Explored by Lewis and Clark, the site of Donald Mackenzie's 1812 fur trade winter post and of H. H. Spalding's Lapwai mission after 1836, Nez Perce County owes its existence to the Idaho gold rush. Mineral discoveries at Pierce, September 30, 1860, led to a major excitement the next spring. Lewiston was established May 13, 1861, at the head of steamboat navigation nearest the new Clearwater mines, and the mining region expanded rapidly. Elk City and Newsome followed as mining camps on the south fork of the Clearwater that summer. At the time of their founding, Lewiston and Elk City were in newly-established Shoshone County (which is more than can be said for Pierce, the county seat), but that winter they were incorporated into Nez Perce County. Created by the Washington legislature, December 20, 1861, Nez Perce is one of the four counties older than Idaho. Originally composed of all the Clearwater drainage south of the Clearwater and of Lolo Creek, Nez Perce County expanded to take in Potlatch Creek as well as a small area (now in Washington) northwest of Lewiston a year later. Then when Idaho was established, March 4, 1863, the area northwest of Lewiston was lost when Idaho got around to defining county boundaries, February 4, 1864, all of the land Nez Perce County had acquired north of the Clearwater was detached again. Along with most of the remnant of Spokane County (running north to the international boundary), this territory remained unorganized, but was attached to Nez Perce County for judicial purposes. At the same time, Nez Perce picked up some mostly-uninhabited country south of the lower Salmon River.

With abrupt and remarkable shifts in population as one gold rush followed another, Nez Perce County did not realize its early promise immediately. Elk City and the south fork mines, which had exceptional possibilities their first summer, were eclipsed by the far more spectacular Salmon River mines at Florence that fall. A rush of more than 10,000 hopeful miners to Salmon River in the spring of 1862, and Lewiston's efforts to route the Boise rush through Lewiston and on up Snake River did not work out too well. When Governor W. H. Wallace organized Idaho territory in Lewiston, July 10, 1863, Nez Perce County still had hopes of retaining the promising start that had been made in the first two years. Two sessions of the legislature met in Lewiston, but when Montana was established May 26, 1864, and when Boise was designated permanent capital of Idaho, effective December 24, 1864, Nez Perce County was left in an isolated North Idaho, separated by the Salmon River mountain barrier from the southern part of the territory, where more than 90% of the population was to be found in 1864. For the next quarter century, Nez Perce County took the lead in a concerted movement to get out of Idaho--preferably into a new territory of Columbia that would include Washington east of the Cascades or of the Columbia River,
along with North Idaho, and if possible, Montana west of the Continental Divide. If a new territory were rejected, North Idaho might compromise on returning to Washington. This Nez Perce County effort to get out of Idaho very nearly succeeded. But when Idaho was admitted to the union in 1890, state boundaries in the Pacific Northwest were fixed permanently with Nez Perce County still in Idaho.

Nez Perce County boundary changes came frequently in the early days. Many were minor. But on January 9, 1867, the county regained the area north of the Clearwater, along with what later became Latah County, so that Lewiston, the county seat, no longer was on the northern (as well as the western) boundary. Another major adjustment came January 8, 1875, when Idaho County expanded into the Clearwater region that makes up most of its present area. At that time, Elk City, Mount Idaho, and Grangeville shifted out of Nez Perce County to Idaho County, and Nez Perce was left with some ill-defined boundaries (overlapping part of Ada County on the southwest, and with an open gap for an eastern boundary: the northern and southern boundaries did not connect) that, despite some revisions, were not perfected until 1889. Meanwhile, a bitter county seat rivalry developed between Lewiston and Moscow. With rapid settlement of the Palouse farms, the Moscow area had enough population for a separate county. This was established by act of Congress, May 14, 1868, largely as a special favor of Fred T. Dubois (Idaho’s congressional delegate) to Willis Sweet and his Moscow political associates. That left the modern counties of Lewis and Nez Perce in Nez Perce County when Idaho became a state. The Lewis County part still belonged to the Indians, along with much of the rest of Nez Perce County, as part of the Nez Perce reservation. When arrangements were concluded, August 15, 1894, to open most of the reservation to white settlement, Nez Perce County gained an opportunity for rapid growth. Construction of the Northern Pacific Railway to Lewiston, September 8, 1898, also helped.

A large acquisition of territory from Shoshone County restored Nez Perce to something like its original large size in 1904. On November 8, the voters of the area eventually to become Clearwater County decided to switch from Shoshone (where access to the county seat at Wallace involved a long, hard trip) to Nez Perce. This increased the area of the county from around 1,320 to over 3,800 square miles. This move was intended to be temporary (an earlier effort simply to create Clearwater County had failed in the courts), and finally in 1911, Nez Perce County was reduced to its present size. This was accomplished through creation of Clearwater County, February 27, and Lewis County, March 11. Nez Perce County was left with a farming area around Lewiston, where a major commercial center and forest products industry developed.

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