tolbutamide group than for either of the other two. Considering deaths from cardiovascular causes, this observation is even more striking: while certainly in all risk categories, the probability of dying from cardiovascular causes in years 5-10 was consistently higher in the tolbutamide group than in the diet group, for those over 60 the probability was also higher in the tolbutamide group than in the insulin group at all risk levels. This observation is not as apparent among those under 60 at entry although in this age group the initial differences in survival between the tolbutamide and insulin groups become negligible.

It has been seen that the delineation of the population by consideration of all risk factors is a sensitive indicator of survival because observed probability of survival decreases as level of risk increases. It has also been seen that within risk factor categories the probability of death from cardiovascular causes is greater for persons on tolbutamide than for those on other treatments. The most comparable group is that of individuals with low risk levels. Even within this sub-group the numbers are small and therefore the standard errors associated with the probabilities are large. The increased risk among those on tolbutamide is nonetheless present.

Discussion

The major purpose of this study was to compare the effects of long term hypoglycemic therapy prescribed in the usual clinical manner with tolbutamide to that of treatment with insulin and to that with diet alone. Specifically, it was desired to assess the effects of the individual therapies on mortality and especially on that portion attributable to cardiovascular causes. Because individuals were not randomly allocated to the specific treatment groups, disease severity within the three groups considered here is not comparable. Evaluation of survival was restricted to individuals with known duration of diabetes = one year prior to entry to the study. However, even in this group disease severity could not be assumed to be comparable. The symptoms of diabetes can be insidious in their appearance and therefore, although symptoms of the disease were noticed in the year previous to the first visit, the true onset of the disease could have been 5 to 10 years earlier. Unmeasured differences between the groups in the true duration of diabetes prior to the first visit could influence the severity of the disease at the time of the first visit and consequently the results observed here. However, in order for any analysis to be performed it must be assumed that the discrepancies between true and observedduration of diabetes were distributed equally among the different groups.

The best available indicator of severity over the course of the study was mean blood glucose level and it has been seen that even in this group of newly diagnosed diabetics the distribution of blood glucose was different. Nonetheless, evaluation of relative survival within 4 blood glucose groups showed (whether or not history of ASHD or hypertension was considered) some positive evidence that for persons with low and moderate mean blood glucose levels treated with tolbutamide, the probability of deaths during the 5-10 year period was greater than in either of the two other treatment groups. This result was most noticeable when considering deaths due to cardiovascular causes. Evaluation of survival within general classes of overall risk supports this hypothesis for cardiovascular causes.

The fact that in the first five years after entry to the study those on insulin appear to exhibit poorer survival than either the tolbutamide or diet groups is most likely related to differences (unmeasured) in disease severity at the time of entry to the study rather than to the treatment itself. This hypothesis is consistent with the way in which treatment is prescribed. Observation made after five years are, therefore, more likely to be related to the effects of long-term treatment of the diabetes.

The results of the UGDP strongly suggested that tolbutamide was not an effective treatment for diabetes. The excess of cardiovascular deaths observed in the tolbutamide group was sufficient to warrant termination of that portion of the clinical trial. The Joslin Clinic data presented here are not directly comparable with the results presented by the UGDP; it cannot be assumed that the underlying populations of diabetics from which each of the study groups was drawn were the same. In addition, the administration of treatment was done randomly in the UGDP project whereas in the Joslin Clinic data treatments were prescribed according to the physician's biases. While from the UGDP data it was possible to quantitate the excess cardiovascular mortality attributable to tolbutamide, the sizes of the groups in the Joslin Clinic data were small and in addition, treatment and blood glucose were highly confounded so that