Report on the Diabetes and Aging Conference
February 12-13, 2001
National Institutes of Health
Sponsored by
National Institute for Diabetes & Digestive & Kidney Diseases
National Institute on Aging
Diabetes Mellitus Interagency Coordinating Committee

The purpose of this conference was to bring together researchers from the fields of gerontology and diabetology to examine issues surrounding the etiology, impact and responses to diabetes in the aging population. Traditionally, researchers in these two disciplines have worked independently, though their research interests often overlap. However, the rapid growth of the population over sixty, taken together with the increasing incidence of Type II diabetes in that population, seem to call for a more collaborative effort. Therefore, we have invited laboratory and clinical researchers from both disciplines to tell us about what they are learning and to help us to define the next phase of needed research.

Overview of the Problem

The Evolution of the "Disease vs. Aging" Controversy –Reubin Andres

Since gerontologists and diabetologists approach the fact of diabetes in the elderly from different points of view, it may be helpful to articulate the basic differences. In general, diabetologists regard the development of Type II diabetes in the elderly as the result of a disease process. Gerontologists are more inclined to see the same development of diabetes as a fundamental consequence of aging. So the question is whether the decline in glucose tolerance seen in elderly diabetics is a primary biological reaction to a given stimulus or set of events, or whether there are other characteristics about getting old that result in such a decline.

This is not an easy question to address, much less answer. Older people develop a large number of medical problems and take a wide array of medications. Further, they are likely to have changes in diet and activity patterns, as well as body composition when compared to their earlier lives. Any of these variables, alone or in combination, have potential for affecting the body's ability to tolerate glucose. We must then be very careful to be comparing apples with apples as we approach the question.

This leads us to the issue of how we measure glucose tolerance. Over time, our ability to measure glucose tolerance has improved, but there is still a divergence of measures used to diagnose the condition in clinical practice and in research. In order to draw meaningful conclusions from the data we collect we need to have some common reference points. We need to know if the same measure of glucose tolerance means the same thing in twenty year olds, fifty year olds and eighty year olds. We need to follow subjects longitudinally if we hope to be able to develop standard reliable measures that may be used as reasonable predictors for diagnosis and management of diabetes in the future. Combining the efforts of the gerontologists and diabetologists can only benefit this research.

Scope and Impact of Diabetes in the Elderly – Maureen Harris

Data from a survey conducted in 2000 indicate that there are 17 million diabetics in the US, half of which are over 60 years of age. This means that almost 18% of those aged 60 and older have diabetes. According to the survey, nearly a third of all cases of diabetes go undiagnosed. Rates of incidence are higher among non-white populations than among whites.

The implications of this epidemic can be seen in the increase in risk factors for macro and micro vascular disease. Half the diabetics in the study had BBP exceeding 140/90, or uncontrolled. More than half also failed to meet the ADA goals for total cholesterol of 200, and half failed to meet the goal of LDL lower than 130. Additional impact from diabetes in those over age 65 can be seen in the incidence of lower extremity amputation, which increases with age. End stage renal disease is another condition experienced by elderly diabetics at a rate much higher than non-diabetics.

Another area where we see the impact of diabetes in the elderly population is in physical disability. When we look at rates of inability to manage ordinary physical tasks such as walking, climbing stairs, and housework, we see that diabetic women had twice the rate of disability as women without diabetes. The final place where the impact shows is in the significantly higher rate of mortality from all causes in diabetic men and women over age 65, when compared to their non-diabetic counterparts.

Presentations

Pathophysiology of Diabetes in Aging
Chair, Josephine Egan

In order to avoid developing diabetes the body must maintain a balance between insulin secretion and insulin sensitivity. In Type I diabetes there is an absolute decline in insulin secretion. Type II diabetes occurs when insulin sensitivity declines for any reason and insulin secretion fails to increase to restore the balance. Type II diabetes is a progressive disease, so control is an ongoing challenge, often requiring an increase in numbers of medications, finally going to insulin.

The progressive nature of the disease is the result of a continuing Beta cell failure inside the islets. In various studies, researchers found that after the rodents reached middle age, the islets no longer enlarged. The number of Beta cells actually declines, and the remaining Beta cells hypertrophy, so the islet size does not decrease. At the same time, there is a decline in the insulin messenger RNA in the islets and a decline in the total pancreatic insulin. There is also a decline in the sensing mechanism of the Beta cells with age in rodents, so that the specific glucose transporter, as well as glucokinase, the message and the protein levels, both decline with age.

Factors Determining Glucose Tolerance in the Elderly- Marilyn Ader

Without trying to account for the reason, we know that insulin sensitivity decreases with aging and that this decrease in insulin sensitivity is associated with increased mortality from all causes. In spite of the number of studies done to try to determine whether the increase in insulin resistance in the elderly is a natural consequence of aging, or a disease process, controversy still exists. In fact, the body of research produces conflicting data on the question.

We see from the literature that investigators approached the question in various ways, each focusing on different variables. They used animal and human subjects, dynamic and steady state measures, and longitudinal as well as cross-sectional data. They focused on insulin sensitivity in both hepatic and peripheral tissue, as well as insulin secretion under a variety of conditions. They used both lean and obese subjects, and they compared old vs. young, as well as healthy elderly subjects vs. diabetic elderly subjects. Though they were all trying to understand the etiology of increasing insulin resistance with age, they were actually asking different questions. It is not surprising then that the data give us conflicting conclusions.

Though there are differences in the literature, there are also some common conclusions we can draw.

- Peripheral insulin resistance likely exists during the sustained hyperinsulinemic conditions of the glucose CLAMP.
- Under dynamic conditions of the OGTT or the IVGTT, the magnitude of the insulin resistance may be greater.
- Hepatic resistance, impaired suppression of glucose production, may be evident in the dynamic condition.
- Visceral adiposity does increase with age, but there have not yet been enough studies done that have corrected the insulin sensitivity for central fat. We need to know more about age-associated changes in insulin sensitivity associated with visceral adiposity.
- We need to pay close attention to how secretory function is measured. All measures are not equal. We get different results for diagnosis and incidence depending on what measure we use.
- Secretory function needs to be assessed in terms of rising insulin resistance with age.

Basic Mechanisms of Insulin Resistance – Nir Barzilai

We are looking for a cause and effect relationship between aging and insulin resistance. We know that the insulin resistance syndrome in the elderly is associated with obesity, disease, and mortality from all causes. In the rodent model we see that visceral fat appears to pose a much greater risk for morbidity than does the total fat in the body mass index.

We are looking at the hypothesis that longevity is limited by lipotoxicity. Rodents in the wild are lean, extremely active, and survive on far fewer calories than do ad libinum fed animals in the laboratory. This kind of caloric thrift gives the genes the greatest chance of being reproduced. If the animal eats more calories than it needs for survival, and begins to accumulate excess fat, the metabolic system is required to compensate for the excess demand. **It is important to note here that the greatest increase in risk of insulin resistance occurs with an increased distribution of fat to the visceral area.**

We see in obese rodents that when we remove the visceral fat, their insulin sensitivity improves significantly, even when less than 15% of total fat is removed**. Since it is possible for a lean looking individual to have a high concentration of body fat in the abdominal region, it is important that we understand the processes at work in both the increased risk for insulin resistance as it relates to visceral fat, and in the decreased risk generally seen in caloric restriction.**

Insulin Secretory Deficits in the Elderly with and without Diabetes – Graydon Meneilly

In spite of the number of studies done in this field, there still exists a large amount of controversy regarding the cause and impact of insulin secretory deficits in the elderly. When life style factors, such as diet, activity level, and body composition are adjusted for in community dwelling older subjects by multiple regression analysis, the effects of aging per se in the OGTT is very small. One area of concern is the European study

that showed that there is a decrease in insulin clearance in older individuals. This would mean that the ability to maintain physiological levels of glucose in the aging may be due to a reduced rate of insulin clearance, not to an appropriate rate of insulin production. There also seem to be changes in more subtle measures in the elderly involving the burst mass and regularity of insulin pulses, both in rapid and ultradian insulin responses, under both fasting and hyperglycemic conditions.

Lean older people with diabetes tend to have a profound impairment in glucose induced insulin secretion when compared to age matched non-diabetic controls. Obese older people with Type II diabetes have an absence of first phase insulin secretion, but they have a relatively modest impairment in second phase insulin secretion when compared to age matched non-diabetic controls. **All older people with Type II diabetes have marked defects in insulin secretion. The magnitude of the secretory defect is greater in lean patients than it is in obese patients, but all older patients have a defect in Beta cell secretion of insulin for various reasons. With GLP, and potentially with many other interventions that we have at our disposal, we can partly or completely reverse some of the defects in insulin secretion that occur in older people in association with diabetes.**

Basic Defects in Insulin Secretion and the Beta Cell with Age – Peter Butler

The traditional belief has been that humans do not grow new islets over time, yet we have autopsy evidence that new islet production occurs even in those over 90 years of age. There is also speculation that Beta cell mass inevitably decreases with aging, but this has not been demonstrated. However, we still see a typical decline insulin sensitivity for various reasons in humans as they age. Some of this can be attributed to possible genetic defects at the level of the islet. We know that there is a minimum Beta cell mass needed to avoid the development of diabetes. We are beginning to learn what happens inside the Beta cell and the islet that may help to explain Beta cell death and the consequent decline in insulin producing capacity.

There are striking similarities between the decline of Beta cells seen in Type II diabetes and the decline of brain cells seen in Alzheimer's. **There is consistent evidence in both diabetes and Alzheimer's research to indicate that amyloid material exists inside the cells prior to their deaths.** The protein is found only in pathological circumstances. Cell death in both diseases is highly correlated with small intra-cellular aggregates of amyloid. In both diseases there seem to be deficits of chaperone proteins necessary to protect the secretory protein from aggregating as it moves within the cell. **The processes of cell destruction in both Type II diabetes and Alzheimer's are so similar that it is quite possible that if we find the cause for one, we will also find the cause for the other.**

Molecular Events of Insulin Signal Transduction
Chair, Mark Lane

The Possible Role of Insulin Signaling in Aging and the Retardation of Aging and Age-related Disease by Caloric Restriction – Mark Lane

There is essentially no literature about molecular events in the development of diabetes in aging. We have a lot of questions, but few answers about the role of insulin signaling in caloric restriction and its relationship to aging and age related disease. We know that there are many genes and processes that are responsive to insulin within the cell. We also know that ad libidum fed animals die earlier and have higher rates of morbidity than do those on caloric restriction. So there is a high correlation between caloric restriction and extended lifespan. **The insulin pathway is a major sensor and transducer of the energetic status of the**

animal, and we may speculate that this pathway plays a significant role in the benefits seen in caloric restriction.

Caloric restriction reduces "energy" intake and may extend lifespan by altering carbohydrate metabolism or stress resistance**.** When animals can find more than adequate food, more of their energy can be devoted to growth, development, and reproduction. When food is scarce, a higher proportion of energy needs to be devoted to repair, maintenance and survival. **In caloric restriction, the energy expenditure ratio changes to emphasize maintenance and survival, making the organism more resistant to stress. So it appears that stress response is greatly enhanced in caloric restriction and may be significant in life extension.**

The DAF-2 Pathway of the Nematode Caenorhabditis elegans as a Homolog of the Insulin Signaling Pathway in Mammals: Similarities and Differences – Thomas Johnson

C. elegans is an excellent organism for the study of aging. It has only 1000 cells and is thoroughly mapped. In addition, it is optically transparent, enabling researchers to tag particular proteins and track them in the animal. C. elegans offers several classes of gerontogenes for study. The generation length is only three days. When the animals are fed ad libidum, they multiply from one egg to 100,000 worms in a week.

When food supplies are exhausted, the animal form an alternative form called "dauer larvae", a migratory stage during which metabolism continues. When food is inadequate, this condition is sensed by a series of genes, whose basic output is the formation of dauers. These DAF (dauer formation defective) genes are involved in a coordinated pathway that starts with a putative insulin receptor, such as DAF-2 that has very high homology to the insulin IGF-1 receptor in mammals. **Proteins in the insulin signaling pathways in c. elegans are homologous to a great degree with identifiable proteins filling similar functional roles in mammals. There is a signal transduction cascade driven by kinase action whose ultimate output is the DAF-16 gene, which is closely associated with stress resistance and extended lifespan in the worm.**

While the c. elegans model is very useful helping us understand the interaction of the genes in this pathway, the output of these different pathways is quite different. Worms respond to the output by forming dauers, while mammals probably experience some metabolic shift in response to the absence of food. In worms, there is an obvious trade off between dauer formation and reproduction. In mammals, the output from this pathway is perhaps more likely to be expressed in terms of the animal's ability to resist stress, which then has implications for morbidity and lifespan.

The Role of IRS Proteins in Growth and Metabolism – Morris White

Insulin action has an enormous influence on mammalian physiology beyond what we ordinarily think of as glucose metabolism measured by glucose uptake in fat and muscle. In mammalian systems up to 80 or 90% of insulin signals are mediated through IRS (insulin receptor signal) proteins. We have identified a range of IRS proteins and other receptors and understand some of their roles in insulin signaling and response.

The insulin signaling pathway involves a large number of proteins that all need to function in a coordinated way in order to achieve optimum gluco-regulation. These proteins perform the additional function of coordinating the physiology and growth in brain, liver, ovary, adipose and muscle tissues. **We need, therefore, to look at the impact of this pathway beyond the disease processes we typically think of in association with diabetes. We need to examine the specific ways that age related alterations in the insulin signaling pathway influence the development of a wide range of age associated diseases and related disability.**

Insulin Signaling and Action in Skeletal Muscle: Effects of Age and Caloric Restriction – Gregory Cartee

Muscle is important for disposing of blood glucose in response to insulin. Muscle insulin resistance is an early defect in Type II diabetes, and muscle function is highly dependent on metabolism. Insulin signaling is therefore, very important to muscle function. In order for insulin to enter the muscle cell, a GLUT 4 transporter must move to the cell surface. We set out to describe the calorie restriction effect on glucose transport in animals at various ages in both calorie-restricted groups and ad libidum fed groups. We used isolated muscle cell preparations for our analyses.

We looked at both long and short- term calorie restriction and found that there were significant improvements in glucose transport in both cases. Though there are declines in GLUT 4 abundance with age, we see significantly more cell surface insulin in elderly CR animals than in the elderly ad libidum fed animals at the same insulin levels**. We have reason to believe then, that age related insulin resistance in skeletal muscle likely involves altered insulin signaling.**

Old animals do respond to single session and chronic exercise with a substantial increase in insulin stimulated glucose transport. Skeletal muscle remains responsive to calorie restriction and to exercise induced improvements and insulin sensitivity during old age. The underlying mechanisms for improved insulin signaling and action with calorie restriction and exercise appear to be different, yet both likely involve amplified insulin signaling.

Prevention and Treatment
Chair, James Meigs

Carbohydrate Metabolism in Dietary Restriction and Aging – Mark Lane

We are testing the hypothesis that caloric restriction will extend life span, prevent or delay onset of age related diseases, and slow the rate of aging in rhesus monkeys. The work is being done at a three labs, using a range of diets, feeding protocols and ages of the animals at the initiation of restriction. In calorie restricted animals we find a decline in total body fat, body weight, and abdominal fat. CR animals have a significant reduction in the peak level of glucose. This goes up with age. Glucose tolerance goes down with age.

When we surveyed the medical records of the monkeys for chronic disease and mortality in both the calorie restricted populations and the controls, preliminary data indicate that calorie-restricted animals have only half the deaths due to chronic disease seen in the control animals**. Data from both rodents and monkeys indicate that caloric restriction is an effective means for improving glucose tolerance and increasing insulin sensitivity. The effects of calorie restriction and gluco-regulation can occur after only a short time on restriction and may not be entirely dependent on changes in body composition.**

Glycemia and Risk for Cardiovascular Disease – James Meigs

We used the Framingham Heart Study to look at the relationship between glycemia and risk for CVD. We looked at data from both the original cohort study and the offspring study and asked the following questions:

1. What is the prevalence of diabetes with age using various diagnostic criteria?

2. What is risk for CVD associated with hyperglycemia among older persons? What is the association between hyperglycemia and CVD?
3. What is the risk for CVD associated fasting and 2-hour hyperglycemia measures according to different thresholds?

Though the data are limited in a number of ways, we are able to draw some conclusions.

- Diabetes is common, even among the very old subjects. If that is true, and people with diabetes tend to die young, then new cases are continually developing, even in the very old.
- Isolated post challenge hyperglycemia is very common in older people, so a fasting plasma glucose screening would fail to identify many in this population at increased risk for CVD.
- Hyperglycemia is an independent CVD risk factor in older people.
- Hypertension is an important modifiable CVD risk factor in the elderly.
- Hypertension is a highly prevalent concomitant of diabetes.
- Post- challenge hyperglycemia is an independent risk factor for CVD, especially in older subjects. In thinking about interventions to reduce CVD, it may be worth focusing on post- challenge hyperglycemia is an attractive target.

The Pathway from Diabetes to Disability: Optimal Targets for Intervention in the Elderly – Helen Hazuda

This talk presents a series of statistical analyses using data from the San Antonio Longitudinal Study on Aging (SALSA). The study contains a nested, case controlled study that follows incidence of functional decline in subjects with and without diabetes. The aim of the study is to better understand the pathways between disease and disability in order to identify optimal targets for intervention. We are using a basic model identifying the stages leading to disablement, which include pathology, impairment, functional limitation, and disability. Data was collected at three different times over 18 months, looking for both trends and causes of disablement.

As different variables are included, the model becomes very complex. We tested the various hypothesized pathways by first adjusting for contextual variables of age, gender, ethnic group, education, and household income. We then begin to see involvements that we did not expect, such as the significant decline in musculo-skeletal function in the presence of diabetes**. Although the percent of disability found to be due to diabetes was modest when compared to that attributable to context, even small percentages have a large public health impact in a population of 8.3 million diabetics. It is therefore important to be able to identify and understand the modifiable variables so that we can begin to develop effective interventions.**

Pharmacological Treatment of Diabetes in Elderly People: Challenges and Opportunities – Jeffery Halter

Establishing appropriate, effective pharmacological treatment for elderly people with diabetes is a challenge because we don't know who has this condition, why they have it, or what we are trying to accomplish for them. We don't have uniform protocols or measures for diagnosis. Our main concerns are the range and rate of development of complications seen in elderly people with Type II diabetes, as well as the increase in risk factors for other diseases**. Many elderly people with diabetes have co-existing health problems, and are on several medications, some with side effects, so controlling hyperglycemia and establishing clear treatment priorities becomes extremely complex.**

The clinical and research picture is further complicated by the varying perceptions of this population held by practitioners. Diabetologists tend to view these people as likely to be frail, dependent, and poor candidates for aggressive intervention, while the image held by most gerontologists is that most older people with diabetes are quite functional, independent, interested in their health and pursuing their interests in life. Clearly, this difference in perception leads to different levels of aggression in treatment, so we need to develop criteria to help clinicians make decisions about appropriate types and degrees of treatment in response to the actual overall condition of the patient.

Type II diabetes is hard to treat over time. It is a progressive disease and requires an increasing number and dose of medications as the patients age. We generally fail to achieve ADA goals in screening for frequently seen complications in this population. For some common circumstances, we have thinly researched guidelines or none at all, as in the case of post-prandial hyperglycemia. With improved screening and diagnosis, we could much more adequately address the needs of the elderly who have diabetes than we now do.

Clearly, the treatment goals appropriate for an independent, active older person with diabetes need to be different from those for a patient in a skilled nursing setting. We have a variety of pharmacological treatment options including the standard collection of sulfonylureas, a growing number of specifically targeted insulins, as well as the newer combination therapies**. We need to work harder to establish and promote appropriate treatment goals for all elderly persons with diabetes. We should not be excluding people from treatment arbitrarily because of age.**

Clinical Overview of Diabetes and Aging - Robert Schwartz

This is a personal view of the current state of diabetes and aging. We can see that the population over age 65 is increasing rapidly as is the incidence of Type II diabetes in that population. This increase carries with it a substantial burden of medical complications, cost, and disability. At present, Type II diabetes in the elderly is seriously under diagnosed, so it is also under treated. We do an inadequate job of employing the tools we have available to screen for and diagnose the disease. We lack a commonly accepted protocol for diagnosis and treatment in the elderly population.

Treatment of diabetes in the elderly is complicated because of the changes in physiology seen in aging, the increase in risk factors for other diseases, the frequent occurrence of other medical conditions, and multiple medications. Type II diabetes is a progressive disease, making it very difficult to treat over the long term. Available treatments typically have either high cost or considerable risk of hypoglycemia associated with them, and they are often inadequate to control the condition in the elderly. We do see promise in the new drug, Metformin.

Finally, appropriate treatment is frustrated by the belief on the part of many clinicians that individuals in this population are frail and have very limited life expectancies, so it is inappropriate to pursue aggressive treatment of their diabetes. In fact, at age 65 many women can expect to live for 19 years and many men can expect to live for 15 years. Under-treatment for diabetes and associated conditions may contribute substantially to portion of the remaining lifespan that will be spent in a dependent state. The public health consequences of untimely and inadequate care of the elderly with diabetes will be enormous unless we can work together to improve both the timeliness of intervention and the level of that care.

Work Groups

Conference participants divided into three topic groups to design and compile lists of questions and topics that describe the most pressing research needs in the emerging field of diabetes and aging. Each group then presented its work to the full conference. The work group reports follow.

Patho-physiology Work Group Report

1. What is the role of body fat distribution in age-related peripheral and hepatic insulin action and glucose intolerance?
2. What is the role of insulin independent processes in age-related glucose intolerance?
3. What are the metabolic consequences of fat products such as free fatty acids and fat derived peptides, and how do they change with aging?
4. What are the metabolic consequences of age-related changes in glucose levels?
5. What are the mechanisms contributing to post-prandial hyperglycemia, that are seen as a function of age?
6. Does Beta cell function change with age, and what are the mechanisms of change?
7. How does Beta cell mass change with age, and what are the mechanisms?
8. Can adverse changes in function and mass be ameliorated?
9. Should we establish a cooperative group in order to obtain human autopsy tissues such as pancreas, liver, fat, muscle?
10. Is there a mechanism whereby we in the Type II DM field can obtain human islet cells for study?
11. What are the mechanisms underlying the change in the relationship between insulin secretion and insulin action with age? Can they be reversed?
12. Given the comparable pathology seen in Alzheimer's disease and Type II diabetes, are the mechanisms leading to the neural and Beta cell dysfunction related?

Insulin Signal Transduction Group Report

General considerations

1. In addition to diabetes, insulin and insulin action are likely to be involved in many age associated diseases and pathologies.
2. It is important to more specifically define the role of insulin action on various age associated pathologies including syndrome x, Alzheimer's, etc.
3. Alzheimer's literature is beginning to discuss Alzheimer's as "diabetes of the brain".

Recommendations

1. We need to describe changes in insulin signaling that occur with aging in rodent models first. This is not necessarily looked upon favorably by study sections, and review boards, etc. Therefore it may require different funding mechanisms than usual.
2. Once the descriptive studies are done, the next step is to utilize those findings to develop targets for enhancing insulin action in peripheral tissues of older and /or diabetic individuals.
3. We need to define the role of tissue specific changes (other than those we typically think of as being involved in diabetes) in insulin action with age, independent of those changes involved solely in carbohydrate metabolism.

4. We need to understand the impact of aging and hyperglycemia, both independently and together on Beta cell function. Then we need to develop targets for improving Beta cell function in older individuals.

Models and Model Systems

1. We need to identify genes and mutations in **humans** associated with insulin resistance in aging, looking at micro-array and classic epidemiological studies.
2. Once those genes are identified, they could then be used in **rodent** models to do more mechanistic studies, either by inserting the human gene, or by altering the expression of a rodent homology to determine the effects or significance of that gene.
3. **Non-human primates** offer some advantages for this work because most of the variables can be controlled in a laboratory setting.
4. More functional (physiological/ biochemical) studies in **c. elegans** are needed to relate genetic studies in the worms to mammalian aging and disease.

Interventions

Both calorie restriction and exercise have been shown to improve insulin action, perhaps even in older individuals, and should be utilized in studies of aging and insulin action.

Miscellaneous

1. Is it better in aging to be more or less insulin sensitive?
2. Are there separate contributions of insulin level vs. insulin sensitivity to age-associated disease? Is it only insulin sensitivity, or is there some worth in considering the impact of hyper-insulinemia or insulin level in the blood itself?
3. If diabetes is a disease of signal transduction, maybe glucose has been over-emphasized in its importance. Should we consider insulin and insulin action in greater detail in diabetes as well as other diseases of aging?
4. We need to better understand the role of signal transduction mechanisms in relation to regulation of insulin secretion.
5. What is the role of nutrient sensing pathways in a variety of age related changes and diseases?

Prevention and Treatment Work Group Report

How do we define Type II diabetes in the elderly?

Research Questions

1. Are there fast vs. slow progressors?
2. Should OGTT screening be performed?
3. Can a combination of fasting plasma glucose and HbA1c be used to identify at risk subjects?
4. Is fasting insulin a useful marker of disease? Goldberg's paper emphatically said no for older people.
5. Should, and how should, insulin assays be standardized?
6. Are there existing population data bases that can be exploited to advance knowledge?
7. What new data should be collected?

What causes the complications of diabetes in the elderly?

- Hyperglycemia is common.
- Coexistent risk factors are common.
- Treating hyper-lipidemia and hypertension is beneficial.

Research Questions

1. What is the significance of isolated post-challenge hyperglycemia as a risk factor? Is this true for hyperglycemia that happens after a meal?
2. What is the marginal benefit of controlling hyperglycemia beyond control of lipids and BP?
3. Are lifestyle interventions (exercise and weight loss) sage and effective in the elderly?
4. Is the observational data sufficiently complete that RCTs can now be recommended?

How should we prevent /treat diabetes in the elderly?

- Goals for treatment overall may not be applicable in the elderly. One size does not fit all.
- We know a lot about how to prevent complications.
- Evidence-based recommendations are not being applied in clinical practice.

Research Questions

1. What are appropriate goals for glycemic control in sub-groups of elderly aimed at preventing death or increasing function?
2. When should treatment be started, with prevention, with onset of symptoms, or with the appearance of complications?
3. What are appropriate goals of treatment? Prevention of mortality? Prevention of complications? Quality of overall life?
4. Poly-pharmacy is a problem with respect to cost, adherence, and side effects.
5. How can we address this?

6. Can we package drugs together to minimize the number of pills?
7. How can evidence be translated into practice?
8. What types of studies will inform better evidence-based care? We need to fund research to study care in managed care settings.
9. How can modern informatics/technology be used to enhance care?
10. How can we develop the clinical, geneological, and epidemiological data to better tailor treatment to individual differences in older patients?

Diabetes Mellitus Interagency Coordinating Committee Meeting on Diabetes and Aging

Program Activities in Diabetes and Aging
Chair, Sanford Garfield

This afternoon we will hear presentations from DMICC agencies telling us what they are working on and what opportunities are available in their organizations for further research.

Program Activities and Research Opportunities

The table below is a summary of the presentations by representatives from DMICC member organizations. It gives a brief description of activities being carried on in each, as well as resources available in the organization for further research. It details available databases, populations, funding sources, etc. mentioned by the presenters. Contacts for each organization are included.

Program Activities and Research Opportunities

Organization	Program Activities and Research Opportunities	Contact
Centers for Disease Control	**Program Activities** • **Surveillance and epidemiology** of incidence of disease, and its causes, treatments, complications and resulting disability. • **Translation research**- study of whether, how, and to what degree of success efficacious interventions are being implemented at the clinical level. • **Implementation of research findings**- Serve as clearinghouse for wide range of research so that it is made available and can be put into practice at the clinical level. **Current Study** Translating Research Into Action in Diabetes-a multi-center of diabetes treatment in managed care settings.	Edward Gregg edg7@cdc.gov
Indian Health Service	**Characteristics of Native American Populations** • Strong cultural identity • High rate of poverty and underinsurance • Generally poor health with high rates of alcoholism • High incidence of diabetes in young and old • Existing diabetes care, prevention, and education programs emphasize service to the elderly. **Research needs** HIS needs data of all kinds related to diabetes in these communities, especially in the elder population.	Lorraine Valdez s.lorraine.Valdez@mail.his.gov
Veterans Health Administration	**Program Description** • Covers 9.3 million people over age 65, primarily male • Largest integrated health care program in the country, comprising 22 regional networks • 13% of $21 billion yearly budget spent on geriatrics • All patients linked to primary care practitioner • Performance measures in place for management of patient care	Judith Salerno judith.salerno@mail.va.gov

Veterans Health Administration cont.	**Research Opportunities** Data mining of completely computerized patient records, as well as information on income and demographics.	
National Diabetes Education Program	**Program Description** • Public and private partners working together to reduce the pain suffering and death due to diabetes. • Trying to reach diabetics and their families as well as those who treat and pay for care • Want to increase awareness of diabetes to improve diagnosis, treatment, lifestyle and testing **Current Activity** "Control Your Diabetes for Life" Campaign, aimed at promoting the message that diabetes is treatable, and that successful treatment is dependent on the involvement of patients in their own care.	Mimi Lising mimi_lising@nih.gov www.ndep.org
American Diabetes Association	**Program Description** Mission is to prevent and cure diabetes and improve the lives of people affected by diabetes through • Supporting research - especially for novel approaches, new investigators, and supplemental studies • Providing information to - • professionals - professional programs, journals, clinical practice recommendations, and recognition and accreditation programs for physicians and organizations. • consumers – website, including all journals and clinical recommendations, call center, publications, and referrals to recognized programs. Outreach focus on children, African Americans, Hispanic Americans, and Native Americans. • Advocacy- to increase funding for diabetes research, improve insurance coverage, end discrimination in schools and in work places **Opportunities** At present trying to expand limited activity on diabetes in aging. Looking for volunteers to serve on a professional council on aging.	Marion Parrot mparrott@diabetes.org www.diabetes.org
National Institutes on Aging	**Biology of Aging Program** funds research in • Non-enzymatic glycation • Caloric restriction	Huber Warner warnerh@gw.nia.nih.gov

National Institutes on Aging continued	• Insulin signaling **Research Opportunities** New animal model – Dwarf mice, extremely long lived, having defective genes involved with pituitary development. Lower blood glucose, higher insulin sensitivity, lower insulin levels that other laboratory animals. **Geriatrics Program** funds research on • Body composition changes • Metabolic changes • Caloric restriction **Research Opportunities** Currently waiting to award funds for study of caloric restriction in non-obese elderly people.	Chhandra Dutta duttac@exmur.nia.nih.gov
National Institute of Diabetes, Digestive and Kidney Disease	**Program Activities** Supports research across divisions that contribute to understanding of diabetes and the aging process **Endocrinology and Diabetes Division** supports • Diabetes Prevention Program- Multi-center randomized controlled trial to determine whether interventions can be designed that can prevent the development and onset of Type II diabetes • Investigator initiated grants **Division of Digestive Diseases and Nutrition** supports • Look Ahead study following the consequences of intentional weight loss in population of individuals with Type II diabetes over the course of the aging process. Recruitment of 45-75 yrs olds, to begin in June 2001. **Division of Kidney, Urologic and Hematologic Diseases** supports • US Renal Data System in developing the database that follows population with end stage renal disease.	Sanford Garfield garfields@extra.niddk.nih.gov
National Heart, Lung and Blood Institute	**Program Activities** • Honolulu Heart Study – observational study started in 1965, including over 8000 Japanese American men. Looking at stroke in men age 45 to 65 at study entry. • Strong Heart Study – study of three geographically diverse groups of 4500 Native Americans age 45-74. Currently in year 12. Plan	Robin Boineau boineau@nhlbi.nih.gov

National Heart, Lung and Blood Institute continued	to study 3600 people from 120 families for genetic linkage analyses. • Cardiovascular Health Study – four US communities, aged 65 and older. • Framingham Heart Study • Action to Control Cardiovascular Risk in Diabetes - multi-center trial to assess rate of major CVD events that can be reduced by intensive control of blood sugar. New study intended to have 10,000 participants. Will compare blood pressure control and diabetes control for individuals aged 45 and older in Native Americans, 55 and older in Asian and Hispanics, and 65 and older in Caucasian and African Americans. Expect 60% of study population will be 65 and older. **Research Opportunities** • Public use data sets available for data collected up to 1996 on longitudinal study of Japanese men in Honolulu. • Cardiovascular Health Study – four US communities, aged 65 and older. Substantial amount of data available for mining. Active diabetes working group.	

Adjournment

Approved by: _____

Date: _____

Allen Spiegel, MD, Chair
Diabetes Mellitus Interagency Coordinating Committee, NIDDK

Approved by: _____

Date: _____

Sanford Garfield, PhD, Executive Secretary
Diabetes Mellitus Interagency Coordinating Committee, NIDDK