
Of Mice and Mongooses... A History of Leptospirosis Research in Hawaii

Charles R. Middleton MS*, Vernon E. Ansdell MD, FRCP, DTM&H**,
and David M. Sasaki DVM, MPH***

Abstract

A history of leptospirosis research in Hawaii is presented, beginning with the first published work in 1937. This account traces the leading researchers who described the organism and the disease, the diagnostic tests developed and used, the reservoir animals identified, methods of disease transmission discovered, prevention programs developed in the state, and research into more effective disease detection and prevention.

Introduction

Leptospirosis was first reported in Hawaii in 1907 in sugar cane workers. Since that time, it has been recognized in a wide range of agricultural workers, most recently in taro farmers. Over the past 50 years, it has been increasingly recognized as a recreational disease related to activities such as hiking, swimming, freshwater fishing and kayaking. Infection is caused by *Leptospira interrogans*, a coiled spirochete that is spread by environmental contamination of the urine of infected animals.

In Hawaii, wild animals such as rats, mice, and mongooses are the primary reservoirs of infection, harboring organisms in their kidneys and shedding them in their urine. Domestic animals, particularly dogs, and farm animals such as cattle and swine, are also important reservoirs of infection in residential and agricultural environments. This article highlights some of the extensive local research conducted over the past 60 years and emphasizes community educational programs to better understand and control this very important infectious disease.

Early Recognition of the Disease

Illnesses resembling leptospirosis have been described since ancient times. Castiglioni¹ quoted the famous Greek physician Hippocrates on a disease that possibly was leptospirosis: "When jaundice supervenes in fevers before the seventh day, it is a bad symptom, unless there be watery discharges from the bowels." In ancient China, rice harvest jaundice ("wei ni" and "lo ya goz fe") probably referred to leptospirosis. Similarly, in ancient Japan, 7-day fever ("odan-eki") and autumn fever ("aki yami") were names given to illnesses resembling leptospirosis.²

The first detailed clinical accounts of illness resembling leptospirosis were in the early 19th century. Larrey³ described an illness with fever and jaundice ("fièvre jaune") among Napoleon's troops during the siege of Cairo in 1800. This was probably leptospirosis. An early study of the disease was made by Adolf Weil, who named it "Infectious Jaundice" in a paper published in a German medical journal in 1886.⁴ Two years later another German researcher, Fiedler, named it "Weil's Disease." Subsequently, physicians around the world referred to icteric leptospirosis as "Weil's Disease."

In 1914, Inada et. al.⁵ made the important discovery of the causative organism of this disease. Noguchi in 1918⁶ described the organism as being 6 to 20 microns long and 0.1 to 0.2 microns wide, a fine tightly wound spiral enclosing an axial filament, and noted that it was rapidly motile. The rat was the most recognized reservoir, but other species such as foxes, cats, pigs, horses, dogs and gophers were also identified as carriers.

Early Research in Hawaii

Leptospirosis was first recognized in Hawaii in sugar cane workers. The earliest medical reports were from plantation doctors. The first death attributed to Weil's Disease was reported to the Territorial Department of Health in 1907.⁷ The Department of Health included leptospirosis as a reportable disease in the 1930's. Throughout the 1950's, however, the disease was reportable as "Weil's Disease," and not leptospirosis. For this period, the incidence was probably grossly understated as, currently, only about 25% of cases would fit the description of Weil's disease (febrile illness with jaundice).

Joseph E. Alicata, a parasitologist at the University of Hawaii, developed a diagnostic test for leptospirosis and was the first to detect the bacteria in animals and humans in Hawaii. He defined the epidemiology of leptospirosis among sugar workers on the island of Hawaii and in residents of Honolulu.

Early Studies in Humans

In 1937, Alicata published a case report documenting leptospirosis in a patient on the island of Hawaii.⁷ Physician Thomas Keay from Pepe'ekeo Hospital, sent him a patient's urine sample which he inoculated into a guinea pig. Alicata subsequently identified the organism from kidney sections of the animal. In the same paper Fred Irwin described the treatment used at the time, which included administration of convalescent sera from recovered cases, or repeated blood transfusions. Prophylaxis consisted of sterilizing the

Correspondence to:
Charles R. Middleton MS
615 Lawelawe St.
Honolulu, HI 96821
Tel: 808-373-2774

fecal and urinary discharges of patients, and “waging war against the rat.” In 1939, James Enright and Eric Fennel⁸ described Weil’s Disease in a case report presented to the Sixth Pacific Science Congress. In the first human serosurvey in 1943, Alicata and Virginia Breaks⁹ reported a 3.8% prevalence among 344 residents of urban Honolulu.

Discovery of Animal Reservoirs

Noguchi observed that many wild and domestic animals were thought to be reservoirs of leptospires in Asia.⁶ Alicata showed that this new occupational health risk was carried by rats and mongooses on the island of Hawaii.¹⁰ He also discovered that kidney cultures were more sensitive in detecting rodent infections than serology; but in mongooses, serology was more sensitive than culture for diagnosis of leptospirosis. In 1942, Alicata and Breaks¹¹ identified dogs (20% prevalence of 100 tested) in Honolulu as a reservoir of leptospires. In 1943, Alicata¹² developed a vaccine for dogs using formalized antigens. The early field studies in Hawaii were the beginning of an extensive series of investigations into transmission cycles involving various reservoir animals, fresh water and soil, and ultimately, humans.

Early Diagnostic Test Development

Alicata in 1942¹³ published “The Diagnosis of Leptospirosis” in *Plantation Health*, describing clinical symptoms and laboratory findings in patients diagnosed serologically by the newly developed microscopic agglutination test (MAT).

Understanding Clinical and Epidemiologic Aspects of Leptospirosis: 1944-1986

Alicata’s and Enright’s early work increased the concern about the disease in the medical community in Hawaii. During this period, the most prominent researcher was Henri Minette, Administrator of the Department of Health (DOH) laboratory in Hilo. In addition to developing a leptospirosis diagnostic laboratory in Hilo, he was involved in many animal and human surveys. With Bruce S. Anderson, he published an important historical summary of studies conducted in Hawaii through 1984.¹⁴ From the review of cases associated with sugar plantations, the need for better diagnostic tests and the scope of environmental sources of infection were addressed. In 1979, a DOH advisory committee was formed under the direction of Robert Melton, the Kauai District Health Officer, following two fatalities on the island in the late 1970’s, including an aquaculture farmer in 1978. In the same year, a fatal case occurred in an aquaculture farmer on Oahu. At the time, current Director of Health Bruce S. Anderson was very interested in this new industry. He enrolled in a Ph.D. program at the University of Hawaii School of Public Health to study the epidemiology of leptospirosis in aquaculture and taro farmers under Professor of Epidemiology, Robert Worth. Anderson’s studies were subsequently published by the DOH.^{15,16}

Human Case Studies

In 1944,¹⁰ Alicata reported a 12.2% prevalence among 860 plantation workers tested on the island of Hawaii. In the same year H. M. Patterson published a clinical review entitled “Weil’s Disease, A Report of Thirty Seven Cases.”¹⁷ Three years later he published a

larger review of 61 cases in the *Journal of the American Medical Association*.¹⁸ These studies, carried out at Ola’a Hospital on the island of Hawaii, were based on cases among cane-cutters of Filipino and Japanese ancestry from Ola’a Plantation. He described the patients with Weil’s Disease as “desperately ill” and unresponsive to sulfonamide compounds. He tried a second treatment consisting of blood transfusions from patients with prior infections. The patients responded dramatically and recovered. He also tried a third treatment, a new antibiotic – penicillin - on the last six patients in this series. It proved efficacious, leading to the rapid recovery of all six cases.

In 1977 W. A. Shrader reviewed 19 cases admitted to Honoka’a Hospital on Hawaii from 1962-1965.¹⁹ He noted that many of the cases had been treated on an out-patient basis, indicating that there were mild forms of the disease that were often self-limiting. He also observed that the illness occurred in two phases, an early septicemic phase followed by a secondary immune phase.

In 1980, Mary Serdula, a U.S. Centers for Disease Control (CDC) Epidemic Intelligence Service Officer assigned to Hawaii, conducted a survey of people who lived and/or worked in Waipi’o valley on the island of Hawaii (unpublished data). Of 82 people sampled, 26 (32%) had significant MAT ($\geq 1:200$) titers. Taro farmers who did not live in the valley and residents of the valley who did not farm taro were identified as being at risk for the disease. This study also identified a hyperendemic geographic area, which continues to be a high risk location for people who live and work there.

Anderson and Minette reviewed 556 cases that were reported between 1936 and 1984:¹⁴ 398 on Hawaii, 82 on Oahu, 53 on Kauai, 15 from Molokai and Lanai, and 8 from Maui. Case distribution by island has since changed; Kauai currently reports the second highest number of cases in the State and the highest incidence. Included in the review were surveys conducted by Anderson, James Brock, Harry Higa, John Gooch, Ned Wiebenga, Nicholas Palumbo, Sam Perri and Vernon Sato on aquaculture farmers, as part of Anderson’s Ph.D. thesis.¹⁵ He found an overall prevalence of 18.7% among 123 freshwater aquaculture farmers sampled statewide, documented a statistically-significant risk of exposure in aquaculture farmers on Oahu, and an extremely high annual incidence of 2.5/100 prawn farmers. Anderson, Higa, Brock, Serdula, Gooch, Wiebenga, Palumbo, and Minette identified a statewide prevalence of 60% in 55 taro farmers sampled, and in four of five watercress farmers tested,¹⁶ documenting a high risk of infection for those engaged in freshwater occupations.

In 1984, State public health veterinarian David M. Sasaki, did his University of Hawaii Master of Public Health field work project at the CDC in Atlanta, Georgia. He conducted a descriptive epidemiologic analysis comparing cases of leptospirosis reported nationwide with those reported from Hawaii for the five years from 1979 to 1983.²⁰ During that time, Hawaii accounted for 22% (118/525) of the cases reported nationally and had an incidence 50 times higher than the rest of the country.

Animal Surveys

In 1947 Alicata²¹ detected antibody titers in swine, identifying the animals as a reservoir and potential source of infection to humans. During this 43 year period, there were at least sixteen field studies of leptospires in feral reservoir animals. The primary species tested

in most of these studies were rats, including the Norway rat (*R. norvegicus*), the Roof rat (*R. rattus*), the Polynesian rat (*R. exulans*). The house mouse *Mus domesticus*, and the mongoose (*Herpestes auro-punctatus*) were also frequently sampled. Anderson and Minette¹⁴ summarized the data from the studies by island, species, number of animals tested and the percent positive. 7,645 small feral mammals were trapped and tested for leptospires during the 40-year period. Composite results for each species showed *R. norvegicus* with a 30% prevalence, *R. rattus*, 23.6%; *R. exulans*, 17%; and *H. auro-punctatus* with 29%. The island of Hawaii, because of the earlier recognition of leptospirosis in plantation workers and the presence of Minette's diagnostic laboratory, was the most actively investigated, accounting for 70% of the animals tested. 1,877 animals were tested on Oahu, and 332 on Maui. Minette's 1964²² and Marie Shimizu's 1984²³ studies described the largest surveys. An increased academic interest in the epidemiology of leptospirosis resulted in other animal studies. They included the aforementioned studies by Anderson et. al.,^{15,16} who also examined rodent infection rates on aquaculture and taro farms, and Masters of Public Health student field work projects by Alan Zahn,²⁴ and Peter Yan.²⁵

Gary F. Beck's Master of Public Health field work project in 1977 studied feral swine in Waimanu Valley on the island of Hawaii.²⁶ A 41% prevalence from 17 feral pigs sampled showed that feral swine were reservoirs of the disease.

Between 1983 and 1985, the State Department of Agriculture (DOA) in conjunction with the Southeastern Cooperative Wildlife Disease Study from the University of Georgia, conducted a survey of feral swine. In 1983, a 28% prevalence was noted from 134 animals sampled from the island of Hawaii. In the same year, an 82% prevalence was found in 56 samples from Molokai. In 1985, a 20% prevalence was noted in 10 samples from Maui. The samples were tested with the MAT.

Diagnostic Test Study

In 1945, Minette published a "A modified technique for reading the rapid slide agglutination test for leptospirosis" in *Science*,²⁷ describing his modification of that screening diagnostic test. This test was used by the DOH laboratory until 1992 when the test reagents were no longer commercially available.

Organized Research: 1987-2001

In 1987, then Director of Health John C. Lewin asked Sasaki to convene a committee to develop a comprehensive report, plan of action, and policy development for leptospirosis control in Hawaii. A community-based Leptospirosis Ad-Hoc Committee, sponsored by the DOH, was formed to promote community-wide participation in development of educational and control programs. State, city, federal, and private healthcare agencies have participated in the Committee from its beginning to the present. The Committee has sponsored epidemiologic and laboratory research, participated in scientific presentations at national and international meetings, published findings in peer-reviewed scientific journals, sponsored visits by internationally recognized experts, and developed a comprehensive health educational program that has gained international attention. In recent years, there has been an increased effort toward development of sensitive, rapid-screening serologic diagnostic tests for disease detection in humans through collaborations with the

Royal Tropical Institute (RTI) in the Netherlands. Most of the published work on leptospirosis by local authors from this period was an outgrowth of the Ad-Hoc Committee's activities.

Human Studies

The Committee's first activity was suggested by Arnold Kauffman of the CDC to more accurately determine the incidence of the disease in the state. A one-year active surveillance study on the island of Hawaii and identification of statistically-significant risk factors for the disease were undertaken. From July 1988 through June 1989, a five-fold increase in incidence was observed as compared with the previous four years of passive surveillance. Annual incidence on the island was estimated to be 128/100,000 population. A new risk factor was also identified, use of household water catchment systems in rural areas. Results of that very important study were published in 1993 by Sasaki, Lorrin Pang, Minette, Chester Wakida, Wallace Fujimoto, Sally Jo Manea, Robert Kunioka, and Charles Middleton in the *American Journal of Tropical Medicine and Hygiene*.²⁸

For her Master of Public Health field work project in 1992, Linda M. Odello compiled a database from DOH records on 404 reported cases diagnosed in the state between 1971 and 1990 and completed a descriptive epidemiologic analysis of the cases.²⁹ Her report was the basis for subsequent presentations at the 1994 International Leptospirosis Meeting in Italy by Sasaki³⁰ and by Vernon Ansdell at the 1995 annual meeting of the American Society for Tropical Medicine and Hygiene in San Antonio, Texas.³¹

At the 1997 annual meeting of the American Society of Tropical Medicine and Hygiene, presentations were made by Hawaii researchers as a part of a symposium organized by the DOH and Kaiser Permanente entitled "Leptospirosis: A Re-emerging Disease." Speakers included Ansdell, who presented an overview of the disease and its importance to residents in the tropics;³² Jeffrey Goodman, who presented "Clinical Leptospirosis in Hawaii: A practitioner's Perspective;"³³ and Sasaki, who presented a "Review of the Epidemiology and Prevention of Leptospirosis in Hawaii: 1992-1996."³⁴

In the 1980s and 1990s a number of small common-source outbreaks were reported, in addition to the normal sporadic cases reported to the DOH. In 1986 two sailors swimming in Kalihi Stream in Honolulu were hospitalized with severe leptospirosis. In 1987, circumstances surrounding an outbreak involving eight teen-aged boys who swam daily for two weeks in the Waimea River on Kauai, were published by Alan R. Katz, Manea and Sasaki in the *American Journal of Public Health*.³⁵ In 1991 investigation of a two case outbreak that occurred among 16 military personnel engaged in repeated recreational swimming at Kapena Falls in Nu'uuanu, Oahu, was published by Katz, Sasaki, Alan Mumm, Joel Escamilla, Middleton, and Sophio Romero in *Military Medicine*.³⁶ In addition to these recreational outbreaks, four outbreaks in agricultural venues were also documented: three ginger farmers in Kea'au, Hawaii, two corn farmers in Kahuku, O'ahu, two pig farmers in Wai'anae, Oahu, and two landscapers in Kapa'a, Kauai.

A retrospective case review also documented multiple infections in residents. From 1977 through 1996, there were records of seven residents with multiple infections. Intervals between infections ranged from one to 10 years. Five of the seven were exposed

Continued on p. 184

occupationally, including a taro farmer who was diagnosed with leptospirosis three times over a six-year period.

Increased numbers of recreationally-exposed cases in Hawaii over the past 50 years prompted Ansdell and Sasaki,³⁷ at the 1993 annual meeting of the International Society of Travel Medicine in France, to highlight the risk of exposure for adventurous travelers to the tropics. They recommended medical counseling and prophylactic doxycycline for travelers prior to recreational activities. Considering the diagnosis of leptospirosis in returned febrile travelers, particularly from the tropics and subtropics, has often been neglected because of the broad differential diagnoses (e.g. malaria, dengue fever, typhoid fever, and typhus). In 1999 at the International Leptospirosis Society Meeting in Australia,³⁸ they summarized six hospitalized cases in returned travelers diagnosed in Hawaii between 1992 and 1998. The study documented the importance of physicians maintaining a high index of suspicion for diseases such as leptospirosis in returned travelers when presenting with non-specific febrile illnesses.

In 1993, James Gollop, Katz, Raul C. Rudoy, and Sasaki published "Rat bite associated leptospirosis: An uncommon mode of transmission."³⁹ This article documented the only known reported case of leptospirosis associated with animal bite transmission in Hawaii.

Animal Studies

During this period, there were no known published animal studies. However, in 1987 and 1988, the DOA conducted statewide surveys of domestic cattle and swine, with MAT testing conducted by the U.S. Department of Agriculture. A 64% prevalence was observed in 139 cattle from Kauai, 70% of 168 cattle tested on the island of Hawaii, 35% of 55 cattle tested on Maui, and 86.2% of 29 cattle tested on Oahu.

In 1988, a domestic swine survey showed a 74% prevalence in 222 samples from the island of Hawaii, 75% of 199 animals from Maui, 76% of 63 samples from Molokai, 63% of 79 samples from Oahu, and 45% of 49 samples tested from Kauai. Although commercial vaccines are available for swine and cattle, none of the animals tested had a history of vaccination against leptospirosis.

In addition, small samples of dogs, bison, elk, horses, sheep and mongooses from the four major islands were tested, with prevalence ranging from 50 to 100%. However, many of these animals were suspected of having the disease. The above surveys documented the presence of widespread infections in domestic and feral animals throughout the state.

Diagnostic Test Development

Important environmental diagnostic studies to develop a rapid, inexpensive, accurate test to detect leptospires in water were carried out by Roger L. Fujioka, water microbiologist at the University of Hawaii at Manoa. He presented a study entitled "Recovery and Characterization of Leptospiral Bacteria from Environmental Waters in Hawaii"⁴⁰ at the Leptospirosis Research Conference in Japan in 1990, co-authored by Laura Young, and Bunnie Yoneyama. He and Richa Wilson presented a paper on isolation, characterization, and identification of saprophytic and pathogenic *Leptospira* at an International Leptospirosis meeting in Italy in 1994.⁴¹ Further work to detect pathogenic leptospires from water while suppressing

saprophytic strains was presented at the 1997 annual meeting of the American Society of Tropical Medicine and Hygiene in Florida.⁴²

A need for more sensitive screening diagnostic tests resulted in a 1994 study of a preliminary evaluation of the Quantitative Buffy Coat Analysis system for leptospirosis, by Kenton J. Kramer, Pang, Minette and Joseph Perrone.⁴³

The need for screening tests that are easier to use and store resulted in a study titled "International Multicenter Evaluation of the Clinical Utility of a Dipstick Assay for Detection of *Leptospira*-Specific Immunoglobulin M Antibodies in Human Serum Specimens."⁴⁴ It was authored by Henk Smits of the RTI and 19 others, including Sasaki and Harry Y. Domen of the Hawaii DOH. The test was evaluated in Hawaii. Studies were published in 2000 and 2001 by Smits et. al., including Sasaki, on latex agglutination^{45,46} and lateral flow assays⁴⁷ that evaluated screening tests that were easy to use and store. Paul Effler, Domen, Sandra Bragg, Tin Aye and Sasaki published "Evaluation of the Indirect Hemagglutination Assay for the Diagnosis of Acute Leptospirosis in Hawaii" in 2000.⁴⁸ In spite of the IHA being the only FDA-approved screening diagnostic test for leptospirosis at the time, the test had an overall sensitivity of only 41% of samples tested with the IHA when compared to the confirmatory MAT.

Educational Programs

The DOH and the Ad-Hoc Committee launched many educational initiatives, most of which continue today.

Public Education programs included the following.

1. Brochures were created in three languages: English, Japanese and Ilocano.
2. Red and white warning signs were posted along streams in state and county parks, as well as at exposure sites of previous cases.
3. Leptospirosis education displays were circulated at public libraries and displayed at health fairs, clinics and a hospital.
4. An educational videotape, sponsored by the DOH and Kaiser Permanente, was developed and distributed to all schools and libraries in the state.
5. A sign was created for display in buses on the islands of Oahu and Hawaii.
6. Presentations to enhance understanding the disease and its prevention were made to groups as requested.

The following medical education programs were developed to increase awareness of the epidemiology of the disease in Hawaii.

1. Presentations have been made at national and international scientific meetings.
2. National and international consultations have been conducted.
3. National and international experts have been hosted for seminars and consultation.
4. Grand round presentations have been made at local hospitals and medical organizations.
5. Frequent articles have been published in the DOH's bi-monthly newsletter, Communicable Disease Report, to update physicians on the epidemiology of leptospirosis.
6. Letters are sent to physicians who submit serum samples for diagnostic testing, and include the test result, and a request for convalescent samples for confirmatory testing.

The New Millennium Studies In Progress

Several studies are being prepared for publication. Clinical and epidemiologic analyses of 25 years of confirmed cases in Hawaii by Katz, Ansdell, Effler, Middleton & Sasaki^{49,50} are in press. Ansdell wrote a book chapter reviewing the disease entitled "Leptospirosis" which will be published in the upcoming 3rd edition of *The Travel and Tropical Medicine Manual*.⁵¹ The DOH is analyzing a study evaluating eight rapid screening tests for the diagnosis of leptospirosis in Hawai'i, in which the overall sensitivity by sample of the tests ranged from 27 (IHA) to 53%.

Concerns For The Future

Great progress has been made during the past century in Hawaii in understanding the nature of leptospirosis; its clinical manifestations, the uniqueness of its epidemiology in the state, its laboratory diagnosis, occurrence in travelers, and initiation of community prevention programs. However, further work is needed to more effectively control and prevent this disease.

There are over 600 people a year tested for leptospirosis in Hawaii. The DOH needs to implement a diagnostic laboratory for human and animal disease diagnosis, including MAT testing (confirmatory serologic test) and serotyping of isolates, to more effectively control and prevent this disease. The MAT is the most sensitive diagnostic test, more so than the recently developed polymerase chain reaction test (PCR), but is labor-intensive and requires paired samples drawn two weeks apart. In addition, a more sensitive rapid screening test is needed to assist clinical management of the disease.

It is still not known why the reported incidence in young children is low, and what role different animals play in transmission of the disease. Leptospirosis is an expensive disease, sometimes fatal, and often requiring protracted patient care (over 60% of identified cases are hospitalized). Because of its non-specific clinical presentation, leptospirosis is a disease that is usually recognized only when it is suspected. As a result, vigilance on the part of primary care physicians needs to be maintained. Continuing a high level of awareness in the community is also important to minimize exposures to the disease.

In 2000, a large outbreak of leptospirosis occurred among participants of the Eco-Challenge Adventure race in Borneo.⁵² Included among the ill were two residents from Hawaii. The 12-day race included jungle trekking, canoeing, sea paddling, canyoneering, scuba diving, mountain biking, and caving. The race reflects the current popularity of environmentally challenging athletic activities. The outbreak illustrated an important risk for travelers from Hawaii, and emphasized the value of consultation with a competent travel medicine specialist prior to departure.

As concerns about leptospirosis were highlighted in former Governor John Waihee's 1991 State of the State address,⁵³ health care institutions should lead in programs limiting the impact of this serious disease in Hawai'i's residents and tourists.

Author's Note

This paper does not describe all the research conducted in Hawaii, or list all published articles authored by Hawaii residents. In researching this document, over 85 articles were reviewed on lep-

tospirosis related to Hawaii. All but seven references cited refer to work conducted in the state. Our intent is to provide the reader an understanding of the history of leptospirosis research in Hawaii, some of the important people and work that has led to our current understanding of the disease. It is our desire that future researchers may find this helpful in seeking to expand the knowledge of leptospirosis and develop more effective control and prevention measures.

Dedication

This article is dedicated to Henri Minette DrPH (1916-2001) who mentored three generations of leptospirosis researchers in his 56 years with the Department of Health - 30 years as an employee and 26 years as an unpaid volunteer. His profound interest in the subject, technical knowledge, work ethic, keen sense of observation, ability to see the "bigger picture" and receptivity to the ideas of others fostered great progress in our understanding of this disease.

Acknowledgements

Grateful appreciation is extended to the following for their review of the manuscript and helpful suggestions: Philip P. Bruno DO, FACP, Chief, Communicable Disease Division, DOH; O.A. Bushnell PhD, Emeritus Professor of Microbiology, University of Hawaii, and Hawaiian historian; Vernon Miyamoto PhD, Chief, State Laboratories Division, DOH; and Robert M. Worth MD, PhD, Emeritus Professor of Epidemiology, University of Hawaii School of Public Health, and retired Chief, Communicable Disease Division, Hawaii Department of Health.

Authors

*Charles R. Middleton MS

Retired, Research Corporation of the University of Hawaii

**Vernon E. Ansdell MD, FRCP, DTM&H

Kaiser Permanente, Hawaii

***David M. Sasaki DVM, MPH

Hawaii Department of Health, Communicable Disease Division

References

1. Castiglioni A. The Golden Age of Greek Medicine. Hippocratic Medicine - A Biologic and Synthetic Concept. In: Krumbhaar EB. ed. *A History of Medicine*, 2nd ed. New York N.Y. Alfred A Knopf, Inc; 1947:169.
2. Faine S, Adler B, Bolin C, Perolat P. *Leptospira and Leptospirosis*, 2nd Ed. Melbourne, Australia: MediSci; 1999:1.
3. Larrey DJ. Memoires de chirurgie militaire, et capagnes. *J. Smith*. 1812, 2:18-32
4. Weil A. Uber eine eignethumlich, mit Mitzumor Icterus un Meijprotos comergejemde acta omfectoprimairamlait. *Deut. Arch. Klin. Med.* 1886, 9:209-232.
5. Inada R, Ido Y, Hoki R, Kaneko R, Ito H. The etiology, mode of infection and specific therapy of Weil's Disease. *J. Exp. Med.* 1916, 23:377.
6. Noguchi H. Morphological characteristics and nomenclature of *Leptospira (spirochaeta) Icterohemorrhagiae* (Inado and Ido). *J. Exp. Med.* 1918, 27:575.
7. Alicata JE. A Study of Trichinosis and Infectious Jaundice in the Hawaiian Islands. Trans. of the 47th Annual Meeting of the Hawai'i Territorial Medical Association. 1937, 95-103.
8. Enright JR, Fennel EA. Weil's Disease in Hawai'i, *Proc. of the Sixth Pacific Science Congress*. 1939, 5:337-343.
9. Alicata JE, Breaks V. A Survey of Leptospirosis in Honolulu. *Hawai'i Med. J.* 1943, 1:137-142.
10. Alicata JE. A Study of Leptospirosis in Hawai'i. *Plantation Health*. 1944, 8(4):1-33.
11. Alicata JE, Breaks V. Incidence of Leptospirosis among dogs in Honolulu as determined by serological agglutination tests. *J. Wash. Acad. Sci.* 1942, 32:305-308.
12. Alicata JE. Active Immunization of Dogs against Leptospirosis by the use of formalized leptospira antigen. *JAVMA*. 1943, CII(795):472-473.
13. Alicata JE. The Diagnosis of Leptospirosis. *Plantation Health*. 1942, 6(3):1-8.
14. Anderson BS, Minette HP. Leptospirosis in Hawai'i: Shifting trends in exposure, 1907-1984. *Int. J. Zoon.* 1986, 13:76-88.
15. Anderson BS, Brock JA, Higa HH, Gooch JM, Wiebenga NH, Palumbo NE et. al. A Study of the Epidemiology of Leptospirosis on Aquaculture Farms in Hawai'i. State of Hawai'i Department of Health. 1982, 153 pp.

16. Anderson BS, Higa HH, Brock JA, Serdula MK, Gooch JM, Weibenga NH et. al. A Study of the Epidemiology of Leptospirosis on Taro Farms in Hawaii. State of Hawaii Department of Health. 1982, 69 pp.
17. Patterson HM. Weil's Disease: A Report of Thirty-seven Cases. *Hawaii Med. J.* 1944, 3:213-221.
18. Patterson HM. Weil's Disease: Observations on sixty one cases with special reference to the use of Penicillin in six cases. *JAMA.* 1947, 134:1077-1080.
19. Shrader WA Jr. Leptospirosis in Hawaii. *Hawaii Med J.* 1977, 36:135-138.
20. Sasaki DM. Leptospirosis Surveillance in the United States and Hawaii: 1979-1983. University of Hawaii School of Public Health. 1984. unpublished observations, 1-22.
21. Alicata JE. Studies on swine leptospirosis. University of Hawaii, Ag. Exp. Sta. Biennial Report:1944-1946. 1947:100
22. Minette HP. Leptospirosis in rodents and mongooses on the island of Hawaii. *Am. J. Trop. Med. & Hyg.* 1964, 13:826-832.
23. Shimizu M. Environmental and biological determinants for the prevalence of leptospirosis among wild small mammal hosts, island of Hawaii. *Int. J. Zoon.* 1984, 11:173-188.
24. Zahn A. A Survey to determine the presence of leptospirosis in rodents and mongooses on the island of Maui, Hawaii. University of Hawaii School of Public Health. 1968, Unpublished observations, 1-25.
25. Yan P. Leptospirosis on Oahu. University of Hawaii School of Public Health. 1970, Unpublished observations, 1-18.
26. Beck GF. A survey of the mammalian fauna in the Waimanu Valley, island of Hawaii, for the prevalence of leptospirosis. University of Hawaii School of Public Health. 1977. Unpublished observations, 1-33.
27. Minette HP. A Modified Technique for reading the rapid slide agglutination test for leptospirosis. *Science.* 1945, 101(2619) 256.
28. Sasaki DM, Pang L, Minette HP, Wakida CK, Fujimoto WJ, Manea SJ et. al. Active Surveillance and Risk Factors for Leptospirosis in Hawaii. *Am. J. Trop. Med. Hyg.* 1993, 48(1):35-43.
29. Odello LM. Epidemiology of Leptospirosis in Hawaii: Analysis of 382 cases, 1971-1990. University of Hawaii School of Public Health. 1992. Unpublished observations, 1-42.
30. Sasaki DM, Ansdell VE, Odello LM, and Katz AR. Surveillance of Leptospirosis in Hawaii 1971-1990 and Changing Epidemiological Trends. VIIIth Meeting of European *Leptospira* Workers. Anzio, Italy. 1994.
31. Katz AR, Sasaki DM, Odello LM, Ansdell VE. Leptospirosis in Hawaii:1970-1990. Clinical and Epidemiological analysis of 189 laboratory confirmed cases. Annual Meeting of the American Society of Tropical Medicine, San Antonio, Tex, 1995.
32. Ansdell VE. Overview of *Leptospira* and the Epidemiology of Leptospirosis. Annual Meeting of the American Society of Tropical Medicine and Hygiene. Orlando, Fla, 1997.
33. Goodman J. Clinical Leptospirosis in Hawaii: A Practitioner's perspective. Annual Meeting of the American Society of Tropical Medicine and Hygiene. Orlando, Fla, 1997.
34. Sasaki DM. Surveillance, Prevention and the Epidemiology of Leptospirosis in Hawaii: 1992-1996. Annual Meeting of the American Society of Tropical Medicine and Hygiene. Orlando, Fla, 1997.
35. Katz AR, Manea SJ, Sasaki DM. Leptospirosis on Kauai: Investigation of a Common Source Waterborne Outbreak. *Am. J. Pub. Hlth.* 1991, 81(10):1310-1312.
36. Katz AR, Sasaki DM, Mumm AH, Escamilla J, Middleton CR, Romero SE. Leptospirosis on Oahu: an outbreak among military personnel associated with recreational exposure. *Military Medicine.* 1997, 162(2):101-104.
37. Ansdell V, Sasaki DM. Leptospirosis in Hawaii: Important Implications for the Adventurous Traveler in the Tropics. Third Conference on International Travel Medicine. International Society of Travel Medicine, Paris, France. 1993.
38. Ansdell V, Sasaki DM. Leptospirosis in travelers: An under-recognized hazard. International Leptospirosis Society, 2nd Mtg. 1999, Marysville, Australia.
39. Gollop JH, Katz AR, Ruddy RC, and Sasaki DM. Rat bite associated leptospirosis: An uncommon mode of transmission. *West J. Med.* 1993, 159:76-77.
40. Fujioka R, Young L, Yoneyama B. Recovery and Characterization of Leptospiral Bacteria from Environmental Waters in Hawaii. In Kobayashi Y, ed. *Leptospirosis: Proc. of the Leptospirosis Research Conference 1990.* Matsuyama, Japan: Hokusensha; 1991:419-430.
41. Wilson RB, Fujioka RS. Isolation, characterization and identification of saprophytic and pathogenic *Leptospira* isolated from environmental waters in Hawaii. VIIIth Meeting of European *Leptospira* Workers. Anzio, Italy, 1994.
42. Fujioka RS. Methods of Recovery of Pathogenic *Leptospira* from Environmental Waters to Assess Human Health Risks. Annual Meeting of the American Society of Tropical Medicine and Hygiene. Orlando, Fla, 1997.
43. Kramer KJ, Pang LW, Minette HP, and Perrone JB. Evaluation of the Quantitative Buffy Coat Analysis (QBC) System for the Detection of *Leptospira* in Human Blood. *SE Asian J. Trop. Med. & Pub.Hlth.* 1994, 25(4):788-9.
44. Smits HL, Ananyina YV, Cheresky A, Dancel L, Lai-a-fat RFM, Chee HD et.al. International Multicenter Evaluation of the Clinical Utility of a Dipstick Assay for Detection of *Leptospira*-Specific Immunoglobulin M Antibodies in Human Serum Specimens. *J. Clin. Microbiol.* 1999, 37(9):2904-2909.
45. Smits HL, van der Hoorn MAWG, Goris MGA, Gussenhoven GC, Yersin C, Sasaki DM, et. al. A Simple latex agglutination assay for the quick serodiagnosis of human leptospirosis. *J. Clin. Microbiol.* 2000, 38(3):1272-1275.
46. Smits HL, Chee HD, Eapen CK, Kuriakose M, Sugathan S, Gasem MH et. al. Latex Based, Rapid and Easy Assay for Human Leptospirosis in a Single Test Format. *Trop Med & Int Health.* 2000, 6(2):114-118.
47. Smits HL, Vestering M, Abdoel TH, Gussenhoven GC, Yersin C, Sasaki, DM, et.al. Lateral Flow Assay for the Rapid Diagnosis of Human Leptospirosis. *Clin. Diagn. Lab. Immunol.* 2001,8(1):166-169.
48. Effler PV, Domen HY, Bragg SL, Aye T, Sasaki DM. Evaluation of the Indirect Hemagglutination Assay for the Diagnosis of Acute Leptospirosis in Hawaii. *J. Clin. Microbiol.* 2000, 38(3):1081-1084.
49. Katz AR, Ansdell VE, Effler PV, Middleton CR, Sasaki DM. Assessment of the clinical presentation and treatment of 353 laboratory confirmed leptospirosis cases in Hawaii, 1974-1998. *Clin Inf Dis.* 2001, in press.
50. Katz, AR, Ansdell VE, Effler PV, Middleton CR, Sasaki DM. Leptospirosis in Hawaii, 1974-1998: epidemiologic analysis of 353 laboratory confirmed cases. *Am J Trop Med Hyg.* 2001, in press.
51. Ansdell VE. Leptospirosis. In Jong EC, McMullen R, eds. *The Travel and Tropical Medicine Manual, 3rd Ed.* Philadelphia, PA: W.B. Saunders Co., Inc; In press.
52. Centers for Disease Control and Prevention. Public Health Dispatch: Outbreak of Acute Febrile Illness among Participants in EcoChallenge Sabah 2000 Malaysia, 2000. *Morbidity Mortal. Weekly Rep.* 2000, 49(36):816-817.
53. Waihee J. 1991 State of the State Address. Honolulu Star Bulletin. January 20, 1991.

Schering/Key Pharmaceutical

Claritin-D 12 Hour
(5 mg loratadine/120 mg pseudoephedrine sulfate, USP)
Extended Release Tablets

Claritin-D 24 Hour
(10 mg loratadine/240 mg pseudoephedrine sulfate, USP)
Extended Release Tablets

Claritin RediTabs
10 mg (loratadine rapidly-disintegrating tablets)

Claritin Syrup
(loratadine) 10 mg per 10 mL



Schering Velvet Agena-Chee
Senior Sales Representative
Voice Mail (800) 782-2347
Box 3858

Schering Donn keoki Arizumi
Pharmaceutical Representative
Voice Mail (800) 544-5420
Box 8058

KEY Shawn Brady
Sales Representative
Telephone (808) 387-1409
Voice Mail (800) 554-5420
Box 1342
FAX (808) 373-1772
E-Mail shawn.brady@spcorp.com

Schering Mark Buquoi
Sales Representative
Telephone (808) 384-3862
Voice Mail (800) 544-5420
Box 9795
FAX (808) 841-6105

Schering Dennis M. Hamamura
Senior Pharmaceutical Rep.
Telephone (808) 671-0225
Voice Mail (800) 544-5420
Box 8774
FAX (808) 671-0817

KEY Carol K. Honda
Sales Representative
Voice Mail (800) 554-5420
Box 8322
FAX (808) 593-1776

Schering Rachelle Hyde
Sales Representative
District Trainer
Voice Mail (800) 782-2347
Box 3861

KEY Caroline Perry
Sales Representative
Voice Mail (800) 554-5420
Box 1274
E-Mail Caroline.perry@spcorp.com

Schering Brian Souza
District Account Representative
Telephone (808) 394-9475
Voice Mail (800) 554-5420
Box 6811
FAX (808) 394-9475
E-Mail brian.souza@spcorp.com