Document #11

Summary of Meeting held with Representatives from UGDP and the Upjohn Company

Present were Drs. Max Miller, Christian Klimt, Genell Knatterud, Curtis Meinert, Martin Goldner. Robert Reeves, Charles Kilo, Lillian Haddock and Theodore Schwartz from the UGDP. Among those present from the Upjohn Company were Drs. Keith Borden and Dr. Ascenzo. Dr. William Brown, statistical consultant to the UGDP was present as was Dr. Alan Feinstein who had served as a consultant to the Upjohn Company.

The meeting was opened by Dr. Miller who stated that, from the point of view of the UGDP, the meeting was justified so that members of the UGDP meeting could have an opportunity to hear all ideas, then when findings were published, questions and possible shortcomings could be dealt with as completely as possible. He mentioned, too, that he looked on the meeting as a dialog rather than a confrontation but that he felt that there was no compelling moral necessity for the meeting to take place.

Dr. Keith Borden then summarized some of the views of the Upjohn Company. He maintained that (1) the excessive mortality for the tolbutamide treatment group lay primarily in 2 or 3 clinics, (2) the difference in structure and results in the phenformin versus non-phenformin clincs was disturbing, (3) the ambiguities inherent in the difference of time of exposure of the patients studied in phenformin and non-phenformin clinics made analysis difficult if not impossible. He emphasized that in his view there was a significant difference in death rates between clinics for the same number of years of study. In effect, he felt there was a difference in mortality in cohort analysis for phenformin versus non-phenformin clinics. (4) He questioned whether simple pooling of data from all clinics was warranted.

Dr. Klimt responded, saying that there was, indeed, a variability in mortality by clinics but that this was to be expected in a large scale study. Dr. Meinert stated that he examined the hypothesis that the excess deaths in the first seven clinics could be the results of variations in a single distribution curve. His results showed that the data were entirely consistent with a single underlying distribution.

Dr. Brown referred to the table in Dr. Feinstein's report in which the tolbutamide group seemed to be worse than the placebo group in 12 of 16 baseline measurements. He stated that this difference was beyond two standard deviations. But, he pointed out that many of the measurements were not independent variables, eg., EKG changes and, that the baseline variables tabulated were a group selected from a much larger population of variables.

Dr. Feinstein summarized his report. He mentioned that he had attacked his task in an entirely unbiased manner. He felt that clinicians had been cowed into abrogating clinical considerations in the structure of the study. He emphasized the differences in baseline variables with the tolbutamide and placebo groups. Dr. Klimt interjected that of the twenty variables only eight are relatively independent. There were forty-eight response variables and therefore, ninety-six possibilities of tolbutamide being greater or less than results with the placebo group. In a random distribution, nineteen should be higher or lower and this is quite close to the twenty such changes described. Drs. Meinert and Knatterud pointed out what they thought to

Document #11

be imprecise chi-square estimations using this table. Dr, Ascenzo, statistician for the Upjohn Company, detailed some of his reservations such as the differences in cardiac score between the two groups, the fact that some glucose tolerance tests included patients who did not meet the admission criteria.

Dr. Goldner asked Dr. Feinstein directly what his explanation for the discrepancies might be. Dr. Feinstein replied that he thought the patients, by unfortunate chance, were "sicker" when admitted to the tolbutamide treatment group than those admitted to the placebo group.

Dr. Brown quoted from Dr. Feinstein's report to the Upjohn Company in which Dr. Feinstein spoke of a "systematic bias" in admitting patients to the study. He asked Dr. Feinstein whether this was an accurate statement. Dr. Feinstein replied that he had not intended to imply that there was bias in selection of patients but rather he felt that despite radomization, chance bias has invalidated the results of the study.

The meeting began at 6:30 and ended at 10:00 PM.

Respectfully submitted,

T B Schwartz

Theodore B. Schwartz, M.D.

TBS:vs