Built in 1923, Mercy Hospital is the oldest surviving hospital building in St. Petersburg. Mercy Hospital was designed by Henry Taylor, a prolific architect in St. Petersburg. He is responsible for designing some of St. Petersburg’s most significant structures including the City Comfort Station, the Vinoy Park Hotel and the Jungle Country Club Hotel (Admiral Farragut). Mercy Hospital also employed Dr. James Ponder, one of the most influential leaders of St. Petersburg’s African-American community. After moving to St. Petersburg in 1924, Dr. Ponder became St. Petersburg’s first African-American physician in 1926. He was recognized as spearheading the construction of a much needed new wing for the hospital, was recognized as the first African-American physician to be elected as an active member of the Pinellas County Medical Society and was generally recognized as a role model to those in the City's African-American community who wanted to become doctors.

As the primary care facility for the City’s African Americans from 1923 to 1966, it played a significant role in the community. Mercy Hospital was the site of protests demanding the desegregation of the City’s hospital facilities during the Civil Rights movements of the 1960’s. By the late 1950's the rapid population growth of the City was overcrowding both Mound Park and Mercy Hospitals; however, a proposed $1.7 million addition to Mercy was rejected by City Council. Consultants to the City urged the integration of the two hospitals, but staff physicians and the administration of Mound Park strongly opposed this plan to City Council. In June 1960, a new City staff report advised the expansion of Mercy Hospital before integration, provoking a strong negative response from the African-American community. The bond issue for the expansion of Mercy was delayed in July 1960, creating further tension. The NAACP became publicly involved in the hospital integration controversy in November 1960 and African-American physicians at Mercy boycotted the hospital. The Mercy expansion was voted down by City Council on November 21, 1960. A plan for devoting one wing to African Americans at Mound Park was suggested by the City Manager's office in December, 1960; this infuriated many in the white community and approximately 300 people protested at a rally in January 1961. City Council still favored the plan and whites started a petition drive to oppose the integration of Mound Park and to force the issue to a public referendum. The doctors on staff at Mound Park also publicly criticized the plan for an African-American wing.

The administration of Mound Park Hospital formally admitted the first African-American patient to the hospital on February 25, 1961 and informed the press the hospital was now integrated. Meanwhile, the referendum petition was certified and the City Council quickly dropped plans for the African-American wing. The City Council eventually voted to expand Mercy in January 1962; the total budget of the project was $865,000 and would increase the capacity from fifty five to seventy-eight beds. The new Mercy Hospital addition opened in February 1963, designed by the architecture firm of Reynolds, Smith & Hill and constructed by Biltmore Construction Company.

Maintaining the racial segregation of the City's hospitals solved the City Council's political problems, but it did little to solve the critical lack of health care facilities in the City. The duplication of expensive modern equipment was too costly for a city struggling to meet the demands of an exploding population. Mercy Hospital tried to meet state accreditation in 1965, but failed. The lack of funding for personnel was one of a number of major problems, which in August of 1965 turned into a crisis. An infant boy was badly burned when an incubator malfunctioned. The parents of the boy brought suit against the City, and Mercy’s quality of patient care became a legal issue. The City requested Pinellas County to take over operation of Mercy Hospital. When they refused, the City closed the hospital on April 1, 1966. The county delayed purchase and ultimately refused to buy the Mercy Hospital property.