Document #18

VETERANS ADMINISTRATION
HOSPITAL
4500 S. LANCASTER ROAD
DALLAS, TEXAS 75216

December 16, 1970 YOUR FILE REFERENCE:

IN REPLY REFER TO:

Dr. Christian Klimt
University of Maryland School of Medicine
Baltimore, Maryland

Dear Chris:

I've been trying to get this letter off to you ever since I was in Ann Arbor with Steve Fajans on Oct. 14-17 and found out the ADA was about to support the UGDP study, which drove me to a word-by-word analysis of the manuscript as soon as I got back. And the opinion I finally ended up with has probably come roundabout to you piecemeal because I've had to write other stuff to hit deadlines and this opus to you just got sandwiched in between everything else -- especially after I decided not to just try and get a shortie off to you, but to pound it out blow-by-blow so you'd know for sure that I worked from the data all the way through and didn't just use intuition or a ouija board. So here goes.

As things have turned out, I seem to be the one guy who is entirely independent of both the study and of Upjohn who happens to know most about the details of the study. After sending the following opinion to Steve Fajans, I also sent it to Bob Osborne and then checked with him several days later by phone to make sure I wasn't making any wild charges, which I wasn't. I had written 12-page letters to both of them and included something like a half dozen charts and figures. As I said, I was going to make this one shorter but changed my mind, so that you'll know exactly how I arrived at my current irrevocable opinion. Finally, before getting down to the nitty-gritty, I told Steve (Fajans) that as soon as the supplement to

DIABETES comes out I'll send a letter to the ADA so that these objections to the study are officially recorded.

First of all, by the time I started plowing through the final manuscript, I had at my disposal (in addition to Feinstein's original critique) Feinstein's supplemental report and Schor's critique, both of which Upjohn sent. Also, a week after Bob Osborne was here Keith Borden came down and snowed me with all kinds of analyses of the UGDP data that he'd been conjuring up during the past few years. HOWEVER: Because I didn't want to be swayed by one side any more than by the other, in this final blistering opinion against the UGDP report, I worked only from the manuscript you sent me, the one that will be published -- with the one exception that I had to get the actual number of cumulative deaths during the study (from the 5th through 8th years) from Keith Borden to compare with your Table 2 and Figure 1 on pages 7-8 of Part II, because you didn't include them in the manuscript. Otherwise, all of my challenges to the following features of the study are based on the percentages for baseline characteristics quoted in Feinstein's first critique -- since they were what established my anti-UGDP opinion in the first place -- and the final manuscript as it will show up in DIABETES. My main bitches are the following:

(A) The changes in EKG criteria.

(B) The changes in baseline risk factors.

(C) True mortality versus calculated cumulative mortality rates.

(D) Correlation of baseline risk factors per clinic and mortality per clinic.

(E) Changes in denominators in some clinics.

(A) OLD VERSUS NEW EKG CRITERIA: As stated in Part 1, page 79, you

originally used all of the first 8 of the 9 categories of Blackburn et. al., in their entirety and presumably any change at all was recorded as "one or more major ECG abnormalities" in the September 1968 UGDP Progress Report, as cited in Feinstein's #1 critique. In the final manuscript, however, you used almost all of the Q-wave changes (1-1-1 through 1-2-7), but only the worst S-T depressions (4-1) and T-wave inversions (5-1); and only complete heart block (6-1), LBBB (7-1), and ventricular tachycardia (8-2) in those three categories. On top of that, categories 2 and 3 were omitted completely despite the fact that Blackburn et al specifically stated that the criteria they used for axis deviation (category 2) and amplitude of R-wave (category 3) would be considered definitely abnormal by everybody. As I told Bob in his letter and again over the phone, if we look at category #8 first just for laughs, how in hell could anyone decide to limit "significant arrhythmias" to ventricular tachycardia! -- which is only one step before ventricular fibrillation and therefore practically the kiss of death? This decision of course meant omitting auricular fibrillation, auricular flutter and flutter-fibrillation, and A-V dissociation (8-3). I won't even argue (although plenty of cardiologists would) that supra-ventricular tachycardia (8-4), idioventricular rhythm (8-5) and A-V nodal rhythm (8-6) should also be counted. Going back to category 5 (T-wave items) -- by only counting 5-1 (T-wave minus 5 mm or more in I, II, V_2-V_6), you deleted 5-2 (T-wave inversion minus 1 to 5 mm in I, II or V-$_2V_6$) as a "significant ECG abnormality;" and as far as I'm concerned (and I think most ECG readers would agree, for that matter), flat T-waves when QRS is normal in amplitude is also bad news, so that even subgroup

5-3 would be significant. In any event, there is NO argument about 1-5 mm T-wave inversions in subgroup 5-2 being clearly abnormal. Turning to category 6 (A-V conduction), the cardiology books I plowed through indicate that partial heart block (6-2) and Wolff-Parkinson-White (6-4) are by no means benign situations (although the latter may be). And in category 7 (ventricular conduction), although RBBB (7-2) is slightly better prognostically than LBBB (7-1), it is not automatically benign, and it is especially more significant when there's reason to suspect arteriosclerotic heart disease (as in diabetics). At the very least, then, the new criteria have eliminated T-wave inversions of 1-5 mm, partial A-V heart block, and auricular fibrillation and flutter, all of which every cardiologist would agree represent "significant ECG abnormalities." But when I questioned Bob about this on the phone -- since, as the "heart man" on the team, he had to be involved in changing the criteria -- he said something about only using those criteria in categories 2 through 8 that would be equivalent to a myocardial infarction, with the latter apparently being represented by all of the Q-wave changes from 1-1-1 through 1-2-7. I think this was the point Dr. Knatterud was trying to ram down my throat when we were eating lunch in Buenos Aries, but it is absolutely not valid to just take some of the worst possible ECG criteria and label them "significant ECG abnormalities," which obviously implies ALL commonly-agreed-upon "significant ECG abnormalities" to anyone who doesn't dig up and plow through Blackburn et al's classification. What I'm getting at of course is: How many patients in each treatment group were dropped from the "one or more major

ECG abnormality" category by using these arbitrarily and irrationally restricted criteria? Meaning that, in September 1968, the actual numbers of patients in PLAC-TOLB-ISTD-IVAR were 30-48-41-39, whereas now they've dropped to 6-8-11-8 (from Part II, Table 6, page 28). The fact that only 157 out of 810 patients (19%) of diabetics averaging 52.7 years of age had "one or more major ECG abnormalities" in Sept. 1968 is amazing enough, since one certainly would expect the percentage to be much higher in such a population of elderly diabetics. But to ask any clinician to believe that only 4% (33 out of 810 patients) had "significant ECG abnormalities" surpasses the bounds of credulity. Ask Kurt Meinert, whom Bob Osborne says is practically a cardiologist via his long experience in statistical analysis of cardiovascular epidemiology, and he'll tell you the same thing. What I'm really getting down to, obviously, is the fact that the elimination of 75% of the patients who originally had one or more major ECG abnormalities at baseline somehow worked out so that the "worst ECG-risk-factor" shifted -- both by actual number of patients and percentage-wise -- from the TOLB group over to the ISTD group. This revelation leads directly to my next main point, namely:

(B) CHANGES IN BASELINE RISK FACTORS: Which refers of course to a comparison of the 20 factors I was originally exposed to in Feinstein's #1 critique (see my Reference (1)), compared to those now used in Part II, Table 6, page 28. In the September 1968 list there were 20 total factors and 11 C-V factors, compared to 11 total factors and 6 C-V factors in the present list. As far as I'm concerned, however, if inter-related factors in Feinstein's #1 list had been condensed into a single one -- as was done in the final paper, and entirely justifiably -- the three blood sugar

values at 1, 2, and 3 hours on the GTT could be reduced to just one factor (as it is now, using a FBS level of 110 mg. % or more), and the 5 ECG changes could be reduced to just the last one ("one or more major ECG abnormalities"), which is now recorded as "significant ECG abnormalities." So just this condensation step reduces Feinstein's September 1968 "total of 20 baseline values in which TOLB patients were higher or lower than all others" to a total of 14 factors, including 7 C-V factors. On top of that, "Systolic BP below 120" can hardly be considered a poor-risk factor, nor can "sum of GTT under 500" (which actually means that there were more non-diabetics in the TOLB group, and we won't go into the glaring fact that there shouldn't have been any non-diabetics in any group in this study). We can also chuck out that uninterpretable "exact 100 R. eye visual acuity" thing, and the "venous pathology in CR fundus photo" business as far as arteriosclerosis is concerned -- and also the "crude creatinine clearance below 150," since everybody has a value below 150 cc/min or liters/day -- thus further reducing Feinstein's original 20 risk factors to a total of 9 and with 6 C-V factors -- which is practically the same as the present total of 11 factors including 6 C-V factors.

However, three of the "old" criteria (Sept 1968, Ref. (1)) have now been omitted (oscillometric measurements, absence of pulse in right femoral artery, and intermittent claudication); and, as noted below, not only have criteria for all but one of the remaining findings been changed (Ref. (2)), but 5 new factors have also been added as "selected baseline characteristics" (Ref. (3)). The effect of these changes upon the treat-

ment group with the "worst percentage" for each baseline risk-factor is seen in my References (2), (3) and (4). Ref. (4) shows how things ended up, i.e., in September 1968 all 9 risk-factors, including the 6 C-V factors were worst in the TOLB group -- whereas in the present Table 6 (Part II, page 28), only 4 of the 11 total risk factors are worst in the TOLB group, and only 1 of the 6 C-V risk factors are worst in the TOLB group, with most of the TOLB risks now having shifted to the ISTD group. Thus, the shift in "worst" groups was achieved by 3 maneuvers, namely (1) by deleting three findings (oscillometric measurements, absent right femoral pulse, intermittent claudication); (2) by modifying the criteria for a given finding (ECG abnormalities, serum creatinine [ostensibly changed but actually not], absent arterial pulse); and (3) by the addition of 5 new criteria, all of which were worst in non-TOLB groups.

The question now comes up whether the changes from "old" to "new" criteria were justified for any other reason than to remove from the TOLB patients the onus of having entered the study with the worst baseline characteristics and especially the worst cardiovascular risk factors; since, even though only 7 out of 20 differences from placebo were significantly different in Sept. 1968 (Ref. (1)), if most of the risk factors were even minimally worse in TOLB group it would suggest that they were in fact "sicker" at baseline than the other 3 groups. At this point, Chris, let me point out that, instead of just using the "percentages" you essentially used throughout, from now on I'll also be comparing the actual numbers of patients represented by percentages multiplied by denominators (as much as it was possible to do so). And as you well know, looking at the actual numbers of patients

involved often revealed interesting or even downright puzzling phenomena. Here are my comments about percentages-versus-actual patients per baseline risk factor:

(1) To get the easy stuff out of the way first, the addition of the first three of the five new criteria in Ref. (3) is perfectly O.K., since they're all valid C-V risk factors and their distribution now is the same as in July 1966. However, new factor #4 ("one or more C-V risk factors listed above") is untenable, because its a redundancy that just milks one more "risk factor" out of HBP plus digitalis plus angina plus significant ECG abnormality plus cholesterol of 300 mg% or more (you even deleted this factor from your calculations on page 29 for this same reason). So there are really only FIVE valid C-V factors in Table 6 instead of SIX. As for your new factor #5 (visual acuity), it's probably O.K. to use it as one of the selected risk factors, since visual acuity is at least definitely defined here whereas it wasn't in the Sept. 1968 report (Ref. (1)).

(2) In contrast to the above area of general agreement, I now object strenuously to the cavalier deletion of two of the three important C-V factors originally used in the Sept 1968 report (Ref. (1)) but now omitted from Table 6 on page 28 (namely, absent right femoral pulse and intermittent claudication; it's O.K. to drop the oscillometric thing because it didn't pan out). And I also object to certain markedly changed values -- both in total patients and/or percentages -- that had the effect of paring down the former preponderant TOLB risk factors until they were leveled off with the other 3 groups -- and with ISTD in particular. To wit:

(a) One or more major ECG abnormalities: We've already talked

about the changes in ECG criteria used, and here we see what they led to. Instead of having from 30 to 48 patients with significant changes, the numbers dropped to only 6-11 patients per treatment group, which add up to only 33 out of 823 patients with significant ECG changes. As already stated, this comes to an incidence of only 4% which is clinically unbelievable in a population of elderly diabetics. And in the process, the "worst percentage" shifted from TOLB to ISTD...

(b) History of digitalis (Ref. (2)): The only factor that remained absolutely unaltered from September 1968 through to the final manuscript.

(c) Serum creatinine (Ref. (2)): Although the criterion is expressed differently, this must actually be the same criterion, but now expressed intelligibly instead of unintelligibly as in Sept. 1968. In that report it was called "serum creatinine over 0.014," a meaningless phrase in that no units were given. The present criterion of "1.5 mg% or more," is correct and precisely states the same cut-off level that was implied by the former expression. But now, since this is the same criterion expressed differently, it's even harder to explain how the total patients in respective groups changed from 7-9-8-6 = 30 patients in September 1968 to the present totals of 5-5-4-4 = 18 patients. If there were 30 patients in September 1968 but now only a total of 18 patients -- all presumably with serum creatinine levels of 1.5 mg% or higher --

what happened to the other 12 patients? Also, there were 9 TOLB patients in 1968 and now only 5 TOLBS, and there were 7 PLAC in 1968 but now only 5 PLACS. What happened to 4 patients in the TOLB group and to 2 of the PLAC patients? And, although it's a tiny difference, with a denominator of 194 for PLAC compared to 199 for TOLB, the PLAC group ends up with a slight percentage edge of 2.6% versus 2.5%. Why did you drop 12 patients who were previously recorded as having serum creatinine levels of 1.5 mg% or more?

(d) Arterial calcification (Ref. (2)): The change from measuring calcification in "right thigh" only in September 1968 to the "entire right leg and foot" in the final manuscript would of course provide more anatomy in which to pick up calcifications and therefore to increase the total number of patients -- as it actually did for ISTD and for IVAR... but which it did not do for PLAC or TOLB, strangely enough. The one explanation might be that all of the PLAC and TOLB films had been read before September 1968 but not all of the ISTD or IVAR -- possibly, but sounds fishy. Another possibility is that more attention was paid to getting leg films of the TOLB group than of the insulin patients and that you guys had to play catch-up ball and belatedly get leg X-rays of the latter two groups which hadn't been insisted upon originally, and in the process you picked up some more patients with arterial calcification. In the long run, although nothing could be done to overcome the undeniable excess of calcification in the TOLB group, the increased incidence in the two insulin groups did

lower the gap between TOLB and the other 3 groups with respect to this clear-cut evidence of cardiovascular disease.

(e) Oscillometric measurements (Ref. (1)): Bob Osborne has already explained the difficulty of getting this measurement in all clinics, especially in a standard fashion, so that it seems entirely reasonable to drop this particular criterion.

(f) Absent arterial pulses (Ref. (2)): By changing from just palpating the right femoral artery to palpating both femorals and both dorsalis pedis pulses (absence of any of the four being recorded as a positive finding in the final manuscript), the number of patients mushroomed from 4-8-5-6 = 23 in September 1968 to 26-27-22-32 = 107 patients in October 1969, a 500% increase (!) and-- to recite the same litany once more -- the highest percentage shifted from the TOLB group to the IVAR group in the process. Who would have ever predicted that, although twice as many TOLB patients as PLACS had no palpable right femoral pulse in September 1968, between that time and October 1969 the PLAC patients would overtake the TOLBS and end up with only one less than the number of TOLBs with absence of at least one of the four pulses; and that the IVAR group would do even better, and actually go from 2-patients-less than TOLB with no right femoral pulse in September 1968 up to 5-patients-more than TOLB, with respect to one of the four pulses absent by the end of the study in Oct. 1969? Arterial disease is admittedly spotty, but how spotty can it get?

(g) Intermittent claudication (Ref. (1)): Since this is a history diagnosis that had to be made during the original work-up of the patient, the incidence of this particular baseline factor in the various groups should not have changed. Despite this obvious fact, the distribution of 40 patients with this finding were 12-13-7-8 in September 1948 whereas in October 1969 they were 13-12-7-8. So the PLAC group increased by one patient and the TOLB group decreased by one patient, thus shifting the worst percentage from TOLB (PLAC vs. TOLB = 6.1% vs 6.6% in Sept. 1968) to PLAC in the final paper (6.4% vs 6.0% in Oct. 1969). Did one of the PLAC patients remember that he had intermittent claudication after all, and one of the TOLB patients confess that he'd just been kidding and rescind his original positive reply about having claudication? What the hell.

(h) Body weight (Ref. (2)): Although the life insurance boys start obesity at 110% of "desirable" body weight, 115% is O.K. (as used in September 1968), but there was really no reason to move the cut-off level up to 125% unless there was a special reason. Actually, nobody uses more than 120% of desirable weight as the lower limit of obesity and I wonder what those values might have shown. As it is, the total numbers group-by-group dropped from 148-153-150-147 = 598 patients in September 1968 (using the 115% criterion) to 108-120-120-110 = 458 patients in Oct. 1969 (using

125%) -- and once again reduced the Sept. 1968 "worst total number" in the TOLB group to a numerical tie-score with ISTD. Although TOLB still had the highest percentage because of its lower denominator (204) compared to ISTD (210), the difference between it and the next highest percentage was reduced from 2.7% in Sept. 1968 to 1.7% in Oct. 1969.

(i) Blood sugar criteria (Refs. ①, ②): As I've already agreed, using just the FBS in the final manuscript is really a better criterion than the three values originally used in September 1968, since you tell the same story with one criterion instead of three. Since more of the TOLB patients had severer glucose intolerance than any other group, both the highest number of patients and the highest percentage remained in that group even though the total numbers of patients dropped from 146-161-156-148 = 611 in September 1968 to 129-147-133-138= 547 total in October 1969.

To summarize the foregoing comments on changes in baseline risk factors, can you blame me for getting the impression that they were juggled around until the cumulative preponderance of both total risk-factors and C-V risk-factors in TOLB patients in Sept. 1968 was bulldozed down to the levels found in one or more of the other three groups, to the extent that it even gave ISTD a worse-than-TOLB baseline for the sum-total of 5 out of 6 C-V factors as shown in Part II, Table 6, page 28 and in my Reference ④? Or for observing that this was a very handy baseline situation to have

ended up with, since it nullified one of the two explanations for the great excess of C-V deaths in TOLB-vs-PLAC (26-10 = 16 deaths difference) compared to the modest gap in All-Cause Deaths (30-21 = 9 deaths difference) -- namely, because the preponderance of baseline C-V disease in TOLB patients in Sept. 1968 had disappeared by Oct. 1969. The other explanation is unalterable, however, and is of course the preponderance of cancer deaths in PLAC, the respective values being 7-2-4-2. Although this was just a fluke, it did show that the PLAC group was also aberrant in one specific respect that itself accentuated the difference in C-V deaths compared to All-Cause deaths. Who knows how many of those 7 PLAC patients might have died of C-V disease if cancer hadn't knocked them off first? As for the five new factors that were added to Table 6, four of them are reasonable but the "one or more cardiovascular risk factors listed above" is an inadmissible redundancy that pads the figures in favor of ISTD.

Finally, here's my overall impression of the changes in the Sept. 1968 baseline factors: Nine of the 20 values cited by Feinstein seemed reasonably related to the risks to life and limb posed by diabetes, including 6 C-V factors. The total number of patients and the percentage incidence was highest in the TOLB group for all 9 of these factors. In contrast, in the present Table 6 (Part II, page 28) -- omitting the demographic characteristics -- and also in my Ref. (4), there are 6 baseline cardiovascular risk factors and 5 additional selected baseline characteristics, with 5 of the 6 C-V risk factors showing most total patients and the highest percentages in ISTD, and only one of the highest percentages in the TOLB group. However, the 6th factor, "one or more cardiovascular risk factors listed above," has already been tagged as a redundancy that stacks baseline C-V risk factors

in favor of ISTD and it should therefore be dropped, thus leaving 5 baseline C-V factors. Moreover, the "arterial calcification" listed below as one of the "other selected baseline characteristics" certainly belong up in the cardiovascular risk factors because it sure as hell is evidence of vascular disease. Since this preponderantly occurs in the TOLB group, we are back to a total of 6 C-V factors (the "new-revised 6"), of which TWO now show the highest percentage in TOLBS and FOUR in ISTD. Now we return to the two omitted factors, namely, intermittent claudication and absent arterial pulses -- both of which occurred most frequently in the TOLB group in Sept. 1968 (distribution for intermittent claudication was 12-13-7-8, and for absent arterial pulse it was 4-8-5-6 patients, respectively). If these two of the "old-revised 9" baseline characteristics (as defined in September 1968 = Ref (4)) had also been included in Table 6 and therefore been added to the "new-revised 6" cardiovascular risk factors, the resulting total of 8 C-V risk factors would now show the highest percentages per risk factor to be equally distributed, i.e., FOUR EACH for the TOLB group and for the ISTD patients. BUT: If the changed figures for intermittent claudication cited elsewhere in the final manuscript -- but NOT included in Table 6 -- were used instead, the addition of one more patient to PLAC (12 ⟶ 13) and the deletion of one patient from the TOLB group (13 ⟶ 12) shifted the highest percentage to the PLAC group (6.4%) instead of the TOLB group (6.0%). Similarly, the 300-500% increase in the number of patients in each group with at least one absent pulse in either femoral artery or dorsalis pedis artery shifted the highest percentage to IVAR (15.8%) and away from TOLB (13.4%). This means that, even if these two former baseline characteristics were reinserted into Table 6, but with the "new" (i.e., changed) percentages being used,

the final distribution of highest percentages of baseline C-V risk factors would still be 4 in ISTD, 2 in TOLB, 1 in PLAC and 1 in IVAR. However, since the changed intermittent claudication figures must be a mistake, the preponderance for this factor should remain in the TOLB group; and the 3- to 5-fold increase in the number of patients with absence of at least one of four arterial pulses, as compared to just an absent right femoral pulse, is inexplicable to say the least. The implication of course is that, although during the baseline physical examination the clinician only had to feel for the right femoral pulse, they would have had to be such meticulous craftsmen (all of them) that they voluntarily took the trouble to also check carefully for the left femoral and both dorsalis pedis pulses as well. Since the weaker dorsalis pulses automatically require more dedication (and time) to rule their existence in or out, who's kidding whom that the other 3 pulses were always recorded as present or absent also, so that the information would be right there waiting for your retrospective search to pick it up -- almost as though all of the examining clinicians had some prescience that they'd be needed some day. Especially in view of what must have been repeatedly frustrating evidences to you that many of the principal investigators were blatantly ignoring the constant baseline criteria you had originally laid down -- the single worst instance of which was the admission of 69 non-diabetics -- i.e. 1 out of every 12 patients -- to a study of 823 diabetics? If I haven't made the point by this time that, by God, you or somebody else did manipulate the baseline risk factors -- by means I've been able to track down for some factors but that remain unfathomable for others -- then I never will. But an even more serious charge is about to come. Read on.

(C) TRUE MORTALITY VERSUS FALSE CUMULATIVE MORTALITY RATES: On the point about to be raised, I particularly had to write Bob Osborne first to see if I'd misinterpreted your Table 2 and Figure 1 on pages 7-8 of Part II. Even then, I only caught on because Keith Borden had mentioned that after September 1968 the number of deaths in the TOLB group had leveled off whereas those in PLAC had increased -- thus narrowing the gap between them. Therefore, when Steve Fajans and I looked at Figure 1 on page 8 a few days later, I couldn't explain either to him or to myself why both TOLB mortality rates still seemed to be increasing whereas the All-Cause and C-V mortality rates for PLAC seemed to have leveled off. When I got back to Dallas, though, and spent about 12 hours analyzing the data in the final manuscript I figured it out. Here's my comment on the picture conjured up by the combination of the text on page 6, Table 2 on Page 7, and Fig. 1 on Page 8 (see my Reference (5)): The table and figure both show "cumulative mortality rates per 100 population at risk..." and the percentages in Table 2 are graphed in Figure 1. However, the last paragraph on page 6 explains that, "cumulative mortality rates per 100 population at risk have been computed with life table methods for each year of follow-up for each of the four treatment groups. The results are given in Table 2 and plotted in Figure 1. The detailed life tables on which these results are based are given in Appendix A-1...." Although I got lost in the shuffle trying to untangle Appendix A-1 (which I've since had translated for me by Clare Mahan), I understood enough of it to answer my basic question. Namely, that the percentages shown in Table 2 and Figure 1 were, as I suspected, calculated from the life tables, and were not in

fact the actual mortality rates. This is still my interpretation despite the fact that in Appendix A-6 on page 94 you have asterisked the column for "Observed Mortality Rate," and then explained below that these values were taken from Table 2 -- which they were, but which in turn implies that the values in Table 2 were actual (observed) values which they were NOT. Meaning that the asterisk is defined erroneously, since the percentages cited in the "Observed Mortality Rate" column of Appendix A-6 are the same values as in Table 2, but those percentages themselves are different from the actual percentages for both total deaths and cardiovascular deaths that you have previously cited in the first paragraph of the text on page 6 and shown in Table 1 on page 5. Specifically, the actual percentages of "All-Causes" deaths were 10.2-14.7-9.5-8.8, in contrast to the Table 2 "All-Cause" percentages of 11.4-19.8-11.7-12.9; and the actual mortality rates for C-V deaths were 4.9-12.7-6.2-5.9, in contrast to the Table 2 values of 6.0-17.6-7.7-8.1. Aside from the fact that you guys apparently mis-labeled your own data in Appendix A-6, your presentation of cumulative mortality and mortality rates throughout the paper is consistently obscure and seems to be purposely misleading. For example, as already pointed out, on page 6 you start out clearly enough by telling us about the actual total of 89 deaths and the actual total of 61 C-V deaths, and both the totals and the percentages jibe with the values given in Table 1 on page 5. These are the final deaths as of October 7, 1969, not the totals of May-June 1969, when there were 2 less PLAC deaths and 1 less TOLB deaths(and also 1 less

ISTD death and 3-less IVAR deaths). These are also, of course, the well known percentages that have gone around the country and have now shown up in the FDA's therapeutic recommendations. However, the final totals tell us nothing about the trends in mortality rates, and presumably in order to show these trends you direct us in the last paragraph of page 6 to the cumulative annual mortality rates per 100 population at risk, both for All-Causes and for C-V causes... and we are referred to Table 2 and to Figure 1 for the values themselves and their graphic plotting for each year of follow-up. HOWEVER the "cumulative annual mortality rates" given in Table 2 and Figure 1 are NOT THE ACTUAL CUMULATIVE ANNUAL MORTALITY RATES -- which almost everyone who reads this paper in DIABETES is going to think they are, despite the fact that you state on page 6 that the cumulative annual mortality rates "...have been computed with life table methods." What you've actually done ——→ is to suddenly switch from a discussion of ACTUAL MORTALITY to PREDICTED MORTALITY RATES -- without clearly notifying the untrained reader of this fact. I gather from Feinstein's and Schor's critiques that, although the use of life-tables to predict mortality rates if everyone in the study were followed the same length of time is theoretically valid, there was something faulty about the way you used them. Which anyone who has the actual deaths available can tell anyway, even without knowing boo about life-tables, since the observed deaths are what count, not what someone predicts the mortality rates might-be-if... And once the reason for the discrepancy between what actually happened and the impression

given in Figure 1 on page 8 became clear to me, I absolutely exploded with rage at what seems to me to be pulling the wool over the reader's eyes. I certainly hope this impression of mine is erroneous and is only due to the obscure way you've presented the data all the way through the paper; but the overriding evidence that makes me think I'm not wrong is that NOWHERE IN THE PAPER DO YOU EVER PRESENT THE ACTUAL CUMULATIVE DEATHS YEAR BY YEAR, which is why I had to get them from Keith Borden. If you had presented them they would have shown that the gap between total TOLB and PLAC deaths was getting smaller after September 1968; and, to a lesser extent, that the gap between their C-V deaths was also narrowing, as shown in my References (2) & (3). Instead, your Figure 1 makes it look as though the TOLB deaths were increasing faster than PLAC deaths at each successive period of observation, so that the gap was steadily widening both for total deaths and for C-V deaths -- which would be a damned good reason to stop tolbutamide, admittedly, but which is the exact opposite of what happened. To translate what your calculated life table mortality rates would mean in terms of actual deaths I figured them up as in my reference 5 and, as you probably know already, instead of the actual total of 30 TOLB deaths there are 40; instead of 21 actual PLAC deaths there are 23 (also, but not shown in my refs), instead of 20 actual ISTD deaths there are now 25; and instead of 18 actual IVAR deaths there are now 26). Similarly, the box score on observed vs. predicted cardiovascular deaths is as follows (see my Reference (6): PLAC: 10 actual, versus 12 "life-table"; TOLB: 26 actual, vs. 36 "life-table"; ISTD: 13 actual, vs. 16 "life-table;" and for IVAR: 12 actual, versus 17 "life-table." Quite some differences -- especially the predicted "All-Causes" gap of 17 deaths

between PLAC-TOLB at your 8th-year end-point of May 1969 in Figure 1 and an estimated difference between PLAC-TOLB of 24 cardiovascular deaths, when converted from the percentages in Figure 1-Part B -- in contrast to the actual differences of only 9 All-Cause and 16 Cardiovascular deaths. For the life of me, Chris, I don't see how the editor of DIABETES ever accepted the paper for publication without making you put down the ACTUAL cumulative deaths somewhere in the manuscript! Since you've been steeped with UGDP findings for 9 long years, it's impossible to conceive that this way of presenting the mortality data was due to carelessness or oversight; and to my personal consternation the only conclusion I can come to, based on the manuscript you sent me, is that whoever wrote it purposely recorded the mortality findings in this obscure fashion so as to give an impression contrary to what actually happened. For example, Figure 1 on page 8 was first shown to us in St. Louis, and was shortly thereafter published in Medical World News, and is now about to be seen by everybody who reads the final paper in DIABETES. And since your cumulative life-table percentages clearly portray a different picture than what actually went on -- coupled with deliberate omission of the actual cumulative mortality that was observed, I have to conclude that the authors want readers to believe that tolbutamide was still causing an increasing number of deaths as of Oct. 7, 1969, instead of showing us that the spurt in TOLB deaths between Jan. 1967 and Sept. 1968 not only leveled off from then until Oct. 1969, but had actually been replaced by a spurt in PLAC deaths -- the very kind of sporadic responses that plague studies on small series of patients like these. I sent all these figures to Bob Osborne, and when I subsequently asked him about them over the phone he didn't say a helluva lot one way or the other, but at the end

of our 90-minute conversation he did say something like, "So all you'd require before accepting the study is a table showing the actual cumulative mortality rates, is that right" -- and I told him no, that was not quite right, because on all counts this is the most incredibly misrepresented mish-mash of data about to be foisted upon the medical community that I've ever seen, and that for the life of me I can't see why the total membership of the UGDP study let the authors get away with it. In any event, once the paper is finally published, the discrepancy between the life-table projections of mortality and observed mortality has to be exposed -- unless the latter does finally end up in print too.

I'm glad I finally had to sit down and phrase my exact thoughts about this absolutely horrible affair and transmit them to you. I'm actually so worked up right now that the other two points I was going to mention seem inconsequential -- except that they're not, because they add still more to the picture of an absolute shambles of a study which has somehow conned so many men of excellent scientific reputation into believing and actually supporting it! Anyway, I'll try to condense the last two points:

(D) CORRELATION BETWEEN BASELINE RISK FACTORS PER CLINIC AND MORTALITY PER CLINIC: In an attempt to determine whether the first two or three highest-mortality clinics had in fact started out with a greater multiplicity of "All-Risks" and/or "C-V Risk Factors," I used Part B and Part C of Table 12 (Part II, pages 53-54), and converted each percentage and denominator into the actual number of patients per factor. For each clinic, I then added all the patient-

numbers for "C-V-risk-factors," and for "Other Selected Baseline Characteristics;" and then added both values to obtain "Total Risk Factors Per Clinic." Although this meant equal-weighting of all factors, it did give some idea of the total risk factors per clinic in order to see if, in the clinics with the highest baseline risks to start with, there was a tendency for more people to die in ALL treatment groups or just in the TOLB-patients. I therefore ranked the clinics from 1 to 12 in descending order of total risks and then compared the baseline ranking of each clinic with its ultimate rankings in actual numbers of deaths per treatment group. ——→ Reference (7) shows that, when ranked from 1 to 12 in descending order of total risk factors, the 3 clinics whose patients had the worst baseline health status when they entered the study were Cincinnati, Minneapolis and Williamson, West Va. The relationship of pre-treatment state of health to subsequent mortality from all-causes is clearly shown by the circles denoting the 3 highest death rankings across the board. Thus, Cincinnati was #1 in total risk factors, and was also #1 in total deaths, in placebo deaths, and in insulin-variable mortality; and it ranked 2nd in both tolbutamide and insulin-standard deaths. Similarily, Minneapolis was #2 in total baseline risk factors; it also ranked 2nd in total deaths, but was actually 1st in both tolbutamide and insulin-standard deaths, and was #2-3 in placebo mortality. And Williamson, #3 in total baseline risk factors, was also 3rd in total deaths and #2-3 in insulin-standard and insulin- variable mortality. Only New York and Boston ranked 4th or

lower in baseline risk factors, yet had disproportionate mortality that ranked them (3rd or higher) in one or more treatment groups. In other words, the clinics whose patients had the greatest amount of pre-existing disease before initiation of any therapy also ended up with the greatest mortality -- in ALL treatment groups, not just in patients on tolbutamide.

Reference (7) also shows similar correlations for cardiovascular deaths. Cincinnati again ranked 1st in baseline cardiovascular risk factors, followed by #2 Williamson and #3 Minneapolis. And again, the circles across the board show that the 3 clinics whose patients had the worst cardiovascular status before treatment subsequently accounted for all but 2 of the 15 "top-3" death rankings. Number 1 Cincinnati actually ranked first in total cardiovascular deaths, and also in tolbutamide, insulin-standard and insulin-variable cardiovascular deaths; and it was #2-3 in placebo-cardiovascular deaths. And 3rd-ranked Minneapolis was actually 2nd in both total and tolbutamide cardiovascular deaths, and 2nd or 3rd in the other 3 treatment groups. As a matter of fact, Reference (8) shows that Cincinnati and Minneapolis together accounted for 39-to-50% of the deaths in all categories across the board. For each of the 10 sub-groups the percentage was obtained by dividing the combined deaths in Cincinnati and Minneapolis by the total deaths in all 12 clinics. The remarkedly constant percentages of both total deaths per treatment group in the top line and cardiovascular deaths in the bottom one show clearly that these two clinics accounted not only for exactly half of both total and cardiovascular deaths

in the tolbutamide patients, but also for almost half of the total and cardiovascular deaths in the other 3 treatment groups as well. In this regard, Cincinnati is known to have culled most of its UGDP entries from the cardiac clinic, but what happened in Minneapolis remains obscure. In any event, deletion of Auschwitz and Buchenwald, as it were, from the study would leave Boston's disporportionate excess of total and cardiovascular deaths in tolbutamide-patients clearly attributable to chance, with an otherwise balanced distribution of mortality among all four treatment groups (see my Reference (9)).

E. CHANGES IN DENOMINATORS IN SOME CLINICS: Without the actual raw data I can't precisely evaluate the significance of this factor, but both in Part I, page 13, Table 5, and in Part II, page 51, Table 11, the denominators per treatment group per clinic are given. Although supposedly the same, they're different, and sometimes the numbers go up and sometimes they go down. Although the total number treated per clinic sometimes changes from Part I to Part II (Baltimore up one, NYC down two, St. Louis down 7, and San Juan up 8), they still add up to 823 total patients in both tables. This naturally entitles a person to ask what the hell's going on, when supposedly a given clinic started out with the number of patients per treatment group shown in the baseline-data paper (Part I, Table 5), and then in the mortality-results paper (Part II, Table 11) some persons in the original study group have been deleted in order to add others. In view of my voluminous comments on the changes in baseline criteria from September 1968 until October 7, 1969, you can't blame me for again being suspicious and suspecting

that maybe a patient was dropped here and another added there -- always adding up to the same total of 823 patients -- in order to alter some of the baseline risk factors and thereby flatten out the preponderance of TOLB baseline risks as of Sept. 1968, the ones to which I was originally exposed. Whether or not this is the actual explanation of the discrepancy in the figures, the manuscript ought to have used the same set of values in both tables. Sooner or later somebody else will probably note the differences between two sets of ostensibly identical values, and it looks bad.

In closing, Chris, as one of the principal authors of the manuscript, you know damned well how you could have avoided all of the confusion and the still-gathering storm about this tolbutamide business, and I'll never understand why the editor of DIABETES didn't demand it. All you had to do was present all of the data throughout in the format shown in my Reference (10), namely, by having <u>three columns</u> for each treatment group, with the <u>denominators</u> in one column, the <u>actual numbers</u> of patients with the positive finding in another, and the <u>percentages</u> in a third column. That way everyone could tell at a glance what was actually going on at all times, and if you or whoever else then wanted to extrapolate with life tables and Monte Carlo and what-not, at least the reader interested only in getting the straight message and the main point would have had it clearly laid out before him. Of course, such a crystal clear approach would have shown that the original scare about excessive C-V deaths in TOLB patients that occurred between

Jan. 1967 and Sept. 1968 had spontaneously subsided; but since that's what had actually happened, that's what the physicians throughout the country and their diabetic patients should have been told.

Sincerely,

Hoe Seltzer

HOLBROOKE S. SELTZER, M.D.
Chief of Endocrinology Section at
Veterans Administration Hospital
and
Professor of Internal Medicine at the
University of Texas Southwestern
Medical School.

Document #18

Reference (1)

FROM FEINSTEIN'S FIRST CRITIQUE, BASED ON UGDP PROGRESS REPORT OF SEPT. 1968

Baseline Values In Which Tolbutamide Group Patients Were Higher or Lower Than All Others

★ = $p < 0.05$, TOLB vs PLAC † = $p < 0.05$, TOLB vs All Others

BASELINE VALUE	(Percent of Patients Per Treatment Group) PLAC	TOLB	ISTD	IVAR
~~1. Exact 100 R. Eye Visual Acuity~~	~~52.4~~	~~46.0~~	~~47.2~~	~~48.4~~
~~2. Venous Pathology in CR Fundus Photo~~	~~2.3~~	~~7.0†~~	~~1.7~~	~~6.5~~
~~3. Systolic BP < 120~~	~~14.4~~	~~17.0~~	~~12.6~~	~~12.1~~
(4) S-T Depression	6.6	12.2†	6.3	11.2
(5) Inverted T Waves	9.6	12.2	8.2	11.2
(6) Significant Arrhythmia	2.5	4.1	3.9	1.5
(7) Large Q Waves	1.5	2.6	1.0	2.5
(8) One or More Major ECG Abnormalities (Includes (4)-(7))	15.2	24.0★†	19.3	19.3
(9) History of Digitalis	4.5	7.6	5.8	5.0
10. Serum Creatinine over 0.014	3.7	4.6	4.0	3.1
~~11. Crude Creatinine Clearance < 150~~	~~5.9~~	~~5.3~~	~~9.2~~	~~8.8~~
(12) Calcification in Right Thigh	14.9	19.6	14.3	13.1
(13) Oscillometric Measurements at Right Knee Under 15	26.0	31.1†	27.0	26.9
(14) Absence of Pulse in Right Femoral Artery	2.0	4.0	2.4	3.0
(15) Intermittent Claudication	6.1	6.6	3.4	4.0
16. Body Weight More Than 115% of Desirable Body Weight	72.6	75.3	71.7	71.8
~~17. Sum of GTT Under 500~~	~~4.2~~	~~9.2★~~	~~7.3~~	~~6.7~~
18. Value Over 300 @ 1 Hr on GTT (‡)	21.6	27.0	23.5	25.5
19. Value Below 180 @ 2 Hrs on GTT (‡)	35.4	27.5†	33.2	32.0
20. Value Below 110 @ 3 Hrs on GTT (‡)	27.8	20.9†	25.9	27.2

C = Cardiovascular Risk Factors = 11 of them

(‡) These 3 values expressed as 1 value (FBS of 110 mg% or more) in final manuscript.

~~~~~ Deletable values as far as I'm concerned, either non-risk factors in TOLB or inconsequential clinically or hard to compare between groups.
~~~~~

Reference (2)

HOW MODIFICATION OF SEPT. 1968 CRITERIA FOR BASELINE RISK FACTORS SHIFTED SOME "WORST PERCENTAGES" FROM TOLB TO OTHER GROUPS

DEGREE OF CHANGE	BASELINE RISK FACTOR	CHANGE IN CRITERIA	WORST % (SEPT '68)	WORST % (NOV. '70)
None	1. History of Digitalis	NONE	TOLB	TOLB
Minimal Change	2. Severity of diabetes	From post-glucose values on GTT to FBS of 110 or more	TOLB	TOLB
	3. Body Weight	From 115% to 125%	TOLB	TOLB
	4. Serum Creatinine	From "over 0.014"(?) to 1.5 mg% or more	TOLB	(PLAC)
Significant Change	5. EKG Abnormalities	As discussed	TOLB	(ISTD)
	6. Arterial Calcification	From right thigh to entire right leg	TOLB	TOLB
	7. Absent Arterial Pulses	From right femoral to any of both femorals or both dorsalis pedis	TOLB	(IVAR)

Reference (3)

TREATMENT GROUPS WITH THE WORST PERCENTAGES FOR THE FIVE NEW FACTORS ADDED TO TABLE 6, PAGE 28.

	BASELINE RISK FACTOR	WORST GROUP JULY 1966 (*)	WORST GROUP NOV. 1970
1.	Hypertension	PLACEBO	PLACEBO
2.	Cholesterol of 300 mg % or more	ISTD	ISTD
3.	History of angina pectoris	ISTD	ISTD
4.	"One or more CV factors listed above" (**)	ISTD	ISTD
5.	Visual Acuity 20/200 or worse	ISTD	ISTD

(*) Values taken from Schor's critique. Source recorded as "6 Year Progress Report, July 1966."

(**) As noted in body of letter, this factor is not permissible because it is redundant and pads the "worst percentages" in favor of ISTD. (You actually omitted it from your tabulation on page 29 for the very same reason, see footnote same page).

Reference (4)

"REVISED 9 RISK FACTORS"

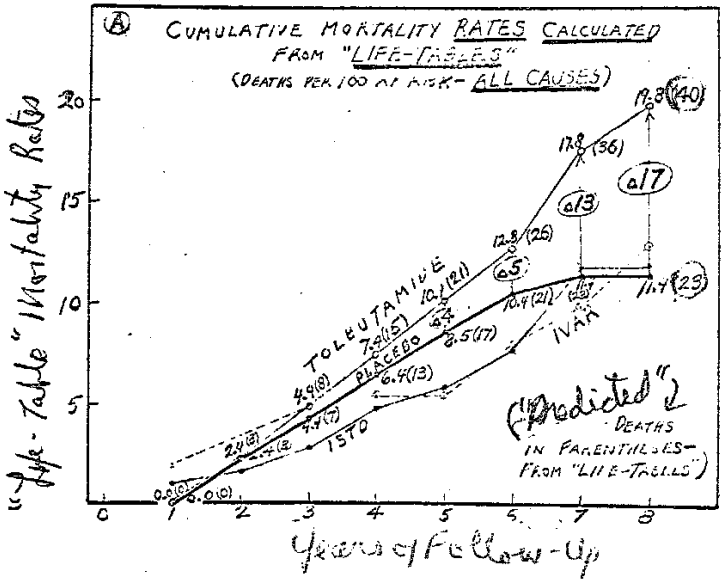
COMPARISON OF FEINSTEIN'S "REDUCED RISK FACTORS" WITH THOSE IN TABLE 6 (Part II, page 28)

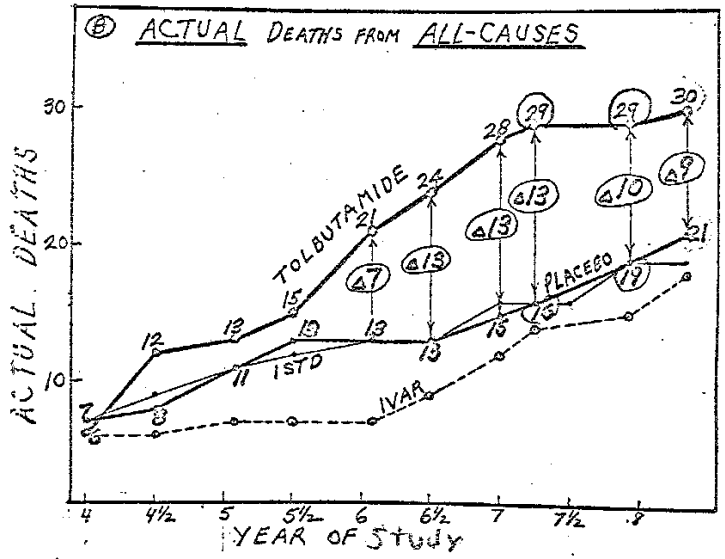
		GROUPS With Worst Percentage
FEINSTEIN'S REDUCED RISK FACTORS (from Sept 1968 UGDP)	(9) TOTAL Risk Factors	(TOLB) = Worst % in ALL (9)
	(6) C-V Risk Factors	(TOLB) = Worst % in ALL (6)
PRESENT RISK FACTORS (Table 6, Part II, page 28)	(11) TOTAL Risk Factors	(TOLB) = Worst % in (4) ISTD = Worst % in 6 PLAC = Worst % in 1
	(6) C-V Risk Factors	(TOLB) = Worst % in (1) ISTD = Worst % in 5

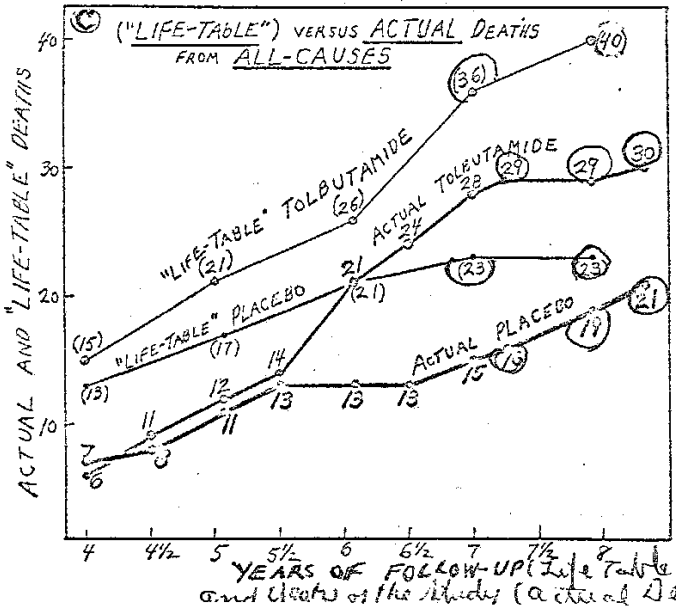
Reference (5)

ALL-CAUSE DEATHS

FIG. 1-Part A (Part II, page 8)







(I KNOW NOW THAT CAN'T SUPERIMPOSE LIFE-TABLES and ACTUAL DEATHS, BUT YOU GET THE IDEA)

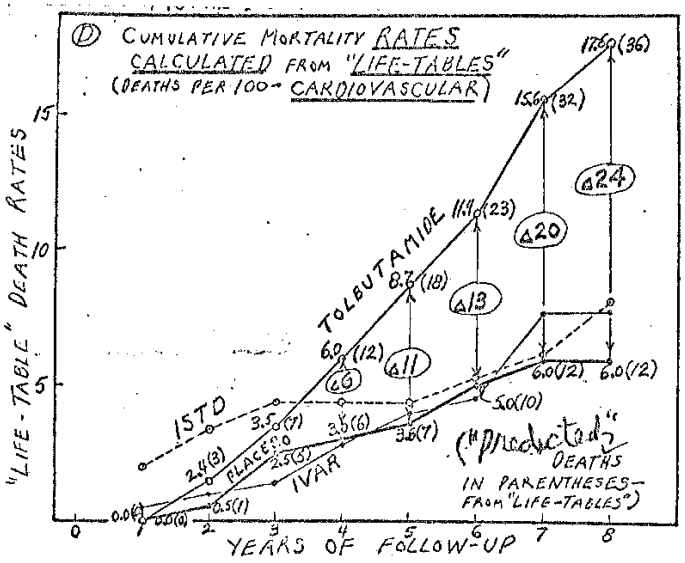
Reference (5)

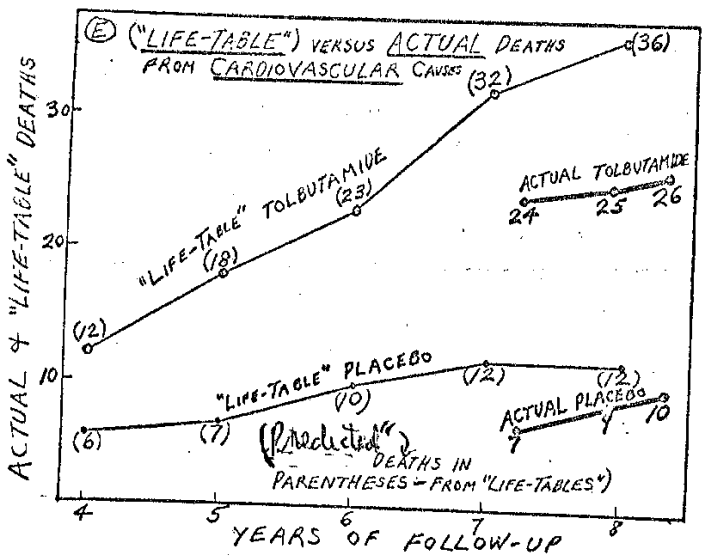
Document #18

Reference (6)

Cardio-Vascular Deaths

FIGURE 1. Part B (Part II, page 8)





Document #18

Reference 7 Correlation between

BASELINE RISK FACTORS AND MORTALITY PER CLINIC

RANKING BY BASELINE RISKS	CLINIC	No. of Pts. Rx'd	No. of Pts. Who Died	Rank by # of Deaths	No. & Rank of Deaths per Treatment Group							
					PLACEBO		TOLBUT.		INS. STD.		INS. VAR.	
					No.	Rank	No.	Rank	No.	Rank	No.	Rank
ALL CAUSES OF DEATH												
(1)	Cincinnati	90	23	(1)	7	(1)	7	(2)	4	(2)	5	(1)
(2)	Minneapolis	94	18	(2)	3	(2-3)	8	(1)	5	(1)	2	4-5
(3)	Williamson	92	12	(3)	2	4-5	4	4	3	(3)	3	(2-3)
4	Cleveland	77	4	6-7	1	6-9	1	7-8	0	10-12	2	4-5
5	Baltimore	87	1	11-12	0	10-12	1	7-8	0	10-12	0	9-12
6	New York	85	10	4	3	(2-3)	2	5-6	2	4-5	3	(2-3)
7	Boston	63	9	5	1	6-9	5	(3)	2	4-5	1	6-8
8	Birmingham	49	4	6-7	2	4-5	2	5-6	0	10-12	0	9-12
9	Chicago	46	3	8	1	6-9	0	9-12	1	6-9	1	6-8
10	St. Louis	44	2	9-10	1	6-9	0	9-12	1	6-9	0	9-12
11	San Juan	52	2	9-10	0	10-12	0	9-12	1	6-9	1	6-8
12	Seattle	44	1	11-12	0	10-12	0	9-12	1	6-9	0	9-12
CARDIOVASCULAR CAUSES OF DEATH												
(1)	Cincinnati	90	17	(1)	2	(2-3)	7	(1)	4	(1)	4	(1)
(2)	Williamson	92	9	(3)	1	4-6	3	4	2	(2-3)	3	(2)
(3)	Minneapolis	94	12	(2)	2	(2-3)	6	(2)	2	(2-3)	2	(3)
4	New York	85	5	5	3	(1)	2	5-6	0	9-12	0	7-12
5	Cleveland	77	2	7-8	0	7-12	1	7-8	0	9-12	0	7-12
6	Baltimore	87	1	9-12	0	7-12	1	7-8	0	9-12	0	7-12
7	Boston	63	7	4	1	4-6	4	(3)	1	4-8	1	4-6
8	Birmingham	49	2	7-8	0	7-12	2	5-6	0	9-12	0	7-12
9	Chicago	46	3	6	1	4-6	0	9-12	1	4-8	1	4-6
10	Seattle	44	1	9-12	0	9-12	0	9-12	1	4-8	0	7-12
11	St. Louis	44	1	9-12	0	9-12	0	9-12	1	4-8	0	7-12
12	San Juan	52	1	9-12	0	9-12	0	9-12	1	4-8	0	7-12

Reference 8

CINCINNATI AND MINNEAPOLIS -- JUST THOSE TWO CLINICS --

ACCOUNTED FOR 39% - 50% OF ALL DEATHS... FROM ALL-CAUSES...

...FROM CARDIOVASCULAR CAUSES... AND TOTAL DEATHS

	PLAC	TOLB	ISTD	IVAR	TOTAL
ALL DEATHS	48 %	50 %	45 %	39 %	46 %
C-V DEATHS	40 %	50 %	46 %	50 %	48 %

Document #18

Reference (9)

MORTALITY IN 10 CLINICS (CINCINNATI AND MINNEAPOLIS DELETED)

(3-or-more Deaths Red-Lettered)

BASELINE RISK FACTORS AND MORTALITY PER CLINIC

Corrected Ranks

RANKING BY BASELINE RISKS	CLINIC	No. of Pts. Rx'd	No. of Pts. Who Died	Rank by # of Deaths	No. & Rank of Deaths per Treatment Group							
					PLACEBO		TOLBUT.		INS. STD.		INS. VAR.	
					No.	Rank	No.	Rank	No.	Rank	No.	Rank
ALL CAUSES OF DEATH												
(3)	Williamson	92	12	(3)	2	4-5	4	4	3	(3)	3	(2-3)
4	Cleveland	77	4	6-7	1	6-9	1	7-8	0	10-12	2	4-5
5	Baltimore	87	1	11-12	0	10-12	1	7-8	0	10-12	0	9-12
6	New York	85	10	4	3	(2-3)	2	5-6	2	4-5	3	(2-3)
7	Boston	63	9	5	1	6-9	5	(5)	2	4-5	1	6-8
8	Birmingham	49	4	6-7	2	4-5	2	5-6	0	10-12	0	9-12
9	Chicago	46	3	8	1	6-9	0	9-12	1	6-9	1	6-8
10	St. Louis	44	2	9-10	1	6-9	0	9-12	1	6-9	0	9-12
11	San Juan	52	2	9-10	0	10-12	0	9-12	1	6-9	1	6-8
12	Seattle	44	1	11-12	0	10-12	0	9-12	1	6-9	0	9-12
CARDIOVASCULAR CAUSES OF DEATH												
(2)	Williamson	92	9	(3)	1	4-6	3	4	2	(2-3)	3	(2)
4	New York	85	5	5	3	(1)	2	5-6	0	9-12	0	7-12
5	Cleveland	77	2	7-8	0	7-12	1	7-8	0	9-12	0	7-12
6	Baltimore	87	1	9-12	0	7-12	1	7-8	0	9-12	0	7-12
7	Boston	63	7	4	1	4-6	(4)	(3)	1	4-8	1	4-6
8	Birmingham	49	2	7-8	0	7-12	2	5-6	0	9-12	0	7-12
9	Chicago	46	3	6	1	4-6	0	9-12	1	4-8	1	4-6
10	Seattle	44	1	9-12	0	9-12	0	9-12	1	4-8	0	7-12
11	St. Louis	44	1	9-12	0	9-12	0	9-12	1	4-8	0	7-12
12	San Juan	52	1	9-12	0	9-12	0	9-12	1	4-8	0	7-12

Document #18

Reference (10)

WHAT SHOULD HAVE BEEN DONE

CUMULATIVE MORTALITY + MORTALITY RATES PER YEAR OF STUDY

YEARS OF THE STUDY	PLACEBO (1) # of Patients (Denominators)	PLACEBO (2) No. of Deaths	PLACEBO (3) Percent Deaths	TOLBUTAMIDE (1) # of Patients (Denominators)	TOLBUTAMIDE (2) No. of Deaths	TOLBUTAMIDE (3) Percent Deaths
"ALL CAUSES"						
June 1965 4	184	7	3.8	176	6	3.4
Jan 1966 4½	200	8	3.9	200	12	5.9
June 1966 5	205	11	5.4	204	13	6.3
Jan 1967 5½	205	13	6.4	204	15	7.3
June-July 1967 6	205	13	6.4	204	21	10.2
Jan 1968 6½	205	13	6.4	204	24	11.7
July 1968 7	205	15	7.4	204	28	13.7
Sept 1968 7¼	205	16	7.8	204	29	14.2
May-June 1969 8	205	19	9.3	204	29	14.2
Oct 7 1969 8⅓	205	21	10.2	204	30	14.7
CARDIOVASCULAR CAUSES						
4						
⋮						
Sept 1968 7¼	205	7	3.4	204	24	11.8
May-June 1969 8	205	9	4.4	204	25	12.3
Oct 7 1969 8⅓	205	10	4.9	204	26	12.7