

The background is a dark blue-grey color with faint, light-colored geometric patterns. On the left side, there is a faint compass rose with a needle pointing towards the top-left. The text is centered and has a slight drop shadow.

LYME DISEASE

An elusive diagnosis

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OVERVIEW

- Introduction
- Clinical diagnosis of early Lyme disease
- Clinical diagnosis of chronic Lyme disease
- Laboratory testing in Lyme disease
- Treatment of Lyme disease

Definition

Lyme disease is an infection caused by *Borrelia* species of spirochaetes carried by ticks of the *Ixodes* genus.

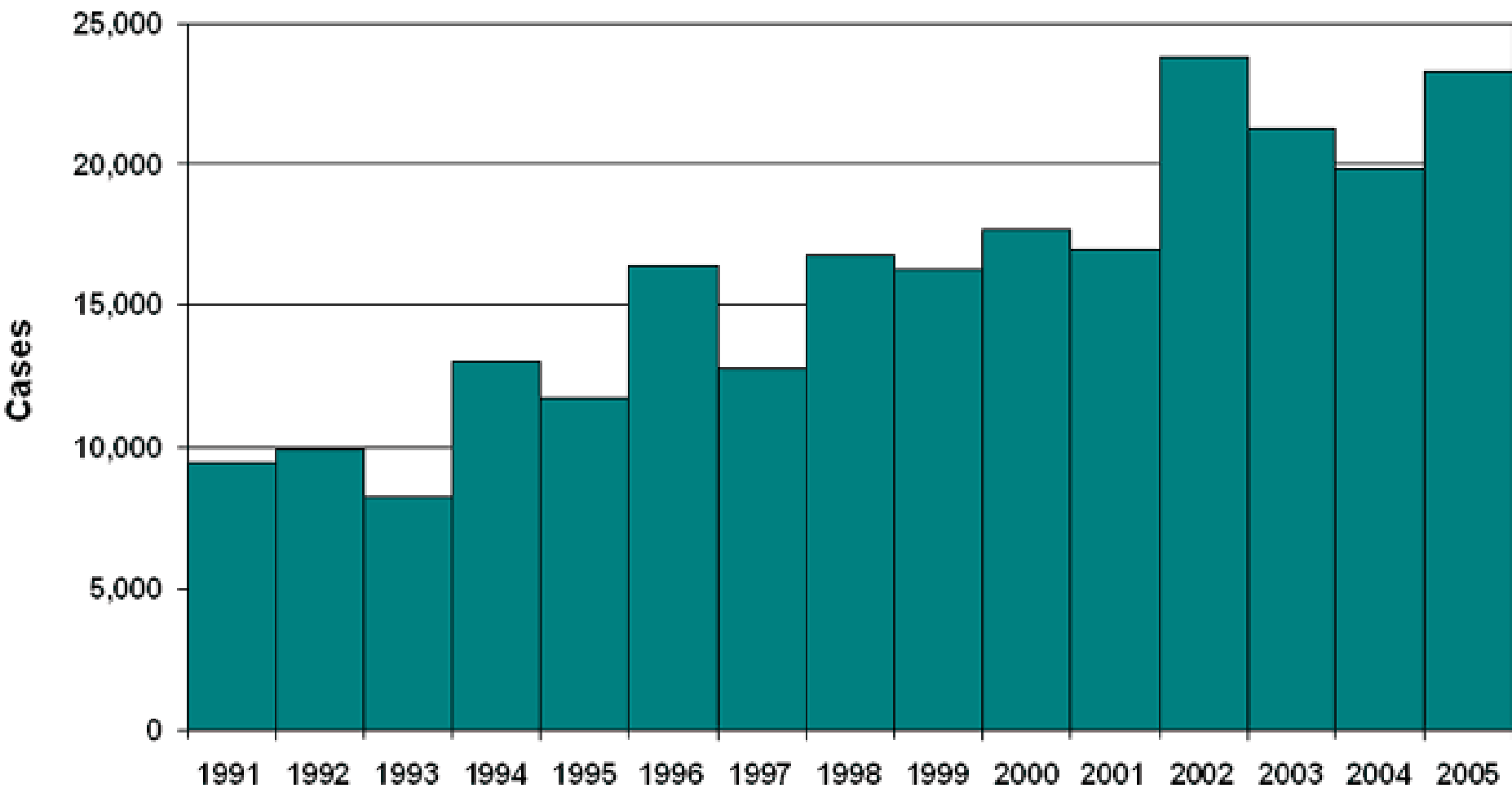
Other definitions of LD

e.g. Burrascano 2007

Lyme disease defined in terms of illness following the bite of an infected tick.

Lyme disease – some terms

- Early LD
- Persistent LD
- Refractory LD
- Recurrent LD
- Sero-negative LD
- Latent Lyme disease
- Neuroborreliosis
- Chronic LD
- Early disseminated LD
- Late Lyme disease
- Neurologic LD
- Lyme arthritis
- Post Lyme syndrome
- Lyme neurosis



Cases in USA 1991-2005 Source: CDC

Number of cases of Lyme disease in England & Wales each year

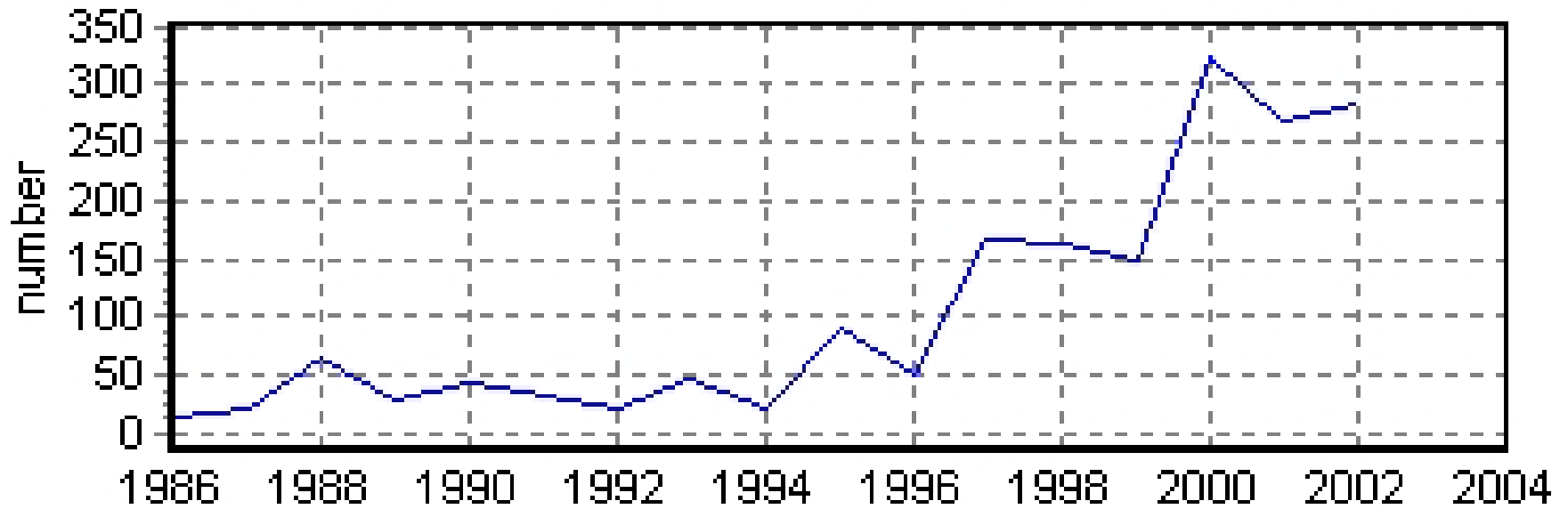
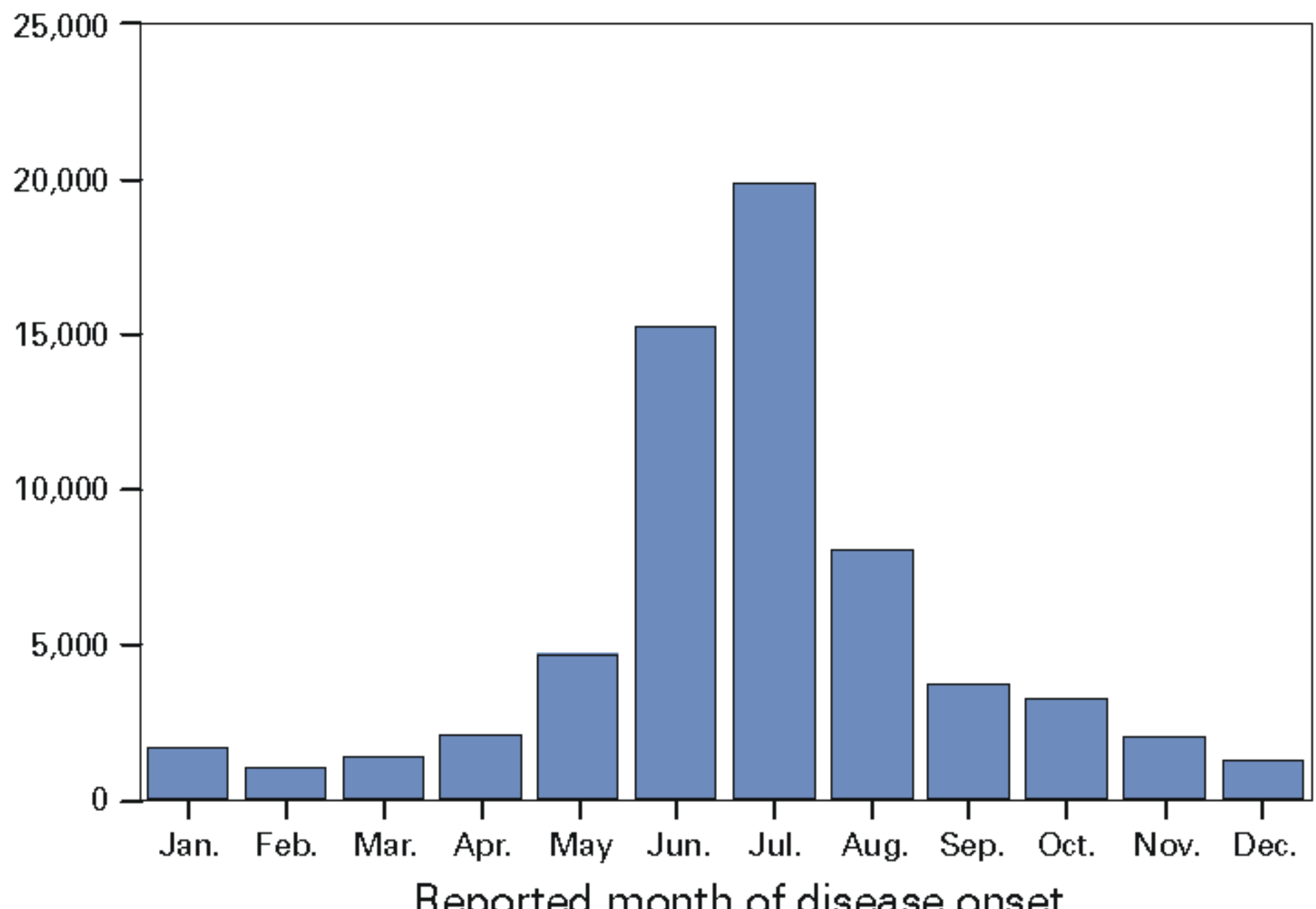
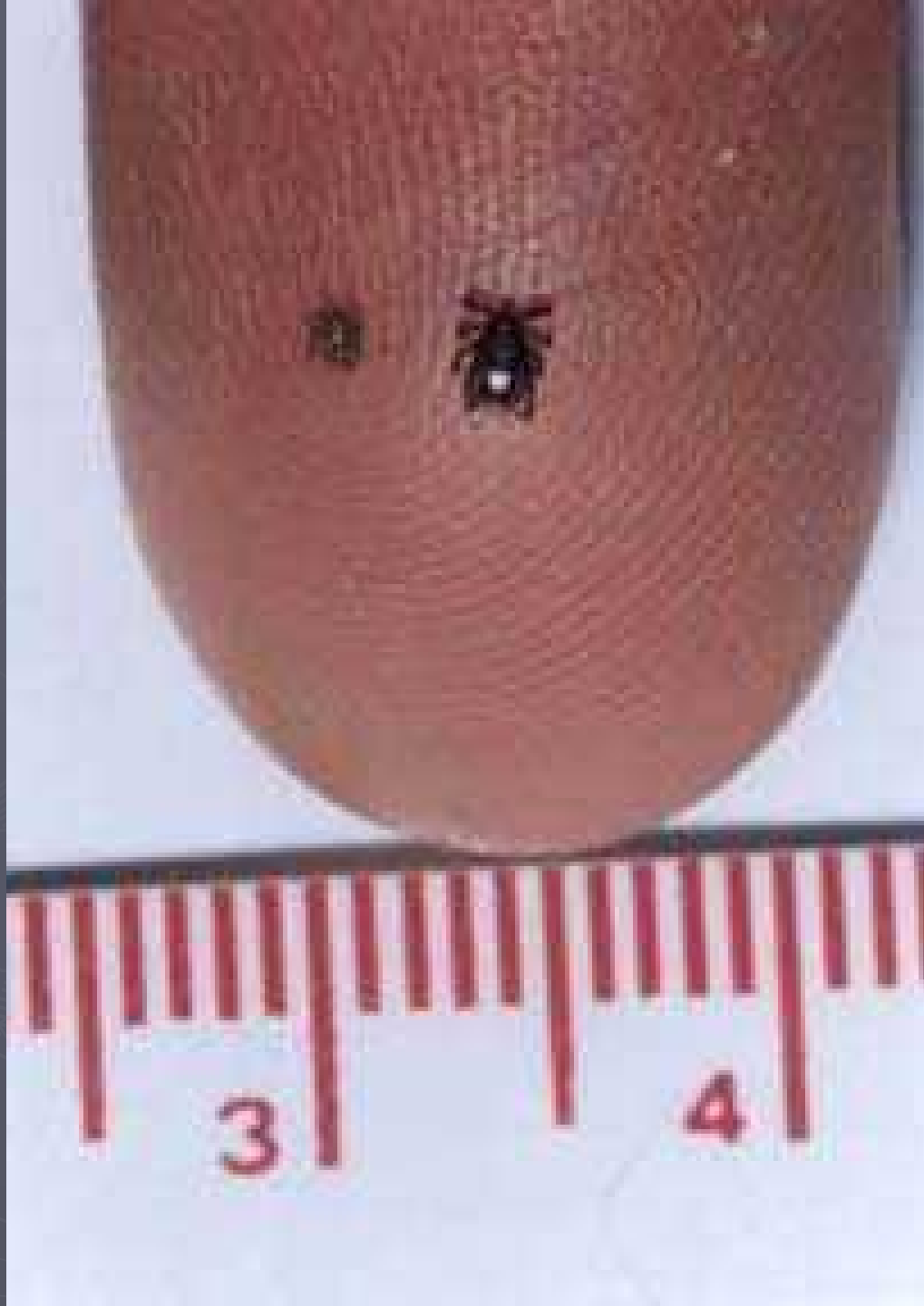


FIGURE 4. Month of Lyme disease onset for reported cases — United States, 1992–1998







TICK BITE

≠

DOOM AND GLOOM !

The bacterium

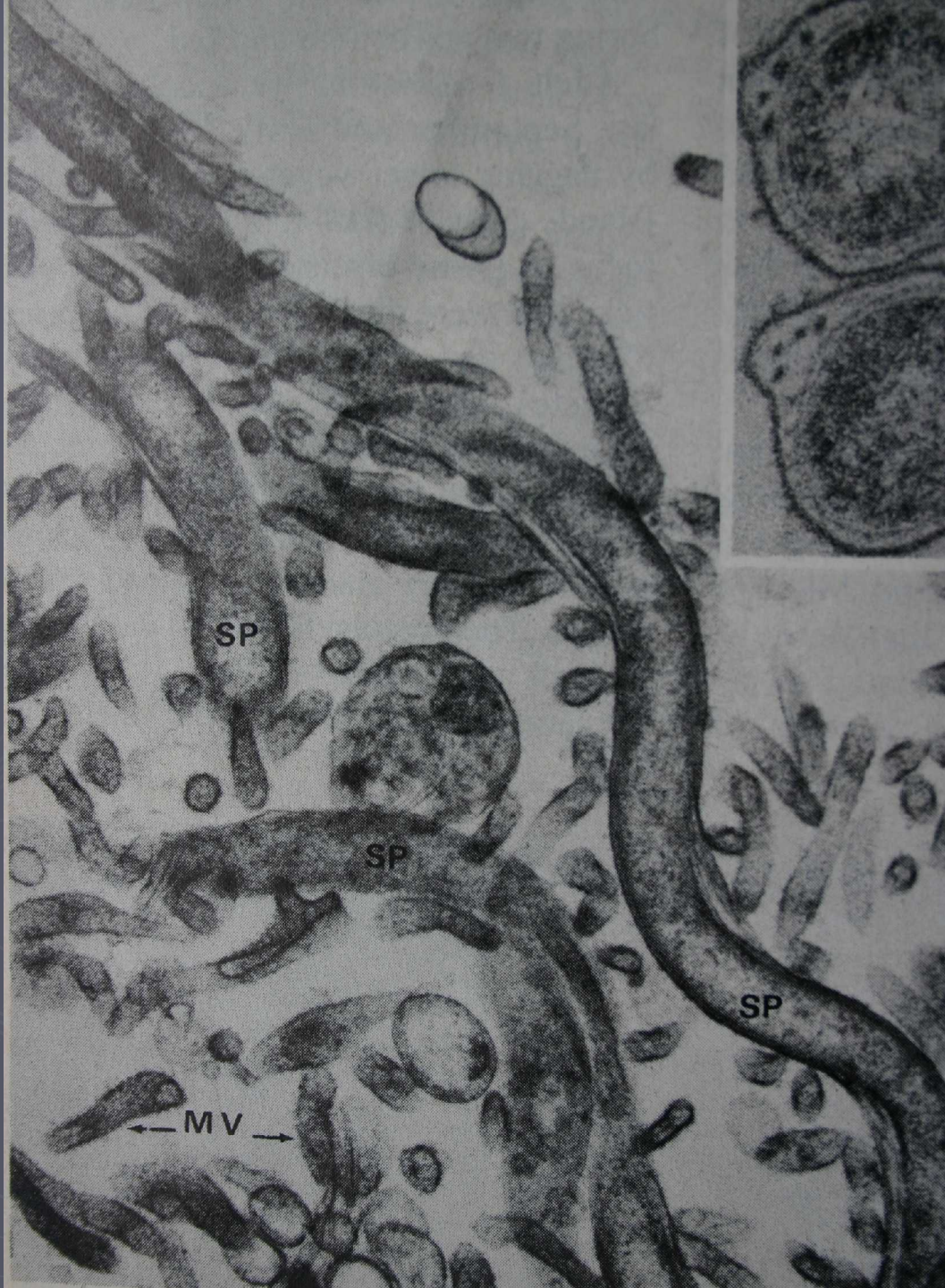
Mainly *B burgdorferi*, *B garinii* and *B afzelii* but numerous other species

Borrelia burgdorferi strain B31 (culture MI) has been fully sequenced. High genetic variability.

910 kbp linear chromosome.

12 linear and 9 circular plasmids total 610 kbp.

More than 3x no. of plasmids of any other bacterium.



Clinical diagnosis of early Lyme disease

Early Lyme disease

Erythema migrans and/or flu-like symptoms occurring within one month of a tick bite.

Source: IDSA Guidelines 2006 (Not explicit)

Typical Erythema Migrans

- Large (> 5cm)
- Slightly raised erythematous border
- Slightly warm border
- Central clearing
- Not itchy
- Persist
- Antibiotic responsive
- May slowly expand





REMEMBER ATYPICAL ERYTHEMA MIGRANS

Tibbles CD and Edlow JA JAMA

2007 297 p 2617-2627

Title: Does this patient have Erythema
Migrans ?

Conclusion:

“Our analysis of the current available literature suggests there is no single element in the history or physical examination that is highly suggestive by itself for the diagnosis of EM. Clinicians should be aware of the wide variability in the clinical presentation of Erythema migrans..”

IF IN DOUBT – TREAT as EM !

Consider serological testing 4-6 weeks
after tick bite.

Clinical diagnosis of chronic Lyme disease



Chronic Lyme disease

Suggested definition:

A state of persistent *Borrelia* infection lasting more than one month associated with incapacitating symptoms.

Does persistent infection occur?

There are numerous human and animal studies which show that persistent infection does occur.

Persistent infection can occur despite intensive anti-bacterial therapy.

What are the symptoms of chronic Lyme disease?

Non-specific and highly variable –

One reason the diagnosis can be elusive

9. Symptoms of Lyme disease

- Fatigue
- Low grade fevers, 'hot flashes' or chills
- Night sweats
- Sore throat
- Swollen glands
- Stiff neck
- Migrating arthralgias, stiffness and, less commonly, frank arthritis
- Myalgia
- Chest pain and palpitations
- Abdominal pain, nausea
- Diarrhea
- Sleep disturbance
- Poor concentration and memory loss
- Irritability and mood swings
- Depression
- Back pain
- Blurred vision and eye pain
- Jaw pain
- Testicular/pelvic pain
- Tinnitus
- Vertigo
- Cranial nerve disturbance (facial numbness, pain, tingling, palsy or optic neuritis)
- Headaches
- 'Lightheadedness'
- Dizziness

- **Autonomic / systemic**

Eg. Sweats, palpitations, chills, bladder disturbance

- **Arthritic**

Fleeting arthralgias, myalgias, enthesopathies, sometimes frank arthritis

- **Neurologic**

Eg. Parasthesiae, dysaesthesiae, muscle twitching

- **Dermatologic**

EM, ACA, Lymphocytoma, other rashes

- **Encephalopathic**

Eg. Cognitive dysfunction, sleep disturbance, air hunger

- **Other systems**

Eg. Respiratory, cardiac, endocrine

The fatigue of Lyme disease

Fatigue - OED: Extreme tiredness resulting from mental or physical exertion or illness.

May be profound; prostration

Typically recurrent / relapsing

Incapacitating

Worse following activity

Clues to the clinical diagnosis of chronic Lyme disease

Tick bite history:

Number of bites

History of high risk bite(s)

EM or illness following bite(s)

Other clues pointing to a diagnosis of Lyme disease

History of tick exposure if not bites

Illness with multi-system involvement

Relapsing symptoms

Numerous normal tests

Prominent systemic features

Exercise intolerance

Chemical / alcohol intolerance

Response to treatment

Conditions which may be confused with Lyme

Chronic fatigue syndrome

ME

Fibromyalgia

Viral Illness

Various psychiatric disorders

Dual diagnosis

The presence of one condition does not preclude the presence of another !

Dual diagnosis refers to the presence of Borreliosis when criteria are already met for another diagnosis.

Conditions in which Lyme has been found

Numerous !

Eg. Neurological eg. MS, MND, Alzheimer's disease

Laboratory testing in Lyme disease

Testing is necessary to prove a diagnosis of Lyme disease.

Testing cannot be used to refute a diagnosis of Lyme disease.

Treatment should not be withheld on the basis of negative tests where there is clinical suspicion of Lyme disease.

Laboratory testing in Lyme disease

Many tests have been developed for Lyme disease and many have, possibly unfairly, been rejected.

The system of testing advocated by the IDSA will miss many cases of Lyme disease.

Tests which have broad acceptance

Borrelia Western blot testing.

Borrelia PCRs.

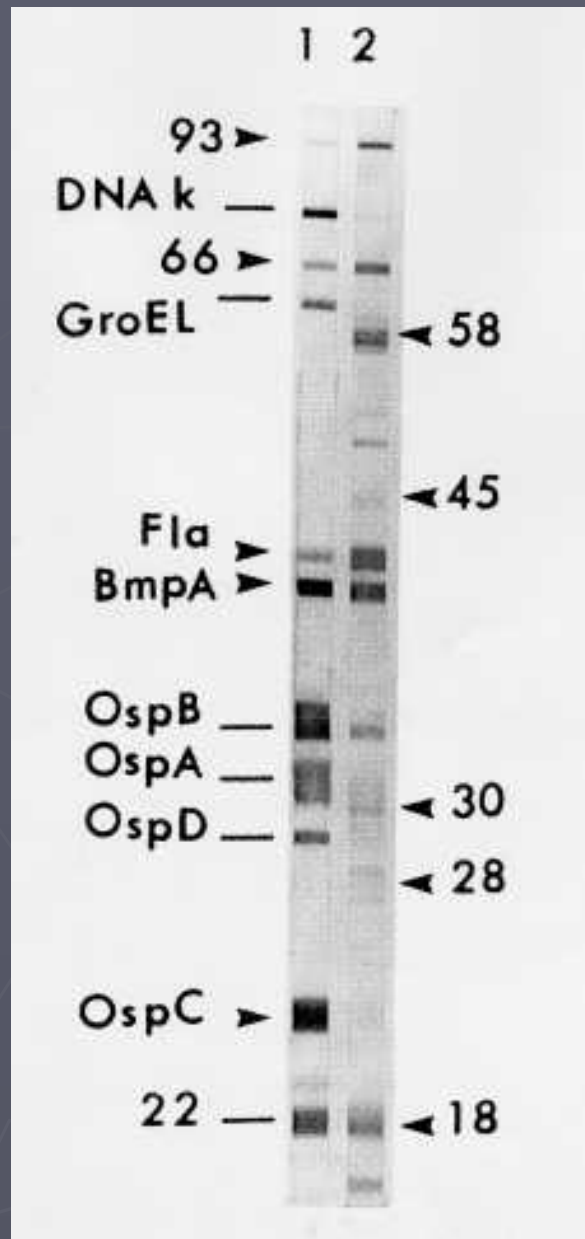
Borrelia Western blot v PCR

Western blot

Indirect test –
Cannot be used to infer
disease activity.
High specificity.
Moderate sensitivity.

PCR

Direct test –
Infer active infection.
Very high specificity.
Low sensitivity.



Western blot test. 1- Bb strain B31 2 calibration strip.

EXAMPLE





Band present at an intensity \geq Weak (1+) Positive (

=====

IGENEX-IGG-RESULT

NEGATIVE

CDC/NYS-RESULT

NEGATIVE

18 kDa	-
22 kDa	-
**23-25 kDa	IND
28 kDa	-
30 kDa	-
**31 kDa	+
**34 kDa	-
**39 kDa	-
**41 kDa	IND
45 kDa	-
58 kDa	+
66 kDa	-
73 kDa	-
**83-93 kDa	-

***FOR IND SEE NOTE ABOVE

Continued on next page

THEREFORE, WE RECOMMEND TESTING WITH ANOTHER METHOD A

BAND INTENSITY: Negative (-): No visible band pres
Band present with intensity < Weak (1+) Positive Cont
Band present at an intensity >/= Weak (1+) Positive C

=====

IGENEX IGM RESULT
CDC/NYS RESULT

NEGATIVE
NEGATIVE

18 kDa.	-
22 kDa.	-
**23-25 kDa.	+++
28 kDa.	-
30 kDa.	-
**31 kDa.	-
**34 kDa.	-
**39 kDa.	IND
**41 kDa.	IND
45 kDa.	-
58 kDa.	-
66 kDa.	-
73 kDa.	-
**83-93 kDa.	-

1 year after appearance of rash

****FOR IND SEE NOTE ABOVE

Continued on next

Band present with intensity < Weak (1+) Positive C
Band present at an intensity >/= Weak (1+) Positiv

IGENEX-IGG-RESULT
CDC/NYS-RESULT

POSITIVE
NEGATIVE

18 kDa	-
22 kDa	-
**23-25 kDa	-
28 kDa	-
30 kDa	+
**31 kDa	++
**34 kDa	-
**39 kDa	IND
**41 kDa	+
45 kDa	-
58 kDa	+
66 kDa	-
73 kDa	-
**83-93 kDa	-

****FOR IND SEE NOTE A

Conclusion from this example.

- 3) Negative IgG WB cannot be used to infer Borrelia exposure has not occurred.
- 4) IgeneX criteria may be more sensitive than CDC criteria.

Questions for the Lyme testing lab in Southampton

Why are only IgG blot results reported in many cases ?

Why are the individual bands not reported in the blots ?

Why is clinical advice given ?

In the laboratory's experience how many IgM positives subsequently test positive on the IgG ?

How can one condition, Lyme disease,
cause so many different symptoms ?

Possible Answer

Lyme disease may be more than one condition.

The complexity of tick borne disease

Some Human pathogens found in ticks:

Borrelia

Anaplasma

Babesia

Bartonella

Mycoplasma

Rickettsia

Coxiella

Francisella

HYPOTHESIS

Is Lyme disease always polymicrobial?



ELSEVIER

Is Lyme disease always poly microbial? – The jigsaw hypothesis

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Received 22 March 2006; accepted 30 March 2006

Summary Lyme disease is considered to be caused by *Borrelia* species of bacteria but slowly evidence is accumulating which suggests that Lyme disease is a far more complex condition than Borreliosis alone. This hypothesis suggests that it may be more appropriate to regard Lyme disease as a tick borne disease complex. Over recent years numerous different microbes have been found in ticks which are known to be zoonotic and can coinfect the human host. The hypothesis suggests that multiple coinfections are invariably present in the clinical syndromes associated with Lyme disease and it is suggested that these act synergistically in complex ways. It may be that patterns of coinfection and host factors are the main determinants of the variable clinical features of Lyme disease rather than *Borrelia* types. An analogy with a jigsaw puzzle is presented with pieces representing *Borreliae*, coinfections and host factors. It is suggested that many pieces of the puzzle are missing and our knowledge of how the pieces fit together is rudimentary. It is hoped that the hypothesis will help our understanding of this complex, enigmatic condition.
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Introduction

Lyme disease is a condition associated with spirochete bacteria of the *Borrelia* genus transmitted by ticks of the *Ixodes* species. This association was made in 1982 [1]. An expanding clinical entity of Lyme disease was already recognised [2]. Since its recognition Lyme disease has caused controversy within the medical profession with frequent lack of agreement about diagnosis and treatment. This paper suggests that a possible source of the

confusion has been the preoccupation with *Borrelia* as the cause of Lyme disease. A hypothesis is presented that *Borrelia* alone does not result in the clinical syndromes we associate with Lyme disease.

The prevalence of Lyme disease in the USA is reported to be increasing [3]. This may partly reflect a true increase in incidence but is also likely to reflect increasing recognition of the disease. The CDC recognises that the reported cases of Lyme disease underestimate the true prevalence of Lyme disease. The true prevalence remains unknown [3].

The CDC criteria for reporting Lyme disease includes two tier serological testing [3] but it is accepted that this may not be appropriate for diagnosis in a clinical setting [3]. Both false posi-

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LYME DISEASE

UNDERDIAGNOSIS
OR
OVERDIAGNOSIS ?

The debate goes on but a condition which causes non specific and variable symptoms and lacks a sensitive diagnostic test would be expected to be under-diagnosed.

Treatment of Lyme disease



—

Is there a **WONDERDRUG** ?





WONDERDRUG

CLICK TO ENTER



Treatment of Lyme disease

Explanation

Discuss supporting evidence

Discuss uncertainties

Treatment of Lyme disease

Optimum treatment of Lyme disease not known at any stage of the illness.

Few case controlled studies for guidance.

Seems to be the case that early treatment is more likely to be successful.

Treatment of early Lyme disease

IDSA guidelines 2006:

Doxycycline, Amoxicillin or Cefuroxime
for 2-3 weeks.

Suggestions: Treat until EM is gone !

Consider higher doses than
IDSA recommends.

Treatment of chronic Lyme disease

Avoid:

Steroids

Stimulants

Depressants

“Stress”

Try:

Graded exercise as in CFS

Consider:

Analgesia

Psychoactive medication

Treatment of chronic Lyme disease

Antimicrobial therapy:

Borrelia very sensitive to many antibacterial agents *in vitro*.

Doxycycline is used most commonly for monotherapy.

Dosage should be high.

Treatment may need to be prolonged.

Justification for long term antibacterial treatment in chronic Lyme disease

Case studies

Animal models

Long doubling time of *Borrelia*

Cystic forms

Analogy with other bacterial infections

Delayed diagnosis

Anecdotal evidence

Clinical trial evidence

Few randomised controlled studies

Klempner et al NEJM 2001 **345** p 85-92.

78 sero-positive and 51 sero-negative patients

Compared 90 day antibiotic treatment in “chronic Lyme disease” (all previously treated).

Conclusion:

No significant difference in outcome in the two groups.

“We did not find evidence of persistent infection with *B. burgdorferi* in these patients”

Fallon et al 2007 Neurology 70
p992-1003

“Randomized placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy.”

37 Chronic Lyme disease patients who had already received at least three weeks IV Ceftriaxone at least four months before the study.

20 Healthy controls.

Neuro-cognitive testing used – not reliant on reported symptoms.

Conclusion of the Fallon study:

IV Ceftriaxone therapy results in short-term cognitive improvement for patients with post treatment Lyme encephalopathy but relapse in cognition occurs after the antibiotic is discontinued.

Also significant improvement in self-reported measures of fatigue pain and physical functioning were found.

Both the Klempner and Fallon studies involved patients already treated for Lyme disease.

Many patients in the UK have clinical evidence of chronic Lyme disease but are offered NO treatment.

WHY NOT ?

Monitoring response to therapy

There is currently no easy way of monitoring therapy in the treatment of chronic Lyme disease-
There is no biomarker.

Unhelpful: Serology
 PCR (Unless chance positive)
 Inflammatory markers

Symptom monitoring is the only practical way of monitoring therapy.

Treatment of Lyme disease- Involvement of the patient

GMC booklet 2008:

“Consent: patients and doctors making decisions together”

Part 2 section 7:

“You should tailor your approach to discussions with patients according to their needs, wishes and priorities.”

When should treatment be stopped?

Consider:

(1) If improvement is not occurring treatment should be discontinued. Problem: How much time to allow ?

(2) If improvement is occurring consider rate of improvement.

(3) If relapses are occurring treat until they have ceased.

(4) Consider late relapses, re-infection, co-infection.

Conclusion

Lyme disease is a diagnosis which can easily be overlooked and can be difficult to confirm. Treatment decisions need to be made on a clinical basis with an emphasis on symptoms since physical signs may be absent.

The future

Patient education

Healthcare worker education

Clinical Research

Scientific research

View of the UK government

The Department of Health does not consider that further research is needed at this time as much is already known about the diagnosis, treatment and mode of transmission of Lyme disease and other tick borne diseases.

Department of Health 2008