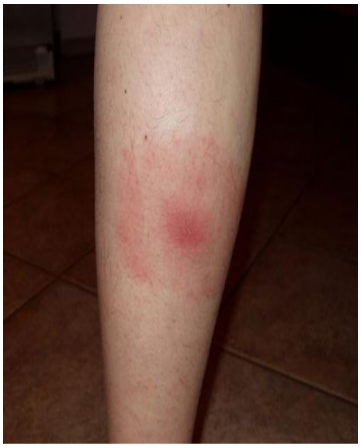
Erythema migrans on day nine



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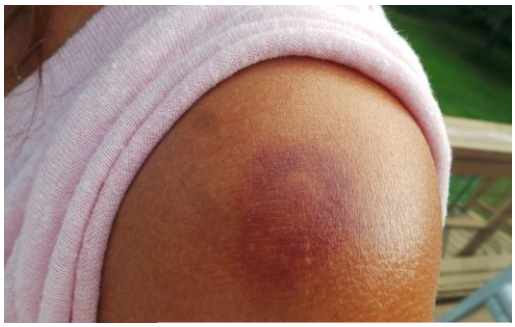
Erythema migrans on day nine



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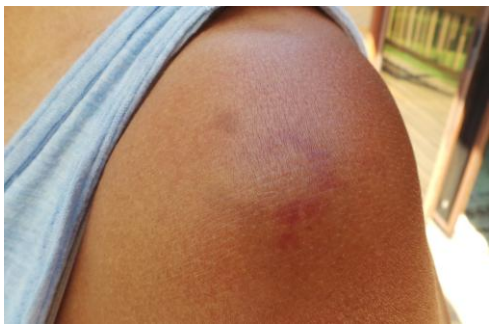

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An EM develops on day four after the tick's engorgement and flares down under Minocyclin treatment on day 10

These few examples of EM's and Lymphocytomata show clearly how different the rashes can be. The skin reaction is sometimes round or oval shaped, with small blisters or pimples and can change color from red to bluish-purple. Sometimes it can be difficult to see if it is hidden in the armpits, between the toes or the buttocks or in the groin area. When such a **skin reaction develops** after a tick was attached to the skin this is **proof of an infection** with Borrelia. The immune system of the skin fights the invading bacteria and this can be seen and felt. On the other hand an infection can go totally unnoticed and without any localized sign, especially when the tick has penetrated directly into a small blood vessel. Then the bacterial load is immediately spread with the blood stream throughout the host's entire body and the infection is generalized from the very beginning (so-called dissemination). This occurs in roughly 50% of all infections. Lyme disease as the underlying cause for a variety of symptoms should always be kept in mind, especially when the onset of LD-symptoms happens much later in life. It is said that the majority of chronic LD patients needs to see approximately eight different family doctors and specialists before the Borrelia infection is diagnosed as the real reason behind their many and varied complaints (For a survey of LD case reports see: www.Borreliose-Nachrichten.de/Datenerhebung, which provides statistics on more than 1000 LD patients, their symptoms, treatment and the social outcome, last update 12/15).

III. What should you do immediately after a tick bite?

If you find a tick latched onto your skin, you should remove it as soon as possible. This can easily be done by using a pair of tweezers or a "tick credit card" with a slit in it to carefully lift the tick straight up off the skin. The blood filled body of the tick should not be squeezed during this procedure to avoid the risk that the tick's saliva and the content of the mid-gut with all its pathogens get injected into the deeper layers of the host's skin. If a camera is available, a photo of the tick should be taken before its removal. Also photos of the sting site both initially and when changes at or around the sting's area develop, should be taken.

The tighter the tick's stinger (hypostome) is glued into the host's skin, the longer the tick has already been drawing blood. Since it takes at least a few hours for a host to become infected, it is important to estimate how long the tick may have been latched onto its host. If, for example, the tick is discovered in the morning, then the minimum time for an infection- about four to six hours- has passed during the night and therefore one should be very careful in observing the skin area as well as the person's general condition for any changes.

An even better way to assess the risk of infection is to send the whole tick to a special laboratory (see lab addresses in the **Appendix**) to have it checked via PCR (**p**olymerase **c**hain **r**eaction) for the DNA of

pathogens like Borrelia burgdorferi s.l. (or e.g. Bartonella, Babesia, Ehrlichia/Anaplasma, Rickettsia, TBE-Virus). Generally, in Germany, it only takes two or three days to receive the PCR results of the tick. This is a quick and easy way of verifying if the tick in question was carrying any pathogen affecting humans. Since roughly 30% of ticks in Germany carry some of the genospecies Borrelia (although this can vary up to 50%-70%, depending on the region), it is wise to take as a precaution, especially in the case of a longer period of attachment, antibiotics for a few days until the PCR results have come back (see "Antibiotic Therapy of early Borreliosis" page 13 ff). Doing so reduces the risk of an onset of a systemic infection considerably. Newly available to the general public in Canada is a test kit for the detection of Borrelia DNA (www.stopthetick.ca), but the reliability of the test is still under investigation by health authorities.

IV. Early symptoms of Borrelia Infection

Even when there is no **Erythema migrans (EM) or a lymphocytoma**, **both typical sign of an infection** with the genospecies Borrelia, there will very often be some other clinical symptoms.

In addition to the EM the most important early symptom is the so-called **Borrelia-flu,** because it feels like the beginning of a bad flu for those affected. Within from a few days up to two to three weeks after the tick has stung unusual symptoms may occur such as fever, fatigue and insomnia. Additionally, there may be a sudden onset of profuse sweating (usually during the nights) and palpitations. If these two symptoms occur simultaneously they are often misdiagnosed as "panic attacks". Also sore throat, severe headaches, irritation of the sinuses (but without a runny nose) and intense muscle- and joint pains may occur. If these "summer flu" like symptoms appear after a tick bite, they should be regarded as an early and definite sign of infection. Therefore they have the same significance as the appearance of an Erythema migrans (EM) or lymphocytoma. But the area of the bite is important, too, in the development of further symptoms, as most symptoms appear in close proximity to the initial bite. An EM is only one amongst these symptoms, but others include painfully swollen lymph nodes close to the bite site (usually at the back of the neck, under the lower jaw, in the groin or under the armpits) and diffuse pain in the bitten extremity and/or itching, numbness or a burning sensation on the skin near the bite site. Most of those infected suffer debilitating tiredness as well as general exhaustion without exertion and lack of energy which often even forces them to stay in bed for a few days. Headache and neck pain are common, especially in children who are often bitten at head or shoulder height (adult ticks can crawl up to 120 cm on grass and shrubs). Children often suffer from facial palsy and in some very rare cases even from a two-sided paralysis of the facial nerves, a symptom only seen so far after Borrelia infection.

A possible early Borreliosis should certainly be considered if such symptoms are present, especially in summer. Too often, symptoms like these are attributed to a viral summer flu which can only be treated symptomatically and not with antibiotics as it must be done in the case of an early Borreliosis, because it is a bacterial disease. It is important to always consider a possible tick sting when symptoms like these show up. If so, a certain group of antibiotics (see below under Antibiotic Treatment of early Borreliosis, page 14 ff), which are effective in treating the genospecies Borrelia, should be started at once, even without the presence of an EM. This opportunity for an efficient early treatment should not be missed!

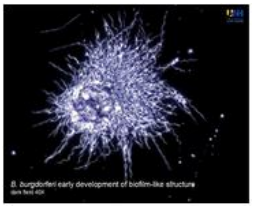
There is no clear pattern as to the spectrum and timing of symptoms, making early diagnosis of a recent infection much more difficult. Even if all these early symptoms are not present in the begin-

ning, the Borrelia infection can, nevertheless, spread throughout the entire body only to show up with symptoms at a much later stage. Consequently, misdiagnoses are very common as the many possible symptoms prevalent in late Borreliosis, are not immediately recognized as LD complaints. This is even more likely when a tick sting is overlooked which is the case in roughly 60% of all those infected according to a survey of LD patients (see www.borrreliose-nachrichten.de/ Datenerhebung).

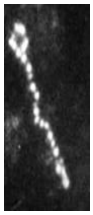
V. How can Borrelia survive in a host?

Borrelia can spread actively moving throughout the host and can therefore cause all kinds of symptoms and complaints. These clever bacteria prefer areas of the body which can't be easily reached by blood and therefore by the immune cells. The bacteria have developed many mechanisms over thousands of years to protect themselves from being attacked and eaten up by the macrophages, the "police force" of the blood, which are always on the lookout for intruders. For that reason, the Borrelia bacteria prefer to retreat to poorly-vascularized tissue like tendons, ligaments, cartilage, inner membranes of the joints (synovia) or to hide in erythro- and leucocytes or within the cells of neurons and connective tissue. Furthermore, Borrelia can change their outer surface to mimic the host's body cells and therefore can no longer be recognized as intrusive by the host's own immune system. They may transform their long and corkscrew-like spirochete form (extended 8µm-30µm in length) into small round bodies (granula) or they may lose their cellular wall and become so-called stealth forms such as the L-shapes or pseudocysts. These can no longer be dealt with by the host's immune system because the antigen properties of the cellular wall are then absent and therefore no antibodies can be produced by the host `s immune system.

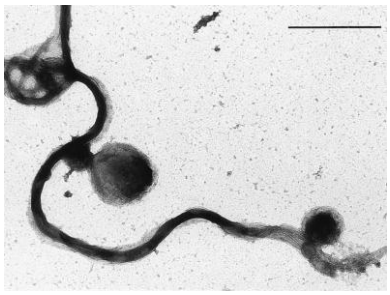
Recent in-vitro-studies by Eva Sapi, Ph.D., Univ. of New Haven, Conn. show that the safest and longest hideout for Borrelia is the so-called **biofilm**, similar to a large beehive in which the Borrelia bacteria "hibernate" in a well-organized unit. To build this survival "ball of wool", spirochetes swim together and intermingle. They then surround themselves with a strong gel-like cover and stay connected like this for a long time, out of reach for the host's immune system. There are many types of bacteria that live in these "survival spheres" (such as E.coli, Streptococcus pneum., Pseudomonas aeruginosa, Candida albicans et al.) Only as recently as 2008 did it become known by in-vitro studies that the genospecies Borrelia, too, build biofilm structures and can survive in that way in their hosts for a long time. These biofilms are well organized and all spirochetes within the "ball" can communicate with each other via a pheromone-like system known for many types of bacteria, which is called "quorum sensing". If the surrounding conditions become more favorable, the spirochetes of the outer layer of the biofilm communicate with those of the inner layer, thereafter they multiply and swarm out into the host's tissues and vessels. Doing this they cause a new inflammatory reaction of the immune system and thereafter a renewal of symptoms. This new flare up of symptoms, so-called relapses, can be observed repeatedly in all chronic Lyme disease patients. Nevertheless, it has still to be shown by scientists that all these actions happen in vivo, too, i.e. under real life conditions.



Spirochetes have built a biofilm ©Eva Sapi, Ph.D.

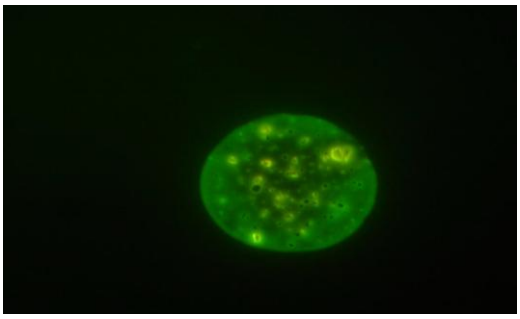


A spirochete disintegrates to granula ©Alan MacDonald, M.D.



© Kersten et al 1995

Development of cysts alongside of a Borrelia in spirochetal form



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Separate cyst of Borr. burgdorferi without extracellular matrix

VI. Antibiotic Treatment of early Borreliosis / LD

The following recommendations for an antibiotic treatment in early Lyme disease are based on my experience after many years of treating patients and of studying the therapeutic proposals of many of my colleagues (R .I. Horowitz, M.D., PD, Dr. Berghoff, J .J. Burrascano, M.D. et al.). This information can be given by patients to those of their doctors who might not be experienced in the treatment of LD. Please note that adequate treatment from the very beginning of the infection is crucial. But these recommendations do not replace a thorough clinical examination and judgement by a doctor, and are definitely not meant as guidelines for, nor an endorsement of, one's self-treatment.

From my experience, antibiotic treatment should be given after a tick bite, if:

the tick has been feeding on its host for more than four hours and was found firmly attached **and**
the site of the tick's sting changes its color or creates any physical sensations (itching, burning etc.)

or

the tick has been found to **contain pathogens,** detected by the PCR-method

and/or the patient starts to feel ill and tired, with symptoms resembling flu-like symptoms.

These are in short the criteria when it is most advisable to begin an antibiotic treatment to prevent the spread of the Borrelia bacteria.

Some General Thoughts about the Choice of Antibiotics

There are different classes of antibiotics which are all effective in treating early Lyme disease. Some may be preferred for treating different age groups and special patients, as described below.

The first choice for antibiotic treatment is **Minocycline,** because it is effective intra- **and** extracellularly and can penetrate the blood-brain-barrier (BBB). It is best in treating cognitive and neurological symptoms. Patients from age nine and older can be treated with Minocycline. It should be given in a slowly increasing dosage for at least 30 days. The dosage for a patient with average body weight (ca 70 kg) is 2 x 100 mg. If the body weight of the patient is well below 70 kg, the maxi-

mum dosage of Minocycline should not exceed 150 mg; the same applies to children. If the body weight, however, is much higher than 70 kg, a dosage of even 250 mg daily may be given, if no side effects occur.

Alternatively **Doxycyclin** can be prescribed, but in a dosage which is double the one normally recommended (i.e. 100-200 mg per day). But it is only with a dosage of **2 x 200 mg Doxycyclin** daily that the necessary blood level is reached to reduce the number of free floating spirochetes. Unfortunately, Doxycyclin does not cross the blood-brain barrier thus making it less effective in cases with neurological and cognitive symptoms. Nevertheless, one advantage of Doxycyclin is that it simultaneously treats co-infections that may have also been transmitted by the blood sucking tick, such as Ehrlichia/Anaplasma, Mycoplasma, Rickettsia and Bartonella, to name a few.

For children from the age of 6 months to 14 years the best treatment drug is **Clarithromycin** in a dosage according to their body weight. It can be given as syrup or in capsules orally twice a day (15 mg/kg body weight per day); it very rarely has side effects. It can also be given in the case of a newly infected pregnant woman who is allergic to penicillin.

During antibiotic treatment lab tests should be performed every other week to control the levels of liver enzymes as to also monitor results for blood, kidney function and inflammation.

Survey of Treatment Recommendations for Early Stage Lyme Disease

A. For adults

Tetracyclines

Minocycline 2 x 100 mg daily

The Minocycline dosage should be increased only slowly, starting with 50 mg once a day, and then be increased by 50 mg every three days up to 2 x 100 mg (i.e. 2 x 50 mg = 100 mg in the morning and in the evening). Dosage may vary depending on body weight and blood level of the antibiotic (required blood-level for effectiveness: > 2.5 µg/ml).

Doxycline 2 x 200 mg

starting with 100 mg twice a day for four days (up to maximum 2 x 300 mg , if obese). Dosage may vary depending on body weight and blood level of the antibiotic (Required blood-level for effectiveness: > 5 µg/ml).

Macrolides (should be taken in case of side effects or allergies to Tetracyclines)

Azithromycin 500 mg or 600 mg 1 x /day. After four days of treatment, a three day interruption is necessary because of the intracellular accumulation of the antibiotic.

Clarithromycin

2 x 250 mg for four days at the beginning then continue with 2 x 500 mg, if there are no side effects. As a precaution, check ECG after 14 days of treatment because sometimes a prolongation of the QT-time can result. In that case, Clarithromycin should be stopped. Be careful simultaneously taking other drugs which have effects on the QT-time.

B. For pregnant women

Amoxicillin

3 x 1000 mg can be taken, if a fresh infection occurs during pregnancy. In case of a penicillin allergy, **Clarithromycin** is a possible alternative.

C. For children under 8 years of age

Amoxicillin, Cefuroxime or Clarithromycin can equally be taken for children according to body weight

Cephalosporins

Cephalosporins should only be given for cases with severe neurological symptoms or serious symptoms in other organs, e. g. facial palsy, paralysis of an extremity or life-threatening heart dysfunctions (AV-Block III, myocarditis and/or pericarditis with efflusion). The two available Cephalosporins can only be given intravenously.

Cefotaxime (Claforan®) 3 x 2 g (up to 4 g) or 200 mg/kg body weight for children or patients who are underweight/overweight (usually with fewer side effects than Ceftriaxon)

Ceftriaxon (Rocephin®, Cefotrix®) 2 g- 4 g or 100 mg/kg body weight for children (only once a day due to the long half-life of Ceftriaxon). Serious side effects may occur such as allergic reactions, pseudomembranous colitis or gall bladder infections/stones.

Even though it is possible to encounter side effects during any antibiotic treatment, such as diarrhea, allergies, sensitivity to sunlight, changes in the ECG or the blood parameters, these are - in my experience with chronic Lyme disease – mostly acceptable side effects. It is most important to treat the disease adequately at a very early stage. Doing so prevents the later stages of a chronic persistent Lyme Disease, which is much more difficult to handle. If clinical signs of Borreliosis persist after the first 30 days of treatment and/or if the Lymphocytes Transformation Test (LTT, see more details page 28) is still positive, the treatment should be continued, perhaps after changing the type of antibiotics.

Despite the fact that statistically 9 out of 10 people who are definitely infected with Lyme Disease, can effectively fight it with their own healthy immune system, I nevertheless recommend the above course of antibiotics. This is because at the time of making the decision for or against an antibiotic treatment, the state of the immune system of the patient is normally unknown. If the immune system is already compromised by another illness or by toxins such as mercury in Amalgam fillings or by a recent vaccination, to mention only a few reasons, the immune system cannot handle an intruder like Borrelia effectively. Therefore it is safer to treat with antibiotics as early as possible.

To ensure that treatment has been successful, the Lymphocytes Transformation Test should be ordered four to six weeks after the end of the antibiotic course, to see whether or not there remains Borrelia activity. If so, a second antibiotic treatment phase with another antibiotic should immediately be started to kill as many Borrelia bacteria as possible. The early infection can only be regarded as fully treated when there are none of the earlier clinical signs of Lyme Disease or inflammation present anymore **and** when the LTT has become negative. But note that the Borrelia IgM- and IgG- antibodies can stay positive for years, even when there is no disease activity anymore.

VII. Chronic Lyme disease or Borreliosis

How can a previous infection with Borrelia burgdorferi s.l. be recognized when neither a tick bite nor a bull's-eye rash can be recalled?

This question might arise at some point in one's life when a set of sometimes strange, often changing symptoms or pain show up. There could be a diverse array of symptoms ranging from physical to psychological including cognitive disorders; these symptoms may seem to be not due to **one** disease but to numerous. Additionally, the myriad of symptoms can vary from patient to patient making it even more complicated to recognize them as symptoms of the same disease. Therefore, to begin, a thorough examination of the overall condition of the patient should be made, including internal, orthopedic, ophthalmological, neurological and psychological aspects in order to try to identify the origin of the different symptoms. Unfortunately, in Lyme disease many of the standard medical tests and routine physical examination usually do not establish a plausible reason for all the pain and complaints. Routine lab tests as well as usual technical methods such as ECG, X-rays, CT-scans, MRI and even the more sophisticated neurological and electrophysiological tests may also not ensure a correct diagnosis. As a result, many stay undiagnosed or get misdiagnosed with diagnoses such as "(Atypical) Rheumatoid Fever", "Fibromyalgia" (FM) or "Chronic Fatigue Syndrome" (CFS).

Even worse, because of some psychological problems associated with Lyme Disease, such as sleep disorders, mood swings and depressive phases, many patients are diagnosed as *solely* psychological cases. They are told, for example, that their symptoms are "all in their head between the ears" or that they are "making them up". Therefore, LD patients often get a **psychosomatic** diagnosis only, even though this far reaching misdiagnosis is made without taking into consideration the many simultaneously presented physical symptoms they are suffering from. This is especially sad because they are thus not treated effectively with antibiotics for LD and subjected to -in these cases- mostly inappropriate psychotherapy and antidepressive drugs.

To prevent this, a doctor should, before making a psychosomatic diagnosis, always keep in mind that, in the case of a genuine psychosomatic disorder such as "somatoform pain disorder" or "psychosomatic illness", symptoms usually begin to appear **after** a severe psychological trauma, that the patient always can recall. The intensity and type of his symptoms normally **remain unchanged** from the very onset and they typically begin between the ages of 16 to 30, more often in women than in men. In contrast, the symptoms of chronic Lyme Disease fluctuate in intensity and may manifest differently at varied times, they can develop at every age and equally in men and women, so it should not be too difficult to differentiate between psychosomatic disorders and chronic Lyme Disease.

It is important to know that almost all chronic and actively persistent Borrelia infections cause some neurological, cognitive and psychological impairment and complaints**.** Therefore, it would be more accurate to speak of *chronic Borreliosis with neuro-psychological symptoms*, rather than of *Neuroborreliosis,* to avoid any confusion. Characterizing the infection correctly helps to prevent a mix-up with the disease pattern of the acute Neuroborreliosis, in which we usually have a cerebrospinal fluid (CFS) with elevated Borrelia antibodies and inflammation markers. However, if the Borrelia infection has been present in the human body for a longer period of time, the immune system may have adapted to it and no longer produces many antibodies against the intruder Borrelia. No signs of inflammation or abnormalities in the CFS will then be found mainly due to the fact, that some time

after infection Borrelia germs are no longer present in their spirochetal form in the CFS, but in their granular form only. However, this life form of the Borrelia is not antigenic at all.

Examination of the CFS is, at the present time, the standard procedure to rule out the possibility of an acute Neuroborreliosis. However, if the CFS results come back negative for LD-antibodies and/or inflammation markers (i.e. elevated cell count, increased protein/albumin etc), then the patient has to have -in the doctor`s opinion- something other than LD. This can cause a real problem for the suffering patient, because he will no longer be considered as a patient with a bacterial infection, but instead will either be seen as suffering from a viral infection or, as discussed above, as a psychosomatic case. Both misdiagnoses lead to incorrect treatments and to a failure to heal from the bacterial infection LD.

Therefore we should always be mindful that lab values and CFS results can be misleading, either because they are not sensitive enough (for example, the ELISA-antibodies) or because they do not take into consideration the development of the variety of symptoms over the years nor the many different life forms of Borrelia burgdorferi.

Clinical symptoms caused by chronic Lyme Disease

Chronic persistent Borreliosis should be considered as a possible cause whenever several, generally more than three, of the symptoms below occur. This is especially true in cases in which the patient is not aware of ever having been bitten by a tick or having had an EM or when certain symptoms come and go (relapses), even without any treatment.

Some of the most common complaints of chronic LD patients

- Strong and unrelenting **fatigue and exhaustion** without any prior physical exertion. This typically includes the urge to sleep several times during the day and/or feelings of exhaustion half way through the day even after a good night's rest.
- Severe **joint pain** which randomly changes in location and intensity, sometimes seemingly disappearing altogether (without treatment) only to reappear at a later date. Sometimes relatively large joint swelling occurs, especially in the knees. The swelling can even be painless when it occurs in the tissue around the knee caps (i.e swelling of the bursa suprapatellaris).
- Intense **headaches**, mostly throbbing, diffused or localized at the front, temples or all around the head. Even combing or brushing of the hair can be painful.
- Pain may also occur in the **throat or tongue**, often only on one side, as well as in the shoulder and neck, in which case it is often mistaken as a "shoulder-neck-syndrome" and gets treated incorrectly with physiotherapy only.
- Chronic **sinus infections** with multiple relapses and slow recovery as well as long-lasting swelling of the mucus membranes. Chronic forehead headache is caused often by a sinusitis frontalis or a neuritis N. supraorbitalis, too.
- **Lymph node swellings,** painless or painful, under the lower jaw (submandibular), along the cervical spine (neck), under the armpit and in the groin, especially if a tick was attached to the leg of the same side.

- **Muscle pain and cramps** throughout the whole body without prior physical exertion, usually associated with an increase of the muscle enzymes (Creatine Phosphokinase (CPK) and/or Lactate Dehydrogenase (LDH)).
- Spontaneous **muscle twitching** (fasciculation), in the arms or legs. These twitches are usually visible and constantly perceptible to the patient.
- Pain in the **ligaments and tendons**, most commonly in the heel (Achilles tendon), but also the elbow (Epicondylitis, also known as tennis or golfers elbow), **C**arpal **T**unnel **S**yndrome (CTS), "Jumping" fingers (also known as Digitus saltans, caused by a swelling of the tendon inside its tendon sheath) or irritation/inflammation of the plantar fascia which causes pain in the sole of the foot, especially during first steps in the morning.
- **Partial or full tendon and muscle ruptures** without adequate prior physical exertion, especially applicable to the Achilles tendon, but also in the tendons of the thigh muscles (M. quadriceps femoris) or the calf muscles (M. triceps surae) and sometimes even of the muscles of the upper arm (M. biceps).
- **Severe pain in the shin and the heel**, especially *during the night*.
- Deeply felt aching pain in the joints of the **ribs and breastbone** (sternum) or at the **lower rib-cage**, often combined with a feeling of reduced respiratory volume and pressure on the rib-cage. This pain can be mistaken with the feeling of "heavy burden on the chest" as often experienced by patients suffering of depression.
- **Irritation in the throat with coughing** and shortness of breath after only minor physical activity (like walking upstairs). These symptoms are most commonly encountered when also suffering from a co-infection such as Chlamydophila pneumoniae or Mycoplasma pneumoniae.
- A burning **pain of the skin** and/or a feeling of **numbness**, which can occur all over the body or in certain areas, or an **itching** and sensation of something crawling under the skin without any visible changes of the skin surface.
- **"Electrifying" or "water flowing" sensations** under the skin, mostly under the scalp.
- Sudden **stabbing pains** in different groups of muscles, but in constantly changing locations.
- Sudden onset of a **racing heart beat (**tachycardia), especially at night, without any previous physical activity, **irregular heart beat** (arrhythmia, extrasystoles) or uncomfortably strong felt heart beats (palpitations).
- In some cases, infestation of the heart with the spirochetes Borrelia causes **dysfunction of the regular transmission of heart impulses** which can be the reason for second or third-degree **AV block** (also known as complete heart block) and arrhythmias. Infection with Borrelia can also cause a fluid build-up around the heart (pericardial effusion), i.e. the patient suffers from a myocarditis in conjunction with pericarditis. Angina pectoris on the other hand, is usually not a part of the spectrum of cardiac symptoms of Borreliosis.
- A change from a normal to a **high blood pressure** (hypertension) mostly with a rise in diastolic values (over 90 mm Hg). Blood pressure will generally normalize after adequate LD therapy and anti-hypertensive medication will no longer be required. The antihypertensive drugs should be reduced slowly as the LD treatment normalizes blood pressure.

- **Neurological symptoms** and complaints are numerous and complex. In addition to strong pain and changes in the sensation (dysesthesia) along the peripheral nerves (**polyneuropathy**), tremors may occur in the extremities and so can (**partial) paralysis** of arms or legs. Other clinical symptoms of chronic persistent LD include **paraplegia** or **hemiplegia** and/or reduced feeling in one half of the body (**hemihypesthesia**). These neurological deficits can all be caused by a Borrelia-induced **inflammation in the upper spinal cord** or **in the brain** (resembling a stroke). In rare cases, **epileptic seizures** can also be seen in cases of chronic persistent LD, especially in children.
- **Garin-Bujadoux-Bannwarth-Syndrome (or "Bannwarth-Syndrome"):** This syndrome is a typical manifestation of a recent Borrelia burgdorferi infection, although it can also be seen in the later stages of the disease. It presents itself as an intense burning and aching, usually in one leg or arm only, **resembling the pain of a slipped (herniated) disc** or, if the upper extremities are affected, of a so-called shoulder-arm-syndrome. By the type of pain only, one can differentiate between the two conditions, as the pain caused by the Bannwarth-Syndrome is **worst at night**, whereas the pain caused by a spinal herniated disc increases with movements and upright position during the day. Commonly-prescribed pain relievers or anti-inflammatory drugs will have little impact on the pain if it's caused by a Bannwarth-Syndrome and physical therapy is similarly ineffective. Due to the Borrelia induced inflammation of the spinal nerve roots, a CFS-analysis may show signs of acute inflammation such as an increased cell count, increased Borrelia burgdorferi antibody index or increased protein values. If the real reason behind the ischiadic pain is not detected, the chronic LD stays on as well as the symptoms of the Bannwarth-Syndrome.
- **Dysfunctions of the autonomic nervous system: Impaired sense of body temperature** with either severe shivering "from deep within" or "hot flashes" like in menopause, but experienced by both women and men. Profuse **sweating,** mostly at night, but also during the day. Often **slight fevers** (sometimes bound to a circadian or monthly rhythm), "**flushed cheeks**" without fever, predominantly in the afternoons and newly-developed **alcohol intolerance** often to only very small amounts of alcohol. Sometimes there are persistent slightly elevated liver enzymes, too.

Some of the possible cranial nerve dysfunctions

- **Irritation of some cranial nerves** is common. **Paralysis of the facial nerve** occurs most often during the early stages of the spirochetal infection, while in the later stages of the infection several of the other 12 cranial nerves can be affected, too.
- **Dysfunction of the eyes:** Pain of the eye muscles during eye movements, slight weakness of an eye muscle with double vision, upper eyelid weakness, light sensitivity and delayed adjustments to light changes, especially at dusk (hampered accommodation), pupil dysfunctions (with a paradoxical undulating mydriasis when exposed to direct light), burning eye (conjunctivitis) and dry eye as well as gritty feeling of the eye. Sometimes even scleritis, (recurrent) retinitis, scotoma and impaired vision fields.
- **Dysfunction of hearing and the labyrinth:** Sudden loss of hearing, tinnitus, dizziness (vertigo) and impaired balance.

- **Dysfunction of the sense of smell and taste:** The ability to smell and taste is impaired; there are unusual sensations in the face. Irritation of the fifth cranial nerve, the trigeminal nerve (N. trigeminus) may cause too much or too little sensation of the skin of the cheeks (and it can even imitate tooth ache or aches of the jaws, Dysesthesia, Hyperesthesia, Hypesthesia)

Hormonal and metabolic dysfunctions

- **Sexual dysfunctions:** Loss of libido, menstrual irregularities, erectile dysfunction as well as pain in the breasts and mammary glands.
- **Urological dysfunctions:** Burning sensation in the bladder and urethra, pain in the testicles and scrotum without any indications of bacteria in the urine ("prostatitis" without the presence of bacteria), frequent urination with only small amounts of urine (pollakisuria) day and night, too (nycturia). Sometimes one even complains of urinary incontinence or pain in the groin, all of which have no detectable urological causes (especially occurring after a tick attachment in the genital area).
- **Gastrointestinal complaints:** Changes in appetite and weight (both increasing and decreasing) without any change in diet. Stomach ache, flatulence, bloated feeling, stool irregularities with diarrhea alternating with constipation (irritated bowels), loss of appetite, newly appearing lactose or fructose intolerance, other food intolerances and very often alcohol intolerance.
- **Changes in metabolism:** Hyperacidity (urine pH-testing can be done with five urine samples in one day by the so-called Sander Test), new increase in cholesterol values, thyroid disorders (often hypothyreoidism with an increase in the Thyroid-Stimulating Hormone (TSH basal)) and the development of autoantibodies against thyroid tissue (Anti-TPO/MAK), causing the so-called Hashimoto-Thyreoiditis. The spirochetes could also be responsible for a change in the activity of the enzyme which converts T4 to T3 resulting in the production of an inactive, inverse form of T3. Even when taking supplemental thyroid medication and when TSH-values have already normalized, the change in enzyme activity can still cause symptoms of impaired functioning of the thyroid gland (hypothyreoidism).
- **Changes in the Serotonin metabolism:** Irritability, panic attacks, anxiety, (latent) aggression, fits of rage, mood swings and emotional instability caused by low levels of serotonin. If the first onset of panic attacks occur suddenly and newly in already older individuals and do so predominantly at night, it is very likely that they are caused by a Borrelia infection, since normally panic attacks belong to the serotonin disorder syndrome and start during adolescence.
- Another **change in the reaction of the immune system**, which is often reported by Borreliosis patients, is a much stronger reaction to **anaesthetics** and **vaccinations,** than before the Borrelia infection. In particular, after a vaccination for Tick borne encephalitis (TBE) LD symptoms can strongly exacerbate. Additionally, it is often observed that other infections, especially virus infections, will flare up. (With the LTT-method these flare-ups can be detected as well as a flare up of Borrelia activity: for details see page 28).
- **Chronic sleep disorders:** Disturbance of sleep patterns with interrupted sleep, trouble falling and staying asleep, light and non-refreshing sleep and nightmares. Each of these disturban-

ces can be caused by the lack of melatonin due to a dysfunction of the Tryptophan-Serotonin-metabolism.

- **Attention deficit disorders:** Lack of ability to focus and concentrate, especially noticeable in children, as well as a predominantly physical restlessness. Many children might be wrongly misdiagnosed with "Attention Deficit Disease" (ADD) or "Attention Deficit Hyperactivity Disease (ADHD)**.** They may also show changes in social behavior such as newly developed anxiety about going to school, irritability and aggression with siblings and friends.
- **Serious but rare psychological changes:** In adults, even more serious psychological conditions may occur in some cases such as psychosis, manic-depressive mood swings, obsessive compulsive disorder (OCD), irritability and uncontrollable aggression.
- **Cognitive dysfunctions.** Almost every patient with chronic LD will suffer from some form of cognitive dysfunction, though with varying degrees. Often patients complain of **short-term memory loss, lack of concentration and of being easily distracted**. Difficulties in **planning and organizing** every day activities and in **abstract thinking** are frequently reported. There are very often difficulties in academic and job-related **learning** and, in general, in absorbing new information. Patients also complain about **reading, calculating** and **writing difficulties** (mixing up letters especially when using the keyboard of their computers) as well as in **speaking** (e.g. mispronouncing words, having trouble finding the correct words) and in **thinking** ("mental fog"). There is a constant feeling of not being "quite right".
- **Pseudo-Dementia**. In rare but severe cases of chronic LD, there may be symptoms similar to those of an organic brain syndrome (Alzheimer's disease). These include disorientation, severe short-term memory problems and even hallucinations and delusions.

Skin changes

- **Skin conditions.** A rare but typical (pathognomonic) skin change, which only 2% of all chronic LD patients develop over time, is the so-called ACA (**Acrodermatitis chronica atrophicans**) stage III with "cigarette paper skin". It normally appears in the lower part of one extremity (leg or arm) only. Stage I and II of ACA is much more common and shows subcutaneous swelling and lilac coloring of the skin. Often you will see in LD patients bluish and white blotchy skin in combination with cold extremities.

  Recently, **Focus Floating Microscopy** (FFM) (for details see the Appendix) has been developed to scientifically examine some rare skin conditions such as Morphea (Sclerodermia circumscripta), fibrotic-like nodules in close proximity to joints as well as Granuloma anulare. The supposition that these skin conditions could be a result of a Borrelia infection has now been confirmed by this new histological method (FFM). In 30% of all of these patients, Borrelia antibodies were also found as well as spirochetes themselves histologically in the tissue samples.
- **Erythema migrans** (or **Erythema chronicum migrans,** if it develops more than four weeks after the infection) has already been mentioned above as a typical LD skin symptom, also commonly known as a bull's-eye rash. Lesser known is the fact that an EM can appear in multiple forms, one after the other or even at the same time. It can also reappear **on different parts of the body** as long as the spirochetal infection is present, particularly during the anti-

biotic therapy. This means that not every EM is a sign of a recent Borrelia infection only but can also indicate **a reactivation** of an already in the body existing LD infection.

- **Lymphocytoma** is another typical skin reaction to the Borrelia infection (see above on page 8 and 9).
- **Skin Rashes** of various types like papules, urticaria, blotches, flakes . Atrophy of the follicles of the skin (Anetoderma) as well as inflammation of the subcutaneous tissue (Panniculitis) or the connective tissue, which can cause painful skin nodules or a dispersed pain, which is easily misdiagnosed as fibromyalgia.
- **Problems with nails or hair.** Nail growth anomalies like brittleness or nail grooves, sometimes profuse diffuse hair loss (mostly in women) or hair loss in spots (Alopecia areata). The increased hair loss will normally be normalized during and after treatment.

Questionnaire for checking if you might be infected with Borrelia burgdorferi and suffering from Lyme Disease

(From: Richard I. Horowitz, MD: Why can`t I get better, NY 2013; Used with author 's permission)

SECTION 1: SYMPTOM FREQUENCY SCORE	
0 None **1** Mild **2** Moderate **3** Severe	
1. Unexplained fevers, sweats, chills, or flushing	
2. Unexplained weight change; loss or gain	
3. Fatigue, tiredness	
4. Unexplained hair loss	
5. Swollen glands	
6. Sore throat	
7. Testicular or pelvic pain	
8. Unexplained menstrual irregularity	
9. Unexplained breast milk production; breast pain	
10. Irritable bladder or bladder dysfunction	
11. Sexual dysfunction or loss of libido	
12. Upset stomach	
13. Change in bowel function (constipation or diarrhea)	
14. Chest pain or rib soreness	
15. Shortness of breath or cough	
16. Heart palpitations, pulse skips, heart block	
17. History of a heart murmur or valve prolapse	
18. Joint pain or swelling	
19. Stiffness of the neck or back	
20. Muscle pain or cramps	
21. Twitching of the face or other muscles	
22. Headaches	
23. Neck cracks or neck stiffness	
24. Tingling, numbness, burning, or stabbing sensations	
25. Facial paralysis (Bell's palsy)	
26. Eyes/vision: double, blurry	

27. Ears/hearing: buzzing, ringing, ear pain	
28. Increased motion sickness, vertigo	
29. Light-headedness, poor balance, difficulty walking	
30. Tremors	
31. Confusion, difficulty thinking	
32. Difficulty with concentration or reading	
33. Forgetfulness, poor short-term memory	
34. Disorientation: getting lost; going to wrong places	
35. Difficulty with speech or writing	
36. Mood swings, irritability, depression	
37. Disturbed sleep: too much, too little, early awakening	
38. Exaggerated symptoms or worse hangover from alcohol	
Section 1: Total Symptom Frequency	

SECTION 2: MOST COMMON LYME SYMPTOMS SCORE	
If you rated a 3 for each of the following in section 1, give yourself 5 additional points:	
39. Fatigue	
40. Forgetfulness, poor short-term memory	
41. Joint pain or swelling	
42. Tingling, numbness, burning, or stabbing sensations	
43. Disturbed sleep: too much, too little, early awakening	
Section 2: Total Most Common Lyme Symptoms	

SECTION 3: LYME INCIDENCE SCORE	
Now please circle the points for each of the following statements you can agree with:	
44. You have had a tick bite with no rash or flulike symptoms. *3 points*	
45. You have had a tick bite, an erythema migrans, or an undefined rash, followed by flulike symptoms. *5 points*	
46. You live in what is considered a Lyme-endemic area. *2 points*	
47. You have a family member who has been diagnosed with Lyme and/or other tick-borne infections. *1 point*	
48. You experience migratory muscle pain. *4 points*	
49. You experience migratory joint pain. *4 points*	

50. You experience tingling/burning/numbness that migrates and/or comes and goes. *4 points*	
51. You have received a prior diagnosis of chronic fatigue syndrome or fibromyalgia. *3 points*	
52. You have received a prior diagnosis of a specific autoimmune disorder (lupus, MS, or rheumatoid arthritis), or of a nonspecific autoimmune disorder. *3 points*	
53. You have had a positive Lyme test (IFA, ELISA, Western blot, PCR, and/or borrelia culture). 5 points	
Section 3: Total Lyme Incidence Score	

SECTION 4: OVERALL HEALTH SCORE

54. Thinking about your overall physical health, for how many of the past thirty days was your physical health not good? _____days Award yourself the following points based on the total number of days: 0–5 days = 1 point 6–12 days = 2 points 13–20 days = 3 points 21–30 days = 4 points	
55. Thinking about your overall mental health, for how many days during the past thirty days was your mental health not good? _____ days Award yourself the following points based on the total number of days: 0–5 days = 1 point 6–12 days = 2 points 13–20 days = 3 points 21–30 days = 4 points	
Section 4: Total Overall Health Score	

SECTION 5: SCORING

Record your total scores for each section below and add them together to achieve your final score:	
Section 1 Total:	
Section 2 total:	
Section 3 total:	
Section 4 total:	
Final Score:	

If you scored 46 or more, you have a high probability of a tick-borne disorder and should see a health-care provider for further evaluation.
If you scored between 21 and 45, you possibly have a tick-borne disorder and should see a health-care provider for further evaluation.
If you scored under 21, you are not likely to have a tick-borne disorder.

Interpreting the Results

We see a high frequency of Section 1 symptoms in our patients, including fatigue, joint and muscle pain that often migrates, sleep disorders, as well as memory and concentration problems, and a high frequency of Section 3 symptoms, especially neuropathic pain that comes and goes and migrates (tingling, numbness, burning, etc.). These form a cluster of presenting symptoms that are characteristic of those with a high probability of having Lyme- MSIDS.

In one recent study conducted in our office of 100 consecutive patients, we found that more than 25 percent reported that the following symptoms were present most or all of the time in the month preceding their office visit. Many of these patients reported that these symptoms affected their quality of life: 71 percent reported that their physical health was not good and 47 percent reported that their mental health was not good on at least fifteen days in the previous month.

Disclaimer:

The Horowitz Lyme-MSIDS Questionnaire is not intended to replace the advice of your own physician or other medical professional. You should consult a medical professional in matters relating to health, and individuals are solely responsible for their own health care decisions regarding the use of this questionnaire. It is intended for informational purposes only and not for self-treatment or diagnosis.

Laboratory tests to confirm an infection with the genospecies Borrelia burgdorferi

The symptoms described above should always evoke suspicion of a possible case of Lyme Disease and laboratory tests should be conducted to determine if their results, such as increased antibodies against Borrelia burgdorferi or some specific bands in the Immuno/Westernblot test, do confirm that the symptoms of the patients are being caused by Lyme Disease.

However, even without positive laboratory test results, the possibility of a Borreliosis shouldn't be excluded because seronegative test results are also possible in some cases. Thus, tests to prove Borrelia burgdorferi directly should always be preferred to the indirect serological tests mentioned above.

The following laboratory tests are presently available to confirm an infection with the spirochete Borrelia burgdorferi s.l.

Indirect serological methods, which measure the reaction of the immune system to a pathogen.

- **Borrelia antibodies**
  The **E**nzyme **L**inked **I**mmunosorbent **A**ssay (ELISA) tests are used to detect Borrelia antibodies. A positive result is evidence that the immune system has had to deal with the spirochete Borrelia s.l. at some time in the past or more recently. It shows the reaction of the immune system to the surface proteins of the Borrelia bacteria. It takes the *B-cells* of the immune system four to six weeks before they can produce the IgM antibodies , and even later the IgG antibodies against B.b.. It is a test to prove, that an infection with B.b. has taken place sometime in the past, but it is not at all a confirmation of a still active Borreliosis.

  Retrospective studies show that roughly 20% of patients who were definitely infected by Borrelia had hardly any Borrelia antibodies. Various reasons for seronegativity are currently known, including: previous use of cortisone or other immunosuppressants; an early antibiotic therapy immediately after the spirochetal infection; a weakening of the immune system due to other diseases; a lack of immunoglobulin; malfunctioning of the white cells; a hypogammaglobulinemia or simply disappearance of the antibodies over the time.

- **Immuno-/Westernblot**
  A more accurate test for identifying if a Borrelia infection has taken place is the Protein Immunoblot test, also known as the Westernblot test. This test is particularly useful for determining the necessary course of treatment for an LD infection as it gives an idea of whether the infection is more recent or older. Typical "**old bands**", highly specific, are for example: **Osp17, p18, p28/29, Osp A/p31/p32, OspB/p34, BmpA/p39, p83, p100.** A more **recent infection** is likely when bands like **OspC/p21/25** show up. The p 41-Band is quite unspecific (all bacteria with Flagellae cause it) but it is the first to show up in the immune reaction process after an infection with B.b. has taken place. A highly specific band, VlsE–IgG, is present only when a host has been intruded by Borrelia. The same applies to the C 6-Elisa test.

  There are, however, so-called "seronegative" patients who show neither antibodies in the ELISA-test nor have specific immunblot bands. Besides the reasons mentioned above this is also the case when the immune system is not able to recognize Borrelia germs in the system

as they are able to “hide” in body regions that have poor blood circulation and furthermore because they are able to exist in different life forms. If the Borrelia spirochetes have transformed themselves into cysts, blebs, granula, biofilm or even into an immunocomplex, then they cannot be detected at all by the immune system. The same applies if the Borrelia in all its possible life forms is located in host tissue with poor vascularization such as ligaments or tendons, so that no antigens of Borrelia will be presented to the immune system and therefore, no humoral defense strategies are implemented. The Borrelia bacteria also have another amazing ability: they can disguise themselves as being “human cells” by using Factor H, a specific cell adhesion protein, which was chemically fully deciphered in 2005. Thus the immune system fails to recognize Borrelia as an attackable antigen.

It should be noted that not all laboratories have the capacity to diagnose the full range of Borrelia antibodies correctly and that in some labs the Borrelia test kits do not contain the highly-specific recombinant Borrelia antigens .Therefore these labs do not always give reliable results. If in doubt about the validity of the test result, consider using a more specialized laboratory for retesting. In North America, including Canada, the *IGeneX* laboratory in California, USA has a good reputation.

In the case of seronegative LD patients with a lack of antibodies or specific bands, a Borrelia infection can still be present. It may be detected by using either the **Lymphocytes transformation test (**LTT) or a **EliSpot** (Enzyme linked immune spot assay). (For laboratory addresses see the **Appendix**).

- **The Lymphocytes Transformation Test (LTT)**
  The lymphocytes transformation test or lymphocytes proliferation test has been in use for 45 years and measures the reactions of the *T-cells* of the immune system to an antigen. All studies to date confirm it to be more sensitive and to give earlier test results than tests which measure *the B-cells* reaction with its late production of antibodies (see above). This immunological reaction of the *specific Memory-T-cells* occurs as the first measurable positive immune system reaction within 10 days after infection, i.e. long before the IgM or IgG antibodies production has started (which usually occurs 4 to 6 weeks after infection). The **Borrelia-LTT remains positive as long as an immunological reaction takes place between the cellular immune system and Borrelia bacteria**. The LTT is currently the most suitable test to prove the *ongoing activity* of Borrelia burgdorferi s.l.. The test is one of the indirect types, as it can only show the immune system’s reaction towards the intruding bacteria rather than being able to detect the presence of the pathogen itself. But if the immune system itself is not healthy, it may fail to produce these indirect parameters.

- **The T-cellspot or EliSpot-Test**
  The EliSpot test for Borrelia measures cytokines (Interferon gamma) released by T-Lymphocytes when they are stimulated by Borrelia specific antigens but does not measure the memory T-lymphocytes themselves. It cannot differentiate well between an active ongoing infection and a condition any time after an infection. But the EliSpot test does detect, with high sensitivity, Borrelia infections in general. The advantage of an EliSpot-test is that the result is more quickly available than that of an LTT (six days versus ten days for the LTT).

- **Cerebrospinal fluid**
  Analyzing the Cerebrospinal fluid (CSF) in the later stages of a Borrelia infection does not often yield any positive results as to Borrelia-Antibody-Index (AI) and cell count because these

are often normalized after Borrelia has been in the human body for some time. Immediately after the onset of the infection the immune system may cause an increased Borrelia antibody-index and higher protein values and elevated cell counts in the CFS, but not always. In the later stages of the disease, signs of a mild dysfunction of the brain-blood-barrier with slightly increased protein and albumin concentration in the CSF can sometimes be detected. Therefore, it cannot be definitely determined by a CFS test alone, if a Borrelia infection has taken place or not. If after a Borrelia infection neither Borrelia antibodies nor Borrelia specific immunoblot bands or any inflammation sign in the CFS are found, this does not "prove" the absence of chronic (Neuro-)Borreliosis (better characterized as chronic Borreliosis with neuro-psychological symptoms). It rather shows that there is actually no spirochetal infection of the meninges and the part of the brain tissue which is located within the proximity of the dural membranes, which produces the CFS.

In addition to these indirect methods to prove the presence of Borrelia, there are also some direct methods available. They would definitely be preferred if they were as sensitive as the indirect tests. Unfortunately, this is not yet the case with the presently available testing methods.

Direct testing methods

- **Blood Culture**
  After an infection, the presence of viable Borrelia bacteria can be directly established by culturing, in a special growth medium for Borrelia, from biopsy material from a patient's skin, synovial fluid or CFS. The growing of Borrelia in the culture medium, however, can take several weeks and is often unsuccessful due to the spirochetes' very slow replication time of 12 to 24 hours. In addition, this culturing method is to my knowledge currently done only by a few specialized laboratories in Germany.

- **Polymerase chain reaction**
  Another possible way of verifying the presence of Borrelia is the Polymerase chain reaction (PCR) method in which the genetic material (DNA) of Borrelia can be detected. The PCR method can be performed using bodily fluids (in order of decreasing probability of a Borrelia DNA-positive result): synovial fluid, CFS, urine, blood. The PCR method can also be used with biopsy material from infected tissue, for example from a biopsy of an EM, ACA, synovia, the inner lining of the bladder, mucous membranes of the sinuses, muscle fibers or tendon tissue. Generally, biopsy material is more likely to give positive DNA-results.

  If a PCR result is positive for Borrelia DNA, one can assume a recent or still active Borrelia infection. As the PCR method does not differentiate between live and dead Borrelia it is scientifically not quite clear if a positive PCR indicates a still ongoing infection or not. Through phagocytosis, dead Borrelia material including its DNA will be removed usually in about four weeks. IGeneX laboratory in California, USA, has developed and patented a new PCR method, called *Multiplex PCR*, which can, in addition to genome-sequence analysis, determine the plasmid-sequences of Borrelia and can thus prove the presence of Borrelia, even if they hide in blebs, cysts or biofilms. As such, Multiplex PCR seems to be much more sensitive than the "nested PCR" in attempts to identify the "genetic fingerprint" of Borrelia. When this method is used, Borrelia DNA can also be found in blood and blood smears, skin samples, CFS and sediments (eluats) obtained by apheresis.

This method can also be used to analyze the ticks for their content of Borrelia DNA or DNA of even other pathogens. This helps to verify whether Borrelia and/or TBE-Virus, Babesia, Bartonella, Rickettsia or Ehrlichia/Anaplasma could have been transmitted at all through the tick bite before. (For laboratory addresses see the Appendix).

As mentioned above (see page 11) the tick should for safety reasons always get checked for Borrelia DNA after it is removed from the skin to know for sure if it carried Borrelia germs or not. This may avoid unnecessary worries if the tick test shows no sign of Borrelia DNA. There is a consumer kit on the market to test a tick for Borrelia DNA, but its reliability is not yet known (see page 11).

Even when DNA analysis of the tick is negative for Borrelia, one should always remain cautious. Even though immediate antibiotic treatment is not necessary, great attention should still be paid to clinical symptoms/complaints for a longer period of time after the tick bite, as one can never be sure if another tick, in addition to the one tested, may have also latched onto the body.

- **Dark field microscopy**

  Another direct method of confirming a Borrelia infection is the almost forgotten Dark Field Microscopy (DFM) which analyses fresh, that is, unstained and not centrifuged blood. A small drop of capillary or vein blood can be used to prepare a blood smear. A small serum vial of blood can also be sent for analysis *by mail* because even after one or two days there are still some liquid parts of the blood sample available for the analysis.

  The blood sample is observed over a period of several days using the Dark Field Microscope to monitor changes in the sample. When the positive surface tension of the blood cells subsides, i.e. when the cells no longer repel each other and the cells get destroyed and break open so that previously intracellular hiding spirochetes will show up.

  In a fresh Borrelia infection, the spirochetes are still moving around freely in the blood and, characteristically, spin around their own axis, making it easy to identify them. In case of a chronic infection, it can take several hours or even days before they are visible under the microscope as they "slip out" of the blood cells (erythrocytes and macrophages). We know that Borrelia can penetrate various tissue cells as well as endothelial and blood cells within hours after infection. In the Microbiology medical literature Dark Field Microscopy is, still today, considered to be a suitable direct method of proving the presence of leptospira and other spirochetes, the relatives to the B.b.-spirochete. For example, it has been predominantly used in earlier times to directly prove the presence of e.g. Treponema pallidum, the spirochete of the Syphilis infection. This method of analysis can, however, also equally be applied to Borrelia recurrentis, the pathogen causing tick-borne relapsing fever, as well as to all sorts of Borrelia genotypes. In addition to Borrelia, Dark Field Microscopy can show other intracellular pathogens such as Chlamydia or Yersinia. Extracellular pathogens can also be seen, for example Candida, Streptococcus, Diplococcus, Staphylococcus and parasites such as Giardia/Lambia. For the latter, this may be quite helpful because the serological detection of antibodies or the LTT for Giardia/Lamblia is not always conclusive.

  Dark Field Microscopy can also identify hyperacidity by the presence of crystalline structures in the patient's blood and, furthermore, it can also show exposure to heavy metals (e.g. mercury, palladium, cadmium or lead etc). Unfortunately, this helpful method of analysis is now

used mostly by naturopaths following the teachings of Professor Enderlein and no longer by laboratories and microbiologists as an established method of verifying pathogens as it had been in the past, for example, used to diagnose syphilis by detection of the spirochete Treponema pallidum.

In seronegative, but clinically suspect cases of LD, Dark Field Microscopy can be used to find evidence of Borrelia and certain co-infections as well as to detect other risk factors (such as heavy metals or hyperacidity). Dark field microscopy can also be done to determine if there is any Borrelia bacteria left after a course of antibiotic treatment. In general, it takes 10 days to get the results of the dark field microscopy. The patient can clearly observe the changes and improvements in their own blood sample because the doctor, as well as the patient, are usually given a print-out of the microscope images and, if desired, even a DVD with video sequences of the (still moving) spirochetes. (See the Appendix for the address of a source for Dark Field Microscopy).

- **Histological methods**
  Spirochete Borrelia can also be detected in skin and tissue samples using histological methods by applying special staining agents. The newest one of these methods is the immune histochemical method of *Focus Floating Microscopy (FFM)* which additionally uses polyclonal Borrelia antibodies. FFM analysis has achieved a sensitivity of 96% compared to the PCR method which has a sensitivity of only 45%. Additionally, FFM has almost the same specificity as PCR, 99.4% for FFM compared with 100% for PCR. Many skin conditions which, until now, could not easily be classified (such as Lichen sclerosus or sclerodermia circumscripta), can now be attributed to a Borrelia infection using this method. (See the Appendix for sources for FFM analysis).

Conclusion

When deciding whether a patient needs LD therapy the practitioner should assess the patient's medical history (tick bite in the past?), the kind of symptoms and complaints of the patient (see the list of symptoms on page 17 ff) and the patient's current clinical condition. Therefore, the decision about a necessary antibiotic treatment should never be based *solely* on lab results. Lab results can support the diagnosis of Lyme Disease, but cannot exclude it.

Some of the factors that can cause an acute Borrelia infection to become chronic

In completely healthy individuals without previous stress to the immune system, the production of antibodies against Borrelia can be sufficient to prevent the onset of further Borrelia-related symptoms. Epidemiological studies have shown that out of 100 Borrelia-infected patients, who developed antibodies, only 10 had clinical signs of the disease. However, the follow-up observation period for these studies was, in all cases, probably much too short to make definite conclusions because many Borrelia-related symptoms appear only years after. This is supported by clinical, longtime observations, made for example by PD Dr. Hassler, a family doctor, who has monitored his patients with a confirmed Borrelia infection over many years. Most of these patients were seropositive but asymptomatic. Nevertheless, many of them began to show their first symptoms and complaints of a Borrelia-related disease as late as eight years after infection.

Inadequate elimination of pathogens could be due to a weakness in the patient's immune system itself. This could be due to an inborn "error" e.g. **lack of immunoglobulin** or to lack or weakness of

Mannose binding globulin (MBL) or due to a previous treatment with **immunosuppressant medication** for another severe illness, thus inhibiting the body's ability to defend itself against invading bacteria.

But the development of a chronic form of Lyme Disease can also depend on some risk factors such as **deficiencies in detoxification ability** due to (genetic) polymorphisms. If toxins of any kind are already present in the body, the additional burden for the immune system is immense. This is because it has to deal, in addition with the bacteria, with toxins which cannot be detoxified if there is a genetic weakness or deletion of enzymes of the detoxification system.

Other factors that increase the risk of development into chronic LD are **environmental toxins** such as **solvents, softeners (phthalates), fungi and heavy metals**. These include, to name only a few, lead (from old pipes), cadmium (manure, cigarette smoke, waste burning) and nickel (jewelry or food), as well as aluminum (in deodorants and antacids). Many vaccinations can be dangerous for those with an **impaired genetic detoxification system** because the vaccines contain, for stabilization purposes, aluminum which cannot be excreted or flushed out by individuals with weak levels of GST-enzymes.

Until recently, many vaccinations (e.g. Twinrix® against Hepatitis B) contained **Thiomersal** (in the USA called Thimerosal or Phenyl**mercury**) as an antibacterial preservative, as well as **Aluminium-hydroxide** (Al-OH) as a stabilizer. These could potentially have very serious consequences, especially for infants and children, as their immature nervous and immune system are often not strong enough to cope with these powerful neurotoxic substances.

Mercury poisoning primarily affects the peripheral and central nervous system resulting in polyneuropathic changes as well as psychological and cognitive dysfunctions. Those suffering from chronic LD often show a **Type IV-allergy** to amalgam composites (i.e. Mercury (Hg), Methyl-Hg and Phenyl-Hg and sometimes tin), even long after the removal of their amalgam fillings. Often, evidence of mercury can be found in the stool from residual deposits in the body, even when the patient has not recently consumed any mercury-containing food such as seafood (especially tuna).

In this connection it is worth noting that in the United States a **triple vaccination** is often given to newborns on their first day of life. The growing number of autistic children has become quite a problem in the USA. Epidemiological investigation by the National Survey of Children's Health (NSCH) of the year 2007 discovered that in the United States almost one in every 100 children, between the ages of 2 and 17, suffered from a form of autism (Autism spectrum disorder or ASD). There has been a drastic increase in the number of previously healthy children who develop autistic or ADD/ADHD behavior patterns after they got a Borrelia infection and/or had additional "Thimerosal load" caused by either vaccinations and/or amalgam fillings of their own or of their mother's where transmission during pregnancy occurs. For further Information about the relationship between **Mercury, LD and ASD, and ADD/ADHD** see:

www.liafoundation.org

http://articles.mercola.com/sites/articles/archive/2009/09/10/1-in-100-now-have-autism-spectrum-disorder.aspx

Cheuk, D.K.L., Wong, V.(2006): Attention-Deficit Hyperactivity Disorder and blood mercury level: a case control study in Chinese children, Neuropediatrics 37: 234-240

The build-up of the toxic effects of these substances is directly related to the degree to which the patient can or cannot excrete them, i.e. to some kind of genetic detoxification dysfunction. There are various genetic tests available to test the enzyme activity to assess an individual's potential for detoxification. Usually **detoxification enzymes of phase II** are analyzed for this, such as Glutathione-S-Transferase -enzymes like GST-M1, GST-T1, GST-S1 as well as SOD2, NAT2 and COMT. Specialized laboratories are testing for some of these genetic polymorphisms, which can be the reason for the chronification of Lyme disease (for addresses see the Appendix).

If a patient shows an intolerance reaction when applying a normal dose of medicines, checking the **phase I enzymes of the Cytochrome P 450-system** (i.e. Cyp 2D6, Cyp 2C19 or Cyp 3 A/4 et.al.) is also recommended to avoid the risk of incorrect dosing of medications**,** either underdosing or overdosing according to the metabolizing ability of these enzymes.

Heavy metals, like so many other toxins, (i.e. pesticides, biocides and fungi) lead to an accumulation of **free radicals**. This causes an abnormal metabolic reaction, the so-called nitrit/peroxynitrite-cycle or better known as **NO/ONOO-Cycle** (according to Martin Pall, Ph.D.). This leads to an increased formation of Nitrogen-Oxide (e.g. peroxynitrite, nitrotyrosine, nitrophenylacetic acid, only to name a few). These metabolites themselves cause *nitrosative stress* in the blood and tissue cells as well as in the immune cells and thus they also can weaken the effective functioning of the immune system.

Even more serious is the **toxic load** of a patient after exposure to **dental/medical interventions**. Several alloy materials used by dentists for tooth inlays or crowns (gold, palladium etc.) and their "glue" (Methylmethacrylat or MMA) can contribute to the development of chronic LD. The worst culprits are amalgam fillings, as roughly 50% of the amalgam is normally mercury, which is a strong (neuro-) toxin.

In short, patients may **become chronic LD** cases because they have a **burden of toxins** (heavy metals et al.) in their system, have a **reduction in their detoxifying enzymes'** activity or even have a total absence (so- called deletion) of certain detoxifying enzymes, especially the ones of Phase II. This results in a **buildup of toxins** and, therefore, a further stress to the immune system, thus weakening its ability to fight against Borrelia. However, in my experience, the immune system can improve and become more effective again after a thorough detoxification implemented either by zeolithes, certain supplements (algae, colestyramine) and herbal medicines or by intravenously applied DMPS or orally given DMSA.

For those with not quite a healthy immune system, the main reason, however, for the progression to a chronic course of Lyme disease, is **the lack of treatment**. This happens if the infection is not recognized at all or if **an insufficient treatment with inadequate antibiotics and/or not of the right dosage of antibiotics** given at the time when an Erythema or a lymphocytoma is present or, equally relevant, at the time of a "summer flu" shortly after a tick bite occurs.

A Borrelia infection is easily missed if there is no tick attachment at all known to the patient. Lately, there have also been reports of Borrelia transmission to humans by fleas, mites, spiders, mosquitos and horseflies. In all of these cases it is much harder to identify a particular condition as Lyme disease because the "culprit" may never be seen by the patient. It should also be remembered (see page 3) that Borrelia infections can be transmitted by blood transfusions and sexually as well and also from mother to child during pregnancy. Even these rare forms of transmission should be considered when examining a complex illness, which cannot be diagnosed otherwise.

Antibiotic treatment is considered insufficient if the antibiotics are given for *too short a period* of time or in *too low a dosage*. This is often the case when the treating doctor strictly follows the current applicable guidelines for the treatment of LD of the medical associations, as these recommendations are often insufficient. Guidelines, published e.g. by the "Deutsche Gesellschaft für Neurologie" make neither a statement about the treatment of a recently acquired Borrelia infection without neurological symptoms nor about the treatment of a chronic persistent LD, if there are no associated neurological symptoms/complaints. These guidelines were formulated only for cases of (acute) neuroborreliosis, which are, however, only **one** of the many possible manifestations of Borrelia infections. There are many other complaints and symptoms of an (acute or chronic) LD such as cardiac, urogenital, cognitive, hormonal, gastro-intestinal or musculoskeletal symptoms, to name a few.

The guidelines of the German medical associations are very similar to those of IDSA (Infectious Diseases Society of America). They provide American doctors with treatment recommendations for LD which are, however, not mandatory. For the treatment of an acute Neuro-Borreliosis, the recommendation is: "treat it intravenously with Ceftriaxon, Cefotaxim, Penicillin G or orally with Doxycycline 200 mg (maximum 300 mg) for 14 days to a *maximum* of 21 days". To treat a recently acquired Borrelia infection (so-called stage 1), most medical textbooks and publications suggest Doxycycline 2 x 100 mg (maximum 300 mg) will be enough if given for 14 (maximum 21) days except for children under 9 years of age and pregnant women. For them, Amoxicillin is recommended (for adults in a dosage of 3 x 1000 mg, for children 50 mg/kg body weight).

However, the suggestion of a maximum of 21 days treatment does not take into consideration the very long replication time of Borrelia (ca 24 hours compared to 20 minute replication time for E. coli bacteria). Borrelia divides by transverse fission and then replicates within 12 to 24 hours. Theoretical calculations by microbiologists suggest a necessary time of at least 30 days for elimination of **one** spirochete generation and therefore an antibiotic **treatment of 30 days** and more is recommended. LD patients often experience a deterioration of their condition every four weeks, possibly because of the one month replication cycle of Borrelia.

In-vitro studies at the University of Wädenswil, Switzerland, by Prof. Martin Sievers, with Borrelia bacteria grown in human endothelial cell structures, have shown that a certain level of antibiotic concentration in the blood is needed to prevent Borrelia from replicating. According to the results of these studies, the necessary so-called **bacteriostatic serum concentration** of Doxycycline in the blood is **5µg /ml.** This, in practical application, is a daily dosage of **400 mg up to 600 mg of Doxycycline**, depending on the patient's body weight. This is more than twice or **even three times the dose suggested by the current guidelines** (200 mg Doxycyclin).

To find the correct individual dosage it would be useful to test the serum concentration of the antibiotic during treatment, especially during prolonged antibiotic therapy for chronic persistent LD. However, with the currently, even for severe neurological cases, recommended antibiotic dosage, the necessary 5µg/ml Doxycycline serum concentration can never be achieved. The dosage recommended by the IDSA guidelines will, at most, simply prevent further replication of the Borrelia.

Each antibiotic therapy with **cell wall synthesis inhibitors** like beta lactame antibiotics (i.e. Amoxicillin or Cefuroxim) as well as cephalosporines (i.e. Ceftriaxon or Cefotaxim) leads to an increasing number of bacteria without cell walls (stealth pathogens*),* which form the biological basis for later relapses. Prof. Sievers as well as others (E. Sapi , Ph.D., A. MacDonald, MD, both Univ. of New Haven,

Conn.) have found that, by using Ceftriaxon or Penicillin G, persister forms such as cysts, granula or biofilms, which they call generally *"round bodies"*, will be formed. These are, most probably, **one of the causes of chronic LD and its relapses**.

There is another disadvantage of a low dose antibiotic therapy. Low dose antibiotic therapy as well as cortisone treatment in the early stages of the infection *prevents a strong initial immune system reaction***.** Consequently, the production of antibodies and immunoblot bands are compromised. Therefore, at a later time, infected patients would not be diagnosed by the presence of Borrelia antibodies and, thus, remain untreated.

But, to date, we know only a few of the possible reasons which cause a severe impairment of the immune system leading to the development of a chronic disease.

A well thought-out and effective first antibiotic treatment, after Borrelia infection has taken place, should take into account all of these facts to avoid the unnecessary risk of the patient becoming chronically ill with LD.

VIII. Some Laboratory Tests

Several laboratory parameters are indicators for the following cell "emergency" situations: a deficiency of intracellular *ATP and glutathione*, increased levels of *peroxynitrite, citrulline, phenylacetic acid* and *methylmalon acid* in the urine, and *homocysteine*, which acts as an indicator for a Vitamin B1, B6, B12 and/or a folic-acid deficiency. *Carnitine, selenium, zinc and coenzyme Q10* are often low in values as well. Low levels of these vitamins and minerals should be supplemented to help the chronic LD patients to recover (see **"Vitamin and mineral supplementation"** p. 41 ff).

Because Borrelia spirochetes cause a **chronic-systemic inflammation** in their host, cytokines (inflammatory markers) are often measurably increased. In the case of Borrelia, which is, in the chronic stage of the disease, typically intracellular, these cytokines of the so-called **Th 1-Cytokines** (*TNF alpha, Interferon gamma, Interleukin 1ϐ et al.*) are steadily produced. They normally help the immune system to fight against viruses and cancer cells, but as well against all intracellular pathogens. Vice versa, if they are elevated this may be a sign of infection with one of these pathogens.

Also, as long as any kind of chronic infection is present, the ***N****atural* ***K****iller(NK)-cells* in the blood are decreased in numbers as they are needed in the tissue to fight the chronic systemic infection. The NK-cells are not specific for LD, but are lowered in any chronic infection with systemic inflammation and in the case of cancer. Nevertheless, the overall number of the NK cells and especially their subgroup, the **CD 57+-NK cells**, can be an additional indicator of a long existing systemic intracellular infection.

If the number of **CD-57+ NK cells is lower than 50/µl** in the blood (the norm being 60 to 360/µl), it could be an indicator of a chronic form of LD (if a Borrelia infection has been previously diagnosed), according to Dr. R. Stricker and J.J. Burrascano Jr. MD (both members of ILADS, the **I**nternational **L**yme and **A**ssociated **D**iseases **S**ociety). If the value is even lower (< 20/µl), it indicates a very severe case of chronic Borrelia infection. Therefore, it is useful at the beginning of laboratory testing to determine the CD 57+-NK cell value, to assess the immune system's ability to react to pathogens. If NK-cell values increase during or after therapy, the treatment can be considered as successful.

A few years ago it was reported that certain manifestations of the **Human Leucocytes Antigen (HLA) system,** the system that represents the immunologic markers of all nuclei-containing body cells, could lead to a resistance against the usual antibiotic therapy or to a lack of the production of specific antibodies (see the Appendix for literature). With the presence of the HLA-DR B1 Subtype-Allele *01:01,*01:02,*01:03, *01:04, *01:05 the *production of antibodies* against Borrelia spirochetes could be *reduced or even fully prevented* and with the presence of DR 1 (HLA-DR B1 *01:01), DR 2 (HLA-DRB1 *15:01), DR 4 (HLA-DRB1 *04:01 ,*04:02 ,*04:03,*04:04, *04:05, *04:07) a *resistance to antibiotics* could result. On the other hand, still some other HLA-subtypes (HLA-DR B1 *0701, *0703, *0704) can cause an *especially strong immune reaction* towards Borrelia surface protein antigens. However, newer studies have moderated these assertions and have called for more scientific research. Nevertheless, these genetic parameters can still give an indication of possible reasons for therapy resistance or for a total lack of antibodies, as well as for an extreme build-up of antibodies against Borrelia spirochetes.

Summary of the present insights into how Lyme disease can become chronic

The chronic form of Lyme Disease (LD) is discussed in several contexts in this article. I would, nevertheless, like to briefly summarize here what is known to date about this **persistent active form of the Borrelia infection,** even if it is still somewhat controversial to the established medical opinion and guidelines.

Chronic LD is a chronic-systemic inflammation with continuous slightly elevated **inflammation parameters** of the **Th 1-type** e.g. TNF alpha, Interferon gamma or IL-1ß. These inflammatory reactions are often exacerbated by other pro-inflammatory factors such as a build-up of free radicals due to heavy metals and/or other environmental toxins.

Free radicals, and consequently the increase of nitric oxide, start to change the metabolism of the body resulting in the so-called **NO/ONOO-Cycle** (nitrite/peroxynitrite cycle according to M. Pall, Ph.D.). Interestingly enough, nitric oxide seems to cause the Borrelia spirochetes to become more mobile, as demonstrated in biofilm matrix observations.

This abnormal metabolism can lead to the following changes at the cellular level: **reduction of intracellular Glutathione** and **Adenosine Triphosphate (ATP); deficiency of Vitamin B 12** as seen by elevated **Homocysteine** in serum and by **elevated Methylmalonic acid** in serum as well as in the urine. Infection with parasites (especially with Giardia/Lamblia), which are easily identified with Dark Field Microscopy, results in an **increase of immunglobulin E (IgE)** and **elevated eosinophilic cells** evidenced in a differential blood count. The increase of the eosinophilic cells reflects the intensity of the allergic process. Elevated IgE is also seen if the immune system fights against heavy metals and/or other toxins. **A low level of the enzyme DAO (Diaminooxidase)** frequently leads to histamine intolerance and allergic, often urticarial skin reactions. Minocycline as well as N-Acetylcysteine (NAC®, ACC®) lowers the DAO activity, so that allergic reactions of this kind are more likely if either one or both of these drugs are taken. If such allergic reactions do occur or if the levels of DAO are low, DAOsin® or other DAO-formulas can be prescribed to increase and stabilize the levels of the DAO enzyme.

Chronic inflammation - due to various reasons including bacteria, heavy metals and other toxins - can lead over time to a progressive **weakness of the functioning of the adrenal glands**. This causes **hormonal changes** (e.g. for cortisol, adrenaline, aldosterone and DHEA-S) and also lowers the levels of

the sex hormones, estrogen, progesterone and testosterone. Therefore, symptoms arise such as severe fatigue and exhaustion, muscle aches, cognitive impairment, sleep disorder and emotional disturbances, just to mention a few. This should always be kept in mind when treating any kind of chronic disease and/or inflammation. Knowing this should avoid diagnosing patients with such symptoms as solely psychological and therefore miss or fail to treat the underlying reasons for their condition.

IX. Therapy Recommendations

As already mentioned, an effective antibiotic therapy is needed as soon as possible after an infection with the genospecies Borrelia (or other pathogens). We now know much more about the life cycles and properties of Borrelia bacteria. Because of their flagellae, the spirochetes are actively moving through their host's body within a matter of only hours and then already begin to replicate. Spirochetes quickly make their way from the blood stream into the cells, for example into erythrocytes, macrophages, endothelial and glia cells as well as into the fibroblasts a bit later. In animal tests, it has been proven that in artificially-infected animal hosts (sheep) the Borrelia spirochetes had spread to the brain, to the liver and even to the lining of the bowels within 21 days.

Once they have penetrated the cell walls, Borrelia spirochetes change into their persister forms (i.e. granula, blebs, cysts or biofilms), and therefore all antibiotics which are extracellularly effective only, e.g. penicillin, amoxicillin, cefuroxime or ceftriaxone, fail to reach the Borrelia bacteria. All of these penicillin derivatives impede the new synthesis of bacterial cell walls after the division of the spirochetes and thus will stop only the normal extracellular replication and re-growth. Only antibiotics which are **able to attack pathogens intracellularily** as well, such as the **macrolides** (e.g. clarithromycin, azithromycin) or the **tetracyclines** (e.g. minocycline or doxycycline) can destroy the intracellular germs. Therefore only these groups of antibiotics should be chosen for therapy of Lyme disease, especially in its chronic form. Antiprotozoal medication such as **Metronidazole** (e.g. Clont®, Arilin®, Flagyl®) or **Tinidazole** (e.g. Trimonase®, Fasigyn®, Tindamax®) is also effective intracellularily and thus can support the antibiotic therapy with macrolides or tetracyclines , especially since an hitherto undetected parasite (especially e.g. giardia/ lamblia or trichomonas) can prolong and intensify chronic Borrelia infection. Studies by Eva Sapi, Ph.D. have shown that round bodies or persister forms of Borrelia also could be treated with Metronidazole and Tinidazole. The newest in-vitro-research of Eva Sapi, Ph.D. (11/15) shows that even a whole leave-Stevia-preparation in alcoholic solution (product by Nutramedix) was able to totally destroy round bodies **and** biofilms of Borrelia, making it the first product to address all persisting forms as well as the spirochetal form of Borrelia.

Hydroxychloroquine sulfate (Quensyl®, Plaquenil®) is an anti-malaria and antirheumatic drug, but it also enhances the intracellular effect of the above mentioned intracellular antibiotics by increasing the intracellular pH to alkaline values. The plant **Artemisia annua** or **Chininsulfate** as a homeopathic preparation (Chininsulfat D4) can also be used as an herbal alternative for Hydroxychloroquine to enhance the effects of the antibiotics administered. On the other hand it has to be kept in mind that study results of Eva Sapi, Ph.D. have shown that by giving Hydroxychloroquine or even Doxycyclin as a treatment, the spirochetes tend to become round bodies even quicker.

The **biofilm-matrix phenomenon** was, only recently, the subject of more intense research (Eva Sapi, Ph.D., Alan B. MacDonald, University of New Haven, Connecticut 7/2008) that shows how effectively the polymeric matrix of the biofilms shields the spirochete Borrelia from antibiotics (up to 1000-fold)

as well as from the immune system. This may be a reason for the often observed ineffectiveness of the currently recommended therapies with their repeated relapses (i.e. reappearances of symptoms) even after previous antibiotic treatment. Almost tragic in this regard is the fact that the IDSA-recommended and therefore often-prescribed antibiotic treatment based exclusively on penicillin and its derivatives, has been proven to be the cause of the later difficult-to-treat persisting forms (granula, blebs, cysts). (Research by Prof. Dr. Sievers, University of Wädenswil, Switzerland).

Therapeutic recommendations for the chronic form of Lyme Disease/Borreliosis

The following antibiotic treatment recommendations and other complementary therapies are based on my experience after years of treating chronic LD patients, on the information and guidelines of the German Borreliosis Society (see www.borreliose-gesellschaft.de) and on the different therapies published by German and, more often, American colleagues. These **therapeutical recommendations are neither complete nor final**, as new findings and insights into the tricky world of LD constantly require changes in the therapeutic proposals and bring forward new ideas. All the following therapy schemata should always be performed by a doctor who assumes responsibility for the treatment. All the following antibiotics should be increased gradually to prevent a so-called **Herxheimer reaction**. The following antibiotic treatment recommendations are in accordance with what we know so far about the biological facts of the Borrelia bacteria and their behavior in the host`s body.

Herxheimer reaction

A Herxheimer reaction is a reaction of the immune system to the destructive effect of antibiotics to Borrelia germs. The lipopolysaccharides of the cell wall of Borrelia bacteria will be released after the attack of the antibiotics. Because these particles are antigenic (i.e. as such they are recognized by the immune system as strange to the host) a “storm of cytokines” will be created by the immune system against them. This happens in general between 48 to 72 hours after the first take-in of antibiotics, but can last for days and in rare cases even weeks. It first was observed when Treponema pallidum, the reason for syphilis, had been treated, but it always happens when spirochetes get treated with antibiotics. The stronger the reaction turns out to be, the better the antibiotic effect normally is and the better the prognosis for the treatment outcome. Mostly the TH 1-cytokines TNF alpha and IL -1 are released and the patient feels as though they had a strong flu with pain all over, aching muscles and joints, severe fatigue and fever as well as sweating and swelling of lymph nodes. Furthermore, all preexisting symptoms of the Borreliosis worsen under treatment. The pains that a patient might have during a Herxheimer reaction are very individual and “detect” all Borrelia-affected areas of the patient’s body. With the help of some anti-inflammatory drugs (e.g. Ibuprofen, Diclofenac or Cox 2-inhibitors) and/or herbs (e.g. Curcumin, African incense like Boswellia, stinging nettle extract, Quercetin et al.) as well as detoxifying preparations (such as algae, zeolithes, colestyramine) the high cytokines level can be lowered and the Herxheimer symptoms wear off. Additionally, physical procedures such as hot baths with basic (alkaline) salts (e.g. Basica) will help. It is very much advised, too, to reduce the amount of antibiotics temporarily until most symptoms have abated.

Treatment for the chronic form of Lyme disease or Borreliosis

Initially, treatment with every chosen antibiotic should last for at least **30 days.** Afterwards, the effectiveness of the antibiotics should be assessed with the Lymphocytes transformation test (LTT) (see page 28). If the result is still positive, the antibiotic treatment should be continued. It should not be stopped until no more clinical symptoms of LD are present and the LTT has become negative.

Tetracyclines

a.) **Minocycline starting with 50 mg in the morning**, staying at this dosage for three days and then increasing the dosage every three days by 50 mg until **2 x 100 mg** is reached. Combine with **Hydroxychloroquine 200 mg** daily (e. g. Quensyl®, Plaquenil®) in order to alkalize the infected cells (or every second day, due to the extreme long half-life time of 30-60 days). Of all the possible suitable antibiotics, **Minocycline is the most effective** in crossing the blood-brain-barrier: 40% can enter the CFS. Thus, in my experience, Minocycline should always be preferred to Doxycycline with regard to neurological, psychiatric, cognitive and vegetative symptoms in the chronic persistent stage of LD.

As an alternative to Hydroxychloroquine, **Tinidazol 500mg-1000 mg** is increasingly more often recommended recently. It should be taken once a day orally with water (more details are provided below).

b.) **Doxycycline 2 x 200 mg** (up to 2 x 300 mg). It is less effective in crossing the blood-brain-barrier (14%) in comparison to Minocycline (40%). It can also be administered intravenously when side effects to the skin/stomach caused by Doxycyline have arisen or just to avoid them. Combinations of intravenous and oral treatment are also possible. For example, 100 mg Doxycycline iv (dissolved in 100 ml of 0.9% saline (NaCl)-solution) in the morning, followed by either 200 mg Doxycycline (or alternatively 100 mg Minocycline) orally in the evening. Obese patients need a higher dosage according to their body weight and patients below 70 kg body weight should get a reduced dosage of 300 mg. For children eight years and older 4 mg/kg body weight is recommended up to a maximum of 200 mg.

Macrolides

c.) **Clarithromycin** (e.g. Klacid®) **2 x 250 mg,** after four days **2 x 500 mg,** combined with e.g. **Tinidazol** or **Hydroxychloroquin 200 mg** daily (or every second day), especially effective in cases with musculoskeletal complaints.

d.) **Azithromycin** 500 mg (e.g. Zithromax®) or 600 mg (e.g. Ultreon®), especially as a second round of treatment after an initial treatment with Tetracyclines in order to further reduce Borrelia numbers and activity. Patients suffering from impaired intestinal flora or from stomach sensitivity will benefit from Azithromycin because it is taken only once a day. The same once-a- day dosage can also work well for those who must go to work. After a four day intake, a pause of three days is necessary, as Azithromycin accumulates **in** the cells. In severe and difficult cases, Azithromycin may also be given intravenously, in order to reach higher blood and tissue levels. To avoid irritation of the veins it should be administered very slowly (over two to three hours).

Depot Penicillin

e.) **Benzathine-Benzylpenicillin** 1.2 Mega (e.g. Tardocillin®) intramuscularly two to four times a month, especially in cases of penicillin-sensitive co-infections such as Strepto-

coccus, Staphylococcus and Pneumococcus. Sometimes it is better to start with it because these extracellular germs are more easily treated than the intracellular Borrelia.

Antiparasitic Drugs

f.) **Metronidazole** (e.g. Clont®, Arilin®, Flagyl®) 400 mg – 800 mg orally or, better yet, 1.2 g intravenously daily for 10 days as additional treatment, especially if a parasitic co-infection such as Gardia/Lamblia is present (often detectable through Dark Field Microscopy or a positive Giardia/Lamblia-LTT). Additionally, Metronidazole is suitable to treat intracellular persister forms (or round bodies) of Borrelia as well as co-infections with other intracellular bacteria such as Chlamydophila pneumonia or Chlamydia trachomatis, Babesia, Bartonella, Coxiella, Rickettsia, Mycoplasma or Anaplasma. A four week pause has to be observed due to possible side effects (e.g. chromosomal damage) before another 10 day treatment can be repeated. Some even state that Metronidazole should only be given once in a lifetime!

g.) **Tinidazole** (e.g. Fasigyn®, Trimonase®, Tricolam®, Tindamax®, Simplotan®) 500 mg 1-2 tablets in the morning is a very effective co-treatment together with Tetracycline and Macrolides. Very recent studies (Eva Sapi , Ph-D. and Alan B. MacDonald of the University New Haven, Conn., 2011) have shown its high efficacy against intracellular persister forms and biofilms as well as against the spirochetal form of Borrelia. In Germany the prescription is off-label and it will therefore not be paid for by the Health insurers because the drug is not on the German market anymore. But in other European countries like Spain, France, Rumania, Italy it is readily available.

Antiviral Drugs

h.) **Amantadine** (e.g. Symmetrel®, Symadine®) 100 mg (up to 200 mg) daily can be quite effective in viral co-infections (e. g. Bornavirus, Parvovirus B 19, Herpes zoster or HSV 1/2) as well as in cases of severe fatigue due to its mild stimulating effects. (Because of that its intake is not recommended past noon.)

Modafinil

i.) **Modafinil** (e.g. Vigil®, Alertec®, Provigil®) can also be effective in cases of chronic fatigue and exhaustion. It is officially registered for treatment of narcolepsy, chronic fatigue in Multiple Sclerosis, shift work sleep disorders and obstructive sleep apnea. The drug may also be effective for other conditions with severe fatigue e.g. chronic Borreliosis or CFS as well as other diseases with chronic fatigue due to mitochondrial dysfunctions. This drug should not be taken permanently but only as a “bridging help” until the fatigue abates.

After the initial antibiotic therapy, **the Borrelia Lymphocytes transformation test** (LTT) should be done to determine therapy effectiveness. It will show if there is still Borrelia activity going on after the antibiotic treatment. But keep in mind that it should not be done until four to six weeks after the end of the antibiotic treatment (this is the necessary time the immune system needs to form new T-lymphocytes). If the LTT is then still positive, i.e. the Borrelia germs are still present and have caused the T-lymphocytes again to react against them, a decision should be made about the further

treatment. Further treatment may be either a continuation with the same antibiotic or starting with another type of antibiotic. This choice also has to be made based on clinical symptoms and if any serious side effects of the first antibiotics are experienced. However, if the Borrelia-LTT is already negative after the first course of antibiotic treatment one can stop to take any further antibiotics and observe how the clinical condition develops.

Alternatively or additional**, Dark Field Microscopy** could also be done after the first course of antibiotics. This test can detect if viable/mobile Borrelia spirochetes are still seen in the blood (more details see page 30).

There is no reasonable argument for (re)testing for Borrelia antibodies or the immunoblot after the antibiotic treatment**,** not only because of the costs, but also because it is unnecessary: the question in chronic LD is not whether an infection with Borrelia has occurred before, to which the build–up of antibodies has been the answer of the immune system, but only whether there is still activity of the Borrelia spirochetes after the antibiotic treatment, detectable by the LTT. Additionally, the amount of antibodies will not change much by an antibiotic treatment and, therefore, this cannot be taken as an indicator for treatment success or failure.

Supplemental therapies

to correct vitamin and mineral deficiency and/or other pathological laboratory findings:

a.) **Reduced Glutathione** 2 cps. 100 mg daily or S-Acetyl-Glutathione powder orally. Tationil® or Ridutox® amps. 600 mg intravenously two to three times per week (depending on the level of the Glutathione deficiency).

b.) **cAMP D 30**, a homeopathic preparation in vials which can be taken subcutaneously, intramuscularly or even orally diluted in water. It is said to be a precursor of ATP and helps to restore energy, especially if ATP is low.

c.) **ACC® or NAC® (i.e. N-Acetyl-Cystein)** 600 mg one to four times daily as a source of Cystein, in combination with Glutamine (e.g. Glutamin Verla®), both effective as Glutathione precursors.

Vitamin and mineral supplementation (mostly available over the counter (**OTC**))

- **Multivitamins :** They should have a high content of Vitamin B, especially Vitamin B 12, B 1, B 2, B 3, B 5 (Niacin), B 6 and B 7 (Biotin = Vitamin H); they should also have Folic acid, Vitamin A, Vitamin C and Vitamin E. Additionally, minerals like Magnesium, Calcium, Selenium, Chromium and Zinc should be supplemented, if there is a proven deficiency. MgCl oil is more effective as Mg orally and can be administered locally on the skin if there are cramps or fasciculations of the muscles.
- **Vitamin B 12**: If Methylmalonic levels in the urine or serum or Homocystein values in the blood are elevated, then this is evidence of a more severe Vitamin B 12 and/or folic acid deficiency. 10 drops (= 1 mg) of Methylcobalamine daily should to be taken orally under the tongue (i.e. sublingually) to avoid the decomposition of Vitamin B 12 by the HCl-acid in the stomach. Alternatively, an intramuscular preparation of Vitamin B 12 (mostly Cyano- or Hydroxycobalamin), often in combination with Vitamin B 6, may be given once or twice a month.

- **Vitamin C** (Ascorbic acid): as powder or tablets, orally, 1-2 g/day or intravenously given in a much higher concentration (e.g. Pascorbin® 7.5 g), once a week. However, Vitamin C should not be given as long as there is a heavy metal load in the body. High dosages of Vitamin C orally can cause diarrhea, too.
- **Vitamin D:** If low levels of the Vitamin D reservoir (25-OH) are found in the blood, Vitamin D preparations, dissolved in an oil base (capsules or liquid), should be given regularly in an amount of ca. **20 000 IU/week** (e.g. Dekristol® 20 000 IE), or twice a week depending on the Vitamin D levels in the blood.
- **Zinc** (mostly 30 mg/day) and **Selenium** (at the most 200 µg/day, if its plasma concentration is lower than 125µg/l) should be supplemented.
- **Coenzym Q 10** (e.g. Ubiquinone or Quinomit fluid®) 200 mg or more (maximum 12 mg/kg body weight) is used as a very effective antioxidant.
- **Acetyl-L-Carnitine** 500 mg twice daily helps to treat muscle pains by correcting the muscle cell metabolism.
- **D-Ribose,** a special kind of sugar**,** ca. 4 x 5 g daily (i.e. 5 tsp. daily) as an additional source of energy, especially for muscles.
- **Silymarin** (Milk Thistle) 300 mg a day to improve the liver function which is often impaired by a Borrelia infection.
- **Melatonin** (1 mg up to 5 mg) for problems falling asleep, with or without Vitamin B 6 (which helps against nightmares). As a natural body hormone it is mostly well tolerated without side effects.
- **L-Tryptophan** 500 mg – 1000 mg is also a natural body hormone and should be given in the evening because it is sedative. It helps to build-up Serotonin. If an antidepressant is already given to the patient it has to be handled with care, because a so-called Serotonin- syndrome can result if too much of Serotonin supplementation is given.

Anti-inflammatory drugs

- **N**on-**S**teroidal **A**nti**r**heumatic drugs (NSAR) such as Ibuprofen (e.g. Advil®), Diclofenac (e.g. Voltaren®), Naproxen (e.g. Anaprox®), Acetaminophen (e.g. Tylenol®), Cox 2-inhibitors (e.g. Arcoxia®, Bextra®), (buffered) Aspirin et al. are all effective in fighting pain. Especially when dealing with a Herxheimer reaction (see page 38), these drugs should be taken for a short period of time to reduce the symptoms (in Germany, by prescription only, but depending on the dosage).
- **Anti-inflammatory herbal preparations** can be taken additionally for the pain management. They can even be used on a regular basis against pain to prevent the known side effects of the NSAR (see above). Effective are such plants like stinging nettle (e.g. Hox alpha®, Natulind®), Curcumin in combination, if possible, with Omega-3-fatty acids and incense (e.g. TNF direkt®) or common teasel (e.g. Kardenminze®) or incense of the African type (e.g. Boscari®) or the Indian type (H 15 Gufic®), Gamma-Tocopherol (Vitamin E), occurring naturally in corn or soja oil, Cat's claw (Samento TOA-free®), Cumanda® and Banderol® (all three products of Nutramedix), or an Omega-3-fatty acid preparation (e.g. Zodin®).

Detoxification drugs against heavy metals, solvents and other toxins

- **Zeolithes** (i.e. very small granules of ground lava stones) like Toxaprevent®, Ferulith® (a combination of zeolithes with ferulic acid, a part of curcumin), or Montillo® to absorb the non-fat-bound toxins in the intestines. They should be taken two hours before or after meals.
- **Algae** can also be very useful in a constant detoxification process of toxin deposits. **Chlorella pyrenoidosa algae** (e.g. Beta Reu Rella®) is quite effective in combination with zeolithes.
- **Colestyramine** (Questran®, Colesthexal®) 2 x 4 g (up to maximum 2 x 8 g) either two hours before or after a meal. Constipation is a very common side effect, so the regularity of bowel movements has to be observed carefully by the patients (in Germany, by prescription only).
- **Cilantro** (e.g. Cilantris®) Coriander is quite effective in detoxifying cerebral mercury deposits, but this should only be taken after some time of enteric detoxification with zeolithes or algae.
- **Alpha lipoic acid (ALA) 600 mg** per day orally or 300 ml intravenously helps to reduce the Nitrostress (NO/ONOO-Cycle), detoxifies of heavy metals and soothes some of the symptoms of polyneuropathiy (in Germany, by prescription only)

To remove heavy metal deposits (e.g. mercury, lead, aluminum, cadmium etc.) from the fatty tissues of the body, **chelation substances** are needed. These help make these deposits water soluble, especially if in the genetic build-up some of the detoxification enzymes are missing (see page 33). The most common drugs for detoxification are:

DMPS (e.g. Dimaval®, Unithiol®) can only be given intravenously (3-10 mg/kg body weight)

DMSA (e.g. Chemet®) can be taken orally in capsules once a week according to body weight (10 mg/kg body weight) with lots of liquids.

But there are also several other therapy protocols available. Zinc supplement should not be taken on the day of a DMSA-intake, but on the days thereafter. Alternatively **EDTA** (20-50mg/kg body weight) or **Na-Thiosulfate** (15-45 mg/kg body weight) can be given according to the type of heavy metal. As long as systemic inflammation caused by heavy metals is ongoing, Vitamin C should not be given because of its pro-oxidative properties. All the chelation substances are available in Germany **by prescription only**.

Hyperacidity

To reduce the hyperacidity of the body cells, mostly caused by the activity of the genospecies Borrelia, different alkalizers can be used (e.g. Bicanorm®, Alka Seltzer®, Sodium Bicorbonate®, Soda Mint®, Basica®). Additionally, an alkalizing diet should be followed. Furthermore, warm baths (about 100 °F) alkalized with “baking soda” (Na HCO3) two to three times weekly for 30-45 minutes will be helpful. Use pH-measuring strips (litmus paper) to ascertain sufficient alkalization of the bathing water, i.e. above pH 8.

Nitrostress (NO/ONOO-Cycle) can be treated with Alpha lipoic acid (ALA) 600 mg /day orally or 300 ml intravenously (in Germany, by prescription only).

Therapeutic Apheresis

In cases of very serious LD manifestations with neurological disorders and/or consequent autoimmune reactions and/or coexistent, severe heavy metal load, mostly due to genetic inability to de-

toxify, a so-called **Therapeutic Apheresis** can be done. This means the blood will be "washed" through special (Japanese) filters for two to three hours to extract certain pathogens like heavy metals or autoimmune complexes. The sediment thus obtained is called **eluat.** Afterwards, in specialized laboratories, the eluat can be examined to determine problematic components present in it that may have contributed to the chronification of LD. By means of therapeutic apheresis, the immune system is relieved of much unnecessary load and it can thereafter work a lot more effectively for the chronically ill patient (for more information see the **Appendix**).

APPENDIX

Laboratory tests

Listed below there are some tests mentioned in this article and the German labs that can perform them. Please inquire with each lab on questions of shipping requirements from abroad. For specialized test every lab provides the necessary test kits and mailing materials (vials, envelopes etc.) when requested. Note that all blood and stool samples have to be sent in unbreakable, shockproof plastic tubes enclosed in specially lined ("bubble") envelopes. Also, pay attention to the necessary shipping time.

Tests, listed in order of time required for correct test results

1. Tests which are non-time critical and can be sent from outside Germany to the labs (Lab addresses are listed below)

- **Nitrosative Stress Test** (Nitrophenyl acid, Methylmalonic acid, Citrullin) of the first urine of the day as well as the test for hyperacidity of the body by measuring several urine samples during the day (so-called Sander test) are available from **Labor Ganzimmun, Mainz and Sension, Augsburg.**

- Borreliosis specific **HLA-DR-subtypes** tests are available from **IMD Berlin** and **Labor Langenhagen**.

- **Heavy metals**, single or so-called **M**ulti **E**lement **A**nalysis (MEA) of the stool or the blood or of samples of dental material, solvents in the urine, analysis of heavy metals before and after the so-called DMPS test in the urine, saliva und stool, are available **from Medizinisches Labor Bremen** and from **IMD Berlin**.

- **Polymorphisms of the detoxification enzymes phase II** (i.e. GST-M1, GST-T1,GST-P1, SOD 2,NAT 2, COMT et al.) as well as the **Cytochrom P 450 enzymes phase I** (i.e. Cyp 2D6, 2C19, 2A4 et al.) from EDTA-blood samples are available from **IMD Berlin** as well as from **Labor Langenhagen**.

2. Tests which need to be at the labs within two days after the blood is drawn

- **Antibiotic blood levels** (Doxycyclin, Minocyclin) are available from **Labor Volkmann, Labor Ettlingen-Karlsruhe, IMD Berlin**. For this test, it is necessary to specify the exact time when the blood was drawn, as well as the actual antibiotic dosage and when the antibiotic therapy was started.

- **CK and LDH with their isoenzymes, all inflammatory values like TNF-alpha, IFN gamma, IP-10, IL 1ß, IL-10, CRP, liver enzymes, intracellular Glutathion and ATP**

(Heparin blood) **and most values of the routine blood work** are available from **IMD Berlin, Labor Volkmann , Labor Ettlingen, Arminlabs et al**.

- **Complete Blood Count (CBC), IgE, Eosinophilic Cationic Protein (**ECP), **Diaminoxydase (**DAO), **immunoblot and antibodies** of Borrelia, Yersinia, Chlamydia trachomatis, Chlamydophila pneumoniae, Giardia/Lamblia, Ehrlichia/Anaplasma are available from **IMD Berlin, Labor Volkmann**, **Borreliose Centrum Augsburg, Labor Ettlingen-Karlslruhe, Arminlabs et al**.

3. Time critical (within 24 hrs) and complicated, costly tests
(They should be sent preferably by courier and arrive at the laboratory no later than on Friday)

- **All types of LTT** tests (needed are 2 x Serum-, 1 x Heparin-vials) such as for Borrelia, heavy metals, dental material, environmental toxins, co-infections like Yersinia, Chlamydophila pneumoniae, Chlamydia trachomatis, Giardia/ Lamblia, Herpes simplex virus 1/2, Varicella zoster virus, Epstein Barr virus; all are available from **IMD Berlin**, **Laborzentrum Bremen** and **Labor Ettlingen-Karlsruhe**.
- **EliSpot** of Borrelia und Ehrlichia/Anaplasma (needed are 2 CPDA tubes) are available from **Labor Ettlingen**, **Arminlabs, Borreliose Centrum Augsburg** and **Labor Ettlingen-Karlsruhe**.

Addresses of the above mentioned laboratories *(in alphabetical order)*

Arminlabs GmbH
Doctor in charge: Dr. Arnim Schwarzbach
Zirbelstr. 58
86154 Augsburg
Tel. 0821/78093150 | Fax: 0821/78093152
E-Mail: info@arminlabs.com | www.arminlabs.com/de

Dedimed GmbH
Doctor in charge: Dr. Waldherr
Heinrich-Hertz-Str. 3 a, 14532 Kleinmachnow
Tel. 033203-879420

Institut für medizinische Diagnostik (IMD) Berlin –Potsdam MVZ GbR
Doctor in charge: Dr. Volker von Baehr
Nicolaistr. 22, 12247 Berlin
Tel. 030-77001-322 (General informations), -220 (Ordering of the LTT-testkit)
E-Mail: info@imd-berlin.de | www.imd-berlin.de

Labor im Borreliose Centrum Augsburg
Morellstr. 33, 86159 Augsburg
Tel. 0821-455471-0

Labor Ganzimmun
Doctor in charge: Dr. Kirkamm
Hans-Böckler-Str. 109, 55128 Mainz
Tel. 06131-72050 | www.ganzimmun.de

Labor Langenhagen
Ostpassage 7, 30853 Langenhagen
Tel. 0511/2030448

Medizinisches Labor Bremen
Haferwende 12, 28357 Bremen
Tel. 0421-2072-0

MVZ Laborzentrum Ettlingen GmbH
Doctor in charge: Dr. Rüdiger Kock
Otto-Hahn-Str. 18, 76275 Ettlingen
Tel. 07243-516 01
E-Mail: info@laborzentrum.org | www.laborzentrum.org

Some laboratories for PCR-testing of ticks

Labor Bremen
Haferwende 12, 28357 Bremen
Tel. 0421-2072-0
E-Mail: info@mlhb.de | www.mlhb.de

Labor Dr. Brunner
Mainaustr. 48 a+b, 78464 Konstanz
Tel. 07531/8173-0
e-Mail: kontakt@labor-brunner.de | www.labor-brunner.de

MZV Labor Enders and colleagues
Rosenbergstr. 85, 70193 Stuttgart
Tel. 0711-63570 E-Mail: info@labor-enders.de | www.labor-enders.de

MVZ Labor PD Dr. Volkmann and colleagues
Kriegsstr. 99, 76133 Karlsruhe
Tel. 0721-85000-152
E-Mail: labor@laborvolkmann.de
www.laborvolkmann.de

Synlab Laboratory for ticks
Zur Kesselschmiede 4, 92637 Weiden, Tel. 018050/93253

Laboratory for pathology and zytology
Postfach 2240, 35578 Wetzlar
Tel. 06441/765510
E-Mail: info@patho-wetzlar.de

Zecklab
Doctor in charge: Dr. Gabriele Liebisch
Up'n Kampe 3, 30938 Burgwedel
Tel. 05139-892447
E-Mail: Liebisch@zecklab.de | www.zecklab.de

Dark Field Microscopy

Dr. Ulrike Angermaier
Traubengasse 19, 91154 Roth
Tel. 09171-851-52-17
(1 serum vial of whole blood or a smear sample enclosed in a shockproof plastic tube should be sent in a "bubble" envelope by mail)

Focus Floating Microscopy (FFM)

FFM can be done with all kinds of tissue, but the samples have to be put into formaldehyde or paraffin. The material should then be sent in a specially lined ("bubble") envelope to Prof. Dr. Bernhard Zilger, Department of Dermatology of the University of Innsbruck, Anichstr. 35, A-6020 Innsbruck (Tel. 0043-512-504-81115 for inquiries)
or
to D.H. Kutzner, Dermatopathology, Siemensstr.6/1,D-88048,Friedrichshafen,Tel. 07541-60440-0 (www.dermpath.de)

Clinic for Dermatology and Dermatological Allergy, Erfurter Straße 35, D- 07740 Jena, Tel. 03641/937375 (www.derma.uniklinikum-jena.de)

Therapeutic Apheresis

INUS Medical Center AG, doctor in charge: Dr. Straube, Gesundheitspark am Regenbogen, Further Str. 19, D-93413 Cham, Tel. 09971/200 3230 (www.gesundheitspark-cham.de)

***Photos and collages of ticks in natural surrounding*:** foto.polack@email.de

Some specialized pharmacies: (alphabetical)

Heck Bio-Pharma, Karlstr. 5, 73650 Winterbach
Tel. 07181/9902960
(Zeolithes-products et al.)

Hohenburg-Versand-Apotheke, Kaiserstr. 15, D-66424 Homburg, Tel. 06841/2500
(Nutramedix products)

Husaren-Apotheke, Kirchenstr. 49, D- 66793 Reisbach, Tel. 06838 86 1420
(S-Acetyl-Glutathione)

Klösterl Apotheke, Waltherstr. 32a, D-80337 München, Tel. 089/54343211
(Methlycobalamin et al.)

Peer Stadt-Apotheke Brixen, Adlerbrückengasse 4, I-39042 Brixen
Tel. +39 04728-6173, Fax -2777 e-mail: info@peer.it
(Glutathione-Amps., Tinidazol et al.)

Viathen: Oll-Daniel-Weg 3, 18069 Rostock
Tel. 0381/808-340-033
(TNF direct, Glutacell et al.)

Further information on (chronic) Lyme disease

Organizations and websites

Borreliose und FSME-Bund Deutschland (www.bfbd.de)

Organisation of German doctors: Deutsche Borreliose-Gesellschaft (www.borreliose-gesellschaft.de)

Borreliosis information website (www.borreliose-nachrichten.de)

Very informative website about LD and the politics around www.verschwiegene-epidemie.de

International Lyme and Associated Diseases Society (www.ILADS.org)

Time for Lyme, Inc. (timeforlyme@aol.com)

Turn the Corner Foundation (info@turnthecorner.org)

Canadian Lyme Disease Foundation (www.canlyme.com)

Lyme action group (www.lymeactiongroup.blogspot.ca)

Some English websites (www.lymenet.org or www.lymedisease.org or www.lymeinfo.net)

www.dr-hopf-seidel.de Information, photos, lectures and much more as well as list of LD doctors in central Europe

Some more informative websites

www.associationlymesansfrontieres.com French Lyme Disease support group
www.borelioza.org – Polish LD support group
www.borrelia-tbe.se – Swedish LD support group
www.borreliose-bund.de – Borreliose und FSME Organization Germany
www.borreliose-gesellschaft.de – German doctor organization for LD
www.borreliose.de – LD support group of Kassel
www.borreliosearzt.de – Information about LD by Dr. H.-P.Gabel, Wolfenbüttel
www.bzk-online.de – Website of the organization for tick-borne diseases
www.daninfekt.dk – Danish LD-support group
www.dieterhassler.de –Information by Dr. Hassler, infectiologist about LD and TBE
www.francelyme.fr – French Website
www.ilads.org – Int. Lyme and Associated Diseases Society, USA
www.laborlexikon.de – Information about laboratory questions
www.lymediseaseaction.org.uk – English LD support group
www.lymenet.de – Information about LD conferences and news of UK
www.lymevereniging.nl – Dutch LD support group
www.med4you.at Informations about laboratory issues, last update 8/12
www.norvect.no - Informations about LD conferences in Oslo since 2014
www.rki.de – German governmental institute of health issues: Robert-Koch-Institut, Nordufer 20, 13353 Berlin,
www.zeckenliga.ch – Swiss Website about LD

Literature, Books

Bean, Constance A. and Fein, L.A.: Beating Lyme, understanding and treating this complex and often misdiagnosed disease, Book Surge Publ. 2008, ISBN-13:978-1-4392-2698-8

Burrascano J.J., Jr, MD: Diagnostic hints and treatment guidelines for Lyme and other tick borne diseases, available at www.ilads.org

Ferrie, Helge (Editor): Ending denial. The Lyme Disease Epidemic. A Canadian Public Health desaster. Kos publ. 2.ed. 2013 ISBN 978-0-9811337-1-3

Hopf-Seidel: Krank nach Zeckenstich. Borreliose erkennen und wirksam behandeln, Droemer Knaur Verlag 2008, 10th ed. 2016, ISBN-13:978-3426873922

Horowitz, Richard I.: Why can`t I get better? Solving the mystery of Lyme and chronic disease, St. Martin`s Press NY, 2013

Jürschik-Busbach, Birgit: Die verschwiegene Epidemie. 9 Leben Verlag 2011, ISBN-13: 978 3981410501

Pall, Martin, Ph.D.: Explaining “unexplained illnesses”, Harrington Park Press 2007

Wilson, James L., M.D.: Adrenal fatigue, Smart publications, Petaluma, USA, 2001

Articles

Articles about the HLA-subtypes and their effect on the immune system of LD patients as well as about the sexual transmission of B.b. spirochetes:

Bach, Gregory about the sexual infection of Laura Bush in: www.canlyme.com/sex.html 4-2001

Carmel, CA: Lyme disease may be sexually transmitted, study suggests in: J Invest Med 2014; 62:280-281 or www.onlineprnews.com/news/454866-1390261 507-Lyme-disease-may-be-sexually-transmitted-study-suggests.html

Kalish, RA et al. (1993): Association of treatment-resistant chronic Lyme arthritis with HLA-DR 4 and antibody reactivity to OspA and OspB of Borrelia burgdorferi. Infection and Immunity 61 (7)

Middelveen MJ et al.: Culture and identification of Borrelia spirochetes in human vaginal and seminal secretions. First publ. 18.12.2014, F 1000 Research 2015, 3: 309 open access article

Steere, AC et al. (1990): Association of chronic Lyme-arthritis with HLA-DR4 and HLA-DR2 alleles. New Engl. J. Med 323 (4)

Steere, AC et al. (2006): Antibiotic-refractory Lyme arthritis is associated with HLA-DR molecules that bind a Borrelia burgdorferi peptide.JEM 203 (4)

Stricker,R., Middelveen MJ (2015): Sexual transmission of Lyme disease :challenging the tick borne disease paradigm in: Expert Rev Anti Infect Ther 2015;13 (11):1303-1306

Wang, P and Hilton, E (2001): Contribution of HLA Alleles in the regulation of antibody production in Lyme Disease. Frontiers in Bioscience 6.

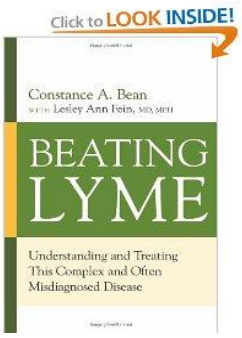

Foto: foto.polack@email.de

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There the whole tick family is waiting for you and **your** blood !!