

Humans first arrived in the Sierra Nevada's of present-day California more than 10,000 years ago. The remains of a Native American dwelling near the Stanislaus River, an oval-shaped site about 12' in width, was estimated by archaeologists to be about 9,500 years old and is the oldest known constructed dwelling in North America. For at least several centuries before the arrival of Spanish explorers, the Stanislaus River basin was inhabited by the Central Sierra, Plains and Sierra Miwok. The Miwok had a predominantly hunter-gatherer lifestyle, although they also practiced some primitive agriculture and controlled burning of grassland to enhance their hunting grounds. The Miwok had their main settlements in the lower elevations of foothills and the Central Valley, where they spent winters. During the summer they traveled into the Sierra Nevada via along the Stanislaus as well as other nearby rivers to harvest vegetable foods in high elevations and escape the summer heat.

Although the Spanish Empire claimed California in the 1770's, much of the Central Valley, then a huge expanse of swamps and rivers, remained unexplored by the Spanish for several decades thereafter. The first Spaniards to encounter the Stanislaus River were Gabriel Moraga's 1806 expedition, who named the river Rio de Nuestra Señora de Guadalupe, "River of Our Lady of Guadalupe". Fray Pedro Muñoz, traveling with Moraga, wrote of "immense quantities of wild grape-vines" along the Guadalupe River. In 1808, Moraga returned to the area to search for suitable mission sites, but was not successful. The river later became known as Río de los Laquisimes, possibly derived from a Native American name for the river or surrounding area. Although the Spanish ultimately did not establish any missions in the Central Valley, they forcibly took thousands of Native Americans to missions along the coast, where they were converted to Catholicism and subjected to agricultural labor. Mission San Jose was the destination of many Miwok from the Laquisimes River area.

There was considerable native resistance to the Spanish mission program, which continued after Mexico gained independence from Spain in 1821. Most escaped Native Americans fled to the Central Valley, which was very difficult for heavily armed Spanish soldiers to traverse due to its swampy terrain. Around November 1828, a Yokuts man named Estanislao, christened after Saint Stanislaus, whose real name is believed to have been Cucunichi, led a revolt at Mission San Jose and fled to the Laquisimes River country with many other natives. There, he raised an army of Yokuts, Miwok and Chumash, who eventually raided the missions and large ranchos, stealing horses and cattle and freeing Native American laborers. The Mexican army, led by Mariano Vallejo, moved to crush the resistance, but was initially defeated by natives on the Laquisimes River, in a place believed to be near present-day Caswell Memorial State Park.

After the initial defeat, Vallejo returned with a force of 107 soldiers, some citizens, and at least fifty mission Indian militiamen, armed with muskets and cannons, but again fought to a draw. Vallejo set fire to vegetation along the river banks to draw out the opposition, but Estanislao and his fighters escaped, and continued to raid Mexican settlements through that winter. According to popular legend, Estanislao would carve an "S" in a tree after his attacks, and was an inspiration for the fictional character Zorro. In June 1829, Vallejo finally defeated him on the Laquisimes River. The vanquished Estanislao ultimately returned to Mission San Jose, where he confessed his sins and was pardoned by the Mexican government. However, the Mexicans never again attempted to control the eastern part of the San Joaquin Valley, and the Laquisimes River was renamed the Stanislaus in Estanislao's honor.