Organization Section

NEW MEMBERS

The following were elected to the Professional Section as of October 1982:

Michael B. Ainslie, MD, Minneapolis, MN
Shoichi Akazawa, MD, Chicago, IL
Nahla Aris-Jilwan, MD, Montreal, Canada
Margaret A. Bergstrom, RN, Boise, ID
James D. Best, MD, Melbourne, Australia
William E. Brown, PhD, Libertyville, IL
Donna C. Carroll, BSN, Burlington, NC
Uday P. Devaskar, MD, St. Louis, MO
Michael P. Diamond, MD, Nashville, TN
Mary J. Essig, BSN, Columbus, OH
Eileen G. Ford, RD, Ardmore, PA
David A. Gapp, PhD, Clinton, NY
Howard D. Gilbert, MD, Minneapolis, MN
Mari K. Haddox, PhD, Houston, TX
Mitchell S. Hamburg, MD, Washington, DC
Edward S. Hanna, MD, Dudley, NC
Norman E. Hendrickson, PhD, Relands, CA
Bruce E. Henson, MD, Kansas City, MO
David A. Hindson, MD, Boise, ID
Lawrence J. Hirsch, MD, Dallas, TX
John C. Holland, MD, Kaneohe, HI
Unen D. Hsu, Phoenix, AZ
Lyman A. Kasselberg, MD, Memphis, TN
Thomas M. Kelly, MD, Salt Lake City, UT
Kathy C. Kirby, BS, Birmingham, AL
Cindy K. Kraus, BA, Wynnewood, PA
Richard A. Levy, MD, Philadelphia, PA
Eric S. Lichtenstein, MD, Greenwich, CT
Peter Mack, Hermosa Beach, CA
Robert K. Maddock, Jr., MD, Salt Lake City, UT
Bruce L. Maloff, PhD, Glenolden, PA
Edmund A. Miller, MD, West Point, MS
Francisco Muguercia, MD, Miami, FL
James H. Myers, MD, Lakewood, OH
Don H. Nelson, MD, Salt Lake City, UT
Margery M. Nettleton, MA, New London, CT
Philip R. Nicol, MBBS, Massillion, OH
Joseph C. Orlando, MD, Towson, MD
Robert E. Ratner, MD, Washington, DC
Marc S. Rendell, MD, Baltimore, MD
Barbara Rossi, BS, Fort Lauderdale, FL
James W. Sawyer, MD, Longview, TX
Kenneth N. Schikler, MD, Louisville, KY
Soon H. Shinn, MD, Seoul, Korea
Brent M. Snow, PhD, Stillwater, OK
Joseph Soufer, MD, Waterbury, CT
John B. Susa, PhD, Providence, RI
John T. Walsh, Houston, TX
Barry P. Wayler, MD, Brookline, MA
David E. Whitney, MD, San Bernardino, CA
Jane C. Williams, MSN, Rochester, NY
Reba K. Wright, PhD, Memphis, TN
W. Patrick Zeller, MD, Maywood, IL

ADA FEASIBILITY GRANT PROGRAM

Applications for Feasibility Grants from the American Diabetes Association are due *February 1, 1983* for funding beginning August 1, 1983. Applications for two years of support for amounts up to $25,000 per year will be considered. Funding for the second year will be provided only upon receipt of a report and progress. Grants are limited to institutions within the United States and U.S. possessions. These grants carry no commitment for overhead costs or tuition. The funds may *not* be used for training stipends, postdoctoral fellowships, professional salaries, or other nontechnical salaries. Otherwise, the funds are unencumbered other than that they are to be used in research activities related to diabetes mellitus for the project described, in the year of the award. The funds may be used for equipment and/or supplies and/or salary for technical assistance. Funds up to $1,000 may also be used for travel to diabetes-related scientific meetings.

The purpose of this program is to assist investigators who want to test the feasibility data upon which a subsequent grant application could be based and submitted to NIH or other funding agencies. The program is intended primarily for new investigators in the field of diabetes who are proposing projects which constitute a major departure from their ongoing research, or for established investigators in other fields who are proposing projects in which they will transfer their special expertise to diabetes-related research.

Descriptive outlines and application forms may be obtained from the Contracts and Grants office of your institution or from Hope Hodson, American Diabetes Association, Inc., Two Park Avenue, New York, New York 10016.

CLINICAL EXPERIENCE IN THE TEAM MANAGEMENT OF DIABETES MELLITUS

The Diabetes Education Center (a component of the St. Louis Park Medical Center Research Foundation), Minneapolis, Minnesota sponsors a comprehensive 5-day "Clinical Experience in the Team Management of Diabetes Mellitus." Health professionals participate in classes with patients and families, observing a model of consumer health education.

The dates of classweeks for the first half of 1983 are as follows: January 31, February 14 and 28, March 21 and 28, April 11 and 25, May 9 and 23, June 20 and 27, and July 11 (juvenile-centered week).

For further information, please contact Helen R. Bowlin, R.N., Health Professional Coordinator, Diabetes Education Center, 4959 Excelsior Boulevard, Minneapolis, Minnesota 55416. Tel: (612) 927-3393.

XIth INTERNATIONAL KARLSBURG SYMPOSIUM ON PROBLEMS OF DIABETES

The Eleventh International Karlsburg Symposium on Problems of Diabetes will be held September 19–21, 1983 at the Central Institute of Diabetes Research and Treatment "Gerhardt Katsch," Karlsburg, German Democratic Republic. Topics will include Etiopathogenesis of Diabetes and Advances in Insulin Therapy. For further information, please contact Dr. Uwe Fischer, Zentralinstitut für Diabetes, DDR-2201 Karlsburg, German Democratic Republic.

HEMOCHROMATOSIS RESEARCH FOUNDATION ESTABLISHED

The Hemochromatosis Research Foundation, Inc., was organized recently to promote the study of hereditary hemochromatosis, an autosomal recessive disease affecting about 2–3 per thousand individuals in Western countries studied. Details available from M. A. Krikker, M.D., P.O. Box 8569, Albany, New York 12208.

PROPOSED PROTOCOL FOR THE CLINICAL TRIAL TO ASSESS THE RELATIONSHIP BETWEEN METABOLIC CONTROL AND THE EARLY VASCULAR COMPLICATIONS OF INSULIN-DEPENDENT DIABETES

One of the critical clinical issues in diabetes mellitus concerns the relationship between metabolic control and the chronic complications of the disease. Debate on this issue has centered largely on two questions:

- Whether, or to what extent, the chronic complications of diabetes are related to the metabolic derangements which characterize insulin-dependent diabetes mellitus; and if so,
- What degree of metabolic control is neces-

sary to prevent the development or ameliorate the progression of such complications.

In its report to the Congress in 1975, the National Commission on Diabetes recommended that appropriate components of the National Institutes of Health (NIH) initiate and support a clinical study to assess the effect of treatment of insulin-dependent diabetes mellitus (IDDM) on the development of microvascular and macrovascular complications. This recommendation has been reaffirmed by the National Diabetes Advisory Board. Extensive discussions between the NIH and the diabetes community led to the development of a consensus that such a study is ethical, desirable, and feasible. Acting upon this consensus, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) has initiated a multicenter collaborative clinical study consisting of the following four phases:

Phase I — Planning (6–12 months)
Phase II — Feasibility Study (2 years)
Phase III— Full-scale Clinical Trial (7–10 years)
Phase IV — Data Analysis/Reporting (1 year).

Twenty-one Clinical Centers in the United States and Canada and a Coordinating Center were selected on the basis of scientific peer review for participation in the study. The investigators elected to identify this study as the Diabetes Control and Complications Trial (DCCT). Phase I (Planning) was initiated in March 1982 for the purpose of developing the Phase II study protocol.

The Phase II protocol describes a two-year, randomized, unmasked, controlled study to determine the feasibility of conducting a seven- to ten-year full-scale clinical trial (Phase III) to assess the relationship between metabolic control and the development or regression of early vascular complications in IDDM. Blood glucose will be used as the primary indicator of overall metabolic control, and diabetic retinopathy will be the primary endpoint because it is a sensitive indicator of disease progression and may be affected by blood glucose control. The objectives of the Phase II feasibility study will include:

- Determination of whether a clinically and statistically significant difference in the level of blood glucose control can be achieved between standard and experimental therapy groups as assessed by hemoglobin A_{1c} and blood glucose measurements.
- Determination of the relative efficacy, utility, patient acceptability, and safety of an experimental and a standard therapy in the management of IDDM.
- Determination of whether biochemical and pathologic characteristics of IDDM can be measured and documented with acceptable precision and accuracy.

If warranted by the results of this Phase II feasibility study, a seven- to ten-year full-scale trial will be undertaken. This full-scale trial would focus concurrently on two categories of IDDM subjects: those who have no evidence of background retinopathy (primary intervention group) and those who have minimal background retinopathy (secondary intervention group). Inclusion of a secondary intervention group has the potential for showing a beneficial effect of one of the treatments sooner than in a primary intervention group. However, a negative result from a secondary intervention group would not address the question posed in a primary intervention group. Thus, study of both groups would be undertaken simultaneously in Phase III.

At time of entry into Phase II, patients will be between age 13 and 40 years; have documented IDDM of 1–15 years' duration; have hemoglobin A_{1c} greater than 3 standard deviations above the mean of a sample of the nondiabetic population; have either no evidence, or a minimal degree, of background retinopathy; and have no serious coexisting disease. Patients without retinopathy must have a duration of IDDM of at least one year but no more than 5 years. Patients with minimal retinopathy must have a duration of IDDM of at least one year but no more than 15 years.

Investigators at each Clinical Center will determine through a preliminary history and physical examination and a series of standardized clinical, psychological, and biochemical determinations, whether a potential study patient is eligible for inclusion in the DCCT. Specific criteria of eligibility for, and exclusion from, entrance into the study have been developed. Patients who are found to be eligible for the study will undergo additional assessments including a standardized history and physical examination and a series of standardized clinical laboratory procedures before randomization into a treatment group. Among these will be hemoglobin A_{1c} determination, blood glucose profile, a standardized ophthalmologic examination including stereo fundus photography and fluorescein angiography, and standardized renal, neurologic, cardiovascular, psychological, and compliance/adherence assessments. Fully informed written consent will be obtained from each participant prior to randomization into treatment group.

A total of 252 patients will be studied in Phase II. Within each Clinical Center, a total of twelve patients will be assigned randomly either to the standard or the experimental therapy group. Two age strata will be employed: 13–17 years and 18–40 years, with a minimum of four and six patients, respectively, in each stratum in each Center.

Standard therapy will consist of not more than two injections of insulin daily; an individualized meal plan, providing for the total nutritional needs of the patient with reinforcement of the dietary program by the dietitian every six months; semiquantitative home urine tests for glucose three to four times per day; an educational program; and a standard schedule of clinic visits and monitoring procedures every three months. The aims of standard therapy include: maintenance of glycohemoglobin less than two standard deviations above the mean value prevailing in a sample of persons with IDDM;* absence of symptoms attributable to glycosuria or hyperglycemia; absence of ketonuria; maintenance of normal growth and development and ideal body weight; semiquantitative home urine tests negative for glucose approximately one-third of the time; and maintenance of general good health. Physicians will be expected to intervene if any of these aims are not being met, using dietary reinforcement or change of type and dose of insulin within the recommended limit of two injections per day and within the standard schedule of clinic visits and monitoring procedures. Self blood glucose monitoring will not be encouraged unless these aims are not being met or unless a patient requests it for reasons of greater convenience or acceptability. In the event that a patient in the standard group cannot be successfully managed by this intervention strategy, the physician may deviate from the standard regimen after obtaining permission from the Treatment Committee of the study. However, when the aims are being met by the standard therapy, institution of self blood glucose monitoring for the express purpose of lowering blood glucose will not be permitted.

Individuals in the experimental treatment group will receive intensive insulin therapy in one of two ways: by continuous subcutaneous infusion, employing a pump (CSII), or administered as subcutaneous injections of short-acting insulin before each meal coupled with one or two simultaneous injections of longer acting insulin (multiple daily injections, MDI). The choice of insulin delivery method shall rest with the DCCT physician and the individual patient. Either CSII or MDI may be tried first and the alternate method employed if treatment goals are not met. For purposes of data analysis, patients treated by CSII only, patients treated by MDI only, and patients treated by both CSII and MDI will constitute a single group whose outcome will be compared with those of the standard treatment group. The same principles of dietary management as outlined in the intervention strategy for the standard treatment group will be followed. Reinforcement of the dietary program will be carried out by the dietitian monthly for the first six months and every three months thereafter. Self blood glucose monitoring will be performed a minimum of four times a day, to include three preprandial and one bedtime sample. A 3:00 a.m. sample will be obtained once a week and repeated the next night if the value is less than 65 mg/dl. Initially, patients will be seen every week at the clinic until a stable treatment program is achieved and at least monthly thereafter. Telephone contact will be made daily for the first week and then weekly thereafter. A system for ready availability of professional staff will be devised by each Center. The aim in the experimental treatment group is to achieve and maintain as near normal glycemic control as possible in the absence of significant hypoglycemia. The goal for fasting and preprandial levels of blood glucose is 70–120 mg/dl; for 3:00 a.m. blood glucose, 65 mg/dl or above; and for 90–120-minute postprandial levels, less than 180 mg/dl. The goal will be to maintain the glycohemoglobin level within two standard deviations of the mean for a nondiabetic sample of persons.† Hypoglycemia will be carefully monitored and limited.

During the course of the study, participants will undergo a set of regularly scheduled procedures for patient follow-up and analysis of study endpoints. A standardized follow-up history and physical examination will be scheduled yearly for each patient. Glycohemoglobin, blood glucose profiles, and a standardized ophthalmologic examination including stereo fundus photography will be determined quarterly; standardized psychological and compliance/adherence assessments will be made annually. Additional visits may be scheduled as needed for clinical care of the patient.

Detailed procedures are specified for the management of diabetic hypoglycemia, ketoacidosis, and pregnancy. The protocol also describes procedures for managing deviations from assigned treatment, for transfers to inactive status, and for protocol changes. Major statistical methods to be employed in the analysis of the data are presented.

Mechanisms for assuring quality control and for monitoring the performance of all DCCT components on a regular basis have been established within the DCCT structure including programs for central laboratory quality control, local laboratory standardization and surveillance of the Clinical Centers and the Coordinating Center. Two groups are specified which are advisory to the NIADDK and are otherwise external to and independent of the DCCT: the Policy Advisory Group and the Data, Safety, and Quality Review Group.

The outcome of this limited feasibility study will determine whether and how the full-scale trial will be initiated.

A limited number of copies of the complete draft of the Phase II protocol are available upon receipt of a written request enclosing a pre-addressed mailing label. Requests will be honored on a first-come, first-serve basis and should be addressed to: Clinical Trial Coordinator, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIADDK, NIH, Westwood, Building, Room 607, Bethesda, Maryland 20205.

* This mean value, as determined from a questionnaire of participating centers, is 11.5% with a standard deviation of 2.0, using preincubated samples and a minicolumn technique. Using this method for reference, the upper action limit would be 15.5%.

† Procedures for calculation of these values will be analogous to those used for the standard treatment group (data are not yet available from the questionnaire survey).