Laysan fever: prevention strategies

Cedric M. Yoshimoto, M.D., Feb 1999

Everything that we know about Laysan fever suggests that it is the result of one or more bites from the avian soft tick *Ornithodoros capensis*. In addition, the bites themselves are irritating, can become infected, and sometimes appear to undergo an allergic reaction. The best approach is to reduce or eliminate the risk of bites in the first place.

PHYSICAL METHODS

Clothing can protect against tick bites. Long-sleeved shirts and long pants prevent ticks from reaching much of the skin, but gaps must be covered, for example by tucking the pants cuffs into socks, and tucking the shirt into the pants waist. Some people (including men) have used nylon pantyhose as a cooler alternative to pants. Even with a complete outfit, some skin will be exposed, such as the hands & wrists, the neck & head.

CHEMICAL PROTECTION

Permethrin sprayed onto clothing is the best way to improve tick protection. This is used to protect people from the tick which transmits Lyme disease; it also is used to treat head lice and scabies in people. It is supplied as a spray can. In a well ventilated area, clothing should be sprayed evenly until damp (the cloth will become a little darker from dampness), then allowed to dry. The other side should be sprayed as well. Pay special attention to the edges of the cloth, where ticks could gain access to the skin. Treated clothing will be protective for weeks to months, even if the clothing is washed. Permethrin spray is not intended to be used on skin; you should promptly wash off any that gets on your skin. Nevertheless, it is very safe when used as intended. But if you develop a rash on an area where the treated cloth touches you, it would be better to stop using the permethrin.

DEET (diethyl toluamide) is the active ingredient in many insect repellents. It can be used sparingly on the exposed parts of your skin. It is safer to use a lower concentration of DEET - 30-35% maximum. The stick form is handy to avoid getting the DEET on the palms & fingers, so that you can eat without getting DEET onto your food.

OTHER MEASURES

Ticks usually rest in the sand, soil, and debris near birds nests, and also in shaded areas such as vegetation zones or under tents, buckets, and other solid objects. You can take extra precautions in these higher risk areas. You can spray permethrin on the **fabric thresholds, window edges, or around any holes in tents.** This will help prevent ticks from entering the tents. It also seems helpful to use a "kneeling cloth" when out in the field especially in vegetated areas or around bird nests. This is a piece of cloth large enough to sit or kneel on, treated with permethrin spray as described above. It reduces the risk for ticks to crawl onto you.

4/13/2007

Hi George -

Here's info on Laysan fever

that we give all our field campers

Brad

QUESTIONNAIRE

Study of "Laysan Fever" in Humans

NAME (will be kept confidential) _____
BIRTHDATE _____ GENDER _____
ALLERGIES (foods, medications, environmental agents) _____
_____
ONGOING MEDICAL CONDITIONS _____
REGULAR MEDICATIONS _____
PRIOR TRAVEL to (or residence in) areas where Lyme disease, Rocky Mountain spotted fever, or exotic diseases are present (place & year) _____
_____
_____
PRIOR ILLNESS related to insects, ticks, animals, or tropical disease (type of illness and year)
_____
_____
PRIOR TRIP(S) TO THE NWHI (islands and years) _____
_____
_____
PRIOR ILLNESS IN THE NWHI No _____ Yes _____ Month & year _____
Please describe briefly _____
_____
_____
ISLAND(S) in NWHI where you spent at least one night on this trip:

ISLAND(S)	_____	_____	_____
ARRIVAL DATE	_____	_____	_____
DEPARTURE DATE	_____	_____	_____

BITES

Did you receive any bites while on the island? _____
What bit you? Bird _____ Seal _____ Tick _____ Mosquito _____
Fly _____ Other _____
For tick bites, what was your reaction to the bite on the day of the bite? _____
_____
How long did the symptoms last? _____
Did any new symptoms develop later? _____
Did the original bite flare up again if you were later bitten by ticks? _____
Did you use any means of avoiding tick bites? _____
How effective do you think these methods were? _____
_____

ILLNESS

Did you become ill while on the island or within two weeks of leaving the island? _____

_____

Lose work time due to illness? _____ How long? _____

Seek medical care? _____ Take medication? _____

What medication? _____

On what day did your illness begin (approx)? _____

On what day did you first feel back to normal? _____

Which of the following symptoms did you have? Which symptoms were major (M), which were minor (m), or if you cannot distinguish between major & minor, which symptoms did you have (x)? On which day(s) of your illness did you have the symptoms? How long did the symptoms last?

SYMPTOM	M	m	x	Dates of Duration
Fever	__	__	__	_____
How High, if you took your temperature? _____				
Tiredness	__	__	__	_____
Rash	__	__	__	_____
Which part of the body? _____ What color? _____				
Separate spots or connected? _____ Size of spots? _____				
Flat or raised? _____ Other description _____				
_____				
Enlarged lymph nodes	__	__	__	_____
Which part of the body? _____				
Swelling	__	__	__	_____
Which part of the body? _____				
Headache	__	__	__	_____
Eyes sensitive to light	__	__	__	_____
Runny nose	__	__	__	_____
Sore throat	__	__	__	_____
Stiff neck	__	__	__	_____
Cough	__	__	__	_____
Shortness of breath	__	__	__	_____
Chest Pain	__	__	__	_____
Loss of appetite	__	__	__	_____
Nausea	__	__	__	_____
Vomiting	__	__	__	_____
Abdominal pain	__	__	__	_____
Diarrhea	__	__	__	_____
Painful muscles	__	__	__	_____
Which muscles? _____				
Painful joints	__	__	__	_____
Which joints? _____				
Restless sleep	__	__	__	_____
Bad dreams	__	__	__	_____
Other _____	__	__	__	_____

Thank you very much for your contribution: I would be happy to discuss Laysan fever with you if you wish. Cedric Yoshimoto, 211- Brown Way, Honolulu, Hawaii 96822.

Laysan fever
a summary of what is known as of October 1997

Cedric M. Yoshimoto, M.D.

"Laysan fever" is the term currently used to designate an illness of uncertain etiology affecting people in the remote Northwestern Hawaiian Islands (NWHIs). This nonspecific syndrome is generally self-limited, although prolonged symptoms occasionally plague some people. Treatment to this point has been empiric, based upon clinical features; no distinctive laboratory findings have been detected.

SETTING

The NWHIs extend to the northwest of the inhabited Hawaiian Islands, ranging from Kure in the northwest to Nihoa 1756 kilometers to the southeast. They are small low atolls or volcanic remnants. Except for Sand Island in Midway Atoll and Tern Island in the French Frigate Shoals, the islands are not inhabited. However, they are home to many millions of seabirds, migratory shore birds, and a few rare endemic land birds. They also serve as hauling out grounds for the endangered Hawaiian monk seal and the green sea turtle.

Most of the islands form the Hawaiian Islands National Wildlife Refuge, established in 1909, and Midway Atoll has recently reverted from the U.S. Navy to the U.S. Fish and Wildlife Service as the Midway Atoll National Wildlife Refuge. Wildlife personnel activities which increased in volume in 1991. Permanent buildings and airstrips exist on Sand Island (Midway Atoll) and Tern Island (French Frigate Shoals). On Laysan Island, management personnel live in tents in a year-round field camp. On other islands, people live in temporary tent camps.

EPIDEMIOLOGY

A retrospective mail survey of people who had been to the NWHIs indicated that people first became ill with Laysan fever in 1990 (Table 1). Surveillance since then shows a clear seasonal trend, with virtually all cases occurring between April and August (peaking in June), coinciding with the time of tick activity and tick bites (Table 2). There is a significant relationship between tick bites and illness. Cases have been reported from most of the islands, but the majority have been from Laysan Island, where attack rates have been about 25%. Men and women appear to be affected equally. The number of cases decreased in 1994 and decreased further in 1995.

Table 1
Cases of Laysan Fever by Year

1960-1898	0
1990	4
1991	7
1992	6
1993	12
1994	3
1995	2
1996	2

Table 2
CASES OF LAYSAN FEVER BY MONTH OF ONSET
through 31 Dec 1996

NUMBER OF CASES	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
15						x						
14						x						
13						x						
12						x						
11						x						
10						x						
9						x						
8						x						
7						x						
6						x	x					
5						x	x	x				
4					x	x	x	x				
3					x	x	x	x				
2			x	x	x	x	x	x				
1			x	x	x	x	x	x	x		x	
0												
Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec

VECTOR BIOLOGY AND ECOLOGY

The implicated ticks belong to the *Ornithodoros capensis* complex, and all individual ticks which have been identified from collections on Laysan Island and Midway Atoll have been *O. capensis*. These are parasites of seabirds and are widely distributed at seabird nesting sites throughout the tropics ad subtropics. They have been found to harbor a variety of avian viruses, including Hughes, Soldado, Johnston Atoll, and Midway viruses on various islands of the central Pacific Ocean. The pathologic effect of these viruses upon humans (or seabirds for that matter) is unknown. The O. capensis ticks have not been studies comprehensively for viruses, toxins, nor for other microbiologic agents of potential pathologic significance such as spirochetal bacteria, rickettsiae, mycoplasmae, etc.

CLINICAL ILLNESS

People who have been ill in this remote setting without another readily-identified illness have tended to have a syndrome characterized by some of the following non-specific symptoms: feverishness, fatigue, headache, nausea, anorexia, myalgia, and arthralgia. A minority of people have other symptoms including diarrhea, lymphadenopathy, and sleep disturbance. Respiratory symptoms and rash have not been a significant feature of this illness (Table 3). To assist study of Laysan fever, a case definition has been used: at least three of the first seven symptoms in a person who is symptomatic while in the Northwestern Hawaiian Islands, or within 14 days of departing the NWHI, with no other identified etiology. This represents a nonspecific syndrome which might describe the symptoms found in a large variety of arthropod-borne viral infections.

TABLE 3
FREQUENCY OF SYMPTOMS IN LAYSAN FEVER CASES
based on 29 cases
as of December 1993

SYMPTOM	PERCENTAGE OF CASES
fatigue	97
nausea	76
headache	69
anorexia	66
myalgia	66
feverishness	59
arthralgia	38
diarrhea	38
adenopathy	31
epig pain	28
chills	24
stiff neck	21
photophobia	17
bad dreams	14
dizziness	14
sweating	14
vomiting	14
abdominal pain	10
swelling	10
cough, slight	7
dyspnea	3

The great majority of persons meeting the case definition of Laysan fever have had a self-limited illness lasting up to seven days (median of four days). Several people have had symptoms which have persisted for prolonged periods, as long as seven weeks. These people with more prolonged illness have generally been treated with doxycycline (see Treatment), and side effects attributed to this medication (particularly sun sensitivity) have sometimes come to dominate the latter part of the illness.

LABORATORY STUDIES

Since people ill with Laysan fever are usually in isolated field camps at the time of their symptoms, there has been no laboratory testing done during the acute stage of illness. Several people who have returned to Honolulu have been tested either during the late stage of prolonged symptoms, or after resolution of their illness. Hemotologic and biochemical testing has generally been within normal limits. Serologic studies have been done on a limited number of patients. A single patient had a four-fold rise in IgM antibody to West Nile virus by hemagglutination inhibition (between pre-exposure and convalescent sera), while several other patients had no such rise. Several patients were tested for antibodies to Hughes virus, with negative results. At least one person had a negative serology for Lyme disease (1995).

TREATMENT

Persons who develop symptoms consistent with Laysan fever are generally treated with simple analgesics such as acetaminophen or ibuprofen, a limitation of activity, and adequate oral hydration. Most people recover within seven days.

In cases of prolonged illness (longer than seven days), people have generally been treated with doxycycline 100 mg bid for 10 days, in addition to the previously-mentioned measures. Some patients report an improvement of symptoms within three days of beginning doxycycline; others have continuing symptoms. To date, there have been no cases with chronic neurologic or rheumatologic illness such as occurs in chronic Lyme disease.

CONCOMITANT PROBLEMS

Local reaction to tick bites has frequently added to morbidity. The bites may be quite pruritic, sometimes requiring systemic antihistamines for relief. Old bites frequently flare with recurrent swelling and itching when new bites are sustained. Bites sometimes take two weeks to heal, and of course are prone to secondary bacterial infection.

The empiric use of doxycycline in a subtropical wilderness with little or no shade has resulted in photosensitivity reactions including sunburn in unexpected sites. One notable problem has been burns under the nails with subungual pain and serious drainage. Preventive measures including sunscreen with UVA protection, protective clothing and hats, and even gloves have been advocated, with some difficulty in balancing protection with personal comfort.

PREVENTION

In the absence of a definite etiologic agent, the prospect for active immunization is remote. Prevention efforts have focused upon the prevention of tick bites among people at risk. Measures have included an orientation to the problem for outgoing field personnel; instruction about clothing protective against tick bite; permethrin spray applied to clothing, sandals, and a "kneeling cloth" to be used while working in the field; and a permethrin-treated ground cloth under field tents. These measures have had some limited success in reducing the number of tick bites and perhaps in reducing the incidence of Laysan fever. The number of reported cases has been only two during each of the years 1995 and 1996, down from a high of 12 during 1993 (Table 1).

Cedric M. Yoshimoto 8 Mar 96

LAYSAN FEVER: SEASONAL OUTBREAK OF A DISEASE OF HUMANS IN THE NORTHWESTERN HAWAIIAN ISLANDS

ABSTRACT

Laysan fever is a newly-described illness of humans who enter into seabird colonies in the Northwestern Hawaiian Islands of the north central Pacific Ocean. Occurring since 1990 primarily between the months of May and August, it appears to be associated with bites of the seabird tick complex *Ornithodoros capensis.* It is a nonspecific febrile illness with two forms, a shorter self-limited one and a longer one which has been treated with antibiotics. Serologic, virologic, and bacterial studies are in progress.

INTRODUCTION

There are scattered reports of human illness among people who come into contact with remote seabird colonies in various parts of the world (1-5). These reports have generally been anecdotal, describe a small number of cases, and lack a solid epidemiologic or medical basis for supporting etiologic conclusions. Nevertheless, there is a common theme in these accounts, a possible association of illness with the bites of avian ticks, some of which have been shown to harbor viruses.

In 1991 I learned of several people who had become ill after being bitten by ticks while on Laysan Island, a small atoll about 709 nautical miles northwest of Honolulu, Hawaii. I began studying the problem at the request of and with the assistance of the U.S. Fish and Wildlife Service. This report describes the clinical illness, its epidemiology, and initial efforts to protect field workers.

SETTING

The Northwestern Hawaiian Islands (NWHI) are small atolls which are remnants of eroded volcanic islands lying northwest of the inhabited Hawaiian Islands in the north central Pacific Ocean (6). Most of these remote islands comprise the Hawaiian Islands National Wildlife Refuge (HINWR) and support seabirds, migratory shorebirds, endemic (passerine) birds, Hawaiian monk seals, and green sea turtles (7). In terms of human access, there are two categories of island. Tern Island in the French Frigate Shoals, Kure Atoll, and the Midway Islands are (or were) occupied throughout the year, have paved airstrips and permanent buildings, and entertain more human traffic. The other islands are accessible only by sea (hence infrequently), have no permanent structures or paving, and are managed to prevent the introduction of exotic life. Laysan Island, the largest island in the refuge, hosts the abovementioned fauna, a variety of insects and other arthropods (including avian ticks *Ixodes laysanensis* and the *Ornithodoros capensis* complex (8)), and endemic and introduced vegetation. Notably, there are no land mammals (besides humans) and no mosquitos. Wildlife workers on the less accessible islands live and labor under fairly rigorous conditions for part of the year, generally in tented field camps with imported water and food and limited human contact via shortwave radio. From about 1980, workers camped on Laysan Island in semi-permanent tents on the beach from about February through August. Beginning in 1991, human occupation became year-round, and in November of that year, a permanent tented field camp was established on higher ground about 200 meters inland (Elizabeth Flint, personal communication).

METHODS

The U.S. Fish and Wildlife Service (FWS), which has jurisdiction over the HINWR, controls access to these atolls and maintains the most nearly complete list of persons who have been there in the last 30 years. This roster was used to identify the people (termed "biologists") who had been to one or more of the NWHI. Additional field workers were identified through the other agency which sends wildlife workers to the NWHI, the National Marine Fisheries Service (NMFS) Endangered Marine Mammals Program. Finally, an environmental consultant identified a number of persons who had conducted a

clean-up of hazardous wastes at French Frigate Shoals during 1991. These people are designated as "clean-up workers , were present only on Tern Island, stayed in permanent buildings, and had less exposure to wildlife and natural areas than did the field biologists.

In December 1991, a survey questionnaire was mailed to everyone for whom an address could be located. The questions covered demographic information, a variety of exposures, animal bites, details of any tick bites, and the symptoms of any illness. This constituted the retrospective survey.

During 1992, prospective surveillance was carried out with the same questionnaire for persons who were going to Laysan Island. These people were informed about the possibility of an illness related to tick bites and were instructed on personal protection measures. During 1993, surveillance was extended to people going to any of the islands in the wildlife refuge as well as to people going to the Midway Islands for wildlife-related work. Also during 1993, these people were asked to volunteer to give a blood sample before and after their time in the NWHI. The 1993 phase of the investigation, which included phlebotomy, was approved by the University of Hawaii Committee on Human Studies (CHS #9240).

RESULTS

Retrospective survey

158 biologists were identified from the various rosters. 113 mailings were done to the persons with identifiable addresses. 104 survey responses were eventually returned from 76 persons (67.3%). Three of these surveys were completed prospectively, covering the 1992 field season; these were not included in the retrospective study. 14 clean-up workers returned one survey each. Table 1 summarizes the demographic description of the survey. Female respondents were more likely to provide information on more than one field season.

TABLE 1
RETROSPECTIVE SURVEY OF BIOLOGISTS IN THE NWHI THROUGH 1991

Number of persons replying retrospectively	73
female	24
male	49
Number of surveys completed retrospectively	101
from females	42
from males	59

(14 persons provided information for two or more separate years)
Median age for 101 surveys: 30 years (range 17-68)
Years covered by replies: 1964 - 1991

There was a variety of illnesses among the people working in the NWHI. Some of these were readily identifiable, including seasickness, skin infections, jellyfish stings, and a spider bite. Others illnesses could be described, but had several possible etiologies: recurrent diarrhea and an eruption of blisters. Finally, there was a series of people who suffered from an illness with non-specific symptoms and no readily identified cause. I have defined this as a syndrome, tentatively named "Laysan fever".

Laysan fever (LF) is defined as an illness characterized by certain symptoms and meeting certain exclusionary criteria (Table 2).

TABLE 2
CASE DEFINITION OF LAYSAN FEVER

1) At least 3 of the following symptoms must have been present while on one of the Northwestern Hawaiian Islands or within 14 days of departure, with no other likely cause: feverishness, fatigue, anorexia, headache, nausea, myalgia, arthralgia.

2) Using this case definition, there were ten cases of LF in eight separate individuals. Two people became ill on two separate occasions each within the same season. LF first occurred during 1990, affected people during the spring and summer (see below), occurred only on Laysan Island and French Frigate Shoals, had a considerable attack rate on Laysan Island (Table 3), tended to affect people in the middle age range (Table 4), and affected both sexes (Table 5).

TABLE 3
LAYSAN FEVER ATTACK RATES BY ISLAND BY YEAR

	Year						
	Unspecified	Multiple	1979-89	1990	1991	Totals	Percent
Unspecified			0/1			0/1	0.0
Multiple	0/1	0/15	0/12	1/1*	0/2	1/31	3.2
Kure			0/3			0/3	0.0
PHR				0/1	0/1	0/2	0.0
Lisianski				0/2		0/2	0.0
Laysan		0/1	0/12	1/3	4/7	5/23	21.7
FFS	0/1	0/2	0/13	1/2	1/9	2/27	7.4
Nihoa			0/1			0/1	0.0
Totals	0/2	0/22	0/44	3/10	5/23	8/101	7.9
Percent	0.0	0.0	0.0	30.0	21.7	7.9	

* This person was on both Laysan Island and FFS. Unspecif = island or year was not specified on survey. Multiple = information on survey covered more than one island or year.

TABLE 4
LAYSAN FEVER ATTACK RATES BY AGE, THROUGH 1991

Age	People with LF/Total	Percentage
15-19	0/1	0.0
20-24	0/16	0.0
25-29	3/29	10.3
30-34	2/25	8.0
35-39	3/14	21.4
40-44	0/5	0.0
45-49	0/6	0.0
60-69	0/2	0.0
Total	8/101	7.9

Note: Interpret with caution. Quality of information not strictly comparable with respect to age.

TABLE 5
LAYSAN FEVER ATTACK RATES BY GENDER, THROUGH 1991

Gender	People with LF/Total	Percentage
Female	3/42	7.1
Male	5/59	8.5
Total	8/101	7.9

Note: Interpret with caution. Females more likely to provide data for more than one survey.

The question of primary interest was whether there was an association with tick bites. This question is addressed in Figures Ia for all the respondents; Ib for the biologists only, because the clean-up workers had a qualitatively different exposure than that of the biologists; and Ic for Laysan Island only, because that island is more isolated, hence more insulated from the confounding effects of introduced human illness. However, the number of people on Laysan is small.

FIGURE Ia
ASSOCIATION OF REPORTED TICK BITE WITH LAYSAN FEVER
All respondents through 1991
All islands

	Tick bite	No bite	
Laysan fever	6	2	8
No LF	47	47	94
	53	49	102

Thirteen persons with unknown bite status,odds ratio (OR) = 3.00.
Fisher's exact test (one-tail) p = 0.162

FIGURE Ib
ASSOCIATION OF REPORTED TICK BITE WITH LAYSAN FEVER
Biologists only, through 1991
All islands

	Tick bite	No bite	
Laysan fever	6	1	7
No LF	47	35	82
	53	36	89

Twelve persons with unknown bite status, OR = 4.47.
Fisher's exact test (one-tail) p = 0.142

FIGURE Ic
ASSOCIATION OF REPORTED TICK BITE WITH LAYSAN FEVER
Biologists only, through 1991
Laysan Island only

	Tick bite	No bite	
Laysan fever	4	0	4
No LF	11	5	16
	15	5	20

Three persons with unknown bite status, OR undefined.
Fisher's exact test (one-tail) p = 0.282

Associations between the development of LF and other potential risk factors (physical contact with birds or seals, bites by birds or seals) were examined in a similar manner. The odds ratio (OR) and p value (one-tailed Fisher's exact test) for these associations are given in Table 6.

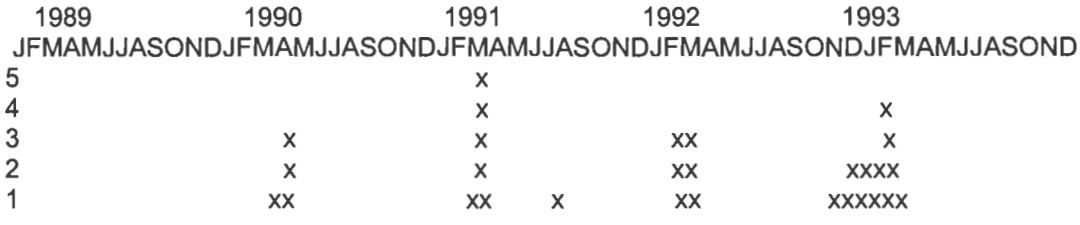
TABLE 6
ASSOCIATION OF FACTOR WITH LAYSAN FEVER

Factor	Biologists, all islands	Laysan Island only
Bird contact	OR = 0.209 p = 0.984	OR = 0.000 p = 0.040
Seal contact	OR = 2.029 p = 0.451	OR = 0.643 p = 0.852
Bird bite	OR = 1.429 p = 0.512	OR = 0.333 p = 0.343
Seal bite	OR = 3.120 p = 0.959	OR = 2.333 p = 0.912

Surveillance during 1992 and 1993

Prospective surveillance of the biologists going to Laysan Island during 1992 or to any of the NWHI during 1993 continued to demonstrate a pattern of illness during the spring and summer (Figure 2). The number of cases tended to increase each year.

FIGURE 2
EPIDEMIOLOGIC CURVE OF CASES OF LAYSAN FEVER
Through 31 Dec 1993
By month of onset



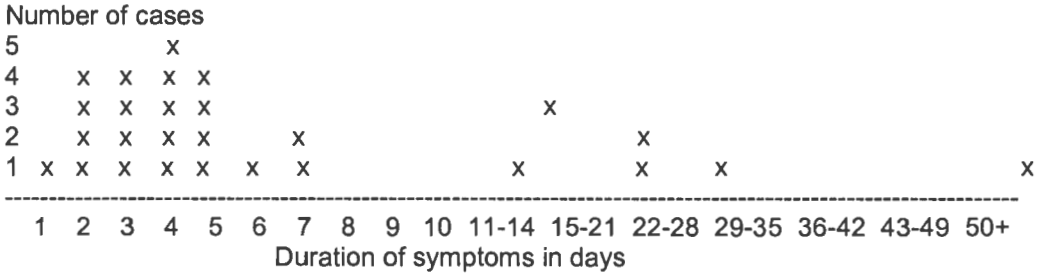
For Laysan Island during 1992, there were five cases of LF in five different people among the 11 who returned a survey, yielding an attack rate of 45.5%. For the first time in 1992, there were cases of LF which lasted for longer than a week (see below).

Clinical features

Including both the retrospective survey and the prospective surveillance through December 31, 1993, twenty different persons reported an illness meeting the case definition of LF. Five of them were ill on more than one occasion (three were ill twice, one person three times, and one person five times), resulting in a total of 29 cases. It is possible that some of the repeat cases represent relapses rather than separate illnesses, although (with one exception) there was a period of at least four weeks between the end of one episode and the beginning of the next. I have arbitrarily designated the episodes as separate cases if they were separated by a symptom-free interval of more than ten days.

The duration of symptoms appeared to fall into two clusters (Figure 3), suggesting either a broad spectrum of duration or that there might be more than one disease. An illness of short duration lasted up to seven days and was self-limited. Beginning in 1992, there was also an illness of longer duration, lasting 10 to 49 days. In four of these cases, empirical treatment with antibiotics was given (see below, treatment).

FIGURE 3
DURATION OF LAYSAN FEVER ILLNESS
As of December 1993



short = 21; long = 6; unknown = 2

The symptoms reported for cases are given in Table 7.

TABLE 7
FREQUENCY OF SYMPTOMS IN CASES OF LAYSAN FEVER
As of December 1993
As a percentage of all cases in the respective category

	All	Duration of symptoms			Island of residence	
Symptoms	cases	Short	Long	Unkn	FFS	Laysan
Fatigue	97	95	100	100	86	100
Nausea	76	71	83	100	71	74
Headache	69	57	100	100	57	68
Anorexia	66	67	83	0	43	74
Myalgia	66	67	83	0	28	74
Feverishness	59	62	67	0	57	58
Arthralgia	38	38	50	0	14	47
Diarrhea	38	19	83	100	43	32
Adenopathy	31	19	83	0	43	26
Epig pain	28	24	17	100	29	26
Chills	24	24	33	0	14	32
Stiff neck	21	14	50	0	29	21
Photophobia	17	14	33	0	14	16
Bad dreams	14	10	33	0	0	21
Dizziness	14	14	17	0	14	16
Sweating	14	10	33	0	0	21
Vomiting	14	14	17	0	43	5
Abd pain	10	0	50	0	14	11
Swelling	10	10	17	0	0	16
Cough, sl	7	0	33	0	14	5
Dyspnea	3	5	0	0	0	5
N =	29	21	6	2	7	19

Six of the seven defining symptoms were present in more than half of the cases. There is a suggestion that LF of longer duration is associated with more gastrointestinal symptoms (abdominal pain and diarrhea). LF on Laysan Island is more often associated with certain constitutional symptoms (myalgia and joint pain) and possible central nervous system involvement (bad dreams). I have not applied statistical tests to these comparisons because so many comparisons were made that some statistically significant differences might be expected by chance alone.

One person was evacuated from Laysan Island with prolonged symptoms and was examined in Honolulu 42 days after onset of her illness. Physical examination revealed marked tenderness of the liver edge with a liver span of 10 cm. in the right mid-clavicular line and a tender right axillary lymph node. Laboratory evaluation including complete blood count, serum chemistries, anti-hepatitis A IgM, anti-hepatitis B core IgM, hepatitis B surface antigen, and urinalysis were within normal limits. No other person with LF could be examined while symptomatic.

TREATMENT

The majority of cases of LF were self-limited and required little more than rest (taking time off work) and analgesics such as acetaminophen, aspirin, or ibuprofen.
However, beginning in 1992, there were several cases of prolonged illness. Of the six cases with symptoms of 10 days or longer duration, four were treated with an antibiotic: two because of prolonged symptoms, one because of initial symptoms similar to that person's previous prolonged illness, and one because of a large red area around tick bites which could not be distinguished (over the radio) from erythema migrans. In each case, the person began to feel better within two or three days of beginning doxycycline or an unidentified "strong antibiotic". In each case, the person eventually made a complete recovery.

TICKS

Several of the biologists who served in the NWHI captured one or more of the ticks which bit them. These were tentatively identified as *Ornithodoros* ticks and a representative sample was submitted to the National Tick Collection in Statesboro, Georgia, where James Keirans identified them as *Ornithodoros capensis (M.* Lee Goff, personal communication). Their accession numbers are RML 120808 (captured while biting), 120809, 120810, and 120811. The author collected ticks on Laysan Island during August, 1993, and Thierry Work collected ticks on Laysan and Tern Islands during November, 1993. All these ticks were tentatively identified as *Ornithodoros.* A sample was deposited as voucher specimens in the Bishop Museum, Honolulu, Hawaii. O. *capensis* cannot be reliably distinguished from O. *Denmark* after the larval stage (8), so field identification of species by non-specialists was not possible.

In the course of collection on Laysan Island, it was observed that ticks tended to concentrate in areas protected from sun and drying. These areas were at the field camp, under tents and plastic containers.

DISCUSSION

Association with tick bites

The retrospective study of association between reported tick bite and symptoms of illness may be distorted by recall bias, particularly for events in the distant past. This may also explain the absence of cases before 1990; a relatively mild illness might have been forgotten several years after the fact. Rumination bias may also distort the association; ill people may tend to recall tick bites or other potential associations to a greater extent than asymptomatic people. Classification bias is another potential problem. Tick bites are initially painless, and bites in people who were not sensitized might easily pass unnoticed.

After the association began to emerge, people going into the field were instructed on protective measures. On the one hand, this introduces the possibility of expectation bias; people who were bitten might be more likely to designate their sensations as symptoms, and people who became ill might be more likely to recall a tick bite. On the other hand, this situation defines a natural experiment: the earlier retrospective survey represents people who were not informed of a potential association of illness with tick bites, while the surveillance data were collected from people who knew of the potential association. Both sets of data point toward the same association, although the numbers are small and the association does not reach statistical significance. But they suggest that expectation bias is not a major factor.

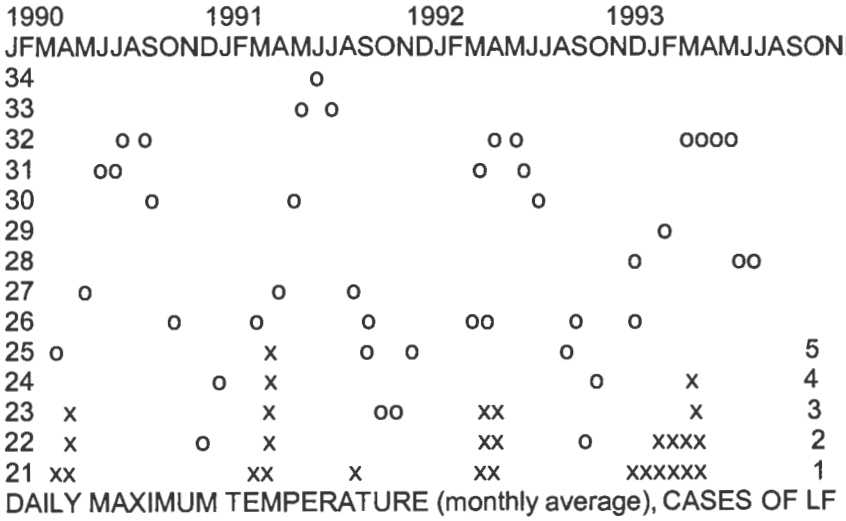
Supporting evidence for an association with tick bites is the occurrence of LF during the late spring and summer, coincident with the time when ticks are observed to be active in the NWHI (personal communication from several field workers) and consistent with the time of highest prevalence - May and June - in a study on Johnston Atoll (9).

The other potential risk factors yielded mixed results. Bird contact tended to appear protective. Since this is opposite to the proposed association, the proper test of association is the two-tailed Fisher's exact test, which yields a p value of 0.079 for Laysan Island only, which is not significant. I know of no biologic reason that physical contact with birds should protect against an illness. I suspect that this is merely a chance finding. Seal contact yielded associations in different directions for the two data sets, and neither approached statistical significance. Bird bites likewise gave conflicting results--which were not significant. Seal bites showed a relatively small association which was not at all significant. In summary, tick bites were the only factor under investigation which showed a robust association with LF and consistently tended toward statistical significance.

ETIOLOGY

There is a wide range of agents which might produce an illness like LF. Environmental stress (heat, cold) can produce many of the symptoms found in LF. However, the biologists did not mention unusual temperature conditions in connection with periods of illness. A check of the weather lows for Laysan Island (unpublished data from U.S. Fish and Wildlife service) showed that monthly averages for daily maximal temperature could be graphed with a clear seasonal pattern. When this is compared with the onset of cases of LF (Figure 4), it appears that LF tends to occur when the maximum temperatures reach about 27°C, and not when the temperature is either cooler or goes above 32°C.

FIGURE 4
CASES OF LAYSAN FEVER BY MONTH OF ONSET AND TEMPERATURE



degrees Celsius (= o) (= x)

Toxic substances may produce non-specific symptoms, including many of those associated with LF. There was a specific site on the northern beach of Laysan Island, the "dead zone," where an unusual concentration of dead birds and flies had been observed. An investigation of this site during 1993 found evidence of carbofuran, a carbamate insecticide (unpublished data). This chemical is a reversible cholinesterase inhibitor and produces an acute illness of short duration with abdominal pain, vomiting, headache, dizziness, excessive salivation, diaphoresis, and possibly muscle fasciculations, ataxia, respiratory distress, or coma (10). This is not the picture of LF. Furthermore, the biologists on Laysan Island avoided the dead zone once it was identified, but cases of LF continued to occur.

Naturally-occurring toxins abound in the marine environment, and ciguatera in particular is well known from Hawaiian waters (11). The illness is contracted by consuming reef fish which contain one or more toxins, and is characterized by constitutional, gastrointestinal, and neurologic (dysesthesias and paresthesias) symptoms (11). These neurologic features have not been reported in LF. Because of the risk of ciguatera, the field biologists are cautioned not to eat the fish from waters around the island, and nobody with LF has reported eating reef fish.

Biting arthropods may introduce toxic substances into bite wounds. The best known example is the paralysis toxin produced by a large variety of ticks (12), but other toxic reactions have been reported (13). In general, these toxins and the associated toxicoses in humans are not well described or understood. Since LF appears to be associated with tick bites, it (especially the short form) might represent a tick toxicosis.

Infectious agents are high on the list of suspects for the etiologic agent(s) of LF. Some agents may be present in the environment. For example, *Coxiella burnetii,* the agent of Q fever, may persist in soil or water for months (14), may infect some wild and domestic birds (15), may infect a variety of tick species (15), and may persist in tick feces for well over a year (16). Many species of ticks may transmit this organism, including at least six species of *Ornithodoros,* at least under experimental conditions (17). The symptoms of Q fever overlap with those of LF to a considerable extent (18).

Other rickettsial infections such as ehrlichiosis, caused by *Ehrlichia chaffeensis* (19,20), and scrub typhus, caused by *Rickettsia tsutsugamushi (21),* are arthropod-related infections which may resemble LF, particularly the longer form (19,22). However, there are no mammalian hosts for these organisms on Laysan Island. The suspected vector tick for ehrlichiosis, *Amblyomma americanum* (19,23) is also absent. The known vectors of scrub typhus are various species of trombiculid mites of the genus *Leptotrombidium* (21), and although *Leptotrombidium intermedium* has been recorded on Laysan (24), this species is unlikely to transmit *R. tsutsugamushi (21).*

Three zoonotic spirochetal diseases share a common set of symptoms - fever, headache, and myalgia - during their bacteremic phase which may be indistinguishable from LF (25). Lyme disease, caused by B*orrelia burgdorferi, B. garinii,* or an unnamed spirochete designated VS461 (26), is transmitted by hard ticks *Ixodes scapularis (27), I. pacificus, I. ricinus,* and I. *persulcatus (28).* It may also be sustained in the absence of mammalian hosts in seabirds and I. *uriae (29).* However, the only hard tick identified in the NWHI has been I. *laysanensis* (~), which is distinctly uncommon and has not yet been associated with bites in humans. Tick-borne relapsing fever is caused by spirochetes of the genus *Borrelia* and transmitted by several species of *Ornithodoros* ticks (30). However all the *Borrelia* associated with human illness to date have mammalian hosts. The only spirochete apparently found in O. *capensis* has been an unconfirmed report of *B. anserina* in penguins off South Africa (16). Leptospirosis is caused by a large number of serotypes of *Leptospira interrogans,* which is excreted in the urine of infected mammals into the environment, and is generally transmitted to humans by penetration of the skin or mucous membranes (31). Leptospirosis is well known from Hawaii (32). Seals and other pinnipeds in other parts of the world may harbor leptospira (33), but monitoring of Hawaiian monk seals has shown no evidence of such infection in these animals to date (William Gilmartin, personal

communication). Aside from Midway, no island of the NWHI supports any other wild mammal which could serve as a source of this infection.

Psittacosis, caused by *Chlamydia psittaci, is* commonly a moderately severe illness with a cough (often mild) and constitutional symptoms (34). The agent is well known in the inhabited Hawaiian Islands, infecting feral and exhibit birds at the Honolulu Zoo and occasionally causing human illness (35). It may be transmitted via aerosol and by direct contact with birds or their secretions (36). It has been isolated from a number of seabirds (36, 37, 38) and an avian soft tick, Argas *arboreus,* in Ethiopia (39), but tick transmission has not been shown.

In some ways the most likely infectious agent of LF is an arbovirus. Human disease from arboviruses commonly fits the syndrome of a nonspecific febrile illness, with fever, headache, malaise, nausea, possible muscle or joint pain, rash, lymphadenopathy, and a mild course of 3-7 days duration (40), which easily fits the case definition of LF.

In the central Pacific Ocean, three viruses have been isolated from seabird ticks of the O. *capensis* complex (O. *capensis* and O. *denmarki):* Johnston Atoll virus, Midway virus, and Soldado virus (41,42). There is no information available about the effects of the first two viruses in humans, although Johnston Atoll virus is related to Quaranfil virus, which causes a febrile human illness (43). Soldado virus in Morocco has been circumstantially linked with human illness (fever, pruritus, and rhinopharyngitis) (4). However, there appear to be several antigenic variants of this virus, one type isolated from O. *maritimus* in Europe and Africa (including the virus associated with the human illness noted above), and a type isolated from O. *capensis or O. Denmark* in the New World (including Hawaii) (44). Any potential pathologic effects on humans may differ according to the viral variant.

There may be other viruses of seabirds and their ticks which are candidates as the etiologic agent of LF. Table 8 lists viruses which have been isolated from either O. *capensis or O. denmarki* ticks in various parts of the world. It is possible that one of these viruses or an as-yet unknown virus is involved in LF.

TABLE 8
AVIAN VIRUSES ISOLATED FROM O. CAPENSIS OR O. *DENMARK*

Virus	Reference
Aransas Bay	(45)
Farallon	(46)
Hughes	(47)
Johnston Atoll*	(41,42,48,49)
Midway*	(41,42,50)
Raza (= Hughes)	(50,51)
Saumarez Reef	(5)
Soldado	(42,52,53,54,55,56,57,58)
Upolu	(49)

* = identified in the central Pacific region
Note: Baku and West Nile viruses were reportedly isolated from O. *capensls (59*), based upon erroneous tick identification (60).

CONCLUSIONS

LF is a nonspecific illness (or group of illnesses) affecting people who work on Laysan Island and other islands of the NWHI. It is usually self-limited, but four people with prolonged symptoms reported improvement after beginning an antibiotic. There is some evidence that LF may be related to the bites of avian ticks belonging to the Ornithodoros *capensis* complex. There is a non-significant (but suggestive) association between reported tick bite and clinical illness on Laysan Island and other atolls in the NWHI. Human illness peaks during the late spring and summer, when ticks appear to be most active. O. capensis complex ticks have been associated with several avian viruses in various parts of the world, including Hawaii.

Although investigation into the specific etiology or etiologies of LF is still in progress, it seemed prudent to begin preventive measures based on the apparent relationship with tick bites. People going into the NWHI are advised to take precautions against tick exposure, including clothing which covers most of the skin, permethrin spray for clothing (61,62,63), repellant for application to exposed skin, and awareness to watch for and avoid ticks. Permethrin-impregnated fabric is being tested as a ground cloth under tents, and also as a tent constructed of such fabric (Graniteville Company, South Carolina), to determine whether this can reduce the frequency of tick bite and of illness.

Determining the etiology of LF and preventing it in field workers will preserve their health and facilitate their work in protecting the wildlife in this unique ecosystem. Their experience with LF in the NWHI may have relevance for people contacting seabirds and avian ectoparasites in other parts of the world.

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