Sarcoidosis Lyme Australia
(SLA)
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Comments

on the

Australian Government Department of Health
Clinical Advisory Committee on Lyme Disease

SCOPING STUDY
TO DEVELOP A RESEARCH PROJECT(S) TO INVESTIGATE THE PRESENCE OR ABSENCE OF LYME DISEASE IN AUSTRALIA

by

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dated

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SLA's Introductory Comments

Any study pertaining to the presence or absence of Lyme(-like) disease in Australia brings with it an inference that the findings of the study could fall on the side of presence or the side of absence.

Current Australian Lyme(-like) disease patients have no doubt that they have a Lyme(-like) disease; their symptoms remind them on a daily basis, as does the devastation the disease has brought into their lives. Many current patients have been consulting doctors for years and receiving symptomatic treatments for their seemingly incurable medical issues. The startling point must be made that most patients have either had a list of sequential, probable/possible diagnoses, or no diagnosis at all, and the treatments offered have not brought a cure or significant, sustained improvement. Probable/possible diagnoses are offered because patients do not actually fit the diagnostic criteria of the putative alternative disease to confirm the diagnosis. It is always useful to test patients for the disease they actually have!

At worst, Australian Lyme(-like) disease patients have been called hypochondriacal, depressive or outright crazy. Anecdotal patient accounts even include accusations from doctors that test results have been falsified.

It is of concern that patients are given incorrect disease labels in an avoidance of investigation or acknowledgement of Lyme(-like) disease. This practice does not foster faith in the Australian healthcare system or the quality of service offered by doctors.

The doubt about the presence or absence of Lyme(-like) disease in Australia lies with the government and most of the medical establishment. There is much discussion of evidence-based medicine but the enormous number of Lyme(-like) disease patients ***are*** the evidence. These patients have lengthy medical records attesting to their Lyme(-like) symptoms, non-specific test results supportive of Lyme(-like) disease, and, in many cases, specific, positive test results from state-of-the-art, specialised laboratories. In view of this, when patients remain ill, it is a riddle why denial of the possibility of Lyme(-like) disease continues. It is a conundrum why the medical establishment would prefer to have so many undiagnosed patients in the system, rather than address the most likely causative disease.

The Scoping Study leans towards the finding of absence of Lyme(-like) disease in Australia, made apparent from choice of wording, negative comments, and choice between studies from which to draw points and which to gloss over. SLA is disappointed by this negative slant but appreciative of the opportunity to comment on the study.

It would be our hope that a more rounded, amended version will supersede the current Scoping Study. The two decade moratorium brought into being by the Russell, Doggett et al (1994) document is a situation that should not be replicated.

Investigations and discussions on the presence or absence of Lyme(-like) disease in Australia need to be collaborative, transparent, unbiased, innovative and precise. To that end, SLA offers the following comments.

Researcher

John S Mackenzie's credentials are not detailed on the report. A quick check of Professor Mackenzie's qualifications and published work reveals he has published at least two papers jointly with RC Russell and SL Doggett. In view of the controversy surrounding *Lyme disease: a search for a causative agent in ticks in south-eastern Australia* (Russell et al 1994) and these authors' later published works, Professor Mackenzie's undeclared connection with these authors may be construed as a conflict of interest.

Title

The Scoping Study title is inadequate for the breadth of the proposed investigations in that Lyme disease and Lyme-like disease may have differences enough to warrant completely separate disease names. Brazil acknowledged this by calling its Lyme-like disease Baggio-Yoshinari syndrome. Australia needs to ensure that all documents in relation to Lyme(-like) disease are comprehensive and correct. We should start with a title that encompasses Lyme and Lyme(-like) disease.

Terms of Reference *Page 4*

(i) Restricting investigations of causative agents to ticks *(Pg 4, 1st sentence)* limits the possibility of identifying the causative agent and this is acknowledged by Professor Mackenzie *(Intro, Pg 5, Para 1-last sentence)* when he states '*with the acknowledgement that an Australian agent responsible for Lyme-like disease might be significantly different from those described elsewhere in the world…might be due to an infectious agent other than a Borrelia species…might extend to differences in modes of transmission....*'

Furthermore, restricting investigations of causative agents to ticks overlooks the possibility of transmission from mother to child during pregnancy, as well as sexual transmission (Middelveen et al 2014) and infection via transfusion (Gabitzsch et al 2006).

(ii) If '*Lyme disease and Borrelia experts, including those overseas*' *(Pg 4, Point 2)* include any pathology laboratories, Igenex USA should be given as much consultation time as other laboratories consulted. Igenex has tested many Australian patients' pathology, so their input is vital.

(iii) Restricting investigations to '*haematophagous arthropod vectors*' *(Pg 4, Point 4)* excludes investigations of other species infected with Borrelia (Mackerras 1959; Pope & Carley 1956; Carley & Pope 1962) passing on the infection to humans. Carriers, including animals and putative patients, are sources for pathology which may enable identification and bacterial characterisation and, hence, should be included in the Terms of Reference.

Introduction *Page 5*

Paragraph 1 refers to '*20,000+ cases in the United States*' whereas the 19 August 2013 CDC Press Release states that '*each year, more than 30,000 cases of Lyme disease are reported to CDC*,' and that the '*new estimate suggests that the total number of people diagnosed with Lyme disease is roughly 10 times higher than the yearly reported number…around 300,000*.'

Paragraph 1 continues on to specify that 'e*arly disease includes erythema migrans…early disseminated disease includes multiple erythema migrans…and late disease presents primarily as arthritis*.' The ILADS guidelines, however, state that '*the EM rash may be absent in over 50% of Lyme disease cases*.' The BCA Clinic, Germany, advises on its website Lyme Disease Information section that '*erythema chronicum migrans [occurs] only in 50-70% of all cases*,' and the BCA's description of disease stages and presentation of symptoms indicates that arthritis is typical of Stage 2 (i.e. early disseminated disease) and that Stage 3 (i.e. late disease) involves far more than primarily arthritis. It is common knowledge that different strains of Borrelia tend toward distinct symptom trends in differing locations, so sweeping generalisations should be avoided. Additionally, '*Lyme neuroborreliosis may occur with or without antecedent erythema migrans or other symptoms*' and '*clinical outcome might depend on infection with strains of different species and pathogenic potentials* (Busch et al 1996).'

Paragraph 1 next highlights that the Murray & Shapiro (2010) study found most patients could be successfully treated in 2 to 4 weeks. No details are given as to time between tick bite or other mode of infection and diagnosis, and at what stage of disease treatment began for the patients described as '*most patients*.'

Next, Paragraph 1 states that '*In Australia, the presence of Lyme disease remains uncertain, equivocal, and evidence for the presence of B. burgdorfferi or any other related aetiological agent remains confused and unsubstantiated*.' This is not an honest depiction of the Australian situation as any study which has presented evidence that Lyme or Lyme-like disease may be acquired in Australia has been downplayed or unjustly ignored. Studies which deserve to be **fairly** included in the picture include: Mackerras (1959); Pope & Carley (1956); Carley & Pope (1962); Alpers (1992); Wills & Barry (1991); Barry (1995); and Hudson et al (1998). As the Scoping Study stands, it presents a negative view of studies finding and/or slanting towards the presence of indigenous strains of Borrelia, while presenting a more comprehensive recount and favourable view of those refuting indigenous strains. The Scoping Study disservices putative Lyme disease patients in Australia and puts question to its credibility with this lack of impartiality. Strict impartiality may have allayed fears pertaining to Professor Mackenzie's conflict of interest, but as the Scoping Study stands, both the lack of impartiality and conflict of interest stand out as red flags.

Paragraph 1 next states that '*This uncertainty and confusion has spilt over into the public arena, fuelled in part by emotive and unsubstantiated reporting by the media, and has resulted in substantial public concern*.' This is an inflammatory statement. The various state and territory health departments' lack of acknowledgement of even the possibility of indigenous strains of Borrelia, and their refusal to consider that patients who have travelled overseas may have Lyme(-like) disease, have left patients no option but to draw awareness to their plight. Government departments could have averted such media reports by showing concern, being respectful of patients and actively investigating the possibility of Lyme(-like) disease. To this day, most hospital infectious disease doctors will not consider Lyme(-like) disease and GPs are fearful of the consequences to their career should they treat patients for Lyme(-like) disease. The public has every right to be concerned, and the media reports will not differ in tone until patients are able to easily, openly and affordably receive adequate treatment.

Paragraph 1 next states that it is '*increasingly important to resolve this issue in order to provide public assurance, particularly for those whose lifestyles or homes are associated with risks for exposure to tick bites, and to provide some degree of certainty to those suffering from symptoms which have been diagnosed as being due to Lyme disease*.' Worryingly, the tone of this statement implies that it is not expected that indigenous Borrelia will be found in Australia and, hence, patients do not have Lyme disease. If indigenous strains are found, the public will not be reassured that they have been exposed for years, and individuals particularly exposed by pursuits or location will require testing if they have unexplained symptoms. The best the government could offer to the public at this stage, should indigenous Borrelia be discovered in the very near future, is assurance that adequate tests will be developed, treatment will be allowed and doctors will receive guidelines. The point must be made that most of the uncertainty lies with government departments. Most current patients have worked their way through differential diagnoses to their best of their ability, given the Medicare restrictions within which they must operate, and have found themselves with various test results and symptoms which point to Lyme(-like) disease.

Continuing, paragraph 1 states that '*investigations should be open and uncommitted*' and that '*all possible scenarios should be canvassed*.' All above comments indicate that the Scoping Study does not meet its own requirement in this respect.

Background: Brief Review of Lyme Borreliosis *Page 6*

(a) Borrelia species in Lyme disease and their vectors, reservoirs and genomes *Page 8*

The Wills and Barry (1991) study, to which paragraph 2 refers, is decades old. A comprehensive experimental vector competence study would necessitate the inclusion of all known species of Borrelia from North America, Europe and everywhere else in the world. Furthermore, a comprehensive experimental vector competence study would necessitate the inclusion of all known Ixodes species found in Australia.

Other vectors may be competent. The Scoping Study mentions that '*B. burgdorferi s.l. have occasionally been found in Ornithodoros* species' but makes no mention of further studies being warranted on Ornithodoros species and other Argasidae. No mention is made of the possibility of investigations broadening to include mites, also in the order Ixodida, and haematophagous arthropod vectors from a wider range of subphyla and classes. If investigations are not exhaustive and comprehensive, we risk creating another situation where a flawed and narrow study (i.e. Russell et al 1994) presents a false picture of the Australian situation. Further to that point, there is no mention of the paper (Alpers 1992) which stated that Doggett had successfully isolated and grown spirochaetes from ticks infesting animals with symptoms similar to those occurring in human sufferers of Lyme disease. Alpers claims that coastal areas from northern Victoria to southern Queensland produced over 70 isolates from 30 locations within that range.

Considering the flawed nature of Russell et al's (1994) study, the question must be asked as to whether the spirochaete-like objects were artefacts as claimed or something of clinical significance which warranted further investigation. The recently discovered Brazilian Lyme-like disease, Baggio-Yoshinari syndrome, is also described as revealing '*spirochaete-like structures*'(Shinjo et al 2009). A comparison between the Australian and Brazilian spirochaete-like structures would seem logical, especially as both countries are in the Southern Hemisphere (partly in Brazil's case, the country being in three hemispheres) and share climates which are not uniform throughout the country. Climate ranges from semi-arid, tropical or temperate, to frosty and snowfall at the other end of the spectrum, depending on location and season.

Page 8, paragraph 2, gives the brown dog tick (Rhipicephalus sanguineus) and the bush tick (Haemaphysalis longicornus) as examples of '*other widespread ticks*.' It is noted that Lyme spirochaetes have been detected in the bush tick in China but neglects to note that Laboratorio de Doencas Parasitarius (LDP) demonstrated that the spirochaete '*B. burgdorferi strain G39/40 adhered, grew, multiplied and showed great motility in cultures of embryonic cells of R. sanguineus tick. Although R. sanguineus is not the species-specific vector of B. burgdorferi, spirochaete culture in the presence of these cells was successful*.' The researchers' objective was in vitro culture of B. Burgdorferi in R. sanguineus to aid in the isolation of Borrelia strains and species in Brazil. Tinoco-Gracia et al (2008) found that 136 of 850 (16%) of dogs were positive for B. burgdorferi in an area where R. sanguineus was the only tick identified to date. These researchers noted that R. sanguineus can be brought into homes and feed on humans, and the entire life cycle can be completed indoors.

Disappointingly, Ornithodoros gurneyi is not mentioned as the favoured potential vector of Borrelia Queenslandica (Carley & Pope 1962). Russell et al (1994) made the same omission and this brings us back to the question of Professor Mackenzie's undeclared conflict of interests. A Scoping Study looking for Lyme disease in Australia should surely recount details of an indigenous strain of Borrelia at each relevant opportunity. There have been similar early accounts of Borrelia species from Ornithodoros vectors in other countries, such as Borrelia graingeri/Ornithodoros graingeri and Borrelia tillae/Ornithodoros zumpti, both of South Africa, as well as Borrelia brasiliensis/Ornithodoros brasiliensis of Brazil (Barbour et al 1986).

(b) The natural reservoirs of Lyme Borrelia species *Page 8*

The reference to Butler et al (2005) is a case of slanted and selective picking. The only credence to Butler's point is that the horses may not have fit the very strict definition of Lyme disease he appeared to be using. There are many strains of Borrelia which produce differing symptom sets. That is true of humans, depending on the strain of Borrelia, so it's logical that horses would have symptom sets according to strain of Borrelia and their own equine genetics.

Conversely, Burgess (1988) found that '*B. burgdorferi infection occurs in horses and cows and can cause clinical illness in some but not all animals…Because spirochetes could be isolated from blood, synovial fluid, colostrum, and urine, these animals could be important in providing an infected blood meal for ticks and bringing B. burgdorferi in direct contact with humans*.' Additionally, '*the most*

frequent clinical signs in antibody-positive horses and cows were lameness and swollen joints, but many also had stiffness, laminitis, abortions and fevers.'

The argument here is not whether disease exists in horses (and cows) but what criteria we are going to use to distinguish between Lyme and Lyme-like diseases resulting from Borrelia infection. Perhaps Australia could learn from Brazil on this topic.

SLA is aware that Mr Richard Isaac is submitting a lengthy report and study proposal on *Borrelia Infection & Avian Transmission in Australia*. No doubt, that will incorporate any comment which may be made in relation to the contents of page 9 of the Scoping Study.

It must be noted, however, that Comstedt et al (2006) present representative figures on migratory passerine birds coming to their breeding grounds in Sweden in spring: '***≈*** *15 million infested birds would disseminate 40 million ticks, of which 5.6 million would be infected with LB group* spirochetes.' Mr Isaac's work may point towards a way to find similar statistics for birds relating to Australia. Comstedt et al (2006) state that the '*American robin , an abundant and commonly tick-infested passerine, is as effective as mice in reservoir competence for this bacterium [B. burgdorferi]. Understanding the contribution of this and other alternative reservoirs in enzootic maintenance of B. burgdorferi is prerequisite for advancing prevention strategies for LB*.' Precisely. It would be negligent to discount birds from the equation in the fashion which the last paragraph of page 9 so clearly does.

(d) Lyme Borrelia and human disease *Page 10*

As noted earlier *(Herein, Pg 2, in relation to Scoping Study Introduction, Paragraph 1)*, as few as 50% of cases may develop erythema migrans *(BCA Clinic website, Lyme Disease Information section)*.

Stanek et al (2012) are quoted as saying that '*As Lyme disease can take various forms, differential diagnosis is essential*.' This is logical, but then the logic must follow that if a patient does not meet the criteria for any of the differential diagnoses, then the consideration of Lyme(-like) disease should move to the top of the list. While specific laboratory tests for Lyme(-like) disease are completely inadequate in Australia, diagnostics must include every tool available, including overseas testing, non-specific but relevant tests, and clinical presentation. The purpose of the Scoping Study is to lead to proof or disproof of Lyme(-like) disease in Australia. Putative patients may have Lyme(-like) disease; it has not been disproved, only discredited.

Highlighting Stanek et al's (2012) belief that '*differential diagnosis is essential*' only highlights the current situation of infectious disease doctors being willing to consider every disease (and more) on the differential list, with the exception of Lyme(-like) disease. Infectious disease doctors are more willing to use such default diseases as Sarcoidosis, expecting patients to accept that possible label, sans the gold standard positive biopsy, than to explore the distinct possibility of Lyme(-like) disease. Some patients have medical reports and consultation notes testifying to this and the continuation of this practice by medical practitioners, especially government-employed, hospital infectious disease doctors, is outright negligence in view of Lyme(-like) disease being not disproved, hence possible.

Paragraph 1, page 11, describes Huppertz et al's (1999) study. The study's diagnostic requirements of Lyme borreliosis are imperfect in that:

(i) erythema migrans is usually a first stage manifestation (Aberer et al 1991) and easily recognisable;

(ii) lymphocytoma is usually an early disseminated stage manifestation (Aberer et al 1991) and easily recognisable; **but**

(iii) other specific manifestations could be characteristic of various disease stages and required serological confirmation. Commercial testing for Lyme disease can be '*relatively insensitive, especially during later stages of the disease*' (Stricker 2007). Burrascano (2008) states that '*when late cases of LB are seronegative, 36% will transiently become seropositive at the completion of successful therapy*.' Wang et al (2001) state that their '*results provide evidence of a correlation*

between certain HLA genotypes and the ability to mount an antibody response to Bb…evidence that HLA alleles are involved in antibody responsiveness or non-responsiveness to Bb infection…Thus, genetic predisposition may be a critical factor in the regulation of the host immune response and the diagnosis and prognosis of Lyme disease.' Not all patients make antibodies or can mount an immune response, so placing two requirements, with one being positive serology, on the 'other specific manifestations' group, suggests that some from this group would be excluded.

The study was slanted towards finding a high rate of erythema migrans, as this one easily recognisable characteristic was all that was required. That does not translate into erythema migrans being characteristic of 92% of Lyme disease patients, as this study finds, but simply says that erythema migrans was an easier criteria to meet than the double criteria of symptom plus positive serology in various disease stages. Consequently, patients with erythema migrans were most likely included in the study in higher numbers.

Furthermore, Huppertz et al (1999) describe 60% of patients as reporting a recent tick bite. This means that 60% of the study's participants were early, localised stage or early disseminated stage, and hence more likely to present with erythema migrans than late stage patients, who may have been excluded due to serological test insensitivity or inability to mount an immune response as a result of genetic predisposition and varying immune response or lack thereof. This again favourably skews the chances of erythema migrans being a frequent patient characteristic finding.

Huppertz et al's (1999) findings are odd in that '*all patients with symptoms other than EM alone experienced improvement or resolution after antibiotic therapy, except one patient with ACA who refused therapy*.' As 279 (89%) of patients had EM alone, this must mean that 89% of the patients did not improve or experience resolution after antibiotics, despite being early localised or early disseminated patients. This contradicts the earlier reference to the Murray & Shapiro (2010) study finding most patients could be successfully treated in 2 to 4 weeks. Conversely, it would appear that antibiotics only improved or resolved symptoms for 33 out of the 34 patients potentially from any disease stage, although the 4 patients with ACA were most likely late stage. Clarity is needed here. SLA failed to find anything beyond the abstract to Huppertz et al's (1999) article. Perhaps the EM alone patients were not given antibiotics at all; the wording here is not clear.

The last paragraph on page 11 discusses the Brazilian Baggio-Yoshinari syndrome (BYS). Considering the purpose of this Scoping Study, the Brazilian experience of Lyme(-like) disease should be studied intently. Yoshinari et al (2010) detail many characteristics of BYS that may be pertinent to the Australian situation:

(i) Vectors in Brazil are recognised as being diverse, with species of ticks involved differing from those elsewhere in the world, and the role of other arthropods, '*such as flies, mosquitoes and louses*,' are recognised as possibly '*being involved in the BYS epidemiological cycle*' (Yoshinari et al 2010).' The possibility of a similar situation existing in Australia is high.

(ii) '*Ticks from the Rhipicephalus microplus species cannot be discarded as participant of zoonosis transmission cycle*' (Yoshinari et al 2010). This species of tick (often called cattle tick) is '*the most serious external parasite of cattle in Australia*' *(NSW Department of Primary Industries website)*. The Queensland Department of Agriculture, Fisheries and Forestry website describes cattle as the '*main host…although they may be found on horses, goats, sheep, deer, camelids and buffaloes*' and describes infected zones as comprising '*the coastal areas east of the Great Dividing Range and north of the Great Northern Rail Line…the northern areas of Western Australia and Northern Territory and sporadically through the northern rivers area of New South Wales*.' The Northern Territory Department of Regional Development, Primary Industry, Fisheries and Resources website advises that these ticks may also occasionally be seen on donkeys, dogs and pigs. Due to its widespread geographical location and numerous hosts, Rhipicephalus microplus species requires study in Australia.

We note that the Queensland Department of Agriculture, Fisheries and Forestry website states that '*cattle ticks are notifiable when they occur outside the Queensland cattle tick infected zone*.' It is surprising that even putative Lyme(-like) disease is not notifiable. It would seem, from the current situation, that cattle and the viability of the cattle industry rate higher than human wellbeing in Australia. It is virtually impossible to know the true possibilities and incidence of a putative disease that is not having its occurrence monitored.

Additionally, the Queensland Department of Agriculture, Fisheries and Forestry website states that '*cattle tick outbreaks can and do occur in Queensland's tick free zones*.' It is reasonable to extrapolate from such a statement that cattle tick outbreaks can and do occur outside tick free zones in all relevant locations. This makes mockery of state government claims that putative Lyme(-like) disease patients cannot have Lyme(-like) disease because they have not been to tick infested areas. This also makes mockery of state government claims that people who have travelled overseas could not have Lyme(-like) disease unless they had travelled to an endemic area. The Queensland Department of Agriculture, Fisheries and Forestry seems to understand that ticks do not stay within their allotted boundaries. Should *Rhipicephalus microplus species* be found to be infected with Borrelia, then vectors of Borrelia will have already been found in non-endemic areas. SLA would suspect that other species of ticks, and in fact most vectors, would have difficulty remaining rigidly within government demarcated boundaries.

(iii) '*The Brazilian biodiversity in reservoir animals and ticks, as well as climatic differences, would be the factors implied in the emergence of latent spirochetes…cystic presentation, very different from spiralled microorganisms found in the Northern Hemisphere* (Yoshinari et al 2010).' The Australian Department of Environment website details both Australia and Brazil as being included in the 17 megadiverse countries of the world. Australia and Brazil have climatic similarities, sharing climates which are not uniform throughout the country. Climate ranges from semi-arid, tropical or temperate, to frosty and snowfall at the other end of the spectrum, depending on location and season, for both countries. Brazil falls into 3 hemispheres (western, northern and southern), while Australia is located in the Southern Hemisphere. Brazil and Australia share enough characteristics to add more feasibility to the possibility that they may share a similar Lyme(-like) disease than the popular belief that the only two countries in the world free from Lyme disease are Australia and the Antarctic, countries completely different in biodiversity and climate.

(iv) Shinjo et al (2009) state that '*BYS has now been defined as a vector-borne disease caused by atypical morphological spirochetes at vegetative presentation and transmitted by arthropods not belonging to the I. ricinus complex, which replicates all the clinical symptoms described in classical LD, with the addition of a high frequency of relapse episodes and autoimmune manifestations*.' The Brazilian researchers embraced the possibility of a Lyme-like disease producing clinical symptoms of Lyme disease but differing enough from Lyme disease in terms of vector, serology and disease course to require its own diagnostic pathway and a separate name. The Scoping Study *(Pg 22, Paragraph 4)* makes note of the point '*that it is always much harder to prove a negative*.' If the Brazilian researchers had focused on Lyme disease as it occurs elsewhere in the world, they would not have made the discoveries they have made.

To find, there has to be a genuine willingness to look. While the Russell et al (1994) study created a situation of denial and close-mindedness for 20 years, Brazil managed to take a similar situation and effect many of the Terms of Reference of this Scoping Study in 15 years. Even if the Australian situation does not prove to replicate or be similar to the Brazilian findings, there is much which may be learned about positive attitude, reshaping the questions and redefining criteria.

(v) Yoshinari et al (2010) state that '*BYS diagnosis is essentially clinical*.' A diagnostic guide based on 3 major and 3 minor parameters has been adopted and a positive diagnosis is made when a patient presents all 3 major parameters *or* 2 major and 2 minor parameters.

Major Parameters (Yoshinari et al 2010):

(1) Compatible epidemiology at the beginning of the infection, including tick bite, visualisation of ticks, visiting areas considered risky and presence of sick animals.

Most Australian patients have had such factors ignored or dismissed. Those who have never travelled outside Australia have never stood a chance of meeting this parameter due to governmental denial of the possibility of Lyme(-like) disease, and those who have travelled outside Australia usually have not travelled to locations the Australian government considers endemic. It takes one infected tick or other vector to transmit disease. As the Queensland Department of Agriculture, Fisheries and Forestry is aware, ticks can be found outside of infected zones.

(2) Positive serology (ELISA or WB). The ELISA test has been modified to Brazilian requirement and the WB is interpreted using Brazilian criteria which focus on the quantity of bands present rather than on the occurrence of specific bands. A WB positive may be achieved through the presence of 4+ IgG bands or 2+ IgM bands or at least 2 IgG and 1 IgM bands.

Most Australian patients have had positive test results dismissed on the basis that they have been provided by international, non-NATA accredited laboratories. NATA accreditation is of no value when a laboratory does not have a specific test for a specific disease. Australian patients are being forced to pay the price of Australian laboratories lagging behind the rest of the world in relation to this disease. Australian laboratories lack of adequate tests for Lyme(-like) disease does not mean Australian patients do not have Lyme(-like) disease. Brazilian BYS patients, negative by CDC standards, are positive by Brazilian standards. Brazilian standards would instantly convert even some internationally tested negative and indeterminate Australian patients into positive for Lyme(-like) disease. Australian laboratory tests have been failing patients for years by not testing for all known strains of Borrelia that may cause Lyme(-like) disease. Adding the issues of interpretation and NATA accreditation to this, highlights that it would be virtually impossible for Australian patients to meet this parameter.

It is of interest that the Brazilians allow the WB 2 IgG and 1 IgM option, noting that the distinction between the acute stage dominance of IgM antibodies and convalescence stage dominance of IgG antibodies tends to disappear in relapsing outbreaks. As many Australian patients have this pattern of WB, it is important to investigate whether a similar relapsing type of disease may be present here, rather than continuing to declare atypical results as false-positives.

The Brazilian studies read as if a positive ELISA **or** Western Blot is enough to meet the positive serology parameter. This would imply that patients are not subject to a rigid 2-tier testing process and that a negative ELISA does not preclude a WB. Additionally, Mantovani et al (2007) stated that '*the diagnosis of Lyme Disease-Like Syndrome* (later renamed BYS) *is based on epidemiological and clinical aspects. Since the etiological agent has not been isolated or cultivated in Brazil, false-positive serology for B. burgdorferi is a helpful laboratory parameter*.' The Brazilians put an interesting false-positive laboratory finding to good use in their quest to narrow down the cause of patients' symptoms.

(3) Pertinent clinical symptoms.

Australian patients are routinely told, especially by hospital infectious disease doctors, that their symptoms are due to other diseases, such as Sarcoidosis. Considering such doctors have failed to adequately explore all diseases on the list of differential diagnoses for Lyme disease, as evidenced by their refusal to consider Lyme(-like) disease, every Australian patient diagnosed with a disease on that differential diagnoses list should be entitled to be re-evaluated for Lyme(-like) disease. At this time, while patients present with pertinent clinical symptoms, most doctors

refuse to assess these symptoms in relation to Lyme(-like) disease, which means that this parameter is routinely ignored in Australia.

Minor Parameters (Yoshinari et al 2010):

(1) Recurrence episodes.

Most Australian patients report flares of symptoms at times. It is unknown whether Australian patients are having recurring episodes, ongoing disease, inadequate treatment, inappropriately delayed treatment, chronic and irreversible disease due to inappropriately delayed treatment, auto-immune disorders subsequent to and/or triggered by Lyme(-like) disease, or some combination of these possibilities. The Brazilians acknowledge this dilemma, also recognising that BYS most especially has a recurrent course if treatment with antibiotics is not commenced within three months of infection. This finding might have enormous implications for Australian patients, who frequently were not treated with antibiotics within years (or even decades) of infection. Outright denial of Lyme(-like) disease in Australia by our governments may have irrevocably determined the course of disease for current patients. While Australian patients continue to present ongoing and reoccurring symptoms, Australian state and territory governments and most doctors continue to deny the possibility of Lyme(-like) disease. Treatment of other misdiagnosed diseases has failed to return Australian patients to health, so it is evident that disease and treatment are being mismatched. Most Australian patients have easily accessible medical records which prove the ongoing and reoccurring nature of their Lyme(-like) disease. Incorrect or absence of diagnosis, lack of appropriate medication and ongoing symptoms have written the patient aspect of Lyme(-like) disease in patient medical records throughout the country for all posterity.

(2) Visualisation of spirochete-like microorganisms at dark field microscopy.

Alpers (1992) claimed that Doggett had successfully isolated and grown over 70 spirochaetes from ticks infesting animals with symptoms similar to those occurring in human sufferers of Lyme disease. The question as to whether the spirochaete-like objects were artefacts as claimed (Russell et al 1994) or something of clinical significance which warranted further investigation should be readdressed.

(3) Chronic fatigue syndrome.

Many Australian patients have been misdiagnosed with chronic fatigue syndrome and nearly all Australian patients report some degree of chronic and excessive fatigue.

(vi) One of the main clinical manifestations observed in BYS is '*immune-allergic dysfunctions with higher sensitivity to drugs and foods*' (Yoshinari et al 2010). This aspect of BYS warrants highlighting in view of recent media reports focusing on the emergence of tick-induced allergies to red meat. In December 2013, the media reported Associate Professor Sheryl van Nunen, a clinical immunology specialist at Sydney's Royal North Shore Hospital, as having about two new such cases each week, bringing the total of her tick-induced red meat allergy patients to 23. It was reported that more new cases of mammalian meat allergy were occurring throughout Australia. In the past 2 years, Sydney's northern-beaches-located Mona Vale Hospital reported that more than 500 cases of tick reactions were treated in their emergency department, and that up to 2% of the daily caseload in tick season is tick related. Dr Andy Ratchford, Mona Vale Hospital's Director of Emergency Medicine, reported the most common allergic reaction seen was to ticks. Australia needs to determine whether the explanation offered here of alpha-gal allergy differs from the Brazilian cause of allergy.

It is of note that:

(1) Brazil leaves room for a purely clinical diagnosis, which may be achieved without positive serology and without visualisation of spirochaetes.

(2) Brazil recognises that physicians should be informed of '*the existence of a severe and highly morbid zoonosis…[with] an infectious initial character…when not recognised and treated early, it develops recurrent systemic complications…especially with neurological and articular symptoms*' (Yoshinari et al 2010). Brazil recognises that lack of full understanding of the vector does not negate or transmute the existence of the Lyme-like disease for the patients.

(3) The Scoping Study did not give more space than 8 lines to Baggio-Yoshinari syndrome when the Brazilian Lyme(-like) disease situation may very well be the best model on which to base Australian investigations and criteria. This is surprising since the purpose of the Scoping Study is to develop research projects investigating the presence or absence of Lyme(-like) disease in Australia.

Page 12, first paragraph, states '*that Lyme is not a fatal disease*.' SLA finds this statement highly insensitive and offensive in view of the fact that the CACLD includes a representative from the Karl McManus Foundation , this foundation bearing the name of an Australian who lost his life from causes directly attributed to Lyme disease. Paralysis of the tongue caused by Lyme disease, caused choking from mucous, caused by the flu. Mr McManus did not lose his life to the flu; Mr McManus lost his life to complications of Lyme disease and lack of appropriate treatment.

The Australian government's steadfast denial of Lyme(-like) disease being present in Australia has created a situation where Australian patients of Lyme(-like) disease are more likely to die than similar patients from other countries where Lyme(-like) disease is recognised and treated. Evidence-based medicine would support the generalisation that patients with progressive, systemic infectious diseases left untreated are more likely to die than patients who are treated appropriately within a short timeframe. Furthermore, evidence-based medicine would decree that representatives of the Australian government cannot statistically support claims that Lyme(-like) disease is not fatal in Australia because no-one with Lyme(-like) disease has been acknowledged as having the disease. If there have been fatalities due to Lyme(-like) disease and its misdiagnosis and lack of or inappropriate treatment, those fatalities have been erroneously attributed to other diseases or causes.

SLA agrees that '*chronic Lyme disease is a widely used but poorly defined* term' *(Pg 12, Para 2)*. It would appear that even the 'experts' have not reached consensus.

Centres for Disease Control and Prevention *(CDC website - Signs & Symptoms of Lyme Disease)*

CDC divide stages of Lyme disease as follow:

(1) Early localised stage (3 to 30 days post-tick bite)
(2) Early disseminated stage (days to weeks post-tick bite)
(3) Late disseminated stage (months to years post-tick bite)
(4) Lingering symptoms after treatment (post-treatment Lyme disease syndrome)

In relation to the early disseminated stage, CDC advise that untreated infection can spread from the bite site to other parts of the body, and note that lack of treatment may result in additional complications. The inference is that appropriate treatment lessens the risk of disease progression and complication for the patient.

In relation to the late disseminated stage, CDC advise that approximately up to 60% of untreated patients may develop articular manifestations, and up to 5% of untreated patients may develop chronic neurological complaints months to years after infection. The inference is that appropriate treatment lessens the risk of disease progression and complication for the patient. It is also inferred that the

patients constituting the articular 60% and neurological 5% would be patients untreated in the early disseminated stage.

CDC describes Post-treatment Lyme disease syndrome (PTLDS) as '*symptoms that last months to years after treatment with antibiotics*' and presenting in approximately 10-to-20% of patients. CDC states the cause of these symptoms is unknown but denies evidence of ongoing infection, claiming some evidence of auto-immune factors.

SLA views this as a sweeping generalisation. Statistics are not provided to break down the 10-to-20% of PTLDS patients by stage at which they commenced antibiotic treatment. It would seem logical that patients who did not commence treatment until late disseminated stage would comprise a larger portion of the 10-to-20% than patients who received treatment in the early localised stage. It would be easier to find evidence for auto-immune causes of PTLDS because knowledge about such genetics as Human Leukocyte Antigen (HLA) is readily available but tests may not be sensitive enough to detect Borrelia in a patient who remained undiagnosed for years. It is possible that Borrelia may be able to modify the immune system favourably to ensure its own survival and avoidance of detection. Anecdotally, some Lyme(-like) disease patients produce elevated amounts of serum Vitamin D (1,25-dihydroxy) which is known to be immunosuppressive, a factor which could produce a very favourable environment for Borrelia. It is impossible to provide references on 1,25-dihydroxy in the Lyme(-like) disease patient because there has been no such research. It is our understanding that Sydney University may have included 1,25-dihydroxy data in their ongoing research on Lyme(-like) disease. While there may not be evidence that infection continues in PTLDS, there is also no evidence that it does not and the whole question warrants extensive investigation.

As stage at which treatment commenced and genetics play roles in the how and why of patients may progress to PTLDS, SLA does not believe that one label suffices to cover all the patients encompassed in the 10-to-20%. SLA recommends that PTLDS would be better broken down into four categories, reflecting the following groups of patients:

(1) Symptoms remaining after antibiotic treatment commenced in the early localised stage;

(2) Symptoms remaining after antibiotic treatment commenced in the early disseminated stage;

(3) Symptoms remaining after antibiotic treatment commenced in the late disseminated stage; and

(4) Symptoms remaining after antibiotic treatment commenced subsequent to one year in the late disseminated stage, and within category four:

   (i) In patients without known genetic disadvantages and/or immune-system complications; and

   (ii) In patients with known genetic disadvantages and/or immune-system complications.

SLA views the purpose of disease staging to be to lead to appropriate treatment protocols, and it would seem that treatment for each of the above four categories and two sub-categories would necessitate protocols specific to each category.

The International Lyme and Associated Diseases Society *(Evidence-based guidelines for the management of Lyme disease)*

ILADS acknowledges that '*the management of chronic Lyme disease must be individualised, since patients will vary according to severity of presentation and response to previous treatment*.' ILADS sub-divides chronic Lyme disease into categories as follow:

(1) Persistent Lyme disease

(2) Recurrent Lyme disease

(3) Refractory Lyme disease

Persistent Lyme disease is described as disease which is resistant to treatment, and recurrent Lyme disease is described as relapsing disease. Refractory Lyme disease seems more a combination of persistent and recurrent than a separate category. The ILADS description for Refractory Lyme disease

suggests that patients benefit from antibiotics, even if not able to tolerate antibiotics or previous antibiotics have failed.

SLA considers that a more suitable name for the refractory category would be Irreversible Lyme disease. As long as symptoms persist, the patient remains ill, whether the symptoms are produced by continued infection, immune-system complications or a combination of both. It may be that the patient requires at least intermittent antibiotic treatment to prevent the infection causing even further irreversible symptoms, while at the same time, the infection may be too widely disseminated and too firmly entrenched to ever completely be eliminated. It may also be that the infection has created a favourable environment for survival.

Anecdotal patient accounts make apparent that some patients with Lyme(-like) disease have a significant 1,25-dihydroxy elevation, ie. the active metabolite of Vitamin D, also known as calcitriol. Calcitriol is known to have potent immunoregulatory properties (Bagot et al 1994; Conron et al 2000;) and much research has studied its immunosuppressive abilities in relation to various diseases, especially autoimmune diseases. The question of whether Borrelia has the ability to activate the macrophage-monocyte line of immune cells into expressing extra-renal 1a-hydroxylase, which converts 25-hydroxy into 1,25-dihydroxy, warrants research. Certainly, the experience of some Australian Lyme(-like) disease patients suggests that their disease and calcitriol have a relationship which impacts negatively on their symptoms. Likely, genetics play a role in which patients present 1,25-dihydroxy elevations, along with the hot Australian summer, warm spring and autumn, and short, mild winter.

SLA is concerned that many Australian patients would fall into this suggested category of Irreversible Lyme disease. Some patients remained without diagnosis or misdiagnosed for years, translating into the infection remaining unchallenged in the body for years (even decades, in some cases). Some patients were given immunosuppressant medications to alleviate symptoms which, most likely, would have allowed the bacteria an environment in which proliferation and movement were given a free pass.

Dr Joseph Burrascano *(Advanced Topics in Lyme disease, 16th Edition, 2008)*

Dr Burrascano holds a broader view of Lyme disease, including co-infections and Borrelia in his definition. He categorises Lyme disease as follows:

(1) Acute
(2) Early disseminated
(3) Chronic

Chronic Lyme disease is characterised by three criteria:

(1) Illness of at least one year's duration
(2) Persistent neurological involvement or active arthritic manifestations
(3) Active Borrelia infection, regardless of prior antibiotic therapy

Dr Burrascano believes that chronic Lyme disease has an '*inhibitory effect on the immune system…[and can] inhibit and kill B- and T- cells and decrease the count of the CD57 subset of the natural killer cells*.' He notes that '*serologic tests can become less sensitive as the infections progress, obviously because of the decreased immune response upon which these tests are based*.'

Dr Burrascano notes that '*not all patients with chronic Lyme disease will fully recover and treatment may not eradicate the active Borrelia infection. Such individuals may have to be maintained on open-ended, ongoing antibiotic therapy, for they repeatedly relapse after antibiotics are stopped. Maintenance antibiotic therapy in this select group is thus mandatory*.'

SLA believes that chronic Lyme(-like) disease is too general a term to use when developing treatment guidelines. Determining patients' stage or category of Lyme disease requires information about:

(1) duration of infection prior to treatment,

(2) response to treatment,
(3) genetic predispositions and immune responses,
(4) symptom pattern, and
(5) pathology results, in tandem with the above four points.

SLA's preferred break-down of general chronic Lyme disease is the 4 category and 2 sub-category model suggested on page 10 *(Paragraph 3)* of this response.

Even in countries where Lyme disease is recognised and treated, there is no consensus about the definition and constituents of chronic Lyme disease. Australia will need to develop its own definition, categories and treatment guidelines according to how Australian chronic Lyme(-like) disease patients are presenting. On that point, attention must be again drawn to the Brazilian BYS, which is characterised by recurrent and relapsing illness if treatment is not initiated within the first three months. It would appear that the Brazilians have readily included the chronic aspect of BYS in their characterisation of the disease. The rest of the world appears to be holding chronic Lyme(-like) disease outside the parameters of what constitutes Lyme(-like) disease. The Brazilians have accepted that recurrent, relapsing disease is a possible and likely consequence of delayed treatment. The rest of the world is presenting chronic Lyme(-like) disease as an aberration from the course of Lyme(-like) disease. Chronic Lyme(-like) disease is so common that this is not logical. As well as categorising subdivisions of chronic Lyme(-like) disease, Australian investigations should focus on the nature of the entire disease. Perhaps an overhaul of staging and definitions is required generally. It would seem preferable to be aiming to make the definitions fit the disease, rather than the converse.

Page 12, second paragraph, states that '*there needs to be confirmatory testing in accredited laboratories to provide scientific evidence-based support*' of chronic Lyme(-like) disease. Preac-Mursic et al (1989) demonstrated that Borrelia burgdorferi '*may persist as shown by positive culture in MKP-medium*' and that '*patients may have sub-clinical or clinical disease without diagnostic antibody titres*.' They concluded '*that early stage of the disease as well as chronic Lyme disease cannot be excluded when the serum is negative for antibodies against B. burgdorferi*.' Embers et al (2012) studied antibiotic efficacy using nonhuman primates (Rhesus Macaques), chosen because of '*their ability to reproduce many of the key signs of human Lyme disease, including neuroborreliosis*.' They note '*reliable procedures to determine that infection has been cleared from Lyme disease patients have not been established*.' Nevertheless, Embers et al were able to detect DNA and RNA in the tissues of treated animals and '*small numbers of intact spirochetes were recovered by xenodiagnosis from treated monkeys. These results demonstrate that B. burgdorferi can withstand antibiotic treatment, administered post-dissemination, in a primate host…appears to become [antibiotic] tolerant post-dissemination in the primate host*.' It is noted that chronic Lyme disease may be attributed to '*several causes, including (1) spirochetes that persist in the tissues, likely in small numbers, inaccessible or impervious to antibiotic; (2) inflammatory responses to residual antigens from dead organisms; or (3) autoimmune responses, possibly elicited by antigenic mimicry*.'

As noted earlier *(Herein, Pg 7, Para 7)*, it is acknowledged that the Brazilian BYS is characterised by a break-down of the distinction between the acute stage dominance of IgM antibodies and convalescence stage dominance of IgG antibodies in relapsing outbreaks, necessitating the need for a third variable of a positive WB, allowing two IgG and 1 IgM positive bands.

While the '*jury is out*' *(Pg 12, Para 2)*, patients continue to be chronically ill with Lyme(-like) disease. Evidence for continued infection is not completely absent and evidence for autoimmune responses is really only guided by genetic predispositions. There is not adequate testing available to determine whether putative autoimmune responses are, in fact, autoimmune responses, or responses to undetected residual antigens from dead organisms. The latter is not an autoimmune response and the inflammatory reaction is not to 'self' but to antigenic derivatives of dead organisms resisting phagocytosis or degradation. Furthermore, Borrelia burgdorferi has uniquely evolved with no requirement for iron, a

characteristic which enables it to evade the immune system's technique of starving pathogens of iron (Aguirre et al 2013).

Page 12, second paragraph, refers to the approach of Germany's national Public Health Institute, the Robert Koch Institute. The report of the project group RKI 2010 makes it apparent that:

* the Public Health Institute should strive to co-operate with universities and research institutes at both the national and international levels;
* the Public Health Institute follows national and international developments with regard to new scientific knowledge, methods and techniques;
* the Public Health Institute sends epidemiologists overseas, if necessary, to collect first-hand information relevant for Germany;
* the modern diagnosis of pathogens requires techniques and expert knowledge offered only by centres specialised for this purpose;
* climate change has the potential to result in an increased spread of zoonoses, with climatic and environmental changes heightening the possibility of increasing numbers of pathogen-transmitting insects and ticks, and heightening the possibility of host animals varying their habitat;
* there is evidence that Germany is experiencing spread of certain tick-borne disease (i.e. encephalitis) to areas not previously affected;
* that rare pathogens have been spreading, including infections with parasites and fungi that are difficult to diagnose and treat, as well as infections transmitted by vectors such as midges, ticks and rodents; and
* climate and landscape changes, as well as increased travel by Germans, all contribute to changes in vector-borne infectious disease patterns.

It would seem that the Robert Koch Institute is focused on collaboration at national and international levels, as well as keeping ahead of new infectious disease trends. The Robert Koch Institute embraces the concept of change in disease patterns and demographics. The continued message of denial of Lyme(-like) disease from Australian state governments and infectious disease doctors, and the lack of interest in collecting data about putative patients, is at complete odds with the practices of the Robert Koch Institute. SLA believes that drawing attention to the approach of the Robert Koch Institute is valuable in that it highlights all that Australia has yet to do in relation to Lyme(-like) disease.

Page 12, third paragraph, states that '*Lyme borreliosis has been reported in Australia but the vast majority of cases were people who had travelled to Lyme endemic areas overseas*.' This one sentence does not do justice to the findings of several studies conducted in the 1980s and 1990s. In view of the controversy surrounding current patients' having positive international but negative Australian test results, the question of test sensitivity and accuracy from two decades ago must be reconsidered. Dickeson's personal communication indicates that NATA-accredited laboratories could not confirm putative positive specimens to international standards. Expecting insensitive and inaccurate tests for perhaps unknown Borrelia strains to meet international standards for diagnosis does not seem like a practical or logical exercise. Furthermore, it is a double-standard that international test results are not accepted but international diagnostic standards are considered the benchmark.

(e) Other Borrelia species associated with disease *Pages 10 to 14*

This section highlights that various ticks can transmit various Borrelia species. As the Robert Koch Institute purports, climate and landscape changes, as well as increased travel, all contribute to changes in vector-borne infectious disease patterns. Climate change has been very topical in the media in recent years and Australia has experienced extremes of temperature, breaking many previous records. Vector-borne infectious disease patterns from a decade or two decades ago may have transformed into new patterns in 2014. It would seem that lice and ticks (soft and hard) should be studied afresh, utilising the

best laboratory tests the world has to offer, and all diseases they carry, Borrelia and otherwise, should also be studied afresh. Such an approach would provide a platform for evidence-based medicine.

Page 13, paragraph 3, notes that '*B. theileri is a pathogen of cattle…transmitted by Rhipicephalus microplus, the cattle tick…found widely in Australia but not believed to infect humans*.' In a Chinese study, Chu et al (2008) detected B. burgdorferi (garinii species) DNA in 3 of 21 (14.29%) Rhipicephalus microplus ticks tested by a nested PCR. They conclude that '*the result of B. garinii infection in R. microplus present[s] additional human and animal infection risks following [a] bite*.' Chu et al also found 16 of 200 (8%) rodents, inclusive of four species, PCR positive for B. burgdorferi DNA, 12 rats positive for B. garinii and the remaining 4 positive with a B. valaisiana-related group. They note it is yet to be determined if B. valaisiana can cause disease in humans.

It is of note that B. miyamotoi was discovered in Japan only eight years ago and its role in human disease demonstrated even more recently in 2011 in Russia.

Page 14, paragraph 2, notes that '*louse-borne and tick-borne relapsing fevers have not been reported in Australia*.' SLA contends that this may not be an accurate summation as few doctors would even think to test for such causes of fevers and illness in Australia, and if such a cause was considered, accurate testing is not available. If the Lyme(-like) disease current patient experience is taken into consideration, any patient reporting an illness they thought came from lice or ticks probably met a wall of denial of the possibility.

(f) Borrelia species in Australia *Page 14*

The tone of this section is dismissive of interesting findings from research of earlier decades. No major efforts have been made to initiate more recent research to investigate the limited but significant results of studies from the 1950s and 1960s.

Although Russell & Doggett et al (1994) had successfully isolated and grown spirochaetes from ticks infesting animals with symptoms similar to those occurring in human sufferers of Lyme disease, these spirochaete-like objects were dismissed as artefacts. While this potentially significant finding was brushed aside, the work of researchers at the Royal North Shore Hospital (Bernie Hudson and Michelle Wills) found that approximately 20% of 1,024 people tested WB blot positive to B. garinii (56% of the positive results), B. afzelii (34% of the positive results) and B burgdorferi (10% of the positive results). Hudson and Wills' results, in view of Russell & Doggett's putative artefacts, warranted further research. Instead, the results and unanswered questions have been brushed aside for two decades.

Apart from the work of Mayne (2012), the most recent Borrelia-focused research to which page 14 can refer is from 1995. Considering that the last few years have seen the discovery of new Borrelia species in several countries and the appearance of known strains in new locations, it does not seem surprising that Mayne's findings suggested three distinct strains of spirochaete. Mayne's finding of a valaisiana-type genotype is interesting in light of Chu et al's (2008) findings, which also included a valaisiana – related group. Mayne's findings may just have answered Chu et al's note of query as to whether B. valaisiana can cause disease in humans.

The last paragraph of page 14 states that '*confirmatory evidence should be obtained in a second NATA-accredited laboratory*.' At this point in time, such an exercise would most likely produce two negative first-line results as Australia does not have adequate tests or interpretative criteria for Borrelia. Not all NATA-accredited laboratories are testing for all strains of Borrelia, i.e. European and American. Even the inclusion of both American and European strains leaves the possibility of novel indigenous strains out of the equation.

(g) Laboratory diagnosis *Pages 15 to 17*

Page 15, paragraph 1, specifies that '*laboratory support is an essential component of clinical* diagnosis.' Conversely, the *ILADS Guidelines for Lyme disease* state that '*treatment decisions should not be based routinely or exclusively on laboratory findings. The two-tier diagnostic criteria…lacks sensitivity and leaves a significant number of individuals with Lyme disease undiagnosed and untreated*.' Burrascano (2008) states that '*LB is diagnosed clinically, as no currently available test, no matter the source or type, is definitive in ruling in or ruling out infection*.'

In relation to the recently discovered Brazilian Lyme(-like) disease, Yoshinari et al (2010) state that '*BYS diagnosis is essentially clinical*.' A diagnostic guide based on 3 major and 3 minor parameters has been adopted and a positive diagnosis is made when a patient presents all 3 major parameters *or* 2 major and 2 minor parameters. These criteria allow a purely clinical diagnosis, which may be achieved without positive laboratory results and without visualisation of spirochaetes.

Page 16, paragraph 1, notes that research shows that '*CDC criteria for the United States are not applicable for European patients as their immune response is restricted to a narrower spectrum of Borrelia proteins compared with that shown by American patients*.' Page 22, paragraph 3, states that one of the two '*obvious [initial] specified reference laboratories would be the Institute of Clinical Pathology and Medical Research at Westmead*.' ICPMR only tests the American B. burgdorferi strain in their first-line test, effectively excluding patients with European strains from returning a positive. Should a patient return a positive and move forward to a second-line WB, then only IgG for B. burgdorferi and B. azfelii is run. This excludes B. garinii and all IgM possibilities. Furthermore, the European B. azfelii is interpreted using American CDC criteria of 5 positive bands rather than the European criteria of 3 bands *(Dickeson, ICPMR/NSW Health, web slides)*. There is no test available which would detect a novel, indigenous strain of Borrelia. Mayne (2012) detected B. valaisiana-type and B. bissettii strains but there is no test available for these and similarly less common strains. If ICPMR (or any Australian laboratory) is to be hand-picked as an initial specified laboratory, SLA would expect that that laboratory would already have the most advanced, sensitive comprehensive tests in use.

Page 15, paragraph 2, notes the questionable sensitivity and specificity of serological tests, commenting that '*the use of newer recombinant antigens rather than whole cell lysates have substantially improved their reliability*.' SLA would consider it highly contentious that ICPMR continues to use the whole cell lysate method, as Dickeson's recent slide presentation makes clear, and interprets this comment as supportive of the unreliable nature of the testing offered at ICPMR. Considering that ICPMR is put forward as innovative and the best Australia has to offer, the fact that ICPMR is not already using the most effective and reliable tests available casts doubt as to why ICPMR should automatically become a reference laboratory in an area in which they have already spectacularly failed.

Page 15, paragraph 1, notes that '*culture of spirochaetes from patient specimens remains the gold standard for specificity*,' lists difficulties associated with culture, then states that '*culture is seldom done or available*.' SLA contends that culture should be reassessed as a viable diagnostic tool, especially for chronic Lyme(-like) disease patients. Lida Mattman, a 1998 nominee for the Nobel Prize in Medicine for her work on stealth pathogens, developed a unique MPM medium and methodology to culture Borrelia from the blood of chronic, late-stage Lyme disease patients. Phillips, Mattman et al (1998) demonstrated reliable and reproducible culture of Borrelia Burgdorferi from the blood of chronic Lyme disease patients who had received extensive antibiotic treatment. All patients had failed or relapsed after treatment. Patients were selected from private practices, from both hyper- and non-endemic areas. While most patients had some serological evidence of Lyme disease, few had positive ELISAs (4/47 9% positive; 3/47 6% equivocal), and only just over half met CDC criteria for WB positivity (26/47 55%). From the 26 WB positive patients, 10 (28%) were IgG positive , 20 (77%) were IgM positive and 4 (15%) were both IgG and IgM positive. Controls were 23 patients from non-endemic areas, with non-Lyme chronic illnesses. Results demonstrated that 43/47 (91%) Lyme patient subjects cultured positive for B. burgdorferi, while 23/23 (100%) of controls cultured negative. Phillips, Mattman et al pursued the organism in its cell-wall deficient state, i.e. L-form. Typical spirochaetal morphology was seen when L-forms reverted to classic parent form, and the cultures showed Borrelia in varying stages of reversion.

The researchers note that L-form variants are fragile and require precise conditions to grow in culture, hence the development of a specifically designed and highly exact MPM medium and methodology. Phillips, Mattman et al not only demonstrated the usefulness of culture, especially pertaining to chronic Lyme(-like) disease, but concluded that their study '*proves that chronic Lyme disease is of chronic infectious etiology*.' The researchers noted that their MPM medium could be useful in culturing a variety of other spirochaetes.

Page 16, paragraph 2, states that it is '*important that the 2-tier protocol is undertaken*.' In complete divergence, the recent Brazilian studies read as if a positive ELISA ***or*** Western Blot is enough to meet the positive serology parameter. This would imply that patients are not subject to a rigid 2-tier testing process and that a negative ELISA does not preclude a WB. Additionally, Mantovani et al (2007) stated that '*the diagnosis of Lyme Disease-Like Syndrome* (later renamed BYS) *is based on epidemiological and clinical aspects. Since the etiological agent has not been isolated or cultivated in Brazil, false-positive serology for B. burgdorferi is a helpful laboratory parameter*.' The Brazilians put an interesting false-positive laboratory finding to good use in their quest to narrow down the cause of patients' symptoms.

Furthermore, the Brazilians include a third WB 2 IgG and 1 IgM option, noting that the distinction between the acute stage dominance of IgM antibodies and convalescence stage dominance of IgG antibodies tends to disappear in relapsing outbreaks. As many Australian patients have this pattern of WB, it is important to investigate whether a similar relapsing type of disease may be present here, rather than continuing to declare atypical results as false-positives.

At this point, no test for Borrelia is reliable enough to hold up as gold standard. Until such a test(s) exists, SLA would prefer that newer tests are made available but are considered another tool in the tool-box, rather than definitive. Page 16, paragraph 3, discusses the C6 peptide ELISA. Embers et al (2012) note that '*to date, the C6 ELISA is the only test in which a decline in antibody titre is statistically associated with outcome of antibiotic treatment…not all animals, however, were spirochaete-free, so the question of what facet of infection is indicated by anti-C6 antibody titres is brought to the fore*.' Embers et al posit that '*anti-C6 titre declines with a significant reduction in spirochaetal burden, but a low number of organisms reside in the host; if these organisms are dormant, than transcription of VlsE also may be negligible, minimising restimulation with antigen*.' There are still unanswered questions about the reliability and sensitivity of the C6 ELISA.

Page 16, paragraph 4, discusses the poor accuracy and reproducibility of commercially produced Lyme disease kits, as well as lack of interassay standardisation and differing test methodologies, all of which may lead to a high number of false-positive and false-negative results. SLA notes that anecdotal patient accounts suggest that all positive Australian patients are told they are false-positive. SLA has never encountered a patient who has been told by an infectious disease doctor that they may be false-negative.

Page 16, last paragraph, notes that false-positives can occur from cross-reactions. Yoshinari et al (2010) state that '*in the absence of a Brazilian isolate, B. burgdorferi strain G39/40 of North-American origin [is used] in serological tests…patients with BYS develop positive serology (ELISA or WB) to B. burgdorferi in approximately 65% of cases, while in normal individuals the frequency of positivity is nearly 16%*.' If the potential 16% false-positive figure is subtracted from the total positive 65% of BYS patients positive for B. Burgdorferi, this leaves 49% of BYS patients positive for B. Burgdorferi. Instead of arguing over the 16% chance of false-positivity, the Brazilians use the knowledge that approximately half all BYS patients return a positive to B. burgdorferi as information which can be used in the essentially clinical assessment of BYS. Mantovani et al (2006) refer to a study by Pirana et al which showed that 39 of 200 (19.5%) serum samples of LDLS (later renamed BYS) patients with peripheral facial nerve palsy had positive serological reactivity to B. burgdorferi. Mantovani et al detail another study where 23.3% of BYS patients with sudden deafness react to B. burgdorferi.

The general discussion on pages 15 through 17 highlights that for the past 20 years, a period in which serious questions have been raised and significant findings have been dismissed in relation to Lyme(-

like) disease, laboratories have been allowed to run insensitive and inadequate tests which do not test for all strains of Borrelia known or suspected to cause Lyme(-like) disease, as well as to compound this insult by interpreting data with inappropriate guidelines. Furthermore, by the time tests are run, the patient is often in a state of immune dysfunction caused by the lengthy duration between time of infection and testing, and unable to produce an immune response. In the chance of a positive result, it is dismissed as a false-positive. There has been continual reference in the Scoping Study to evidence-based medicine but that seems to be very one-sided. It is enormously difficult for patients to 'prove' their Lyme(-like) disease when the main diagnostic criteria are laboratory tests but appropriate laboratory tests are not provided. The tests and methodologies are ensuring negative results. Evidence-based medicine would posit that the chances of returning positive results increase significantly when the correct tests are run, in appropriate timeframes for the nature of the test, in relation to the interaction of the disease and the patient's immune system. Evidence-based medicine would posit that if patients do not meet the criteria for other diseases on the differential diagnosis list, then they most likely do not have those diseases. Infectious disease doctors continue to misdiagnose patients with other diseases, such as Sarcoidosis, based on symptoms but without any ***specific*** laboratory evidence. SLA considers this unethical and a double-standard. The irony of using Sarcoidosis as a default position, is that in genetically predisposed people, having Lyme(-like) disease may be the trigger for a Sarcoid-like immune response. Judson *(Sarcoidosis:A Primer-Patient Education Guide, American College of Chest Physicians)* notes that '*while the cause of sarcoidosis is not known, medical professionals believe that Sarcoidosis results from an interaction between the patient's immune system and an unknown exposure. Researchers have found evidence that Sarcoidosis may have many causes; it may be triggered when a specific agent "fits" an individual patient's immune system and triggers the formation of granulomas. A useful analogy to describe this process is finding the right key that "fits" a specific lock. This may explain why several different exposures are associated with some, but not all, cases of sarcoidosis. These include bacterial exposures (including organisms thatresemble tuberculosis), metals, combustible wood products, and mould*.' It is entirely possible that some Australian patients have Sarcoidosis secondary to or triggered by Lyme(-like) disease. In such cases, the road to remission from Sarcoidosis would include controlling the Lyme(-like) infection. It may yet be proved that Sarcoidosis is not a disease in its own right but more a cluster of symptoms produced by an immune reaction. Hudson points out that genetics may play a role in Sarcoidosis: '*HLA molecules (the Human Leukocyte Antigen) and T-lymphocytes probably have important roles as elements of the immune system in the development of Sarcoidosis*.'

The anecdotal count of patients encountering elevated 1,25-dihydroxy is considerable, and the relationship between macrophages/monocytes and 1,25-dihydroxy can morph into a cycle which results in the formation of granulomas. Patients' anecdotal accounts also indicate that infectious disease doctors refuse to consider Lyme(-like) disease in the differential diagnosis and would prefer to leave patients without any diagnosis, rather than investigate Lyme(-like) disease. Many patients continue to be refused laboratory testing at all for Lyme(-like) disease, with this refusal extending to tests for co-infections. Many Australian patients have lengthy and long-standing medical records detailing their attempts to reach a diagnosis. The multiple probable diagnoses and misdiagnoses therein are testimony to the failure of our healthcare system. SLA contends that Australian patients diagnosed with any disease on the differential diagnosis for Lyme(-like) disease should be offered a review, including testing for Lyme(-like) disease. Current Lyme(-like) disease patients have experienced doctors offering unlikely and unsubstantiated diagnoses, with those doctors seemingly having no accountability.

The National Association of Testing Authorities, Australia, *(A Guide to using NATA Accreditation in Legislation, Regulation and Specification, 2nd Edition)* states that '*a measurement, test or inspection is not an end in itself but a means of collecting information on which to make a decision. It is also self evident that if the information is not correct, any decision based on the information is likely to be incorrect*.' The translation of this is that tests for Lyme(-like) disease in Australia are too inadequate to produce reliable results on which treatment decisions may be made. SLA would like to be advised where responsibility for this falls.

The NATA guide states that the government stakeholder role takes three forms, the first being '*government as regulators mandating/encouraging the use of NATA accredited facilities as a means of*

providing confidence that activities such as testing, measurement and inspection will contribute to achieving regulatory objectives.' SLA fails to see the logic in encouraging the use of NATA accredited facilities which do not have appropriate (let alone state-of-the-art) tests. SLA will also be interested to learn the responses from NATA, the NATA accredited laboratories and the government when Lyme(-like) disease ***is*** demonstrated and acknowledged in Australia, and it is clearly evident that patients have been denied diagnostics and treatment for years.

Many Australian patients have positive tests from Infectolab, Germany, and Igenex, America. In view of these laboratories being highly specialised, state-of-the-art facilities, SLA recommends that both are consulted and a study be initiated comparing the results of tests on various samples. It would be logical to include Australian Biologics and the NATA accredited laboratories put forward as reference laboratories by the government in such a study. The ***only*** way NATA accreditation can be of use to Lyme(-like) disease patients in the current situation in Australia is if NATA accredited laboratories adopt the test materials, methods and interpretation criteria of the international Laboratories.

'*NATA is Australia's only ISO/IEC 17011 compliant, laboratory accreditation body recognised both nationally and internationally. This position is recognised by the Commonwealth through a Memorandum of Understanding. As such, NATA has been given sole responsibility for laboratory accreditation and also for the accreditation of reference material producers*.' This arrangement has completely failed Australian Lyme(-like) disease patients. The ultimate responsibility for this needs to be specified, and NATA standards and guidelines need to be amended in such a manner as to prevent such a situation arising again. The rationale and prerequisites for the continuance of the Memorandum of Understanding need to be amended. All these documents need to specify procedures for ensuring appropriate tests are used in the first place, even if this means sourcing such tests from non-NATA accredited international labs. A policy needs to be put in place to allow Australian patients access to international tests when Australia cannot provide the required tests. NATA accreditation noted on the negative results of Australia's long-suffering Lyme(-like) disease patients is little solace, especially when they are holding positive results from international state-of-the-art laboratories in the other hand. NATA states that reliability of data is a prerequisite but is condoning inappropriate interpretation of unreliable results from inappropriate tests. The government has given NATA sole responsibility for laboratory accreditation, thus condoning NATA's mode of operation. The 2006 Productivity Commission review based continuance of the government's recognition of NATA on '*NATA appear[ing] to do an effective job*.' Who is going to take responsibility for the situation in relation to Lyme(-like) disease tests in Australia…NATA or the government?

The section on laboratory diagnosis does not address non-specific tests which may be useful in arriving at a clinical diagnosis of Lyme(-like) disease. Yoshinari et al (2010) note that standard markers of acute inflammatory activity such as ESR, CRP and mucoproteins may be normal '*even under inflammatory processes such as arthritis, meningitis or neuritis. This clinical-laboratorial dissociation is a common aspect of BYS and it indirectly shows how much the latent microorganisms are adapted to survive in the host…anaemia, leucopenia, transaminases elevation or bilirubins in BYS patients may suggest coinfections with other tick-borne zoonoses, such as babeiosis and ehrlichiosis*.' Mantovani et al (2006) notes that there may be high levels of circulating IgE antibodies, hypergammaglobulinemia and antinuclear antibodies present.

Red Laboratories, Belgium, states CD14, expressed in monocytes/macrophages and playing a critical role in the recognition of bacterial cell well components, may be elevated in patients suffering from Lyme disease. Red laboratories also state that an American study found that C4a complement was an early marker for Lyme disease in tick bite patients. Red laboratories acknowledges that patients with a very low CD57 cell count have more persistent immunologic defects and coinfections than patients with higher cell counts.

Burrascano (2008) notes that chronic Lyme disease infections are known to suppress the immune system, decreasing the quantity of the CD57 subset of natural killer cells. Burrascano states that a normal CD57 cell count is above 200 and that the aim is to return chronic Lyme disease patients to a

cell count above 60. Infectolab, Germany, notes that research and case studies have shown that chronic Lyme infections are often accompanied by changes in the cellular immune defense, particularly a decreased absolute number and parts of the activated NK-cells (CD3-CD56+CD57+), with chronic Lyme disease patients often having a parameter of 100 CD57 cells in the blood or less.

Douglass Hanly Moir Laboratories has a CD57 reference range with the lower limit at 30 cells. The lower limit has been decreased from 60 to 30 at some point in the last year or so. Such a low entry reference range contradicts the figures provided by Burrascano and Infectolab, with the figure most likely having been skewed by large numbers of Lyme(-like) disease patients being tested.

In the same way as Angiotensin Converting Enzyme *may* indicate Sarcoidosis, while not specific to Sarcoidosis, the CD57 cell count *may* indicate chronic Lyme(-like) disease, while not specific to chronic Lyme(-like) disease.

It would seem prudent to review the abnormal, non-specific pathology results presented by Lyme(-like) disease patients. Anecdotal patient accounts suggest that inflammation may present with such markers as low to moderate elevations in ANA, 1,25-dihydroxy and ACE, co-existing with normal, even low normal, ESR and CRP. Patterns warrant investigation, along with the role that genetics play.

Iliopoulou et al (2009) found that chronic Lyme arthritis is linked to HLA-DRB1*0401 (DR4) and related alleles. Patients whose arthritis resolved showed an increased frequency of HLA-DRB1*1101 (DR11). Kovalchuka eta l (2012) found that HLA-DRB1*04 and HLA-DRB1*17 (03) '*may contribute to the Lyme borreliosis development in Latvian* population.' Infectious disease doctors (in denying the possibility of Lyme(-like) disease) are comfortable in highlighting HLA genetic susceptibility to patients in terms of other HLA associated diseases, such as Coeliac disease, but not in relation to Lyme(-like) disease. HLA and other genetic susceptibilities warrant research as they impact on diagnostic test effectiveness and individualised patient treatment plans.

Sarcoidosis is virtually unknown (one case appears in the literature) in full-blooded Australian Aborigines. MacGinley & Allen (1997) note that Australian Aborigines who have developed Sarcoidosis are found to have a European (Celtic) ancestor in their family tree. This would suggest that Australian Aborigines have unknown genetic factors which are protective from the development of Sarcoidosis. SLA failed to find any studies on Lyme(-like) disease in Australian Aborigines. On the basis that Australian Aborigines most likely have genetic factors affecting the immune system significantly enough to prevent Sarcoidosis, SLA considers it would be worthwhile to study Lyme(-like) disease in full-blood and non-full-blood Australian Aborigines. The questions to be considered are:

(1) Do Australian Aborigines develop Lyme(-like) disease at all?

(2) Do Australian Aborigines experience similar manifestations and course of disease as non-Aborigines?

(3) Which co-infections do Australian Aborigines most frequently present?

The answers to these questions could be very productive. If there are indigenous strains of Borrelia in Australia, perhaps Australian Aborigines have evolved an immunity; perhaps they are genetically less susceptible to all Borrelia, in the same manner as to Sarcoidosis. It would be interesting to study people who have non-Borrelia infections from vectors, without the co-existent and complicating factor of Borrelia.

Barker et al (2012) studied tick-borne haemoplasma infections, and their correlation with other haemoparasites, among free-roaming canine populations associated with Aboriginal communities. These canine populations have endemic Rhipicephalus sanguineus infestation and the associated infections Anaplasma platys and Babesia vogeli. As a naturally occurring model, it would be useful to investigate the Lyme(-like) diseases and co-infections presented by free-roaming canine populations associated with Aboriginal communities from varying locations, and the same in the Aboriginal communities

associating with the canines. The free-roaming nature of the canines would ensure that a wide range of vectors would be encountered.

(h) Co-transmission of tick-borne organisms *Pages 17 to 20*

The reliability of the tests for Borrelia available in Australia is very questionable, with most Australian patients remaining negative serologically. In view of this, it would be naïve to expect tests for co-infections to be reliable. Furthermore, anecdotal patient accounts reveal that most have been denied testing for co-infections by infectious disease doctors as "they don't have Lyme disease."

Anaplasma & Babesia *Pages 17 to 18*

SLA has noted *(Herein, Pge 4, Paragraph 3)* that there is a possibility that Rhipicephalus sanguineus may be implicated in transmission of Borrelia, and if this proves true, Anaplasma and Babesia could easily be co-transmitted *(see previous paragraph, this page)*. Yoshinari et al (2010) state that '*ticks from the Rhipicephalus microplus species cannot be discarded as participant of zoonosis transmission cycle*' *(Herein, Pages 6 to 7)*. Mayne (2011) found that 16% of 25 patients were positive for Anaplasma phagocytophilum, and 13 of 41 patients (32%) were positive for Babesia species, with one patient who had never been out of Queensland positive for Lyme disease, Babesia duncani, Babesia microti and Bartonella hensalae. Mayne found 3 other patients with the same co-infections from the east coast of Australia.

Bartonella *Page 18*

Mayne (2011) found 9 of 41 patients (22%) positive for Bartonella.

Candidatus Neoehrlichia mikurenis *Page 18*

Many infections supposedly not in Australia have been demonstrated in Australia. This organism has now been found in several countries, so warrants investigation in Australia.

Ehrlichia *Page 18*

Barker et al (2012) found 3% of dogs positive for Ehrlichia canis from Pmara Ti Tree, Northern Territory.

Co-infection concerns *Page 20*

The Scoping Study acknowledges the problematic issue of co-infections, including viral infections, and notes that multiple infections may lead to more intense and prolonged symptoms. In view of this, SLA recommends that testing for Borrelia should include testing for co-infections. It is of concern that most Lyme(-like) disease patients, even those with positive laboratory results, have not been tested for co-infections. Burrascano (2008) describes Lyme as the '*illness that results from the bite of an infected tick. This includes infection not only with B. burgdorferi, but the many co-infections that may also result*.'

Major gaps in our knowledge of Lyme-like disease in Australia *Page 21*

Two glaring omissions to the list of eleven essential questions are:

(1) Why have Australian patients with Lyme(-like) disease been ignored for so many years?

and

(2) How has the current situation of patients with Lyme(-like) disease come into being in a first-world country, with state and commonwealth governments in jurisdiction overseeing public health, and a government endorsed system of laboratory accreditation in place?

A further question is:

(3) With whom or what department does the responsibility fall for keeping abreast of worldwide

change in infectious diseases?

The undated *(although contents indicate most likely 2007/8)* Wildlife Health and Biosecurity Workshop document *The need for improved disease detection, diagnosis, risk assessment, communication and response* notes that 60% of all human pathogens are zoonotic globally, 75% of emerging and re-emerging diseases in the past 30 years have been zoonotic, and most of the emerging diseases over the past decade have originated in wildlife. Lyme disease is included in the list of global examples of emerging zoonotic disease from wildlife reservoirs. Considering these figures were known around 2007/8, it is hard to comprehend how Lyme(-like) disease in Australia could be so completely ignored and actively denied for the subsequent six or seven years, especially when patients continuously produced positive test results to match their symptoms.

The Executive Summary of the report notes that '*historically, wildlife and invasive species health surveillance in Australia has fallen into gaps between agriculture, conservation and human health agencies. There is no direct agency responsibility for wildlife and invasive species health. Thus, we lack an integrated policy approach, along with operational tools, and critical resources for nationally coordinated wildlife health surveillance, risk assessment, education, communication and research*.'

SLA contends that perhaps the answer to Question 3 above lies in the two paragraphs beneath it.

The report states that lessons learnt from previous experiences '*include the need for a program for early intervention and ongoing monitoring and surveillance*,' as well as '*a database of wildlife health and disease*.' It would appear that refusal to acknowledge and monitor the growing incidence of Lyme(-like) disease in Australian patients is a direct aberration from these acknowledged needs.

The Australian Registry of Wildlife Health is described as '*a diagnostic and resource centre that improves Australia's ability to detect and diagnose endemic, emerging and exotic diseases of wildlife that could have negative impacts on Australia's…human health*.' It would seem that investigations of wildlife vectors and hosts of Borrelia and co-infections should have fallen into the parameters of this function. Why have investigations not already been initiated in view of the ever-growing number of Lyme(-like) disease patients?

The gaps and problems section of the report states that '*the current system of wildlife and invasive species biosecurity is disjointed and under-resourced…The current stand-alone nature of wildlife and invasive species health increases our vulnerability to undetected and undiagnosed disease. There is a clear need to improve relationships, communication, and collaboration among wildlife health, human health, livestock health, plant health, aquatic health, and environment sectors*.'

Distressingly, for current Lyme(-like) disease patients of Australia, the report continues on to identify as problems:

* '*delays of between 1 and 15 years between disease detection and diagnosis in wildlife*;'
* '*lack of available tests for key wildlife diseases within Australia, and a difficult process to export samples*;'
* '*the long process to characterise emerging disease agents in wildlife*;'
* '*the issue of who pays – need to consider a cost sharing agreement between states and commonwealth*;' and
* '*personal ownership of data and intellectual property issues*.'

It is not comprehensible to SLA how such a report, identifying roles, needs, and gaps and problems, can exist, when the entire experience of current Lyme(-like) disease patients of Australia contradicts every word of the report. SLA would like to know where the blame for this falls and where the responsibility lays.

One Biosecurity, A Working Partnership
The Independent Review of Australia's Quarantine and Biosecurity Arrangements
Report to the Australian Government
30 September 2008
Beale / Fairbrother / Inglis / Trebeck

The Executive Summary of this review states that the task of managing Australia's complex biosecurity regime has recently become even more challenging, due to several reasons including:

* '*population spread into new habitats and increasingly intensive agriculture, which increases the risks of zoonoses*;'
* '*climate change, which adds to the spread of pests and diseases (expanding range or habitats, changing migratory bird patterns, and weather events supporting the spread of disease vectors)*;
* '*an emerging shortage of highly qualified plant and animal pest and disease professionals*;' and
* '*financial constraints, as governments allocate scarce revenue among many competing demands*.'

The Applying Biosecurity section identifies emerging risks as:

* '*the urbanisation of rural regions, leading to a heightened risk of pest and disease incursions and zoonoses due to the increasing interaction of urban communities with agricultural production areas*;'
* '*increases in the international movement of people and goods*;'
* '*intensification of agriculture*;'
* '*the global movement of genetic material*;'
* '*skill shortages in critical areas*;' and
* '*the challenges from climate change, including increasing numbers of viable natural pathways for exotic pests and diseases to enter Australia*.'

The review notes that since the 1996 Nairn Report, there has '*been a deterioration in cooperative arrangements and a level of fragmentation within the Commonwealth…evidence of a reduced flow of biosecurity information between the Commonwealth and the states…A new approach is needed…a common understanding between the Commonwealth [and] the states*.'

The review advises that the '*Commonwealth's powers to legislate arise from the Australian Constitution…To date, the Commonwealth has not exercised its full Constitutional power*.' While post-border activities have generally been understood to be the responsibility of state governments, the Commonwealth may extend its reach and regulation of biosecurity by exercising powers, such as the quarantine power. The review advises that '*the quarantine power is likely to support Commonwealth legislation that is designed to prevent the spread of pests and diseases from one part of Australia to another, regardless of whether the pest or disease is exotic or endemic. The quarantine power would also support measures to control and eradicate the pest or disease*.'

Preliminary Commonwealth Government Response to the Independent Review

The Commonwealth Government indicated the following in its preliminary response:

* '*The Commonwealth intends to negotiate with states and territories to develop and implement a national system, with the aim of achieving an agreement on the new system by end-2009. The government intends to address the issue of roles, responsibilities and decision making arrangements as part of the legislative development process*.'
* Agreement-in-principle to all recommendations pertaining to use of Commonwealth powers in biosecurity issues.

SLA's Request

The Scoping Study makes apparent the enormity of the task of investigating the presence or absence of Lyme(-like) disease in Australia. Designing and implementing research programmes and then developing guidelines for diagnostics and treatment will likely take years.

The Scoping Study maintains that '*the jury is out.*' This translates into Australian patients may or may not have Lyme(-like) disease. Despite Commonwealth communications to doctors advising of the CACLD's existence and purpose, the message seemingly received is that Lyme(-like) disease is not in Australia and so patients cannot and do not have it. State and territory governments appear set on denying Lyme(-like) disease and refusing its treatment until the CACLD delivers its recommendations. This is an untenable situation for current Lyme(-like) disease patients.

SLA requests that:

(1) A sub-committee or working party is formed, with a Commonwealth representative and a representative from each state and territory, for the express purpose of communication about Lyme(-like) disease and the treatment of current patients in the interim between now and the CACLD delivering its findings.

(2) An interim policy for management of current patients becomes an immediate priority.

(3) The Commonwealth exercise its full constitutional power, in respect of the quarantine power, in the event that the states and territories continue to deny the possibility of Lyme(-like) disease in Australia and continue to refuse consideration of the disease and its treatment for current patients. Current Australian Lyme(-like) disease patients have suffered long enough. It is unethical and inhumane to leave patients without means to easily accessible and affordable medical assistance and medications, especially in view of Lyme(-like) disease being not *disproved* in Australia.

Research Programmes to Detect/Confirm/Disprove the Presence of Lyme Borreliosis in Australia
Pages 21 to 22

The first paragraph of this section refers to lack of '*evidence-based scientific information…to come to an evidence-based answer which fulfils the criteria of Lyme disease or otherwise*.' SLA considers this a contentious statement, as there are many patients who have come forward with positive serological results for Lyme(-like) disease and/or symptoms matching the disease criteria of various strains of Borrelia. It is possible that evidence-based scientific information may have been discovered from studying these patients but instead they were ridiculed and shunted. ***Current Lyme(-like) disease patients are an untapped source of evidence-based scientific information***. It has been the government's choice to leave this pool of potential evidence-based scientific information untapped.

At this point, apart from patients identifying themselves and stepping forward, the government does not have a database of putative Lyme(-like) disease patients. SLA maintains that it was erroneous and a breach of biosecurity to neglect to add putative Lyme(-like) disease to the list of notifiable diseases, even if in the first instance only for reasons of collecting data to implement investigations.

The criteria for '*Lyme disease or otherwise*' would be hard to fulfil as the position acted upon in hospitals and by most doctors, especially infectious disease doctors, is that there is no Lyme disease in Australia and returned travellers have not been to endemic areas. SLA would suggest that the government and medical profession be open to considering the criteria of any known Lyme(-like) illness in the world at this point, including European and American strains of Borrelia, as well as Baggio-Yoshinari syndrome. When more is known about Lyme(-like) disease in Australia, Australian criteria will be determined.

Two initial actions are specified: (a) sharing of specimens and (b) confirmatory testing of positive clinical specimens using a NATA-accredited laboratory.

Action (b) is problematic in that:

1. Not all NATA-accredited laboratories have the most sensitive, accurate tests available;
2. Non-NATA- accredited laboratories may have more sophisticated, sensitive, state-of-the art tests then NATA-accredited laboratories;
3. NATA-accreditation has not prevented NATA-accredited laboratories from using insensitive, outdated, non-comprehensive tests to date, so amendments to policy/standards will be required to demonstrate that this issue has been resolved;
4. Policy needs to be created that specifies the process by which all strains of Borrelia will be incorporated into tests;
5. A hierarchy of responsibility needs to be implemented for keeping abreast of discovery of Borrelia strains worldwide and the various new diagnostic techniques employed in their testing, and for ensuring Australian laboratories offering testing for Lyme(-like) disease regularly update their tests and procedures accordingly; and
6. **All** testing for Lyme(-like) disease needs to be confirmed at a laboratory testing for all strains of Borrelia, using sophisticated, state-of-the-art, sensitive and reliable tests, both positive and negative results. Confirming only positive specimens means that all false-negatives will remain undiagnosed. It is time for the laboratories to prove their reliability.

Page 22, paragraph 2, invites the comment that greater involvement with global experts, not just European experts, would be a valuable resource. SLA would consider contact with Brazilian experts in relation to Baggio-Yoshinaro syndrome an integral tool in assessing the Australian situation, as the Brazilian experience may prove to be the best model on which to base Australian investigations and guidelines.

Concerns about the Institute for Clinical Pathology and Medical Research at Westmead being chosen as a specified, reference laboratory have already been noted herein. This NATA-accredited laboratory has failed Lyme(-like) disease patients. Any laboratory offering Lyme(-like) disease testing would need to meet the six criteria listed above in relation to '*initial action (b)*.'

Page 22, paragraph 4, neglects the question of what ails the many ill people in Australia, who display many of the characteristic features of Lyme disease, and who do not fit the criteria for other diseases. The core of the problem is ill people…it is irrefutable that they exist. This paragraph very much implies 'no Lyme(-like) disease until proven Lyme(-like) disease' and puts forward '*that it is always much harder to prove a negative!'* Proving a negative would involve finding definitive (including gold standard diagnostic measure) alternative diagnoses for all the current Lyme(-like) disease patients, explaining their positive Lyme-specific and Lyme-non-specific laboratory results within the context of the alternative disease, and eliciting improvement in condition through medications appropriate for the alternative disease. Failing to find the vector(s) does not prove a negative.

Major Research Programmes required to accomplish the Terms of Reference

1. **Experimental programme to determine whether there is a Borrelia species in ticks in Australia causing Lyme(-like) disease, or whether another tick-borne pathogen is involved in human Lyme(-like) disease.** *(Pages 22 to 24)*
   (i) Restricting investigations of causative agents to ticks limits the possibility of finding the causative agent. All biting vectors should be investigated.
   (ii) Vectors (ticks and otherwise) should be sourced from areas where Lyme(-like) disease has been reported or contracted, but also from varying terrains and climates throughout the country.
   (iii) Vectors (ticks and otherwise) sourced from veterinary clinics, general practice clinics and such, should be sourced from as wide and varied locations as possible throughout the country.
   (iv) Vectors (ticks and otherwise) should be sourced from free-roaming dogs who associate with

Australian aborigines, as well as the Aboriginal communities who associate with the free-roaming dogs, in several differing locations.

(v) An exhaustive investigation of all possible vectors should occur. Finding Borrelia in ticks should not preclude investigating other vectors, and finding Borrelia in a particular species of tick should not preclude investigation of the remaining species of ticks.

(vi) Vectors (ticks and otherwise) should be investigated for infections other than Borrelia, especially those frequently transmitted as co-infections.

2. Are Australian ticks competent to maintain and transmit B. burgdorferi s.l. genospecies, or other Borrelia species associated with relapsing fever? *(Page 24)*

(i) Competence studies should include vectors other than ticks.

(ii) Competence studies should include all known strains of Borrelia.

(iii) Competence studies should address the issue that there may be unknown, indigenous strains of Borrelia, or distinct variations of known strains.

(iv) Relapsing fever may be included in Lyme(-like) disease, so parameters need to be defined specifying the criteria of relapsing fever.

3. Do we have the best reagents for detecting novel Borrelia species, including B. miyamotoi, especially in clinical specimens? *(Pages 24 to 25)*

(i) It would seem logical to consult with experts from countries who have detected novel Borrelia species or have research in progress aiming to do so.

(ii) It would seem logical to consult the specialist tick-borne pathogen laboratories around the world, especially those which have appropriate tests for detection of novel species.

(iii) Most Australian patients with positive laboratory results have used Igenex, Infectolab or Australian Biologics. Extensive consultations should be initiated with all three laboratories and comparison studies run to investigate differences in results between the three laboratories. It may be that part of such an investigation could include the results current patients already have, with another part testing fresh specimens simultaneously with all three laboratories.

(iv) Sydney University has samples and raw data for many Australian patients of Lyme(-like) disease. The Sydney University Tick-Borne Disease Project should be prioritised for funding.

4. Clinical studies of patients presenting with symptoms suggestive of Lyme or Lyme-like disease. *(Page 25)*

(i) Current (especially long-term/chronic) patients and newly infected patients are two completely separate groups of patients.

(ii) There potentially could be three distinct groups of Lyme(-like) disease patients in Australia, including patients with an: (a) indigenous strain of Borrelia; (b) typical presentation of known Borrelia strains, with infection during overseas travel or perhaps domestically; and (c) atypical presentation of known Borrelia strains, adapted to Australian conditions, with infection during overseas travel or more likely domestically. Furthermore, some patients may be infected with more than one strain of Borrelia.

(iii) Studies of patients with Lyme(-like) disease should focus on symptomatology and non-specific-to-Lyme laboratory findings, equally as much as Lyme-specific laboratory findings.

(iv) Australia does not have reliable and up-to-date testing for Lyme(-like) disease and it may be that international laboratories need to fill the gap until Australian laboratories can match their reliability and sophistication.

(v) Not all newly infected patients develop EM.

5. **Retrospective investigation of chronic cases of Lyme borreliosis.** *(Page 26)*

   (i) Chronic Lyme(-like) disease is poorly defined. SLA recommends the term be divided into four categories and two sub-categories, as detailed in the discussion of PTLDS *(Herein, towards end page 11)*.

   (ii) Seeking evidence of past infection through serological tests for IgG to Borrelia antigens is a methodology which will miss many chronic patients. Brazil has found that the distinction between the acute stage dominance of IgM antibodies and convalescence stage dominance of IgG antibodies tends to disappear in relapsing outbreaks.

   (iii) Models of other bacterial infectious diseases known to have chronic and/or relapsing aspects should be studied. Whipple's disease is known to require antibiotic treatment for one to two years, and neurological involvement can lead to a chronic, relapsing path which requires at least ongoing intermittent antibiotic intervention.

   (iv) International expertise is clearly required. SLA notes that the Karl McManus Foundation holds an annual conference for the purpose of bringing international expertise to Australia and disseminating information.

SLA's Prioritisation of Research Programmes to Detect/Confirm/Disprove the Presence of Lyme Borreliosis in Australia

SLA agrees that all the components of the five suggested research programmes to detect/confirm/disprove the presence of Lyme Borreliosis in Australia are important but does not feel that they are actually five separate research programmes.

It would seem that programme 2, focusing on competency, and programme 3, focusing on reagents are essentially part of programme 1, which focuses on the pivotal question of the existence or absence of Lyme(-like) disease in Australia. Programme 1 cannot roll out and be resolved, without the concomitant initiation of programmes 2 and 3…information from these is needed to effectively carry out the first programme.

SLA views the suggested research projects as divided into four categories, based on focus:

1. Vector *(Programmes 1 to 3)*
2. Patient of three months or less *(Programme 4)*
3. Patient of more than three months *(Programme 5)*
4. Laboratories and tests.

Ideally, investigations should commence into all four areas as matters of priority.

The Vector Programme should answer questions pertaining to causative agents, important knowledge for prevention of infection, as well as developing diagnostic tests and treatment guidelines.

The Patient of <1 Year Programme is important in that it should maximise the chances of future patients arriving at a diagnosis in a timeframe which increases the chances of their Lyme(-like) illness being resolved, and not progressing to any form of chronic stage.

The Patient of >3 Months Programme is important because these patients may have a stealth form of Lyme(-like) disease, complicated by genetics and immune processes, which may be extremely difficult to eradicate or even irreversible. This complicates treatment and may become a lifetime burden for the patient.

The Laboratories and Tests Programme is vital as an aid for diagnosing patients in a timely fashion and confirming the disease. Identification of Borrelia strain and coinfections would allow treatment plans to be individualised to patient requirements.

If one programme must be prioritised, then SLA would recommend the Patient of >3 Months Programme.

Priority One: Patient of >3 Months Programme

Current patients cannot wait for the CACLD to reach conclusions, make recommendations and initiate guidelines on diagnosis and treatment.

SLA requests:

1. That an interim policy for management of current patients becomes an immediate priority.
2. That information is disseminated to GPs, hospitals, and particularly infectious disease doctors, detailing that Lyme(-like) disease is neither proven nor disproven in Australia, and remains under investigation. The message needs to be conveyed that it is possible that indigenous disease might exist, as well as known overseas strains, and that many patients have a credible symptom match and to-be-verified serology supportive of the diagnosis. The message needs to be conveyed that patients with a diagnosis should be assisted to embark upon or continue treatment.
3. That interim information about clinical symptoms, non-specific pathology tests, and specific tests is disseminated to GPs, hospitals, and particularly infectious disease doctors.
4. That interim treatment guidelines are disseminated to GPs, hospitals, and particularly infectious disease doctors.
5. That medications for the treatment of Lyme(-like) disease are added to the PBS list if not already on it and that the same medications are also available at the reduced Healthcare Card prescription cost. Restricted benefits need to be removed from the selection of Lyme(-like) disease treatment medications or Lyme(-like) disease needs to be included in the restricted benefit. Minocycline, for example, one of the basic mainstays of treatment for many patients, currently is listed as a restricted benefit for the treatment of teenage acne not responsive to other tetracyclines.
6. That investigative research start with this cohort of chronic or late-stage Lyme(-like) disease patients.
7. That doctors be given a government point of contact to whom they may direct questions and enquiries about the diagnosis and treatment of Lyme(-like) disease patients.
8. That a sub-committee or working party is formed, with a Commonwealth representative and a representative from each state and territory, for the express purpose of communication about Lyme(-like) disease and the treatment of current patients in the interim between now and the CACLD delivering its findings.
9. That the Commonwealth exercise its full constitutional power, in respect of the quarantine power, in the event that the states and territories continue to deny the possibility of Lyme(-like) disease in Australia and continue to refuse consideration of the disease and its treatment for current patients.
10. That as no method exists currently to disprove international test results, that these results be viewed as part of supportive evidence for a diagnosis of Lyme(-like) disease, rather than with ridicule.

Current Australian Lyme(-like) disease patients have suffered long enough. It is unethical and inhumane to leave patients without means to easily accessible and affordable medical assistance and medications, especially in view of Lyme(-like) disease being not *disproved* in Australia.

Priority Two: Patient of <3 Months Programme

The above points are applicable to this cohort of patients as well but information needs to be disseminated to GPs, hospitals, and particularly infectious disease doctors, conveying the message that prompt treatment with antibiotics can spare patients from a more persistent, long-term and devastating form of Lyme(-like) disease.

Patients of less than 3 months' duration should constitute the basis of a separate investigative process to that of the study of chronic, long-term patients.

Patients of less than 3 months' duration should be tested only by laboratories which can offer testing of all strains of Borrelia, using the most reliable methods.

Priority Three: Laboratories

A research project is warranted in which laboratories including, but not limited to, Igenex, Infectolab, a Brazilian laboratory recommended by BYS researchers, Australian Biologics and at least two NATA-accredited laboratories run tests on the same samples. It is imperative to determine why these laboratories are returning differing results.

This exercise is necessary to determine the most appropriate and reliable test materials and methods for Australia as:

1. Not all NATA-accredited laboratories have the most sensitive, accurate tests available;
2. Non-NATA- accredited laboratories may have more sophisticated, sensitive, state-of-the art tests then NATA-accredited laboratories;
3. NATA-accreditation has not prevented NATA-accredited laboratories from using insensitive, outdated, non-comprehensive tests to date, so amendments to policy/standards will be required to demonstrate that this issue has been resolved;
4. Policy needs to be created that specifies the process by which all strains of Borrelia will be incorporated into tests;
5. A hierarchy of responsibility needs to be implemented for keeping abreast of discovery of Borrelia strains worldwide and the various new diagnostic techniques employed in their testing, and for ensuring Australian laboratories offering testing for Lyme(-like) disease regularly update their tests and procedures accordingly; and
6. **All** testing for Lyme(-like) disease needs to be confirmed at a laboratory testing for all strains of Borrelia, using sophisticated, state-of-the-art, sensitive and reliable tests, both positive and negative results. Confirming only positive specimens means that all false-negatives will remain undiagnosed. It is time for the laboratories to prove their reliability.

Priority Four: Vectors

1. All biting vectors, not just ticks, should be investigated as causative agents of Lyme(-like) disease.
2. Vectors (ticks and otherwise) should be sourced from areas where Lyme(-like) disease has been reported or contracted, but also from varying terrains and climates throughout the country.
3. Vectors (ticks and otherwise) sourced from veterinary clinics, general practice clinics and such, should be sourced from as wide and varied locations as possible throughout the country.
4. Vectors (ticks and otherwise) should be sourced from free-roaming dogs who associate with Australian aborigines, as well as the Aboriginal communities who associate with the free-roaming dogs, in several differing locations.
5. An exhaustive investigation of all possible vectors should occur. Finding Borrelia in ticks should not preclude investigating other vectors, and finding Borrelia in a particular species of tick should not preclude investigation of the remaining species of ticks.
6. Vectors (ticks and otherwise) should be investigated for infections other than Borrelia, especially those frequently transmitted as co-infections.

Competence Studies

7. Competence studies should include vectors other than ticks.
8. Competence studies should include all known strains of Borrelia.

9. Competence studies should address the issue that there may be unknown, indigenous strains of Borrelia, or distinct variations of known strains.
10. Relapsing fever may be included in Lyme(-like) disease, so parameters need to be defined specifying the criteria of relapsing fever.

Reagents

11. Consult with experts from countries who have detected novel Borrelia species or have research in progress aiming to do so.
12. Consult the specialist tick-borne pathogen laboratories around the world, especially those which have appropriate tests for detection of novel species. *(See Priority Three above)*
13. Most Australian patients with positive laboratory results have used Igenex, Infectolab or Australian Biologics. Extensive consultations should be initiated with all three laboratories, a Brazilian laboratory and two NATA-accredited laboratories, and comparison studies run to investigate differences in results between all of the laboratories. It may be that part of such an investigation could include the results current patients already have, with another part testing fresh specimens simultaneously with all of the laboratories.
14. Sydney University has samples and raw data for many Australian patients of Lyme(-like) disease. The Sydney University Tick-Borne Disease Project should be prioritised for funding.

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