St Gregory's beginnings are entangled with various charitable aspirations of the Catholic philanthropist, Mr Thomas Donovan. He wished to establish a farming school for destitute boys who would be trained in agricultural skills to enable them to support themselves well in life. He had in mind the model of St Vincent's Boys’ Home at Westmead, namely a partnership between the Marist Brothers, the St Vincent de Paul Society and himself. The clientele were to be boys over the age of 14.

With this in mind, in 1921 Mr Donovan purchased the property on which the College now stands together with Badgally House.

The Marist Brothers became involved when they, together with Mr Donovan and the St Vincent de Paul Society, signed an agreement to realise this project on 8 March 1923. The first director of the Marist community at Campbelltown was Brother Methodius Watson.

When the original project did not eventuate and the St Vincent de Paul Society withdrew, Mr Donovan suggested to the Brothers that, with his support, they found a College, along the lines of the English Benedictine Colleges. He planned to endow poor students with bursaries to attend this College. The Brothers agreed to this and the first boarders of St Gregory's College arrived on 2 February 1926. The first Principal of St Gregory's College was Br Felix Rogers.

In 1927 St Gregory's presented its first candidates for the Intermediate Certificate.

After the death of Thomas Donovan it was unclear who had ownership of the College and the property. Following several years of legal negotiations the Marist Brothers were eventually recognised as sole owners of both. This happened on 13 July 1934. Mr Donovan's death also enabled the Brothers to deviate from his original plan for the school and in 1937 St Gregory's registered with the Department of Education as a Junior Agricultural College. In 1939 the school was given full secondary registration and presented its first candidates for the Leaving Certificate.

Until 1963 St Gregory's was essentially a boarding school. In this year the policy changed and St Gregory's took in its first significant group of day students. Since then it has become predominantly a day school for secondary boys with a smaller intake of boarders.

In 2001 Mr Marshal McMahon became the first lay headmaster of the College.
St Gregory’s College Campbelltown 1950

For many years, as this cover of the annual magazine shows, St Gregory’s put great stress on its identity as an agricultural college.

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