

where  $\lambda(t)$  and  $\{\beta_s\}$  are unknown parameters to be estimated and  $\{x_{s\alpha}\}_{s=1,2,\dots,p}$  and  $p$  covariables associated with the  $\alpha^{\text{th}}$  patient. The  $x$ -variables for the four protocol treatments were taken to be equal to the proportion of time the  $\alpha^{\text{th}}$  individual was on the particular protocol treatment. That is, if the first four  $\beta$  coefficients refer to the treatments in the standard order, then  $x_{s\alpha} = w_{s\alpha}$  for  $s=1,2,3,4$ . If a patient receiving standard-dose insulin had an altered dose of insulin, this was regarded as contributing information to the variable-dose insulin group.

The estimates of  $\beta_s$  ( $s=1,2,3,4$ ) correspond to the logarithm of the ratio of the failure rate of the  $s^{\text{th}}$  treatment to that of the period for which no medication is taken. The differences  $\beta_s - \beta_1$  estimate the logarithm of the ratio of the  $s^{\text{th}}$  treatment to placebo. These ratios are "adjusted" ratios that have been adjusted for base-line and demographic variables as well as institutions. The model is based on the work of Cox, (27) utilizing a modification suggested by Kalbfleisch and Prentice. (28)

## REFERENCES

TABLE 1.—UGDP STUDY: TREATMENT GROUPS AND CAUSES OF DEATH

| Treatment group            | Number of subjects | Percent dead |                       |
|----------------------------|--------------------|--------------|-----------------------|
|                            |                    | All causes   | Cardiovascular causes |
| Clinics using tolbutamide: |                    |              |                       |
| Placebo.....               | 205                | 10.2         | 4.9                   |
| Tolbutamide.....           | 204                | 14.7         | 12.7                  |
| Standard dose insulin..... | 210                | 9.5          | 6.2                   |
| Variable dose insulin..... | 204                | 8.8          | 5.9                   |
| Clinics using phenformin:  |                    |              |                       |
| Placebo.....               | 64                 | 9.4          | 3.1                   |
| Phenformin.....            | 204                | 15.2         | 12.7                  |
| Standard dose insulin..... | 68                 | 8.8          | 8.8                   |
| Variable dose insulin..... | 65                 | 6.2          | 4.6                   |

TABLE 2.—BEDFORD STUDY (6): CARDIOVASCULAR EVENTS AND TOLBUTAMIDE

|                               | Placebo            |            |         | Tolbutamide        |            |         |
|-------------------------------|--------------------|------------|---------|--------------------|------------|---------|
|                               | Number of subjects | With event |         | Number of subjects | With event |         |
|                               |                    | Number     | Percent |                    | Number     | Percent |
| Both risk groups:             |                    |            |         |                    |            |         |
| Both sexes.....               | 123                | 46         | 37.4    | 125                | 34         | 27.2    |
| Male.....                     | 69                 | 25         | 36.2    | 62                 | 19         | 30.6    |
| Female.....                   | 54                 | 21         | 38.9    | 63                 | 15         | 23.8    |
| High risk group: <sup>1</sup> |                    |            |         |                    |            |         |
| Both sexes.....               | 34                 | 19         | 55.9    | 41                 | 21         | 51.2    |
| Male.....                     | 14                 | 10         | 71.4    | 14                 | 11         | 78.6    |
| Female.....                   | 20                 | 9          | 45.0    | 27                 | 10         | 37.0    |
| Low risk group:               |                    |            |         |                    |            |         |
| Both sexes.....               | 89                 | 27         | 30.3    | 84                 | 13         | 15.5    |
| Male.....                     | 55                 | 15         | 27.3    | 48                 | 8          | 16.7    |
| Female.....                   | 34                 | 12         | 35.3    | 36                 | 5          | 13.9    |

<sup>1</sup> The high risk group consisted of those who, on coming into the trial, had clear clinical evidence of cardiovascular disease or clinically significant hypertension.

TABLE 3.—BEDFORD (5) AND UGDP STUDIES: AGE DISTRIBUTIONS

| Age              | Bedford study |         |             |         | UGDP study |         |             |         |
|------------------|---------------|---------|-------------|---------|------------|---------|-------------|---------|
|                  | Placebo       |         | Tolbutamide |         | Placebo    |         | Tolbutamide |         |
|                  | Number        | Percent | Number      | Percent | Number     | Percent | Number      | Percent |
| 20 to 29.....    | 7             | 5.6     | 6           | 4.9     | 7          | 3.4     | 3           | 1.5     |
| 30 to 39.....    | 7             | 5.6     | 12          | 9.8     | 25         | 12.2    | 23          | 11.3    |
| 40 to 49.....    | 22            | 17.6    | 22          | 17.9    | 51         | 24.9    | 45          | 22.1    |
| 50 to 59.....    | 25            | 20.0    | 34          | 27.6    | 60         | 29.3    | 74          | 36.3    |
| 60 to 69.....    | 27            | 21.6    | 27          | 22.0    | 46         | 22.4    | 51          | 25.0    |
| 70 to 79.....    | 30            | 24.0    | 20          | 16.3    | 16         | 7.8     | 8           | 3.9     |
| 80 and over..... | 7             | 5.6     | 2           | 1.6     | 0          | 0       | 0           | 0       |
| All ages.....    | 125           | 100.0   | 123         | 100.0   | 205        | 100.0   | 204         | 100.0   |
| Mean age.....    | 58.6          |         | 55.4        |         | 52.2       |         | 53.0        |         |