**National Institute of Diabetes and Digestive and Kidney Diseases**
**Diabetes Mellitus Interagency Coordinating Committee**

# Opportunities for Diabetes Clinical Research

**Natcher Conference Center**
**National Institutes of Health Campus**
**Bethesda, Maryland**
**January 18–19, 2007**

***SUMMARY MINUTES***

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## WELCOME, INTRODUCTIONS, BACKGROUND AND GOALS OF THE MEETING

*Judith E. Fradkin, M.D., Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Bethesda, MD*

Dr. Fradkin welcomed participants and provided background information on the need for a meeting to discuss future clinical trials. The DMICC, the Federal government's lead entity for coordinating diabetes research, includes representatives from many other NIH Institutes as well as representatives from across the Department of Health and Human Services (DHHS) and other Federal agencies. Many past NIDDK-sponsored diabetes clinical trials have been collaborative efforts involving other NIH Institutes, the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA), for example. We expect future clinical trials will be collaborative efforts with many of these same agencies.

Both practical and societal considerations are relevant in considering opportunities for clinical trials in diabetes. For the practical, just as NIDDK began planning for the Diabetes Prevention Program (DPP) when the Diabetes Control and Complications Trial (DCCT) was coming to an end, it is prudent to begin planning for the next major clinical trial. Several NIDDK clinical trials will be ending around 2009. One example is the "HEALTHY" trial, a middle-school-based trial of physical activity and dietary intervention, which because of its design can not be continued as a followup study. In addition, NIDDK is continually asked by Congressional and NIH leadership to identify opportunities for diabetes research if funding was available.

In terms of societal considerations, the Nation faces a paradox with regard to diabetes care and treatment. Although new drugs and diagnostic tools that can predict the risk of type 1 (T1D) and type 2 diabetes (T2D) exist, individuals are still not receiving interventions that have been proven to reduce diabetes complications and the burden of diabetes in society is mounting.

This is an opportunity to identify key areas where a well-designed trial can make a difference in the lives of individuals. It is important to discuss not only new technologies such as sensors, but emerging technologies such as genomics that might lead to individual or personalized treatments.

## HOW FAR WE HAVE COME IN ANSWERING CRITICAL QUESTIONS IN DIABETES

*David Nathan, M.D., Professor of Medicine, Harvard Medical School, Boston, MA*

Dr. Nathan, Chair of the meeting, presented slides describing controlled clinical trials and the types of outcomes that may be investigated (slides 1-2). The "ontogeny" of multicenter clinical trials includes epidemiology to generate associations; physiology to generate mechanisms; and small-scale experiments, which should precede planning and initiation of multicenter trials (slide 3). These trials involve a large investment that must be justified by consistent and convincing preliminary data. As powerful as clinical trials are, they rarely answer all clinically relevant questions (slide 4). What they can do is provide a quantitative measure of the effects of interventions, including both benefits and risks. In addition to providing an estimate of risk to benefit ratio, they assess the tolerability of intervention and provide the substrate for economic analyses.

In a chronic degenerative disease such as diabetes, clinical trials can study interventions during pre-diabetes (primary prevention), during overt diabetes but before complications occur (secondary prevention), or during early complications before morbidity and mortality occur (tertiary prevention) (slide 5). Clinical trials have established the following (slides 6-7):

- Most cases of T2D can be prevented.
- Intensive therapy leading to lower glycemic exposure over time results in improved outcomes.
    - Results from T1D clinical trials have been persuasive.
    - Interventions are most effective when implemented early; this appears to apply to all complications of T1D, including microvascular, neuropathic, and cardiovascular complications.
- Progression to more advanced complications, including severe morbidity and mortality can be reduced. The complications include blindness (by laser surgery and vitrectomy); renal disease (by reducing blood pressure with ACE-I and ARB), dialysis, and transplantation; amputations (by foot care); and CVD (by glycemia control in T1D, blood pressure and lipid control, bypass surgery using stents, and aspirin).

Clinical trials, however, have limitations (slide 8). By virtue of their experimental nature (e.g., selected experimental cohorts, interventions applied in academic centers, non-standard resources applied), clinical trials usually establish principles of therapy. They do not compare all available therapeutic options, establish the most cost-effective interventions, or determine the translation potential of interventions in the community ("second translational block").

Dr. Nathan presented existing data from evidence-based reviews of clinical trials that show progress made in diabetes prevention and treatment (slide 9). A compilation of data from completed clinical trials shows impressive risk reductions can be achieved in retinopathy (26−76 percent), nephropathy (39−84 percent), neuropathy (25−60 percent), CVD (10−58 percent), and amputations (10−30 percent).

Despite the impressive knowledge base generated by clinical trials, Dr. Nathan suggested that the implementation of this knowledge base fell short of "delivering" the improved care to much of the vulnerable population. These data were illustrated in the format of the "Diabetes Report Card" (slides 10-18).

Dr. Nathan listed a series of questions that still need to be addressed if we are to improve health care delivery, expand and refine the considerable knowledge base already generated by clinical trials, and improve public health in the diabetic and pre-diabetic population, which amounts to almost one-third of the adult population. For diabetes management, these include the best means of achieving normoglycemia for either T1D or T2D; the role of intensive therapy in the elderly; and how to increase the level of control for diabetes care in inpatients (slide 19). For diabetes prevention, these include the best strategies for prevention; the difference between prevention and early intervention; and how to implement clinical trial results most effectively (and cost-effectively) in the community setting (slide 20).

The advantages that NIDDK is working within as it begins planning for the next phase of diabetes clinical trial(s), whether for management or prevention, include the following:

1. There are established surrogates for diabetes prevention and the amelioration of disease or preservation of long-term health (slide 21).
2. Therefore, it is not necessary to incorporate hard endpoints (e.g., mortality or severe morbidity) that require very large scale, long-term expensive trials, especially if the goal is not to establish a principle of therapy for the FDA. Endpoints could be factors such as levels of Hb1Ac, microalbuminuria, blood pressure, lipids, or other CVD endpoints.
3. Highly experienced clinical trial centers and investigators have been established in prior studies.
4. NIDDK now has extensive experience in conducting clinical trials.
5. Diabetes is a common disease with a large population at risk for diabetes development and complications. The high profile of the disease has major public health, economic, and policy implications (slide 22). The importance of studies is self-evident.
6. Patients with diabetes and advocates provide a very motivated constituency for addressing the topics above.

There are, however, limitations for NIDDK in designing and conducting future clinical trials (slide 23).

1. There is little experience in designing and conducting studies that examine translation;
2. Little interest by industry in performing (?helping to support) balanced comparison studies;
3. Although the clinical science community is convinced of the merits of experimental methods, designing valid, high yield experiments at the community level is potentially problematic.

Dr. Nathan introduced potential goals of the next major NIDDK trial(s) (slide 24).

- The trial(s) must have a positive impact on public health.
- The trial(s) must build on our current knowledge base, expand and refine our knowledge regarding currently effective interventions, and improve translation/application of current interventions.
- The trial(s) should aim to maximize benefits and target applications.
- The trial(s) should aim to minimize cost.
- The trial(s) should be designed as approximately a 5-year study with moderate funding available.

For today's meeting, the goal will be to develop clinical trial concepts that NIDDK can use to help create future clinical trials for management or prevention of diabetes, both for T1D and T2D. Dr. Nathan explained the process to be used to develop recommendations (slides 25-26).

- Unanswered questions in the management and prevention of T2D, management of T1D, and management of diabetes in the elderly will be presented.
- Participants will discuss and come to a general consensus on 4-6 potential projects in the areas of management and prevention.
- There will be a review of the compiled list of projects during the plenary session.
- A supplemental list of recommendations by meeting participants can be considered on any topics that fulfill the criteria.
- A poll will be conducted to gauge the relative enthusiasm for specific topics.
- The most "popular" potential project areas (probably 3-4) will be given to each of the two working groups (management and prevention) for further discussion in breakout sessions.
- During breakout group sessions, the projects will be discussed in detail by the working groups with the goal of preparing initial outline proposals for 2-3 studies from the Management Breakout Group and 2 from the Prevention Breakout Group for the NIDDK to consider.
- The breakout groups will reconvene in a plenary session for the studies to be presented and discussed.

**Discussion**

Dr. Tamborlane commented that it might be beneficial to have discussions with the insurance industry, because many of the issues discussed here will have relevance for them. Dr. Mangione cautioned that surrogates in the elderly should be considered carefully because there is little understanding of surrogates (e.g., Hb1Ac) in patients over 65 years of age. Dr. Haffner commented that there are drugs that may improve some drugs that surrogates, but do not reduce endpoints. He said that for an NIH-funded trial, the use of these surrogates should not be considered. Dr. Narayan asked about the slide on unanswered questions and whether the mention of glycemia obviated the need to study lipid reduction or other risk factors. Dr. Nathan responded that he only listed glycemia as an example and did not mean to eliminate other risk factors.

**TREATMENT AND PREVENTION OF TYPE 2 DIABETES: UNANSWERED QUESTIONS**

*Bernard Zinman, M.D.C.M., Professor of Medicine, University of Toronto, Toronto, Canada*

Dr. Zinman reviewed the pathophysiology of T2D and illustrated how an understanding of the pathophysiology could be used to help design clinical trials and in particular determine what metabolic and hormonal intermediates may be useful select to measure (slides 1-2). Also discussed were the natural progression of T2D and the issue of whether to intervene early or late, and how to intervene (slide 3). He commented that there are many studies using surrogates endpoints for macrovascular disease but few with clinical outcomes.

It is impractical to study T2D without also targeting obesity, which has a dramatic effect on increasing the risk of T2D (slide 4). Potential pathophysiologic targets for studying T2D and obesity include the alpha and beta cell, the liver, muscle, adipose tissue, the gastrointestinal tract, and the brain (slide 5). In addition, in any study of T2D must consider the effect of ethnicity, family history, phenotype, pharmacologic interventions, and lifestyle changes (slide 6). T2D is a heterogeneous disease that likely has a different underlying basis in different populations. Dr. Zinman commented that because of the interaction between environmental changes and genetic susceptibility, any clinical trial for T2D should consider incorporating high risk populations (e.g. American Indians, Hispanic, African American, and South Asians) (slide 7).

Dr. Zinman reviewed the stages of prevention (slide 8). In considering the types of trials to recommend, it is important to remember that lifestyle changes are very effective in primary prevention, but are difficult to implement clinically (slide 9). This also applies to pharmaceutical agents for primary prevention, especially in a community setting (slides 10-11). Remaining questions for primary prevention include the following (slide 12):

- What are the best predictors of progression to diabetes mellitus in "high risk individuals"?
- What is the impact of lifestyle combined with newer pharmacologic interventions?
- What are the benefits of low-dose combination therapies?
- What is the impact of diabetes prevention on clinical outcomes?
- How do we implement community-based primary prevention strategies?

It is still unclear which strategies for treating T2D (secondary prevention of complications) are optimal and in which order they should be used (slide 13). There are diabetes therapies that target the increased hepatic glucose output, insulin secretion, and insulin resistance, characteristic of T2D (slide 14). Remaining questions for secondary prevention include the following (slides 15-16):

- What are the most effective combination therapies to use?
- What is the impact of early aggressive therapy on diabetes progression?
- What is the most effective model to implement diabetes therapy in a community setting?
- What are the most effective therapies for adolescents and young adults with diabetes?
- What is the role of glycemic control in reducing morbidity in the elderly?
- What is known about the safety and efficacy of various glycemic strategies in the elderly?

For tertiary therapy of advanced diabetes complications, there is a lack of information on the most effective therapy for the established complications of T2D (slide 17). Remaining questions for tertiary therapy includes the following (slide 18):

- There is a need to define the optimal therapy for patients with diabetes and CVD.
- There is a need to define the optimal therapy for patients with diabetes and renal disease.

**Discussion**

Dr. Tamborlane commented that the FDA has difficulty approving drugs for prevention. He suggested one strategy may be to treat IGT as a disease and normalize glucose to overcome these concerns. Dr. Zinman pointed out that interventions for prevention will by necessity expose a much larger population to pharmacologic agents He agreed that treating IGT as a disease is important concept, but there need to be studies that document changes in clinical outcomes; this represents an important focus for future clinical trials.

In response to a question from Dr. Rubin on bariatric surgery, Dr. Zinman responded that there is no doubt that significant weight loss dramatically improves glycemic control, blood pressure, and lipids. If bariatric surgery could be demonstrated to be effective, economic feasible and safe it will be considered an important therapeutic option.

Dr. Narayan interjected that he agrees that it is reasonable to attack multiple pathways and simultaneously alter multiple risk factors. Such an approach could be studied in a community setting. He added that there is evidence that organs such as the heart can suffer microvascular disease. Dr. Zinman responded that a study of the polypill may be able to address this, although what you put in the polypill would be open to discussion. This relates to translation of complex therapies to the clinical setting.

Dr. Howard said she was concerned about conducting a long-term trial in young people–5 years will not be enough. Dr. Haffner added that several ethnic groups should be included, but that would make it even more difficult to have enough statistical power to test the effect in each such group. He suggests using a separate analysis for subpopulations but not designing the trial with high power for each group. Dr. Zinman suggested creating cohorts of subpopulations within a larger trial. Dr. Haffner added that once people get diabetes, the progression is the same regardless of the population group. Dr. Fradkin addressed the issue of Dr. Howard's concern about needs for a long-term trial. She said that although the trial may be designed for only 5 years, there is no problem with having intermediate endpoints that can power a 5-year trial– these would provide evidence to justify continuation for longer periods to conduct followup studies. Dr. Haffner asked for a clarification of the 5-year study period, and if this included followup. Dr. Fradkin responded that the NIDDK could consider a 5-year trial with very rapid start-up.

Ms. Brown said it is important to educate the community on how to interact with the physician. Dr. Zinman agreed and said that there is a need to have a trial that can clinically relevant address the unanswered questions that can be translated to a community setting.

Dr. Mangione commented that she agrees with the concept of head-to-head comparisons for therapies, but she would expand such a trial to look at interventions for controlling lipids rather than just glycemic control. She added that it would be hard to have an adequately powered trial for all subgroups at high risk for diabetes, but from a public health perspective it makes sense to enroll those from high risk groups.

Dr. Dagogo-Jack said that it is important to remember the role of guideline developments that have occurred in the past that impacted the scope of diseases. For example, in 1997, the recommended level of blood pressure for those with diabetes changed from 140 Hg/mm to 130 Hg/mm; this change meant that in one day, more than 2 million individuals became eligible for interventions who were not eligible the day before. This type of change in other measures could have a similar impact. Lowering the intervention level of IGT to 101, could help treat and prevent pre-diabetes. Dr. Nathan said everyone involved in diabetes research has discussed this issue, although there may not currently be enough data to make that change.

Dr. Nathan thanked participants for the discussion. He added that no one has recommended a potential trial studying remission of T2D. Some small studies have given encouraging results for this.

## TREATMENT OF TYPE 1 DIABETES: UNANSWERED QUESTIONS

*William V. Tamborlane, M.D., Professor and Chief, Department of Pediatrics, Yale University School of Medicine, New Haven, CT*

Dr. Tamborlane presented information on unanswered questions in T1D, focusing on better treatment of children and adolescents (slides 1-2). This group is the most difficult to treat and is at the highest risk for ultimate development of vascular and neuropathic complications of T1D, and there is an immediate need to do something for this group. He said he would not be presenting information on immune interventions to prevent T1D or preserve beta cell function, or islet transplantation because there already is significant ongoing research in these areas (slide 3). He reviewed the DCCT, which resulted in the recommendation that most children and adolescents should be treated with intensive therapy to lower HbA1c levels as close to normal as possible (slides 4-5). The subsequent Epidemiology of Diabetes Interventions and Complications Study (EDIC) added that treatment should begin as early as possible. Dr. Tamborlane added that results from DCCT and EDIC have not been adequately translated into practice HbA1c values remain far above the ADA target of $\leq$ 7.5 percent and severe hypoglycemic events occur all too frequently in this population (slides 6-7).

Dr. Tamborlane reviewed two other studies in children and adolescents with T1D, the Hvidore Study from Denmark and a Western Australia population-based study (slides 8-11). Results from these studies indicated that intervention did not reduce the levels of Hb1Ac in these populations. The Australian study showed a dramatic increase in hypoglycemic events.

Since DCCT, insulin analogs and insulin pumps have been developed (slide 12). Studies of insulin pumps have shown small reductions in Hb1Ac compared to insulin injections, and reduction of hypoglycemia insufficient to satisfy diabetologists (slides 13-14). Another

promising advance has been in continuous glucose monitoring (CGM) systems (slides 15-17). Studies have shown that they improve bolus dosing and overnight glucose control.

Dr. Tamborlane described the Diabetes Research in Children's Network (DirecNet), which is comprised of 5 research centers (slide 18). A completed pilot study on the Navigator pump system has indicated that the system is reasonably accurate and has improved glucose control (slides 19-20). Some results however, were not encouraging, including the percentage of patients with glucose values < 70 mg/d, and the number (50 percent) of patients who discontinued the use of the sensors during the 14-26 week continuation phase of the pilot study (slide 21). Another small trial, the open-loop Medtronic GuardControl Trial, sponsored by industry, had similar results. It illustrates the reality that no treatment for diabetes will ever be perfect until there is feed-back control of insulin delivery that is regulated by fluctuations in plasma glucose (slides 22-24).

Studies in adults using an external, closed-loop system indicated that exaggerated post-meal excursions and a tendency to late post-prandial hypoglycemia occurred because of lags in carbohydrate absorption, increases in interstitial glucose concentrations, and insulin absorption from subcutaneous sites (slides 25-29). In this study, there was excellent overnight control, but there were lingering concerns regarding sensor accuracy. Dr. Tamborlane provided some suggestions for addressing post-prandial hypoglycemia and sensor accuracy.

Dr. Tamborlane presented data from the Yale Full versus Hybrid Closed-Loop Study in adolescents with T1D (slides 30-32). Preliminary observations showed that short-term closed-loop control is feasible in children with T1D; night-time control is outstanding; and meal-related excursions are as good, or better, than traditional open-loop therapy, and improved with use of a manual priming bolus. He also described a study being started by the Juvenile Diabetes Research Foundation (JDRF) on open-loop use of CGM. The trial is a large-scale, relatively short-term (6-12 months) RCT to define the effects of CGM in continuous subcutaneous insulin infusion and multiple daily injection treatments on HbA1c levels, with behavioral and psychosocial outcomes, and the prevention of hypoglycemia (slide 33).

Unanswered questions that can be addressed by a new clinical trial include the following (slide 34):

- Will open-loop use of CGM reduce the frequency of hyper- and/or hypoglycemia in very young children with T1DM, and will there be a beneficial effect on brain development and cognitive function?
- Can open-loop use of CGM help define the independent role of glucose variability on vascular complications of T1D or T2D (oxidative stress hypothesis)?

In-patient studies using a closed-loop insulin delivery system should test improved insulin infusion algorithms; better control of meal-related glucose excursions; and gain a better understanding of the robustness of the system under more "real-life" conditions regarding exercise, variable timing of meals, and multiple days of use (slide 35). For out-patient studies, it is possible to investigate the closed-loop systems at night time only and to study 24-hour control (slide 36). Dr. Tamborlane suggested that industry has a role in addressing some of the issues

with closed-loop systems using CGM (slide 39). There is a need for smaller, more accurate monitors and systems.

**Discussion**

Dr. Nathan commented that the transition from smaller single-center studies to larger multi-center trials would establish what the smaller studies are beginning to show. Dr. Tamborlane responded that many of the earlier studies need to be redone with new technologies. Dr. Palmer said that a concern is how to design a clinical trial that will test what you want to test. People who participate in these trials are highly motivated and get training on the use of the technologies. This makes it difficult to determine how much progress is attributable to the pump or how much is due to an open-loop sensor; it would be easier to tell about a closed-loop sensor. Dr. Tamborlane responded that this is not always the case, although people who use pumps also tend to do better with CGM systems. They just may be more attuned to technology.

Dr. Buse commented on the JDRF study that is beginning soon. He said that there is a financial interest for industries to do the studies correctly so they have the necessary data to interest the insurance industry in the benefits of their products. In addition, details of how effective these devices are in real people in the community are very broad, and NIH should be careful in designing a clinical trial. Dr. Tamborlane said he disagreed that industry may not be able to produce results that are important for the research community.

## TREATING THE ELDERLY WITH DIABETES: UNANSWERED QUESTIONS

*Frederick Brancati, M.D., M.H.S., Professor, Department of Medicine, Johns Hopkins University, Baltimore, MD*

Dr. Brancati reviewed the 2001 Prevention and Treatment Work Group Report produced after the Diabetes and Aging Conference, which was co-sponsored by NIDDK, the National Institute on Aging (NIA), and the DMICC (slide 2). This report asked questions that were relevant then, and are relevant today in the elderly (age 65 years and older):

- When should treatment start?
- How aggressively to treat glycemia?
- What is the right endpoint: death, function, or QOL?
- Can polypharmacy risk be reduced?
- Can informatics improve care?
- How to better tailor treatment?
- Is lifestyle modification effective in the elderly?
- Is oral glucose tolerance test (OGTT) screening useful?

Dr. Brancati presented data showing the prevalence of diabetes in the elderly in the United States; the number of newly-diagnosed cases in the United States; the prevalence of diabetes in the elderly in Mexico; and prevalence among women in selected Asian countries (slides 3-6). Data on the distribution of elderly people with diabetes in the United States by age of diagnosis indicates that middle age is the most common time for onset, although significant numbers are

found in those over 65 years of age (slide 7). Data from Medicare show that diabetic complications are some of the most common reasons for hospitalizations in older people (slide 8). It also is true that patients suffering from diabetes and congestive heart failure have high rates of hospitalization (slide 9). There also is a strong association between diabetes and idiopathic cardiomyopathy (slide 10), and a significant excess of mortality associated with diabetes among Medicare recipients (slide 11).

Six geriatric syndromes have been identified in elderly patients with diabetes (slide 12): polypharmacy, depression, injurious falls, urinary incontinence, cognitive impairment, and neuropathic pain.

The 2007 ADA guidelines for standards of care for elderly individuals (55 years and older) with diabetes include the following (slide 13):

- There are no long-term studies in those older than 65 years of age.
- There is a higher risk for death, disability, and conditions of aging.
- Comorbidity, function, and life expectancy are variable at the level of the individual.
- Patients who are not frail and whose life expectancy is greater than 10 years should be treated as if they were younger.
- There should be a multi-disciplinary approach to improve glycemia.
- It may be more important to focus on blood pressure.
- If an individual is ill from diabetes or other diseases, restrict aggressive treatment.
- There is a greater risk for hypoglycemia, and the patient is less likely to enjoy the benefits of glycemic control.
- Consider the elevated adverse effect risk from all prescriptions taken by the elderly patient.

Dr. Brancati presented evidence showing that disease profiles differ among those with earlier and later onset of diabetes (slide 14). For example, patients whose disease is diagnosed in elder years have lower Hb1Ac levels, less insulin use, and a lower prevalence of diabetic complications in than those diagnosed in middle age. Among risk factors, uncontrolled high blood pressure is a major risk factor (slide 15). Recommendations from the American Geriatric Society were presented to show that many have not been developed using strong trial-based evidence (slides 16-20).

There are technical advantages and disadvantages inherent in conducting a potential NIDDK trial in the elderly. Advantages include the following (slide 21):

- The NIH has a track record for recruitment in the elderly population.
- The NIH has a track record for conducting trials for behavior change.
- There are more endpoints, there is more variety in endpoints, and endpoints occur sooner in the elderly.
- It is easier to track the elderly by Medicare benefits.
- Economic endpoints are more compelling,
- There is the possibility of developing a partnership with CMS.
- Few practices have been tested in RCTs in the elderly.

Technical disadvantages for conducting a trial in the elderly include the confounding and complex nature of comorbidity; a clean test of simple intervention is difficult to achieve; and there is a higher risk of adverse effects (slide 22).

**Discussion**

Dr. Narayan commented that the major outcome in the elderly would be improvement in quality of life and reduced morbidity. He asked if it would be appropriate to intervene in late adulthood to achieve compression of morbidity. Dr. Brancati said his general impression is to treat earlier, but economic and practical issues dictate that it may be better to treat those at high risk first.

Dr. Zinman commented that it will be critical to decide early whether to study the development of diabetes in the elderly with a management strategy, or to study people who have had diabetes for a long period but are now elderly. Dr. Haffner said this important issue that will have consequences for the type of trials to conduct. Dr. Buse added that there are large studies ongoing at this time in the elderly including ACCORD with 10,000 participants largely between 55 and 79 with a mean age of 62 at baseline. He asked if results from those studies should be completed before undergoing another trial. Dr. Brancati responded that he has looked at these trials and thinks that it will be important to see what they are measuring, what they are using as endpoints, and what exclusion criteria they used.

## SUMMARY PRESENTATION, PRIORITIZATION OF PROPOSED TRIALS USING THE NOMINATIVE PROCESS, AND INSTRUCTIONS TO THE BREAKOUT GROUPS

*Dr. Nathan*

Dr. Nathan provided background on the development of the lists of potential clinical trials and the modified nominative process.

In the past decade, clinical trials have provided significant new information for diabetes management and prevention. In the next few years, many of these ongoing trials will be completed or near completion, with only follow-up studies still to be conducted. Although these trials produced results that will improve the management and prevention of T1D and T2D, they also left many questions unanswered. In order to continue adding knowledge to the understanding of the etiology and progression of diabetes, NIDDK is beginning to review past research results and important questions still left unanswered to plan for the next decade of diabetes clinical trials. The number of advances in genomics, proteomics, and other "-omic" technologies and approaches allows a broad array of clinical studies to be designed that may result in answers to questions raised in previous clinical trials.

The DMICC in its role in coordinating the research activities of the NIH and other Federal agencies relating to diabetes and its complications also contributes to the adequacy and technical soundness of these activities by providing a forum for communication and exchange of information. In planning for future clinical trials for diabetes, the DMICC, in the summer of 2006, recruited 17 leading diabetes researchers to participate in a planning committee for a meeting of the DMICC. Dr. David Nathan chaired the planning committee. After months of

preliminary discussions on the best approach for designing future clinical trials, planning committee members were asked to submit their recommendation for a trial. DMICC members also were asked to make recommendations. To assist planning committee members, a list of ongoing and completed diabetes clinical trials, including design elements and results if available, was provided as background.

In December 2006, more than 20 suggestions were collected by NIDDK. These were reviewed by Dr. Nathan and NIDDK staff, combined together if suggestions were similar, and divided into "Management" and "Prevention" categories. The compiled suggestions were circulated among planning committee and DMICC members for their review before the January 18-19, 2007, meeting of the DMICC.

During the morning of January 18, DMICC members and planning committee members heard background presentations on what is known regarding T1D and T2D based on past clinical trials and basic research. After these presentations, Dr. Nathan reviewed the suggestions for 14 management trials and 7 prevention trials developed prior to the meeting. After discussions, a modified nominative process was used for a vote by DMICC and planning group members to identify those potential trials in each category that would be discussed in breakout sessions. After the vote was taken and counted, the following potential trials were listed for the breakout sessions (listed by rank from the modified nominal process).

## BREAKOUT SESSION: PREVENTION CLINICAL TRIALS

### Summary of discussion and final presentations

William Knowler led the discussion for the prevention group. He first identified the three prevention trials that received the most votes in the nominative process (by rank) as follows:

Option 1: Combined drugs to prevent diabetes plus lifestyle versus lifestyle alone.
Option 2: Pharmaceuticals plus lifestyle versus lifestyle alone, with cardiovascular endpoints
Option 3: Community-based interventions to achieve behavioral changes, with the goal of decreased weight and diabetes prevention

The group discussed the intent of the proposed trials and further refined there design. Participants pointed out that both DPP and DREAM have shown that it is possible to revert IGT to normal glycemia and not just prevent or delay diabetes with the important issue being can one prevent progression to IGT and DM for a prolonged period by achieving normal glycemia. Additional questions were: 1) could normalization of glucose change disease progression and improve insulin resistance and insulin secretory reserve? 2) Would lower levels of glycemia lead to better clinical outcomes?

There was some discussion about the value of a drug wash-out phase in Option 1 to determine if benefits persisted, but most felt that the drug would not work if not present.

There was considerable discussion as to whether Option 1 and Option 2 could be combined. A few individuals advocated for a large, simple trial for CVD prevention with a smaller sub-group

arguing for more in-depth diabetes and metabolic evaluations. Another suggestion was to do the intensive glucose trial first followed by the large simple trial for CV events. Ultimately the group was split about keeping them separate or combining them, but it was decided to present them to the larger group as two separate studies.

The group discussed what Option 1 or 2 added to what the DPP demonstrated and what DPPOS was now following. It was noted that DPP did not seek to normalize glucose. Treating IFG would allow for simpler and less costly screening which would allow for earlier treatment in a more easily translated manner plus there are agents with new mechanism of action available now.
The intervention that would be used in a large simple trial would need to be very different in intensity from DPP but would potentially be more translatable.

The discussion then turned to option 3, community-based interventions to achieve behavioral changes leading to decreased weight and reduced diabetes risk. Dr. Knowler admitted this was his proposal as he felt this was really an important issue that need more study. A community cluster design was proposed and significant care would need to be taken to identify comparable communities and minimize contamination. Small isolated towns or similar neighborhoods in dispersed parts of a large city were discussed as possibilities.

A community based participatory research approach was proposed. However the group was concerned that the relevant scientific expertise was not represented at the meeting. Also some worried that changed infrastructure takes too long and rather, communities with existing positive lifestyle infrastructure could be compared to communities without those changes. Others argued that working with local leaders could make positive infrastructure changes happen. Other types of changes will likely also need to be considered, and scientists working on this type of research should be included in the discussion. It was clear that researchers with expertise in this type of research would need to be involved in its design. Involving community leaders and scientist involved in this type of research is critical to provide input about reasonable study designs and interventions.

One participant indicated that the recent review of the literature on structural interventions, and the results were not impressive. Another participant stated that this was the most noble, but least feasible of the studies proposed. Many in the group felt that the behavioral-directed interventions are more feasible than conducting studies dependent on structural changes. Ultimately, the group decided that Option 3 could only be proposed as a pilot study due to the number of as yet unanswered questions.

Dr. Knowler then presented the group's discussion to the broader group attending Day 1.

**Top 3 Options**

| | IFG/IGT | |
|---|---|---|
| **Subjects** | **Option 1** | **Option 2** |
| Outcomes | Normal Glucose (short) | Vascular Disease (VD),<br>Diabetes Mellitus (DM) (long) |
| Treatments | LS<br>LS + TZD + metformin<br>LS + TZD + DPP4 | LS<br>LS + metformin<br>LS + DPP4<br>LS + metformin + DPP4 |
| Option # 3: Communities — Randomized Clinical Trial —> minimal<br>—> intervention | | |

**<u>Option 1</u>. Normalizing fasting glucose – based on the original "Combined drugs to prevent diabetes versus lifestyle changes"**

This trial was renamed by the breakout to include a more aggressive goal of returning patients to normal glucose tolerance. Interventions would include various to be determined lifestyle and pharmacologic strategies.
There are a number of short-term ways to normalize glucose and insulin secretion in people with diabetes or IGT. The objective of this trial focuses on the best way to have normalization be persistent over the long term. The study would have a physiologic focus, measuring insulin action, insulin secretion, and try to understand the mechanism leading to glucose normalization. This would be a relatively small and short-term study performed in a limited number of sites.

***Discussion***

The decision to keep Options 1 and 2 separate was based on each having different physiologic endpoints. Integration could occur by having the two options being a different phase of the same study.

**<u>Option 2</u>. Pharmaceuticals versus lifestyle changes, with cardiovascular endpoints.**

This trial is a study to prevent vascular disease in people with IFG or IGT. The immediate treatment goal is to prevent the increase in glycemia that is causing people to become diabetic. The main outcomes are cardiovascular, cerebrovascular, and renovascular complications of diabetes. Interventions would be patterned after the DPP, but with newer drugs added. Lifestyle would be an important part of this study.

The study would be larger and more long-term study than Option 1.

***Discussion***

Although sample sizes have not been calculated, it is likely that trials of vascular endpoints it would take thousands of people.

**<u>Option 3</u>. Community-based interventions to achieve behavioral changes, such as to decrease weight and diabetes.**

Such studies would randomize small communities rather than individuals, with minimal intervention and follow-up. The goal would be to facilitate physical activity and healthier diet in these communities. A pilot study may need to be designed before the main study, as well as collaboration with other NIH Institutes.

## BREAKOUT SESSION: MANAGEMENT OF DIABETES CLINICAL TRIALS
## Summary of Discussion and Final Presentation

### <u>Option 1</u>: Selecting optimum intervention strategies for T2D

This proposal reflected a combination of 3 proposed trials using elements of each, with the goal being to establish principles of therapy that would promote glycemic control and preserve beta cell function. The group decided to choose a population that was early in the disease course, such as new-onset patients, or even individuals with pre-diabetes. The group did not agree on a design but discussed several possibilities, including: 1) testing weight gaining therapy versus weight neutral/weight loss therapies; 2) a factorial design to test a series of drug combinations with metformin; and 3) testing aggressive early management versus staged therapies. The group discussed the value of extensive phenotypic characterization of patients to identify those patients who optimally benefit from specific therapies.

***Discussion***

This study would be a first step, which would lead to additional studies based on results of this trial. The group debated whether HbA1c would be the appropriate endpoint. Some individuals argued that it is not appropriate to compare multiple drug therapy to single drug therapy, as subjects on multiple drugs should do better than those on a single drug. Areas that must be considered are cost effectiveness and the effect of diabetes treatment on blood pressure and lipids.

### <u>Option 2</u>: Glycemic control and intensive therapy in the elderly.

The goal would be to determine whether aggressive metabolic control in elderly patients without microvascular disease is beneficial. The intervention might include using the new ADA treatment algorithm, but modifying the HbA1c action level (e.g., .7% v. > 8%). The group would have to be chosen to address the ethical concern of allowing patients to have HbA1c levels greater than 8 percent.

The group did not agree on endpoints, but felt that, for generalizability and statistical power, there would be a need to have very broad cardiovascular endpoints, in addition to glycemic control. Others argued that inclusion of outcomes related to cognition and functional status would be important.

***Discussion***

DPP results raise the question of whether metformin is effective in the elderly, although a specific study has not been conducted to answer the question.

**<u>Option 3</u>: Weight control: lifestyle versus bariatric surgery.**

An evolving body of clinical experience and some literature suggests that bariatric surgery is extremely powerful treatment for type 2 diabetes, though no long-term, randomized clinical trial has been conducted. Discussion centered on the use of bariatric surgery as a bold approach to the treatment of type 2 diabetes, because conventional medical therapy is often not successful. Nevertheless, there was concern that the surgical techniques are currently evolving (e.g., bypass versus "lap band"), and that it would be premature to conduct such a trial.

**<u>Option 4</u>: Development of a closed loop insulin pump for type 1 diabetes.**

This project was discussed by Dr. Tamborlane in his presentation, and did not engender much discussion.

***Discussion***

Some preliminary data suggests that closed loop systems may have an impact on T2D, although Dr. Tamborlane thought this was premature. More work may need to be conducted on sensors for T2D; this could be conducted in pilot studies.

**<u>Option 5</u>: Determining Appropriate Management and Goals for Everyday Control in non-ICU diabetic inpatients (DAMAGE CONTROL study).**

The group agreed that this could be a potentially important question but tabled the proposal because of methodological concerns (e.g., heterogeneity of patients; too short a period of time for effective intervention, ill patients may not be receptive to intervention).

Dr. Buse then presented the group's discussion to the broader group attending Day 1.

**FRIDAY JANUARY 19, 2007**

**INTRODUCTIONS AND WELCOME**
*Dr. Fradkin*

Dr. Fradkin explained the process that occurred in yesterday's meeting resulting in recommendations for the types of management and prevention clinical trials to consider in the future. She introduced speakers who would review the results of yesterday's meeting.

**SUMMARY AND DISCUSSION OF PREVENTION CLINICAL TRIALS**
*Dr. Nathan*

Dr. Nathan reviewed the modified nominating process used to winnow down proposed clinical trials submitted before yesterday's meeting, and presented the trials selected by the Prevention Breakout Group. He began by presenting slides from his introductory address at yesterday's meeting. These will not be summarized here other than discussions and comments that are new; please refer to pages 2-4 and the slide presentation referenced above for details regarding this presentation.

Dr. Nathan provided overall insight to the problem trials for the prevention of diabetes and complications from diabetes face. In effect, the kinds of surveillance and the types of interventions that are necessary to accomplish the goals of prevention are not being uniformly applied across the total population of people at risk for diabetes or with diabetes.

After his overview, Dr. Nathan presented the 3 recommended prevention clinical trials. These were described in detail above (see pages 12-15) and are summarized below (Dr. Knowler's slides 1-4).

**#1: <u>Normalizing fasting plasma glucose</u>**

- Patient population: Patients with above-normal IFG and/or IGT.
- Goal: Normalize glucose over time and influence physiologic factors.
- Design: This could be a relatively short term and small trial.

During the presentation of the first choice (Normalized fasting glucose), Dr. Brancati commented that the concept put forward for the trial on normalizing glycemia was meant to treat patients aggressively at the beginning of the trial and follow that with a wash-out period to see if glucose can remain normalized. He added that some people wanted a more physiologic-oriented study.

Dr. Fradkin asked about using physiologic outcomes. Dr. Brancati responded that the protocols are not fleshed out, but there must be serious consideration about the possible interventions and outcomes before the trial is designed. It would be difficult to characterize exactly how to conduct the trial without a lot more thought.

**#2: Prevent Vascular Disease**

- Patient population: Patients with above-normal IFG and/or IGT.
- Goal: Prevent an increase in glycemia.
- Interventions: Similar to DPP, with stepped intervention if participants develop diabetes.
- Design: This could be a large and long-term trial, randomized to usual care and aggressive treatment.

For the second trial (Pharmaceuticals versus lifestyle changes, with cardiovascular endpoints), after a brief presentation by Dr. Nathan, Dr. Brancati added that this study has physiologic endpoints but could be a larger trial than the previous trial. It would be possible to randomize to usual care or to aggressive treatment.

**#3: Community-based intervention trial**

- Patient population: Small communities.
- Intervention: Cluster randomization to minimal or higher levels of intervention.
- Goal: Facilitate increases in physical activity and adherence to a healthy diet.
- Outcomes: Individual outcomes could include body size and glycemia.
- This trial would need developmental and feasibility work.

The third selected trial (Community-based interventions to achieve behavioral changes, such as to decrease weight and diabetes) aroused a lot of discussion in the breakout group yesterday. Dr. Brancati commented that individual interventions are expensive; community interventions sometimes can give the same information, especially for lifestyle interventions. The outcomes could be weight, disease risk levels, and glycemic markers. Dr. Nathan described a worksite weight program at a hospital that reported a total loss of 16 tons in weight among all workers; this is truly impressive, but he doesn't know how this translates for individual workers.

Dr. Fradkin commented that it may be possible to use to use an R18 funding mechanism for this type of project on community lifestyle intervention. Dr. Brancati added that this could be done on a smaller scale, because it would be difficult to do this as an RCT. It might be possible to randomize by blood pressure (i.e., a medical model) or for tobacco control (i.e., tobacco control). As a collaboration, there could be State involvements, such as CDC uses for other public health approaches. In either case, there is a need to have translation as part of the trial.

Dr. Nathan commented that for glycemic levels in this study the ADA guidelines should be used. Dr. Buse interjected that clinicians have difficulty following guidelines, especially in patients who already are on multiple drugs, with a HbA1c or 7.2. He asked whether there any sense in adding another drug. He noted that some patients are taking as many as 20 drugs for diabetes and other conditions. Dr. Nathan expressed the conviction that physicians need to use common sense when following guidelines for prevention or treatment.

## SUMMARY AND DISCUSSION OF MANAGEMENT CLINICAL TRIALS

*John Buse, M.D., Ph.D., Chief and Professor, Division of Endocrinology, Department of Medicine, University of North Carolina, Chapel Hill, NC*

Dr. Buse presented background information on treatment algorithms for type 2 diabetes, based on the ADA recommendations (slides 1-2). In addition, he reviewed anti-hyperglycemic drugs used in the treatment of T2D and their impact on HbA1c reduction, hypoglycemia, weight change, and dosing (slide 3). After a discussion of treatment options, Dr. Buse presented the five proposed trials recommended by the Management Breakout Group (slides 4-8). General criteria are described for each of the selected clinical trials on pages 15-16 and will only be summarized in this section, including the discussion following the presentation.

### #1: Selecting optimum interventions strategies for type 2 diabetes

- Patient population: Early patients with newly-diagnosed T2D, perhaps in those who are managed by lifestyle recommendations (e.g., diet and exercise) or those on one-drug therapy with HbA1c less than 7.0 or 7.5. It also could be extended to patients who have not been diagnosed with T2D but have a IFG or IGT very close to the diabetic range.
- Interventions: Comparison of agents or techniques of administration could be varied, and could include different agents or comparisons of techniques of delivery of agents. The focus would be on beta-cell (e.g. ADA algorithm versus metformin ± TZD ± incretin based therapy); a study based on weight (e.g. ADA algorithm versus metformin ± incretin based therapy); or an investigation on the speed of initiation (e.g. triple therapy versus staged therapy).
- Design: The study should be no more complicated than a 2 x 2 factorial design.
- Endpoint: This would need a lot of thought, but HbA1C as an index of beta-cell preservation could be used; long-term extension of the study could look for harder endpoints.

### #2: Glycemic control in the elderly

- Primary Goal: Would less intense A1C management than current guideline care provide for better outcomes in the elderly?
- Patient population: Patients over the age of 65 years without microvascular complications; blood pressure <140/80 Hg/mm; and treated with statin and/or aspirin therapy. Patients would be selected so that a substantial number in the protocol are just on metformin therapy.
- Interventions: Use of the ADA algorithm, with the action level set at HbA1C at 8 percent versus 7 percent.
- Endpoints: Broad CV endpoints (e.g., MI, CVA, revascularization, CHD, or microvascular), as well as geriatric-focused endpoints (e.g., functional status, cognition, falls, and bone health).

**#3: Bariatric surgery versus maximal medical therapy**

- Patient population: Patients with diabetes and morbid obesity (possibly with a BMI of 35 or 40) meeting indications for bariatric surgery (e.g., psychological, behavior, cardiopulmonary, or failed medical therapy)
- Interventions: To include the best available surgical intervention (may not be known at this time) and maximal medical therapy (metabolic and weight-loss).
- Endpoint: Long-term health/functional status outcomes (e.g., CVD, functional status, cost, and quality of life).

**#4: Intervention in non-ICU hospitalized patients to improve long-term outcomes**

- Patient population: Hospitalized patients, excluding those in ICUs.
- Interventions: Usual care versus diabetes education, plus treatment intensification.
- Endpoint: Twelve month post-discharge HbA1C; economic costs; quality of life; and self-efficacy.

**#5: Continuous glucose sensors in type 1 diabetes**

This was added because there was a need to have a trial in T1D.

- Overarching goal: Establish the utility of sensor-augmented care and closed-loop systems on intermediate term outcomes.
- This could actually be a series of studies.

**Discussion**

Dr. Fradkin asked if there was a misinterpretation on what was listed for bariatric surgery. Dr. Buse indicated that it should have been listed as providing maximal medical therapy for all patients.

Dr. Penn commented that she is concerned about the lack of a study on neuropathies, which contribute to amputations. Dr. Buse said that a study on neuropathy was proposed but not selected. Dr. Nathan added that there are clinical implications, especially in minority patients. The problem for having this in a clinical study is that it is difficult to identify a group that is so far advanced that a lot of events would occur. Everyone recognized that this is an area of concern in communities. Dr. Buse indicated that the number of below-the-knee amputations has gone down in the past decade. This makes it difficult to find enough patients for a large study.

**UPDATE ON DMICC INITIATIVES**
*Dr. Fradkin*

Dr. Fradkin thanked Dr. Nathan for chairing the meeting and provided updates on current DMICC initiatives.

***NIH Reauthorization:*** The 2006 DMICC Annual Report will be completed this year, but may not be required for 2007. Dr. Fradkin said there may be a different type of report next year.

***Type 1 Diabetes Strategic Plan:*** The report has been completed and is now posted on the NIDDK website at http://www2.niddk.nih.gov/AboutNIDDK/ResearchAndPlanning/Type1Diabetes/. Dr. Fradkin thanked DMICC members for their help in producing and marketing the report. She thanked Dr. Mary Hanlon, NIDDK, for her guidance in producing the Strategic Plan, as well as her efforts to produce a Congressional report in January on the use of T1D special funds.

Dr. Fradkin said that a Program Announcement is being developed by Dr. Sanford Garfield, DMICC Executive Secretary, and Dr. Mark Chavez, National Institute of Mental Health, after the September 2006 meeting of the DMICC, which focused on psychoactive drugs and T2D.

**NEW BUSINESS**
*Dr. Fradkin*

Dr. Fradkin presented plans for upcoming DMICC meetings. The next meeting will be to review efforts to improve the health of American Indians. This will include hearing from representatives from the Diabetes Education for Tribal Schools (DETS) program, on which Dr. Garfield, CDC, and the Indian Health Service have been collaborating. Dr. Fradkin asked if other DMICC members have information that may be applicable to the program, or any other topic for the DMICC, to let her know.

Dr. Martha Hare said that she would be interested in hearing from community-based programs. Dr. Fradkin responded that NIDDK has been discussing the possibility of a meeting to hear from these programs, and it may be possible as the first of the R18 researchers have completed their projects. She said there is a need to bring together researchers from different venues—employers, State health officials, schools, or worksites—to see if there are opportunities for partnerships.

Dr. Fradkin thanked participants for attending and adding their voice to these important topics. The meeting adjourned at 10:30 a.m.