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Minutes of the Principal Investigators' Meeting of the UGDP
June 5-6, 1969, Williamsburg, Virginia

Present were two representatives from each of the Clinical centers, with the exception of San Juan and Cleveland, from which only the principal investigators attended. Drs. Klimt, Meinert and Knatterud served as hosts from the Coordinating Center and Dr. Jerry Cornfield, statistical consultant, was present and participated in the discussion on June 5. Drs. Whedon and Remmert were present as representatives from the NIH.

As is the custom in the UGDP, the meeting was opened by Dr. Max Miller, with exortations and admonitions which served to remind the group of the importance of their deliberations.

Dr. Curtis Meinert then launched into a detailed analysis of the data concerned with tolbutamide, placebo, insulin-standard, and insulin-variable treatment groups. It was suggested by Dr. Schwartz that an effort be made to prepare Monte Carlo boundaries for the cardiovascular deaths. The Coordinating Center agreed that this effort be made. Dr. Cornfield, then summarized his analysis of Relative Betting Odds. He stated that this was, in general, a more conservative approach to determinations of the meaning of the data and that his analysis was based on person-years of observation. With regard to cardiovascular deaths and comparing tolbutamide versus placebo, he reported the following:

Interval	Relative Betting Odds
4 - 5	0.33:1(1:3)
5 - 6	0.22:1(1:5)
6 - 7	0.05:1(1:20)
7 - 8	0.017:1(1:60)

He also stated that for all causes of deaths, after 8 years of observation, the relative betting odds were between 1:15 to 1:30 that tolbutamide caused more deaths than did placebo.

Dr. Cornfield also calculated relative betting odds on projections of deaths from all causes (projected into 1972 and 1974 for tolbutamide group versus placebo.

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	1972	1974
Present trends continued	0.17:1	0.12:1
Placebo deaths reduced-all others increased	0.028:1	0.04:1
Placebo deaths increased-tolbutamide reduced	0.62:1	0.57:1

Dr. Cornfield concluded that (1) there is no edivence that tolbutamide has exerted any beneficial effect in any of the end-points examined and (2) that the tolbutamide segment of the study should be discontinued. When pressed as to whether tolbutamide could be designated as a toxic drug, Dr. Cornfield balked at an unequivocal reply. Instead he remarked that, "If it were offered to me, I would refuse to take tolbutamide". A letter from Dr. Brown, another statistical consultant, was read and is attached. He also recommended strongly that the tolbutamide segment of the UGDP be discontinued.

Dr. Goldner pointed out that while we have learned that there is a difference between thos patients taking tolbutamide and those taking placebo we have not learned why there was a difference. He agreed that there was no evidence that tolbutamide was beneficial but he thought it would be important to learn more about the specific causes of death in each patient. He and Dr. Weisenfeld urged that a careful analysis be carried out of all the drugs which the patients had been taking at the time of death. Dr. Goldner also asked for specific data on (1) how many patients were actually taking tolbutamide at the time of death since all patients, once assigned to the tolbutamide group remain members of it; (2) For similar reasons he wanted to know which patients were taking tolbutamide just before death; (3) A further detailed analysis of causes of cardiovascular death such as case 9, a patient who died with calcific aortic stenosis. (It was pointed out that this case was matched by case 4, a patient taking placebo,) and (4) Dr. Goldner asked that further information be obtained in those patients who had "sudden death". He questioned the certainty that these can be listed as cardiac death. Dr. Knowles emphasized that autopsy data should be examined critically.

Dr. Prout cautioned that it would be "dangerous to beautify the data" and that predetermined protocols must be followed. Dr. Goldner retorted that he was not at all suggesting that death categories be changed. Rather, he was insistent only that data of patients in this category be more closely examined. Dr. Levin suggested that all members of the UGDP who have questions which they feel might

elucidate the data should send them to the Coordinating Center and the Death Committee, chaired by Dr. Osborne. He suggested as an example, an examination of the cardiac scores at baseline within clinics with regard to possible differences in those patients taking tolbutamide and those taking placebo.

Dr. Goldner thought that other data in the literature should be examined. He quoted, as examples, the long term study of Dr. Fajan's in Ann Arbor, and studies in alloxan diabetic rats performed by Dr. Arnold Lasro.

It was decided that the June 5 meeting should be adjourned at 5 p.m., that the members ponder the massive data presented to them and that decisions would be deferred until the following morning.

The meeting was re-convened at 8:30 a.m. on June 6. Dr. Donald Whedon was asked for his views and he mentioned that in his opinion, the UGDP could recommend (1) the discontinuance of tolbutamide in the study, and (2) could recommend to the Federal Drug Administration that tolbutamide be removed from sale in the United States. He pointed out that these were two separate recommendations and should be dealt with independently. After further discussion, Dr. Klimt made the following motion: That the University Group Diabetes Program discontinue the prescription of tolbutamide in the study now and to place patients taking tolbutamide on known placebo for the duration of the study. In a discussion of this motion it was tentatively proposed that perhaps the patients taking tolbutamide should be switched to the insulin-variable group but this did not gain much suppoert. Dr. Goetz raised the question of whether the fact that they were now taking placebo should be revealed to the tolbutamide patients. Dr. Osborne strongly recommended that the patients in the AB groups, that is those patients presently taking tolbutamide and/or placebo be both given an identical placebo but a tablet which is different from what they had been provided by the Upjohn Company up until the present time. Dr. Reeves raised questions regarding the validity of the data concerning the toxicity of tolbutamide.

Dr. Goetz strongly endorsed Dr. Osborne's recommendation. The motion was voted upon and passed with 21 voting members for and 5 members against.

With the passage of this motion, Dr. Levin asked what guidelines should be offered to individual investigators returning to their home centers. Dr. Miller suggested that the decision be kept confidential until after the forthcoming meeting with the FDA on June 16. Dr. Klimt suggested that the data summaries be forwarded promptly to all three drug houses and the FDA. He also suggested that a committee be set up promptly to prepare a tolbutamide paper. Dr. Goldner emphasized that, with decisions being made rapidly, that there be rapid communications among the members of the UGDP so that all are kept appraised of what is transpiring.

Dr. Miller mentioned that a meeting has been scheduled with the FDA. It was agreed that the attendance at this meeting should include from the UGDP Coordinating Center, Drs. Klimt, Meinert and Knatterud, from the Clinical Centers, Drs. Miller, Schwartz and Goldner, and from the National Institutes of Health, Dr. Carl N. Leventhal, Special Assistant to the Deputy Director for Science, NIH and Dr. Lamar Remmert, Diabetes Program Director, Extramural Programs NIAMD. This group will meet with Dr. Edwin Ortiz, Director, Division of Metabolic and Endocrine Drug Surveillance, FDA.

A motion was made, seconded and passed unanimously to hold this meeting on June 16.

Dr. Klimt then made a motion, seconded by Dr. Prout, that a report of our findings and our decisions be sent to the three interested drug companies. In this report it was to be stressed that the information forwarded was to remain confidential. Dr. Goldner then made a motion, seconded by Dr. Reeves, that the group inform the FDA and the three Drug companies promptly of our decision regarding the discontinuance of tolbutamide therapy. This motion too was seconded and passed unanimously.

It was suggested by Schwartz, in view of the fact that the phenformin data and other important matters were not considered at this meeting, that an additional meeting of the Principal Investigators be held on Monday, June 30 in New York, at the time of the meetings of the Endocrine Society and the American Diabetes Association. Arrangements to bring this meeting into being were to be made by Dr. Goldner. It was suggested that the meeting be held from 8:30 a.m. to 5 p.m. The UGDP investigators will be notified as soon as arrangements are definitive.

Dr. Klimt composed a letter of transmittal to be sent along with the data to the three drug companies and the FDA. It is attached. The letter was approved by the Principal nvestigators. Dr. Goldner had earlier suggested that guidelines be prepared for use during the meeting with the FDA in Washington. Dr. Prout suggested that the guidelines be constructed so that the overall mortality data, the cardiac mortality data, and fatal and non-fatal events only be considered. Dr. Goetz advised strongly that non-fatal not be considered at that meeting since the investigators themselves had considered these only in passing. It was the sense of the group that Dr. Goetz's advice be followed and that in terms of presentation, there would be emphasis only on overall and cardiac mortality. A Statement of the Guidelines is attached.

At noon of June 7, the meeting was adjourned.

Respectfully submitted,

Theodore B. Schwartz

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