Although the idea of a waterway crossing the upper Delmarva peninsula was suggested in the 1600s, the canal did not become a reality until 1829. Over 2,600 workers, including many Irish immigrant and African-American laborers, dug the canal with picks and shovels for wages of 75¢ a day. When they were done, they had created a 14-mile long ditch that was ten feet deep and sixty feet wide, with four locks to carry ships over high and low waters, shortening the water route between Philadelphia and Baltimore by more than 300 miles.

The United States government purchased the canal from the private corporation in 1919. By 1927, the Army Corps of Engineers relocated the Delaware River entrance of the canal to Reedy Point, two miles south of Delaware City. The Corps also eliminated the need for locks by dredging the waterway into a sea-level passage. The branch of the original canal that passes through Delaware City connects with the main C&D Canal two miles inland.

The canal opened on October 17, 1829, with great celebrations. All manner of craft used it. Initially horse- and mule-drawn barges predominated, but eventually steam powered vessels made up the majority of canal traffic.