Introduction
Proceedings of a Conference on Insulin Pump Therapy in Diabetes
Multicenter Study of Effect on Microvascular Disease

THE KROC COLLABORATIVE STUDY GROUP EDITORIAL COMMITTEE:
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To the individual investigator, participation in a multicenter trial usually involves long hours, hard work, and little recognition. The compensation obviously lies in the prospect of achievement by the collective of a worthwhile major objective that could not be tackled by its individual parts. Along the way there is the prospect of a new sort of interaction with fellow investigators. To the salt of criticism and competition is added the sugar of collaboration. In the case of the Kroc Collaborative Study, nine independent groups joined forces, held working meetings diverse in time and place, set and achieved scientific objectives, and for a time enjoyed the cameraderie of common purpose. It was appropriate that the most important of the series of meetings, a detailed examination of the results of our trial, was at the conference facility of the J and R Double Arch Ranch, one of the last of a succession of notable scientific meetings which marked the life of the Kroc Foundation. Surely there could be no better place to exercise both the psyche and the soma than this well-appointed complex in the beautiful and remote Santa Ynez Valley in California.

Conceived in 1979, the planning, execution, and analysis of the Kroc Study had been completed by early 1983. It was time to examine the results. Members of the Study Group were delighted with the generosity of Drs. R. L. Kroc, Walter Garey, and G. Donald Whedon of the Kroc Foundation, who made it possible for all the constituent groups to be represented.

It was fitting that the major examination of the results of the trial took place at the Kroc Foundation. In late 1979, after a meeting of the National Conference on Diabetes in Reston, Virginia, Dr. Harry Keen and others initiated a series of conversations that culminated in December 1979 in an application to the Kroc Foundation for grant support of a study entitled, "Metabolic Normalization and Microvascular Disease." In his introduction, Dr. Keen said, ". . . the generous support of the Kroc Foundation is sought to carry these centers through a first year of protocol planning, methodology development, 'end-point' evaluation and pilot infusions. As well as being a vital preparation for the definitive clinical trial, important new information is expected to emerge from this year of activity."

In the proposal, it was recognized that several of the techniques for assessment and treatment of diabetes and its complications, when combined appropriately, might be exploited to provide at last the answer to the long-standing question of the relationship of metabolic control to microangiopathy.

But were we indeed ready yet? Could we achieve and hold adequate glycemic improvement? Were our methods of outcome measurement sensitive enough, clinically significant enough? If we proposed to look at these questions in an organized way would we find backing enough? From this background, the trial now known as "The Kroc Collaborative Study" was formulated. Looking back, the comments of the referees are of interest: from one reviewer, ". . . the proposal sets some very ambitious and worthwhile goals, but is lacking in the methods of procedure . . . the study does not really compare continuous subcutaneous insulin infusion (CSII) with traditional therapy;" from another, ". . . there is no indication that the study can really be done. Five centers in four countries on both sides of the Atlantic are to be included;" and yet another, ". . . financing is requested for a project that is very open-ended;" and finally, ". . . the degree of control that can be obtained in a cross-section of the population should be of particular interest to NIH." These comments illustrate the intellectual and the practical concerns felt as much by the proposers as by the reviewers. There was concern with respect to the efficacy of separate methodologies, many still evolving in the individual centers; there was concern about communication problems, recruitment problems, and even ethical problems. Despite general recognition of the importance of the questions asked, could we induce enough support to see us through?

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Notwithstanding these concerns, the Kroc Foundation allowed itself to be persuaded by Dr. Harry Keen, now joined by Drs. Robert Sherwin, Phil Felig, John Dupre, Eva Kohner, Arthur Rubenstein, George Alberti, and Torsten Deckert. The timetable was ambitious. By the first organizational meeting in New Haven in April 1980, Dr. Keen's proposals had already been formulated into a very workable scheme, details of which were examined systematically by representatives from Guy's and Hammersmith Hospitals in London, United Kingdom; the Steno Memorial Hospital in Gentofte, Denmark; Yale University; University of Chicago; and the University of Western Ontario in Canada. Dr. Malcolm Champion emerged as the keeper of the protocol and was still adding the final touches to it as the study came to its conclusion. The planning of the study continued, with meetings in Aarhus, Denmark, and at the meeting of the American Diabetes Association in Washington, D.C., in June 1980. Dr. George Alberti agreed to contribute his resources at the University of Newcastle to the formation of a central laboratory. The Steno Hospital group decided to proceed independently using a similar protocol but have maintained contact throughout. To facilitate communications, the number of treatment centers was intentionally kept small, but with the Danes gone, the group at Hammersmith (under Dr. Eva Kohner) assumed responsibilities as a treatment center as well as a resource center for the assessment of fluorescein angiograms. It was at this time that the term "Oligomulticenter Trial" emerged, sometimes to be replaced by the term, "MC MC Trial," standing for Multicenter Trial of Metabolic Complications (although some inferred a relationship to McDonalds). A series of bulletins and newsletters from the secretary, Dr. Malcolm Champion, provided periodic updating and encouragement to the planners. In October 1980, the consortium was completed when the group at Mayo Clinic (under Dr. John Service) became the sixth treatment center. In the following month, approximately a year after the initiation of discussions, the first patients were randomized.

Continuing uncertainties as to the specification of the precise retinopathy requirement for entry were resolved at a meeting (again at Yale) in March 1981, and the group agreed to some adjustments to other eligibility criteria (see page 13). The last pair of patients entered the trial in November 1981 and the first treatment phase was completed in August 1982.

In retrospect, the overlap of the planning and recruitment phases was intrinsic to the nature of the trial, and had been predicted in the proposal on the grounds that organization should, within set limits, be responsive to initial experience with respect, for instance, to recruitment criteria and to analysis of outcome variables. The methodologies of data analysis and outline of policies for publication were initiated before the end of the treatment phase, with meetings of June 1982 in Toronto, and January 1983 at the O'Hare Airport in Chicago. It was at the latter meeting that Dr. Garey and others proposed the major presentation conference at the Kroc Foundation, which took place in March 1983. Subsequently, an approach was made to the Fundus Photograph Reading Center in the Department of Ophthalmology of the Medical School, University of Wisconsin, Madison, Wisconsin, for assistance in the assessment of the retinal photographs.

The members of the group attending the conference may be identified in the photograph and in the list of participants elsewhere in the proceedings. Guests included Dr. Robert Frank of the Kresge Eye Institute in Detroit, Michigan; Dr. Fred Ferris of the Office of Biometry and Epidemiology, National Institutes of Health, Bethesda, Maryland; Dr. Richard Goldsmith of Cathedral City, California; Dr. Paul Palmberg, Bascom-Palmer Eye Institute, University of Miami, Florida; Ms. Carolyn Siebert of the Division of Diabetes, Endocrinology and Metabolic Diseases, NIADDK, at the National Institutes of Health in Bethesda, Maryland; and Dr. John Lachin, the Biostatistics Center, George Washington University, Bethesda, Maryland.

The program was organized and co-chaired by Drs. Harry Keen, R. S. Sherwin, and M. C. Champion. The meeting took the form of morning and late afternoon sessions, mid-day being dedicated to rest and relaxation, no doubt reflecting the enlightened life-style of the American West. The initial session, presented in the four initial chapters of these proceedings, included consideration of the purposes of the study, its design, recruitment problems, characteristics of the study population, organization and application of the laboratory facilities, and an analysis of the levels of glycemic control achieved. Subsequent sessions dealt with the clinical consequences of pump treatment, as reported on pages 37–41 (the "Pump Life"), effects on serum lipids (pages 27–30), and the very important observation of the response of microalbuminuria to treatment (pages 69–73). A major concern of the study was the effect of improved diabetic control on retinopathy. These presentations are summarized on pages 42–49 (methodology), pages 50–55 (analysis of stereoscopic pair fundus photographs), pages 56–60 (results with the fluorescein angiograms), and pages 61–68 (correlation of metabolic variation with ophthalmologic outcome).

That afternoon the Steno Hospital group discussed their parallel studies, presenting their longer 2-yr experience, which they have generously included in these proceedings on pages 74–79.

In the final morning session, the group indulged in some introspection, aiming to refine and articulate its initial conclusions; in this, it enjoyed the advantage of the comments of several of the invited observer-discussants. The editors of these proceedings were fortunate in having, as a resource, a transcription of those discussions, carefully prepared by Mr. Tom Parker.

After its debut with a paper entitled, "Is a Multicenter Trial of Diabetic Control and Complications Feasible?", presented to the American Diabetes Association in June 1982,[1] the Kroc Collaborative Study Group has reported these results in a number of verbal presentations in the United States, Europe, and elsewhere at meetings of ophthalmologists and diabetologists. Citations to the abstracts of these presentations are provided below.[2-11] The first major report of our findings was published in August 1984.[12] Pursuing the publication policy agreed at the conference, an editorial committee was struck to prepare and edit these proceedings for submission as a supplement to DIABETES, to follow the appearance of the primary publication, and to provide the detailed documentation required for a more complete evaluation of the study. The committee, chaired by Dr. N. Wilson Rodger at the University of Western Ontario, was ably assisted by Ms. Catherine Solly and also received generous support from the Kroc Foundation.

In preparing these proceedings, we have preserved the individuality of each contribution, imposing editorial prerog-

atives with respect to economy, chapter organization, and terminology. This has necessarily meant reducing to a minimum repeated descriptions of the study protocol and, when possible, cross-referencing within the symposium proceedings rather than duplicating findings. Some of the papers describe aspects of the study which, while not primary targets in the study structure, are nonetheless of great importance and value to many concerned with clinical trials and with the improved care of diabetes (e.g., patient acceptance, adverse effects, and recruitment problems). All of the presentations were submitted to independent peer review and we express our gratitude to the reviewers whose comments (sometimes extensive) have been dealt with systematically.

There have been two conferences on the microangiopathy of diabetes in the last few years at the Double Arch Ranch, proceedings of which have been reported in supplements to DIABETES.[13,14] In these, the editors have presented analogies based on animal models, illustrating the variability of approach (and those who instigate them) to the solution of a common problem. Bearing in mind the multicenter, multidisciplinary, multinational approach which we felt to be necessary, and which the Kroc Study has shown to be possible, we choose to add the analogy of an orchestral ensemble. One might imagine conductors Keen and Sherwin, chalk in hand, directing a string ensemble of great capability and consummate skills but small in number. The product could be perhaps considered an overture to an opera yet to come,[15] the findings perhaps to confound those who considered formal clinical trials of the effects of diabetes control to be unnecessary.

For the group, we express gratitude to the Kroc Foundation and in particular, Dr. Robert Kroc, Dr. Walter Garey, and Dr. Donald Whedon for the hope they showed in their initial decision to provide funds for this unusually constituted trial, for their faith in providing continuing encouragement and support, and for their charity in taking us as guests into their home to tell the story.

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