

Diabetes in Elderly Adults

Graydon S. Meneilly¹ and Daniel Tessier²

¹Division of Geriatric Medicine, Department of Medicine, University of British Columbia, Vancouver, Canada.

²Division of Geriatric Medicine, Department of Medicine, University of Sherbrooke, Quebec, Canada.

Diabetes is common in the elderly population. By the age of 75, approximately 20% of the population are afflicted with this illness. Diabetes in elderly adults is metabolically distinct from diabetes in younger patient populations, and the approach to therapy needs to be different in this age group. Diabetes is associated with substantial morbidity from macro- and microvascular complications. Several lines of evidence suggest that optimal glycemic control and risk factor modification can substantially reduce the risk of complications in elderly patients. In the past, treatment options were limited. However, recent studies have delineated several new and exciting therapeutic opportunities for elderly patients with diabetes.

EPIDEMIOLOGY

Numerous studies have evaluated the incidence and prevalence of type 2 diabetes in the elderly population. The most recent Health and Nutrition Survey, HANES III, suggests that approximately 20% of the population develop diabetes by the age of 75 (Figure 1) (1). At least half of these patients are unaware they have the disease (2). The prevalence of diabetes is much higher in some ethnic groups, especially Native Americans, Hispanics, blacks, and Micronesians. Because elderly patients with diabetes are living longer and are likely to use increasing amounts of scarce health care resources in the next several decades, diabetes in aged adults may ultimately prove to be the most important epidemic of the 21st century.

PATHOGENESIS

There are several lines of evidence to suggest that type 2 diabetes in elderly adults has a strong genetic predisposition. Elderly patients with a family history of diabetes are more likely to develop the disease as they age (3). The prevalence of diabetes is increased in certain ethnic groups, implying that genetic factors play an important role. In elderly identical twins, the prevalence of diabetes is markedly increased in siblings of affected patients (4). In addition, in sibling pairs that are discordant for diabetes, nondiabetic siblings clearly have evidence of disordered glucose metabolism.

Several other factors contribute to the high prevalence of diabetes in the elderly population (5). There are a number of age-related changes in carbohydrate metabolism (such as alterations in glucose-induced insulin release and resistance to insulin-mediated glucose disposal) that interact with genetic background to explain the progressive increase in the incidence of diabetes with aging. Lifestyle factors are also important. Individuals who are obese (especially if the distribution of body fat is central), who consume diets that are high in saturated fat and low in complex carbohydrates, or who are inactive are more likely to develop diabetes as they age. Lower testosterone levels in men and higher values in women also appear to be risk factors for the development of diabetes in elderly persons, although the mechanistic significance of these abnormalities is uncertain.

A number of studies have carefully evaluated glucose metabolism in middle-aged patients with type 2 diabetes (6). These studies have shown that patients have several metabolic abnormalities, including increased fasting hepatic glucose production, altered glucose-induced insulin release, and marked resistance to insulin-mediated glucose disposal. Recently, investigators (7–9) have also carefully assessed the metabolic changes in lean or obese older subjects with type 2 diabetes. In contrast with younger patients, hepatic glucose production was within the normal range in elderly patients (Figure 2). Lean older patients with type 2 diabetes had a marked impairment in glucose-reduced insulin secretion (Figure 3), but relatively normal insulin-mediated glucose disposal (Figure 4). It has recently been suggested that thin elderly diabetics have a syndrome intermediate between type 1 and 2 diabetes, which might properly be thought of as type 1 1/2 diabetes (10). In contrast, obese older patients have relatively normal glucose-induced insulin secretion (Figure 3), but marked resistance to insulin-mediated glucose disposal (Figure 4). Tumor necrosis factor α (TNF- α) is a cytokine produced by adipocytes that is believed to contribute to the insulin resistance seen in younger patients with diabetes. Of interest, there is a strong correlation between TNF- α levels and insulin resistance in obese elderly patients with diabetes (11), although the therapeutic relevance of this finding is unclear. The previously described data suggest that diabetes in elderly persons is metabolically distinct and may require a different therapeutic approach than is commonly applied to middle-aged patients.

Other metabolic defects have recently been defined in elderly patients with diabetes. Glucose uptake in men occurs by insulin-mediated and non-insulin-mediated mechanisms (12). In normal subjects, approximately 50% of glucose uptake after a meal occurs as a result of non-insulin-mediated glucose uptake (NIMGU). In younger subjects with insulin-resistant conditions, NIMGU may be responsible for an even greater proportion of postprandial glucose disposal. Studies that have evaluated non-insulin-mediated glucose uptake in middle-aged patients with diabetes have produced conflicting results (12). Recently, we demonstrated that non-insulin-mediated glucose uptake was significantly impaired

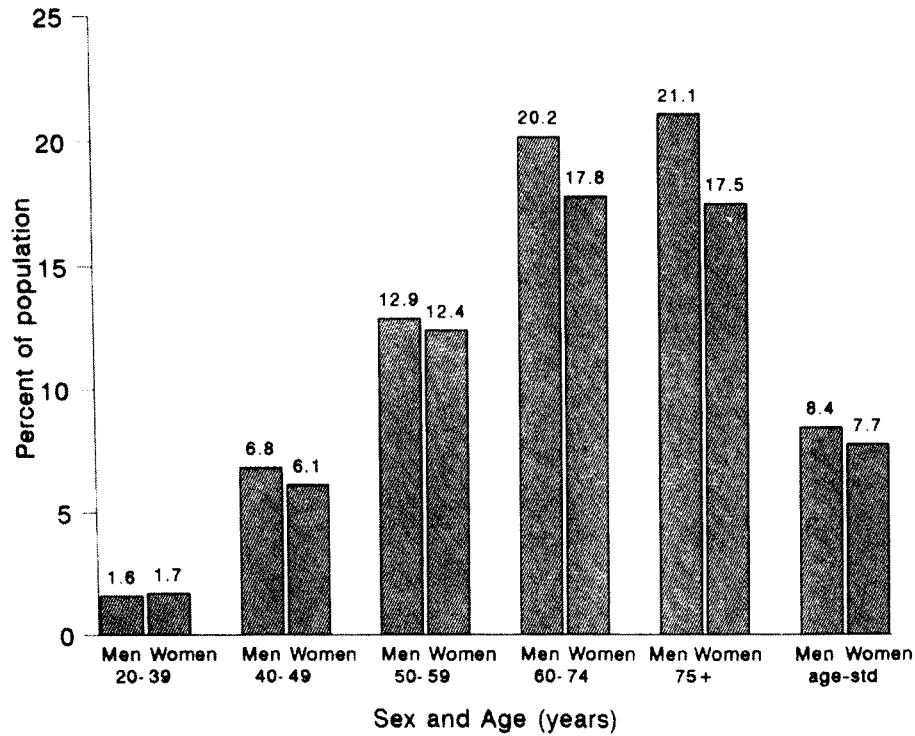


Figure 1. Prevalence of diabetes in men and women in the U.S. population, based on the Health and Nutrition Survey, HANES III. Reprinted with permission from Harris and colleagues (1).

in elderly patients with diabetes (13). Interventions that may enhance NIMGU are currently being tested in clinical trials, and these interventions may ultimately prove to have important therapeutic relevance to aged adults.

It is well known that diseases characterized by insulin resistance (such as hypertension, obesity, and type 2 diabetes) are associated with endothelial dysfunction and an increased incidence of atherosclerosis (14). Insulin is known to stimu-

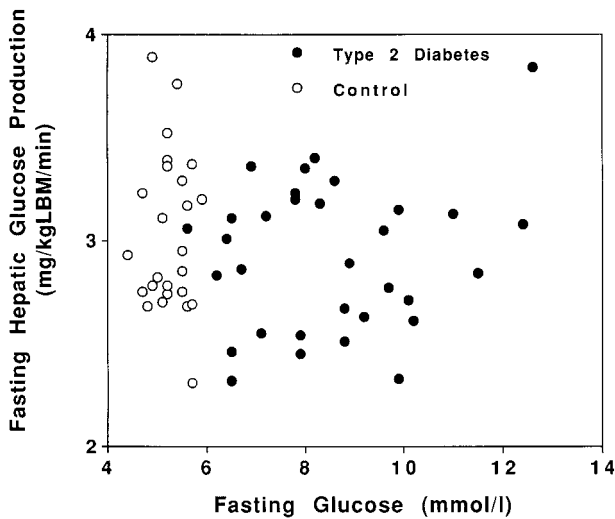


Figure 2. Fasting hepatic glucose production in relation to fasting glucose values in elderly controls and patients with diabetes.

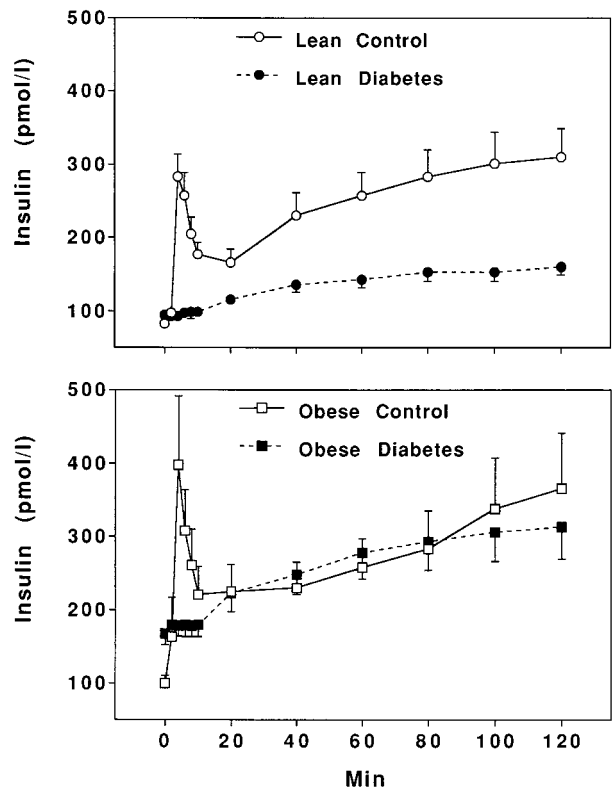


Figure 3. Glucose-induced insulin release in elderly controls and patients with diabetes.

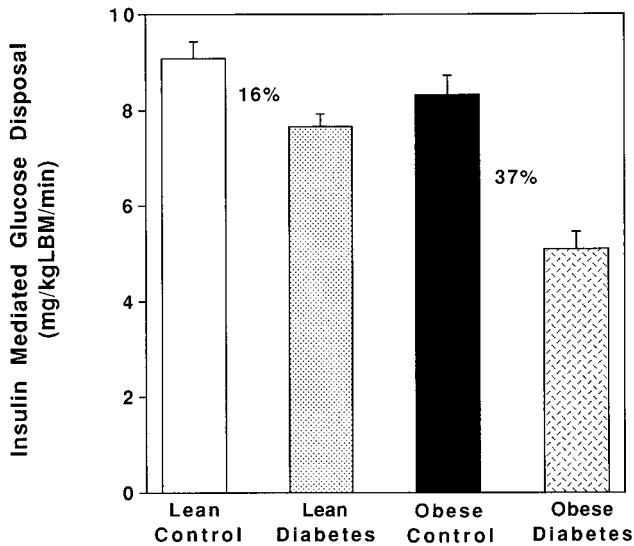


Figure 4. Insulin-mediated glucose disposal in elderly controls and patients with diabetes.

late blood flow by an endothelium-dependent mechanism. Insulin-mediated vasodilation may be impaired in younger subjects with diseases characterized by insulin resistance, although the data are controversial. It has also been implied that insulin-mediated blood flow may be an important component of insulin-mediated glucose uptake, although studies in normal subjects and younger patients with diseases characterized by insulin resistance have again produced conflicting results. Recently, we demonstrated that insulin-mediated blood flow is impaired with normal aging, and there is an even greater impairment in this parameter in elderly patients with diabetes (9,15). Although the role of the alteration in insulin-mediated vasodilation in the insulin resistance that occurs with aging and diabetes is uncertain, it is clear that reduced insulin-mediated vasodilation is a marker of endothelial dysfunction in elderly patients with diabetes. Further studies are needed to determine whether enhancing insulin-mediated vasodilation will alter insulin resistance, improve endothelial function, or reduce the risk of atherosclerotic events in this population.

Autoimmune phenomena are an important contributing factor to the insulin deficiency that occurs in younger patients with type 1 diabetes (5). Autoimmune factors may also have a role to play in the insulin deficiency that occurs in lean elderly patients with diabetes, but the data are conflicting (5,16–18). Further investigations are required to resolve this issue.

Molecular abnormalities that occur in elderly patients with diabetes have not been fully elucidated (5). The glucokinase gene is the glucose sensor of the β cell. Theoretically, alterations in this gene could explain defects in insulin secretion, but it is not clear whether the function of this gene is impaired in older people with diabetes. Insulin-receptor tyrosine kinase activity in skeletal muscle has been reported to be altered in elderly patients with diabetes and insulin resistance, but it is uncertain whether this is the cause or the result of the elevated glucose levels in these patients.

PRESENTATION AND CLINICAL FEATURES

One half of older persons with diabetes are unaware they have the illness, suggesting that symptoms of hyperglycemia are rarely present in this patient population (5). This may be because the renal threshold for glucose increases with age, so that no sugar is spilled into the urine until the glucose level is markedly elevated. In addition, because thirst is impaired with normal aging, polydipsia is unlikely in elderly patients with diabetes, even if they are hyperosmolar as a result of marked hyperglycemia. If symptoms do occur, they are generally nonspecific (confusion, failure to thrive, incontinence, etc.). Often, diabetes presents for the first time in an elderly person who is hospitalized with a complication that may be related to diabetes, such as a myocardial infarction or a stroke. In frail elderly nursing home patients, non-ketotic hyperosmolar coma may be the first sign of diabetes.

Several unique syndromes occur in elderly patients with diabetes (5). Diabetic neuropathic cachexia presents with weight loss, depression, and painful peripheral neuropathy, and generally is resolved without specific treatment in a few months. Diabetic amyotrophy occurs almost exclusively in older men with diabetes. Malignant otitis externa, a necrotizing infection usually caused by pseudomonas, occurs primarily in elderly patients with diabetes. The papillary necrosis that can occur with pyelonephritis develops primarily in elderly patients with diabetes. Spontaneously resolving intradermal bullae of the feet and the painful limitation of shoulder movements occur more commonly in elderly patients with diabetes. Finally, diabetes in elderly persons has been associated with an increased risk of accidental hypothermia.

Community-dwelling elderly patients with diabetes are less obese and more likely to be hypertensive when compared with younger patients with this illness (5). When compared with community-dwelling elderly persons with diabetes, elderly nursing home patients with diabetes are more likely to be treated with diet, less obese, less likely to be treated with insulin, and have a higher incidence of macro- and microvascular complications and skin infections. Finally, when compared with nursing home residents without diabetes, elderly nursing home patients with diabetes have a higher incidence of infections and micro- and macrovascular complications.

COMPLICATIONS

Diabetes is the sixth most common cause of death among elderly adults. However, its role in mortality in the elderly population is probably understated, because when patients die of cardiovascular causes, diabetes is often not listed as a contributing cause of death (5,19,20). The principal cause of death in elderly patients with diabetes is cardiovascular disease, and these patients have nearly twice the mortality rate of age-matched controls without diabetes. It has been estimated that in patients who develop diabetes over the age of 65 years, life expectancy is shortened by at least 4 years (19). Mortality in elderly patients with diabetes is strongly correlated with long-term variability of plasma glucose and Hgb A1C values (5,21,22). People with diabetes have a poorer quality of life and a higher frequency of chronic disease than do age-matched controls

without diabetes, and diabetes is one of the strongest predictors of functional decline in longitudinal studies (5,23–26). Finally, elderly patients with diabetes use almost twice as many inpatient and outpatient resources as elderly people without diabetes (5).

The risk of macrovascular events (cardiovascular disease, cerebrovascular disease, and peripheral vascular disease) is doubled in elderly patients with diabetes when compared with controls (5). The risk of these events is related to duration of diabetes, Hgb A1C values, and the presence of traditional risk factors such as smoking, hypercholesterolemia, and hypertension (5). Although randomized trials are required to definitively address this issue, the data imply that risk-factor modification and improved glycemic control will result in improved outcome in elderly persons (5).

The risk of microvascular complications is also increased in elderly persons, and, again, there is a strong correlation between the risk of these complications and Hgb A1C, duration of diabetes, hypertension, and hyperlipidemia (5). Although no randomized controlled trials have been conducted in this regard, the previously described data again suggest that improved glycemic control and risk-factor modification may be of value.

The risk of severe or fatal hypoglycemia associated with the use of oral agents or insulin increases exponentially with age (5,27). This increased risk of hypoglycemia in elderly persons is related, in part, to reduced responses of glucagon, the most important counter-regulatory hormone (Figure 5). Because of this glucagon deficiency, elderly subjects are critically dependent on epinephrine to prevent hypoglycemia (28). Other contributing factors to the high prevalence of hypoglycemia include lack of knowledge of the warning symptoms of hypoglycemia and reduced awareness of autonomic warning symptoms, even when the patient has been educated regarding the nature of these symptoms (5). When elderly subjects do experience symptoms of hypoglycemia, the symptoms tend to be less intense and more nonspecific (29). It has been suggested that hypoglycemic awareness may be enhanced in older people treated with animal insulin

rather than human insulin, but these data are controversial (30,31).

Elderly patients with diabetes have a higher incidence of depression and impaired cognitive function when compared with age-matched controls without diabetes (5). Depression in elderly patients with diabetes is a strong predictor of hospitalization and death (32). The changes in cognitive and affective function are closely correlated with lipid, blood pressure, and Hgb A1C values, and recent studies suggest that improved glycemic control may enhance cognition and mood in this patient population (5). Diabetes in elderly persons is clearly a risk factor for vascular dementia and may also be a risk factor for Alzheimer's disease, although the latter is controversial (33).

DIAGNOSIS

The diagnostic criteria of the American Diabetes Association (ADA) for diabetes mellitus have recently been revised as follows (34): Symptoms of diabetes plus a casual (any time of day without regard to time since last meal) plasma glucose value of ≥ 11.1 mmol/l (the classic symptoms of diabetes include fatigue, polyuria, polydipsia, and unexplained weight loss); a fasting plasma glucose value of ≥ 7.0 mmol/l (fasting is defined as no caloric intake for at least 8 hours); or a plasma glucose value in the 2-hour sample of the oral glucose tolerance test (OGTT) of ≥ 11.1 mmol/l. The test should be performed using a load of 75 g of anhydrous glucose.

The criteria were changed because they lacked sufficient sensitivity. In addition, the values used for diagnosis were not concordant between fasting glucose values and the OGTT. The fasting glucose level used in the earlier criteria (7.8 mmol/l) defined a greater degree of hyperglycemia and a greater risk of macrovascular events than the 2-hour glucose value from the OGTT that was diagnostic of diabetes (11.1 mmol/l). Because a substantial number of elderly patients have undiagnosed diabetes, and these patients appear to have an increased incidence of macrovascular events, the current criteria recommend that a fasting glucose value be performed every 3 years in elderly patients at low risk for diabetes and yearly in patients at high risk. Patients at high risk include those with obesity, hypertension, ethnicity, family history, or the presence of complications commonly associated with diabetes. If the efforts to standardize Hgb A1C measurements come to fruition, this test may ultimately supplant the fasting glucose value as the preferred screening method (35). In addition, some studies suggest that substantial numbers of elderly subjects have fasting glucose values < 7 mmol/l, but also have a diabetic glucose tolerance test, and these subjects have an increased risk of macrovascular events when compared with nondiabetic controls (36–38). It is possible that OGTT may also be considered in the future for screening, particularly in high-risk patients or subjects with impaired fasting glucose levels (6.1–7 mmol/l). Further studies are needed to determine the optimal screening method in aged adults.

TREATMENT GOALS

All clinicians agree that blood glucose should be controlled well enough in elderly patients to prevent symptoms

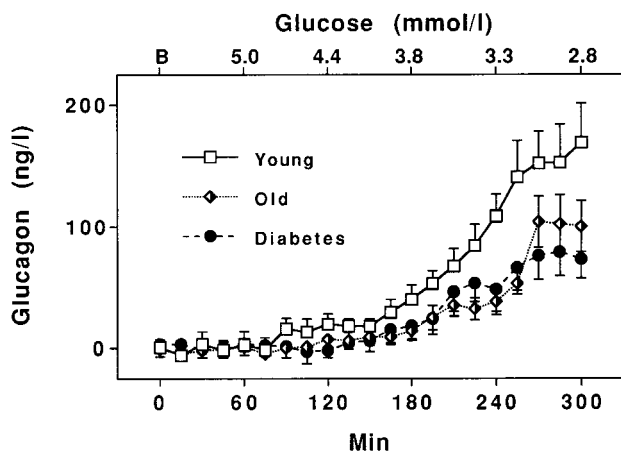


Figure 5. Glucagon responses to hypoglycemia in healthy young, healthy elderly, and elderly patients with diabetes.

associated with hyperglycemia. The UK Prospective Diabetes Group (39) demonstrated that control of diabetes in middle-aged subjects reduces the risk of microvascular, and possibly macrovascular, complications. As yet, there are no data from randomized controlled trials in elderly subjects to determine the level of glycemic control in this patient population that maximizes benefit but minimizes the risks of therapy, in particular, hypoglycemia. However, numerous prospective epidemiologic studies have shown a strong correlation between Hgb A1C values and the risk of complications in this patient population (5). If improved glycemic control alters the risk of complications and associated functional disability in aged adults, this intervention could have a profound effect on the quality of life for elderly persons.

Recent cost-benefit analyses have called into question the cost effectiveness of aggressive glycemic control in aged adults (40–42). Before these analyses are widely applied by health-policy makers as a justification for a nonaggressive approach to the care of the elderly diabetic, the assumptions underlying these studies must be critically evaluated (5). The analyses were based entirely on data from investigations in younger patient populations, the authors only assessed the benefits of control for patients who did not have complications to begin with, and only microvascular complications were considered. Diabetics tend to engender increased costs to the health care system for non-diabetes-related illnesses (respiratory infections, etc.). The improved control of diabetes has been found to reduce costs in this area for middle-aged patients, and the potential benefits of improved control on costs for non-diabetes-related illnesses were not evaluated in these analyses. In addition, it has been demonstrated that the assumptions underlying traditional cost-benefit analysis tend to discriminate against elderly populations (43). Ultimately, properly randomized controlled trials will need to be conducted to determine the benefits and cost of optimal glycemic control in elderly persons. Based on the evidence available, we have developed guidelines for the control of diabetes in elderly persons as follows:

Goals of therapy for the healthy elderly patient with diabetes: a fasting plasma glucose level of <7.0 mmol/l; a 2-hour plasma glucose value of <11.0 mmol/l; and Hgb A1C values of <15% above the upper limit of normal.

Goals of therapy for the frail elderly patient with diabetes: a fasting plasma glucose level of <10 mmol/l; a 2-hour plasma glucose value of <14 mmol/l; and Hgb A1C values of <40% above the upper limit of normal.

Clinicians will need to modify the guidelines for each individual patient based on their comorbidity and functional status.

THERAPEUTIC OPTIONS

According to current ADA guidelines, diabetes in elderly persons is undertreated (44,45). Because elderly patients with diabetes are often complicated as a result of multiple pathologies, social factors, and polypharmacy, a team approach to management is essential. Multidisciplinary programs, particularly if they involve family members caring for the patient, have been shown to result in improved compliance with therapy and better glycemic control (5). Nurs-

ing homes often have few guidelines for the care of elderly residents with diabetes, and knowledge of diabetes tends to be relatively poor among the staff of these facilities. Improved outcomes for elderly nursing-home patients can occur as a result of educational programs for the staff.

Since elderly diabetic persons with conventional risk factors have an increased risk of vascular complications, risk-factor modification may be of benefit. Recent large-scale studies (46,47) suggest that treatment of isolated systolic hypertension will reduce the risk of complications in these patients independent of glycemic control. Studies (48,49) also suggest that in elderly patients without diabetes or patients with type 2 diabetes in their 60s who have evidence of cardiovascular disease, lipid-lowering therapy reduces the risk of subsequent cardiovascular events. The Heart Outcomes Prevention Evaluation, or HOPE, Study (50) showed that angiotensin-converting enzyme inhibitors reduce the risk of macrovascular complications and death in older patients with diabetes and one other risk factor independent of the effects of these drugs on blood pressure). The previously described data argue for a more aggressive approach to risk-factor modification in elderly persons than has previously been applied.

Diet and Exercise

There are few original studies of dietary interventions in elderly patients with diabetes (5). It appears that elderly patients with this illness avoid simple sugars but do not adhere to current dietary recommendations regarding fat and fiber composition. A dietary intervention that results in weight loss has been found to improve glycemic control in ambulatory obese elderly patients with diabetes. However, diabetic diets complicate the care and increase the cost of looking after frail elderly nursing-home patients, and these diets do not appear to significantly improve glycemic control in this patient population. Elderly patients with diabetes are at risk for deficiency of trace elements, and magnesium and zinc supplementation results in improvements in glycemic control. Hyperglycemia in elderly patients with diabetes is associated with increased oxidative stress (51). Small-scale studies have demonstrated that supplementation with antioxidant vitamins (C and E) may improve glycemic control (5). Unfortunately, the effect of exercise programs on glycemic control in elderly patients with diabetes has been incompletely assessed, and the results of the studies that have been done are conflicting (5). Clearly, further investigations are needed to evaluate the role of dietary and exercise interventions in the management of diabetes in the elderly population.

α -Glucosidase Inhibitors

α -Glucosidase inhibitors act by inhibiting the digestion and absorption of simple sugars from the gastrointestinal tract. The major side effects of these drugs are gastrointestinal, particularly flatulence and diarrhea. A recent randomized controlled trial of glyburide versus the α -glucosidase inhibitor miglitol in elderly patients with diabetes demonstrated that miglitol reduced Hgb A1C by about 0.5%, whereas glyburide reduced Hgb A1C by about 1%. However, the patients who were treated with glyburide had more weight gain,

a higher frequency of hypoglycemia, and an increased incidence of cardiovascular events (52). In a recent randomized multicenter trial of the α -glucosidase inhibitor acarbose in obese elderly patients with diabetes, acarbose reduced Hgb A1C by about 0.8% when compared with the placebo and also resulted in an improvement in insulin sensitivity (53). α -Glucosidase inhibitors are useful drugs as primary therapy for elderly patients with modest fasting hyperglycemia, especially if they are obese. They can also be used in patients taking other oral agents to enhance glycemic control.

Metformin

Metformin is currently the only biguanide available in North America. Aging does not appear to be a risk factor for lactic acidosis with metformin, provided that careful attention is paid to the contraindications for this drug (significant liver, renal, and cardiac disease) (5). Limited nonrandomized clinical studies suggest that the drug is safe and effective as monotherapy in obese older people (5). A recent randomized controlled trial demonstrated that metformin was also effective when added to glyburide in poorly controlled elderly patients with diabetes. In this study, Hgb A1C was reduced by approximately 1.6%, without a significant increase in the risk of hypoglycemic events (54). In our view, metformin is an ideal drug for first-line therapy of obese older patients, because it increases insulin sensitivity, assists with weight loss, reduces lipid levels, and rarely causes hypoglycemia. In addition, it is a useful adjunct for patients who are inadequately controlled on maximum doses of sulfonylureas.

Thiazolidinediones

Drugs in this class improve glycemic control by enhancing peripheral insulin sensitivity. Troglitazone was the first drug of this type released for clinical use. This drug was recently removed from the market because of concerns regarding hepatic toxicity. A randomized controlled trial of troglitazone in elderly patients with diabetes found that the drug was safe if patients were carefully monitored for hepatic toxicity. Troglitazone resulted in significant improvements in insulin sensitivity and glycemic control (55). Two more drugs in this class have recently been released for use. There are no data yet available on the effect of pioglitazone in elderly patients. The kinetics of rosiglitazone are not significantly altered in elderly patients (56). Pooled data on elderly subjects from the clinical trials that have been done with rosiglitazone have recently been published in abstract form (57). Rosiglitazone appears to be as effective in older patients as in younger patients and results in an approximate 1.5% reduction in Hgb A1C. Hepatic toxicity has not been reported in elderly subjects, although all elderly subjects who are started on rosiglitazone should have liver function tests monitored regularly until further studies are forthcoming. The incidence of edema and anemia was substantially higher in elderly patients than in middle-aged patients treated with this drug, and volume status and blood count will need to be carefully monitored in patients started on rosiglitazone. Rosiglitazone can be a useful first-line therapy in obese elderly patients, particularly for those patients who cannot tolerate metformin or have a contraindication to it. In addition,

rosiglitazone may be a beneficial adjunct in elderly patients who have suboptimal glycemic control, despite insulin requirements of >50 units per day.

Sulfonylureas

The absorption and elimination of glyburide is impaired with age, and elderly subjects appear to have enhanced insulin responses to the drug as well (5). This may explain, in part, the age-related exponential increase in the frequency of severe or fatal hypoglycemia with this drug. The kinetics of other sulfonylureas do not appear to alter importantly with age (5). In our opinion the use of chlorpropamide is relatively contraindicated in elderly persons because this drug is associated with an increased frequency of hypoglycemia, and can interact with multiple drugs and cause an antabuse effect and syndrome of inappropriate secretion of antidiuretic hormones, or SIADH. The risk of hypoglycemia associated with sulfonylureas in aged adults appears to be reduced with tolbutamide, gliclazide, and, possibly, glipizide (57). In addition to the type of sulfonylurea, other potential risk factors for hypoglycemia with these drugs in elderly persons include black race, multiple medications, male sex, renal dysfunction, and ethanol consumption (27,58). Sulfonylureas should be considered as a first-line therapy in lean elderly patients with diabetes.

Insulin

Elderly subjects often make errors when trying to mix insulin on their own. The accuracy of insulin injections has been shown to be improved in older patients when they are treated with premixed insulin (5). Small-scale studies suggest that as long as a premixed insulin is used, the portion of regular to long-acting insulin in the mixture (i.e., 50:50 vs 30:70) does not significantly alter glucose or insulin levels (59). Due to compliance problems in older individuals, some clinicians have recommended using one injection of insulin per day. However, hypoglycemia appears to occur more commonly with one injection rather than two daily injections in this patient population. One study (60) suggested that a combination of a sulfonylurea with insulin is probably more effective than the same dose of insulin alone in elderly patients. However, another study (61) failed to show a difference from the efficacy point of view between two doses of insulin, one dose of insulin at bedtime plus sulfonylureas, compared with one dose of insulin at breakfast plus sulfonylureas. In this latter study, weight gain was comparable between groups. Some differences between regimens may have been masked because one third of the patients who were started on one dose of insulin daily needed a second injection to control glycemia. No studies have evaluated the effectiveness of bedtime insulin along with daytime metformin in elderly persons. Our clinical experience suggests that this strategy is effective in some patients who are reluctant to inject insulin twice a day. We have also had extensive clinical experience with the use of metformin in elderly patients with diabetes treated with bid insulin. In obese patients, this combination appears to reduce weight gain associated with insulin treatment, reduce insulin requirements, and improve glycemic control. To date, no studies have

evaluated the effect of lispro insulin in the treatment of diabetes in elderly patients.

Other Drugs

Repaglinide is a nonsulphonylurea drug that has a distinct β -cell binding profile and stimulates insulin secretion from the β cell by a mechanism similar to that of sulphonylureas. The potential advantage of this drug is that it has a rapid onset and very short duration of action. As a result, it is felt to be of value because it results in a more physiologic insulin profile and because it can be given just before a meal in patients who tend to have irregular eating patterns. In addition, in younger patient populations, repaglinide has been associated with a lower frequency of hypoglycemic events when compared with conventional sulphonylureas, presumably because of its shorter duration of action. The kinetics of repaglinide are not altered with age (62). Data on elderly subjects from the clinical trials that have been done with this drug has been published in abstract form (63). The drug resulted in a similar change in fasting glucose and Hgb A1C values in middle-aged and elderly subjects, suggesting that it has similar efficacy in each age group. In addition, when compared with younger patients with diabetes, elderly patients treated with repaglinide had a similar frequency of hypoglycemic events, suggesting that this drug may be associated with a lower frequency of hypoglycemia in elderly persons than conventional sulphonylureas. Pending the results of properly randomized controlled trials in the elderly population, repaglinide may be considered for elderly patients who have irregular eating habits, or have frequent hypoglycemic events on conventional sulphonylureas. These potential benefits must be balanced against the cost of the new drug and compliance problems that could result from having to take the drug three times a day.

Depression is common in older people with diabetes. A recent randomized controlled trial (64) demonstrated that fluoxetine can assist with weight loss and improve glycemic control in obese elderly patients with diabetes. This drug should be considered for therapy of depression in obese elderly patients with diabetes, particularly if they are in need of improved glycemic control. Because fluoxetine has a very long half life, caution should be used when administering this drug to older patients, since excessive weight loss could occur before the drug is cleared from the system. For this reason, fluoxetine should never be given to lean elderly patients with diabetes. Orlistat is the first of a new class of anti-obesity agents, the lipase inhibitors, which have been developed for the long-term management of obesity. This drug acts by selectively inhibiting the absorption of dietary fat. Limited data from studies in middle-aged patients with type 2 diabetes suggest that orlistat can result in clinically meaningful weight loss, improve glycemic control, and improve lipid profile (65). Because elderly persons with diabetes tend to have diets that are high in saturated fat, this drug may prove to be useful in obese patients. However, there are no data as yet from studies in the elderly population, and caution should be used until further information is forthcoming. Glucagon-like peptide (GLP-1) is a peptide hormone secreted from the intestine in response to food ingestion. This peptide has been shown to enhance glucose-induced insulin

release and reduce appetite in middle-aged patients with diabetes. Recent data from our laboratory suggest that GLP-1 maintains its ability to enhance glucose-induced insulin release in elderly patients and may also increase insulin sensitivity and NIMGU (G.S. Meneilly and D. Elahi, unpublished observations). Long-term clinical studies are required to determine the role of this peptide in the therapy of diabetes in aged adults. No data are currently available on the use of pramlintide in aged adults.

Monitoring Glycemic Control

Because the renal threshold for glucose increases with age, urine glucose testing is not reliable in aged adults. Most studies have found that elderly patients can successfully be taught to monitor blood sugar at home, and such monitoring does not alter their quality of life. Hgb A1C is the standard measure of long-term (2–3 mo) glycemic control in this patient population, although serum fructosamine can be used to measure changes in glycemic control over a shorter period (2–3 wk) (66,67).

CONCLUSIONS

Because of the dramatic increase in its prevalence, diabetes in the elderly population may ultimately prove to be the most important epidemic of the 21st century. Fortunately, our increased understanding of the pathogenesis and treatment of this illness should allow us to improve the outcome of the large numbers of elderly patients that will be afflicted with this illness.

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Address correspondence to Dr. G.S. Meneilly, Room S 169, Vancouver Hospital and Health Sciences Centre, UBC Site 2211, Wesbrook Mall, Vancouver, BC V6T 2B5, Canada. E-mail: meneilly@interchange.ubc.ca

REFERENCES

- Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults. *Diabetes Care*. 1998;21:518–524.
- Harris MI. Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care*. 1993;16:642–652.
- Feskens EJM, Boer JMA, van Dam RM, Ritsema MJ, Kromhout D. Diabetes prevalence in offspring of elderly men with known and newly diagnosed diabetes. *Diabetes Care*. 1999;22:1919.
- Vaag A, Henriksen JE, Madsbad S, Holm N, Beck-Nielsen H. Insulin secretion, insulin action, and hepatic glucose production in identical twins discordant for non-insulin-dependent diabetes mellitus. *J Clin Invest*. 1995;95:690–698.
- Meneilly GS, Tessier D. Diabetes in the elderly. In: Morley JE, van den Berg L, eds. *Contemporary Endocrinology, Endocrinology of Aging*. Totowa, NJ: Humana Press; 2000:181–203.
- DeFronzo RA. Lilly Lecture 1987. The triumvirate: β -cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes*. 1988;37:667–687.
- Meneilly GS, Hards L, Tessier D, Elliott T, Tildesley H. NIDDM in the elderly. *Diabetes Care*. 1996;19:1320–1375.
- Arner P, Pollare T, Lithell H. Different aetiologies of type 2 (non-insulin-dependent) diabetes mellitus in obese and non-obese subjects. *Diabetologia*. 1991;4:483–487.
- Meneilly GS, Elliott T. Metabolic alterations in middle-aged and elderly obese patients with type 2 diabetes. *Diabetes Care*. 1999;22:112–118.

10. Morley JE. Diabetes mellitus: a major disease of older persons. *J Gerontol Med Sci.* 2000;55A:M255–M256.
11. Nilsson J, Jovinge S, Niemann A, et al. Relation between plasma tumor necrosis factor alpha and insulin sensitivity in elderly men with non-insulin-dependent diabetes mellitus. *Arterioscler Thromb Vasc Biol.* 1998;18:1199–1202.
12. Best JD, Kahn SE, Ader M, Watanabe RM, Ni TC, Bergman RN. Role of glucose effectiveness in the determination of glucose tolerance. *Diabetes Care.* 1996;19:1018–1030.
13. Forbes A, Elliott T, Tildesley H, Finegood D, Menielly GS. Alterations in non-insulin-mediated glucose uptake in the elderly patient with diabetes. *Diabetes.* 1998;47:1915–1919.
14. Scherrer U, Sartori C. Insulin, nitric oxide and the sympathetic nervous system: at the crossroads of metabolic and cardiovascular regulation. *J Hypertens.* 1999;17:1517–1525.
15. Meneilly GS, Elliott T, Bryer-Ash M, Floras JS. Insulin-mediated increase in blood is impaired in the elderly. *J Clin Endocrinol Metab.* 1995;80:1899–1903.
16. Ylihärsilä H, Tuomilehto J, Mackay IR, et al. GAD antibodies in elderly men in different categories of glucose tolerance. *Diabetes Care.* 1999; 22:996–997.
17. Pietropaolo M, Barinas-Mitchel E, Pietropaolo SL, Kuller LH, Trucco M. Evidence of islet cell autoimmunity in elderly patients with type 2 diabetes. *Diabetes.* 2000;49:32–38.
18. Meneilly GS, Tildesley H, Elliott T, Palmer JP, Juneja R. Significance of GAD positivity in elderly patients with diabetes. *Diabetic Med.* 2000;17:247–248.
19. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the US population, 1971–1993. *Diabetes Care.* 1998;21:1138–1145.
20. Sinclair AJ, Robert IM, Croxson SCM. Mortality in older people with diabetes mellitus. *Diabetic Med.* 1996;14:639–647.
21. Muggeo M, Zoppini G, Bonora E, et al. Fasting plasma glucose variability predicts 10 year survival of type 2 diabetic patients. *Diabetes Care.* 2000;23:45–50.
22. Groeneveld Y, Petri H, Hermans J, Springer MP. Relationship between blood glucose level and mortality type 2 diabetes mellitus: a systematic review. *Diabetic Med.* 1999;16:2–13.
23. Hoeymans N, Feskens EJM, Kromhout D, van den Bos GAM. The contribution of chronic conditions and disabilities to poor self-rated health in elderly men. *J Gerontol Med Sci.* 1999;54A:M501–M506.
24. Fillenbaum GG, Pieper CF, Cohen HJ, Cornoni-Huntley JC, Guralnik JM. Comorbidity of five chronic health conditions in elderly community residents: determinants and impact on mortality. *J Gerontol Med Sci.* 2000;55A:M84–M89.
25. Tucker KL, Falcon LM, Bianchi LA, Cacho E, Bermudez OI. Self-reported prevalence and health correlates of functional limitation among Massachusetts elderly Puerto Ricans, Dominicans, and a non-Hispanic white neighborhood comparison group. *J Gerontol Med Sci.* 2000;55A:M90–M97.
26. Miller DK, Lui LY, Perry HM, Kaiser FE, Morley JE. Reported and measured physical functioning in older diabetic African Americans. *J Gerontol Med Sci.* 1999;54A:M230–M236.
27. Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y. Drug-induced hypoglycemic coma in 102 diabetic patients. *Arch Intern Med.* 1999; 159:281–284.
28. Burge MR, Kamin JR, Timm CT, Qualls CR, Schade DS. Low-dose epinephrine supports plasma glucose in fasted elderly patients with type 2 diabetes. *Metabolism.* 2000;49:195–202.
29. Jaap AJ, Jones GC, McCrimmon RJ, Deary IJ, Frier BM. Perceived symptoms of hypoglycaemia in elderly type 2 diabetic patients treated with insulin. *Diabetic Med.* 1998;15:398–401.
30. Altman JJ, Elian N, Bonnemaire M, Calmar S, Feldman S. Safety of human insulin in poor sighted elderly diabetic patients. *Diabetes Care.* 1999;22:2089.
31. Feldman S, Bonnemaire M, Elian N, et al. Transferring aged type 1 diabetic patients from animal to human insulin: a randomised study. *Diabetes Care.* 1998;21:196–197.
32. Rosenthal MJ, Fajardo M, Gilmore S, Morley JE, Naliboff BD. Hospitalization and mortality of diabetes in older adults. *Diabetes Care.* 1998;21:231–235.
33. Tariot PN, Ogden MA, Cox C, Williams TF. Diabetes and dementia in long-term care. *J Am Geriatr Soc.* 1999;47:423–429.
34. American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care.* 1998; 21(suppl 1):S5–S19.
35. Rohlfing CL, Little RR, Wiedmeyer HM, et al. Use of GHb (HbA1c) in screening for undiagnosed diabetes in the US population. *Diabetes Care.* 2000;23:187–191.
36. Wahl PW, Savage PJ, Psaty BM. Diabetes in older adults: comparison of 1997 American Diabetes Association classification of diabetes mellitus with 1985 WHO classification. *Lancet.* 1998;352:1012–1015.
37. Barzilay JI, Spiekerman CF, Wahl PW, et al. Cardiovascular disease in older adults with glucose disorders: comparison of American Diabetes Association criteria for diabetes mellitus with WHO criteria. *Lancet.* 1999;354:622–625.
38. Barrett-Connor E, Ferrara A. Isolated postchallenge hyperglycemia and the risk of fatal cardiovascular disease in older women and men. *Diabetes Care.* 1998;21:1236–1239.
39. UK Prospective Diabetes Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet.* 1998; 352:837–853.
40. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM. I. *Diabetes Care.* 1997;20:725–734.
41. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM. II. *Diabetes Care.* 1997;20:735–744.
42. Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. *Ann Int Med.* 1997;127:788–795.
43. Avorn J. Benefit and cost analysis in geriatric care. *N Engl J Med.* 1984;310:1294–1301.
44. Smith NL, Heckbert SR, Bittner VA, et al. Antidiabetic treatment trends in a cohort of elderly people with diabetes. *Diabetes Care.* 1999; 22:736–742.
45. Shorr RI, Lonneke VF, Resnick HE, Di Bari M, Johnson KC, Pahor M. Glycemic control of older adults with type 2 diabetes: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *J Am Geriatr Soc.* 2000;48:264–267.
46. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *JAMA.* 1996;276:1886–1891.
47. Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med.* 1999;340:677–684.
48. The Long-Term Intervention With Pravastatin in Ischaemic Disease Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* 1998;339:1349–1357.
49. Pyorala K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. *Diabetes Care.* 1997;20:614–620.
50. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. *N Engl J Med.* 2000;342:145–153.
51. Tessier D, Khalil A, Fulop T. Effects of an oral glucose challenge on free radicals/antioxidants balance in an older population with type 2 diabetes. *J Gerontol Med Sci.* 1999;54A:M541–M545.
52. Johnston PS, Lebovitz HE, Coniff RF, Simonson DC, Raskin P, Munera CL. Advantages of alpha-glucosidase inhibition as monotherapy in elderly type 2 diabetic patients. *J Clin Endocrinol Metab.* 1998;83: 1515–1522.
53. Meneilly GS, Ryan EA, Radziuk J, et al. Effect of acarbose on insulin sensitivity in elderly patients with diabetes. *Diabetes Care.* 2000;23: 1162–1167.
54. Gregorio F, Ambrosi F, Manfrini S, et al. Poorly controlled elderly type 2 diabetic patients: the effects of increasing sulphonylurea dosages or adding metformin. *Diabetic Med.* 1999;16:1016–1024.
55. Kumar S, Prange A, Schulze J, Lettis S, Barnett AH. Troglitazone, an insulin action enhancer, improves glycaemic control and insulin sensitivity in elderly type 2 diabetic patients. *Diabetic Med.* 1998;15:772–779.
56. DiCicco R, Freed M, Allen A, et al. A study of the effect of age on the pharmacokinetics of BRL 49653C in healthy volunteers. *J Clin Pharmacol.* 1995;35:926.
57. Beebe KL, Patel J. Rosiglitazone is effective and well tolerated in patients over 65 years with type 2 diabetes. *Diabetes.* 1999;48:111A.

58. Burge MR, Zeise T-M, Sobhy TA, Rassam AG, Schade DS. Low-dose ethanol predisposes elderly fasted patients with type 2 diabetes to sulfonylurea-induced low blood glucose. *Diabetes Care*. 1999;22:2037-2043.
59. Brodows R, Chessor R. A comparison of premixed insulin preparations in elderly patients. *Diabetes Care*. 1995;18:855-857.
60. Kyllastinen M, Groop L. Combination of insulin and glibenclamide in the treatment of elderly non insulin-dependent (type 2) diabetic patients. *Ann Clin Res*. 1985;17:100-104.
61. Wolffenbuttel BHR, Sels JPJE, Rondas-Colbers GJ, et al. Comparison of different insulin regimens in elderly patients with NIDDM. *Diabetes Care*. 1996;19:1326-1332.
62. Hatorp V, Huang W-C, Strange P. Pharmacokinetic profiles of repaglinide in elderly subjects with type 2 diabetes. *J Clin Endocrinol Metab*. 1999;84:1475-1478.
63. Muller P, Hedberg T. Efficacy of repaglinide in elderly vs younger patients with type 2 diabetes: HbA1c and FPG parameters in long-term trials. *The Gerontologist*. 1998;38:99A.
64. Connolly VM, Gallagher A, Kesson CM. A study of fluoxetine in obese elderly patients with type 2 diabetes. *Diabetic Med*. 1994;12:416-418.
65. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. *Diabetes Care*. 1998;21:1289-1294.
66. Cefalu WT, Prather KL, Murphy WA, Parker TB. Clinical evaluation of serum fructosamine in monitoring elderly outpatient diabetics. *J Am Geriatr Soc*. 1989;37:833-837.
67. Negoro H, Morley JE, Rosenthal MJ. Utility of serum fructosamine as a measure of glycemia in young and old diabetic and non-diabetic subjects. *Am J Med*. 1988;85:360-364.

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Braceland Center For Mental Health and Aging The Institute of Living: Hartford Hospital's Mental Health Network

The Braceland Center for Mental Health and Aging at the Institute of Living/Hartford Hospital conducts research and education aimed at improving mental health care and other types of services for older persons.

Research, evaluation and education projects address the following major areas: clinical mental health services and policy (primarily focusing on depression and dementia), organization, financing and quality of long term care, and ethical/legal issues in aging. Projects are funded through a variety of federal and state sources and private foundations. The Center also has a substantial and growing endowment to support its activities. The Center is formally affiliated with the Center on Aging at the University of Connecticut Health Center.

Director—The Director will ensure achievement of the Center's mission by:

- providing direction and oversight for all aspects of the aging health policy and clinical mental health research agendas;
- identifying potential funding and directing grant and contract proposal preparation in order to secure adequate support for Braceland Center programs;
- and promoting the Braceland Center as a scholarly research and education institute through applied research in the Hartford Hospital system, national dissemination of original research and faculty appointments.

Required credentials include a Ph.D. or M.D. or its equivalent; a history of extramurally funded scholarly research relevant to mental health and aging; qualifications appropriate for rank as Associate Professor including publications; and experience in research administration.

Senior Scientist—Will enhance the Center's research program through:

- developing a program of scholarly research;
- competing successfully for external grants;
- collaborating with colleagues in a multidisciplinary environment

Required credentials include a Ph.D. or equivalent degree in a health related/behavioral science area with specialization in gerontology. Demonstrated ability to secure independent funding in the field of aging, skills in research design and data analysis and a record of peer-reviewed publications are essential. Experience with mental health services and/or policy research is preferred.

Salary commensurate with experience. The Institute of Living is an equal opportunity employer. Review of applications for both jobs will begin January 1, 2001. Applicants should submit 2 copies of a letter of application and vita. The letter of application should specify the following: 1) a summary of research and teaching experience/interests, and 2) recent samples of scholarly work. Please send application materials to:

Harold I. Schwartz, MD
Psychiatrist-in-Chief
The Institute of Living/Hartford Hospital
400 Washington Street
Hartford, CT 06106