LETTERS

Diabetes Drugs: Clinical Trial

The News and Comment article by Gina Bari Kolata (9 Mar., p. 986) about the controversy surrounding the University Group Diabetes Program (UGDP) contains a number of erroneous and misleading statements. Like so much that has been written about the study, it focuses on the toxicity issue. It is simply incorrect to suggest, as is implied in the article, that the UGDP drew any conclusion with regard to toxicity. The use of oral hypoglycemic drugs was terminated in the study because of lack of efficacy, not proved toxicity. As a matter of fact, ethical constraints make it impossible to reach a conclusion regarding toxicity from a trial such as the UGDP. It is necessary to stop use of a drug in a clinical trial before a definitive conclusion can be reached regarding toxicity.

The suggestion by Kolata that the Food and Drug Administration (FDA) acted in the absence of data is incorrect. The reporting requirements of a drug trial covered by an investigational new drug application (IND) from the FDA meant that the project supplied the FDA, at regular intervals, with updated reports containing summary analyses of accumulated data on the study treatments.

The nature of the reporting regarding Christian Klimt's participation depicts an incorrect role for him in the trial. The University of Maryland, through the Division of Clinical Investigation with Klimt as its director, serves as the repository for the data from the study. The data belong to the study and not to Klimt, as implied. Further, decisions regarding the format and types of analyses to be performed were made by the entire leadership of the study, not by Klimt or any other individual acting alone. Any suggestion that he was able to manipulate the data is irresponsible. It not only assumes conspiratorial behavior by him, but also by a host of independent people in the Coordinating Center who, in fact, carried out the coding and data analyses. In addition, it assumes complicity, naïveté, or stupidity on the part of the other investigators in the study, since they participated in the data review.

The article raises questions concerning access to raw data. The approach followed by the study represents a balance of rights: the rights of the patient to anonymity, the rights of the public to all relevant information, and the rights of the investigators to perform and complete analyses of data before they are analyzed elsewhere by others.

The *Science* article leaves the impression that the study has not revealed important information from its data files. In fact, quite the reverse is true. Much of the fuel for the controversy has come from data supplied by the study and is a direct result of the high standards set by it in making data available to the scientific community. Few if any trials have done as well in this regard. The study has generated seven key papers, all of which have appeared in peer-reviewed scientific journals (*1*, *2*). The 1970 paper on tolbutamide contained an appendix listing the cause of death and baseline characteristics of deceased patients. The 1975 paper on phenformin contained 20 pages of individual patient data as well as updated information on the tolbutamide study. Baseline and follow-up data on all 1027 patients enrolled in the trial were made available in early 1978 through an announcement in the December 1977 issue of *Diabetes*.

There is no basis for Kolata's value judgments regarding the quality of patient care and data processing. It is suggested that the care provided for patients was substandard. The facts indicate quite the contrary. Mortality experience in the study for the placebo and two insulin treatment groups was less than that expected for a comparable group drawn from the general U.S. population (*2*). The use of hyperbole and anecdote is to be expected of critics attempting to make a point, but there is no justification for its perpetuation by a publication of *Science*'s stature. It is unfortunate that neither critics nor Kolata note the time frame for the treatments to which they refer. Patient recruitment and follow-up started in 1961. Data for the tolbutamide report were assembled over the time period from 1961 to 1969, before the initiation of nationwide campaigns in the 1970's to identify and treat systolic hypertension. The much-discussed patient with sickle cell anemia was treated in the time period from 1964 to 1969, before there was a specific warning against the use of phenformin under these conditions.

The data file for the UGDP contains more than 30 million characters of information. Since they have been collected and processed by humans, the files do contain some errors, but if anything, the data entry and coding process is a source of pride instead of disappointment. The use of a magnifying glass on a particular study, with no denominator for comparison, can lead to lasting misconceptions. All evidence points to superior, rather than substandard performance in this regard. Neither of the two indepen-

dent audits found any significant errors in the coding, data processing, or analyses of the study. Further, an FDA audit of a 15 percent sample of patients in the UGDP found no evidence of significant errors in converting raw data to published tables.

The general questions raised in the article regarding the amount of time and money to be devoted to clinical trials are important. Ultimately, the public, through their elected representatives, must decide what the answers are. There is no doubt that clinical trials are expensive, but so is the misuse and overprescription of drugs of questionable value. The cost of the trial ($8.5 million) is small compared to expenditures by consumers for oral hypoglycemic agents. The drop in consumption noted by Warner, Wolfe, and Rich (*3*) since publication of the UGDP results corresponds to a savings of more than $100,000,000 for consumers.

The main difficulty with the UGDP is not its design, execution, or analysis, but rather that it reached an unpopular conclusion. The unfortunate aspect of the controversy is that it has served as a distraction from the real implications of the study concerning the absence of efficacy of the treatments tested. No amount of criticism, no matter how vitriolic, can alter the findings of the UGDP or obscure the fact that no other study has refuted its conclusions. Opponents and proponents alike would do well to expend their energies on generating new information rather than rehashing the old.

THADDEUS E. PROUT*
School of Medicine,
Johns Hopkins University,
Baltimore, Maryland 21205
GENELL L. KNATTERUD*
CURTIS G. MEINERT*
School of Medicine,
University of Maryland,
Baltimore 21201

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2. ———, *Diabetes* **19** (Suppl. 2, part 2) (1970).
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* Member, University Group Diabetes Program Steering Committee.

. . . The UGDP controversy illustrates indeed how shameful it is if challenging scientific evidence is met with disbelief instead of evidence disproving or contradicting the challenge and if insinuations of scientific dishonesty are continued even after the data in question have

been vindicated and upheld by two independent juries of peers, that is, two independent audit committees.

The UGDP data, of course, are open to challenge, as are most all scientific data, but probably somewhat more so. The UGDP investigators have been well aware of this fact. Therein lies a story which goes to the core of the controversy. It is the story of the ethical conflict which is confronted in almost all research involving humans—the question of whether a significant trend toward a threat to health or life is a signal strong enough for termination of a clinical investigation, or whether it is permissible ethically to continue such an investigation until the evidence is indisputable. How great an individual sacrifice is ethically defendable in the search for advancement of the common welfare and the scientific truth? We came face to face with this question when we were confronted with evidence suggestive of a proportionally higher incidence of death due to cardiovascular complications in two of the five treatment groups—those treated with the oral agents. We decided on the first answer, but not before we had asked for advice from independent special consultants who reviewed the evidence, analyzed it with new and different methods, and assured us that the observed trend was significant and in all likelihood irreversible. Some investigators regretted that the necessity of termination would weaken the final evidence; they would have preferred to see the period of data collection extended. Nobody, however, doubted the significance of the risk. That, by the way, was the extent of the disagreement described by Angela Bowen; most certainly it had not the connotation which she ascribed to it and to which Kolata refers. In retrospect one may wonder how much of a greater risk the investigators should have accepted in order to satisfy not only the two peer committees which concurred with the findings but also the profession at large and the public, which remained unconvinced. . . .

One may ask, also, why Kolata concentrates so much on the recital of proved and unproved plots and subplots surrounding the UGDP, and why, at the same time, most of the important aspects of the UGDP story are overlooked or misrepresented. The accusations against Klimt are not new; his consultantship with the U.S. Vitamin Pharmaceutical Corporation was known and so was his FDA assignment during his sabbatical. Both actions caused great concern to the investigators and were considered imprudent and regrettable, but no grounds were found to assume that either jeopardized the integrity of the study. . . .

Kolata omits any reference to the fact that all UGDP publications have appeared in the refereed medical literature, while the critics of the UGDP, and particularly the members of the "Committee for the Care of the Diabetic" (CCD), used the pages of the privately owned and privately supported, nonrefereed *Medical Tribune* for their pronouncements. It should be widely known by now and should not have escaped the attention of your reporter that the *Medical Tribune* is not so ready to print corrections or refutations as it is to accept accusations and rumors. . . .

Kolata quotes many critics of the UGDP who misstate the purpose of the UGDP and ascribe to it conclusions and generalizations which are not correct. The purpose of the UGDP was decidedly *not* to investigate whether the oral antidiabetic agents were "safe and effective" means "of lowering blood sugar," nor were the conclusions "that the drugs are not efficacious and that they were probably toxic." The title of the program and the headings of all seven UGDP publications state that the study concerns "The effect of hypoglycemic agents on vascular complications in patients with maturity-onset diabetes." Clearly, not only the oral agents were involved, but also the other hypoglycemic modalities, insulin and diet; clearly also, the hypoglycemic potency of these agents was not under study, but their effect upon the vascular complications; and clearly, this effect was to be investigated in one special type of diabetes only, albeit the most common one. The conclusions of the UGDP were that, in the type of diabetes under study and with regard to the vascular complications of the disease, neither insulin nor the two hypoglycemic agents employed were more effective than diet alone (plus placebo); and that insofar as mortality from cardiovascular causes is concerned, the two oral agents were less effective than insulin or diet (plus placebo). There is no reference to toxicity. The investigators abstained intentionally from describing the nature of the cause or causes that were responsible for the increased proportional death rates. The design of the study did not permit any such investigations. It was hoped that this would be done by other, more qualified investigators. The UGDP investigators emphasized, however, in all their publications that their findings and conclusions applied only to the type of disease under study and to the agents employed in the study. Moreover, it was stated repeatedly that the findings re-

sulted from a study design which attempted to duplicate as closely as possible the management of the ambulatory diabetic patient prevailing when the program started. At that time, no means were available to achieve ideal, that is continuous, physiological blood sugar homeostasis in the ambulatory patient. Thus the UGDP results apply only to the less-than-optimal control attainable under the design of the program. In recent years much progress has been made to develop means by which a more nearly ideal control may become possible and can be placed into the hands of the practitioner. If it is found in the future that such ideal control has better effects than those observed in the UGDP, the investigators will gladly acclaim this progress and will be satisfied that the UGDP controversy has accelerated this step forward in the care of the diabetic. After all it is not only the CCD who cares!

MARTIN G. GOLDNER
1597 Edgewood Drive, Palo Alto, California 94303

Although I have admired Kolata's reporting in the past, her article on the UGDP is marred by incomplete and one-sided presentation of several key points. Among the many issues which call for comment, let me mention three.

Kolata formulates the controversy as a battle between those who "sharply attack" the findings of the UGDP on the one side, and those who "evangelically promoted" it on the other. She fails to point to the far larger group who share the view that the findings of the UGDP are not in themselves decisive, but that they raise a legitimate concern about the oral drugs tested. That concern cannot be resolved by further debate about the UGDP alone, but only by assessment of it along with other evidence, or by further clinical study. On these matters the review is silent.

Kolata describes the UGDP as "one of the first large-scale trials ever conducted" and says that "it served as a model for the large crop of clinical studies that followed it." These remarkable statements ignore the long history of clinical trials, both here and abroad. If a beginning date for "large-scale" clinical trials must be found, it would be at least 10 years before the start of the UGDP, when the Veterans Administration initiated its ongoing program of clinical trials, among which the trial demonstrating the effectiveness of streptomycin in treating certain types of pulmonary tuberculosis is perhaps preeminent. Nor should the contemporaneous British studies and the celebrated field trial of the Salk poliomyelitis vaccine in 1954 be overlooked. The UGDP is a model for later trials only in the sense that those who plan new trials strive to improve on those of the past. However, it is no more of a model than are those mentioned above and the host of additional trials conducted over the last 20 years.

Kolata quotes me as pointing to the unusually complete reporting of detail as a source of some of the criticism of the UGDP, and she goes on to infer from my remark that all or most clinical trials collect data of inferior quality. I am, no doubt, at fault for failing to emphasize to her that my remarks apply to *all* scientific experiments, and not just to clinical trials. When a great many variables are measured simultaneously in a comparative experiment, it is nearly certain that, as a matter of chance, some variables will appear to favor one group over another. Were it the general custom to publish experimental data in so much detail, the scope of criticism—both valid and misguided—would be virtually unlimited. If my comment is seen as a basis for such criticism, the target will have to be the whole of experimental science, not just clinical trials.

In sum, the issues surrounding almost any public policy decision are difficult and often controversial. There is room for strong differences of opinion in the present instance, and that should cause neither surprise nor alarm.

PAUL MEIER
Department of Statistics, University of Chicago, Chicago, Illinois 60637

Misplaced Nuclear Plant

Luther J. Carter's briefing "Nuclear reactors and eastern earthquakes" (News and Comment, 30 Mar., p. 1320) is accompanied by a map that, because of its inaccurate location of the James A. Fitzpatrick nuclear power plant, owned by the Power Authority of the State of New York (PASNY), may cause undue consternation to the citizens of western New York.

The map shows the PASNY reactor near Buffalo at the eastern end of Lake Erie, an area having historical and instrumentally recorded seismicity, whereas the reactor is actually situated near Oswego, at the eastern end of Lake Ontario, in a region of relative seismic quiescence.

ROBERT H. FAKUNDINY
Geological Survey, New York State Museum and Science Service, State Education Department, Albany 12234