OBJECTIVE - Several methods have been proposed to evaluate insulin sensitivity from the data obtained from the oral glucose tolerance test (OGTT). However, the validity of these indices has not been rigorously evaluated by comparing them with the direct measurement of insulin sensitivity obtained with the euglycemic insulin clamp technique. In this study, we compare various insulin sensitivity indices derived from the OGTT with whole-body insulin sensitivity measured by the euglycemic insulin clamp technique. RESEARCH DESIGN AND METHODS - In this study, 153 subjects (66 men and 87 women, aged 18-71 years, BMI 20-55 kg/m²) with varying degrees of glucose tolerance (62 subjects with normal glucose tolerance, 31 subjects with impaired glucose tolerance, and 60 subjects with type 2 diabetes) were studied. After a 10-h overnight fast, all subjects underwent, in random order, a 75-g OGTT and a euglycemic insulin clamp, which was performed with the infusion of [3-³H]glucose. The indices of insulin sensitivity derived from OGTT data and the euglycemic insulin clamp were compared by correlation analysis. RESULTS - The mean plasma glucose concentration divided by the mean plasma insulin concentration during the OGTT displayed no correlation with the rate of whole-body glucose disposal during the euglycemic insulin clamp (r = -0.02, NS). From the OGTT, we developed an index of whole-body insulin sensitivity (10,000/square root of [fasting glucose x fasting insulin] x [mean glucose x mean insulin during OGTT]), which is highly correlated (r = 0.73, P < 0.0001) with the rate of whole-body glucose disposal during the euglycemic insulin clamp. CONCLUSIONS - Previous methods used to derive an index of insulin sensitivity from the OGTT have relied on the ratio of plasma glucose to insulin concentration during the OGTT. Our results demonstrate the limitations of such an approach. We have derived a novel estimate of insulin sensitivity that is simple to calculate and provides a reasonable approximation of whole-body insulin sensitivity from the OGTT.