

# 100 Years of AAI: A Look Back at Two Early Immunologists in Hawaii

*On the occasion of its centennial meeting in Honolulu, AAI reflects on the association's long ties to Hawaii.*

“Hawaii,” for most AAI members, including those who attended IMMUNOLOGY 2013™, conjures up images of vast white sand beaches and palm trees swaying in gentle sea breezes. These Edenic images, however, belie the islands’ history as a setting for pioneering immunological research and their longstanding connection to AAI.

In fact, one Hawaiian physician, Archibald N. Sinclair, was among the 52 charter members of AAI in 1913. Sinclair, an established authority on tuberculosis, pioneered an immunological-based method for its treatment.

Another early AAI member in Hawaii, Nils P. Larsen, spearheaded massive reforms to improve public health on the islands as early as the 1920s.

We profile below the lives and careers of these two distinguished early AAI members.

## Archibald Neil Sinclair, M.B.C.M., AAI '13 Career Overview

Archibald N. Sinclair was born in New York City on January 20, 1871, just two years after his parents emigrated from Scotland to the United States. Before he was 10 years old, the family moved to Hawaii, when his father, a building contractor, was hired to help build ‘Iolani Palace, the residence commissioned by King Kalākaua, the last Hawaiian king. The family remained in Honolulu after construction of the palace was completed in 1882, and Sinclair attended Oahu College (now known as the Punahou School), a college preparatory school that includes President Barack Obama among its alumni.

After graduating from high school in 1889, Sinclair moved to his parents’ homeland and studied medicine at the University of Glasgow. Upon earning his M.B.C.M.



‘Iolani Palace, 1898

*Hawaii State Archives, Digital Collections, Photograph Collection*

(Bachelor of Medicine, Master of Surgery) in 1894, he practiced medicine in Yaxley, England, for three years before returning to Hawaii. He began a private practice in Waianae, Oahu, in 1897, but by 1901, he had fully dedicated himself to public health. That year, he was named city physician of Honolulu, a position he held until 1908, and was appointed the first medical superintendent of the Leahi Home, the recently opened tuberculosis sanitarium in Honolulu, where he was to spend the rest of his career. He served

concurrently as acting assistant surgeon for the U.S. Public Health Service from 1900 to 1919 and as physician in charge of the tuberculosis bureau and the bacteriological department of the Territorial Board of Health from 1911 to 1916. Resuming his private practice in 1916 while retaining his position at the Leahi Home, Sinclair continued to specialize in the treatment of tuberculosis and other pulmonary ailments until his death on October 21, 1930.<sup>1</sup>

Well-respected among Hawaiian physicians, Sinclair was twice elected president of the Hawaiian Territorial Medical Society, first from 1907 to 1908 and again from 1926 to 1927.

## Making the Case for Tuberculin

A remarkable clinician whose case studies were reported in the *Journal of the American Medical Association*,<sup>2</sup> Sinclair garnered a national reputation for his success in treating tuberculosis with tuberculin. He first presented his “Case for Tuberculin” before the Hawaiian Territorial Medical Society in 1914.<sup>3</sup> The use of tuberculin to treat pulmonary tuberculosis was one of the most controversial immunological issues of the day and had been among the topics debated at the first AAI annual meeting held

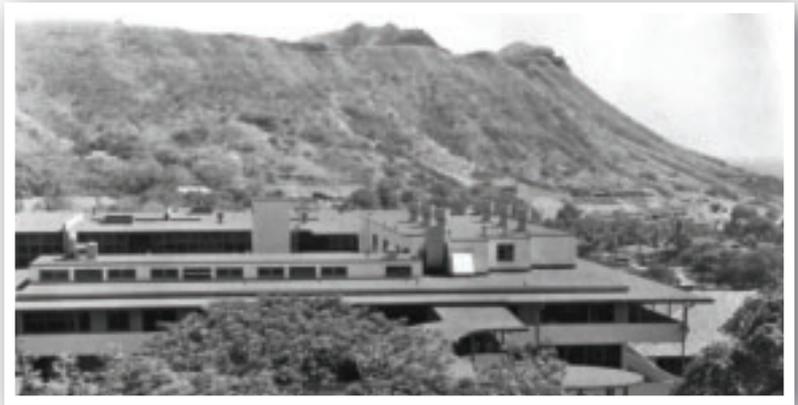
1. “Sinclair, Archibald N.,” *Men of Hawaii: A Biographical Reference Library, Complete and Authentic, of the Men of Note and Substantial Achievement in the Hawaiian Islands*, vol. 2, ed. by John William Siddall (Honolulu: Honolulu Star-Bulletin, 1921), 363; “Archibald Neil Sinclair,” In Memoriam—Doctors of Hawaii—XI, *Hawaii Medical Journal and Inter-Island Nurses’ Bulletin* 17, no. 2 (1957): 152; Gwenfread Allen, *The Story of Leahi: Fifty Years of Service, 1901–1951* (Honolulu: Trustees of Leahi Hospital, 1951), 10; “Dr. Archibald Neil Sinclair House,” Nomination Form, National Register of Historic Places, U.S. National Park Service, <http://pdfhost.focus.nps.gov/docs/NRHP/Text/83003557.pdf>.
2. A. N. Sinclair, “Yersin-Roux Serum in the Treatment of Plague,” *Journal of the American Medical Association* 56, no. 5 (1911): 332–35; A. N. Sinclair, “The Diazo and Urochromogen Reactions in Pulmonary Tuberculosis,” *Journal of the American Medical Association* 66, no. 4 (1916): 247–48.
3. A. N. Sinclair, “The Case for Tuberculin,” *Transactions of the Medical Society of Hawaii* 23 (1914): 79–97.

in Atlantic City, New Jersey, the same year that Sinclair reported his positive findings.<sup>4</sup> The reason for the controversy was that prior attempts to use tuberculin as a treatment, notably those by Robert Koch in the 1890s, had low success rates and often produced unexpected, negative outcomes, even death. Sinclair conceded that tuberculin treatment was a very complicated, precise process that was ineffective if not administered properly and “in inexperienced hands, even dangerous.”<sup>5</sup>

He cited two schools of thought on administering tuberculin. He dubbed one method the “rules on the bottle method” for treating each patient with a fixed, and often too intense, recommended dosage. He referred to the other method as the “immunizing” method, which he attributed to Sir Almroth Wright (AAI ’14).<sup>6</sup> Sinclair, having spent four months at St. Mary’s Hospital in London observing Wright prepare and administer tuberculin in 1911, had further refined the process at Leahi Home.<sup>7</sup> Sinclair’s therapeutic immunizing method involved administering small, regulated tuberculin doses over a long interval and varying those doses based on Wright’s “opsonic index,” which measured the opsonin content in patients’ blood. There was no single dosage that was suitable for all patients nor could tuberculin be expected to cure all patients. Such promises, Sinclair asserted, were “what makes the patent medicine man his living” and were not made by responsible medical practitioners.<sup>8</sup>

Nevertheless, he was convinced that when meticulously administered, tuberculin produced incomparable results. He reported that 67.6 percent of patients who had received tuberculin treatments were able to leave Leahi and return to work, a dramatic increase from the 27.2 percent able to do so before he began administering tuberculin.<sup>9</sup> Sinclair encountered harsh opposition from a Hawaiian colleague who declared that Wright’s opsonic index was “not accepted in this country,”<sup>10</sup> but he remained sanguine about the prospects for tuberculin treatment and, in May 1916, traveled to Washington, D.C., to report his findings at the third AAI annual meeting.<sup>11</sup>

Despite Sinclair’s efforts and optimism, his method of treating tuberculosis was never widely adopted. Most clinicians were concerned that the potential was too great for negative side effects from improper administration.<sup>12</sup> According to Arthur Silverstein (AAI ’63), although



Sinclair Building on the Leahi Hospital campus, built in 1949 and named for Archibald N. Sinclair

*Courtesy of Leahi Hospital*

Wright’s opsonic index was initially met with a great deal of enthusiasm among some immunologists, particularly those in his native England, “the techniques proved so difficult and unreproducible in practice as to become unfashionable within a decade.”<sup>13</sup>

Nevertheless, Sinclair could take pride in the success he had encountered while treating tuberculosis patients at the Leahi Home. Reflecting on the progress that had been made in the treatment of tuberculosis in the first decade of the twentieth century alone, he noted, “One familiar with the [Leahi] Home and its conditions during the past few years cannot but be struck by the change—a few years ago people looked upon it as the last resort of the hopeless—a walk through its wards encountered almost bed-ridden patients entirely; now it is coming to be looked upon as the hope and salvation of the afflicted, and a walk through its wards will frequently show not a single patient in bed—or at the worst of times but an extremely small percentage of bedridden patients.”<sup>14</sup>

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Archibald N. Sinclair, ca. 1927  
*Courtesy of Queen’s Heritage Collection, Queen’s Medical Center*

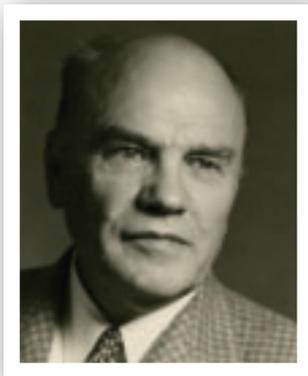
4. “Science at the First AAI Annual Meeting,” *AAI Newsletter*, May/June 2012, 30.
5. Sinclair, “The Case for Tuberculin,” 79.
6. *Ibid.*, 86.
7. *Ibid.*, 85; Allen, *The Story of Leahi*, 12–13, 15.
8. Sinclair, “The Case for Tuberculin,” 97.
9. *Ibid.*, 80.
10. J. T. McDonald, “Discussion,” in *ibid.*, 94.
11. Evidently, tuberculin treatment proved slightly less successful in the two-year interim between presenting his findings at the Medical Society of Hawaii meeting and the AAI meeting. He now reported a success rate of 50.1 percent compared with his earlier rate of 67.6 percent. Abstract of A. N. Sinclair, “Treatment of Tuberculosis Pulmonalis by Tuberculin,” in “Proceedings of the American Association of Immunologists: Third Annual Meeting, Held in Washington, D. C. May 11, 1916,” *The Journal of Immunology* 1, no. 4 (1916): 489–90.
12. “Science at the First AAI Annual Meeting,” 30.
13. Arthur M. Silverstein, *A History of Immunology*, 2nd ed. (New York: Elsevier, 2009), 38.
14. A. N. Sinclair, *Fighting the Great White Plague* (Honolulu: Hawaiian Gazette Co., 1914), 11.

## Nils Paul Larsen, M.D., AAI '23

### A Religious Upbringing

Although Nils P. Larsen did not call Hawaii home until well into adulthood, his impact on Hawaiian medicine and public health was no less significant than Sinclair's. Born in Stockholm, Sweden, on June 15, 1890, Larsen was the sixth of seven children born to a tailor struggling to support his growing family. Overpopulation and successive crop failures were impoverishing life in Sweden, impelling approximately 330,000 Swedes to immigrate to the United States during the 1880s. When Nils was only three years old, the Larsen family joined the ranks of those who hoped to find a better life in the New World. After settling briefly in Peeksville, New York, Nils's father, a devout man, relocated the family to Bridgeport, Connecticut, where he helped start a church for the Swedish Evangelical Mission Covenant, a Lutheran denomination founded in Chicago in 1885. While attending public school in Bridgeport, Larsen held part-time jobs to help support his family, including work in a steel mill during the summers of his high school years.<sup>15</sup>

Larsen attended the Massachusetts Agricultural College (now the University of Massachusetts, Amherst), where he intended to study forestry. Although he began to abandon the formal religious dogmas embraced by his pious father, Larsen remained committed to the Christian ideal of helping others that lay at the heart of the Social Gospel movement of the era. He became actively involved in student religious groups on campus, including the YMCA and the College Christian Association. While attending one religious conference, at which missionaries relayed accounts of their travels, Larsen learned that there was only one doctor for every one million people in China. He decided then that he wanted to become a physician, not out of any special yearning to solve scientific problems but out of his deep-seated commitment to social justice and community service.<sup>16</sup>



Nils P. Larsen, ca. 1955  
Courtesy of Queen's Heritage  
Collection, Queen's Medical Center

### Early Career, War, and Marriage

After graduating from Massachusetts Agricultural College in 1913, Larsen attended Cornell Medical School in New York City, earning his M.D. in 1916. He then interned in the pathology department at New York Hospital and took additional courses in biological chemistry at Columbia University. When the United States entered the First World War in April 1917, Larsen was commissioned as a first lieutenant in the Medical Corps of the U.S. Army and was deployed to Belgium the following May. While in Belgium, he received news that his younger sister had died of tuberculosis. Absorbing this loss during the influenza pandemic that ravaged families across the globe likely motivated his later work to combat tuberculosis.

In the spring of 1919, Larsen was promoted to major, awarded the Silver Star for his valor during combat, and released from active duty. That summer, he made his first trip to Hawaii, where he visited his older brother David, a plant pathologist, who was now a manager of a sugar plantation. Following his vacation, he returned to New York to teach at Cornell Medical School and serve as assistant visiting physician in pediatrics at Bellevue Hospital. These years in New York, from 1919 to 1922, proved to be some of Larsen's most productive for clinical research and writing. He published case studies on allergic reactions, asthma, and pneumonia in the *Journal of the American Medical Association* and *The Journal of Immunology*.<sup>17</sup>

In September 1921, Larsen married Sara "Sally" Lucas, whom he had met two years earlier during his Hawaiian vacation. Although the two had not kept in touch following Larsen's return to New York, Sally was apparently impressed by Larsen during his visit to Hawaii and contacted him upon her arrival in New York from Honolulu to start a confectionary. The extent to which the confectionary materialized is unclear, but, within months, the couple wed.

Sally's mother appears to have been equally decisive and proactive as her daughter. Upon learning of an opening for a pathologist at Queen's Hospital in Honolulu, she mentioned Larsen to the administrators. If she was seizing upon a possible means of bringing her daughter back to Hawaii, she succeeded. Larsen was offered the position in July of 1922 and promptly accepted it.<sup>18</sup>

15. Janine A. Powers, "Worlds Beyond Medicine: Nils P. Larsen's Impact on Hawai'i," *Hawaiian Journal of History* 39 (2005): 92–93.

16. *Ibid.*, 93–94.

17. Russell L. Cecil and Nils P. Larsen, "Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia," *Journal of the American Medical Association* 79, no. 5 (1922): 343–49; Nils P. Larsen, Royce Paddock, and H. L. Alexander, "Bronchial Asthma and Allied Conditions: Clinical and Immunological Observations," *The Journal of Immunology* 7, no. 2 (1922): 81–95; Nils P. Larsen, A. V. R. Haigh, Harry L. Alexander, and Royce Paddock, "The Failure of Peptone to Protect against Anaphylactic Shock and Allergic Conditions," *The Journal of Immunology* 8, no. 5 (1923): 409–24.

18. Powers, "Worlds Beyond Medicine," 96; Janine A. Powers, "From Medicine to Art: Nils Paul Larsen (1890–1964)" (Ph.D. diss., University of Hawaii, 2003), 22.

## At Queen's Hospital

Larsen immediately impressed the administrators of Queen's Hospital. In 1924, he was appointed the hospital's medical director, a position he held until 1942. Named for Queen Emma, its most enthusiastic champion, Queen's Hospital was founded in 1859 to provide medical care to a rapidly dwindling Hawaiian population.

Occupying a major port of call on trade routes across the Pacific, the Hawaiian population was, at that time, besieged by diseases borne by foreigners, most recently a smallpox epidemic that swept across the islands in 1853.<sup>19</sup> At the time of Larsen's appointment more than 60 years later, the hospital had failed to keep pace with the medical advances on the mainland.

Larsen immediately set out to modernize Queen's Hospital. His first reform was to arrange weekly clinics in which medical practitioners from all over the island came together to share and discuss their cases, including the week's deaths. Often, Larsen recruited notable visiting physicians to lecture and consult with the local doctors, and word of the effectiveness of his clinics began to spread nationally, earning Larsen praise in the pages of the *New York Times*.<sup>20</sup> He also significantly improved living conditions for the nurses—usually women who were recruited from plantations—raising \$125,000 for the construction of new nurses' quarters in 1931.<sup>21</sup>

## Reforming Hawaiian Public Health

Larsen's reforms extended well beyond the walls of Queen's Hospital. He made several significant contributions to improving public health in Hawaii. Shocked by the high infant-mortality rate on the islands, Larsen spearheaded a clean-milk campaign in November 1922. His investigations into the Hawaiian milk industry uncovered widespread unsanitary conditions and resulted in new laws regulating milk production. The successful campaign became a national story when it was reported years later in *Reader's Digest*.<sup>22</sup> In the late 1920s, he also called for "preventorium," camps where pre-tubercular children would receive medical care and be provided with a proper diet. With the support of Archibald Sinclair and others at Leahi Home, the first preventorium in Hawaii opened its doors in 1930.<sup>23</sup>



Queen Emma, ca. 1880

Photo by A. A. Montano; Hawaii State Archives, Digital Collections, Photograph Collection

Perhaps Larsen's greatest reforms came in his work with the Hawaiian Sugar Planters' Association. In 1928, he criticized the planters for allowing their workers to live in substandard conditions. Improvements in living conditions and diets could prevent the suffering and even death caused by diseases such as beriberi and gastroenteritis, argued Larsen. He soon convinced planters that these reforms were not only a moral obligation but also a sound economic investment. New meal plans were implemented, and health centers were established on plantations where workers could receive treatment and consultation on nutrition, hygiene, and even birth control.<sup>24</sup>

## A Change of Direction

In 1939, Larsen contracted typhus and was hospitalized for 20 days. Shortly after his recovery, he wrote to Hans Zinnser (AAI '17, president 1919–1920) at Columbia University, an authority on typhus and author of *Rats, Lice and History*. The playfully familiar tone of his letter suggests that Larsen knew Zinnser from his time in New York: "I had occasion recently to meet your good friend with whom you have been so intimately associated . . . throughout your professional life—namely typhus fever."<sup>25</sup>

The typhus left Larsen with angina, for which he decided to seek treatment in Boston. The decision was a fortunate one, for he and his wife departed Hawaii on December 5, 1941, just two days before Pearl Harbor was attacked. When he returned in 1942, he stepped down from his position as medical director of Queen's Hospital and began a private practice.

Larsen continued his research and began pursuing new topics, including the effects of diet on aging.<sup>26</sup> He also became interested in native Hawaiian medicine, pointing out that the traditional remedies of the *kahuna lapa'au*, Hawaiian medicine men, were often more scientific than those of the nineteenth-century Western doctors who so easily dismissed them as primitive. Larsen even developed a supplement made of taro, a plant

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19. Richard A. Greer, "The Founding of the Queen's Hospital," *Hawaiian Journal of History* 3 (1969): 110–45.

20. Russell Owen, "Massie Will Take Stand Again Today," *New York Times*, 18 April 1932, 5; "Cited for Hawaiian Work: Dr. Nils Paul Larsen to Receive Cornell Alumni Award," *New York Times*, 14 April 1952, 21.

21. Powers, "Worlds Beyond Medicine," 100–101.

22. *Ibid.*, 99; Blake Clark, "Plantation Babies Okay Now," *Reader's Digest*, January 1947, 127–30.

23. Powers, "Worlds Beyond Medicine," 99–100.

24. *Ibid.*, 101–104.

25. *Ibid.*, 106.

26. *Ibid.*, 110–11; Nils P. Larsen, "Animal Fat Diet and Atherosclerosis," *Hawaii Medical Journal and Inter-Island Nurses' Bulletin* 14, no. 6 (1955): 485–90; Walter Sullivan, "Survey of 500,000 Will Study Role of Diet in Heart Disease," *New York Times*, 31 August 1961, 1.

common in the traditional Hawaiian diet that he believed promoted dental health.<sup>27</sup> Perhaps it was his eagerness to synthesize Eastern and Western traditions that made him popular with Hawaiians and won him election to the 1950 Constitutional Convention charged with preparing for Hawaiian statehood.<sup>28</sup>

Although he officially retired in 1955, Larsen continued to treat patients until his death of a heart attack, at the age of 73, on March 19, 1964.<sup>29</sup>



Queen's Hospital, ca. 1925

Courtesy of Queen's Heritage Collection, Queen's Medical Center

### Hawaii—A Researcher's Paradise

Speaking before the Hawaii Medical Association at Queen's Hospital in April 1935, Nils Larsen noted, "The type of observations possible here are endless and many of them cannot be made anywhere else in the world."<sup>30</sup> Not only Larsen but also Archibald Sinclair before him and dozens of AAI members since have taken advantage of the unique setting Hawaii offers for immunological research. Even immunologists who were far removed from the islands geographically have long benefited from the presence of AAI members there, as when Arthur F. Coca (AAI '16) and Ella F. Grove (AAI '24) obtained tropical pollen samples from Larsen for their "Studies in Hypersensitiveness" in 1924.<sup>31</sup>

Hawaii may be at once an island paradise and, in the words of Larsen, "the best biological test tube in the world."<sup>32</sup>

27. Powers, "Worlds Beyond Medicine," 107–10.

28. Arthur V. Molyneux, "Nils Paul Larsen, M.D.," *Hawaiian Medical Journal* 23, no. 5 (1964): 388.

29. *Ibid.*; Powers, "Worlds Beyond Medicine," 111.

30. Nils P. Larsen, "Cancer," *Transactions of the Hawaiian Territorial Medical Association* 45 (1935): 48–52, quote from 48.

31. Arthur F. Coca and Ella F. Grove, "Studies in Hypersensitiveness. XIII. A Study of the Atopic Reagents," *The Journal of Immunology* 10, no. 2 (1925): 445–64.

32. Larsen, "Cancer," 48.

### A Chronological Overview:

**300–500 AD**—Polynesians first inhabit Hawaiian Islands

**1778**—British explorer Captain James Cook lands in Hawaii; his published account provides the earliest documentation of European contact with islands

**1785**—First trading ship lands in Hawaii on way to China; sandalwood trade and whaling soon become major industries

**1810**—Kamehameha formally establishes Kingdom of Hawaii and proclaims himself king after 15-year struggle with *ali'i* (chiefs)

**1819**—King Kamehameha II abolishes the *kapu*—the traditional religious and legal system that governed all aspects of Hawaiian life

**1820**—First Protestant missionaries arrive from the United States

**1835**—First commercially successful sugar plantation is opened by Ladd and Company

**1848**—King Kamehameha III enacts the *Mahele*, a land division act that introduces legal provisions for private ownership of land; opens way for rapid growth of sugar plantations

**1859**—Queen's Hospital, named for Queen Emma, is founded to provide medical care to Hawaiian people

**1872**—King Kamehameha V dies without heir, ending the House of Kamehameha

**1874**—Riots during the subsequent succession crisis are suppressed by U.S. and British troops; Kalākaua becomes King of Hawaii

**1875**—Reciprocity Treaty signed between the United States and Kingdom of Hawaii cedes Pearl Harbor to the United States in return for duty-free importation of Hawaiian sugar into the United States

**ca. 1880**—Archibald N. Sinclair moves to Hawaii with his family as a young boy

**1887**—King Kalākaua is forced to sign new constitution that strips monarchy of power by the Hawaiian League, a group of American and British businessmen who favor annexation by the United States

**1891**—King Kalākaua dies and is succeeded by his sister, Queen Lili'uokalani who calls for new constitution

**1893**—U.S. Marines arrive in Hawaii at request of the Hawaiian League, making it impossible for Queen Lili'uokalani to continue her rule; although U.S. Congress found no party guilty of overthrow in 1894, Congress issued a joint Apology Resolution in 1993 accepting U.S. responsibility for overthrowing the sovereign kingdom

**1894**—Republic of Hawaii is established

**1897**—Sinclair returns to Oahu and opens private practice after spending eight years in the United Kingdom, where he received his medical training

**1898**—Hawaii is annexed by the United States and becomes the Territory of Hawaii

**1901**—Sinclair is appointed city physician of Honolulu and the first medical superintendent of the Leahi Home

**1919**—Nils P. Larsen visits his brother in Hawaii after returning from the First World War

**1922**—Larsen accepts position as a pathologist at Queen's Hospital and moves to Honolulu from New York; he is soon appointed medical director of the hospital

**1930**—Sinclair dies in Honolulu at the age of 59

**1941**—The United States enters the Second World War after the attack on Pearl Harbor

**1942**—Larsen steps down as medical director of Queen's Hospital and begins private practice

**1950**—Larsen serves as member of the convention that drafts the Hawaiian constitution in preparation for statehood

**1954**—Democratic Party takes control of Territorial Legislature and pushes for statehood

**1959**—Hawaii becomes the 50th state of the United States

**1964**—Larsen dies of a heart attack in Honolulu at the age of 73