Document #10

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June 27, 1969

Gentlemen:

Attached is a review of the most recent data from the UGDP Meeting of May, 1969. It is obvious that since we have had the data only two weeks and since there is a rather large amount of data, it has in this time been impossible to complete an in depth evaluation. It is also obvious that we do not have the original patient forms, hence any trends or differences we note must, of necessity, be based on the tabulated data without, in most cases, the possibility of statistical evaluation.

The thoughts and observations expressed are based on the data up to the fifth to sixth year in the phenformin clinics and not beyond the sixth or seventh year in 'all clinics'. Our preliminary review of the data indicates some remarkable and inexplicable findings and conclusions in this study and it would seem that these conclusions can only be explained by peculiar and undefinable groups at baseline.

I regret that it is impossible to be able to complete and make available to you before your June 30th Meeting an in depth evaluation and critique of the study. The attached was accomplished with some haste and hence I beg your indulgence for the lack of polish and the possibility of discovering errors.

Sincerely,

E. Keith Borden

E. Keith Borden, M.D.

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Enc.

Document #10

Preliminary Evaluation of the UGDP Report of May 9, 1969

The Stop Judgment

The data available to us upon which apparently the judgment to discontinue tolbutamide in the study was based consists of the crude death rates, the Monte Carlo procedure, designed by Dr. Klimt, Dr. Meinert and Dr. Knatterud, and the matched pairs analysis. In reviewing these it is difficult to understand the judgment to discontinue treatment. Regarding the actual number of deaths and the crude death rates, since the last report of October 1968 three further deaths had occurred on the placebo group, causing the differential between tolbutamide and placebo to be diminished, so that at the present time the total excess mortality on tolbutamide consisted of ten deaths, a difference of 5% spread over a period of eight years. Quite surprising was the fact that a decision was made to discontinue the drug when in fact three further subjects had died on placebo and no further subjects had died on tolbutamide, suggesting that perhaps the differences were going to disappear.

The Monte Carlo technique for tolbutamide versus placebo showed that over the last two years the tolbutamide group appeared to be parallelling the upper boundary and, in fact, by definition the boundaries are at the 10% significance limits, so that according to the Monte Carlo procedure the differences were not significant even at the 10% level. Thirdly was the matched pairs analysis. The results of this analysis were, in fact, equivocal and also there is some question about the basis for matching. As described in the tan text the basis for matching consisted of matching primarily

on exposure period to drug and secondarily on age. No allowance was made for any of the risk factors which are known to produce cardiovascular disease. It would seem that this matching was based on a biostatistical judgment rather than a medical judgment and that the judgment was that the length of exposure to drug was the critical variable in the study. This would indicate that the matched pairs analysis was purely to see whether or not the differences between the tolbutamide and placebo deaths had reached statistical significance. It would seem to me that a system using matching on the risk factors at baseline as well as drug exposure would have been considerably more informative and would have helped to solve the problem of whether, in fact, the excess mortality was due to tolbutamide rather than approaching the question of whether the excess mortality had become statistically significant.

Point two is the distribution of deaths within the various clinics. Table U-I (attached) is a breakdown of the actual number of deaths for each of the clinics. It can be seen that the excess mortality for tolbutamide occurred in clinics E and K. If clinics E and K are removed the death rate on tolbutamide is reduced by 13 deaths, whereas the placebo is reduced by only four deaths. In fact the crude death rate, after removal of E and K from 'all clinics', does not significantly change the crude death rate in 'all clinics'. However, it makes a remarkable difference in the tolbutamide clinics. Clinics E and K account for 21% of the placebo

deaths in 'all clinics' and 45% of the tolbutamide deaths in 'all clinics'. This would strongly suggest that at least as far as tolbutamide goes these two clinics are different than the other ten clinics. It might be worthwhile to consider for a moment the expected distribution among the clinics if, in fact, the excess mortality seen in the tolbutamide clinics was due to tolbutamide. The probability of observing five clinics with an excess number of deaths in the tolbutamide group, assuming there are no treatment differences and equal numbers of patients, is 0.36. In order for one to have a high degree of confidence, that is a p-value of .05, that the excess mortality is treatment related one would have to observe at least one excess tolbutamide death in each of ten or more of the 12 clinics. In fact, there is an excess tolbutamide death in five clinics, an excess placebo death in three clinics, and no difference in deaths in four clinics.

This would certainly raise the serious possibility that the excess mortality on tolbutamide seen in these two clinics is a function of the clinics, and some peculiarity which has occurred in these clinics in the tolbutamide treated patients, rather than a function of tolbutamide treatment.

Differences between the phenformin or non-phenformin or all clinics

These differences are a matter of serious concern and suggest, in fact, that the populations in the phenformin and non-phenformin

clinics are at different risks of mortality. It would appear that there are statistically significant differences in survival rates for the fourth to fifth year in the phenformin versis the non-phenformin clinics (after taking phenformin clinic data out of 'all clinics'). Certainly in looking at the survival rates for tolbutamide treated patients in the phenformin clinics, without extending the data beyond the fifth year as suggested in the tan book, tolbutamide seems to be favorable. This is certainly not true in 'all clinics'. We were previously advised that this difference was due to period of exposure. It would seem that there are two answers to this question of exposure. First is that it is the survival rates which are different and survival rates by definition are supposed to account for period of exposure. The other answer, however, is that the rate of acceleration that was seen between the second and fourth years in mortality in the tolbutamide clinics has not yet appeared in the phenformin clinics. In 'all clinics' between June 1965 and July 1967 the tolbutamide mortality increased by 6.8% (see Table U-III). Between the period of July 1967 to May 1969* the mortality rate increased only by 4%, which was comparable to the other modes of therapy. This suggests that the accelerated rate of mortality in the tolbutamide clinics seen early is being dissipated. However, of even more significance is the fact that since the phenformin clinics are approximately one and a half years to two years behind the 'all clinics' it would seem that the period between July 1967 to May 1969 for the phenformin

* in 'all clinics'

clinics (Table 1.1 UGDP) should show the same accelerated increase that was seen in 'all clinics' between the period of June 1965 to July 1967. In fact the increase in mortality rate in the phenformin clinics for these comparable two years was an increase of 2.6% (see Table U-III), not any where near the 6.8% seen in 'all clinics'. This suggests that not only are there significant differences in the actual rates between the phenformin and non-phenformin clinics, but that the increased death rate seen in 'all clinics' is not occurring in the phenformin clinics. One wonders how great the differences would be if, in fact, phenformin and non-phenformin clinics were compared. It would seem, then, that the differences in the phenformin and non-phenformin clinics are functions of the populations in the phenformin and non-phenformin clinics and not a function of period of exposure.

If one reviews the many various tables for mortality, risk factors, etc. presented in this extensive report (UGDP of May 1969), and compares the performance of tolbutamide in the phenformin clinics and 'all clinics', it becomes obvious that the rate of increase of mortality in 'all clinics' (which includes the phenformin clinics) seen between the end of the third and the end of the sixth year is not parallel in the phenformin clinics. Some of this material has been tabulated in Table U-IV (attached). In just about every instance tolbutamide in 'all clinics' shows a change in mortality events from the end of the third to the end of the sixth year, which is consistently higher than the events

occurring in the phenformin clinics. In no other treatment group does this finding appear to be so consistent. The events in Table U-IV are taken from the various tables in the UGDP report for cardiovascular deaths with the addition of the table on good and poor adherence.

Consideration of the causes of death

When one compares the causes of death between tolbutamide and placebo it becomes obvious that many fewer patients in the placebo group died of cardiovascular causes. The placebo population had the highest occurrence of cancer deaths, while the tolbutamide and insulin variable had the lowest number of cancer deaths. The ratio of cancer deaths in the placebo versus the tolbutamide group was 7 to 2. Certainly no-one would suggest that this is evidence that tolbutamide reduces the occurrence of cancer or that placebo causes cancer. However, it is legitimate to suggest that the risk factors at baseline for the two groups were different and that in fact the placebo group had a greater likelihood of getting cancer and a smaller likelihood of cardiovascular disease, while the tolbutamide group had very little likelihood of developing cancer and a relatively high likelihood of developing vascular disease. This would seem to be quite important since the analyses for cardiovascular deaths eliminate the cancer deaths from the comparison and make tolbutamide look considerably worse than it does when all deaths are compared. If one arbitrarily eliminates the cancer deaths in an off-hand manner, since it is illogical to

think that tolbutamide prevents cancer or that placebo causes cancer, it would seem equally illogical, if one is to pursue an objective approach, to assume that the excess mortality in the tolbutamide group was caused by tolbutamide, or conversely, prevented by placebo. If one is going to eliminate the cancer deaths in order to evaluate cardiovascular disease in the two groups, one should also perform the analyses with the cardiovascular deaths removed in order to evaluate cancer in the two groups.

Observations on all deaths and cardiovascular deaths by baseline risk factors - and risk factors and mortality

Several interesting and confusing points come up which make it difficult or impossible to define populations at baseline, to believe the likelihood of comparable populations at baseline and to explain the methodology used in evaluating baseline risk factors and their follow up. The placebo group in this study is indeed a remarkable group. According to the data in this study, elevated cholesterol or peripheral vascular disease both increase mortality rates. However, the presence of hypertension causes a decrease in mortality rates. This is greater when all deaths are looked at, but the trend persists even in cardiovascular deaths. This finding is even more remarkable when one compares the differences between no hypertension and borderline hypertension (Table 6) with systolic blood pressure less than 160 and systolic blood pressure greater than 160. When subjects with

no hypertension on placebo are compared with subjects with borderline and definite hypertension on placebo, the mortality rate is much higher in the subjects with no hypertension. When the group of borderline hypertension is added to the no hypertension to form Table 7, then the addition of this group of borderline hypertensive subjects reduces the mortality rate in the no hypertensive subjects (Table 6) so that the group with systolic blood pressure less than 160 (Table 7) in fact has a lower mortality than the group with no hypertension. When cardiovascular deaths are assessed for hypertension, the trend persists. This is seen again in the tables on risk factors and mortality where, on placebo, presence of systolic hypertension reduces the mortality, for subjects with either a low or a high age. Similarly the presence of diastolic high blood pressure (Table 41.11) reduces mortality. These findings in the placebo group are not consistently found in the various treatment groups in 'all clinics' nor are the findings between the phenformin clinics and 'all clinics' always consistent in the various treatment groups, although for the most part they are in the placebo groups.

The baseline cardiac score

Perhaps most dramatic of all is Table 41.16 which, in fact, shows that patients with a low heart score on placebo are better off with hypertension than without it and, even more dramatic, although the numbers are small, that patients with a high heart score are

better off with hypertension than without it on placebo. The data on the various tables on baseline cardiac score again clearly demonstrate that the apparent excess of deaths occurs in subjects with a baseline cardiac score of zero and, in fact, there is a suggestion that tolbutamide is beneficial in subjects who have a baseline cardiac score of 1, 2 or 3 (see Table 8). It seems totally incomprehensible that a drug which can cause cardiac disease to occur in a group of subjects with no cardiovascular disease would not cause an even greater acceleration of cardiovascular disease in those subjects who already have it.

Baseline sum GTT

Again here is the remarkable finding that a baseline sum GTT under 750 in those subjects on placebo results in a higher death rate than a baseline sum GTT over 750. This table is not presented for cardiovascular deaths but is confirmed in the section on risk factors and mortality. In fact, as demonstrated in Table 41.13 the addition of a high GTT to subjects with no high blood pressure and a low GTT causes a decrease in mortality in the placebo treated group. In fact the addition of a high GTT, either to subjects with low or high cardiac scores, results in a decrease in mortality (Table 41.15). This is confirmed in Table 41.8 where the subjects on placebo with a low fasting blood sugar have a higher mortality rate than subjects with a high fasting blood sugar at baseline.

Body weight

Table 41.6 shows that on placebo the mortality rate for subjects without obesity is four times what it is for subjects with obesity, and again we are presented with the problem that obesity in this placebo group is apparently beneficial. These findings are quite remarkable and contrary to all the available published data, especially the very recent data of Chiang et al who demonstrated that the population at risk for sudden death was characterized by obesity, high blood pressure and elevated blood sugar. Again in Table 41.17, looking at cardiac score, hypertension and glucose tolerance test, in those subjects with a low heart score the combination of no high blood pressure and a low glucose tolerance test was the group that had the highest mortality of all four possible combinations of these three variables.

It should be pointed out, as mentioned above for hypertension, that peculiarities of these risk factors for placebo are not consistent in the treatment groups and show some variation between the phenformin clinics and 'all clinics'. It is also suggested in some places that where there appears to be an inversion of the mortality rates on the placebo, some of the excess mortality for tolbutamide is related to this peculiar effect of the placebo. Thus, as an example, tolbutamide was better than placebo for subjects with no hypertension. However, when the borderline hypertensives on Table 6 were added to the no hypertensives to form a group with systolic blood pressure less than 160 tolbutamide

was no longer better than placebo. The reason was that the numbers for tolbutamide treatment had not significantly changed from no hypertension (Table 6) to systolic blood pressure less than 160 (Table 7) but that the addition of the borderline hypertensives on placebo to the no hypertensives on placebo caused a significant reduction in the mortality rate for the placebo group with blood pressure less than 160. Another phenomenon which appears to occur on occasion can be demonstrated in Table 41.8, where risk factors are glucose and age. With low glucose, either at a low or a high age, tolbutamide is better than placebo. With a high glucose, either with low or high age, tolbutamide is worse than glucose. The reason for this appears to be that the rate on tolbutamide has gone up from low glucose to high glucose, as one might expect, but the rate on placebo has gone down. Another observation that can be made which raises questions concerning the populations is comparing the tables for risk factors between the phenformin and the non-phenformin clinics. For instance, in comparing tolbutamide based on reported deaths by baseline hypertension for 'all clinics' (Table 6) with the events in Table 6 for phenformin clinics, the results appear somewhat peculiar. With no hypertension in 'all clinics' tolbutamide is slightly better than placebo. In the phenformin clinics between the third and the sixth year tolbutamide is considerably better than placebo. With borderline and definite hypertension in 'all clinics', between the third and sixth year tolbutamide is worse than placebo, whereas in the phenformin

clinics for borderline and definite hypertension tolbutamide is the best mode of therapy. These kinds of relationships between 'all clinics' and the phenformin clinics can be seen scattered throughout the data.

Adherence and mortality

A section of this book and several graphs in the Risk Factors and Mortality have been dedicated to the significance of drug adherence. In Table 16.1 it is quite apparent that good adherence to tolbutamide is worse than poor adherence to tolbutamide. This would be terribly bothersome until one looks at placebo and finds that poor adherence to placebo is much worse than good adherence to placebo. It would seem inappropriate then to attempt to interpret the relationship between good adherence and poor adherence on tolbutamide until one explains the relationship between good adherence and poor adherence on placebo. Again here one sees the peculiar inverted ratio that seems to occur in the data between placebo and tolbutamide. Thus, with good adherence to placebo the death rate is down, with poor adherence it is up; with good adherence to tolbutamide the death rate is up and with poor it is down.

Blood sugar control

Table 20.1 shows that tolbutamide with good blood sugar control is better than placebo and that tolbutamide with poor blood sugar control is worse than placebo. Again, in this section there are

peculiarities between the phenformin and the non-phenformin clinics. With poor blood sugar control in phenformin clinics tolbutamide is comparable to all other modes of therapy, excluding phenformin, whereas in 'all clinics' it appears to be by far the worst treatment. Table 42.2 points up the fact that good control of blood sugar with tolbutamide is apparently beneficial, is better than good control of blood sugar with placebo, and better than poor control of blood sugar with tolbutamide. Again, however, there is a peculiar inversion of the placebo, so that poor control of blood sugar with placebo has a lower mortality than good blood sugar control with placebo. This inversion is different than all other treatment groups. In every treatment group except placebo, good blood sugar control is better than poor blood sugar control.

The importance of fixed dosage

Some time ago we noted our concern over the fixed dosage of tolbutamide in this study. We received the answer that if a fixed dosage of drug was demonstrated to be hazardous the burden of proof to show that some other dosage was not hazardous would be upon the proponent of such a concept. Several things have happened in this study to indicate that the fixed dosage of tolbutamide may be very important in this study. If one assumes that the groups can be compared, it would appear that the best mode of therapy in this study is insulin variable. Also, it is evident that good control on tolbutamide (Table 20.1) is better

than poor control and better than placebo, and in fact in the phenformin clinics compares favorably with insulin variable and is somewhat better than insulin standard. This certainly raises the serious question that if the drug had been used appropriately and control aimed for, that it might have behaved much better in the study.

Evaluation of non-fatal events

To date we have not had the opportunity to review in depth the non-fatal events. At least for certain of the events, the method of defining absent or present seems inappropriate. For instance, for blindness - to say that blindness was absent at entry and subsequently present is inappropriate. The important question is not that it was absent at entry and then present, but rather how many people at entry who were not blind were at risk of going blind.

Observations on those subjects who died in the study

Table U-V compares certain of the risk factors in the subjects who died of cardiovascular causes in the placebo and tolbutamide groups. It can be seen in this table that the period of drug exposure was greater for subjects who died on tolbutamide than for subjects who

N.B. Page 15 has been omitted

died on placebo. A higher percentage of subjects were 70 or over. A higher percentage of subjects had a sum GTT greater than 750. A higher percentage of subjects were 125% or more of ideal body weight. A higher percentage of subjects had diastolic blood pressure at 90 or greater. A higher percentage of subjects had a diabetes score at 7. Approximately the same percentage of subjects in each group had a cholesterol greater than 240. One remarkable difference is the cardiac score of zero. Only two of the subjects who died of cardiovascular causes on placebo had a cardiac score of zero, whereas 13 of the subjects who died while on tolbutamide had a cardiac score of zero. Table U-VI tabulates some of the risk factors involved in those subjects who died with a cardiac score of zero on tolbutamide. It can be seen that most of these subjects had combinations of risk factors. Five of the subjects were over 70, ten of the subjects had sum GTT greater than 750, eight of the subjects had a baseline body weight greater than 120% of ideal body weight, seven of the subjects had a cholesterol greater than 240, four of the subjects could be classified as hypertensive and ten of the subjects had a diabetes score of 7.

Looking at the combination of risk factors for cardiovascular disease it can be seen that all these subjects were at high risk.

General observations and questions

It would appear from the foregoing that the placebo group in this study is a remarkable group and that, in fact, for the placebo group high blood pressure, high blood sugar, overweight, lack of control of blood sugar, and good adherence to placebo, are all beneficial. It is also obvious that this effect of these ordinarily deleterious variables is not consistent in the various treatment groups. There is evidence that the effect of the variables is different within treatment groups and different between the phenformin clinics and the non-phenformin clinics. It would appear that the excess mortality in the tolbutamide group occurs only in people who have no cardiovascular disease at baseline, that there appear frequently to be inverse relationships between the placebo and the treatment groups, that poor adherence to placebo is deleterious and that good adherence is beneficial.

I believe that this study has raised a question but I do not believe that this study, as presented, can answer it. That the differences in the various treatments are related to the modes of therapy is based on the concept that randomization will result in groups that are similar at baseline. The coordinating center has demonstrated that this is not true when they showed that the cardiac scores for the different groups were different at baseline. It would seem unreasonable to conclude that if the cardiac scores were different at baseline that other variables would automatically be the same. In fact the peculiar results and odd relationships

between the phenformin and non-phenformin clinics, and between treatment groups, would seem to be explained only by differences of populations at baseline.

If one looks at the people who died of cardiovascular disease with baseline cardiac score of zero, it would seem that these were in fact not low risk subjects. Thus a cardiac score of zero cannot be equated with low risk for cardiovascular disease, and the cardiac score is only one risk factor.

If the cardiac score is different between groups, is it possible that other risk factors might also be different?

This raises a question about the number of subjects and the source of subjects. What are the chances in five groups of 200 subjects, who were not screened from a general population but from a group of people who were motivated to see a physician, that risk factors would be equal?

In view of the suggested differences in groups at baseline, I would like to see the groups stratified, based on all risk factors and combinations of risk factors, so that the effect of treatment in the various groups can be seen in patients at comparable risk. It would be necessary to define all the risk factors and [redacted] the groups should be compared not only for individual risk factors but for combinations of risk factors.

I should also like to suggest that the data be handled in such a way that the groups are not divided into groups with risk or without risk, since it has been well demonstrated in the literature that a risk may be greater or less. Thus, if one arbitrarily groups subjects as high cholesterol and low cholesterol using a cut-off point of 240^{+}_{-} it has been well demonstrated that a large number of people without cardiovascular disease would be included in the high group. If one raises the level to a much higher level then one removes the many normals from the high group but now has a large number of events in the subjects who are classified as low. Thus the grouping should be done not only based on the presence or absence of an event, but on the degree of the event.

Also, we would like to see a breakdown of the reason the patients attended the clinics initially, the source of the patients, associated diagnoses or abnormalities at baseline and medications which the patient was taking at baseline. We would like to know also about intercurrent illnesses and medications taken during the period of the study.

We should like to see a breakdown by degree of blood sugar control, if this were possible, since it would seem inappropriate to group all subjects with a blood sugar over 110 together. [redacted] Thus it would seem inappropriate to group together subjects who have a fasting blood sugar of 200 with

subjects who have a fasting blood sugar of 150 and subjects who have a fasting blood sugar of 115.

There is a potential risk in doing this sort of analysis that one would sub-group the patients in to such small groups that no meaningful results could be obtained. However, hopefully there would be several larger populations with similar risk and then a scattering of subjects in the smaller sub-groups which perhaps could or could not be evaluated. In the event that this happened, however, one would feel secure in knowing that the treatment effects were being compared in like populations. The other problem in this type of analysis is whether or not the baseline risk factors, which are now known to be important in the diagnosis of arteriosclerotic cardiovascular disease are available in the data at baseline.

On three previous occasions we have raised the question of baseline differences and the necessity of evaluating and correcting for them.

In view of the findings in the study we should again like to request that the original patient forms and the follow up forms for those subjects treated, at least with tolbutamide and placebo, be made available to us for our own or other independent statistical analysis.

We would like to get, if possible, a breakdown of all deaths and cardiovascular deaths by clinic, i.e. the number of subjects who died in each clinic, the total number of subjects in each clinic,

and a breakdown by year on these subjects, along with copies of the original patient data from each clinic, so that we can see if there are differences between clinics for risk of cardiovascular disease.

We should also like to obtain a description of the method of randomization which was used. The placebo group, for some reason, appears to be a low risk group, particularly for high blood pressure, elevated blood sugar, obesity, lack of blood sugar control, and adherence to placebo.

We would like to see a separate analysis for the phenformin and non-phenformin clinics.

We would like to know the opinions and recommendations of the biostatistical consultants. Did the biostatistical consultants look at the differences between the tolbutamide group and the placebo group with a view to seeing whether these differences had become statistically significant, or was their point of view to see whether the differences were treatment related?

The greatest contribution of this study has been its pioneering effort. In fact the study itself is an experiment and has laid the ground work for those who come after. I do not believe, however, that from the presently available data it is possible to reach a conclusion.

E.K.Borden/so
June 27, 1969

TABLE U-I

NUMBER OF DEATHS BY CLINIC

	Placebo	Tolbutamide
	Non-Phenformin Clinics	
A	2	4
B	0	1
C	7	7
D	2	2
E	3	8
F	0	1
	Phenformin Clinics	
G	1	0
H	2	1
I	0	0
J	1	0
K	1	5
L	0	0
Total		
All Clinics	19 (9.3%)	29 (14.2%)
All Clinics less E & K	15 (8.9%)	16 (9.2%)
Phenformin Clinics	5 (6.9%)	6 (7.9%)
Phenformin Clinics less K	4 (6.9%)	1 (1.7%)
E & K Percent of Deaths All Clinics	4/19 (21%)	13/29 (45%)
K Percent of Deaths Phenformin Clinics	1/5 (20%)	5/6 (83%)

TABLE U-II

CHANGES IN MORTALITY PERCENT IN 'ALL CLINICS'
(DERIVED FROM TABLE 1.1, UGDP 'ALL CLINICS')

	June 1965-July 1967	July 1967-May 1969
Placebo	2.6%	2.9%
Tolbutamide	6.8%	4.0%
Insulin Standard	3.0%	2.8%
Insulin Variable	0.1%	4.0%

TABLE U-III

CHANGE IN MORTALITY PERCENT IN 'PHENFORMIN CLINICS' BETWEEN JULY 1967-MAY 1969 (OBTAINED BY SUBTRACTING PERCENT IN JULY 1967 FROM PERCENT IN MAY 1969)
(TABLE 1.1 UGDP PHENFORMIN CLINICS)

Placebo	Tolbutamide	Insulin Standard	Insulin Variable	Phenformin
+4.1%	+2.6%	+5.2%	+2.7%	+2.5%

TABLE U-IV

CHANGES IN EVENT RATES FROM THE END OF YEAR 3 TO THE END OF YEAR 6

	All Clinics	Phenformin Clinics
(i) (Adapted from Table 10)		
Life Table Rates by Cardiovascular Deaths		
Placebo	+ 2.76	+ 5.68
Tolbutamide	+ 7.81	+ 3.22
I. Std.	+ 3.41	+ 5.07
I. Var.	+ 0.76	0
(ii) (Adapted from Table 11)		
No Hypertension		
Placebo	4.67	11.76
Tolbutamide	6.38	3.47
I. Std.	0	0
I. Var.	0	0
Borderline or definite hypertension		
Placebo	1.86	3.17
Tolbutamide	9.37	2.94
I. Std.	5.93	7.61
I. Var.	1.45	0
(iii) (Adapted from Table 12)		
Cardiac Score 0		
Placebo	0	0
Tolbutamide	6.26	4.12
I. Std.	3.44	6.06
I. Var.	0	0
Score 1, 2, 3		
Placebo	18.51	23.91
Tolbutamide	13.85	0
I. Std.	3.31	0
I. Var.	4.01	0
(iv) (Adapted from Table 16.1)		
Good Adherence (all deaths)		
Placebo	2.17	1.81
Tolbutamide	8.46	4.22
I. Std.	6.52	2.45
I. Var.	0	0

over/...

TABLE U-IV (continued)

	All Clinics	Phenformin Clinics
	Poor Adherence (all deaths)	
Placebo	15.60	34.55
Tolbutamide	5.28	0
I. Std.	2.70	13.33
I. Var.	5.42	0
	(v) (Adapted from Table 17) Good Adherence (cardiovascular deaths)	
Placebo	0	0
Tolbutamide	8.63	4.30
I. Std.	3.78	2.45
I. Var.	0	0
	Poor Adherence	
Placebo	10.37	28
Tolbutamide	5.28	0
I. Std.	2.70	13.33
I. Var.	1.51	0

TABLE U-V

COMPARISON OF CERTAIN RISK FACTORS IN SUBJECTS WHO DIED OF CARDIOVASCULAR CAUSES
(PERCENT DEAD IN EACH GROUP)

	Placebo	Tolbutamide
Subjects 70 or older	22.2% (2)	32% (8)
Period on drug	3.2 years (mean)	4.2 years (mean)
Sum GTT 750 or > 750	33.3% (3)	56% (14)
125% or > Relative Body Weight	22.2% (2)	52% (13)
Cholesterol > 240	66.6% (6)	58.3% (14)
Diastolic Blood Pressure 90 or > 90	22.2% (2)	37.5% (9)
Diabetes Score 7	55.5% (5)	84% (21)
Cardiac Score 0	22.2% (2)	52% (13)

TABLE U-VI

CHARACTERISTICS OF SUBJECTS WITH CARDIOVASCULAR DEATH ON TOLBUTAMIDE AND BASELINE CARDIAC SCORE OF ZERO

Subject	Age	GTT	Relative Body Weight	Cholesterol	B.P. Systemic	B.P. Diastolic	Diabetes Score
1	67	808	121.7	196	114/55		7
2	60	862	114.9	325	134/77		7
6	71	1085	80.6	227	135/86		7
7	72	909	148.2	234	141/70		7
8	53	1152	120.5	231.5	109/67		7
9	71	727	139.4	241	147/90		7
10	72	824	125.8	215	185/90		7
11	71	726	114.1	281	138/73		3
12	54	517	122.8	262	136/80		1
14	57	901	135.2	267	140/95		7
17	57	856	106.8	208	151/95		7
18	68	723	106.9	296.5	141/82		3
25	69	1182	206.9	265.5	130/70		7