(concomitant) variables that affect the outcome are present. Both analyses led to the conclusion that women receiving tolbutamide have higher total mortality and higher cardiovascular mortality than women receiving placebo. This holds especially for the older women (over 53 years of age).

Relative allocation method.—The basic idea of this method is explained in appendix B. The problem is to allocate the number of patients, and the deaths, to the treatments when individuals have not been receiving the initially assigned treatment for the full follow-up time. The method of relative allocation assigns numbers of both patients and deaths to the treatments in such a way that they are proportional to the length of time the patients have been taking each treatment. Suppose a subject has been in the study for ten years, half of them with the initially assigned treatment and half with no treatment. This subject would contribute half an observation to each of these categories. If the subject had died, half a death would be allocated to each of the two categories. The sum of these allocations defines an effective sample size, n′, and an effective number of deaths, d′. We then define as follows:

$$\text{death rate} = 0' = \mathrm{d}'/\mathrm{n}'$$

If time of follow-up is allocated in a similar way to the various treatments, and T is the total follow-up time for a subgroup, then

$$\text{failure rate} = \mathrm{Y}' = \mathrm{d}'/\mathrm{T}$$

Appendix Table A.7.1 presents data on total deaths (d′), cardiovascular deaths (d′′) and effective sample size (n′) by initially assigned treatment and by treatment received; and in Table A.7.2, the calculation of $0'$ and of Y′ is illustrated.

Table A.7.2 summarizes the death rates and failure rates corresponding to assigned treatment without modification, treatment modified by change of dose, and no treatment. The cardiovascular mortality associated with tolbutamide is highest among the four assigned treatments, regardless of whether the treatments are pursued with modification or without. A comparison of the cardiovascular mortality in the tolbutamide vs the placebo groups results in statistical significance at $P=.015$ (no treatment modification), $P=.06$ (doses changed), and $P=.50$ (no drug); using the Fisher test for combining tests of significance, one finds that the overall result is significant at the $P=.007$ level.

Since there appeared to be a randomization anomaly with regard to the allocation of treatments with respect to sex, it is of interest to examine the effects of dose modification for each sex. Table A.7.3 summarizes the cardiovascular mortality by sex and dose modification. It is clear that the largest difference in cardiovascular mortality between the placebo and the tolbutamide groups occurs in the female group not having any dose modification ($P=.004$). A simple, overall statistical analysis can be carried out on the mortality rates given in Table A.7.3 by ranking then for each of the six dose-modification groups (rows) and assigning to treatments within a group the ranks 1 through 4. Since those receiving tolbutamide have the highest mortality in five groups and the next highest in one group, this group has a rank sum of $5(4)+3=23$; the rank sums for the other treatments are as follows: placebo, 12; standard-dose insulin, 12; and variable-dose insulin, 13. The probability of obtaining a rank sum equal to or higher than 23 if there were no difference between the treatments is $P=.007$. (This probability is the ratio of the number of ways of obtaining a rank sum equal to or greater than 23 to the total number of possibilities, ie, $28(6(6))/(24)(6)$). If one were to make a two-tailed statistical test, the P value would be multiplied by 2; ie, $P=.014$.

Another way to analyze the effect of adherence is to partition the data according to both (*a*) dose modification and (*b*) whether the patients adhered to the initially assigned drug for the complete follow-up period. Table A.7.4 summarizes the cardiovascular death rates according to these two variables. The highest death rate is found in the tolbutamide group who were 100% adherers, and had no dose modification. The comparison of placebo vs tolbutamide for this subgroup is significant at the $P=.003$ level. The comparison of placebo vs tolbutamide in the case of the other three subgroups is not significant. The cardiovascular death rate for the three tolbutamide subgroups who either did not adhere completely to the medication or had a dose modification is $7.6/93.9=.08$. A comparison of this proportion with that for the subgroup that adhered completely and had no dose modification (21) gave significance at the $P=.002$

References at end of article.