Diabetes Mellitus Interagency Coordinating Committee (DMICC)
The Science of Translation Research: Outcomes and Opportunities

September 27, 2002

Summary Minutes

Dr. Sanford Garfield, Executive Secretary of DMICC, opened the meeting and announced that Dr. Saul Malozowski, Senior Advisor for Clinical Trials and Diabetes Translation, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) would become the new Executive Secretary at the next DMICC meeting. Dr. Allen Spiegel, NIDDK Director, welcomed the attendees and stated "NIDDK's mission is to conduct and support research on diseases such as diabetes in order to increase knowledge to improve the public's health. NIDDK's goals will not be completely achieved until the knowledge gained from the research it supports is translated and fully applied."

Dr. Spiegel pointed out that understanding translation can sometimes be confusing because it is made up of two blocks. The first block is "from bench to bedside," from laboratory research to impacting on the patient's care. The focus of this meeting was the second translational block, the *science* of translation research that goes from scientific understanding to adoption and community practice. He emphasized that there is no sharp demarcation in the NIH mission; rather it is a continuum, a critical aspect of which is the partnership with academic partners and agencies of the U.S. Department of Health and Human Services (DHHS), many of whose members were represented in the audience. Dr. Spiegel said that the role of DMICC is to ensure that the entire continuum is realized from the most basic NIH-supported research out to the distal levels of clinical care, quality of care, and application. This meeting celebrates the 25th anniversary of the Diabetes Research and Training Centers (DRTCs) program and the initiation of the translation activities mandated to be a part of these DRTCs.

Dr. Spiegel also announced that Dr. Judith Fradkin, Director of NIDDK's Division of Diabetes, Epidemiology, and Metabolism, is the recipient of the 2003 American Medical Association's Nathan Davis Award for Career, Executive Branch, Public Service, a Government-wide award that recognizes her role as co-chairperson of the National Diabetes Education Program (NDEP) and in the framing of a trans-NIH strategic plan for diabetes research, and for her efforts, along with that of other NIDDK program staff, with the 1999 congressionally mandated Diabetes Research Working Group (DRWG) for research planning in type 1 and type 2 diabetes. DMICC participants received copies of a draft Executive Summary of the updated DRWG report and a summary of the May 16, 2002, meeting of external advisors on the special statutory funding program for type 1 diabetes research.

Morning Presentations and Discussions

National Diabetes Mellitus Research and Education Act, Diabetes Research and Training Centers, and Diabetes Translation— The First 25 Years

Dr. Roland "Red" Hiss, Director of Prevention and Control Division of the Michigan DRTC, University of Michigan Medical School, Ann Arbor, presented an historical overview of the DRTCs and their role in translation research, beginning with the National Diabetes Mellitus Research and Education Act of 1974 (Public Law 93-354, July 23, 1974). This far-reaching and informed act enacted by the 93rd Congress resulted from a 1970's national groundswell that was beginning to recognize diabetes as a serious disease, as had happened previously with hypertension. The act established the regional DRTCs and recommended establishment of a National Commission on Diabetes to develop a long-range plan to combat diabetes. The Act also established the DMICC. In December 1975, the Commission, chaired by Dr. Oscar Crofford, submitted a four-part report consisting of nine volumes. The first volume was the mandated long-range plan, updated in 1976. The plan was intended to expand and coordinate national research on diabetes; advance the education of patients, health professionals, and the general public; and disseminate updated information.

The NIH agencies impacted by the report included the National Institute of Arthritis, Metabolism, and Digestive Disorders (NIAMDD, now NIDDK); the National Eye Institute (NEI); the National Institute of Neurological, and Communicative Disorders and Stroke; the National Institute of Dental Research; the National Institute of Child Health and Human Development; the National Heart and Lung Institute (now the National Heart, Lung, and Blood Institute (NHLBI)); and the National Institute of Mental Health (NIMH). Inclusion of NIMH suggested that research be conducted on the behavioral aspects of diabetes. Also included was the Center for Disease Control (now CDC, the Centers for Disease Control and Prevention); the Veterans Administration; and the Bureaus of Indian Affairs, Quality Assurance, and Community Health Services. The report recommended the creation of a National Diabetes Data Group, the National Diabetes Information and Education Clearinghouse, and the CDC Diabetes Control Programs in each of the States' departments of health.The first Request for Applications (RFA) for a DRTC was issued in June 1976 by NIAMDD. The RFA stated two principal functions—research and translation. It stated that a key function "will be to translate, rapidly and effectively, appropriate results of research into health care so that particular activities can become standard practice, not only in the community in which it is demonstrated, but in other communities as well." Dr. Hiss said that the statement sounds clear, but it was not. For some 10 years, "what is translation" was argued about at site visits and annual meetings. He pointed out that we have come a long way from that early concept.

Dr. Hiss mentioned a number of barriers to adoption of new science and to the development of consensus regarding the science's message in its adaptation to clinical care and practice. Among these barriers are the asymptomatic nature of diabetes; attitudes, beliefs, and misconceptions on the part of clinicians and patients; the health care system's emphasis on acute, not chronic illness, and health care economics; the influence of obesity; and the difficulties of instituting and maintaining behavior change in adults. He stressed the importance of consensus in delivering a clear message and the resistance created by mixed messages from different groups. Following barrier identification, the big challenge is barrier removal or circumvention. Incorporation of feedback from clinicians and patients is also necessary.

Asked to provide an example of a good piece of science that has become bogged down in barriers, Dr. Hiss selected NEI's 1981 diabetes retinopathy study that showed that photocoagulation of periferative and pre-periferative retinopathy saved sight. Unfortunately, the

report was publicized primarily in opthalmologic literature and meetingsOther health care professionals did not learn about it for about 3 years. Now a strong effort has been made to have an annual or biannual examination of a dilated pupil included in standard diabetes care. However, in Michigan, which Dr. Hiss believes is typical of the rest of the United States,40 percent of patients with diabetes have never had this examination—21 years after the science was reported.

An example of what the DRTCs' translation components have accomplished collaboratively is the 1993 publication "Metabolic Control Matters," a nationwide translation analysis and recommendations based on the Diabetes Control and Complications Trial (DCCT). The report included recommendations for diabetes care from the DCCT, strategies and models for translation, and implications of the DCCT findings on the structure of the health care system. It also covered professional practice and training, implications of the DCCT for patient education and for social systems, and financing issues of intensified management of diabetes. In 1995, the six DRTCs provided an updated report on the recommendations.

Based on the DRTCs' 25 years of experience, Dr. Hiss offered a definition of translation. He echoed Dr. Speigel's comments that translation is not a one-time event; it is a sequence of many events divided into two distinct phases. Phase I is the development (from the bench) and application (to the bedside) of new biomedical science to patient care. This is the clinical research or bench-to-bedside phase, the "R" in DRTC. Phase II is the application of new clinical science through clinical trials, the product of phase I, to community care. This second phase—the "T" role of the DRTC—involves the identification and overcoming of barriers to widespread adoption of the improved practices. Dr. Hiss stressed that these phases are different, essential, and sequential and performed differently by different people, who *must* remain in touch with each other to resolve their problems if we are to realize the social value of new biomedical science. Phase I benefits several hundreds of patients. Phase II benefits millions of patients.

Discussion. In the discussion following his presentation, Dr. Hiss described how obesity serves as a barrier to better diabetes care because of the perception that the patient's weight is his/her own fault. Obese persons are seen as failures by their families and society in general, and thus obese patients with diabetes may receive less attention in the health care system and also may avoid the health care system because of their fear of being blamed or stigmatized.

It was suggested that translation and translation research are not identical. In addition to the phase I research, research can be done in phase II by studying how to foster the application of phase I research. Dr. Hiss agreed that there is an enormous amount of translation research that needs to be done in phase II.

Experimental Design Elements of Translation

Dr. Lawrence Green, Director of the Office of Extramural Prevention Research, CDC, gave two statements from a recent NCI conference on dissemination research to frame his presentation. The first quotation was "An ounce of prevention takes a ton of office system change" (Thomas Kottke). This relates to the need to bring research methods to bear that allow for working with complex systems. The second was about the culture of the research community itself. One of the cultural aspects of researchers is their conditioned concern about having their best ideas stolen.

The second quotation was "Don't worry about people stealing your ideas. If you have a really good idea, you will have to cram it down their throats."

Because of the increased potential to address diabetes at the primary level, as well the secondary and tertiary levels, Dr. Green said he planned to go beyond the bedside in his presentation to examine the community population-based considerations that influence reaching the millions, both patients and those not yet patients, who deserve the health care system's attention. First, he presented five ideal elements of experimental design as aspired to by researchers in randomized clinical/controlled trials (RCTs). He considered only one element—one or more posttests to measure effects after the experimental intervention—as essential. The others are ways to control threats to internal and external validity. He feels that preoccupation with maximizing internal validity—threats to the validity of the conclusions about the causal effect of the intervention—has neglected external validation. Thus a lot of research is less than convincing to practitioners because it does not relate to their situation.

Dr. Green said he did not come "to bury experimental design, but to praise it." There are problems in applying "best practices" from RCTs because of the inability to achieve their controls in translation to the community. Better use needs to be made of other evidence beyond the clinical setting where there is such strict control. Other problems include generalizing from one population, place, or circumstances to another. Although there is a high degree of generalizability across the human species, because of its relative homogeneity, physiologically and pathologically. In social groups, there is heterogeneity. This makes generalization from one study setting or population to others increasingly difficult as one moves up the biopsychosocial spectrum.

Practitioners face three problems (identified by Brick Lancaster) in translation that cause them to question the high standards suggested by "best practices" based on research conducted elsewhere:

- **Accessibility gap**: Do I have the same resources as the experimenters had?
- **Credibility gap**: How different is their practice situation (i.e., university or large hospital setting with grant money) from mine?
- **Expectations gap**: Do I need to strive for such lofty goals in my practice?

Dr. Green noted that CDC has named 10 areas of great public health achievements in the 20th century. In the last third of the century, the smoking problem accumulated in the first two-thirds of the century was reduced by 50 percent. Similar public health success was achieved in stroke and cardiovascular disease deaths and in automobile crash-related deaths, especially alcohol-related crashes. Dr. Green described the various economic, social, regulatory, and historical events affecting the changes related to cigarette consumption. Strong influences on the decline in smoking included the Surgeon General's Reports on the hazards of smoking, the nonsmokers' rights movements, the ban on broadcast advertising and Federal tax increases, the development of over-the-counter cessation aids, and the master tobacco settlement.

Lessons learned from the smoking cessation achievement include:

- **Surveillance** data systems are needed to track population trends, to establish baseline and trend lines, put an issue on the public policy agenda, show change, and compare progress. The Behavioral Risk Factor Survey System maps showing the growth in the prevalence of obesity from 1985 to 1999 are an excellent example. They clearly indicate the growing epidemic in obesity over time and across jurisdictions. Dr. Green said we are more fortunate than smaller countries to have a 50-State laboratory with variations in policies and programs to compare treatment across jurisdictions and populations.
- **Comprehensive** programs using a combination of methods are more effective than individual methods; the more components, the greater the effectiveness and the better the coverage. In tobacco control programs, only tax increases could stand alone as an essential component. Successful components included community, statewide, chronic disease, cessation, and school programs; enforcement; surveillance and evaluation; counter-marketing; and administration and management. Dr. Green suggested that these same components apply to diabetes.
- The **ecological imperative** means that a problem must be addressed at all levels—individual, organizational, institutional, community, State and regional, national and international—and these levels must be mutually supportive and complementary.
- There is a level of **threshold spending** below which there is little effect. A critical mass of personal exposure is needed to influence individuals and a critical mass of population exposure is needed to effect community response. To reach the less motivated, a critical distribution of exposure is needed. Dr. Green said the RE-AIM model demonstrates this well. Reach is a critical component of the effect of a program. In smoking, anything below $2 per capita achieved little effect. Local ordinances are another critical component.
- The **environmental imperative** addresses the opportunities, cues, and choices provided by the environment, the social reinforcement of positive behaviors and punishment of negative ones, and legal penalties and financial incentives. These create new social norms. Dr. Green reminded the group of how in the past the current room would have been heavy with smoke.
- The **educational imperative** includes public awareness of the risks and benefits, interest in lifestyle options, understanding of behavioral steps, attitudes toward options and steps, outrage at conditions putting them at risk, and personal and political actions. An informed electorate is necessary to get changes in public policy and legislation.
- The **evidence-based imperative** is the need to bridge best practices from research to application in practice. This means reaching the underserved, special populations, the less affluent, the less educated, and the community-centered practitioners. Most research occurs amongst highly motivated persons and off the shelf protocols do not translate well to other populations. Practitioners and health care systems need the tools of research to do their own immediate evaluation.

According to Dr. Green, viable alternatives to the strict RCT-based interpretations, the gold standard that has driven most "best practices" manuals, are beginning to gain increased credibility with practitioners. While the RCTs provide a valuable foundation, there is no single best practice that is appropriate for all patients and practitioners, or even for some of them all the time, as they go beyond the bedside. Behavior is influenced by a combination of forces—predisposition, enabling, and reinforcement. Paying attention to all three is necessary for sustained change, even with highly motivated persons, who, without support and reinforcement, can become frustrated and rationalize away the credibility of the source of the motivation. Different sources of evidence

need to build on the initial structure and provide a menu of appropriate possibilities for different patients and populations.

Dr. Green recommended that the intervention-based research and planning habit be broken. This habit has grown out of the pharmaceutical model of testing specific drugs as interventions by assessing the response, increasing the dose to get a response, and evaluating the response. This tends to increase resource costs without necessarily ensuring they are the appropriate resources for the population being studied. The alternative is a population-based diagnostic planning approach in which the needs and capacities of the population are assessed and a program is designed and implemented based on these and a set of priorities and objectives. The program is then evaluated through a short-loop feedback process to reassess the assumptions, and the program is redesigned. The short-loop cycle becomes a management tool to improve performance in particular settings with specific populations. This approach uses evidence from the community or population; from behavioral, economic, and social research in addition to epidemiological and medical research to help assess causes of behavior and social change; from experimental studies and research and development; and from evaluations in other settings similar to the intended study.

Discussion. Dr. Hiss strongly supported Dr. Green's statement that translational efforts must be very specific to the target audience, the setting, and the situation. As an example, he pointed out that a translational effort with a 35-year-old primary care physician 4 years out of school working in a large hospital that has an active internal medicine residency with a large number of subspecialists in a large community is very different than that effort with a 58-year-old general internist who has been out of school for 25 years working basically alone in a small community hospital with few subspecialists and no in-house educational program.

Asked how the approach would be different, Dr. Green responded that in the hospital setting with an in-house educational program, one works with the house officer and builds into the training the changes in care with this captive audience and this works back through the attendees.

In response to a question as to what approach should be used in what situation to direct the translation, Dr. Leonard Pogach, Veterans Administration (VA), commented that it is the system of care that drives the approach. In the VA system there are a variety of types of hospitals, rural and academic, that are guided by a system of care with integrated electronic medical records, nationally promulgated evidence-based guidelines, quality improvement efforts, and performance measures that drive the system.

Dr. Spiegel pointed out that the obesity issue cannot be viewed solely from the provider perspective, because there are important environmental influences. Although there is arguably a difference between smoking and eating as addictive or non-addictive behaviors, one does have to eat to live. He recommended *Food Politics*, recently published by Dr. Marion Nestle, head of the nutrition department at New York University, that presents a table showing that many of the major tobacco companies have now taken over many of the large food production/processing companies and food industry agri-business. This action has relevance in advertising to children and to underprivileged minority groups. However, rather than smoking cessation as an example for translation research for diabetes, Dr. Spiegel prefers the example of the decline in cardiovascular mortality. He asked if this decline indicated a public health success in reducing

cardiovascular disease or are individuals developing congestive heart failure in larger numbers or other outcomes that are more lingering. Dr. Spiegel posed two related questions. Does the decline reflect control of blood pressure, control of cholesterol, and changes in diet and exercise? If so, then why do we have this increased obesity epidemic over the past two decades?

Dr. Green responded that tobacco cessation was the effort he knew best and it had contributed to the cardiovascular success, but obviously had run in the opposite direction from the obesity problem. The cardiovascular effort was much more complicated.

Dr. Denise Simons-Morton, NHLBI, answered that it was true that along with decline in mortality, there have been dramatic increases in heart failure. Over the years, improvements in quality of care has resulted in improvements in all the risk factors, except obesity, in spite of improvements in diet, in smoking, and some in activity and treatment improvements in blood pressure and cholesterol. There has been a positive impact on cardiovascular disease (CVD) mortality, but there is still a problem in CVD with obesity and the burgeoning diabetes epidemic, an important risk factor for CVD. There remains the relevant issue of competing risks: if people live longer, then what will they develop.

Dr. Garfield mentioned that the initial presentations and discussions had described barriers to translation. The later discussions would address how to revise translation research to combat those barriers.

Translation Research at the University of Chicago DRTC

Dr. Marshall Chin, Associate Professor of Medicine, University of Chicago, discussed the importance of collaborative community-academic-government partnerships in diabetes translational research, especially to improve care in vulnerable or hard-to-reach populations. He offered the Public Health Service's Community Health Centers (CHCs) and the MidWest Clinicians' Network (MWCN) of CHCs as examples and as a basis for later discussion on what types of translation research might be funded by NIH and the other DMICC agencies, many of whom are key partners in the current efforts. He stated that community-based participatory research has come to the forefront in the efforts to find innovative ways to reduce racial and social-economic disparities in health care and outcomes.

CHCs were created by Public Health Service Acts 329, 330, and 340 to provide a broad community health perspective, serve the medically underserved, and focus on community participation. In 1995, MWCN chose diabetes as their number 1 priority for improvement and established a 55-member research network with pilot funding from the Agency for Healthcare Research and Quality (AHRQ) and the Bureau of Primary Health Care (BPHC). The mission was to conduct credible, meaningful research on health care access and delivery issues in special populations served by CHCs. In 1997, MWCN sought an academic partner through NIDDK and the University of Chicago became that partner in the research group along with BPHC.

Reviewing CHC performance against the American Diabetes Association's (ADA's) quality of care guidelines, the committee determined in its first study that improving quality care meant achieving the difficult goals of critical self-examination, courage to adopt new ideas, and rigorous evaluation of interventions. The second study was a needs assessment at the CHCs to determine

barriers and produced three major findings: Physicians wanted help in facilitating behavior change in patients., wanted improved efficiency in the CHC, and wanted macro health policy issues (insurance, access) addressed. At about this time, BPHC, CDC, NIDDK, and others developed a three-prong diabetes breakthrough series (BTS) that included continuous quality improvement cycles, a chronic care model, and learning sessions to work collaboratively and share lessons learned.

A study of 19 midwest CHC's that applied the diabetes BTS showed improvement in key ADA recommendations of care such as eye and foot exams and urine microalbumin testing, improvement in A1c levels, and enthusiastic support for the intervention. In interviews, physicians noted several issues that impacted their ability to improve standards of care in the community and that are relevant to translation: They needed more time and resources to provide the intervention, paper registries needed to be converted to electronic recording, and lack of senior leadership and support and staff turnover were problems. Another major concern was how to sustain gains after the first year. In response to these studies, Dr. Chin listed current intervention efforts of the group including an RCT-based study of the BTS intervention, provider training in behavioral change, patient empowerment, and hypertension and lipid projects. One evaluation technique was audio tapes of patient-doctor encounters to assess if patients asked questions based on the ADA standards.

As an example of some of the diabetes translation questions and issues at the CHCs, Dr. Chin next described evaluation of a BPHC-sponsored 6-year initiative to improve chronic care in CHCs, with an emphasis on diabetes. The evaluation was based on a conceptual model of a health disparities collaborative that was assessed at two sites, Chicago DRTC being one them. Incentives and assistance flowing between BPHC, the CHC leadership, and the CHC collaborative team, providers, and staff are key components of the model. Organizational and environmental characteristics are recognized as affecting the next level of the model, the improved organizational structures and processes, which then impact the clinical processes of care and patient outcomes, the sustainability and distribution of the interventions, and the costs.

The evaluation of the health disparities collaborative model had three aims: (1) to determine if the model improved health care quality and outcomes; (2) to determine if it enhanced effectiveness, sustainability, and spread by providing understanding and improving incentives and assistance for leaders and staff; and (3) to evaluate costs and cost-effectiveness. Dr. Chin said the second aim might be the most important in providing answers to the translation challenge of how to get something to work in the real world over time.

Dr. Chin characterized diabetes translation research issues as being diverse and complicated, involving quality of care, outcomes, access, and costs across the multiple intervention levels of patients, including children and older persons, providers, centers, and health care systems. They require multiple methods from multidisciplines. Methodological resources include biostatistics, economic analysis, and database management, along with a large variety of research areas. From the funding agency perspective, a major challenge is how to evaluate proposals and encourage innovative, creative research that takes advantage of multidisplinary approaches.

In summary, Dr. Chin named the following three issues faced by community-based participatory research:

- Developing and funding relationships of trust and equality that recognize the partners' different goals, needs, and skills and accepting that building such relationships takes time.
- Dealing with the time constraints and need for flexibility required by the real world and recognizing which partners are ready to change.
- Promoting a common vision across the partners' agendas and obtaining senior leadership's buy-in.

Discussion. Since not all standards are equally evidence-based and those that are can vary by populations, especially by age, the question was asked whether there was a need to prioritize delivery of services within constrained systems and related costs, and if so, how should they be prioritized. Dr. Chin responded that there is a lot that needs to be done in several areas at this time. A primary determining issue currently is what is practical. In CVD and diabetes management, Dr. Chin sees hypertension control as being be easier to work on than glucose control. As progress is made, there may be more of a role for prioritization. CMS, for example, is considering whether outpatient quality indicators for the Medicare population should vary by age. In diabetes risk factors, should some areas require more attention than others. Dr. Chin said, possibly, but on the other hand, there is so much room to grow that group autonomy needs to be respected. Groups may have different priorities for very good reasons, so it may not make sense to apply the same standards in the VA and the health centers and the Medicare population. Some may overlap and some may be different.

Dr. Russell Glasgow, Kaiser Permanente AMC Cancer Research Center in Colorado, raised the point that there is considerable variability in success across the centers in applying the BTS approach. Dr. Chin agreed and attributed this to issues of leadership and culture, although on the whole all are enthusiastic and idealistic groups. He emphasized that the CEO or the medical director is crucial to supporting the changes needed in the organization and in making the sustainability of the approach a strategic priority and to ensure incentives are developed to combat burnout over time.

Dr. David Stevens, Health Resources and Services Administration (HRSA) commented that translation involves system change, not just removal of barriers. He noted that three main tools have been effective so far in promoting system change. One of these is moving from an acute care model to a multi-element chronic care model, that is population-based as well as patient-based. The assumption is that one cannot change or improve a system by maximizing only one element, as was illustrated by the tobacco interventions. Teams need to work on all the elements simultaneously to make changes. A second tool is an improvement model that relates to taking a general idea proven in research and applying it in various settings. The model provides measures acceptable to the research field to test the idea in the settings. The third tool is the learning model that allows for learning and changing over time, such as a year, rather than attending one or two CME courses.
Dr. Chin stated that placement of the focus depends to some extent on the individual organization. For example, for the individual practitioner or health care organization, the system is where one must get the most result from their investment. An agency such as NIDDK can take a broader viewpoint.

Translation Research: Insights from Cardiovascular Research

Dr. Harlan Krumholz, Professor of Medicine and Epidemiology, Yale University School of Medicine, said that those who are interested in diabetes are a special community of people who focus on a large population in the country, are concerned with the acute stages in diabetes care, and then follow up with efforts to manage the chronic nature of the disease. In carrying out their mission, they are used to working in multidisciplinary teams and thinking about a populations' health and about individual patient care decisions from initial diagnosis through the patient's lifetime. There is so much that researchers and providers need to know to inform the way to bring about change. He stressed that as NIH's budget is increased and applied to support discovery, the application side needs equal enthusiasm. Dr. Krumholz gave two examples of how little is known about promoting behavior change. It is not clearly understood why there is a stigmatism of bad health behaviors amongst health professionals, but this change was not because of legislation, or adaptation of quality measures, or educational sessions. Likewise, dress fads sweep the country, especially amongst teenagers, but there is no understanding or documentation on how this happens.

Dr. Krumholz asked "What is the paradigm?" The conventional paradigm is ththat great discoveries happen, research is conducted to demonstrate that something should be done, and then the discovery is applied. This is rarely a linear process. It goes backwards and forwards. There are also terminology issues—translation research, translational research, differences between type 1 and type 2 translation research, outcomes research, and so forth. He defined outcomes research as "applied clinical research that generates knowledge to improve clinical decision making and health care delivery to optimize patient outcomes." This research has a broad focus related to providing evidence applicable to enhancing and promoting quality patient care and population health. It strives to understand factors and consequences of patterns of care and to develop strategies to address current deficiencies and knowledge. Outcomes research is about questions, not methods, and takes advantage of observational, quasi-experimental, and clinical trial approaches to address the challenges and do timely, relevant research. He stressed the necessity of embracing a broad range of approaches in a variety of areas and in moving to develop models to gather information quickly, process and evaluate an intervention, and get it to the public, and then evaluate its effect on the next generation. This will require thought and a change in the paradigm of what constitutes good research. The traditional journals do not always appreciate such real world approaches because they do not fit easily into a current paradigm.

Applying public health discoveries will always present challenges. It is thus important to study and develop an infrastructure to do this translation. Dr. Krumholz stated one goal is to have evidence-based health policy, acknowledging that there will never be absolute evidence of the right thing to do. A second goal is appropriate adoption of innovation. Surveillance, knowledge of what is taking place, is important to this goal. Finally, rigorous evaluation of changing practices at the community and clinical level is a necessary aim to understand the implications of the process changes being made. He cited the example of the change in hospital stay for bypass patients from 10 days to 4 days, without any requirement for monitoring the effect of this earlier dismissal, unlike the stringent requirements on prescription drug usage. Domains to be considered include safety, effectiveness, efficiency, equity or access, patient-centeredness, and timeliness.

The good news/bad news, according to Dr. Krumholz, is that there is great progress in diabetes but not as great as it could have been, advances in knowledge along with substantial gaps in

applied science, and a focus on discovery with a relative neglect of application research. He recommended that NIH take the lead in showing Congress and the public the value of not only research to find a cure for cancer, for example, but research to find a way to better apply the cure. This will draw the best people to the field, identify the best problems, and obtain the best answers.

The age-adjusted incidence of CVD has dropped dramatically for a variety of reasons, including health care changes and secular changes. However, prevalence of CVD cases is expected to explode because of the epidemics in diabetes and obesity and the aging of the population. The issue is not just mortality or years of life, but morbidity, quality of life.

Applying discoveries is not as simple as "just do it." Variations in population characteristics and settings affects the generalizability and validity of an intervention as well as changes that take place between the time of the initial discovery and study and the present day. Besides the cost of the intervention, there is usually a question of just what part or strategy of the intervention actually caused the positive result. Dr. Krumholz gave the use of beta-blockers after an acute myocardial infarction event as an example of these translation challenges. Following the NIHLBI-funded trials in 1981, guidelines were issued with a number of contra-indications, and basically it was left up to physicians what to do, with no surveillance of practices for a long time. Then in the 1990s, a few studies showed that less than half of those who were ideal candidates for the beta-blockers were receiving them. Further studies showed that in 1995, this was still true. Questions were also raised about effectiveness, so observational studies were done with the elderly and with diabetics. Finally, additional application issues have been raised. What are the key success factors to adopting this? How can we do studies to enhance this approach? Currently, about 75 percent of prime candidates are being treated.

Other trials have been conducted in management of heart failure, lipid management, and the role of diet in CVD. In general, each disease management intervention has shown approximately a 50 percent reduction in readmission rates. A major issue is who will pay for an intervention that may actually reduce the health care system's revenue stream. Therefore, a number of potentially valuable applications are not being used in practice or being evaluated for effectiveness. With regard to diet, there is not a clear definition of what the right diet is. Billions are spent on diets, but the knowledge of what works for whom is not being collected. If known, there would remain the question of how to get people to do it.

Effectiveness involves both efficacy and knowledge of what in the setting, the population, the intervention, or the administration of the intervention is working or not working, during the trial and beyond in the community practice. Dr. Krumholz cited reperfusion therapy as an example. There were many trials, but few studies on the right way to organize the hospital in order to administer the medication and successfully replicate the trial results. He suggested that such studies would result in more "bang for the buck" from funding these trials. Hypertension has similar issues. Treatment efficacy studies compare drugs that the pharmaceutical industry chooses to compare, which leaves providers confused about which are the most efficient strategies. Also, there are few studies on the most efficient way to screen. Should everyone have a blood pressure measure by age 45? Screening and identification strategies do not have the attention that treatment does. In addition, measurements in a trial are administered much differently than they

are in a doctor's office. In other words, there is a whole range of questions and issues that are downstream from the original discovery or knowledge.

Dr. Krumholz listed several issues of particular significance to him. These included decision making based on the patient's characteristics and preferences and the complex world in which the person lives. Should we assume that everyone wants to minimize risk regardless of the level of their risk and their circumstances? He quoted Dr. Feinstein's statement that "clinical judgment depends not on a knowledge of causes, mechanisms, or names for disease, but on a knowledge of patients." He noted that the quality of the research spanned a large spectrum. He asked that NIH recognize that implications for the field include external perceptions, training needs, and enhanced funding opportunities.

In the hierarchy of research, RCTs, according to Dr. Krumholz, are not necessarily the best way to answer questions. It depends on whether the question is one of comparing direct medical treatment procedures or one regarding effective care in general, for example. The first calls for an RCT, the second for a real-world observational study. He urged that existing data, even if it is still debatable, be made available more rapidly, citing the 7-year delay since the Framingham study. Partnerships with agencies and quick grant mechanisms are needed to take advantage of the data sets already collected. He also recommended that although industry has contributed much to research, NIH should look at opportunities and challenges that industry is not interested in, ones that are important to patients even though not profit-making.

In summary, Dr. Krumholz presented a set of perspectives or needs. These included:

- Directing resources toward application and surveillance as a complement to the investment in discovery.
- Training future clinical investigators.
- Using multidisciplinary approaches.
- Forging public policy links.
- Making improved health a paramount goal.
- Gaining insight into enhancing translation of the best science.
- Continuously evaluating and refining the definition of best science as applied in the real world.
- Relying on parallel efforts, not perfect science, for appropriate evidence to implement practices in the community.

Discussion. It was observed that a large part of NIH efforts seems to be based on a model that there will be a breakthrough that will lead to a cure. Although there has been some modification of this, this is still the driving force. In CVD and stroke, the age-adjusted death rates have declined 70 percent without understanding all the genetics underlying the disease risk. There is likely to be a breakthrough in type 1 diabetes, but in type 2 diabetes, due to its being intricately intertwined with obesity and metabolism and environmental influences, the benefit may be incremental and dependent on studies about how to do things in the real world.

Dr. Spiegel added that an intriguing scenario in type 2 diabetes is when the University of Pennsylvania's Dr. Mitchell Lazar discovered that insulin resistance is possibly affected by a

secreted hormone coming from fat from an endocrine organ. It was thought that perhaps a pill, not lifestyle, could uncouple being fat from insulin resistance. If so, then there might be obesity, but not type 2 diabetes. He noted that it is interesting to contemplate if that would be a good thing.

Regarding using case studies to promulgate information, Dr. Pogach said that the VA did a gap analysis and performance measures and learned that heart patients were not getting the proper education, or at least it was not documented. The VA implemented a performance measurement mandating the delivery of the information, developed health tip tools for patients and templates for providers, and sampled the 140 facilities over several months. Improvement varied between 20 and 100 percent. The agency has researched rigorous tools to reevaluate risk-adjusted readmission rates for heart failure nationwide using administrative data sets. Now the group is prepared to conduct observational studies. Dr. Pogach agreed that perhaps it is now time to get the information out more quickly, recognizing that there is role for case studies as well as observational studies and well-conducted health services research.

Dr. Krumholz agreed that such publication is important, along with rigorous collection of data to accompany the intervention and rigorous, systematic evaluation of exact impacts. It is important to be able to trust the data.

Diabetes Translation Research: The Next 25 Years

Dr. Russell Glasgow, Senior Scientist at the Kaiser Permanente AMC Cancer Research Center in Colorado, opened his presentation by quoting Yogi Berra who said "In theory, there is no difference between theory and practice. In practice, there is." In looking at the next 25 years for diabetes translation research, he reviewed the key accomplishments and lessons learned from the initial 25 years, discussed needed changes based on the RE-AIM model and recommended responsive new approaches, and identified key areas and opportunities for future translation focus.

In looking back, Dr. Glasgow noted there has been almost a paradigm shift in diabetes management to a patient-centered focus that did not exist as late as 10 years ago. There have also been guidelines and systems change interventions that share such commonalities as having nurses do diabetes care management; using proactive, planned, population-based interventions; and recognition that the fault is not the patient's or the provider's, it is a systems issue. It has been shown that practical behavioral and office-based interventions do bring about effective change.

Dr. Glasgow cited successful robust, replicable interventions across populations and settings and programs to reduce health disparities that have provided valuable lessons in spreading and generalizing knowledge. For the latter, he referred particularly to the Diabetes Prevention Program (DPP), the CHC partnerships, the VA and the Indian Health Service, and the National Diabetes Education Program. He emphasized that diabetes and its management are extremely complex. Accompanying the many attributes of self-management are the impact of individual, social, and environmental variables. A person may do well in one self-management area and less well or poorly in others. The relationship of the variables and performance to outcomes is also complicated.

Using aspects of the chronic care model and the RE-AIM model, Dr. Glasgow listed changes that need to take place. These included:

- **(R)Reach**: expand the focus on creating and documenting broadly applicable interventions for diverse populations and persons with comorbid conditions (who are usually excluded from studies, even those most diabetes patients have multiple chronic problems). Dr. Glasgow noted that designing a perfect intervention does not mean people will choose to use it.
- **(E)Effectiveness**: broaden the outcomes so they are more sophisticated and comprehensive; include economic outcomes and quality adjusted life years (QALYs) from the patient's perspective.
- **(A)Adoption**: pay more attention to settings and agents, particularly to learn who can most effectively deliver the program.
- **(I)Implementation**: pay more attention to issues such as what level of intervention can non-professionals implement, the consistency of the intervention as a variable, and the error in concluding that the intervention was not successful when, in fact, it was never truly delivered. Accurate delivery of a research discovery is a challenge in the real world.
- **(M)Maintenance**: pay more attention to social/environmental factors influencing maintenance, conduct long-term followup studies of participants and settings, and better understand the effects of policies and the interaction of policies and behavioral treatment.

Dr. Glasgow prefaced his recommendations for future translation research by quoting Einstein's statement that "The significant problems we face cannot be solved by the same level of thinking that created them." It is necessary to "think out of the box." Future interventions need to reach those who can most benefit, be adaptable to different settings, be implemented consistently by staff with moderate levels of training and expertise, and produce replicable, long-lasting effects with minimal negative impacts and at a reasonable cost. Dr. Glasgow said there needs to be a cultural change on the part of all relevant parties, not just researchers, but funding agencies, reviewers, and policymakers. He then listed specific recommendations for each of these groups.

Researchers need to reach large, representative populations, especially the underserved. They also need to report on implementation and outcomes across a range of interventions, agents, and settings. Funding agencies should support studies in multiple settings representative of real world practice and report both mediator and moderator effects. They should fund innovative ways to enhance reach, adoption, implementation, and maintenance and require and fund a maintenance/sustainability phase. There should be standardized reporting of exclusions, participation rates, and representativeness of participants and settings.

Reviewers need to undo bias and old learning, provide greater balance in looking at internal and external validity, relax criteria on long-term maintenance, and include the potential for translation as a standard, as has been done with innovativeness. In policymaking, it is time to "put our policies and money where our mouth is." Rather than talking about the importance of translation and patient-centeredness and other issues, we should include behavioral counseling indices in performance measures and provide incentives for individuals and systems.

Dr. Glasgow stated that there are incredible opportunities at this crossroads in translation research. Key areas for future diabetes translation research include:

- Comprehensive evaluations of interventions that address social context, noting that "things are not always what they appear."
- Genetic and behavioral issue interfaces, especially gene-environment interactions and the future of genetic counseling, shared decisionmaking, and risk perception science.
- Prevention issues learned from DPP, including cost-effectiveness and less-motivated populations.
- Integrated technology applications to facilitate and support patient/provider interactions and enhance reach, implementation, and maintenance.
- Health care systems change, including policy factors that impact systems.

Proponents of the chronic care model believe changes are needed in all components of the model in order to see lasting, significant change. The ultimate goal is to see productive interactions between a prepared, proactive practice team and an informed, activated patient. For the future, the impact of policy and the social environment also needs to be evaluated.

Dr. Glasgow offered an exercise looking at a future discovery of an amazing weight-loss intervention to deal with the obesity issue on a population basis. If an unprecedented 40 percent of the clinics adopted the intervention in their setting and 40 percent of the agents adopted it, the overall effect on the population would be only 16 percent. If a phenomenal 40 percent of the patients who tried the intervention were successful, the population effect would still drop to 6 percent. Including the factors of consistent delivery, behavior change, and sustainability, the cumulative effect would fall to less than half of 1 percent. The good news is that with greater attention to these factors, there can be a greater public health impact and perspective.

Dr. Glasgow said that if we are serious about seeing greater translation change, then we must require fundamental improvement and change in the culture at all levels of participation. The stepped care pyramid model illustrates this. To date, the largest amount of research has been at the top of the pyramid at the level of a very small segment of people, some at the primary care and health care systems levels, but relatively little at the community/ neighborhood, media, and policy levels at the base of the pyramid. Whereas reach is highest at the lower levels, intensity and cost are highest at the upper level. Dr. Glasgow suggested that it might be more cost-effective and efficient to do more interventions at the lower levels for everyone.

In conclusion, Dr. Glasgow recommended, "the best way to predict the future is to create it" but to keep in mind that as H.L. Mencken said, "to every complex question, there is a simple answer—and it is wrong."

Discussion. Dr. Green identified that one thread running through the presentations and discussions was the degree to which those present really believe, as one moves out beyond the bedside, that there are interventions that can be packaged and made generalizable. The attendees fall along a continuum with respect to this thread. He said he took the position that no off-the-shelf, generalizable interventions exist. Interventions must vary with the person and the

circumstances. However, RE-AIM seems to imply that there is something concrete, specifiable, exportable, and generalizable. He asked if Dr. Glasgow would be revising the RE-AIM model.

Dr. Glasgow replied that what we should learn from research, if it is cumulative, is some generalizable principles, not just theories or hypotheses, and this result can be enhanced by studying mediators and moderators. There are some common principles in self-management education that apply across settings, such as collaborative goal setting, followup, or integrating self-management into primary care. Dr. Glasgow did agree that one cannot take an intervention, even one as successful as DPP, off the shelf and apply it exactly the same. It must be tailored to the setting, working with partners to apply the principles of the intervention in the setting.

Dr. Stevens asked that in order to have a concept implemented or replicated, does it not have to be specific and not so generalizable that it is "messy" to apply. Dr. Glasgow said that the level of specificity is a good challenge. Most people cannot take the general principle, such as collaborative goal setting, and do it. Everyone thinks they do that, but actually few really do it in a way that is patient-centered. People need options, concrete examples, and tools in order to not have to reinvent the wheel. By being creative and willing to try things, centers have taken the principles of goal setting and having an action plan from the study setting and made them work in their settings. They have taken ideas and examples from academic researchers and adapted them to a lower literate, even almost illiterate level, to be used as tools for interventions.

Dr. Glasgow was asked if he would recommend the use of QALYs to set areas of priorities for interventions, and if so, what would be the implications for DMICC. Dr. Glasgow said one clear implication was that number one on the list would be redoubling efforts for smoking cessation for anyone with diabetes who smokes. That would be the single most cost-effective intervention, and there is a lot of information on how to produce system change in smoking. The questioner agreed and said that blood pressure would probably be second. Dr. Glasgow concurred and addded that one of the important lessons learned is that diabetes is about more than just Alc, although we must continue to improve our efforts to control that while broadening our focus.

Afternoon Presentations and Discussions

Dr. Saul Malozowski, who has been appointed as the new DMICC Executive Secretary, announced that the afternoon's format would vary from that of previous meetings. Rather than agency representatives providing a position statement and update of their current and proposed activities in relation to the meeting's subject, they would be discussing a set of questions posed by the speakers about emerging issues in diabetes translation research and implementation. The exception would be a presentation by Dr. Desmond Williams, Centers for Disease Control and Prevention (CDC).

Desmond Williams, MD, PhD, Division of Diabetes Translation, CDC

Dr. Williams began by stating that many people at CDC have been working to learn new techniques and strategies to address the complex issues of diabetes research translation. CDC views translational research as a way to identify and test strategies of change aimed at achieving

optimal diabetes care, to assess the level and quality of care practices, to explore factors affecting variations in care, and to identify barriers and enablers of change.

Dr. Williams presented a CDC graphic depicting translation research in the context of other models of research, such as basic science/epidemiology, surveillance, and clinical trials, that are used together to better characterize and understand problems and track changes over time. CDC sponsors, conducts, and participates in clinical trials to understand solutions to problems. There is an ongoing translational process in which progress is made from one step to another and much is learned from mistakes made.

Current translational efforts embody a variety of approaches at different governmental levels. Translating Research Into Action for Diabetes (TRIAD) is a health system's approach, Diabetes Control Programs (DCPs) are administered by State health departments, Diabetes Collaboratives take place at the CHCs, Project DIRECT (Diabetes Interventions Reaching and Educating Communities Together) is another community level effort, and the U.S.-Mexico Border Study is an international project.

The CDC/NIDDK multi-center TRIAD study, funded by a 5-year cooperative agreement, involves 11 plans and 63 provider groups and 194,000 persons with diabetes. The TRIAD centers are located in Hawaii, Texas, Indiana, California, Michigan, and New Jersey. The study uses baseline and longitudinal analyses to investigate structural factors, processes and quality of care, and health outcomes issues and interactions. This ongoing study is expected to produce information on the status of diabetes care in managed care organizations.

Levels of funding distinguish core and comprehensive nationwide DCPs ; with cores receiving up to $240,000 and comprehensives, up to $800,000. Although CDC-funded, the groups operate as autonomous bodies, so all have different activities of concentration. CDC encourages the establishment and maintenance of statewide diabetes coalitions and each State has a Diabetes Advisory Committee. Examples of activities include diabetes surveillance and services, community-based programs to control complications, and public and provider education. The groups strive to identify barriers and enablers to changes in diabetes care and develop outreach programs for minority populations.

Project DIRECT is the largest community-based diabetes project in the United States. It is an equal partnership among CDC; the community of southeast Raleigh, North Carolina; the Division of Public Health in the North Carolina Department of Health and Human Services; and North Carolina's Wake County Human Services. The community has developed a coalition, supported by the partners, that guides intervention activities. The coalition-written goals are to improve quality of care and self-management practices, detect undiagnosed patients and ensure persons with diabetes are in the health care system, and reduce risk factors by advocating and encouraging lifestyle changes.

The 5-year U.S.-Mexico collaborative study will be taking place in medically underserved communities on both sides of the border. The study communities have high poverty levels and many of the Hispanic members are uninsured or underinsured. The project's purpose is to determine the prevalence of diabetes along the border and to develop bi-national prevention and

control programs. Besides CDC, international partners include the Pan American Health Organization, the U.S.-Mexico Border Health Association, the Secretaría de Salud de México, State Health Authorities and DCPs, Paso del Norte Health Foundation, El Paso Diabetes Association, the Border Health Foundation, and the California Endowment/Project Concern International.

Other CDC research activities used to support translation efforts include surveillance and evaluation projects using both quantitative and qualitative methods.. Along with efforts to learn more about barriers and enablers, CDC is trying to find ways to institutionalize activities in the community to make them more self-sustaining. CDC is committed to and actively engaged in translational research as a way to reduce the burden of diabetes and its complications. The agency sees translation research as a necessary bridge between basic and clinical research and diabetes care practices. It is an ongoing process of developing, testing, and implementing new strategies. Dr. Williams said CDC believes it is important to have opportunities like the DMICC meeting and other forums in which to share experiences with other agencies.

Discussion. Dr. Green spoke about the announcement of a new urban research center to be established in El Paso, funded by his office and the epidemiology program office. There are currently three such centers engaged in participatory research. Asked if the U.S.-Border Study was connected to this, Dr. Williams replied that it was a separate project. In response to the status of Project DIRECT, he said a contract for evaluation had recently been awarded and that CDC feels they have learned a great deal from this project, including lessons learned about collaboration. The evaluation will look at the study's achievements, analyze methods both qualitatively and quantitatively, look at differences in diagnosed and undiagnosed diabetes, and examine other issues set up by the primary study objectives. Important items to assess will be about how was the community accessed, what were the initial problems and how were they resolved, what was learned from this, and what lessons can be gained from the study to share with others. The study is ongoing with final results expected in approximately 3 years.

Emerging Issues in Diabetes Translation

Dr. Malozowski said that speakers had submitted about 20 questions earlier. These thoughts were used to form the following set of issues to be discussed by the DMICC representatives:

- What is the most important translation issue for your agency?
- What do you see as the unique role of your agency related to diabetes translation and how do you envision your agency responding to the outcome of today's meeting?
- What are the barriers to diabetes translation that your agency faces and what is the single most important thing that can be done to accelerate the translation of research to practice?
- At your agency level, what can be done to address the challenges of diabetes translation involving:
  - patient and provider,
  - health care organizations, and the
  - health care system?
- At your agency level, what can be done to ensure that there is the breadth of expertise needed to develop, nurture, and evaluate diabetes translation initiatives, such as:

- health services research,
- behavioral research,
- organizational theory.
- epidemiology, and
- economics, etc.?

- How can your organization form collaborative partnerships with other funding agencies, academic institutions, and community partners to work on diabetes translation efforts?

Veterans Administration. Dr. Leonard Pogach referred the audience to www.oqp.med.va.gov where the VA's performance measures are posted on the Web. For diabetes care, the VA average nationwide, is equal to or exceeds the 90th percentile of all NCQA reporting plans. The VA embraces change in translation at every level—systems, management, and research—which is why they are successful, according to Dr. Pogach, along with the Indian Health Service and the U.S. Department of Health and Human Services.

Dr. Pogach said that the VA's primary translation issue at this time concerns the nature of its patient population, which is economically disadvantaged, with 10 percent homeless, and 30 to 40 percent with a mental health condition. Even with the mental health problems, their process measures and intermediate outcome measures for diabetes are comparable. With distal outcomes, mortality, amputations, and so forth, there are still disparities. Understanding that is a challenge for the agency. Another issue is that the VA cares for about 800,000 persons with diabetes, of whom 70 percent are Medicare eligible, with attendant policy-level considerations. The VA has a computerized system of medical records, computerized reminders, outcome information, and nationwide automated data sets. This enables him to have a research set of all diabetes patients with their Medicare data, which offers extraordinary opportunities to look at the delivery of health care within their system.

Competing resources for the patients' wide range of health problems, such as stroke and mental health conditions, can be a translation research barrier. Hepatitis C affects about 12 percent of the population. The VA is also the Nation's largest provider of AIDS care. There is tension between quality improvement and research. There is also a lack of consensus often as to what measures most need to be tightly controlled in seniors—hypertension, hyperlipidemia, or glycemia. Glycemia usually wins, which Dr. Pogach disagrees with, and he challenged DMICC to send out a unified message that for seniors, while not demeaning glycemic control, it is blood pressure and smoking that should be the priorities in using the health care systems' limited time and resources.

The VA has a quality improvement research initiative, which is funded for eight or nine disease entities, of which diabetes is one. The research coordinator is Dr. Rod Hayward at Michigan. Dr. Pogach is the clinical director. There was a Medicare supplement report on the initiative in June 2000. The goal throughout the VA is to systemize the quality of care. To accomplish this, the query groups are integrated as much as possible with operations, with efforts made to overcome research/operations barriers as much as possible. Both researchers and policymakers serve on the executive committees for the query groups. This system helps to bring the efforts of the whole VA health services community to bear on problems. In addition, a number of query investigators serve on the VA/DoD national guideline council that integrates guidelines and performance measurements and implementation evaluations for both agencies.

In summary, Dr. Pogach said the VA has a unique system of care that, although sometimes somewhat bureaucratic and para-military and, like most of the other agencies, responsible to Congress, it does embrace change and innovation.

Discussion. Dr. Speigel asked if the VA was considering primary prevention of diabetes. Dr. Pogach answered that revisionary guidelines were coming out that would incorporate the ADA position statement on screening as a consensus-based statement. The VA population's average age is 67 and even among non-diabetics, there is 40 percent hypertension and hyperlipidemia is endemic, so the agency is looking for opportunistic screening in the population. Primary prevention has not been addressed directly, just implicitly. Because of the Institute of Medicine's finding that Agent Orange is possibly related to diabetes, it is now enshrined and benefited as a service-connected disease, so there might be some politically motivated possibilities to target some appropriate populations.

National Heart, Lung, and Blood Institute. Dr. Denise Simons-Morton said the most important issue for NHLBI regarding diabetes is that diabetes is a CVD risk factor. In translation research, NHLBI has projects related to prevention such as diet, weight control, and physical activity programs. The most important challenge is balancing the portfolio with all the basic science that needs to be done along with the translational research. NHLBI also has a research continuum, with feedback loops, that goes from basic research to epidemiological studies to efficacy RCTs to effectiveness trials to translation and dissemination research that then results in translating and disseminating interventions. In this context, NHLBI is sponsoring the TAAG and ACCORD trials and the National High Blood Pressure Education Program and the National Cholesterol Education Program, which are not research programs but are translational.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) is partly an efficacy and partly an effectiveness trial asking if intensive control of glycemia in adults (less than 6 percent HbA1c vs. the average 7.5 percent) would prevent CVD events. This study of 10,000 participants also will ask blood pressure and lipid questions. It will be implemented in 60 clinical sites across the United States and Canada, including HMOs, VA sites, Canadian health systems sites, and private doctors' offices. Thus, ACCORD will test the HbA1c reduction intervention in settings where patients are normally seen. Patient characteristics have been selected to be generalizable also.

The Trial of Activity in Adolescent Girls (TAAG) is another relevant study that is being implemented in 36 schools nationwide with a representative sample of minority students. TAAG's purpose is to study a school-community link to intervention to prevent the decline in activity seen in adolescence, particularly in girls. It is really a primordial prevention study of sedentariness. Phase I was a needs assessment. After the intervention, there will be a sustainability evaluation, which is important for programs to be implemented in the real world.

An example of translation research is the Activity Counseling Trial, an RCT to test patient education and counseling approaches for physical activity. The interventions were designed to be feasible and appropriate for delivery in primary care settings. The completed study was published in 2001 and showed an effect in women but not in men. CATCH-ON is an example of an observational study of the implementation and institutionalization of the previous CATCH (Child

and Adolescent Trial for Cardiovascular Health) school-based intervention. These are examples of an RCT that tested real-life interventions in real-life settings and an observational study to identify the characteristics of schools that would make them adopt an intervention that was successful in improving diet and physical activity in children. The major characteristic identified was having a person in the school who was dedicated to behavioral change.

NHLBI just released and funded a Request for Applications (RFAs) for trials to assess innovative strategies to improve clinical practice through guidelines. The purpose is to test multi-faceted interventions delivered in clinical practice with the outcomes being the provider practices. The interventions are intended to help providers use guidelines that are evidence-based in heart, lung, and blood diseases. RCTs were not required, but quasi-experimental designs were requested in order to have comparison groups. Needs assessments were encouraged for phase I. Eight studies have been funded that are going to provide a lot of experience relevant to diabetes. Other investigator-initiated studies are testing similar events.

NHLBI recently had a retreat on translation to discuss both the bench to bedside and bedside to community steps. One of the results of that retreat is a new policy, which has been posted on the Web, that NHLBI will require dissemination plans in RFAs, Request for Proposals (RFPs), and large investigator-initiated studies for clinical or public health research.

NHLBI is making a strong effort to make data available for epidemiologic studies and clinical trials. There are a number of data sets that are available now from Framingham and the epidemiologic studies. Within the next year, additional clinical trial data will be available from NHLBI.

Dr. Simons-Morton noted that NHLBI also has training programs for clinical researchers, as do other NIH groups.

Discussion. Dr. Glasgow mentioned that each group has a research model going from basic research to translation and these models are useful. However, because of time, occasionally there is a problem going from one stage to another, particularly from efficacy (tested under experimental design conditions) to effectiveness (Does it work in the real world.).
Dr. Simons-Morton agreed that these were excellent points and ones NHLBI staff had discussed frequently in designing studies. In ACCORD, they conducted a vanguard phase in all 60 clinics because they wanted to know, although this was an efficacy study, that the intervention being tested could actually be implemented in the real world. It takes time and resources to reduce HbA1c to 6 percent and stay there, so the next question may be will it be implemented. In the history of CVD, researchers have asked in efficacy trials the causal question or proof of principle question: Is hypertension a risk factor for CVD and stroke? The way one proves evidence of causality is to have experimental evidence that lowering blood pressure prevents or reduces CVD and stroke events. Internal validity has been considered the most important thing, but now, there is a move toward valuing external validity and generalizability.

Dr.

Dr. Simons-Morton stated that NHLBI is putting a lot of resources into ACCORD to do intensive glycemia treatment. If the study finds that there is a significantly positive effect, there will be a

question of whether or not providers will or can do this. If the effect is not positive, then they will know that it is not worth their time.

In response to Dr. Green's query about the results of CATCH, and what CATCH-ON will do differently, Dr. Simons-Morton explained that CATCH was a randomized school-based trial of 96 schools randomized to intervention and control. The intervention being tested was a health promotion intervention to improve diet and physical activity in elementary school-age children. The primary outcome was identified as blood cholesterol. Improvements were achieved in diet and physical activity, but there was not a significant effect in blood cholesterol. Still the intervention was considered worthwhile because of the improvements in the health behaviors. It was then decided to do a followup observational study of three groups, the original CATCH intervention schools, the original CATCH control schools, and a naïve group of schools selected to be roughly comparable. For the original intervention schools, the questions were "was the intervention institutionalized, was it maintained, and what were the factors associated with that, if it was." The control schools were given all the materials and brief training and the question was whether or not the program was adopted. The third group was used for comparison for secular trends. As mentioned earlier, the most important factor for maintenance, institutionalization, or adoption was a change agent or a dedicated person who was committed to having the program happen in the school.

NIDDK. Dr. Garfield reiterated that studies such as DCCT clearly have no purpose unless they are translated. One approach NIDDK has taken is to implement a translation research program. A recent program announcement is asking for studies that involve translation of known effective interventions. The proposals are reviewed by the Institute's review branch. There is also an R21 small grant program to make it easier for persons to develop pilot data to feed into the translation research program. NIDDK is clearly emphasizing translation and setting up programs to promote that. The NDEP that NIDDK and CDC co-fund is also a translation program and is actively developing plans to disseminate and implement the DPP results.

Discussion. Dr. Williams asked how NIDDK sees the implementation of the DPP results in the general population. Dr. Garfield responded that HRSA is developing interventions to try to study that in their community centers and NIDDK's translation research program will assist with that. NIDDK is also working with the Indian Health Service, which is developing plans to implement DPP lifestyle intervention programs. NIDDK is also working with ADA to develop recommendations based on the DPP results. Dr. Malozowski added that NIDDK is working with the DPP nutritionists and those who implemented the intervention to put together a toolbox based on DPP to distribute to practitioners to help them implement the intervention.

Dr. Spiegel commented that Dr. Williams' question touches on the crux of the issue with DPP. In a clinical trial population, motivation is always a factor that limits generalizability. However, in DPP, by selecting 45 percent of the participants from minority groups, the rationale was that it should be generalizeable to the U.S. population, in contrast to the earlier Finnish study, with the caveat of having to motivate individuals. The two critical challenges to real-world effectiveness are first, identifying those at risk , which was done in DPP through the formal oral glucose tolerance testing, an issue we have been in dialogue about. The second issue is about implementing the highly structured, individualized, intensive lifestyle intervention that was shown to be effective; the calculations are that that cannot be done on a population basis simply

in terms of available trained individuals and cost. Other interesting implications are that metformin, which is now generic, was shown to be equally effective to lifestyle in a subset of individuals with a body mass index (BMI) over 34 or 35 and age 25 to 44. So one issue will be pharmacological intervention and the cost effectiveness and implementation of that, which does not raise all the lifestyle issues. Returning to the first challenge, the identification of the target population, Dr. Spiegel said that it is not the message of DPP to suggest that there is no need to select individuals since the lifestyle changes would be good for everyone. The question is should persons be identified by a checklist or a questionnaire, as has been done for cardiovascular risk, in which family history, obesity, membership in a minority population, sedentary behavior, and so forth are assessed. How would such a questionnaire track as a surrogate for formal glucose tolerance testing, which raises more complex questions about which test is appropriate.

Dr. Williams said that CDC is discussing these issues and as Dr. Spiegel clearly illustrated, there are no easy answers to the questions. Eventually, there probably would have to be some surrogate measures developed for administering the oral glucose tolerance test, possibly specific items in the patient's history that would indicate increased risk for impaired glucose tolerance. Those at risk might—only might—then be included in a testing program. Dr. Williams thought that developing such surrogate measures are a major stumbling block in translating DPP's results to a broader population.

Dr. Spiegel stated that the studies in the NIDDK translation research program that Dr. Garfield referred to are potentially important vehicles for testing hypotheses for identification and for modified lifestyle interventions.

Dr. Pogach said that one of his concerns about DPP implementation and generalizability issues was that the control groups did as well as they did, even thought poorly, they had access to one annual session with a diabetes educator, which is more than most people ever have, and they seemed to be a highly motivated, self-selected group who exercised more than most Americans do, although they had no significant weight loss. Also, for some persons in the VA population, vigorous exercise might be difficult because of knee problems and other health problems.

Dr. Spiegel and Dr. Garfield pointed out that 11 percent of the control group per year developed diabetes and that the intervention group attained an overall 4 to 5 percent weight loss and actually exercised more minutes per week than requested. In fact, exercise was the most adhered to component of the lifestyle intervention.

Dr. Simons-Morton commented that the issue of the control group comes up over and over in CVD trials. What is appropriate to deliver to the control group is one issue and another are the changes seen over time in the control group, but the internal validity of the study is still a comparison between the control and intervention group. In randomizing people who agree to go into one or the other group, there is often a highly selected group in terms of motivation whether or not they are representative in terms of gender, minority status, or other characteristic. Clinical trials in general have to deal with this issue.

Dr. Malozowski added that in drug trials, the patients tend to be more homogenous than they were in DPP. An interesting result in DPP was that patients in the control group did not gain weight as it had been expected they would, possibly due to the difference of participating in a

study and not participating in a study. He felt that it was very important information that elderly patients in particular benefited substantially from the exercise

Dr. Peter Savage, NHLBI, stated that DPP was an extremely valuable study because no one would even be talking about preventing diabetes if the time and effort had not been taken to do a study of this sort. This is a good illustration of why there is a need for fairly complex clinical trials to change the mindset. The speculation is, however, that it was a complicated enough study in terms of effort and cost so if these data are turned over to relatively low-level efforts in routine clinical settings, there is a likelihood that there is might not be a major reduction in development of type 2 diabetes. He asked if there was a need for some other type of more formal research studies, maybe treatment for 6 months or a year with an insulin sensitizer—which drug companies are studying— plus some form of weight loss regimen and then stopping to see if persons can be kept non-diabetic for a period. Such a study could bridge the gap between an expensive, complicated intervention and something more affordable that could be done in a clinical setting.

Dr. Speigel responded that Dr. Thomas Buchanan had just published in *Diabetes* his study of the insulin sensitizing drug troglitazone, which has now been withdrawn, in gestational diabetes in Hispanic women. He had strikingly positive effects, which offers a theoretical framework of beta cell preservation. There was an arm of DPP that involved troglitazone that was discontinued after 9 months due to safety concerns and the group given modified lifestyle. The data from that group is not yet publicly available, but it will be at some point and it may be a test of what Dr. Savage just proposed because the group will have been treated with medication for a while and then lifestyle. A paper on data from this group is nearing completion, according to Dr. Garfield.

Dr. Pogach referred to a screening issue in the European __UKPDS____ study about whether early detection for type 2 diabetes will actually improve outcomes. In general, it is thought that there is insufficient evidence to recommend screening for type 2 diabetes in the general population because it is unknown whether or not outcomes will be improved. Hypotheses could be posed that more rigorous treatment of the risk factors would improve outcomes. But these are questions for which there are not yet answers. The intensive nature of DPP has meant that there is a sense of caution about its adaptation. The question remains as to where the effort and resources should be put. That is different than saying who should lose weight and who should exercise.

Dr. Garfield said that the outcome study from the DPP is following all of the newly diagnosed patients and is the only cohort for which it is known, within a 6 month window, when a person became diabetic.

Dr. Glasgow suggested the group consider the situation if the DPP results had been reversed and the pharmacological intervention had been dramatically more effective than the behavioral intervention. The current discussions would probably not be taking place. There would not be much concern about the run-in period. There would not be any consideration about the fact that drugs are never implemented in the real world the way they are in an efficacy studies. There is a huge multi-billion dollar industry out there to support their implementation. This is a cultural mind-shift issue that is real and needs to be studied, but often different standards and issues arise because of how we have been trained in our culture.

Dr. Simons-Morton supported this point by commenting that there was an extensive effort in DPP to achieve the level of compliance for the metformin arm that they needed. Dr. Garfield added that just as there was a lifestyle corps to help people adhere, there was a drug corps for adherence..

Dr. Savage said that exercise may be more efficacious in preventing diabetes than in helping those who already have diabetes in terms of the levels at which people are likely to exercise, although some people may do spectacular things with diet and exercise. There are spun-off questions from the DPP that are not likely to be asked in the community and need to be followed up by NIH. Another question is the use of the fasting glucose test to screen for high-risk people. There are some large data sets from people who have been tested and followed for some time that are becoming available for public use from NIDDK and NHLBI. These will provide an opportunity to analyze that data and see if there is some combination of obesity and fasting glucose that would be a reliable predictor of diabetes risk and substitute for a formal oral glucose tolerance test. Dr. Garfield said they were also analyzing the effects of exercise versus weight loss.

Agency for Healthcare Research and Quality (AHRQ). Dr. Daniel Stryer said that AHRQ is a relatively small agency that is tasked with research on all problems within the "ICD9 book" for all populations and in all settings, which becomes a bit overwhelmingTherefore, AHRQ cannot concentrate too many resources on diabetes, although it is obviously a major cause of morbidity and mortality. AHRQ is focused on the delivery of health care, so the agency is looking at clinical issues, but also at organizational and structural factors, which is important in translational research. In AHRQ studies, the agency is looking at these factors to understand the interplay between the organizational and structural levels and to understand some of the subtleties in interventions that may them work in one setting and not another.

AHRQ does go through the efficacy and effectiveness stages mentioned by the other speakers and other DMICC members. The agency refers to translation as implementation or TRIP, Translating Research Into Practice. The TRIP 1 initiative focused on efficacy. TRIP 2 was more of an effectiveness model. The agency is now in a third generation of implementation research and has issued a TRIP 3 Public Announcement in partnership with the VA. AHRQ is also a partner with NIDDK in its new RFA for translational research in prevention and control of diabetes. In this third generation, AHRQ is especially interested in the factors that account for variability in success or failure from one setting to another. This is considered important for generalizability and for adjusting or selecting one intervention or another in a particular setting.

Dr. Stryer said that the research base is important, but tools are also needed. There is no off-the-shelf intervention, most need to be adapted, but a lot of good work is taking place and it is unnecessary for everyone to reinvent the wheel. AHRQ is developing a tool box—or maybe a tool shed—that is going to come out in about a year to put these tools in the public domain.

Dr. Stryer stressed that partnerships are another important level in translation research. There is a chasm between what is known from research and what is being put into practice. A key in implementing findings is going to be developing partnerships between those on the front line of health care to understand their needs and address them, but also to get them involved early in the

process in the research so they will come to the agencies with their needs and learn what is available. Dr. Styer said that establishing this level of partnership does not just happen; there is a science to it.

AHRQ's partnership with HRSA will assess the Health Disparities Collaboratives to enhance the research basis for quality improvement. It will look at real world situations; it is not an efficacy model. It is getting at the failure and success factors, generalizability, sustainability, and return on investment. All of which are important next steps for translation.

Discussion. In response to Dr. Green's inquiry about AHRQ's activities in community-based participatory research, Dr. Stryer said this sprung up from the disparities initiative but is also a part of implementation. This is really a subset of user-driven research. The communities are one of the types of users that AHRQ feels it needs to reach out to and ensure that their needs are being met. It is very important that these users are incorporated into all stages of the research process from identifying a topic, to development of the question, the development of the hypothesis, the actual choice of methods, the analysis, and the implementation. This is a key component of AHRQ's implementation research.

Health Resources and Services Administration (HRSA) Dr. David Stevens said that the most important issue in translation research for HRSA is the change in practice from the acute to the chronic care model. To do that involves four main elements. First, HRSA is using a learning model and Dr. Ed Wagner's improvement model that relies on productive interactions between a prepared, proactive, practice team and an informed, activated patient and interactions with community resources and policies and the health system. Second, the agency has a leadership program at the national and local levels. The third element is the agencies strategic partnerships. Fourth, and of major importance, is a heavy investment (nearly $20 million) and effort in building infrastructure at the State and national levels.

Dr. Stevens said there is a difference between research and quality improvement. HRSA does not do research to generate knowledge; they do evaluation, so their methods are different than those of researchers. One difference is that research uses blinded tests, and HRSA's are observable. Other differences are researchers are looking for no bias, whereas HRSA studies have a stable bias; researchers collect all possible data and HRSA wants just enough data to know if they are accomplishing what they want. Research works from fixed hypotheses; HRSA studies have changing hypotheses. In research, there is one large test and HRSA has many hundreds of sequential small tests. Research has stable cohorts; HRSA has a changing population.

In answer to the question about HRSA's unique role, Dr. Stevens explained that 86 percent of the patient population the agency works with are low income persons, 40 percent are uninsured, 28 percent are African American, 30 percent are Hispanic, and 8 percent are Asian. This is a very important population to be serving. HRSA has gone into many clinical areas with its model—diabetes, depression, CVD, asthma, and cancer. There is a potential synergism and HRSA has found a tremendous affinity with changes across the conditions, which is good news for a provider, because it means there is a finite number of things to do to produce multiple good results.

Dr. Stevens said he believed that DMICC can do a great deal in providing national leadership on the importance of translational research. This can help in removing barriers and making change in policy. It says that what agencies like HRSA is doing is important; it is not marginalized. It also provides HRSA with access to information. Dr. Stryer said that HRSA is actually a researcher's customer. There is no reason for HRSA to duplicate the expertise of the research agencies, and they are not equipped to do so. That is why HRSA wants to partner with the research groups. In return, HRSA can provide access to populations and provide information on spreading innovation to change and improve health care practices to complement what researchers are doing.

Dr. Stevens stressed that it is important to involve early on those to whom the research is going to be applied. This should be as early as at the hypothesis stage in the clinical research stage. HRSA is translating DPP now, but Dr. Stevens wishes they had been involved when the study was being designed. He said that the use of the DPP results is exciting, even though there are problems to be resolved. However, they wish that the study had considered a non-biological test to identify the target population or tested less than a 150-minute per week exercise intervention, even those this would have cost more money. It would be good to build in collaboration earlier. It could shorten the time. Currently, it has been found that 14 percent of original research takes 8 years to get into practice. It would help to have persons who can straddle the world of research and the world of application. If they do not exist, they should be trained.

Dr. Stevens said he sees translation research as a developing inter-disciplinary discipline. If the translation units within NIH and CDC would form a collaborative themselves and had an overall strategy for moving the field forward, that would be tremendously helpful to HRSA. There would be less duplication and more synergism and it would be easier for those who are in systems to get more feedback to the collaborative. This could be an ongoing activity, where the translation work results can be evaluated. Dr. Stevens said that every month he has outcomes and does not have time to look at the data. He suggested that this is true for the VA and NIDDK and it could be of interest and use to a larger group such as a collaborative.

HRSA does expect to have outcomes from its prototype of five CHCs on the DPP translation by July or August 2003. There will also be important outcomes from the work with AHRQ. Dr. Stevens said he would like to share those results in a group such as DMICC where it might influence research questions of colleagues in other agencies or in academia.

Discussion. Dr. Spiegel expressed his appreciation to the speakers and the attendees for their participation and acknowledgement of the 25th anniversary of the DRTCs and their important work. He said he felt a renewed sense of partnership and of the importance of collaboration. It needs to be made meaningful and Dr. Speigel intends to work with the group in that capacity.

Dr. Pogach asked if there would be another meeting on translation that might bring together other NIH groups with DMICC. Dr. Spiegel responded that such a forum need not be limited to DMICC meetings. Dr. Williams said that CDC would strongly support such a meeting or conference, and it could include scientists from other organizations and from academia also.

The meeting was adjourned at 2:35 p.m.