In 1821, Mexico won its independence from Spain after a decade of war. The revolution had bankrupted the national treasury, and funds that had supported missions, presidios, and Apache peace camps nearly disappeared. Apaches once again began raiding, running off horse herds, and killing anyone caught outside presidio walls. As missions began to wither, Mexico began auctioning off more land, causing the Pimería Alta and the Apachería to shrink. Some presidio soldiers became so poor that they had to sell their weapons to feed their families.

Tucson in the 1830s was as much an Apache as a Mexican community. Sonoran census of 1831 listed only 465 Mexican inhabitants, whereas Tucson's Apache Manso community in 1835 was said to include 486 individuals. Many lived north of the presidio along the east bank of the Santa Cruz cultivating their own fields or occasionally working for Mexican farmers, and they also moved freely back and forth between Tucson and the surrounding mountains, hunting deer and bighorn sheep, gathering cactus fruit, and roasting agave. During the first half of the nineteenth century, their way of life remained Apachean despite the fact that they were allies, not enemies, of the Mexicans living along the Santa Cruz. In 1840 and 1841 the Mexican government campaigned against the Tohono O'odham of the western deserts, their former allies. The colony reached its nadir at midcentury.

The Spaniards had feared that other European powers were planning to invade their sparsely populated northern frontier. After Mexico won its independence from Spain, it was the growth of the United States that proved most significant. The process began with Texas in 1836. Desperate to fill empty spaces, Mexico invited Americans and other foreign colonists to settle in Texas in 1824. By 1830 there were already more than twice as many Anglos as Mexicans there. By 1836 the ratio had changed ten to one. Texas remained an independent republic until 1845. Mexicans of Texas soon became a minority in their native land.

Many citizens of the United States felt they had a God-given mandate to extend their "area of freedom" across North America. They believed it was "our manifest destiny to overspread and to possess the whole of the continent which Providence has given us for the development of the great experiment of liberty and federated self-government entrusted to us." Mexico broke off relations with the United States in March 1845 after the annexation of Texas. Six months later, President Polk sent John Slidell to Mexico City to buy California and New Mexico. When the Mexicans refused to negotiate, Polk ordered General Zachary Taylor to occupy disputed territory between the Nueces River and the Rio Grande. A Mexican attack on U.S. troops preceded a U.S. declaration of war on Mexico in May 1846.

A primary U.S. objective in the war was the acquisition of California. General Stephen Watts Kearny, commander of the Army of the West, led the first group of soldiers. After conquering New
Mexico, Kearny and a detachment of "wilderness-worn dragoons" left Santa Fe in 1846, descended the Gila, and spent the next two months following the river's passage to the Colorado. They marched through the villages of the Gila Pimas, but completely bypassed Tubac and Tucson and avoided any confrontation with Mexican troops.

The Mormon Battalion, a company of Latter Day Saints from the Midwest who volunteered for duty in order to prove their patriotism and diffuse the religious hatred of their neighbors, swung farther south and went through Tucson on its way to California. They intended to blaze a wagon trail across the southern Great Plains and the Southwest. When they reached Santa Fe, Lieutenant Colonel Philip St. George Cooke took command and led the battalion to San Diego. They left Santa Fe in October 1846 and had to double-team their wagons to get over the Sacramento Mountains in south central New Mexico and lower them by rope down Guadalupe Pass in the northern Sierra Madre. While Mormon encounters with the Indians were generally peaceful, the wild bulls of southeastern Arizona charged their caravan and gorged their mules.

The Mormons were the first representatives of the U.S. government to meet the Mexican population of Arizona at a mescal distillery between the San Pedro and Santa Cruz valleys. There the tee-totaling Mormons met a sergeant and several soldiers from the Tucson presidio. The sergeant politely requested that Cooke and his men make a detour around Tucson. Cooke politely declined.

Several days of sparring followed as Tucson's veteran commander, Antonio Camadurán, attempted to persuade the battalion not to enter the community. When all threats and pleas for an armistice failed, Comadurán withdrew his outnumbered garrison to San Xavier. The result was a peaceful day of trading between the Mormons and the Mexican inhabitants of Tucson. The battalion lumbered into town on December 17. The residents of Tucson offered the soldiers food and water, and the soldiers responded by bartering clothing for the beans and flour they needed.

After General Winfield Scott seized Mexico City in September 1847 following bloody hand-to-hand combat, Nicholas Trist sat down with Mexican authorities and helped to write the Treaty of Guadalupe-Hidalgo, which Congress ratified the following March. In return for $18,250,000 in cash payments and claims assumed by the U.S. government, the United States won confirmation of its title to Texas. It also annexed California and New Mexico, which included Arizona north of the Gila River.