Bishop O'Connor asked the Jesuits to operate the college that same year and the University's first president, Rev. Romanus A. Shaffel, S.J., arrived in Omaha in July and the school was opened on September 2, 1878. One priest, three scholastics, a layman and woman formed the faculty when classes began. On August 14, 1879, Bishop O'Connor surrendered his trust to the Missouri Province of Jesuits that incorporated "The Creighton University" under Nebraska law. Because at the time of its opening there were few institutions in Omaha that prepared their students for college level work, much of the initial teaching in the college was at a secondary school level. It was not until 13 years later, in 1891, that the first baccalaureate degree was awarded. A brief history of Creighton University follows.

- In 1878, the Creighton College of Arts and Sciences, the University's oldest and largest division, was founded.
- In 1892, John Creighton established the John A. Creighton Medical College and funded a 200-bed hospital, the Creighton Memorial St. Joseph Hospital. The hospital became and continues to be the primary resource for clinical instruction in the medical school. The hospital actively served patients until 1978 when a new facility was opened at 30th and California.
- In 1904, the Creighton University School of Law was established, also by John Creighton.
- In 1905, the Creighton University School of Dentistry was begun.
- In 1905, the University purchased the Omaha College of Pharmacy which had opened in Fremont five years earlier.
- In 1920, the Creighton College of Commerce, Accounts and Finance was opened in direct response to the educational needs of World War I Veterans. In 1956, the College's name was changed to the College of Business.
- In 1926, a Dean of Graduate Studies was appointed marking the beginnings of a graduate school. (The first master's degree had been awarded in 1893 but between then and the appointment of a Dean of Graduate Studies, post-baccalaureate work was primarily an extension of the undergraduate schools). In 1971, the Graduate School conferred its first Ph.D.
- In 1928, Nursing was added to the curriculum. The initial program provided two years of liberal studies to be taken in conjunction with the nursing programs at various Catholic hospitals. In 1955, Creighton severed its ties with the hospitals and began to offer a full B.S.N. program within the College of Arts and Sciences. In 1971, a free standing college of Nursing was established, and the name was changed to the School of Nursing in 1978. The School of Nursing has advanced practice programs leading to MSN degrees.
- In 1969, a separately administered Summer Sessions division was established and in the mid-seventies that office expanded to become the Summer Sessions and Lifelong Learning Center, which was responsible for meeting the needs of a growing number of nontraditional students. The Lifelong Learning Center offered only noncredit programs.
- In 1982, the School of Pharmacy expanded to become the School of Pharmacy and Allied Health Professions. The reorganized school assumed responsibility for several medically related undergraduate programs previously organized as a division of the School of Medicine and enlarged its programs to include academic preparation for other health-related careers.
- In 1983, University College was opened to make credit courses and degree opportunities available to nontraditional students. University College absorbed the Lifelong Learning Center's noncredit programs. Summer Sessions joined University College in 1990.
In 1985, the School of Pharmacy and Allied Health Professions started a B.S. program in Occupational Therapy. In 1995, the School initiated the nation’s first clinical doctoral program in Occupational Therapy. In 1993, the School expanded by adding the nation’s first doctoral program in Physical Therapy. A significant change for the School occurred in 1994, when the Pharmacy program converted from undergraduate studies to a doctoral degree program.

In 1986, a B.S.N. program was started at The Mary Lanning Hospital in Hastings, Nebraska, at its request. While the curriculum is identical with that in Omaha, Hastings students must spend a minimum of one semester at the junior level on the main campus.

In 1986, Creighton and the Saint Joseph Education Center of the Diocese of Des Moines, Iowa, joined together to offer a Certificate/Diploma Program in Ministry. The classes are taught by Theology faculty from Creighton and resource theologians from the St. Joseph Education Center in Des Moines, Iowa.

In 1999, the Milton R. Abrahamson Law Clinic opened.

In 2003, construction was completed on the Hixson-Lied Science Center.

In 2004, Morrison Soccer stadium was completed. Also, the women's basketball team became the first Creighton athletic team to win a national championship besting the University of Nevada Las Vegas 73-52 in the Women's National Invitational Tournament (WNIT).

In 2008, the Mike and Josie Harper Center for Student Life and Learning opened.

As Mary Lucretia Creighton’s will stipulated that the school she endowed be a school to educate boys, women were not admitted to undergraduate education until 1913, when they were enrolled as part-time students in summer sessions. In 1931, women were enrolled as part of University College as degree-seeking students. In 1951, University College was merged with the College of Arts and Sciences making it a co-educational division of the University. However, from the beginning, women were admitted to professional schools as they were established. The first woman student was enrolled in the Medical School in 1892.

One of the most far reaching and dramatic changes in the structure of Creighton University occurred in 1968 when the Board of Directors, which consisted of five members of the Society of Jesus, voted to expand and restructure itself to include thirteen laymen and eight Jesuits. The Board may consist of 33 members but must include seven Jesuits, one of whom is the President of the University. The Board remains primarily a policy making body and has been effective in increasing the financial support of the University. Consistent with generally accepted corporate practices, the management of the University remains in the hands of the officers who have received authority from and are responsible to the Board of Directors.

In 1971, the Creighton Omaha Regional Health Care Corporation with its own Board of Directors was established. In 1973, it purchased St. Joseph’s Hospital, which remained the University's teaching hospital. In 1984, that Board sold the hospital to American Medical International, Inc. The proceeds were used to establish the Health Future Foundation for the support of research in the health sciences at Creighton and for the care of the indigent sick at the hospital. In 1995, the University and American Medical International, Inc. agreed to Creighton’s purchase of 26% ownership in AMI’s assets in Omaha including Saint Joseph Hospital, the Center for Mental Health, and existing medical practices. The settlement agreement was signed February 28, 1995. On March 1, 1995, AMI was merged with National Medical Enterprises into a new corporation entitled TENET Healthcare Corporation.

Creighton University is committed to being a national leader in preparing students in a faith-based setting for responsible leadership, professional distinction and committed citizenship. The Creighton Jesuit education has always been focused upon the development of the total person. Creighton educates men and women to be leaders in the careers and professions and to be of service to society.