could be made on the basis of the observed blood glucose levels from the short times of the glucose tolerance test. Since some patients did not adhere completely to the assigned treatment, they may have gone for periods of time without any medication or with a modified dose, or they may have switched to another therapy.

It is clear that the interpretation of the UGDP data could be influenced by such variation in the assigned treatment. The UGDP analysis and the analysis discussed in the preceding part of this report are based on the assigned treatments. In this section * * *

Caution must be taken, however, in the interpretation of these results. It is quite possible that adherence is related to importnt base-line or other unknown variables for some treatment groups and not for others. If such were the case, subgroups having a particular pattern of adherence might not yield fair comparisons of treatment. The analyses presented in this section are designed to account for the known base-line influences. owever, without the use of randomization to form treatment groups, there is no assurance that an unknown prognostic variable is present that affects adherence patterns selectively for different treatment groups and thus invalidates the treatment comparisons.

6.1.4.1 *The extent of the problem*

Table 4 summarizes the number of patients who continued taking their assigned treatment for the entire follow-up period, and the number who, for at least one quarter, changed to other treatments or none. Thus, for the 205 patients initially assigned to the placebo group, 76 (37%) continued receiving placebo for the entire period of follow-up, and the remainder had at least one quarter of nonassigned treatment as follows: 1 (0.5%) received tolbutamide; 7 (3%), insulin at a variable dose; 92 (45%), no treatment; 4 (2%), tolbutamide and no treatment; and 24 (12%), insulin and no treatment. (One patient did not fit any of these categories.) An interesting point is that 168 (82%) of the patients initially assigned placebo were receiving either the placebo or no medication for the entire study. Since the initial treatment groups were assigned to their treatment by chance, these patients could be regarded as representative of the UGDP patient population. Thus, over the average follow-up time of 6.15 years, a very large proportion of the patients could be maintained without medication.

Another consideration in evaluating the extent of the problem of adherence is the proportion of follow-up time individuals continued receiving their initial therapy exactly as prescribed in the protocol. Table 5 classifies the patients by the proportion of their total follow-up time spent receiving treatment initially assigned. In order to compare the extent of adherence of receiving standard-dose insulin with the adherence of other patients treated with insulin, a dose modification of variable-dose insulin after the initial titration dose was regarded as a "modification." Note that 26% (218/823) of the entire population were 100% adherers for the total follow-up period and some 23% of the patients were receiving the initial treatment less than 50% of the total follow-up time.

Table 6 summarizes the total follow-up time (patient-years) with treatment exactly as assigned, with the assigned treatment at a modified dose, and with other treatments. Note that for each of the treatmetn groups, 14% to 16% of the follow-up time was spent receiving no medication at all. Further, the proportion of follow-up time that patients spent receiving the fixed dose of tolbutamide was 58% and receiving the fixed dose of insulin, 55%. It is interesting that for 25% of the follow-up period, the tolbutamide patients were taking a dose other than that specified by the protocol; similarly, for 30% of the follow-up period, the standard-dose insulin group was taking an altered dose of insulin.

6.1.4.2 *Statistical analysis*

The statistical analysis of the UGDP data in relation to adherence to treatment is divided into two portions. The first part uses a nonstandard method that was developed for the problem at hand and will be called the *relative allocation* method. It takes into consideration (1) time spent receiving no medication, (2) time spent receiving modified doses of the initially assigned therapy, and (3) time receiving other than the initially assigned medication. The second method of analyss is called the *survival modeling* method and is based on techniques recently developed by Cox (27) for modeling survival data when base-line

References at end of article.