disease.[8] Thus, the presence of asymptomatic pathology in newly diagnosed adult-onset diabetics cannot be used as a telling argument against a relationship to the metabolic abnormalities associated with diabetes mellitus.

The failure to consistently observe improvement in specific diabetic complications following the institution of "stricter control" is frequently used as evidence that the pathogenesis of these conditions is unrelated to the consequences of an impaired insulin secretory mechanism. To cite but one example of the limitations of this reasoning, recent studies have demonstrated that the majority of a group of newly diagnosed adult-onset diabetics with normal standard neurologic examinations and without symptoms of neuropathy could be shown to have widespread functional abnormalities in their peripheral nervous system when suitably sensitive techniques were employed.[9] Biopsies of peripheral nerves from asymptomatic adult-onset diabetics without clinical evidence of neuropathy have also revealed pathological changes similar to those found in the nerves of patients with clinical neuropathy (although of a lesser degree).[10] Thus, the development of the clinical manifestations of diabetic neuropathy may represent a late stage in the pathological process and have irreversible elements. Whether or not patients with clinically apparent peripheral neuropathy respond to efforts to improve "control" can provide little information concerning its pathogenesis or its prevention. The host of invasive techniques which would be required to assemble suitably characterized subjects for study (e.g., coronary angiography, renal and peripheral nerve biopsies, fluoroscein retinography, and so forth) almost precludes meaningful large scale clinical trials.

Many physicians also believe that the controversy over the relationship between the metabolic derangements that result from an altered insulin secretory mechanism and alterations in the capillary basement membrane in diabetics has been resolved and that the two are clearly unrelated. This stems from the provocative studies of Siperstein and associates, who were the first to apply quantitative techniques to the assessment of capillary basement membrane thickness (CBMT).[11] They recognized the inherent technical problems in attempting to measure CBMT in many organs and demonstrated that skeletal muscle biopsies provide a means of obtaining suitable material for study from large numbers of patients. Their data indicated that muscle CBMT was significantly greater in diabetics and that the degree of thickening appeared to be unrelated to the duration of known disease or to its "severity." Moreover, their studies suggested that in patients genetically at high risk for the development of diabetes mellitus, increased muscle CBMT was present prior to the development of a detectable abnormality in glucose tolerance. Siperstein's work has been a major contribution and stimulus. However, some of his observations and interpretations have been seriously challenged by Kilo et al., who have concluded that muscle CBMT is usually within normal limits at the outset of clinical diabetes mellitus and increases with duration of disease.[12] There are differences in methodology and in patient selection in these studies, and the resulting controversy has not been resolved. The studies of Østerby suggest that in the kidney the alterations in glomerular capillary structure are not present at the outset of clinical diabetes in young adults but progress with increased duration of the disease.[13] Thus, it would be premature to conclude that the demonstrable metabolic abnormalities