In the summer of 1849, Father Leo Meyer and Brother Charles Schultz, the first Marianist missionaries to America, journeyed from Alsace in France to Cincinnati, Ohio, where they intended to establish a base for the order in this country. They arrived, however, during a cholera epidemic, so Bishop John Purcell of Cincinnati soon sent Father Meyer to Dayton to minister to the sick of Emmanuel Parish. Here he met John Stuart, whose little daughter died of cholera the year before. Mr. Stuart wanted to sell his Dayton property and return with his wife to Europe. On March 19, 1850, the feast of St. Joseph, Father Meyer purchased Dewberry Farm from him and renamed it Nazareth. Mr. Stuart accepted a medal of St. Joseph and a promise of $12,000 at 6% interest in return for 125 acres, including vineyards, orchards, a mansion and various farm buildings. Meanwhile, more Marianists arrived, and Nazareth became the first permanent foundation of the Society of Mary in the Western Hemisphere.

The University of Dayton had its earliest beginnings on July 1, 1850, when St. Mary's School for Boys, a frame building that not long before had housed farm hands, opened its door to fourteen primary students from Dayton. In September, the classes moved to the mansion, and the first boarding students arrived. Father Meyer served as administrator, Brother Maximin Zehler taught, Brother Schultz cooked, and Brother Andrew Edel worked as farmer-gardener.

Five years later the school burned to the ground, but within a year classes resumed. By 1860, when Brother Zehler became president, enrollment approached one hundred. The Civil War had little direct effect on the school because most of the students were too young to serve. St. Mary's grew as college preparatory courses were started in 1861. Then came a novitiate and a normal school for Marianist candidates. An old history refers to the period of 1860-75 as "the brick-and-mortar years." The Chapel of the Immaculate Conception was completed in 1869. In 1870, visitors marveled at new St. Mary Hall, the largest building in Dayton, and called it "Zehler's Folly." The new "college department" moved into it in 1871. (St. Mary Hall is now listed in the National Register of Historic Places.)

In 1882, the institution was incorporated and empowered to confer collegiate degrees under the laws of the State of Ohio. In 1883, another devastating fire visited the campus, but this time some of the buildings were saved. The statue now known as Our Lady of the Pines was erected in gratitude, and the following year St. Joseph Hall was built, symbolizing the renewed confidence of the Dayton Marianists. In a more famous emergency, the school was spared by water as it had not been by fire. Because of its hillside location, it survived the Great Flood of 1913 untouched and was able to give shelter to 600 refugees.

In 1920, the school was incorporated as the University of Dayton. The same year, the elementary division was closed, the Division of Education was organized, and the University started its tradition of evening and Saturday classes to serve adults in the surrounding community. In 1922, the College of Law opened, also with evening classes. Other graduate programs followed, to augment the professional degree programs which distinguished the University from many of Ohio's other independent institutions of higher learning. In 1923, the first summer session was held; its classes, like those of the law college, were open to women as well as men.

The 1930s, with the Great Depression, were in many ways a time of retrenchment for the University of Dayton as for most other American schools. The Dayton Marianists had survived cholera, smallpox and influenza, wars, fire and flood and (in 1924) a Ku-Klux-Klan cross-burning on the campus. In 1935, even as the University turned its preparatory school functions over to Chaminade High School and graduated what was to be its last class in law for almost forty years, it inaugurated a college for women, with sisters of Notre Dame in charge of twenty-seven entering female students. Two years later, the college for women closed; all divisions opened to women, and the University became fully coeducational.

Enrollment had passed a thousand when World War II broke out. By 1950, with the return of the veterans, it reached more than 3,500. In 1967, it topped 10,000. But then, with the expansion of a community college and the establishment of a state university nearby, enrollment declined, and the resulting retrenchment was exacerbated by rising inflation and the energy crisis. Nor did the social turbulence and activism of the late 1960s and early 1970s bypass the University of Dayton. Some students and faculty protested against the Vietnam War, compulsory ROTC, and defense-related research activities. They campaigned also for changes in the curriculum, seeking more opportunities for meeting personal needs and goals. In response, the University gave greater responsibility to students for their own academic decisions, and it initiated interdisciplinary programs, self-directed learning and various experimental courses and methods. Meanwhile, the profile of the student body changed. The 1960s saw significant increases in female and minority students. In the 1970s, there was a shift to a largely residential student body, and at the same time, many more "nontraditional" (older) students matriculated. By the mid-1970s, total enrollment steadied at more than 10,000, with about 6,000 full-time undergraduates.

The University held its first general public fund-raising campaign in order to erect Wohlleben Hall in 1958 and Sherman Hall in 1960. Both campus and off-campus residences, residence halls, apartments and houses were added and improved as such emergency accommodations as surplus Army barracks and an adapted Army hospital (renamed the West Campus) were phased out.

Long-range planning has helped integrate new buildings and old and made the campus more livable by increasing its beauty as well as its efficiency. In 1986, old and new combined in the design of the Anderson Center between Rike Hall and Miriam Hall. When fire ravaged St. Joseph Hall in 1987, the University was able to rebuild and restore it without harming the architectural integrity of that historic corner of campus. Keeping pace with the needs of the University, the Jesse Philips Humanities Center opened in 1993, and Joseph E. Keller Hall was built for the School of Law in 1997. In addition, the University has renovated Miriam Hall, converted its child care center into an early childhood demonstration school called the Bombeck Family Learning Center and completed the first phases of a modern Science Center. In 2002, the University of Dayton Arena underwent a modernization, placing it among the best venues for basketball in the country. The Donoher Basketball Center, a major addition to the UD Arena giving UD a premier basketball facility for both playing and training, was dedicated in 1998.
As the University of Dayton entered the 21st century, it built modern student facilities, including ArtStreet and Marianist Hall (2004) and RecPlex (2006).

The edifices are not the only changes on campus. In 1960, the University reorganized academically and administratively. Administrative changes saw the formation of the College of Arts and Sciences from what had been two separate units. Other divisions became the Schools of Business Administration, Education and Engineering. In 1970, the University charter was amended and lay members now joined the Marianists on the Board of Trustees. In 1974, the School of Law reopened.

Academically, the University has continued to expand and enrich its offerings and support services, especially since mid-century. Graduate studies, abandoned during World War II, resumed in 1960, with the School of Education leading the way. In 1969, the Department of Biology inaugurated the first doctoral program since 1928. The School of Engineering introduced two doctoral programs in 1973, and in 1992, the first doctoral degrees in educational leadership were awarded. In 1997, the Board of Trustees approved a doctoral program in theology with a focus on the Catholic experience in the United States. It was the first such doctoral program on a Catholic campus nationally.

In 1975, the Marian Library, which had grown to international renown since its inception in 1943, founded the International Marian Research Institute (IMRI), which was incorporated in 1984 as a branch of the Marianum in Rome. IMRI was empowered to confer licentiate and doctoral degrees in theology, with a specialization in Mariology. The Marian Library now holds the world’s largest collection of print materials on Mary, the mother of Jesus.

For all undergraduates, a general education plan was adopted in 1983 to foster integration of the liberal arts in a professional education. In 1990, the Academic Senate approved a revision of the general education requirements that called for an integrated base of four humanities courses complemented by clusters of other courses, requiring various disciplines to focus on a single theme. The Academic Senate revised and renamed the general education requirements again in 2010 to emphasize seven mission-related student learning outcomes: scholarship, faith traditions, diversity, community, practical wisdom, critical evaluation of our times, and vocation. The Common Academic Program (CAP), taken by all undergraduates, integrates all aspects of students’ University experiences beginning with courses in the Humanities Commons and culminating in a Capstone experience. The University has always maintained a tradition of innovation. In 1874, St. Mary’s Institute’s new Play House gymnasium was the only one of its kind in Ohio, and it is probable that the first organized basketball game in the state took place there. A system of elective studies was inaugurated in 1901. In 1924, the University was the first school to be granted a charter by the National Aeronautical Association. It was one of the first in the nation to offer a course in biophysics (1935). In 1948, it was a pioneer in student ratings of professors, and in 1952, it invited persons over 60 to attend its evening classes as guests. Its graduate program in laser optics was one of the earliest in the country. It was one of the first educational institutions to adopt electronic data-processing equipment and to offer degrees in computer science. In 1999, the University of Dayton was the first in the nation to offer an undergraduate degree program in human rights.

More than just a breeding ground for academic excellence, the University also responds to the needs of society and the region. Sponsored research at the University began in 1949 with a few faculty members and student assistants doing part-time research for industry and government agencies. In 1956, the University of Dayton Research Institute (UDRI) was formed to consolidate the administration of the growing research activities. Annual research volume has increased from $3,821 in 1949, to more than $130 million today. The University of Dayton ranks second in the nation in funding for materials research.

Named for Brother Raymond L. Fitz, S.M., the University’s longest-serving president, the Fitz Center for Leadership in Community, founded in 2002, connects students and faculty to the community through service learning, social justice and ongoing involvement.

Among the University’s other community collaborations is the Dayton Early College Academy, a public high school founded in partnership with the Dayton Public Schools. DECA, whose first class graduated in 2007, is the only charter school in the country operated by a Catholic university.

The University's long-range plans include incorporating nearly 50 acres purchased from NCR in 2005. The land, lying between the academic core of campus and the Arena Sports Complex, increased the size of campus by nearly a quarter.

From its humble roots as a private boarding school for boys, the University of Dayton today ranks among the best Catholic universities in the country. It is the largest independent university in Ohio and draws students from around the country and the world.