

June 12, 1969

Max Miller, M.D.
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Cleveland, Ohio 44106

Dear Max:

Your letter has just arrived and in view of the imminence of your June 16 meeting I am answering now, even though I have turned my calculations over to the coordinating center and do not expect them back until Friday.

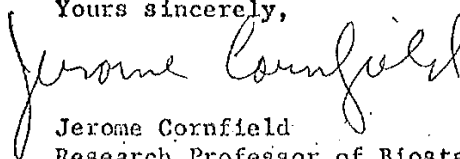
I recommended the discontinuance of tolbutamide because of the progressive increase in mortality from cardiovascular disease among those on this drug as compared with those on placebo. After eight years of use the estimated mortality among those on drug ($19.5 \pm 2.5\%$) was more than $3\frac{1}{2}$ times that among placebo users ($5.3 \pm 2.5\%$). Even after allowing for the multiple testing involved in selecting the most extreme of three drugs and the most extreme of the cumulated eight year mortalities it seems quite unlikely that tolbutamide and placebo really have the same mortality from cardiovascular diseases under the conditions of this trial. The actual statistical analysis used is summarized in an article to appear in Biometrics later this year and described in greater detail in a memorandum prepared for the Data Monitoring Committee of the National Heart Institute sponsored Coronary Drug Project.

I would rather not commit myself to a detailed design for another study at this point, other than to say that a placebo-tolbutamide study with several-fold more patients than now supplied by the UGDP would have high probability of picking up a difference well before eight years, if the present indication of early differences is in fact correct.

Although I know that you and your colleagues are aware of the delicate ethical issues involved in a repetition of this trial, I must state as a matter of record my belief that informed consent requires acquainting potential participants in a future trial with present results.

With best regards,

Yours sincerely,



Jerome Cornfield
Research Professor of Biostatistics