Fortnightly review

Lyme disease in the United Kingdom

Susan O'Connell

Lyme disease is caused by a tickborne spirochaete, *Borrelia burgdorferi*. Infection may be asymptomatic, may cause only erythema migrans (the classic rash around the site of a tick bite), or may cause disseminated disease that can affect many organs and tissues. The term was first used after a cluster of arthritis, associated in some cases with tick bite and rash, occurred in people living around Old Lyme, Connecticut, in the mid-1970s.[1] Subsequent investigations have shown a broad range of clinical presentations associated with the infection.[2] Although the condition has received widespread professional and public recognition only in recent years, descriptions of various skin and nervous system manifestations have appeared in European medical journals for over 100 years under a variety of terms, including erythema migrans, acrodermatitis chronica atrophicans, and Bannwarth's syndrome.[3-6] A tickborne infection was suspected in many of these conditions, and penicillin was used empirically nearly 50 years ago. This article focuses on practical aspects of the diagnosis, management, and prevention of Lyme borreliosis from a British perspective.

Summary points

- Routine prophylactic antibiotic treatment of tick bites is not recommended—most ticks are unlikely to be infected with *Borrelia burgdorferi*, a bite from an infected tick may not cause human infection, and many human infections do not cause serious illness
- A negative history of tick bite does not exclude infection—establish whether there has been possible exposure to ticks and ask about risk associated with residence, work, recreational activities, pets, and holidays
- Erythema migrans is the most common clinical presentation of Lyme borreliosis, and neurological presentations are probably the most common complications in Britain (chronic Lyme arthritis is uncommon in Europe but may be a major feature of infection contracted in North America)
- Lyme borreliosis responds well to adequate treatment with antibiotics, but full recovery may be slow with longstanding infections
- Negative antibody tests are rare in late stage Lyme disease, and alternative diagnoses must be rigorously investigated

Ecological, environmental, and epidemiological aspects

B burgdorferi can be transmitted during the blood meal of an infected hard bodied (ixodid) tick. Ixodid ticks have a worldwide distribution, principally in woodland, pasture, and heath. The main species are *Ixodes ricinus* in Europe and the *I scapularis* group in North America.[7,8] Ticks have a three stage life cycle—larva, nymph, and adult—that lasts two to three years and feed once only during each stage. Their host range is wide, but small mammals such as field mice and voles seem to be commonly parasitised by larvae and nymphs whereas adult ticks tend to feed on larger animals such as sheep, deer, and horses.

The borrelial reservoir is maintained by infected nymphs introducing the spirochaete to uninfected hosts. Large animals play an important role in maintaining tick numbers but are probably not an important reservoir for *B burgdorferi* since they tend to be final hosts in the tick's life cycle. Humans can be an incidental host for the tick at any stage but are least likely to acquire borrelial infection during the first feed, as larvae are unlikely to be infected. Nymphs provide the main transmission risk for humans because they remain very small, even after a feed, and may not be noticed by their host. An adult tick that has taken a blood meal resembles a coffee bean and is therefore likely to be seen and removed (figs 1 and 2).

Ixodid ticks are found in many parts of Britain. Their activity is seasonal, with peak periods in late spring, early summer, and autumn. They become inactive at temperatures less than about 5°C and cannot tolerate desiccation; hence the tick population will crash after a prolonged drought. The risk of human infection mirrors tick activity, with peak periods in early summer and autumn.[7] A low level of tick activity can persist throughout the winter months in areas with a mild climate, such as the New Forest. Variations in tick population density also contribute to yearly variation in the incidence of human infection. Methods of controlling tick populations have been studied, but results so far suggest that they are unlikely to make a substantial impact on the incidence of infection in Britain.[9]

INCIDENCE OF LYME DISEASE

Assessing risk of infection from an individual tick bite is almost impossible. Rates of *B burgdorferi* infection in ticks can vary widely, even in neighbouring areas,[10] and the bite from an infected tick may not result in infection. Risk of transmission tends to be higher if an infected tick has been attached for more than 24 hours, as borrelial activity inside the tick may have been stimulated by the blood meal. The tick may

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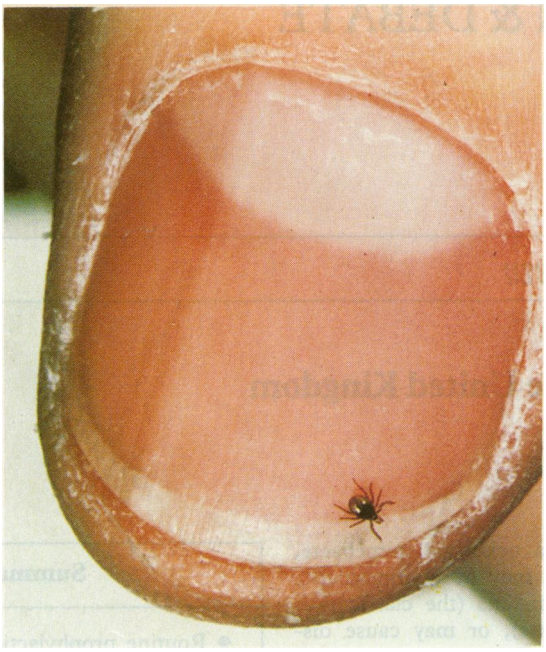

FIG 1—*Adult tick (courtesy of Dr E C Guy)*

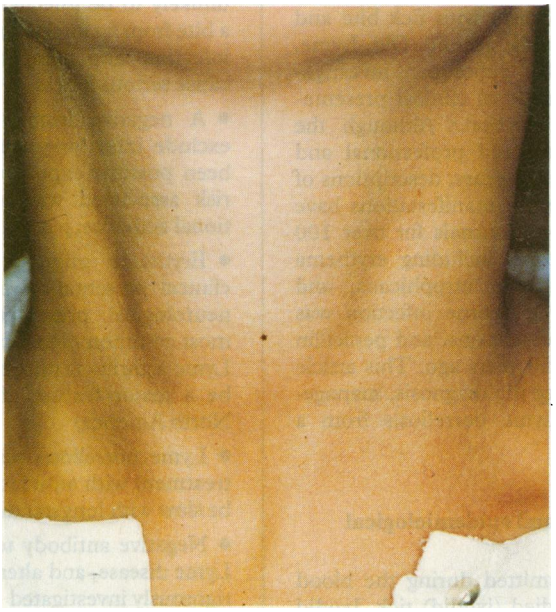

FIG 2—*Tick on neck of forestry worker (courtesy of Dr E C Guy)*

also regurgitate some gut contents containing borreliae into the site of the bite as it completes its feed, usually after 48-96 hours.

The incidence of Lyme borreliosis in Britain is not well documented, but studies of prevalence and clinical experience suggest that serious disease is uncommon. In 1993 44 infections were voluntarily reported by laboratories in England and Wales and four cases were notified by Scottish laboratories. Several studies of seroprevalence have been performed in the New Forest, Hampshire, where the disease is endemic. Forestry workers with a mean work experience of 24 years had a seroprevalence of 25%. None was symptomatic at the time of the survey, and only two recalled a spreading rash or other clinical finding compatible with a diagnosis of Lyme disease, suggesting that asymptomatic infection was common in a population with a high exposure risk.[11] Healthy blood donors resident in villages in the New Forest had an overall seroprevalence of 4%, whereas a survey of blood donors living in cities found no seropositive subjects.[12]

More recently, a case search was undertaken in the New Forest and surrounding districts. This area forms part of the catchment of Southampton General Hospital, a teaching hospital with neurological and cardiac regional units, and local general practitioners and many of the residents are aware of the condition. Only 37 cases were identified in 1992 from a population of about 200 000 that was potentially at risk. The main presenting features were uncomplicated erythema migrans (21 cases), erythema migrans with facial palsy (2), isolated facial palsy without recognised erythema migrans (6), erythema migrans with arthralgia (3), arthralgia without recognised erythema migrans (2), meningitis with cranial nerve palsies (2), and radiculopathy (1). No cases of carditis, chronic arthritis, or chronic neurological problems were found. Two infections were probably acquired abroad, one in France and the other in Connecticut.

Infections have also been acquired in many other parts of Britain, including rural areas throughout the south and west of England, Thetford Forest, Yorkshire, Lancashire, Cumbria, and the Scottish highlands. British residents have also acquired Lyme disease while visiting other parts of the world, especially northern Europe and North America.

Borrelia burgdorferi

B burgdorferi was first isolated in 1982 from ticks in the United States and later from skin biopsies and other clincial material.[13] It is a slow growing spirochaete, fastidious in its nutritional requirements, and is usually cultured in Barbour-Stoenner-Kelly medium. Analyses of isolates from ticks and patients from different parts of the world have found variations. *B burgdorferi sensu lato* is currently subdivided into three genospecies that have been associated with disease and a fourth (*B japonica*, a Japanese tick isolate) that at present does not appear to be pathogenic. North American isolates are almost exclusively *B burgdorferi sensu stricto*. This genospecies is also found in Europe, but two other genospecies, *B afzelii* and *B garinii*, are also often isolated from European specimens.[14]

There seems to be a good correlation between the type of clinical presentation and genospecies of isolate. *B afzelii* predominates in patients whose manifestations are mainly dermatological (early or late) whereas *B garinii* is more strongly associated with neurological complications, suggesting differing organotropic and pathogenic potentials.[15] These findings also support

Measures to reduce risk of infection when visiting areas where ticks are found

Prevention of tick bite

- Keep skin covered
- Use an insect repellent; pets should wear tick collars
- Examine clothes and exposed skin for ticks every 3-4 hours, and again when returning home (remember that larvae and nymphs are small and easily missed)

Removing a tick

- If possible cover attached tick with petroleum jelly, suntan cream, or other oily substance to suffocate it and make it easier to remove
- Aromatic oils may be useful, as they seem to have repellent effect on attached ticks
- Lighted cigarettes or glowing match heads should not be used
- Gently remove attached tick by grasping it as close to the mouth parts as possible and gently lifting with a twisting motion—try to avoid squeezing gut contents into site of bite
- Ensure that tick has been completely removed, and apply skin disinfectant to help prevent bacterial skin infection (staphylococcal or streptococcal infections can occur, especially if mouth parts are left in situ)

earlier clinical and epidemiological observations which suggested that the clinical spectrum of European Lyme borreliosis is more diverse than that seen in North America, where arthritis is often a striking feature of early disease and chronic arthritis is the most common late manifestation.

The spirochaete can invade the endothelium and adhere to many cell types. Live bacteria can exert a direct toxic effect on cells, and inflammatory mediators induced by the spirochaete can also contribute to tissue damage.[14] Autoimmune mechanisms and molecular mimicry may also play a part in pathogenesis: Lyme arthritis is more commonly seen in patients with certain HLA phenotypes, notably HLA-DR4 and HLA-DR2,[16] and antibody to the flagellin protein of *B burgdorferi* has been shown to bind to human nerve axons and neuroblastoma cell lines.[17 18]

Live organisms have been isolated from patients with untreated Lyme disease years after initial infection despite a good humoral immune response.[19] Antibodies are produced to new spirochaetal antigens late in the infection, suggesting exposure to new antigens over time. Modification or down regulation of surface antigens may contribute to the organism's ability to evade the immune system, and its ability to invade relatively sequestered sites such as connective tissue, synovium, and the central nervous system may also protect against humoral and cellular response.

Clinical features of Lyme disease

Clinical presentations are rather artificially divided into three stages,[2 20] but progression from an early to later stage is not inevitable, even in the absence of antibiotic treatment. Also, patients may occasionally present with symptoms and signs of later disease without recalling any earlier features.[14]

EARLY LOCALISED LYME BORRELIOSIS

The early, and in most cases only, clinical feature of Lyme disease is the classic erythema migrans rash.[21] This is an area of erythema migrating out from the site of a tick bite, which may have occurred from about two to 40 days previously (fig 3). The rash can be very faint and easily missed but may become more apparent after a bath or heavy exercise. As the leading edge of the rash advances, the previously affected skin gradually returns to normal. There may be accompanying findings such as pyrexia and local lymphadenopathy, but more severe symptoms or signs suggest some secondary spread. Erythema migrans lesions can cover a large area, with diameters of over 70 cm being reported. Spirochaetes may be cultured or their DNA detected in skin biopsies, especially of the leading edge. Antibody tests are likely to be negative for several weeks after onset, but the diagnosis can be confidently made on clinical grounds if there is a history of possible exposure to ticks. Erythema migrans will clear spontaneously, but antibiotic treatment is strongly recommended as it can shorten the process and should prevent possible progression to a later stage. Cellulitis, especially associated with an insect bite, may be confused with erythema migrans. Other differential diagnoses include erythema annulare, annular tinea infections, fixed drug eruptions, and reactions to insect bite.[21]

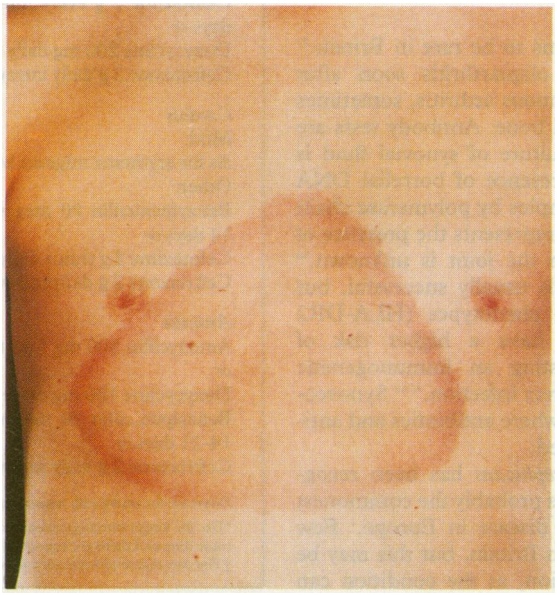

FIG 3—*Erythema migrans (courtesy of Dr J E White)*

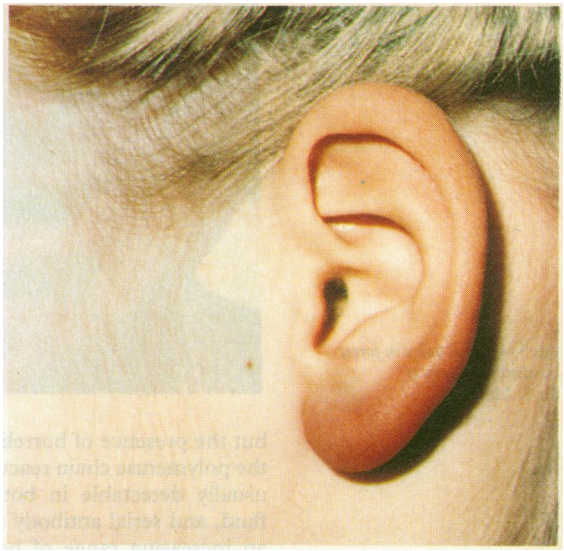

FIG 4—*Borrelial lymphocytoma*

A rare presentation of early localised infection is borrelial lymphocytoma, a bluish-red nodule or plaque which may last for a few months to over a year if left untreated.[21] It is more often seen in children (usually on an earlobe (fig 4)) than in adults, where it is more commonly seen on a nipple. As this presentation tends to occur rather later than erythema migrans, antibody tests are likely to be positive.

EARLY DISSEMINATED LYME BORRELIOSIS

The second clinical stage of Lyme disease occurs some weeks to months after initial infection and results from the spirochaete spreading to more distant sites via the bloodstream and lymph system. Many organs and tissues are potential targets, especially the skin, nervous system, heart, and joints. Clinical features depend on the affected system and the severity of damage. Patients may complain of a flu-like illness, with sweats and myalgia accompanying or preceding other findings.

Skin manifestations—Multiple areas of erythema migrans may appear some weeks after exposure and usually follow a solitary erythema migrans. The individual lesions tend to be smaller than a single erythema migrans, but the patient usually has considerably more accompanying systemic upset.[21]

Cental nervous system—Isolated facial palsy (fig 5) may present soon after erythema migrans, but a preceding rash may not have occurred or may have been missed. It may be bilateral and last for some weeks but should gradually resolve completely. Other neurological presentations include facial and other cranial nerve palsies, often accompanied by some meningitic symptoms.[18] Examination of the cerebrospinal fluid usually shows lymphocytosis, normal glucose concentration, and mildly elevated protein concentration. Borrelial culture has a very low yield,

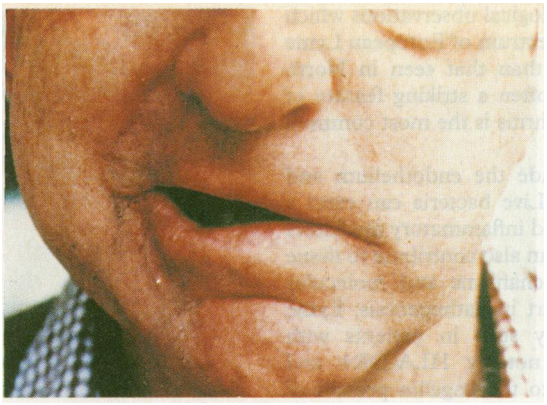

FIG 5—*Facial palsy in forest resident (courtesy of Dr D Markby)*

but the presence of borrelial DNA may be detected by the polymerase chain reaction. An antibody response is usually detectable in both serum and cerebrospinal fluid, and serial antibody tests will show a response to an increasing range of borrelial antigens. Meningitis may also be accompanied by a mild encephalitis, presenting as difficulties in concentrating and persistent fatigue, with mild generalised slowing on electroencephalography.

Peripheral nervous system may also be affected. Peripheral neuritis may resemble a mononeuritis multiplex if several nerve roots are affected. Sensory radiculitis presents with burning pain and paraesthesia in the area supplied by the affected spinal nerve roots. Some patients have described the condition as feeling like a bad sunburn. There may be a mixed sensorimotor radiculitis.[18] These changes tend to appear later than the central nervous system manifestations, up to a year or more after initial infection.

Musculoskeletal system—Myalgia and arthralgia, especially of the small joints, are often experienced by patients who have early disseminated infection. Frank arthritis is unusual; it first presents as intermittent inflammatory arthritis of one or more large joints, usually the knee. A few patients will progress to chronic arthritis.[18] This feature of Lyme borreliosis is more often seen in North America than in Europe.

Heart—Carditis is an unusual feature of Lyme disease in Britain.[22] Conduction disturbances, mainly varying degrees of heart block, are usually short lived, but temporary pacing may be required. Cardiomyopathy is rare, but several European studies have shown borreliae in myocardial biopsies from affected patients.

Other presentations—Hepatitis, myositis, orchitis, anterior and posterior uveitis, and panophthalmitis have all been reported in patients with Lyme disease.[2 18]

LATE LYME BORRELIOSIS

Chronic Lyme arthritis seems to be rare in Britain.[23] Patients with intermittent oligoarthritis soon after infection may develop continuous arthritis, sometimes with erosion of cartilage and bone. Antibody tests are usually strongly positive. Culture of synovial fluid is rarely successful, but the presence of borrelial DNA has been shown in some samples by polymerase chain reaction. Whether the DNA represents the presence of living or dead organisms in the joint is unknown.[18] Treatment with antibiotics is usually successful, but patients with certain HLA phenotypes (HLA-DR2 and HLA-DR4) seem to have a higher risk of continuing arthritis, suggesting an immunogenetic mechanism in addition to direct infection.[16 18] Synovectomy may be useful in cases where antibiotics and anti-inflammatory drugs have failed.

Acrodermatitis chronica atrophicans has been recognised for over 100 years and is probably the commonest late manifestation of Lyme disease in Europe.[1] Few cases have been diagnosed in Britain, but this may be partly due to underrecognition, as the condition can resemble circulatory insufficiency. It occurs most commonly in elderly, usually female, patients and the most common site is the lower leg (fig 6). Initially, there is bluish-red discoloration of the skin, with subsequent gradual development of epidermal atrophy (fig 7). There is often an accompanying myalgia and mild to moderate sensory neuropathy.[21] Borrelial culture of skin biopsies from untreated patients has occasionally been successful, indicating continuing active infection years after acquisition.[19] Antibiotic treatment should give a good result in the earlier stages of the condition, but the late atrophic damage is irreversible.

Chronic neurological syndromes—Lyme encephalopathy is rare; it presents primarily as impairment of memory, depression, spastic paraparesis, or sensory polyneuropathy and probably results from direct infection of the nervous system. Abnormalities are usually seen with examination of cerebrospinal fluid, magnetic resonance imaging of the brain, and electromyography. Symptoms gradually improve after treatment with intravenous antibiotics. It is important to distinguish this rare manifestation of chronic Lyme infection from chronic fatigue syndrome, as the latter will not respond to antibiotic treatment.[24]

LYME DISEASE IN PREGNANCY

A few cases of maternal-fetal transmission of *B burgdorferi* that resulted in stillbirth or neonatal death have been reported, usually in women who had

Recommendations for antibiotic treatment

Erythema migrans

Amoxycillin 500 mg thrice daily orally for 10-21 days*
or
Doxycycline 100 mg twice daily orally for 10-21 days*
or (if these antibiotics are contraindicated)
Oral cephalosporin or new macrolide such as azithromycin† (erythromycin is not recommended because it is associated with high rate of treatment failure)

Borrelial lymphocytoma and acrodermatitis chronica atropicans

As for erythema migrans but for 21-30 days

Isolated facial palsy

As for erythema migrans but for 21-30 days
Ensure there are no other manifestations of central nervous system; if in doubt treat as given below

Other manifestations of central nervous system

Benzylpenicillin 20 megaunits daily intravenously for 14 days *or*
Cefotaxime 2 g every four hours intravenously for 14 days *or*
Doxycycline 200 mg daily orally for 21 days
Ceftriaxone 2 g daily intravenously for 14-21 days

Carditis

Mild:
As for erythema migrans but for 21 days
Other:
Benzylpenicillin 20 megaunits daily intravenously for 14 days *or*
Cefotaxime 2 g thrice daily intravenously for 14 days *or*
Ceftriaxone 2 g daily intravenously for 14 days

Arthritis

Amoxycillin 500 mg four times daily orally for 30 days *or*
Doxycycline 100 mg twice daily orally for 30 days *or*
Benzylpenicillin 20 megaunits daily intravenously for 14-21 days *or*
Ceftriaxone 2 g daily intravenously for 14-21 days

Doses are for adults with normal renal and liver function

*Use for longer duration recommended if condition has been present for some time or if there are important systemic symptoms.
†The new macrolides are not currently licensed in Britain for this use.

untreated or inadequately treated infection during pregnancy. Retrospective studies of women who were infected in pregnancy have shown no uniform pattern of congenital anomaly. Until further information is available aggressive antibiotic treatment (benzylpenicillin, amoxycillin, or a cephalosporin) is advised for suspected or documented Lyme disease during pregnancy.[2 18]

Laboratory investigations

Diagnosis of Lyme borreliosis is primarily based on clinical observations and a history of exposure to ticks.[14 18 25] The main laboratory diagnostic method is detection of antibodies. Culture has a low yield and is slow, taking three to four weeks. Its main use is in obtaining clinical isolates which can be investigated to expand knowledge of the microbiology, pathogenesis, clinical spectrum, and epidemiology of the infection. Detection of DNA with the polymerase chain reaction can be extremely valuable, especially in research and in some cases where the presentation is atypical, but it requires meticulous technique to prevent false positive results through contamination. False negative results may be caused by the presence of reaction inhibitors in a clinical specimen.[14 25]

Methods of detecting antibodies include enzyme linked immunosorbent assay (ELISA) and western blotting or immunoblotting. Most ELISA methods require the use of whole cell sonicates as antigen. Unfortunately, cross reactions often occur in the presence of rheumatoid factor, antinuclear antibodies, and infectious mononucleosis and other conditions. Antibodies to other flagellated organisms—including other borreliae, *Treponema pallidum*, oral spirochaetes, and other organisms—may also produce a positive result.[18 25 26] Western blotting permits observation of antibody responses to a range of antigens of *B burgdorferi* and is used mainly as a confirmatory method to assess the specificity of ELISA. It is particularly useful in serodiagnosis or exclusion of later Lyme disease because chronic infection gives a highly characteristic blotting pattern.[25] It may also be useful in some cases of early infection, when the antibody response may be insufficient to produce a reaction with ELISA.[27] However, western blotting requires a high degree of skill and is labour intensive, and it is available in only a few reference centres in Britain.

There is a slow early humoral immune response to *B burgdorferi*, but most patients should have a good IgM response and detectable IgG response by about six weeks after infection.[25] Positive antibody tests are not essential to confirm the diagnosis of Lyme disease in a patient with classic erythema migrans and a history of possible exposure to ticks. Early antibiotic treatment may prevent a full antibody response but, if an adequate course is given, should forestall later complications. Later stages of Lyme disease are rarely seronegative, and this seems to occur primarily in patients who had received inadequate early treatment, preventing a humoral immune response but allowing progression to attenuated later disease.[28]

There is a danger of Lyme disease being overdiagnosed through overreliance on serology, especially if risk of exposure has not been properly evaluated.[25 26] Many of the conditions that can produce false positive results with ELISA can present with symptoms and signs that might suggest Lyme disease. Further tests are necessary, and the results should be interpreted in the light of symptoms and a detailed history of possible exposure. True positive results, consistent with past infection, may also cause confusion when patients are

Considerations with antibiotic treatment

- Jarisch-Herxheimer reactions may occur shortly after start of treatment
- Few controlled trials have fully assessed efficacy of the various treatments—those given here are based on recommendations of major centres[18 30 31] and clinical experience at Southampton General Hospital
- Length of treatment is important because organism is slow in metabolism and replication, offering fewer chances for antibiotic activity if a shorter course is used
- Response to treatment should be assessed on clinical grounds—patients with longstanding neurological complications may recover only slowly
- Some cases of refractory arthritis are associated with certain HLA types, and antibiotics will not be fully effective
- Antibiotic prophylaxis is not routinely recommended after tick bites, but in special circumstances—such as tick bite during pregnancy—a short course of antibiotics could be used[18]

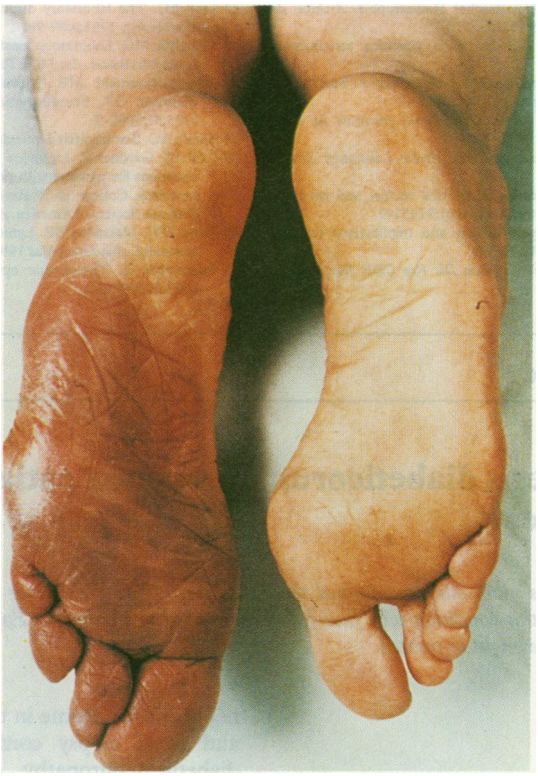

FIG 6—*Acrodermatitis chronica atrophicans of lower limb (courtesy of Dr J E White)*

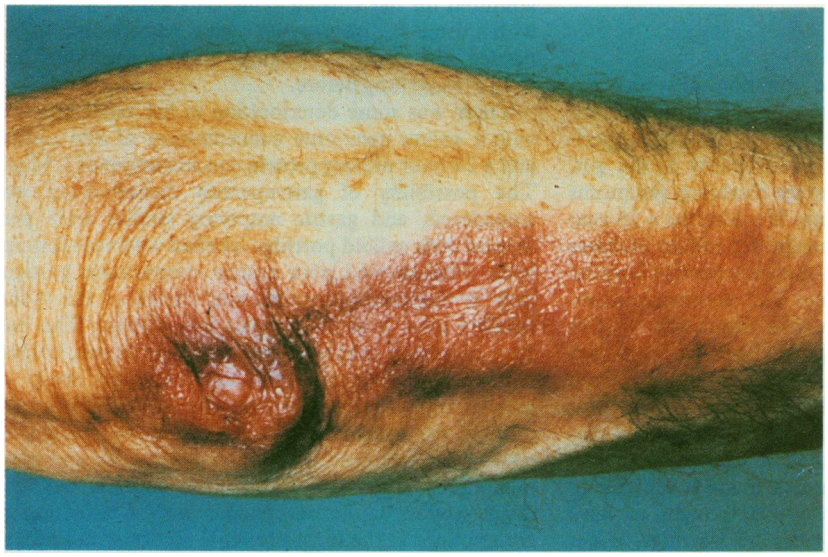

FIG 7—*Skin discoloration from acrodermatitis chronica atrophicans (courtesy of Dr J E White)*

being evaluated for another current illness. This is most likely to occur in patients from areas where *B burgdorferi* is endemic. Misdiagnosis is by far the most common reason for an apparent lack of response to antibiotic treatment.[24] The American College of Rheumatologists and the Council of the Infectious Diseases Society of America have recommended that patients with non-specific symptoms such as chronic fatigue or myalgia without a history of classic features of Lyme disease but with positive serology do not receive parenteral antibiotic treatment: cost effectiveness analysis has shown that treating such patients results in many more cases of antibiotic toxicity and other complications than cures of atypically symptomatic Lyme disease.[29]

I thank Dr E C Guy and Professor P J Watt for their constructive criticism and help in preparing this manuscript.

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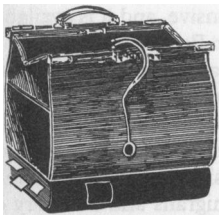
A Difficult Case

Severe gastroparesis diabeticorum in a young patient with insulin dependent diabetes

"Gastroparesis diabeticorum is more often overlooked than diagnosed."[1] C J Dowling and colleagues present a difficult case of a young woman with this condition who had failed to respond to treatment. Four experts not concerned with the case give their views on how she might be treated.



Case report

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Abnormalities in autonomic function affecting the gastrointestinal tract can often be shown by quantitative testing but only a few diabetic patients experience symptomatic autonomic neuropathy of the gut. Occasionally patients have severe disabling symptoms that may be difficult to manage. We describe a 28 year old woman found to have insulin dependent diabetes mellitus in 1979 and who has currently been in hospital for almost a year with severe and resistant gastroparesis. In the years before her admission to this hospital she had been investigated elsewhere for nausea and vomiting and had been labelled as suffering from anorexia nervosa. Subclinical nausea had been present for several years, and the vomitus she produced was seen to contain food that she had consumed a few days earlier. The vomiting and nausea made it difficult to control her diabetes, and she was thought to have "brittle" diabetes because of the wild swings in her glycaemic control. She was diagnosed as having the nephrotic syndrome in the year before her arrival here, and renal biopsy confirmed that this was due to diabetic nephropathy. At that time her serum creatinine concentration was 137 μmol/l. She was first admitted for her current symptoms almost a year ago with a three day history of a severe exacerbation of her nausea and retching, although milder symptoms had been present long before.

There was some deterioration in her renal function with a serum creatinine concentration of 204 μmol/l and a 24 hour urinary protein concentration of 4·52 g/l. The possibility of gastroparesis diabeticorum was considered, and gastric emptying studies were performed with colloid porridge labelled with technetium-99m. This showed poor gastric contractions particularly at the gastric antrum, and transit of the radiolabelled meal into the pylorus was slowed. The half time of gastric emptying was over two hours, consistent with gastroparesis. A later repeated study of gastric emptying showed some improvement of peristalsis in the antral area but confirmed delayed gastric emptying consistent with gastroparesis. Oesophageal manometry studies showed normal motility over the distal section of the oesophagus with a reduction of contractions at the most proximal section, but this was not affecting propagation of contractions distally.

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