Mr. Chairman, Ladies and Gentlemen:

A most difficult job has been entrusted to me this afternoon. I must compress 10 years work into 20 minutes. ----- I must speak to a group of colleagues many of whom have already made up their minds on the basis of fragmentary information which has reached their patients and themselves before they have had an opportunity to hear the facts.

I would like to have you maintain a neutral frame of mind until the facts have been laid before you. If I do not answer all of your questions in the talk and the question period that follows, your judgement may have to be postponed until you have the full paper now in the hands of the editors.

~~Mr. Chairman, Ladies and Gentlemen:~~

Most patients with adult onset diabetes have glucose intolerance of a relatively mild degree and should be able to maintain blood glucose in a satisfactory range simply by following an appropriate diet. Failure to maintain control by dietary means is common, however, and such patients may be offered oral agents. Since these are not life-saving drugs, but medications of convenience, it is necessary that the long-term effects of such therapy be known.

First slide, please.

The University Group Diabetes Program was initiated in 1960 and was designed to evaluate the relative effects of treatment on the course of the vascular complications of the maturity onset type of diabetes.

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The participants of the University Group Diabetes Program are listed here. This give me the opportunity to point out that I am honored to be the spokesman for the large group of investigators whose cooperative efforts have made this report possible. It is also important to point out that the study population drawn from these twelve centers provides a diversity of patients that is quite impossible to find in a single center. We have here a wide geographic representation; a mixture of urban and rural people; representatinn of middle as well as lower economic groups and many ethnic divisions. The heterogeneity of this study population will permit a wider generalization of findings than would be the case were results obtained from a single clinical center.

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In keeping with our objectives, it was determined that a sample size of at least 200 pateints for each study group would be essential to draw valid conclusions within a feasible period of study. It was, of course, mandatory that the patients be allocated ~~by~~ random ~~distribution~~ to the various study groups and that there be balance not only throughout the study but within each clinic as well. ~~It is also axiomatic that~~ The study ~~must be~~ was double blind for the oral agents so that the agent ~~is~~ was unknown to both patient and physician. ~~A cooperative study could not exist if examinations, both clinical and in the laboratory, were not objective~~. All tests were performed in each clinic in the same manner. Quality control was maintained both locally and centrally. Laboratories and all results were given routine quality checks. Data from the study collected at ~~the study~~ the coordinating center were monitored, coded, verified and stored for analysis.

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The principle criteria for eligibility of patients included the following: 1. The diagnosis of diabetes must have been made within 12 months of entrance into the study. 2. The diagnosis was confirmed by a glucose tolerance test, standarized for this study. 3. The patient must have stable adult onset diabetes without significant ketonuria after one month on diet alone. 4. Patients were screened for life expectancy of at least five years by clinical estimate and 5. the patient must be willing to participate in the study and be cooperative in following the instructions of their clinic physician.

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After this selection for study, patients were allocated by random distribution to one of five selected treatment groups. In the insulin-variable group, (IVAR), insulin was used as it is ordinarily used in practice to normalize blood glucose and to keep the patient under the best possible clinical control. A second group was given ~~a standard~~ insulin on a standard dosage ~~of insulin~~ scale, a fixed dosage etc. to determine the effect that insulin might have on vascular complication ~~used on a standard scale unrelated to blood sugar~~. In this group, (ISTD), patients received from 10 to 16 units of insulin, the dosage being based on body surface. Tolbutamide (TOLB) was selected as the representative of the sulfonylurea family. Experience with tolbutamide at the inception of the study was greater than with any of the other sulfonylureas. Moreover, it had the advantage of being rarely hypoglycemic except under unusual circumstances and having a rather fixed narrow dosage range ~~of effectiveness~~. Thus, it has been determined that dosage over 2.0 grams is rarely useful, ~~if effect is not seen prior to that dosage~~. A fixed dose of 1.5 gm. per day was used to preserve the double blind design of the study. A divided dosage was given ~~used~~ since available evidence indicated that better control of blood was obtained by this means. Phenformin (PHEN) was selected as the representative of the biguanides and given as a fixed dose of 100 mgs. daily, in divided dosage. This group was added 18 months after the other groups had been started, when it became clear at that time, that Phenformin had become widely accepted clinically as a useful therapeutic agent. Because of the late entry of this group, the effects of therapy on these patients will not be discussed this afternoon.

One of the most important study features was the inclusion of an oral placebo as a treatment group (PLBO). In this group the dose of placebo corresponded to the oral agent used. ~~Through~~ This group, treated on diet plus placebo, ~~we have~~ gives us an opportunity to follow the natural history of diabetes unaltered by a hypoglycemic agent; a most important part of this study. Little basic information has been accumulated heretofore in a long-term prospective manner on a large group of patients balanced among treatment regimes in this way.

Next slide, please.

At baseline and at quarterly intervals thereafter, patients were brought in for history and physical examinations, and evaluation of treatment. ~~and~~ at each such quarterly visit, one system, such as the Eye or Heart, was reviewed more thoroughly than the others and special data collected. The rate of change for the non-fatal response variables listed was small and did not give any definite evidence of superiority of one form of therapy over another. More extensive reports on ~~each of these~~ non-fatal events will be submitted at a later time. Special reports were submitted to follow drop-outs, treatment failures and, of course, death itself.

Data collected from patients monitored regularly at the Coordinating Center were reported to the clinical investigators at semi-annual meetings.

Next slide, please.

As the fatal events were reviewed alone, sequentially over time, there was a disquieting and quite unexpected possibility that one of the treatment groups was experiencing a mortality rate consistently higher than was true of other groups of patients. This trend appeared to begin somewhere around the third year and did not reverse itself, ~~during the time of observation~~.

Next slide, please

On this slide we see the cumulative rate of mortality for cardiovascular disease alone. Again, the higher instance of cardiovascular death in the group treated with tolbutamide is clearly shown. In reviewing the mortality experience all analyses of the cause of death were made without reference to therapy and, in the death of patients on oral treatment, without knowledge of whether the patient was on tolbutamide or placebo. These deaths were first reviewed by physicians in the clinic and a the cause of death was assigned. Impartial observers were then asked to review the events of death independently and without knowledge of any treatment and the assignment of the cause of death was made final. In reviewing the experience of the 823 patients in these 4 treatment groups, note should be taken of the fact that the life-death status was unknown in only 5 patients and these were assumed to be alive.

Next slide, please.

In reviewing the causes of death, we see the numerical basis of this concern. Of the 89 deaths that have occurred during the period of study, approximately 1/3 of this number have occurred in the tolbutamide treatment group. The difference in death for all causes between tolbutamide and placebo ~~is~~ given a Pvalue of .17 and is not considered statistically significant.

In the tolbutamide group 26 out of 30 deaths, or 87% could be attributed to a cardiovascular cause. Looking ~~more specifically~~ at diagnoses, myocardial infarction ~~seems to take precedence over~~ is numerically more important than the more general category of sudden death, the latter being shared equally be all treatment groups. There is no significant difference in the numbers of death

for cardiovascular cause, between placebo and insulin standard or insulin variable. However, there is a highly significant difference between the total number of cardiovascular deaths in the tolbutamide group when compared to those treated with placebo and diet alone, with a p-value of .005, ~~that is, .005.~~

The Chi-square test of significance should not be used at selected times and does not take into consideration the interplay of many other factors related to the disease itself nor does it project observations continually over time. This leads us to a second method by which these results can be reviewed in a more composite way. This involves the comparison of ~~two study~~ treatment groups with a standard population of the same composition. The mortality experience observed in ~~the study~~ a treatment group is then compared with that expected in the standard population. By comparing the ~~study~~ treatment groups populations to a standard population it is possible to show the relative mortality experience between the ~~study~~ groups.

As shown on the next slide, this is expressed as a ratio between the observed mortality in the patients under study to that which would be expected in the standard population. In viewing this you will recall that the study population was selected with an expected life of at least 5 years. This may account for the fact that the values seen for placebo and the two insulin groups are less than one, that is, the observed mortality was better than that expected. ~~This is not true of the tolbutamide population. Let me emphasize however, that the overall mortality for the entire study population is less by this measure than expected.~~ Tolbutamide, on the other hand, is 30% lower than expected. It is of some interest to note that UPG is continuing to hold or even improve its position - in reference to the other treatment groups.

Thus far these differences have been reviewed at set points in time or in overall aspects of total mortality. What is clearly needed

is some expression of a trend over time or a sequential ~~study~~ analysis in which differences in mortality can be measured against bounds of significance. These bounds of significance can be generated from the expected mortality rates previously used. The next slide will be a useful model on which to make these comments. Boundaries have been set at the upper and lower levels of significance for expected differences in mortality between two treatment groups. If there is no difference between placebo and the insulin standard group as shown here, deviations from the midline will be slight. As the differences between the treatment groups increased one of the boundaries is approached. If the boundary is crossed, the observed difference in mortality has a level of significance of approximately ~~5.0%~~ 2.5% Thus, if the observed difference between placebo and treatment exceeds the upper boundary, the treatment is worse than placebo at a level of significance of approximately 1 to 40. Exceeding the lower bounds on the other hand would mean that the treatment was significantly better than placebo at approximately the same level of significance. I would re-emphasize that this model is used to allow a sequential analysis over time and to make use of all data generated. One would conclude from this example that insulin was not significantly better or worse than placebo as regards cardiovascular deaths.

On the next slide, we see the bounds that have been generated in the same manner as before. The line represents the differences in mortality between placebo and tolbutamide. It is noted that tolbutamide has done consistently worse than placebo as viewed in this sequential manner since the fourth year and has in fact crossed the upper bounds in this analysis.

In trying to determine a basis for this difference in mortality experience, the investigators have carefully scrutinized the characteristics of the various treatment groups at baseline, and we are unable to find any differences in the composition of the various treatment groups which would account for these differences.

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The baseline characteristics have been reviewed and some of these are shown here. An asterisk has been placed beside those differences which approached a level of significance of .05. All other that have been studied have even less differences. The age composition was approximately the same. There were slightly more males and more Caucasians in the insulin variable group. The number of patients with blood glucose above 110 were slightly higher in tolbutamide. Tests of significance were also run for the other response variable and no sizable differences were found.

On the next slide...are shown a similar tabulation of the cardio-vascular risk factors at the time of entry. Both TOLB and ISTD have a slight numerical disadvantage in 10 out of 14 factors listed on this and the previous slide. Except for serum cholesterol, these differences have not proven to be significant in either the TOLB or the ISTD treatment groups.

From these tests of no difference one would conclude that these patients were members of a single population. There is no reason to believe that either TOLB or ISTD were different from each other or that TOLB treatment group was more susceptible to cardiovascular death at the onset on this study than were the patients in other treatment groups.

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In fact, if one divides the group on the basis of the present's or absent's of the risk factors just noted, it can be noted that patients without the risk factor also died in greater proportion than did the

similar tolbutamide group. They were without a history of hypertension, without a history of angina, without major EKG abnormalities, with serum cholesterols below 300 mgs.% and with normal body weight.

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A very careful review was also undertaken to see whether the groups were treated in any way that was different. Adherence to therapy was equally good. In fact, adherence was better in the group on tolbutamide who died than in the survivors. Patients were equally attentive to the clinic. The drop-out rate was equally low. The response of clinicians to symptoms interpreted as hypoglycemia was of interest. The dosage level of the therapeutic agents used in this study was purposely selected to avoid episodes of hypoglycemia. Study physicians were permitted to modify the study medications whenever symptoms believed to be due to hypoglycemia were detected. This occurred in 9 patients both in the placebo and the tolbutamide treatment groups. Hypoglycemic symptoms were most frequent in the patients in whom insulin was advanced to control blood sugar optimally. None of the deceased patients had recorded blood sugars below 50 mgs. per ml.

Only five patients were lost to follow-up. These were considered alive for mortality statistics. Thus, there is no evidence that any group of patients received a different grade of care than did any other group.

Clinic differences have been reviewed. Although there was variability in mortality experience between clinics, the tolbutamide deaths were higher than placebo deaths in 7 of the 12 clinics. In only 2 clincs were placebo deaths greater than those in tolbutamide.

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Of particular interest are the changes in blood sugar from baseline on sbusequent follow-up visits. The same patients were followed over a period of almost five years. The percentage change of blood glucose from baseline is shown. Note is taken of the fact that there is an initial fall in blood glucose in all groups. For the placebo group this is due to the careful scrutiny by physician and patient during the early treatment of diabetes whether the pateint is on active treatment or not. Over the period of the next five years blood glucose gradually tended back towards baseline in both insulin standard and the tolbutamide treatment group. Note the striking similarity of the behavior of the blood glucose in these two groups and contrast this with the previously noted differences in cardiovascular mortality. In patients treated with variable quantities of insulin in an attempt to normalize blood glucose there was no significant upturn in the fasting blood sugar over the period of time studied. One should conclude from this that the differences between tolbutamide and the other treatment groups as to mortality is not related to changes or lack of changes in blood glucose.

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Thus, we return again to the fundamental observation that the differences in mortality for cardiovascular death between tolbutamide and placebo could not be accounted for by any factor which we have been able to study. All investigators have agreed that the findings of this study provide no evidence that the combination of diet and tolbutamide therapy as described and used for mild noninsulin dependent diabetics is more effective than diet and placebo except as regards the lowering of blood glucose. Moreover, the findings suggest that tolbutamide and diet may be less effective, at least in so far as cardiovascular mortality is concerned, than diet and placebo or diet and insulin. For this reason, tolbutamide therapy has been discontinued in the UGDP. It is important

to emphasize that this decision was reached because the cause or causes of the excess mortality due to cardiovascular disease in the tolbutamide group had remained obscure in spite of serious search of the available study data. It has not been proven that tolbutamide is the sole factor responsible for this difference in mortality experienced. As clinicians, however, we cannot detect at this time which of our patients may be at risk. The study clearly indicates that there is a need for careful re-evaluation of current management of patients with adult onset diabetes who are not insulin dependent.