Metabolism, and Digestive Diseases of the National Institutes of Health sponsored a long term, prospective clinical trial. The study, begun in 1961, was conducted by the University Group Diabetes Program (UGDP) in 12 university medical centers. Patients selected for the study were maturity-onset diabetics who had been diagnosed no more than 1 year prior to entry into the study and did not require insulin to remain symptom-free.

All patients were given an appropriate diabetic diet and were randomly assigned to one of four different treatment groups: (1) Fixed dose of tolbutamide (1.5 grams/day), (2) Fixed dose of insulin (10 to 16 units based on body surface area), (3) Variable dose of insulin adjusted to control the blood glucose, or (4) Placebo. Eighteen months after the study began, a fifth group was added in which the treatment was a fixed dose of phenformin hydrochloride (100 milligrams/day). Patient recruitment was completed in 1966 with a total of 1,027 patients in the entire study and approximately 200 patients per treatment group.

By 1969 the unexpected finding of a significantly higher mortality due to cardiovascular causes was present in the tolbutamide group (12.7 percent or 26 out of 204) compared to the placebo group (4.9 percent or 10 out of 205), the fixed-dose insulin group (6.2 percent or 13 out of 210), and the variable insulin group (5.9 percent or 12 out of 204). After evaluating the available data, the investigators decided to discontinue use of tolbutamide in the study because they concluded that no benefit had been shown for these patients and there was evidence that the long term use of this drug was associated with a serious side effect.