Document #12

Minutes of the Principal Investigators' Meeting of the UGDP
Roosevelt Hotel, New York, June 30, 1969

Dr. Miller opened the meeting at 8:30 a. m. and presided. Present were Drs. Brown, Kilo, Knowles, Miller, Klimt, Newberry, Remmert, Haddock, Vega, Whedon, Osborne, Knatterud, Meinert, Goetz, Jacobson, Kreines, Boshell, Barrett, Reeves, Goldner, Weisenfeld, Jones, Martin and Schwartz.

Dr. Knatterud reported on drop-outs. With renewed efforts, seven of the eighteen drop-outs were located and all are alive. Of those remaining with status unknown, there are two in the placebo group, two in the tolbutamide group, three in the insulin standard group, three in the insulin variable and one in the phenformin group. She then proceeded to summarize supplementary tables for the UGDP report for tolbutamide dated May 9, 1969. Dr. Osborne then reviewed the genesis of the UGDP definition of cardiac scores. Dr. Goetz suggested that we pursue further the possibility of including cardiovascular risk factors in the cardiac scores. Dr. Goldner maintained that the cardiac score serves its function and that the question of risk factors for death was a separate problem which should be investigated separately. Dr. Meinert then spoke to his calculations of the likelihood that the differences found in deaths in the tolbutamide and placebo groups are different from clinic to clinic. He found that such a hypothesis could not be supported statistically (P= 0.75 for all deaths, P=0.90 for cardiovascular deaths). His analysis of variability of placebo tolbutamide differences among clinics is attached.

Dr. Miller then asked for consideration of the possibility that tolbutamide be continued in the six clinics which last entered the study. He thought that these six clinics could be considered as a "another experiment". Dr. Klimt replied that the placebo group in the last six clinics was too small to provide definitive information and Dr. Brown remarked that this would simply multiply defects rather than provide definitive conclusions. Dr. Brown thought that more would be gained by initiating a new study than by perpetuating the present one.

Dr. Goetz pointed out that his was one of the clinics that had a relatively large number of deaths and he outlined his reasons for believing that his patients were at a greater risk for mortality than those in other clinics. His patients were referred from throughout the State of Minnesota and selection of patients was limited so that perhaps patients who were more ill than the average were admitted. They came from a low, socio-economic status and because of the distance from his clinic, deaths away from the clinic and outside the hospital were more likely to occur. Dr. Klimt remarked that it was fortunate that such relatively high risk patients were permitted to enter the study since it probably enabled the group to show the increased cardiovascular deaths in the tolbutamide group.

Dr. Reeves and Boshell both asked why tolbutamide would not be continued in the phenformin clinics and Dr. Klimt replied that projections show that no definitive conclusions could be drawn in the study if these clinics were continued. Dr. Goldner asked whether decisions might be modified by the availability of new data from other independent investigators. Dr. Miller replied that he was doubtful that any other studies were comparable. Dr. Knatterud mentioned that tables had been prepared which included a listing of all other drugs taken by the patients who had expired. A superficial examination did not reveal that any other individual drugs

were given inordinately frequently in this group.

Dr. Brown commented on Dr. Feinstein's report in which a selected table showed variations at baseline between the tolbutamide and placebo groups. Dr. Brown stated that, had the baseline data been available at baseline times before treatment was initiated, the UGDP would probably have been pleased because (1) no significant differences exist and (2) if the tolbutamide treated patients had been found to fare better, the study could not have been criticized on the basis of weighting baseline data in favor of tolbutamide.

Dr. Donald Whedon, when asked to comment, mentioned that long-term drug trials were extremely important and probably would become more so in the future. He felt that the efforts of the UGDP investigators were at least partly responsible for this widely held view. He thought that modifications would be appropriate in future trials. With regard to the substantive issue, he reminded the group that the purpose of the study was to determine whether the cardiovascular complications of diabetes could be prevented or ameliorated. And that one could justify continuing the tolbutamide treatment group only if based on a further examination of non-fatal events. In terms of the ethical position of the study, he felt that the increase in cardiovascular deaths found is not unequivocal but that drug risk is a very important consideration in the view of the National Institute of Health in studies such as the UGDP.

After a recess for lunch, Dr. Goetz revealed some second thoughts following Dr. Whedon's statement. He expressed doubt that there could be any clear resolution of the issues by further post hoc study of cardiovascular deaths but he thought that we might consider the possibility of continuing tolbutamide to evaluate non-fatal events. He was greatly concerned about the ethical aspects of the problem. He discussed this with Dr. Robert Ebert, Chairman, Department of Medicine at the University of Minnesota who he said was not "frightened by the mortality figures and would have no compunction about continuing the studies".

Dr. Goetz then made a motion that "after appropriate discussion, the investigators of the UGDP take another vote on the decision to discontinue tolbutamide". The motion was seconded by Dr. Boshell and after considerable discussion and the reading of a statement by Dr. Meinert from the Coordinating Center (Which is attached) those in favor were 5 and those opposed were 17. There was one abstention and it was pointed out that the Baltimore group was absent. The votes were counted by Dr. Brown.

It was the general consensus that the editorial committee (and others involved) proceed with all deliberate speed to publication, not only of the baseline data paper, but of the results obtained in the tolbutamide study. Dr. Klimt then made a motion suggesting that "a set of slides be prepared based on mortality and cardiovascular deaths for the tolbutamide group, which would be used for disseminating information at the institutions of the principal investigators at an appropriate time". The motion was seconded by Dr. Haddock that the appropriate time of release be considered when the manuscripts being prepared for publication go to press. This motion was passed by a vote of 17 to 5. Dr. Reeves then made another motion, seconded by Dr. Kilo, that the guidelines statement used for presentation to the FDA be distributed to the clinical centers now and disseminated with discretion. This was passed with a vote of 19 to 2. In sum, this tortuous (and rather

silly) set of motions are interpreted to mean that each principal investigator will distribute within his institution the guidelines statement. He would discourage any wider distribution but would also stand ready to defend the guidelines if pressed by his colleagues. This action would be taken shortly after his return to his institution.

The distribution of the new placebos was then discussed. The group was told that all placebo tablets would be the same, in bottles marked No. 88. They were admonished to be sure to remove the tab which shows that the bottles contain 100 mg. of lactose. After some debate, it was decided that the patient should instructed to take two tablets in the morning and one in the evening because to do otherwise might provoke some concern about evening "spills" as pointed out by Dr. Maynard and also, as pointed out by Dr. Schwartz, to change the dosage schedule might make for changes in evaluation of adherence. When Dr. Kilo proposed that patients take one tablet per day in the AM (the motion being seconded by Dr. Reeves) the motion was not carried by a vote of 8 to 14. The investigators were urged to (1) destroy all the medication for the AB group when the new capsules arrive, (2) to change over to the new placebo as the patients appear and to record the No. 88 in the patient's file, and (3) at the request of Dr. Miller, to obtain a blood sample that would yield 5 cc. of serum from each patient at the time of changeover for measurement of a sulfonylurea concentration.

Dr. Klimt made a motion that the UGDP continue the phenformin group and placebo group for one more year and to reappraise findings at that time. The motion was seconded by Dr. Miller and was passed unanimously with essentially no discussion.

After consultation with Dr. Remmert it was suggested that the UGDP defer a competitive renewal request until January 1st, 1971, at which time further evaluation of the data will have been completed.

Finally, Dr. Remmert informed the group that with the non-competitive forthcoming renewals, each individual investigator would have to renegotiate for a projected 10% reduction in grant funds. The meeting was adjourned at 5:15 p. m.

Respectfully submitted,

TB Schwartz

Theodore B. Schwartz, M.D.