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LYME DISEASE: THE TIP OF THE ICEBERG?

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ABSTRACT –

Most prevalent in the United States, this zoonotic disease is primarily caused by the spirochete *B. burgdorferi. Ixodes* ticks serve as the bacterial vector and are responsible for infection in humans as a by product of the feeding cycle. Ticks are found in three life stages, with nymphs accounting for ¾ of all cases. Three stages of the disease also occur and early treatment is key to quick recovery, if left untreated bacterial dissemination leads to both a systemic and invasive infection whereby symptoms may last years.

INTRODUCTION –

For those of us who are alive today the world is a vastly different place from one our ancestors knew, cultural and technological changes have enhanced, expanded and enriched our lives however, with new changes come new challenges, one of which is Lyme disease.

LYME HISTORY -

Since 1883 the clinical symptoms of Lyme disease have been scattered throughout medical literature (*table 1*[1]) but it was not until 1975 in Old Lyme, Connecticut[2] that a cluster of misdiagnosed juvenile rheumatoid arthritis cases lead to the name we know today. Six years later the main causative agent was identified as *Borrelia burgdorferi (B. burgdorferi)* during 1982-2002, 157,000[3] cases of Lyme disease have been reported in the United States of America (*USA)* with additional cases throughout the world, typically in Europe and Asia.

TABLE 1 – HISTORY OF LYME DISEASE

YEAR	LOCATION	COMMENT
1883	*Breslau, Germany*	*Physician describes degenerative skin disorder.*
1909-1919	*Sweden*	*Association made between Ioxdes tick bite & ring like skin lesion.*
1922	*Sweden*	*Link between EM rash & neurological problems.*
1970	*USA, Wisconsin*	*Man bitten by Ixodes tick while hunting, first know US acquired case.*
1975	*Old Lyme, Connecticut*	*First clustering of cases, misdiagnosed as juvenile rheumatoid arthritis.*
1981	*USA, Rocky mountain laboratory*	*Willy Burgdorfer identifies causative agent.*
1998	*USA*	*FDA approves Lyme vaccine.*
2001	*USA*	*FDA withdraws vaccine.*

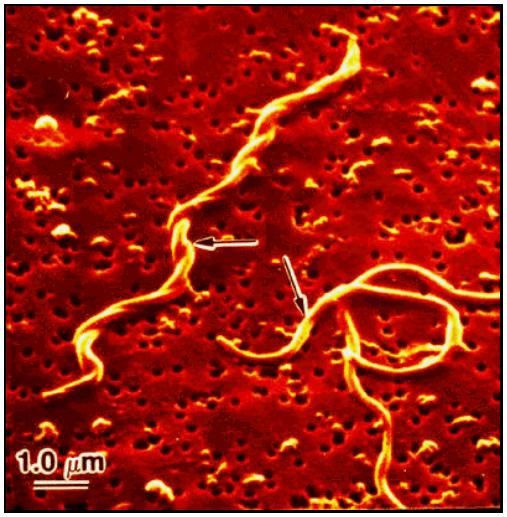
MICROBIOLOGY OF *B. burgdorferi* –

B. burgdorferi (figure 1[4]) is one of 37 spirochetal species[5] found in the *Borrelia* genus; other spirochetal diseases are shown in table 2[6].

TABLE 2 – SPIROCHETAL DISEASES

DISEASE	CAUSATIVE AGENT
LYME DISEASE	*Borrelia garinii / Borrelia afzelli/ B. burgdorferi*
SYPHILIS	*Treponema pallidum*
TICK-BORNE RELAPSING FEVER	*Borrelia recurrentis*
LEPTOSPIROSIS	*Leptospira interrogans*

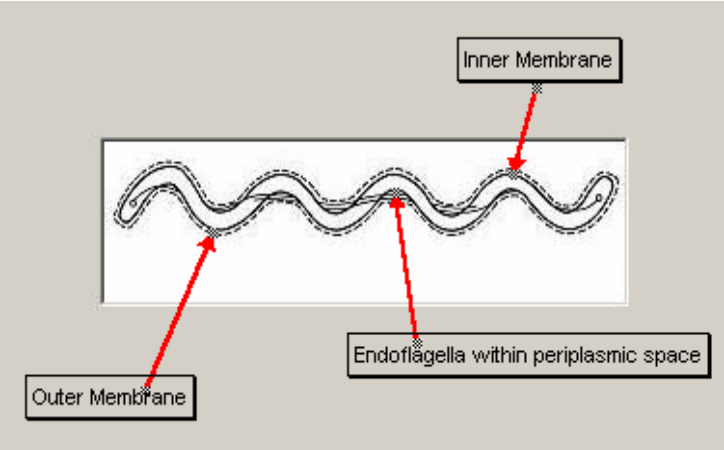
FIGURE 1 – ELECTRON MICROGRAPH



MORPHOLOGY -

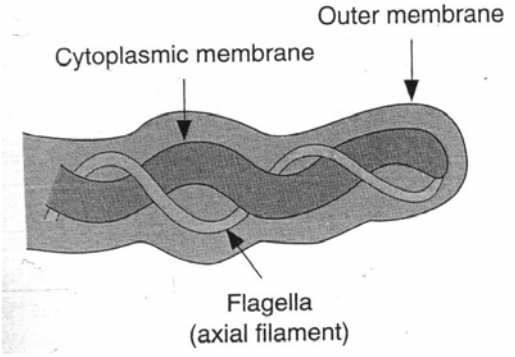
B. burgdorferi has a characteristically long *(20-30µm)* spiral shaped morphology with a diameter of 0.2-0.3µm[7]. Motile in tissue and blood it has 7/11 periplasmic flagella, located between the cytoplasmic and outer membranes; propulsion occurs in a cork-screw like manner *(figure 3[8])*.

FIGURE 2 – SCHEMATIC DIAGRAM OF *B. burgdorferi*



Visually the most distinguishing feature is length. This meandering, morpholical configuration (*figure 2[9]*) most likely complements the cork-screw movement producing a spinning, twirling effect which may be useful in migrating through fluid or tissue.

FIGURE 3 – FLAGELLA ARRANGEMENT



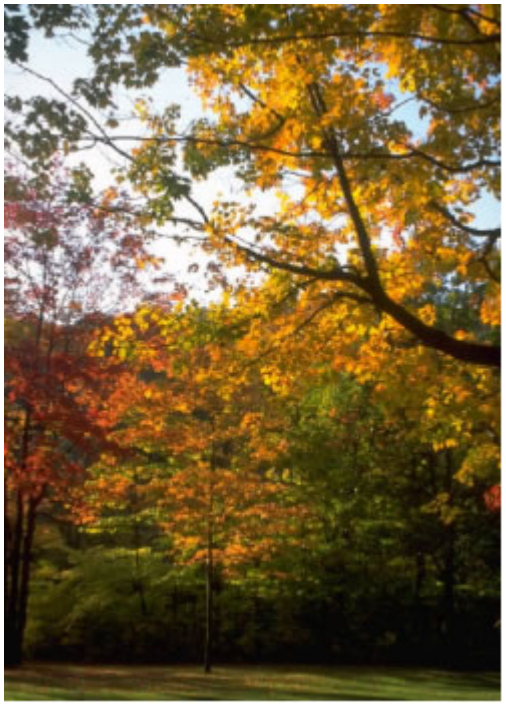
GENETICS -

Six varieties of outer surface proteins (*Osp*) exist on the outer membrane with plasmid encoded OspA/OspB most abundant. Surrounding this membrane a slimy S-layer is found.

B. burgdorferi contains a 950 kilobase linear chromosome with 9 circular and 12 linear plasmids[10], the latter encoding proteins; bacterial division typically takes 12-24 hours at an optimal temperature of 33°C.

TRANSMISSION

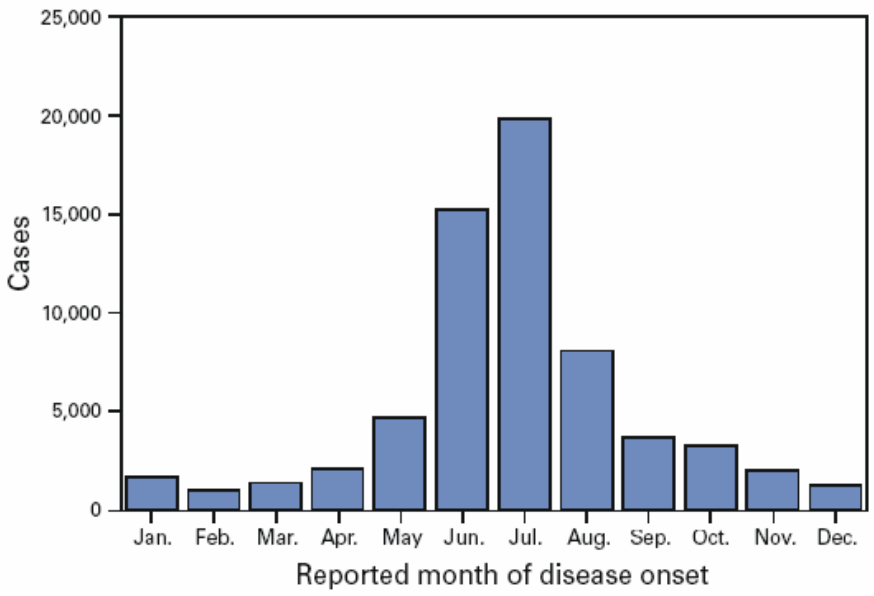
FIGURE 4 – POTENTIAL INFECTION AREA



This zoonotic disease is not contagious, it can however be aquired in humans by 'hard' *Ixodes* ticks, commonly present in woodland areas (*figure 4*[11]), gardens or nature reserves; most reported cases occur June to July (*figure 5*[12]).

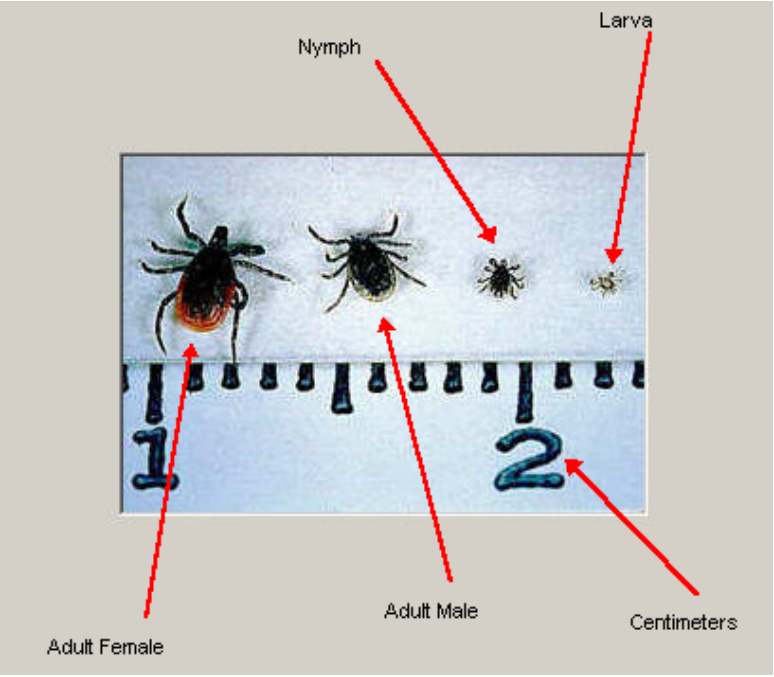
Traditionaly individuals most at risk included agricultural or forestry workers thou with increased lesuire time and acessibility to remote regions children, hikers or tourists increasingly become infected; a social change in lifestyle which has brought man to disease rather than disease to man.

FIGURE 5 – REPORTED CASES OF LYME DISEASE (1992-1998 *USA*)



VECTOR –

FIGURE 6 – *I. SCAPULARIS*

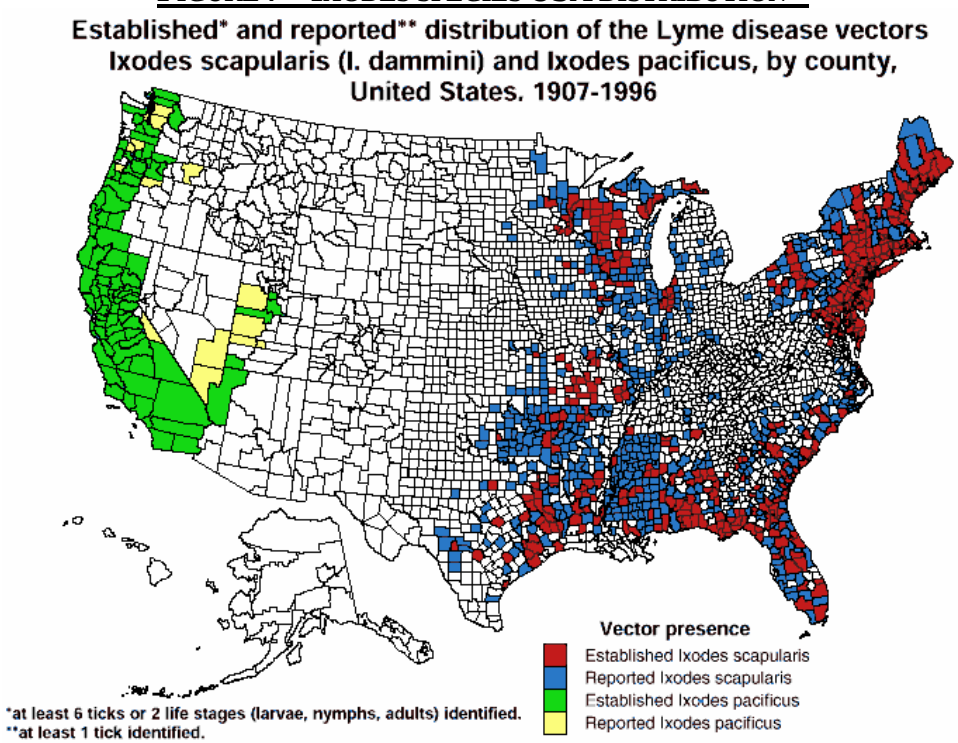


Two species of tick are found in the USA; *Ixodes scapularis (I. scapularis) (figure 6*[13]*)* and *Ixodes pacificus (I. pacificus) (figure 7*[14]*)*. In Europe *Ixodes ricinus* is dominant and *Ixodes persulcatus* in Asia.

COINFECTION -

Whilst the *Ixodes* tick is associated with Lyme disease, it may also be possible to acquire other forms of tick-borne diseases like Colorado tick fever[15] which the arthropod could be carrying, resulting in a combination of diseases.

FIGURE 7 – IXODES SPECIES USA DISTRIBUTION –



Distribution of tick species shows the importance of animal hosts during transmission. In the eastern half of the USA *I. scapularis* feeds mainly on mice[16] and deer which readily become infected with *B. burgdorferi* sustaining it in an animal reservoir. On the western coast *I. pacificus* feeds primarily on lizards which are less susceptible to infection, thus resulting in a reduced animal reservoir and bacterial population.

***B. burgdorferi* TRANSMISSION TO *Ixodes* TICK –**

FIGURE 8 – WHITE-FOOTED MOUSE

ANIMAL RESERVOIRS -

Larval *I. scapularis* feed on small rodents like the white-footed mouse (*figure 8*[17]) and adult ticks on larger mammals such as the white-tailed deer (*figure 9*[18]), piercing skin with the mouthpart allowing blood to be drawn.

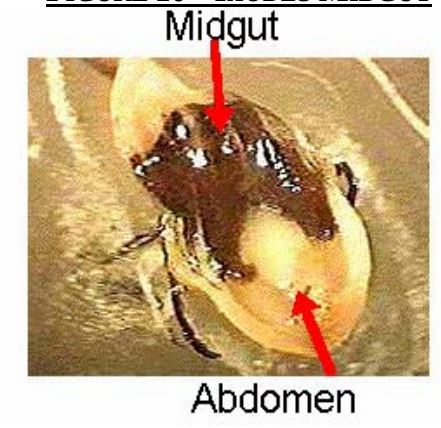
During this process the bacterium may be acquired by the tick or spread to the host if the tick is already infected, however these natural reservoirs do not exhibit any clinical symptoms.

FIGURE 9 – WHITE-TAILED DEER

POPULATION NUMBERS -

As the tick feeds around 500 ingested bacteria are transferred to the lumen of the midgut (*figure 10*[19]). During a subsequent feeding period *B. burgdorferi* multiply, climaxing at a population of 170,000[20].

FIGURE 10 – *IXODES* MIDGUT



In an attempt to reduce outbreaks, environmental conditions and animal reservoirs, have been subject to regulation (*table 3*[21]).

TABLE 3 - METHODS FOR TICK ERADICATION IN NATURE

METHOD	COMMENT
1) SPRAYING PESTICIDE IN WOODED AREAS	*Using pesticide in a wooded area during the spring and fall can help reduce numbers of adult ticks for a year. Generally confined to local areas it may not be economically viable on a large scale. Environmental concerns may limit widepsread use of chemicals.*
2) REDUCE DEER POPULATION	*Computer models suggest completely erradicting deer would have a substantial effect on tick populations, however public opinion would be against this.*
3) DIVERSIFYING THE ECOSYSTEM	*Diversifying an ecosystem lowers the risk of Lyme disease as ticks will feed on a wider range of hosts such as lizards or birds which don't sustain B. burgdorferi well. Nymphal ticks are more likely to become infected in simpler ecosystems.*
4) CLEARING ACORNS IN OAK FORESTS	*Tick numbers peak during good acorn harvest years[22]. Acorns attract deer and mice which also bring ticks. These ticks will drop off the host, mate and lay eggs. Therefore a large acorn crop may signal a high risk of potential Lyme disease cases.*
5) CLIMATIC FACTORS	*Moisture is needed to prevent larval ticks from drying out as they moult into nymphs. Nymphal tick populations swell when winter and spring precipitation are high. This may be used as a means of prediction.*
6) BIOLOGICAL CONTROL	*Natural predators such as parasitc wasps and wolf spiders provide an eco-friendly solution in localised areas, widespread control is ineffective.*
7) DEER FEEDING STATIONS	*Stations which feed deer are equiped with a machine that places a collar onto the neck during feeding[23]. This collar is designed to kill ticks and may be effective over a large scale; eco-friendly and does not harm deer.*

LIFE STAGES –

Ticks are found in 3 life stages (*table 4*[24]*).*

TABLE 4 – THE VARIOUS STAGES OF TICK DEVELOPMENT

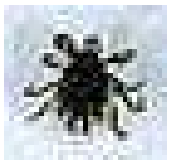
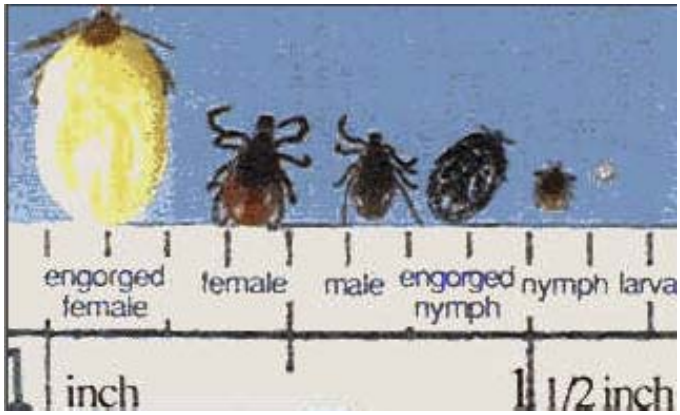
STAGE	PICTURE (*NOT TO SCALE*)	COMMENT
LARVAL		*Ingest bacteria from host, molts and becomes nymph. 6 legs, weak climber; host must make close contact.*
NYMPHAL		*Larger though still small; around size of pinhead. Feed twice as fast as adults, attach readily, difficult to spot on skin. 8 legs, actively seeks out host. Account for ¾ of all Lyme disease cases. Feed May-July.*
ADULT MALE		*Larger than nymph, easy to spot, most active October-June + December – February. 8 legs, adults climb higher, more mobile.*
ADULT FEMALE		*Larger than male and produces eggs therefore needs more blood during meal, may be more likely to transmit B. burgdorferi due to this requirement. 8 legs.*

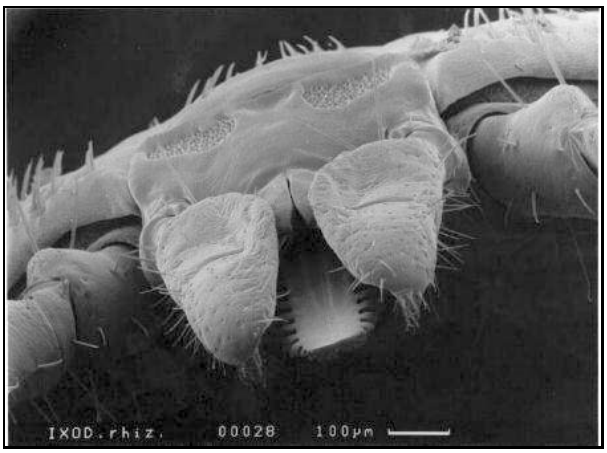
FIGURE 11 –REGULAR AND ENGORGED TICK



ENGORGEMENT -

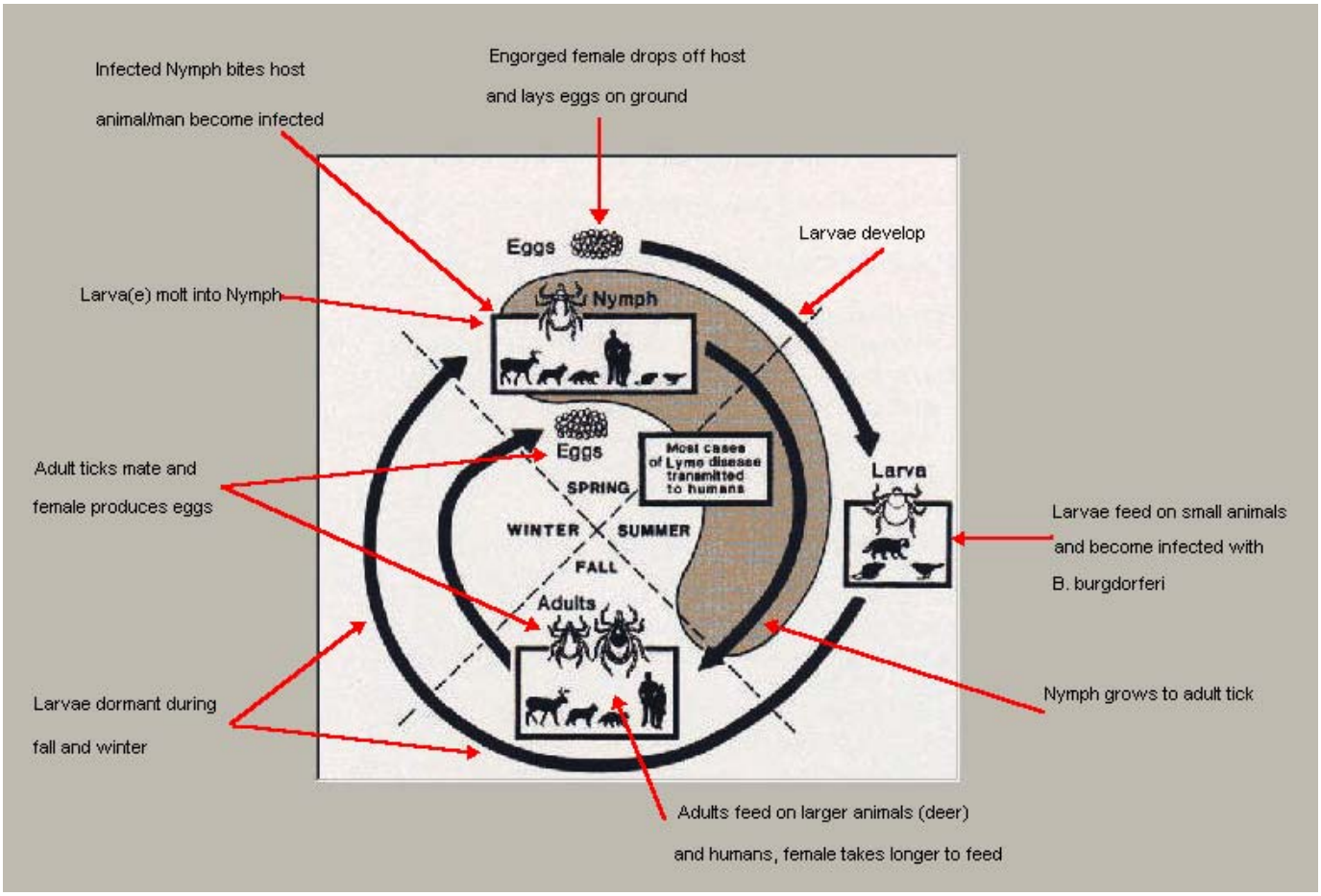
Prior to each feeding period the tick will migrate to a soft, moist area of the body before inserting its mouthpart (*figure 12*[25]*)*; feeding lasts between 2-4 days.

Figure 12 – Tick mouthpart



Approaching the end of feeding, ticks increase in size and become 'engorged' (*figure 11*[26]*)* once complete it drops off the host and progress to its next stage. Life cycles (*figure 13*[27]) take 2 years and feeding must occur once at each stage.

FIGURE 13 – LIFE CYCLE OF *Ixodes* TICK



DANGER PERIOD -

Maximal transmission of *B. burgdorferi* to host occurs when the tick fully completes its feeding period, allowing multiplication of bacteria in the midgut and dissemination via the hemolymph and salivary glands[28] onto the skin; thus it is imperative to remove the tick as soon as possible (*table 5*[29,30]*).*

TABLE 5 – TICK REMOVAL –

PICTURE	REMOVAL METHOD
	*Using tweezers is the safest method of removing an attached tick. Using matches, cigarettes or chemicals may cause contents of the gut including B. burgdorferi to be ejected onto the skin.* *Grasp at its mouthpart close to the skin and tug gently until the tick removes its mouth. Occasionally the mouthpart may still be attached to the skin however as B. burgdorferi is present in the midgut this should not pose a risk of infection, although an allergic reaction to saliva may ensue.* *Save the tick in a jar of alcohol with the date and location it was found on body. Take the tick to be examined for the presence of B. burgdorferi and wipe wound with antiseptic.*
	

TICK HABITAT –

As the *Ixodes* tick is unable to fly and lacks eyes it relies on changes in carbon dioxide, scent and body heat with close contact in order to climb onto the host. For transmission to occur three essential elements are needed in nature *(table 6[31]).*

TABLE 6 – TRANSMISSION FACTORS

FACTOR	COMMENT
B. burgdorferi	*The bacterium must be present in order for ticks to become infected and initiate the cycle.*
INFECTED TICKS	*Not all species of ticks are suitable vectors of the bacteria, only those infected possess the ability to infect animals or humans.*
SUITABLE HOSTS	*Hosts such as mice, deer or humans provide blood the tick needs to feed and harbour the bacterium well, other hosts like lizards are not so readily infected.*

ENVIRONMENTAL CONDITIONS -

The ticks natural environment varies between species, although generally they are found at ground level with moisture and shade in leaf litter or grass which provides shelter from external elements such as wind, cold and rain (*table 7*[32]*).*

TABLE 7 – ALTERED HABITATS BETWEEN *IXODES* SPECIES

TICK	HABITATS
I. scapularis	*Temperate regions, high ground humidity, e.g. deciduous forest with ground leaf litter cover.*
I. pacificus	*Forests, north coastal scrub, open grasslands.*

FIGURE 14 – NYMPHAL TICK -

Several factors make nymphal ticks more likely to transmit *B. burgdorferi;* a shorter feeding time than adults and physical size (*figure 14*[33]*)* making them difficult to spot (*figure 15*[34]*).*

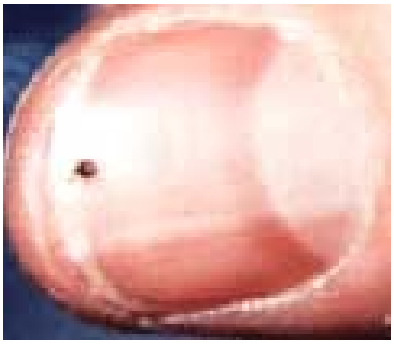
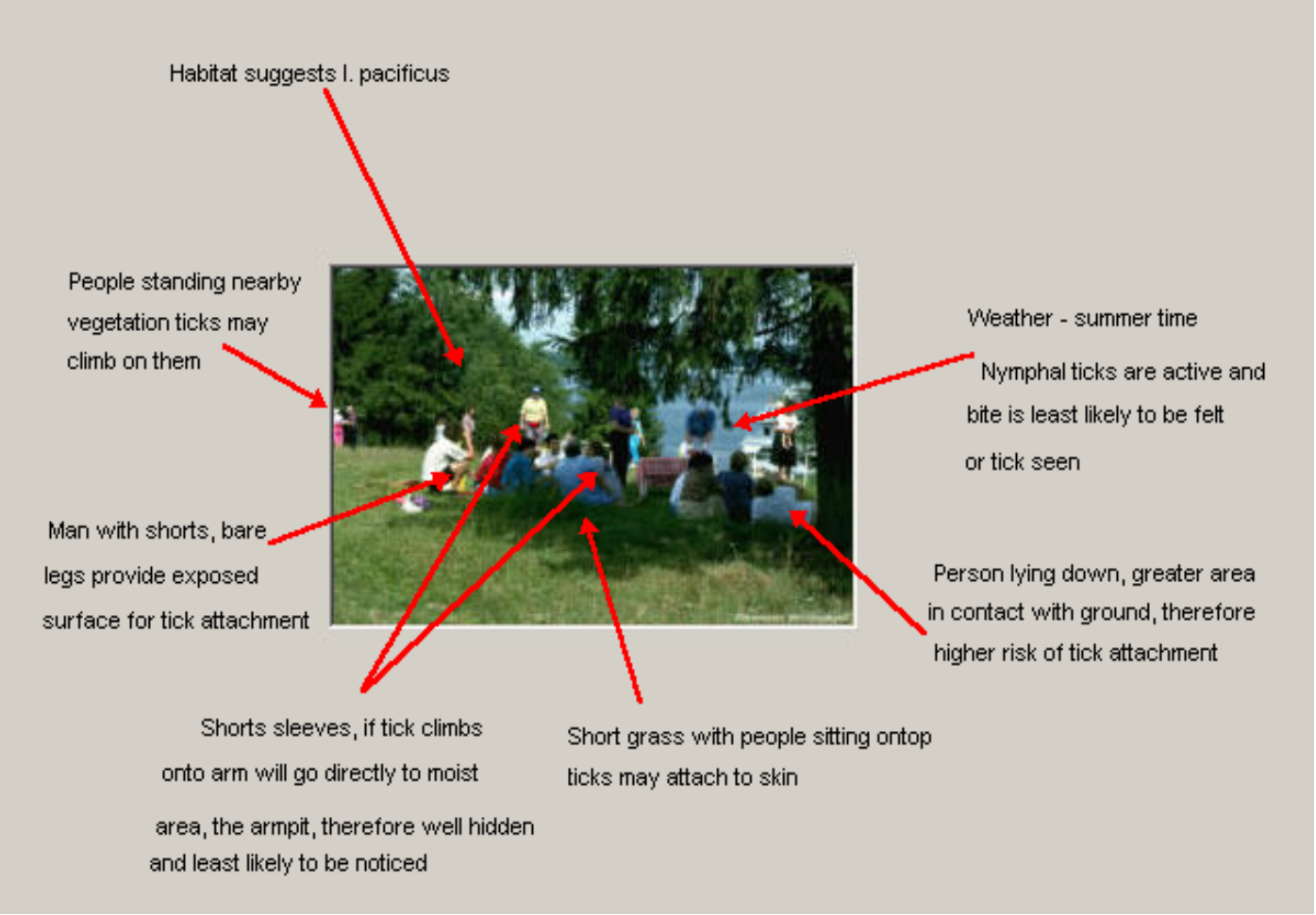


FIGURE 15 – NYMPH ATTACHED TO SKIN –

Figure 16[35] displays and area in nature with individuals who may be at risk.

FIGURE 16 –INDIVIDUALS AT RISK FROM TICK ATTACHMENT



PETS–

FIGURE 17 – DOGS MAY ACT AS TICK VECTOR

Pets are a possible vector of the tick which may bring *B. burgdorferi* closer to home. Dogs (*figure 17*[36]) are likely to come into contact with vegetation during leisure activities. Once a tick attaches itself it may then be brought inside the home or into the garden, well hidden in the fur. After 2-4 days the tick will drop off and possibly lay eggs if an adult female. Therefore homeowners may be particularly at risk and should take various preventative measures when venturing outdoors or owning pets (*table 8*[37]).

TABLE 8 – PREVENTATIVE MEASURES WHEN VENTURING OUTDOORS-

PREVENTATIVE MEASURE	COMMENT
1) WEAR LIGHT COLOURED CLOTHING WITH TROUSERS TUCKED INTO SOCKS AND LONG SLEEVED SHIRTS WITH HAT	*It is easier to see ticks on light coloured clothing, tucking trousers in socks prevents ticks from climbing onto the skin.*
2) SPRAY CLOTHES WITH INSECT REPELLENT	*Using a long lasting repellent confers a great deal of protection, repellents such as Duranon contain permethrin a chemical which is neurotoxic to ticks.*
3) BODY CHECKS	*Important as most people do not feel being bitten and removal of ticks in early stages of attachment minimise risk of infection. Check all over body espically in moist, warm areas such as armpits or behind the knee.*
4) LEARN TO IDENTIFY TICKS WHICH HARBOUR *B. BURGDORFERI*	*Not all ticks will give you Lyme disease so this will help to prevent false alarms. The female Ixodes tick is redish brown/ and the adult male or nymph black with a slight bland on its rear tip.*
5) TAKE APPROPIATE MEASURES TO PROTECT PETS	*There are various repellents for pets to prevent bringing ticks inside the home or garden. Checking pets for ticks may also help, thou this may be difficult with long haired animals. Pets may develop clinical symptoms.*
6) AVOID KNOWN TICK HABITATS	*During spring and summer nymphal ticks are active and most difficult to spot. Avoid moist, shaded areas in woods with low lying bushy vegetation you would brush past. Areas where deer are present may pose a high risk area.*
7) TAKING ANTIBIOTICS WHEN INFECTION IS SUSPECTED	*Taking antiobiotics early on will greatly reduce the risk of bacterial dissemination and prevent further more serious symptons.*
8) TAKE PREVENTATIVE MEASURES AROUND THE HOME	*Removing leaf litter, mowing long grass and introducing more light into the garden by triming trees may help to keep tick populations low.*
9) TREAT CAMPING EQUIPMENT WITH REPELLENT	*Treating tent fabric with permethrin kills ticks on contact and minimises risk of attachment during sleep.*

PATHOGENESIS –

Many factors influence the risk at which an individual is exposed to an *Ixodes* tick and subsequently become infected. Unlike animal reservoirs which exhibit an asymptomatic infection, humans develop Lyme disease (*table 9*[38]*).*

Whilst a pathogen may possess varying degrees of virulence, it is not solely this factor in isolation which determines clinical symptoms; of equal importance is general health and state of the host immune system.

TABLE 9 – STAGES OF LYME DISEASE –

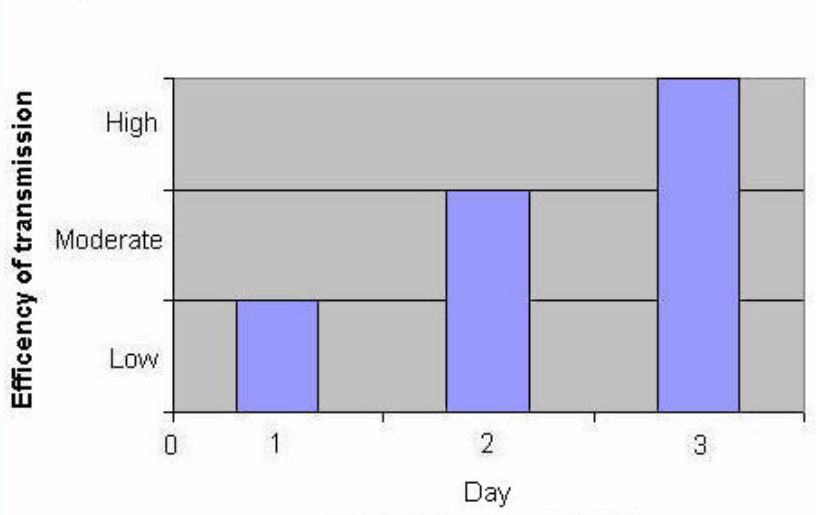
STAGE	COMMENT
STAGE 1 – EARLY INFECTION	In *60-80% of infected individuals Erythema Migrans (EM) appears as a circular red rash 5-6 inches in diameter maturing to a bull's eye ring. B. burgdorferi may be isolated from the leading edge of the rash and cultured for diagnosis. Not all rashes may occur at site tick bite. EM appears 3-30 days after infection and usually disappears within 4-5 weeks. Rash may itch or burn and be accompanied by flu like symptoms. EM rash may be less visible on dark or tanned skin.*
STAGE 2 – DISSEMINATION STAGE	*May occur days to weeks after initial infection whereby B. burgdorferi migrates from the skin and disseminates throughout the body via circulatory or lymphatic systems targeting host cell tissues or invading the central nervous system. Secondary EM rashes may appear.*
STAGE 3 – PERSISTANT INFECTION* ***** *May imitate other diseases such as Chronic fatigue syndrome, Multiple Sclerosis, Mental illness and Fibromyalgia leading to misdiagnosis.*	*Long term symptoms occur months-years after initial infection as B. burgdorferi is able to evade the immune system by antigenic variation and hide inside host cell tissues like fibroblasts or the brain. Antibiotics can eliminate bacteria in the blood but relapses may occur if B. burgdorferi is lying dormant/hidden in the host. Chronic Lyme arthritis may develop and erode cartilage/bone. Treatment at the early stage reduces likelihood of third stage.*

EXIT FROM TICK AND ENTRY TO HOST –

During initial infection of the tick, bacterial numbers peak at 500 and OspA is expressed serving as an adhesive mechanism to the midgut lumen. At the next feeding period multiplication occurs and bacterial population peaks at 170,000, coinciding with decreased expression of OspA and an increase in OspC[39].

OspC serves to release the bacteria and allow migration through the midgut epithelium, transference via the hemolymph to the salivary glands and onto the skin. Down-regulation of OspA may be influenced by temperature and pH[40] changes during feeding concurrently promoting up-regulation of OspC.

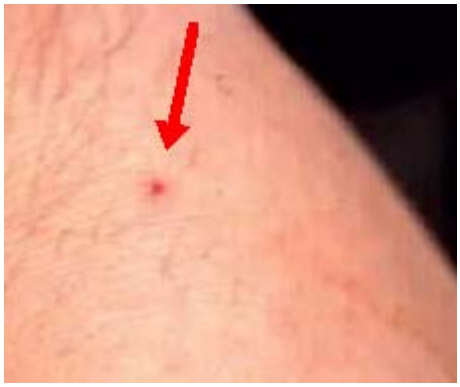
FIGURE 18 – EFFICIENCY OF TRANSMISSION



Therefore not all individuals bitten will automatically become infected with *B. burgdorferi*, as the length of feeding time is directly proportional to the risk of becoming infected (*figure 18)*. This correlates to OspC expression and release from the midgut, climaxing at 48 hours.

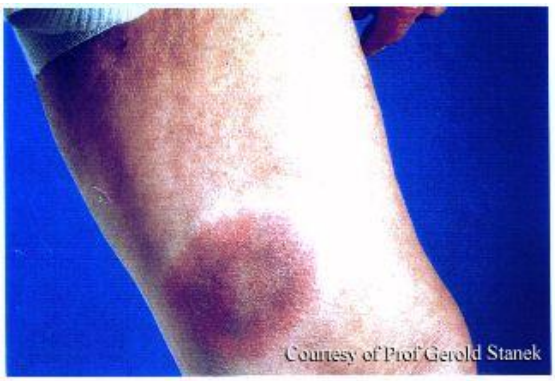
ESTABLISHMENT OF INFECTION –

FIGURE 19- INITIAL TICK BITE –



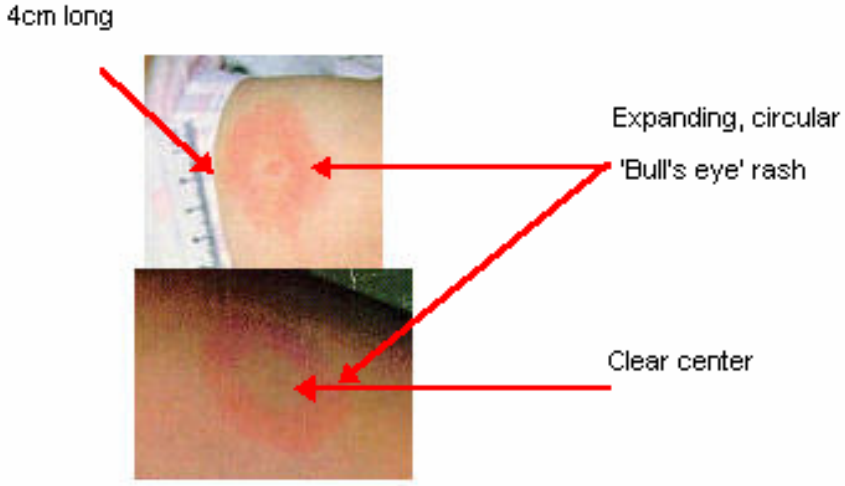
After deposition onto the skin with tick saliva, bacteria multiply and establish a foothold for further infection (*Figure 19*[41]).

FIGURE 20 – EARLY STAGE EM RASH



However this foothold may not be immediately evident before EM occurs 3-30 days after the initial bite (*figure 20*[42]*).*

FIGURE 21 – 'BULL'S EYE' RASH



This early stage is the most obvious external sign of infection, whereby treatment now (*table 10*[43]*)* will greatly minimise the risk of a systemic infection. However 20–40% of those infected will not exhibit EM, they are asymptomatic.

In fact some cases may be due to an allergic reaction with tick saliva generating false alarms. This is distinguished from a bacterial infection as it remains solely a red rash disappearing within days whereby infection with *B. burgdorferi* matures into an expanding 'bull's eye' rash sensitive to touch (*figure 21*[44]*).*

TABLE 10 – ANTIBIOTIC TREATMENT –

ANTIBIOTIC*	FORM	SIDE EFFECTS	GUIDELINES
DOXYCYCLINE (100MG)	*Capsule/tablet / taken oraly*	*Diarrhea, nausea, vomiting, skin rash, light sensitivity, chest pain*	*Children – 2mg / adults 100mg - every 12 hours for 10-21 days – may speed healing of EM rash*
AMOXICILLIN (250/500MG)	*Capsule/tablet / taken oraly –*	*Anemia, anxiety, hyperactivity, confusion, dizziness, insomnia*	*Children 15mg / Adults 500mg -every 8 hours for 10-21 days – may speed healing of EM rash*
**Antibiotic destruction of B. burgdorferi results in release of a toxin which may react with and stimulate the immune system by a process called the Jarisch-Herxhmeimer (J-H) reaction. J-H symptoms range from fever, chills, joint pain or headaches. The J-H reaction may be mistaken for an allergic reaction to the antibiotic (J-H reactions are x10 more likely than allergic reactions to antibiotics). Generally oral tablets are given for early stage symptoms whilst intravenous is given for later stages such as heart symptoms. Some doctors believe chronic Lyme disease should be treated with antibiotics for 6-12 months to take into account periods when the bacteria are hidden and longer if symptoms reappear and there is evidence of B. burgdorferi.*			
BENZYLPENICILLIN (600MG)	*Powder for injection / Intravenous*	*Stomach upset, breathing difficulties, rash*	*Adults – every 4-6 hours for 14-21 days*
CEFTRIAXONE (250MG)	*Powder for injection / Intravenous -*	*Facial swelling, rash, nausea, vomitting, diarrhea*	*Adults – every 24 hours for 14-21 days*

***B. burgdorferi* IN THE BLOOD –**

If left untreated, *B. burgdorferi* may disseminate into the blood where it is vulnerable to immune attack. It will now rely on its own mechanisms to evade immune cells and journey to intracellular locations where shelter and protection are provided, acting in both a systemic and invasive manner. However since no clinical infection is seen in animal reservoirs this may indicate that the action of the immune response itself could trigger virulence factor expression, in order for the bacterium to survive.

DELAYED ANTIBODY RESPONSE -

Flagella are highly antigenic, however as these are 'hidden' within the periplasm surrounded by an outer membrane and slime layer, phagocytic attack and subsequent antigen presentation are therefore largely hindered and ineffective. The resulting consequence is a delayed antibody and membrane attack complex (*MAC*) response, becoming efficient in action 3-5 weeks after initial infection[45]. This means the innate branch will be responsible for protecting the host early on, however limited this may be, effectively allowing ample time for the bacterium to disseminate and seek shelter before the might of the adaptive branch gains momentum; thus laboratory testing may produce negative results in early infection (*table 11*[46]*).*

TABLE 11 – LYME DISEASE ASSOCIATED TESTS

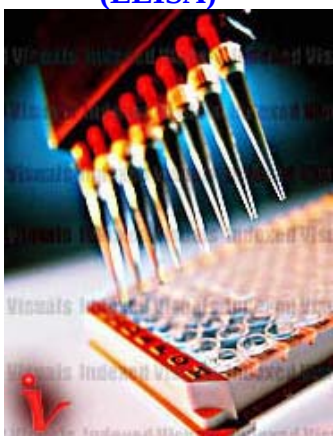
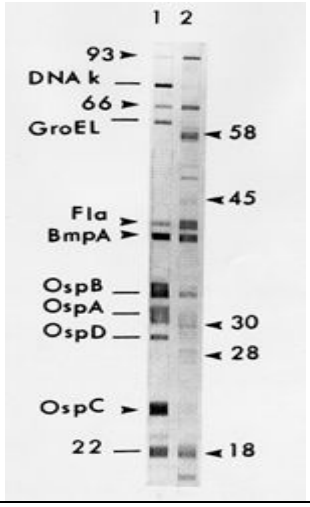
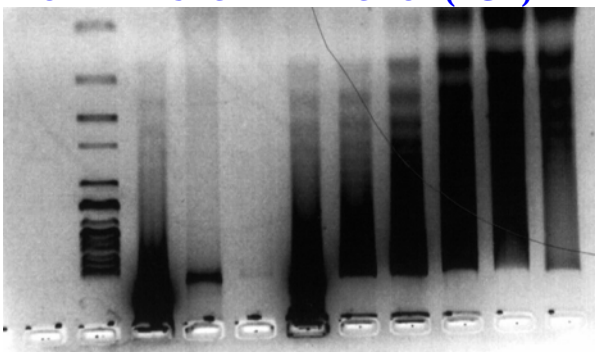
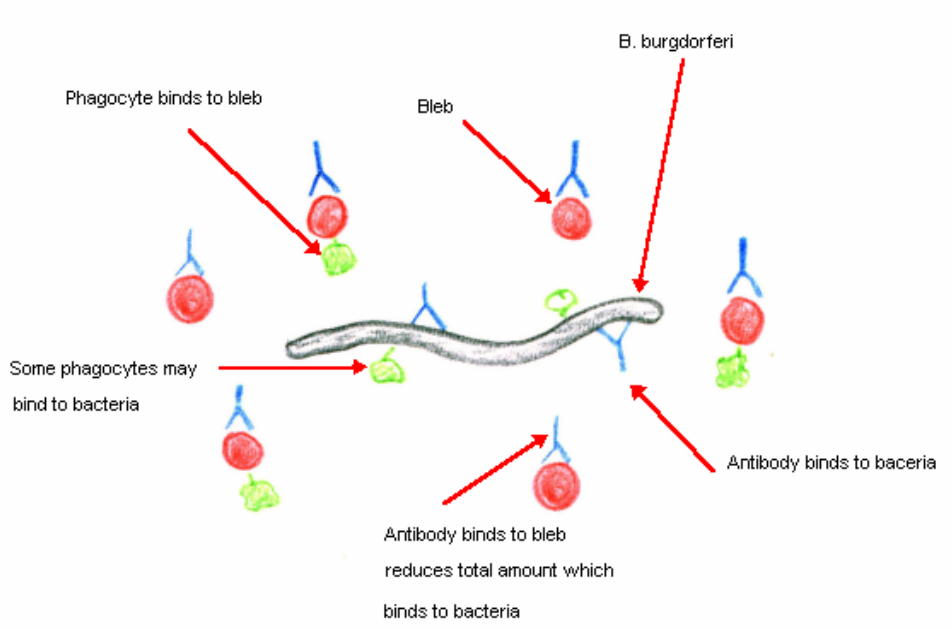
TEST	COMMENT
ENZYME-LINKED IMMUNOASSAY* (ELISA)[47]  ***Picture for example only**	*First step in confirming Lyme disease in patients with and without expanding rash. Screens for elevated blood antigens in response to B. burgdorferi. Performed 4 weeks after tick bite, 5/7% of infected individuals may test positive and 40% of infections may be missed. All positive results must be confirmed by western blot assay. Should include knowledge of when tick bite occurred, symptoms experienced, and possible growth of bacteria from leading edge of EM.*
WESTERN BLOT [48] 	*Specifies which Lyme associated antibodies are present in blood. Used to confirm/contradict ELISA assay. Positive ELISA followed by negative western blot indicates individual is not infected. Together with ELISA is considered a realiable test. As antibodys may not be present until a few weeks after infection this test immediately after tick bite may not be accurate, thus symptons and tick bite must be taken into account. Report should include readings on all bands especially bands 31 and 34. Lane 1 - monoclonal antibodies defining selected antigens to B. burgdorferi. Lane 2 - human serum.*
POLYMERASE CHAIN REACTION (PCR)* [49]  ***Picture for example only**	*Sensitive assay which detects and amplifies DNA of of B. burgdorferi. Skin, blood, cerebro-spinal and synovial fluid samples may be used. PCR of spinal fluid*[50] *may be positive in early neurological disease e.g. Lyme meningitis, usually negative in patients with long-term central nervous damage. PCR may be easily contaminated and produce false positives.*
PREVUE	*Antibody detection assay producing visually read colour results using serum or blood samples. Quick results within an hour, thus treatment may begin sooner, however must be confirmed by western blot.*
LYME URINE ANTIGEN (LUAT)	*Antigen capture assay detecting certain proteins of B. burgdorferi. Not FDA or commercially approved, may lead to misdiagnosis and unnecessary treatment.*

FIGURE 22 – BLEBS



BLEBS –

Blebs could be described as counter measures analogous to those released by fighter jets when evading missile targetting (*figure 22*).

Created by replication of specific genes inserted into the cell wall, blebs are pinched off from the outer membrane as vesicles containing OspA and OspB[51], are highly immunogenic, assist likelyhood of dissemination and generate inflammatory responses which may persist even after complete clearance leading to autoimmune responses.

***B. burgdorferi* AND B-CELLS –**

When surrounded by B lymphocytes the bacterium possesses the ability to enter, replicate and destroy the cell, stripping away some of the membrane and coating itself with it, becoming to some degree immunologicaly invisible disseminating in a stealth[52]. Due to this ability it was thought prevention was better than cure prompting development of a vaccine (*table 12*[53]*).*

TABLE 12 – LYME VACCINE HISTORY –

YEAR	COMMENT
1975	*First clustering of cases reported in USA.*
1981	*B. burgdorferi identified as causative agent.*
1989	*OspA discovered and cloned.*
Early 1990s	*Antibodies to OspA found in chronic Lyme disease patients.*
1990-1992	*Vaccinations with (recombinant) rOspA found to protect mice against Lyme disease infection.*
1992-1995	*Vaccinations with rOspA tested in other animals.*
1995	*Vaccine found safe and effective in persons with Lyme disease.*
1995-1998	*Vaccine called LYMErix found safe and effective in persons without Lyme disease, manufactured by SmithKline Beecham*
1998	*FDA approves Lyme vaccine for those frequenting tick habitats, 3 doses – day 0, 1 month, 12 month with yearly boosters, 70% effective.*
2001	*FDA withdraws vaccine due to complaints about arthritis in individuals with HLA-DR4 gene.*

ANTIGENIC VARIATION –

Another evasive mechanism comes via antigenic variation[54], occuring during immune attack. By altering antigens antibody production must begin again in order to be specific against the new set, since this takes 3-5 weeks the bacterium is able to disseminate again. Consequently infections in the blood may be immunologicaly different to those in other bodily regions, keeping the bacterium one step ahead of the immune response.

DIVISION TIME AND ANTIBIOTICS –

As the adaptive immune response is delayed, administration of antibiotics during early infection is imperative, of equal importance is the course given being fully completed to prevent relapses should the bacterium be lying dormant.

However a feature to consider is the division time of 12-24 hours[55], since most antibiotics serve as cell wall inhibitors by binding to ribosomes, they are only effective during cell division resulting in a longer course of antibiotics.

MIGRATION -

As antibody numbers rise the bacterium becomes increasingly vunerable to destruction and will eventually be overcome. In order to survive it must therefore migrate to intracellular locations where it will be hidden from immune survalence and either replicate or remain non metabolically active.

Medicaly this is of great importance in treating Lyme disease and its related disorders (*table 13*[56]) as a person may appear to be symptom free for some period only to relapse at a later date.

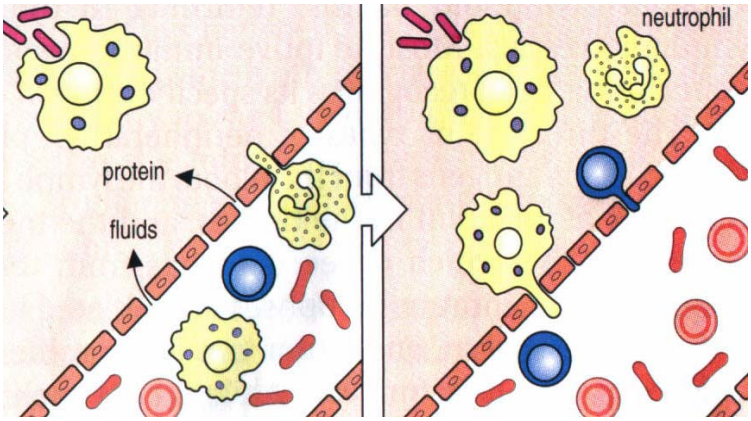
TABLE 13 – RELATED DISORDERS OF LYME DISEASE -

STAGE	SYMPTONS			
STAGE 1 – EARLY INFECTION	*Annular skin rash*		*Erythema migrans*	
STAGE 2 – DISSEMINATION	*Fever*	*Chills*	*Headache*	
	Malaise	*Fatigue*	*Lymphadenopathy*	
	Splenomegaly	*Pain*	*Stiff joints*	
	Joint pain	*Sore throat*	*Cough*	
	Conjunctivitis	*Iritis*	*Carditis*	
	Hepatitis	*Orchitis*	*Meningitis*	
STAGE 3 – PERSISTANT INFECTION * SYMPTONS MAY LAST FOR UPTO 4 YEARS OR LONGER	*Photosensitivity / double vision*	*Bell's palsey – one sided facial paralysis* 	*Memory loss / confusion / problems concentrating / 'brain fog' / speech problems*	
	Lyme arthritis	*Leukocytosis*	*Neurological changes – neuroborreliosis (inflammatory + neurodegenerative disorder)*	*Dermatitis*

LEAVING THE BLOOD VESSEL -

In order to leave a blood vessel and cross the endothelial monolayer, *B. burgdorferi* wriggles between tight junctions and disrupts their association crossing in a similar pattern to granulocytes (*figure 23*[57]), a process which is highly complement by its morpholical structure, possibly using OspB as an adherence mechanism.

FIGURE 23- LEAVING THE BLOOD VESSEL



ENTRY INTO HOST CELL

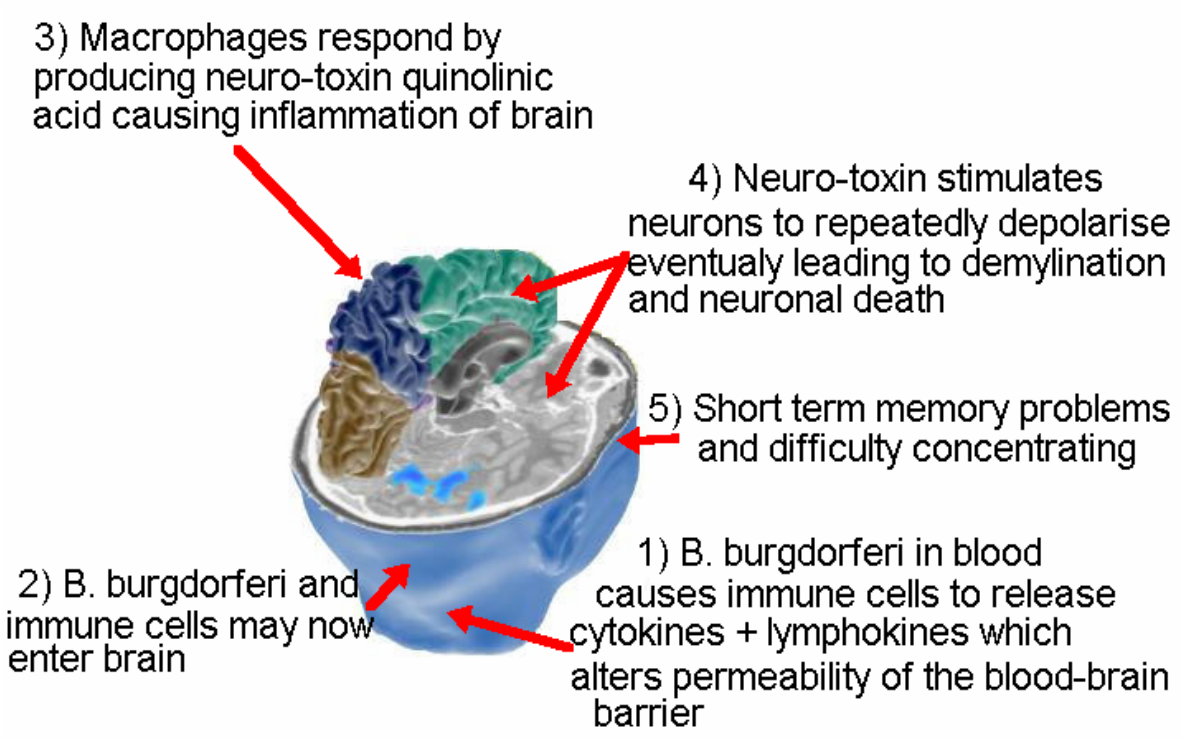
Entry occurs by attachment to the tip of the cell and wiggling in a cork-screw like manner. To assist this process the cell is caused to release digestive proteases which dissolve the plasma

membrane and facilitate entry into the cell. Genetically this allows the bacterial genome to contain only essential genes, such as for replication, hijacking host cellular mechanisms to assist its progression.

IMMUNO-PRIVILEGED AREAS -

Found in eyes, heart, scar tissue, spleen, and with the ability to cross the blood-brain barrier (*figure 24*[58]*) B. burgdorferi* is both systemic and invasive.

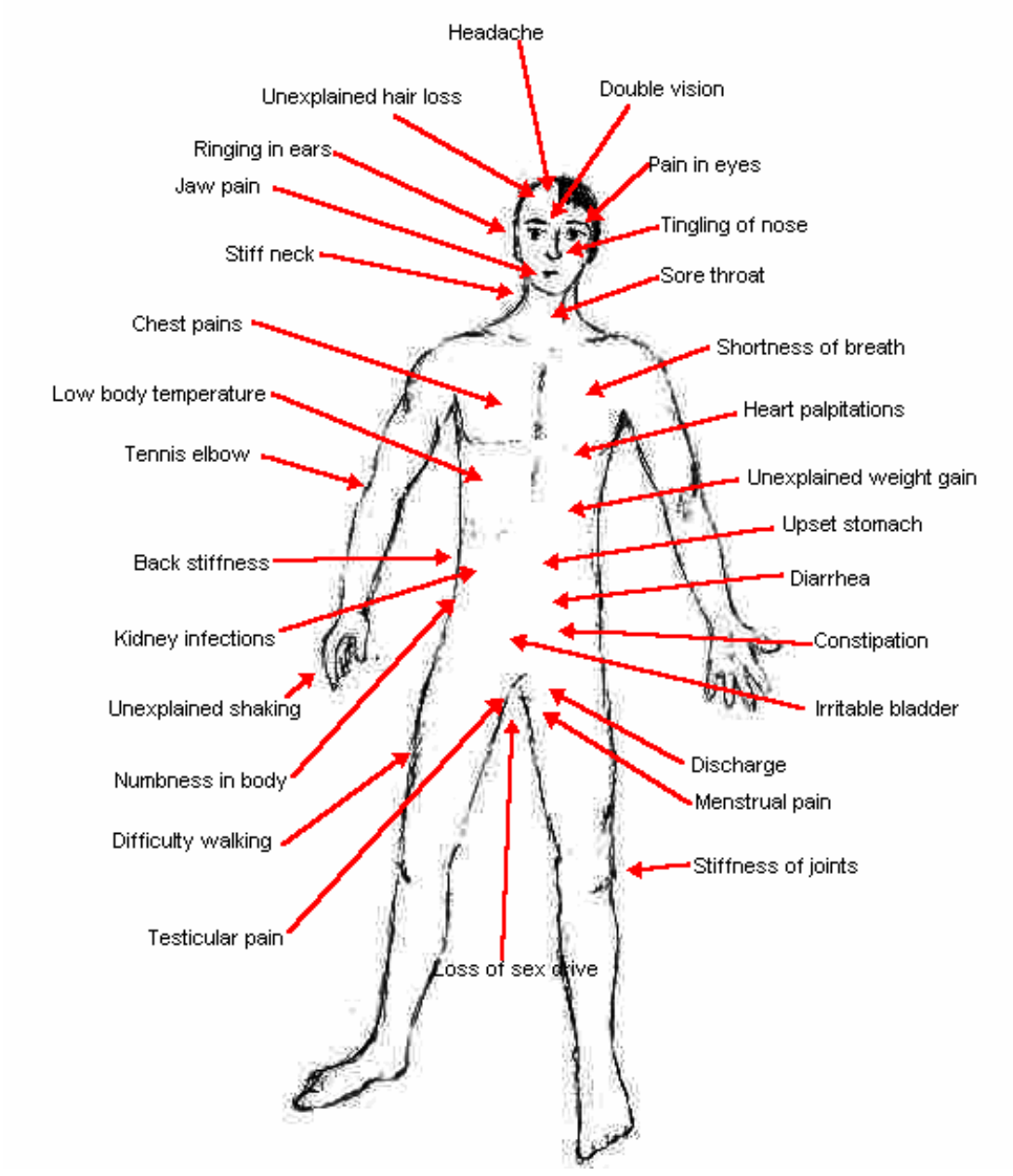
FIGURE 24 – ENTRY INTO THE BRAIN –



LYME DISEASE, THE TIP OF THE ICEBERG?

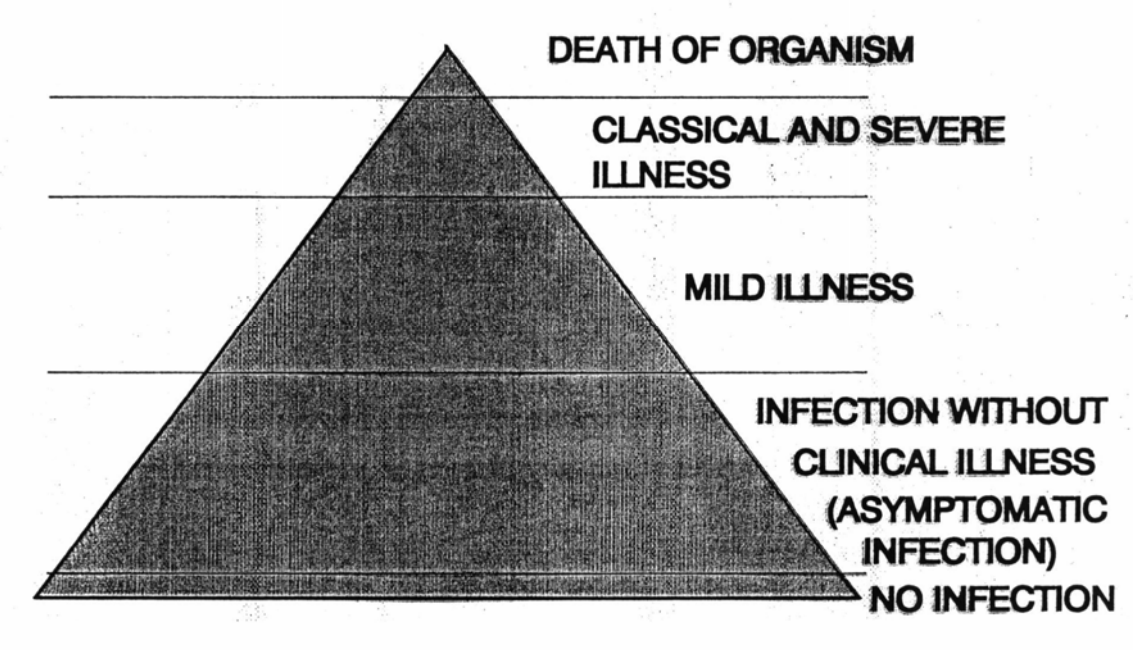
To describe an individual as suffering from Lyme disease seems a rather vague and inadequate description, rather the term should be used collectively as a name for a series of related disorders which may affect virtually any region of the body (*figure 25).*

FIGURE 25 – RANGE OF LYME DISEASE RELATED DISORDERS



Symptoms vary according to the stage of disease, whereby in some cases asymptomatic infections occur in stage 1, subacute in stage 2 and chronic infections in stage 3; this pattern lends itself well to the iceberg principle of infection *(figure 26*[59]*).*

FIGURE 26 – THE ICEBERG PRINCIPLE OF INFECTION -



NO INFECTION -

At the base of the pyramid individuals are uninfected as they have not been bitten by a tick or conversely bitten by an uninfected tick, either case no infection occurs due to the absence of *B. burgdorferi*.

ASYMPTOMATIC INFECTION -

Should the bacterium be brought into the equation, 20-40% of individuals will migrate to the next level and exhibit an asymptomatic infection, showing no characteristic EM rash and appearing symptom free. This may indicate that strength of the immune system could be important in determining the range of clinical symptoms experienced. Also if the tick is removed early after attachment a reduced quantity of *B. burgdorferi* is transferred and the immune system may be able to cope, possibly indicating the infectious dose is relatively high.

MILD ILLNESS -

This level correlates to stages 1 and 2 of Lyme disease progression, whereby infected individuals exhibit a disorder due to acquisition of *B. burgdorferi.* However the width of the pyramid is narrowing, indicating most individuals will not reach this stage and experience no or an asymptomatic infection.

Either through ignorance or misinformation a person may ignore these early clinical signs as they often resemble something experienced before, such as headaches or fever. At this level an infected person will therefore either seek medical advice or do nothing in the expectancy of ‘getting better soon’, exemplifying the importance of public education in preventing bacterial dissemination.

CLASSICAL ILLNESS -

Those who expected to 'get better soon', misdiagnosed or received inappropriate treatment may exhibit a classical and severe illness. The width of the pyramid suggests most with mild illness received appropriate treatment and the bacteria were cleared.

At this level people will most likely seek medical advice as they may now be experiencing symptoms which they have not had before. However at this late stage dissemination has already occurred and a systemic infection is likely, this has two implications; 1) incorrect diagnosis e.g. Lyme arthritis and rheumatoid arthritis both with similar effects but different causes, 2) correct diagnosis with ineffective treatment due to dormancy or hidden from immune system causing prolonged relapses and symptoms possibly lasting years.

DEATH -

A small percentage of infected individuals eventually die, their body has been hijacked by *B. burgdorferi*, organs infected with their functioning disrupted and a compromised immune system increasing risk of opportunistic infections. So suffers can reach the tip of the iceberg, however proper diagnosis and early treatment greatly reduces this risk.

SO WHY IS LYME DISEASE A PROBLEM?

Many complexities associated with the disease result in cases going unreported or taking years to be correctly diagnosed. Symptoms may resemble other disorders leading to inappropriate treatment and medication which could cause side-effects. Compounding these problems are laboratory testing procedures which are not entirely accurate.

Controlling infected ticks is difficult, it is not feasible to simply spray pesticides over acres of nature reserves nor is it feasible to eradicate animal reservoirs. Increased leisure time and social activities put people at an increasingly greater risk and one cannot restrict a person's freedom.

Most bitten do not feel the bite or see the tick and unless informed about early signs bacterial dissemination may be allowed to occur, making later treatment difficult. Inside the host, evasion of the immune system, delayed antibody response, penetration of immuno privileged areas and dormancy, all work in favour of the bacterium. Slow division ensures a long course of antibiotics, but relapses may still occur, and problems with the last vaccine may limit uptake of new offerings.

However most problematic is suffering to the host and a degenerating quality of life. Some are infected young when most active and least aware of dangers; if misdiagnosed, they suffer during the most important years of their life.

To beat the disease people most at risk must be informed about early warning signs as removal of a tick even up to one day after attachment means almost no risk of

infection. Equally important is to educate the medical profession that absence of proof is not proof of absence.

SUMMARY –

FEATURE	COMMENT
CAUSATIVE AGENTS	B. burgdorferi / Borrelia garinii / Borrelia afzelli
MICROBIOLOGY	7/11 periplasmic flagella, Osp A-F, 950kb linear chromosome, 9 circular, 12 linear plasmids, 12-24 hour division
VECTOR	Ixodes tick
ANIMAL RESERVOIR	Small rodents / Large mammals
TICK LIFE CYCLE	Larvae – Nymph – Adult
LYME STAGES	Stage 1 – early infection Stage 2 – Dissemination Stage 3 – Persistent
PATHOGENESIS	Blebs, evasion of immune system, antigenic variation, B-cell killing, delayed antibody response
SYMPTOMS	Vary, may last days, months, years

2,670

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