CHAPTER 2

LITERATURE REVIEW

2.1 DIABETES

Diabetes mellitus is a group of common metabolic disorders. All types of diabetes mellitus are characterized by hyperglycemia, caused by defective insulin secretion, defective insulin action, or both. A simple and still formally correct way of subdividing most diabetic diseases is into type 1 and type 2 subcategories (Gavin et al. 2000). Type 1 diabetes accounts for 5-10% of diabetes cases in the population, and is characterized primarily by the autoimmune destruction of pancreatic islet cells, usually resulting in absolute insulin deficiency (American Diabetes Association 2006). Due to historical selective survival (i.e. that persons diagnosed with type 1 diabetes historically did not survive into old age), combined with low average age of diagnosis, type 1 diabetes prevalence is higher in younger than in older age-groups. Type 2 diabetes accounts for 90-95% of all diabetes cases in the population, and is more common in older than younger age groups (American Diabetes Association 2006). Prevalence of type 1 and type 2 diabetes also varies across different ethnical and cultural groups. In Sweden, data indicate that type 2 diabetes accounts for about 90% of diabetes cases (Henriksson et al. 2000).
2.2 CLASSIFICATION OF DIABETES

A. Based on insulin dependence
   a. Type 1 diabetes mellitus / Insulin dependent diabetes mellitus
   b. Type 2 diabetes mellitus / Non-insulin dependent diabetes mellitus

B. Diabetes due to genetic defects
   a. Genetic defects of β cell function
   b. Genetic defects in insulin action

C. Malnutrition related diabetes mellitus

D. Diabetes associated with diseases of pancreas like pancreatitis, neoplasm etc.

E. Diabetes associated with certain diseases and conditions
   a. Endocrinopathies - Acromegaly, Cushing’s syndrome
   b. Abnormalities of insulin or its receptors

F. Diabetes induced or chemical induced diabetes mellitus
   e.g: nicotinic acid, glucocorticoids and thiazide derivatives

G. Gestational diabetes

H. Diabetes due to impaired glucose tolerance.
2.3 TYPE 1 DIABETES

A. Epidemiology

Type 1 diabetes is caused by an absolute deficiency of insulin, and it represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide (American Diabetes Association 2001). Although Type 1 diabetes affects all age groups, the majority of individuals are diagnosed either at around the age of 4-5 yrs, or in their teens and early adulthood. The incidence of Type 1 diabetes is raising across Europe, the average annual increase in the incidence in children under 15 years old is 3.4%, with steepest rise in those under 5 years old.

B. Etiology

The etiology of Type 1 diabetes remains poorly understood, but it is likely that an environmental factor triggers an autoimmune process in a predisposed individual. Although genetic susceptibility to Type 1 diabetes is inherited, only 12-15% of Type 1 diabetes occurs in families. Several environmental triggers, including viral infections, nutritional factors, parental age and low birth weight have been implicated.

C. Pathogenesis

Type 1 diabetes mostly affects juveniles and also occurs in adults. It is characterized by an absolute deficiency of insulin caused by β cell lesion or necrosis. Loss of β cell function may be due to invasion of virus, the action of chemical toxins or due to autoimmune antibodies directed against β cell.
2.4 TYPE 2 DIABETES

A. Epidemiology

Type 2 diabetes is a heterogeneous disorder that results from an interaction between a genetic predisposition and environmental factors. It accounts for around 90% of all cases of diabetes. The incidence of diabetes increases with age, with most cases being diagnosed after age of 40 years. The prevalence of Type 2 diabetes is increasing rapidly. The World Health Organization (2003) has predicted that by 2030 the number of adults with diabetes will have almost doubled worldwide, from 177 million in 200 to 370 million.

B. Aetioloogy

The factors which contribute for Type 2 diabetes mellitus are lack of exercise, obesity, excessive calorie intake, sedentary lifestyle, diseases like Cushing’s syndrome, pheochromacytoma, glucagon, phenytoin, estrogens etc.

C. Pathogenesis

Under normal physiologic conditions, plasma glucose concentrations are maintained within a narrow range, through a tightly regulated and dynamic interaction between tissue sensitivity to insulin and insulin secretion. In type 2 diabetes these mechanisms breakdown, the two main pathophysiological defects in type 2 diabetes are, impaired insulin secretion through a dysfunction of the pancreatic β-cell and impaired insulin action through insulin resistance.
2.5 COMPLICATIONS OF DIABETES

Since the introduction of effective treatment allows patients with diabetes to live through the acute metabolic consequences of the illness, it has become apparent that diabetes is associated with a number of chronic micro vascular complications, which affect the eyes, kidneys, and nervous system and macro vascular complications which lead to an increased risk of myocardial infarction, stroke and peripheral vascular disease.

A Short term complications

- Diabetic ketoacidosis
- Hyper osmolar non ketotic coma
- Hypoglycemia

B Long term complications

- Diabetic neuropathy
- Diabetic nephropathy
- Diabetic retinopathy
- Heart disease
- Stroke
2.6 DIABETES AND COGNITIVE FUNCTION

Diabetes mellitus is a complex endocrine disease that can lead to many complications particularly when untreated. The association between type 2 diabetes mellitus and dementia has been of great interest, this is particularly relevant with increase in prevalence of both diabetes and dementia with increasing life expectancy. Diabetes Mellitus is associated with slowly progressive end-organ damage in the brain. Mild to moderate impairments of cognitive functioning has been reported both in patients with Diabetes Mellitus Type 1 and in patients with Diabetes Mellitus Type 2 (Biessels 2005).

Several lines of evidence suggest that ‘toxic’ effects of hyperglycemia are involved in the development of diabetic end organ damage to the brain. Hyperglycemic rodents, for example, express cognitive impairments and functional and structural alterations in the brain. Toxic effects of high glucose levels are mediated through an enhanced flux of glucose through the so-called polyol and hexamine pathways, disturbances of intracellular second messenger pathways, an imbalance in the generation and scavenging of reactive oxygen species and by advanced glycation of important functional and structural proteins. These processes directly affect brain tissue and leads to micro vascular changes in the brain (Biessels 2005).

An increasing amount of evidence links insulin itself to cognitive decline and dementia in Type 2 diabetes mellitus. First, alterations in cerebral insulin receptor signaling may be involved, as a cerebral equivalent of peripheral insulin resistance. Secondly, insulin may affect the metabolism of Aβ (β-amyloid) and tau, two proteins that represent the building blocks of amyloid plaques and neurofibrillary tangles, the neuropathological hallmarks
of Alzheimer’s disease. Insulin and its receptors are widely distributed throughout the brain, with particular abundance in defined areas, such as hypothalamus and hippocampus. In addition, insulin appears to act as a 'neuromodulator'. It influences the release and reuptake of neurotransmitters, and also appears to improve learning and memory. Thus the concepts of ‘cerebral insulin resistance’ and ‘insulin-induced amyloid pathology’ are an attractive explanation for some effects of Type 2 diabetes in brain (Biessels 2005).

In Type 2 diabetes condition, elevated levels of blood glucose and insulin may provide a pro-oxidant environment. Thus people with poor glucose regulation are exposing their systems to potentially harmful oxidative stress and also as age increases, the harm continues to accumulate unless we actively counteract (Arvanitakis et al. 2006).

Yeung et al. (2009) conducted study in diabetes group (n = 44; M = 69.33 years, SD = 7.64) and a pool of non diabetes control participants (n = 522; M = 68.13 years, SD = 8.68). Global cognitive competence assessment was carried out using the standard 18-item MMSE (Folstein et al. 1975). Scores were generally high and clinically insignificant for both groups. The results showed that healthy controls significantly outperformed the diabetes group only on markers of executive functioning and speed.

Okereke et al. (2008) has conducted prospective cohort study in 5,907 men and 6,326 women with a mean age 74.1 and 71.9, at their baseline cognitive assessment. Cognitive function assessments were carried out by the Telephone Interview for Cognitive Status (TICS). The study concluded that Type 2 Diabetes Mellitus and longer duration of diabetes Mellitus are similarly related to cognitive impairment and decline in men and women.
Esther et al. (2008) Cognitive functioning was compared cross-sectionally between diabetes mellitus type 2 patients (n = 64), patients with metabolic syndrome but without diabetes mellitus type 2 (n = 83) and control subjects (n = 100) participating in the prospective population-based study. Participants performed an extensive neuropsychological examination. Both the diabetes mellitus type 2 group and the metabolic syndrome group performed worse than controls on the domains of information processing speed and attention and executive functioning.

Debling et al. (2006) conducted study to examine the association between diabetes and cognitive function in the elderly. From January to December 2003, all 740 participants, aged 70 years or more, were eligible for a telephone interview on cognitive function. Cognitive function was assessed using validated instruments, including the Telephone Interview of Cognitive Status (TICS) and the East Boston Memory Test (EBMT). Information on diabetes was available from prior questionnaires and was validated in 2002. The study concluded that diabetes should be considered to be a risk factor for cognitive impairment in the elderly, which might be attenuated by antidiabetic treatment.

Seyfaddini (2006) conducted cohort study to distinguish relation of diabetes mellitus and cognitive decrements. Fifty diabetic patient and 48 control participants were included to study. Patients were 25 to 65 years old and their disease had been diagnosed in the last 5 years. These patients were in different educational levels. The Wisconsin Card Sort Test (WCST) and Mini-Mental Status Exam (MMSE) were conducted for evaluation of cognitive problems. Cognitive problems were 8 times more in diabetics than control group (RR = 8.2 95%CI = 2.15 - 31.4). The findings of study strongly confirmed relationship between diabetes mellitus and cognitive decrements.
Yaffe et al. (2001) conducted study to investigate the association between diabetes and impaired fasting glucose (IFG), cognition and risk of developing both dementia and mild cognitive impairment (MCI) in older women. A total of 267 (3.8%) women had diabetes and 297 (4.2%) had IFG. Women with IFG had worse baseline cognitive scores compared to women with NG but better scores than diabetics (age-adjusted composite z score based on five tests: NG 0.40, 95% CI 0.30 to 0.49; IFG 0.14, 95% CI -0.36 to 0.64; diabetics -0.78, 95% CI -1.23 to -0.33; P < 0.001). Diabetic as well as pre-diabetic women have impaired cognitive performance and greater risk of developing cognitive impairment.

Arvanitakis et al. (2004) has conducted a longitudinal cohort study in 824 older persons aged >55 years for upto 9 years. Diabetes mellitus was present in 127(15.4%) of the participants. During a mean of 5.5 years of observation, 151 persons developed Alzheimer’s Disease (AD). In a proportional hazards model adjusted for age, sex, and educational level, those with diabetes mellitus had a 65% increase in the risk of developing AD compared with those without diabetes mellitus (hazard ratio, 1.65; 95% confidence interval, 1.10-2.47). The study concluded that diabetes mellitus may be associated with an increased risk of developing AD and may affect cognitive systems differentially.

Hassing et al. (2004) has conducted a study in 274 elderly participants (36 with diabetes and 238 without diabetes) aged 80-93 years. The test battery included tests of speed, visuospatialability, short-term memory, semantic memory, episodic memory, and the Mini Mental Status Examination. The study concluded that Type 2 diabetes is associated with accelerated cognitive decline in old age that may result in dementia.
Jasmanda et al. (2003) examined the association of diabetes with decline in global cognitive function and memory function over a 2-year period. Study subjects were derived from an existing cohort of Latinos aged 60 (n = 1,789). Logistic regression analysis indicated that baseline diabetes was a significant predictor of major cognitive impairment in Modified Mini Mental State Exam (3MSE) (OR = 1.68, 95% CI = 1.21, 2.34) and word-list test (OR = 1.31, 95% CI = 0.99, 1.75).

Gregg et al. (2000) has conducted a prospective cohort study in community dwelling white women with diabetes of 65 years and older (n = 9679). Three tests of cognitive function, the Digit Symbol test, the Trials B test, and a modified version of the mini-Mental State Examination (m-MMSE) were administered at the baseline and 3 to 6 years later. The study concluded that diabetes is associated with lower levels of cognitive function and greater cognitive decline among older women.

Worrall et al. (1993) compared the cognitive function of elderly persons with Non-Insulin-Dependent Diabetes Mellitus with a matched sample of persons without NID Diabetes Mellitus. Ninety outpatients over 50 years of age with NID Diabetes Mellitus and 90 matched non diabetic patients were recruited for the study. The Modified Mini-Mental State (3MS) and the Delayed Word Recall (DWR) test were used to assess cognitive function. On the 3MS test, the mean score of persons with NID Diabetes Mellitus was 75.6, and that of non diabetic persons was 79.5 (two-tailed t = 3.04, P = 0.013). On the DWR, the mean score of persons with NID Diabetes Mellitus was 3.9, and that of persons without NID Diabetes Mellitus was 4.7 (two-tailed t = 3.52, P = 0.012). The study concluded that the persons with NID Diabetes Mellitus had significantly poorer scores on two tests of cognitive function.
Grodstein et al. (2001) examined the relationship of type 2 diabetes on cognitive function in community-dwelling women. From 1995 to 1999, they administered four tests of cognitive function (Telephone Interview of Cognitive Status (TICS), immediate and delayed recall of the East Boston Memory Test, and verbal fluency) by telephone to 2,374 participants (70-78 years of age) of the Nurses’ Health Study. After multivariate adjustment, women with type 2 diabetes scored lower on all our cognitive tests than women without diabetes. On the general test of cognition (TICS), the mean difference in score between women with and without diabetes was 20.60 (95% CI 21.18 to -0.03, P=0.04) and the relative risk of a low TICS score was 1.98 (95% CI 1.06 to 3.69). In these women, diabetes was related to lower scores on several aspects of cognitive function. Longer duration of diabetes may be associated with poorer scores, but hypoglycemic therapy may ameliorate scores.

Wessling et al. (2005) conducted randomized double blind, placebo-controlled trial in frail, white adults (n = 101) aged 65 years or older who received either an enriched drink or a placebo product for a 6 months. The cognitive function was assessed using word learning test (WLT), WLT delayed, category fluency. The study concluded that nutritional supplementation may improve neuropsychological performance.

Kalmijn et al. (1997) examined the association of polyunsaturated fatty acids and antioxidants with cognitive function in 476 men aged 69-89 years. The 30-point Mini-Mental State Examination was used to assess cognitive impairment. The study concluded that intakes of β-carotene, vitamin C and E, and flavanoids were not inversely associated with cognitive impairment or decline.
Jama et al. (1996) examined the cross-sectional association between cognitive function and dietary intake of β-carotene, vitamin E and C in 5182 community participants aged 55-95 years from 1990-1993. Cognitive function was measured with Mini Mental State Examination (MMSE). The study reported that β-carotene rich foods protect against cognitive impairment in older people.

All conditions labelled as type 2 diabetes share the characteristic of relative insulin deficiency, i.e. the pancreas cannot produce enough insulin to give the desired effect in peripheral tissue. This deficiency may be primarily caused by abnormal insulin secretion or reduced insulin sensitivity (Zimmet et al 2001). Thus, in the development of type 2 diabetes because peripheral tissue does not respond to “normal” insulin levels the pancreas often increases insulin production. As the disease progresses, both the insulin sensitivity of peripheral tissue and the secretion of insulin from the pancreas become more impaired. Finally, the pancreas is unable to produce enough insulin to counter the insulin requirement, and the patient loses glycemic control. The loss of glycemic control constitutes the diagnostic criterion for diabetes (American Diabetes Association 2006). Importantly, there is not a single pathogenetic process that explains all instances of type 2 diabetes.

Type 2 diabetes is a common disease among the elderly, with diagnosed prevalence figures as high as 10% in the 60+ population and 20% in the 80+ population (Lipson 1986). A studied sample of the general population in Australia, where the diabetes diagnoses were set as a part of the study examination, demonstrated prevalence figures of 0.3% in the 25 to 34 age range, with a gradual increase with increasing age, up to 13.1% in the 55 to 64 age range, and 23% in the 75 and older age group (Dunstan et al. 2002). The present thesis focuses mainly on the older segments of adult life.
Several aspects of aging and type 2 diabetes are worth mentioning. First, the proportion of undiagnosed to diagnosed type 2 diabetics increases with increasing age. Among those diagnosed with diabetes in the Dunstan et al. (2002) study, about one third of the diabetics in the youngest age group, and more than half of the diabetics in the oldest age group were unaware of their diabetic status. Because there is such profound underdiagnosis in the general elderly population, it is desirable for most studies to include some form of objective measure of diabetes risk. Second, type 2 diabetes is part of a risk-factor complex that also includes hypertension, obesity, and cardiovascular disease. As these conditions are risk-factors not only for cognitive impairment but also for each other, it is essential to have good comorbidity data particularly given that comorbidity increases with increasing age.

The issue of comorbidity will be more thoroughly discussed in a later section of this thesis. According to extant literature, disease severity is often difficult to grade in data from studies not specifically designed to assess diabetes. However, a proxy for studying the effects of disease severity may be to study the effects of fulfilling some of the laboratory criteria for diabetes without actually having received a diagnosis. This strategy is used in Study III, where persons with diabetes are contrasted with (i) persons with elevated glycated hemoglobin (HbA\textsubscript{1C} above normal range) in the absence of a diabetes diagnosis, and (ii) persons with normal HbA\textsubscript{1C}.

HbA\textsubscript{1C} is not presently recommended as a diagnostic test for diabetes (American Diabetes Association 2006), an elevated level in the absence of a diabetes diagnosis is certainly a good risk indicator for diabetes. Even if persons that have elevated levels of HbA\textsubscript{1C} would not fulfill clinical diagnostic criteria, the elevated levels represent an early indicator of prodromal diabetes or insulin resistance. In fact, a large proportion of the population in western countries can be expected to have
impaired glucose tolerance, based on the fact that a body mass index (BMI) above 30 is common, and a high BMI is correlated with insulin resistance (Williams and Pickup 2004). Although waist circumference is a better indicator of insulin resistance than BMI (Janssen, Katzmarzyk, and Ross 2004), the latter index is more common in large cohort- or population based studies.

2.7 AGING, COGNITION AND DISEASE

In the study of diseases (Type 2 Diabetes) that increase in prevalence with increasing age, comparisons to normal aging are inevitable. However, the concept of “normal aging” is not easily defined. A nice summary of the potential pitfalls of viewing aging and disease as either dichotomous concepts or as endpoints of a continuum can be found in Blumenthal (2003). Should normal aging be defined as healthy aging?

The World Health Organization’s definition of health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (Page 2, WHO, 1946) implies that aging and disease cannot be evaluated separately. Perhaps it is after all possible to consider aging - be it normal or not - as a continuum reaching from biological aging to pathological aging with regard to age-related functioning. Distinguishing between biological and pathological aging, rather than between normal and pathological aging, underscores the point that the term “normal” excludes the possibility of simultaneous pathological aging, whereas the term “biological” does not. It is reasonable to view aging as composed of interrelated biological and pathological changes, or even to consider biological changes as passing over a pathology threshold when they limit function to a certain degree. For example, a common occurrence in aging is reduced circulation in extremities. This may be due to biological
aging, such as reduced flexibility in blood-vessels, but may also be exacerbated by pathological conditions such as diabetes. Even the biological component - the age-related reduction in vessel flexibility - may be considered pathological if it impairs function. Of course, we may not be able to distinguish a “pure” biological aging component in any person, but it is conceptually helpful to consider biological aging as a factor that interacts with numerous pathological aging factors for any specific individual.

Thus, “normal” aging need not be defined in relation to the WHO-definition of health, or even the absence of disease. Rather, “normal” aging, in the sense that I will use it throughout this thesis, refers to the biological aging component and whatever pathological aging components not known or specifically targeted by research questions or comorbidity control. Clearly, it is a difficult proposition to construct a definition of normal aging that hold true under all conditions. However, a definition that works in the context of a specific argument, or in the context of a specific study, may be a reasonable goal (e.g. Definition of normal aging that is practical in the context of cognition, diabetes, an aging). Characterizing normal aging as the absence of specific diseases means that there will be an artificial increase in the difference between the group of diabetics and the group of “normally aged”. It is uncommon for a group of old people to be disease free, and failure to impose similar inclusion criteria on both the diabetics and the normally aged comparison group introduces bias into the study. Identifying a group of older type 2 diabetics who are free of other disease processes is, in most cases, not practically possible. It is more reasonable to define normal aging in this context as the absence of specific neurodegenerative diseases. Although it is difficult to argue that a given neurodegenerative disease is more pathological than other diseases (e.g. myocardial infarction), neurodegenerative diseases are clearly relevant...
to consider in the context of cognition.

After defining normal aging in the context of cognition, diabetes, and aging, it is necessary to discuss how aging in itself influences cognition. There is, of course, a plethora of studies showing that chronological age is a good predictor of cognitive function. However, I believe that a portion of the variance in cognitive function that is presently attributed to aging can in fact be better explained by specific disease processes. Even so, variance will remain unaccounted for by specific diseases despite improvements in diagnostic proficiency. This variance may in fact be best explained by age. Further evidence for age as an influence separate from disease is provided by analyses attempting to partial out the influence of health and age on cognition, showing relatively little overlap between health-related variance and age-related variance for most cognitive outcomes (Earles and Salthouse 1995). Thus, when I use the term “normal aging” to refer to the absence of specific neurodegenerative disease, it is important to realize that it may be necessary to also control for other known comorbidity.

2.8 COMORBIDITY

Prevalence figures of certain chronic diseases (e.g. diabetes) increases with increasing age. For example, European data indicate that prevalence of hypertension grows dramatically between the ages of 35-44 (27% prevalent hypertension) to the 65-74 year old cohorts, who have 78% prevalent hypertension (Wolf-Maier et al. 2003). As the risk of having any specific disease increases with age, so does the risk of having more than one disease. The concept of multiple diseases in a single patient is referred to as comorbidity, and this is an important factor to consider in studies of health and cognition in the elderly. Importantly, in subjects who are 80 years of age and older, the majority suffer from more than one diagnosed medical
condition (Cauley et al 1996). Whereas incidence of disease tends to increase with increasing age, the prevalence of diseases that cause a large increase in mortality increases up to a point, but then decreases. Since most diseases are associated with increased mortality, the seemingly paradoxical finding that centenarians (admittedly an extremely select sample) are actually healthier than those slightly younger has been reported (Hitt et al 1999).

Since the maximum prevalence age is different for different diseases, it may be informative to include prevalence data for an age-matched stratum of the general population when assessing the prevalence of diseases in a specific data set. Since comorbidity becomes more common with increasing age, it may be relevant to consider whether even those diseases that in themselves do not explain much variance in cognitive test performance may interact with other diseases and biological changes that have not crossed the pathology-threshold to explain age-related variance in performance. More elaborate descriptions of potential interaction effects are provided in the section describing diabetes as a part of total comorbidity burden.

2.9 \hspace{1cm} COGNITIVE EFFECTS OF DIABETES

Effects of diabetes on cognitive functioning were first described in the 1920’s (Miles and Root 1922). However, very little happened in the field until Bale (1973) published the first modern study on diabetes and cognition. Between the 70’s and the 90’s, a trickle of studies was put forth, and by the end of the 90’s the field started growing at a fast rate.
2.10 COGNITIVE IMPAIRMENT

Cognitive impairment has in the last decades got quite some attention. One conceivable reason for that is that we live in a society with increasing demands on cognitive functioning - faster and faster information exchange, rapid developments in technology, not least information processing - which could reveal even quite subtle cognitive deficits. Cognitive impairment is quite frequent in many states of ill-health, but often to some degree neglected and insufficiently surveyed, even though cognitive deficits may complicate treatment and follow-up.

Significant cognitive impairment has been reported in Parkinson’s disease (Caballol et al. 2007; Riedel et al. 2008), multiple sclerosis (Roca et al. 2008), diabetes (Luchsinger et al. 2007), heart failure (Vogels et al. 2007), neuropsychiatric disorders (Chamberlain et al. 2005; Hale et al. 2006; Loo et al. 2004), chronic fatigue (Goshorn 1998; Jason et al. 2005), chronic stress or distress (Oei et al. 2006; Wilson et al. 2007), schizophrenia (Joyce and Roiser 2007; Keefe and Fenton 2007), cancer survivors who have undergone chemotherapy (Jansen et al. 2007). These conditions may contribute or lead to more severe cognitive impairment and eventually promote the one condition that is characterized and defined by disabling cognitive impairment.

2.11 MECHANISMS OF DIABETES-RELATED COGNITIVE IMPAIRMENT IN NON-DEMENTIA AGING

How diabetes specifically affects the brain to impair cognitive functioning is not well understood. Given the complex end-organ effects of diabetes that are known, diabetes’ effects on the brain are likely to be multifactorial, similar to the causes of peripheral neuropathy. Also, evidence for
the brain being an insulin-sensitive organ has recently emerged. Because of
the impermeability of the blood-brain barrier to insulin, the brain was long
thought to be independent of insulin. Insulin and insulin receptors have,
however, been demonstrated throughout the Central Nervous System (CNS)
(Schulingkamp et al 2000). Since the hippocampus is known to be sensitive
to hypoxic conditions it is likely that decreasing vascular supply, causing
inadequate oxygenation of brain tissue, is responsible for some of the
hippocampal volume reduction that has been found in diabetics (Den Heijer
et al. 2003). However, even persons without diabetes diagnosis, but with
reduced glucose tolerance, have been shown to have reduced hippocampal
volume (Convit et al. 2003).

Even though reduced glucose tolerance (postprandial
hyperglycemia) in itself may cause vascular damage that may in turn lead to
hypoxic conditions, perhaps another mechanism is also at work. Insulin and
insulin receptors may play modulating roles in synaptic transmission in the
brain. High densities of insulin receptors have been found in the
hippocampus, olfactory bulb, cerebral cortex, cerebellum, and hypothalamus
(Park 2001; Unger et al. 1991), structures that are known to play important
roles for memory proficiency (Squire 1992). Acute elevation of serum
insulin levels have been shown to increase insulin levels in the CNS
(Wallum et al. 1987), and increased levels of brain insulin during
euglycemic conditions have been demonstrated to improve cognitive
function in healthy humans (Kern et al. 2001).

Since vascular insulin levels are often higher in type 2 diabetes
patients than in persons without diabetes, this would ostensibly be a
protective factor against cognitive impairment in type 2 diabetes. However,
there are two factors that are important to take into consideration regarding
the biological situation in diabetic brains. First, there is mounting evidence
that the effects of chronically raised levels of peripheral insulin may actually induce a down-regulation of brain insulin. Chronic hyperinsulinemia causes down-regulation of the blood-brain barrier insulin receptors, leading to reduced brain insulin availability (Kaiyala et al 2000). Second, the improvement of cognitive function that has been shown under euglycemic insulin administration has not been possible to replicate under hyperglycemic conditions (Watson and Craft 2006). For further discussion regarding how different pathogenetic processes may explain how diabetes causes cognitive impairment in non-dementia aging Biessels (1999).

Aside from the direct pathogenetic effects of diabetes, one must also consider the possibility that diseases that are associated with diabetes may influence cognitive performance. Diseases associated with both diabetes and cognitive impairment includes stroke, hypertension, depression (Stewart and Liolitsa 1999), and cardiovascular disease (Barclay et al. 1988).

Diabetes-associated visual impairment influences performance in cognitive testing, and may indicate greater risk of central nervous system damage, but is not likely a cause of cognitive impairment. There is always a risk of confounding due to a common cause, but there is no proof of a common cause of diabetes and neural damage with the exception of hypertension. Although available data do not confirm a causative link between hypertension and diabetes, they do tentatively indicate that hypertension is a risk-factor for diabetes (Sowers et al 2001). I do not believe that type 2 diabetes is caused by any specific agent in very many cases, but rather by a complex interplay between genetic and lifestyle factors. Even if a diabetes-causing specific agent could potentially induce neural damage, it is unlikely to be a good explanation of the overall pattern of neuronal damage observed in diabetic patients.
2.12 DIABETES AS A PART OF TOTAL COMORBIDITY BURDEN

Several medical conditions, such as cardiovascular disease and symptoms thereof, vitamin deficiency, thyroid disturbances, mood disorders, and diabetes, have been shown to affect cognition. As mentioned in the section on comorbidity, having more than one diagnosed chronic disease becomes increasingly likely with increasing age. In relation to comorbidity, it is important to discuss disease severity. For diseases that are risk-factors for each other, comorbidity could be considered a measure of disease severity. Diabetes is a risk-factor for vascular disease, and the risk of vascular complications is related to the degree of diabetes severity. Thus, vascular disease could be viewed as a proxy of diabetes severity, as well as a risk factor for cognitive impairment in its own right, in diabetic patients. It is not uncommon for related diseases to show this type of relationship. For example, higher blood-pressure leads to increased risk of stroke, and both hypertension and stroke are associated with cognitive impairment. Thus, comorbidity as a proxy for disease severity is always a consideration when diseases serve as risk-factors for each other.

However, diabetes and vascular disease are both risk factors for cognitive impairment, even when they are modelled simultaneously (Kalmijn et al. 1995), so obviously this cannot be the whole story behind comorbidity effects. It is important to realize that different combinations of diseases may act in different ways on cognition. The sum of diseases, or disease burden, does not always maximize explained variations in cognitive test performance. Instead, it may prove worthwhile to examine different types of interaction effects in the context of comorbidity.
There are, for practical purposes, three different ways in which two diseases may affect cognition:

(i) The effect on cognition in subjects with both disease A and disease B approximately equals the sum of effects found in subjects that have either disease A or disease B. This is actually a common finding (Wahlin et al. 1996), that is probably due to the fact that there are cognitive processes that are influenced to a certain degree by either disease, although the variance produced is not shared. Importantly, an additive interaction effect is not likely to be significant if examined as a cross-product interaction term.

(ii) The effect on cognition in subjects with disease A and B is greater than the sum of effects in subjects that have either disease A or disease B. This type of effect is statistically difficult to validate (McClelland and Judd 1993), but has been shown in the context of effects on cognition of diabetes and hypertension (Elias et al. 1997; Hassing et al. 2004).

(iii) The effect on cognition of disease A overshadows the effect of disease B (i.e. the effect of disease A alone is similar to the effect of disease A and B, even though disease B by itself has demonstrated an association with cognition). This type of effect is often found when examining other diagnoses in the context of post dementia diagnosis changes in cognition, such as in Study IV of this thesis. As already mentioned, the absence of a statistically significant interaction means that there is no detectable difference between the sum of effects in subjects that have either disease A or disease B and the sum of effects in
subjects that have both diseases. Of course, data that point in this
direction are by far the most common, since lack of significant
interaction effects is the most common result. Non-significant
interaction effects can either be caused by a true lack of
meaningful effect modification of comorbidity, lack of power to
detect such differences (due to small sample size, small effect
size, or relatedly a large proportion of unexplained to explained
variance in the data). For a more complete discussion on
morbidity interaction effects and cognition, Wahlin (2004)
Comorbidity may, as mentioned, in some cases serve as a proxy
of disease severity.

Thus, controlling for comorbidity (either statistically or through
excluding persons with certain diagnoses from the study) may lead to
unwanted dilution of effects in analyses of diabetes and cognition. On the
other hand, if comorbidity effects are simply ignored, results are often
trivial. For example, if no control for vascular diseases is done, a very strong
association between diabetes and cognitive impairment may be
demonstrated.

However, because this association may result to a large extent
from the “confounding” influence of vascular diseases, and thus does not
imply a direct causative link, it is not as informative as an association
demonstrated whilst controlling for known covarying conditions.
The challenge in dealing with known comorbidity, therefore, is to
simultaneously model diabetes and relevant comorbid conditions. I have
dealt with this in different ways in the studies that form the empirical base of
this thesis.
In Study I, a correlation analysis was performed initially, and all predictor variables that were either correlated with diabetes or cognition were included in the main hierarchical regression analysis. In Study II, known vascular conditions and signs thereof were reduced into clusters by means of a factor analysis, and the factor-scores were then included and controlled for in the main hierarchical regression analysis. In Study III, similarly, a factor analysis was performed, and the resulting factor score was entered as a covariate in the main repeated measures analysis of covariance. In Study IV, several sets of potentially important comorbid conditions, or proxies of such conditions, were controlled for in separate models but not included in the final analysis since they influenced neither model fit nor main results. A last aspect of comorbidity that I will briefly mention is unknown comorbidity. It is likely that all diagnoses that could potentially have been made are not made in all individuals participating in a study. Such undiagnosed conditions could potentially be related to both diabetes and cognitive impairment. Because type 2 diabetes is an exclusion diagnosis of sorts, it is also possible that several different subtypes of type 2 diabetes are represented in the group of diabetics, and that different comorbidity patterns are present for the different subtypes.

2.13 GLUCOSE AND MEMORY

Glucose is the primary substrate for brain energy metabolism (Raichle et al. 1984). Neurons in the brain are unable to store or synthesize glucose, and therefore, the needed glucose is obtained from the systemic circulation and subsequently transported across the blood brain barrier (Mc Call 1992). The hippocampus, which plays a critical role in conscious acquisition and recall of new information (i.e. declarative memory) (Squire et al. 1992), is vulnerable to excitotoxic damage during periods of glucose insufficiency (Mc Call 1992). Other medial temporal lobe structures for
declarative memory include the entorhinal cortex, the parahippocampal cortex and the perirhinal cortex. Together with the hippocampus, these areas work in concert with neocortex (Zola-Morgan and Squire 1993).

Decreased glucose utilization has been hypothesized to play a role in the mild decline in memory function observed in normal aging (Gold et al. 1986, Gold and Stone 1988). This idea has been supported by findings that elevating plasma glucose levels through glucose administration in elderly human and rodents improves memory without affecting motor and nonmemory functions (Gonder-Frederick et al. 1987, Manning et al. 1990). The specific way this occurs is still unclear, but a few mechanisms have been suggested. One hypothesis is that increased availability of glucose may increase the production of acetyl-CoA, a cholinergic substrate and thereby enhance cholinergic mediation of memory function (Gold and Stone 1988). Not only memory, but also attentional function are affected by the basal forebrain cholinergic system innervation, therefore attentional function may be improved by stimulated cholinergic system (Lawrence and Sahakian 1995). An alternative hypothesis is that hyperglycemia may modulate opiate inhibition of acetylcholine turnover in the hippocampus (Stone et al. 1991). Wenk (1989) presented a hypothesis that some cognition enhancing drugs produce their beneficial effects on memory through increasing the availability glucose in the brain.

2.14 ACUTE INSULIN ADMINISTRATION AND COGNITIVE FUNCTION

Insulin receptors have been identified in different brain regions, e.g. in the hypothalamus (Shibata et al. 1985) and the hippocampus (Palovick et al. 1993). The former is an important factor in regulating Insulin receptors have been identified in different brain regions, e.g. in the
hypothalamus (Shibata et al. 1985) and the hippocampus (Palovick et al. 1993). The former is an important factor in regulating raising plasma insulin levels by an intravenous infusion, causes a secondary reduction in plasma glucose level, which itself can impair cognitive function. Hyperinsulinemic euglycemic clamp technique, in which plasma glucose level is maintained at a stable baseline level, provides a way of investigating the independent effect of acutely raised insulin level (Craft et al. 1996).

Kerr et al. (1991) studied the cognitive changes in nine patients with insulin dependent diabetes, aged 21-50 years. During the euglycemic hyperinsulinemic clamp study, no differences were found in cognitive function. However, no appropriate test of declarative memory was included. Fanelli et al. (1994) investigated the relative roles of insulin and hypoglycaemia on cognitive function in 22 young nondiabetic subjects. During a three hour hyperinsulinemic euglycemic clamp study, the sum score of cognitive function did not change, but during the hypoglycaemic condition cognitive impairment was detected. Craft et al. (1996) studied the effect of hyperinsulinemia on cognitive function in patients with mild Alzheimer disease and in normal control subjects. They showed that raising the plasma insulin level via an intravenous insulin infusion while keeping glucose level at the baseline level produced a striking declarative memory enhancement in patients with Alzheimer disease but not in the control subjects. In the nonmemory tests word fluency, Stroop tests, line orientation, digit span) no improvement was found. These results suggest that neuroendocrine may factors play an important role in the pathophysiology of Alzheimer disease. In the patients with incipient Alzheimer disease, acute insulin administration may have significant effects on memory, whereas in the control subjects this would be less likely.
CLASSIFICATION OF COGNITIVE FUNCTIONS

Memory is not a single entity, but is composed of separate systems. Memory can be divided into declarative (explicit) and nondeclarative (implicit) memory. Declarative memory refers to memory for facts and events, whereas nondeclarative memory refers to skill and habit learning, priming, simple classical conditioning and nonassociative learning. Structures of the medial temporal lobe and diencephalon are essential for intact declarative memory function, whereas for nondeclarative memory function they are not necessarily needed (Squire and Knowlton 1995). Through the book, memory refers to declarative memory, unless other indicated. Lezak (1995) has classified cognitive functions into four major classes using analogies with computer systems. Firstly, receptive functions which cover the abilities to select, acquire, classify and integrate information. Secondly, memory and learning, which refer to information storage and retrieval. Thirdly, thinking which is related to the mental organization and reorganization of information. Fourthly, expressive functions which refers to ways through which information is communicated or acted upon. Each of these functional classes comprises many discrete activities, and these classes normally work in concert and interdependence (Lezak 1995). In addition to this crude classification, it presents a compendium of tests and assessment techniques. These are divided into the major classes: orientation and attention, perception, memory, verbal functions and language skills, construction, concept formation and reasoning, executive functions and motor performance (Lezak 1995).

Strachan et al. (1997b) used a classification based on that of Lezak (1995) when reviewing the literature concerning non-insulin-dependent diabetes and cognitive functions. Since very many psychological
tests had been applied in their studies, they summarized the results for practical reasons into six major categories. These categories were:

1. Attention and concentration
2. Frontal lobe / executive function
3. Visuospatial memory
4. Verbal memory
5. Psychomotor / performance intelligence quotient (including variety of subtests of the WAIS performance scale)
6. Mini-Mental State Examination (representing overall cognitive level rather than any specific cognitive domain).

Although still crude, this classification provides the opportunity to compare results obtained in previous studies and gives signposts for future research. Although psychomotor/performance intelligence quotient and Mini-Mental State Examination are not separate cognitive functions these aggregate scores are widely used, and therefore they improve comparability across different studies. The classification of cognitive functions used in the present study was based on that of Strachan et al.

2.16 MILD COGNITIVE IMPAIRMENT (MCI)

In the second half of the last decade Mild Cognitive Impairment (MCI) (Petersen et al. 1997) emerged as the predominant target for studies on early signs and symptoms of dementia. MCI is conceptualized as a boundary or transitional state between normal aging and dementia.
In the original criteria MCI was defined as memory impairment with other cognitive domains relatively spared (Petersen et al. 1999). The memory impairment should be both subjective and objectively significant for age; confirmed by a significantly reduced memory test score. According to a number of studies, individuals with that kind of memory impairment, but with normal general cognitive function, converted to AD at a rate of 10-15% per year (Bowen et al. 1997; Guarch et al. 2004; Morris et al. 2001; Petersen et al. 1997; Petersen et al. 1999; Tierney et al. 1996).

Although the focus of these studies was memory impairment, other cognitive impairments also were reported, for example naming deficits (Petersen et al. 1999), impaired concept formation (Guarch et al. 2004) and executive impairment (Chen et al. 2000; Guarch et al. 2004). Eventually it was suggested that the risk of dementia, including AD, was significantly increased when other cognitive impairment was present, and that isolated memory impairment was not the best predictor of dementia. According to some studies, subjects with memory impairment alone were very rare and rarely progressed to dementia (Ritchie et al. 2001).

These findings led to an amendment of the MCI criteria in 2001, the criteria were widened to encompass three MCI subgroups: amnestic (isolated memory impairment); multiple domains slightly impaired; single non-memory domain impaired (Petersen et al. 2001). This model with three subgroups was, however, soon replaced by new criteria and a model with four subgroups. In 2004 the International Working Group on Mild Cognitive Impairment published a consensus report in which the following criteria were proposed for MCI: (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measure decline over time and/or subjective report of decline by self and/or informant in conjunction with
objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired (Winblad et al. 2004). In accordance with the increasing heterogeneity of the concept, the MCI subgroups were increased with one; subjects could now be designated to one of four subgroups: amnestic; amnestic with multiple domains impaired; non-amnestic multiple domains impaired; non-amnestic single domain impaired.

The notion of different aetiologies causing MCI was also introduced: degenerative, vascular, psychiatric and traumatic (Petersen 2004). A model with MCI subtypes of different aetiologies representing different prodromal dementia disorders was put forward. Amnestic MCI (aMCI) of degenerative aetiology was suggested to represent prodromal AD; amnestic MCI with multiple domains impaired (maMCI) of degenerative aetiology would also represent prodromal AD; maMCI of vascular aetiology would represent vascular dementia (VaD); non-amnestic MCI with multiple domains impaired (mDMCI) of degenerative aetiology dementia was suggested to be prodromal dementia with Lewy bodies (DLB); mDMCI of vascular aetiology VaD; non-amnestic MCI with single domain impaired would be prodromal frontotemporal dementia (FTD) or DLB (Petersen 2004). Thus, it was suggested that a combination of clinical subtypes and aetiologies would be useful in predicting the specific dementia disorder that a person with MCI would progress to.

There are numerous, discordant, reports on which MCI subtype constitutes the greatest risk of conversion to dementia. There is some agreement on that amnestic MCI - with or without other domains impaired - typically represents AD. Some studies report the risk of AD to be increased when domains other than memory also are impaired (Alexopoulos et al. 2006; Tabert et al. 2006) and conclude that pure aMCI has a more
favourable prognosis than maMCI. Others report lower conversion rates for maMCI than aMCI and state that individuals with multiple domain or non-amnestic MCI “include a substantial number of individuals who may not progress to dementia” and that neuropsychological variables other than memory are not instrumental to predict progression to dementia (Schmidtke and Hermeneit 2008).

2.17 BIOMARKERS AND MCI

Since 1995 two biochemical markers in the cerebrospinal fluid (CSF) for AD have emerged, total-tau (T-tau) and amyloid-β42 (Aβ42) (Andreasen et al. 2003). Tau protein is located in the neuronal axons and the concentration of T-tau in the CSF is thought to reflect the intensity of neuronal degeneration in chronic neurodegenerative disorders (Blennow 2004). Aβ42 is the major component of senile plaques and the decreased level of Aβ42 in the CSF in AD may be caused by deposition of Aβ42 in plaques, with lower levels being transported to CSF (Blennow 2004). Lately these biomarkers - increased levels of T-tau and decreased levels of Aβ42 - have been used to predict AD in MCI subjects with some success (Andreasen et al. 2003; Hansson et al. 2006; Ivanoiu and Sindic 2005).

Recently the biomarkers have even been used to predict MCI in seemingly healthy individuals (Li et al. 2007). Some studies on MCI, examining the relation between CSF biomarkers and neuropsychological findings, have been conducted (Ivanoiu and Sindic 2005; Schoonenboom et al. 2005). Both studies found elevated T-tau concentrations primarily to be associated with poor performance on episodic memory tests, whereas decreased Aβ42 concentrations were associated with poorer general neuropsychological performance. In a recent study, both patients with amnestic MCI and MCI with a dysexecutive syndrome had abnormal
biomarkers and progressed to AD to approximately the same extent, with T-tau as the biomarker with the strongest predictive power (Herukka et al. 2007).

2.18 COGNITIVE FUNCTION AND PHYSICAL ACTIVITY

2.18.1 Evidence from Prospective Cohort Studies

Two studies of women only show strong associations between physical activity and cognitive function (Weuve et al 2004; Yaffe et al. 2001). Both include walking, have large sample sizes, controlled for typical potential confounding factors, and have long follow-up periods. With data from the Nurses’ Health Study, (Weuve et al. 2004) included 18,766 women ages 70 to 81 years to ascertain whether greater participation in leisure-time physical activities, as measured by energy expenditure (mean of biennial reports during 8 to 15 years), resulted in better cognitive function, as measured by a global cognitive function score created by combining scores from six different tests.

In another study of women only, (Yaffe et al. 2001) followed 5925 women age 65 years and older for 6 to 8 years to determine whether walking and kilocalories (or energy) used during physical activity (assessed at baseline) were associated with less cognitive decline, as measured by the modified Mini-Mental State Examination (3MS). The women, part of the Study of Osteoporotic Fractures, were all cognitively unimpaired at baseline. After adjusting for potential confounders such as age, education, and functional limitations, at follow-up, women in the highest quartile of blocks walked per week (median, 175; range, 113 to 672), compared with those in the lowest quartile (median, 7; range, 0 to 22), were 34% (odds ratio, 0.66; 95% confidence interval, 0.54-0.82) less likely to experience cognitive
decline, defined as a score on the 3MS 3 points lower than at baseline. One block was estimated to be about 160 meters, so women in the highest quartile walked approximately 17.4 miles per week. Those in the highest quartile for kilocalories expended, compared with those in the lowest quartile, were 26% (odds ratio, 0.74; 95% confidence interval, 0.60-0.90) less likely to have cognitive decline at follow-up (Yaffe et al. 2001).

Several studies have examined the relationship between physical activity and cognitive function for men only. Both studies have small sample sizes, which might explain the weaker links between physical activity and cognitive function that their results indicate. In one such prospective cohort study, 295 men, part of the Finland, Italy, and the Netherlands Elderly (FINE) Study, age 70 years and older, were assessed at baseline and 10 years later for both physical activity, such as walking, bicycling, gardening, and chores, and cognitive function, by using the Mini-Mental State Examination (MMSE). A cutoff point of more than 18 on the MMSE, which the authors note as “not severely cognitively impaired”, was used as part of inclusion criteria along with an absence of stroke, diabetes, cancer, and heart attack. Physical activity data were not available from Finnish subjects at the 10-year follow-up, leaving 243 subjects for those analyses. After adjusting for potential confounders such as age and education, no measures of duration or intensity of physical activity at baseline were associated with differences in baseline cognitive functioning. However, results indicated linear trends between cognitive decline and changes in both duration of activity (P < .02) and intensity of activity (P < .002). One strength of this study is the long follow-up period of 10 years; however, the sample size for these analyses was quite small. In addition, only those who were “severely cognitively impaired” were excluded from the analyses (Van Gelder et al. 2004).
In another study of men only, 347 men from the Netherlands who were part of the Zutphen Elderly Study were followed for 3 years. Subjects were considered more active if they engaged at baseline in self-reported physical activity for more than an hour per day; less active subjects reported physical activity of an hour or less per day. Cognitive decline was defined as a decrease greater than three points during the 3-year period on the Dutch version of the MMSE, wherein the highest score is a total of 30 points. Analyses of those with and without the apolipoprotein were also performed. After adjusting for possible confounders such as age and education, comparing all more active men with all less active men, those who were less active were twice as likely to experience cognitive decline, although this finding was not significant (odds ratio, 2.0; 95% confidence interval 0.9-4.8). However, men with the apolipoprotein who were less active were 3.7 times (95% confidence interval, 1.1-12.6) more likely to experience cognitive decline in adjusted models at follow-up when compared with those who were more active. It should be noted that the sample size for this study is small, and there were only 37 carriers in the less active group and 47 in the more active group (Schuit et al. 2001).

In a study of Chinese elderly who were followed for 3 years, (Ho et al. 2001) found an association between not exercising (self-report) at baseline and incident cognitive impairment, as measured by questions extracted from the Clifton Assessment Procedure for the elderly. Analyses were adjusted for age and education, and the odds ratio was 2.1 (95% confidence interval, 1.3-3.3). When the data were analyzed separately for men and women, the relationship held for women only (odds ratio, 2.2; 95% confidence interval, 1.2-3.8). Of note, the women in this sample of 988 study subjects age 70 years and older were quite different than their male counterparts. All women and men were cognitively unimpaired at baseline,
but the women at baseline had less education and were more financially dependent on others, compared with the men. The women also reported poorer health and had greater functional limitations. At follow-up, 6.7% of the men in the sample had cognitive impairment, but 22.2% of the women were cognitively impaired; women were 2.7 times (95% confidence interval, 1.6-4.4) more likely to be cognitively impaired at follow-up.

The studies described above are all based on self-reported physical activity. To overcome the limitations associated with self-reported data, such as potential errors as a result of recall, Barnes et al (Barnes et al. 2003) examined possible associations between cognitive function and fitness by measuring peak oxygen consumption, a measure of physical fitness, with a sample of 349 adults age 55 years and older. Levels of fitness as well as cognitive function, as measured by the 3MS, were assessed at baseline. They found no association between 3MS scores and peak oxygen consumption at baseline ($P_{.22}$ for trend).

### 2.18.2 Evidence from Randomized Trials

All three of the identified randomized trials support the prospect that engagement in physical activity will result in improvement or maintenance of cognitive function. Two studies (Kramer et al. 1999; Colcombe et al. 2004) found that aerobic, versus anaerobic, activity resulted in improved executive function, and one study (Fabre et al. 2002) found that overall cognitive function improved for subjects who engaged in aerobic activity, even though the intervention lasted for only 2 months. In a randomized trial of 124 sedentary older adults (age 60 to 75 years), (Kramer et al. 1999) were able to show an impact of aerobic exercise on executive functioning (i.e. planning, problem-solving, scheduling).
After a pretest, study subjects were randomly assigned to either a walking (aerobic) intervention or a stretching and toning (anaerobic) intervention. After participating in the exercise interventions for 6 months, subjects were given a post-test. Results indicated that the scores on cognitive tests requiring greater executive processing improved for the group assigned to the aerobic intervention but not for the anaerobic group. For cognitive tests requiring less executive control (eg, reaction time to a command to stop), both groups showed similar results. In a later study conducted by (Colcombe et al. 2004), 29 adults, age 58 to 77 years, were again randomly assigned to an aerobic (walking) or anaerobic (stretching and toning) exercise intervention group. Both the aerobic group and the anaerobic group met three times a week for 6 months. Aerobic sessions initially lasted for 10 to 15 minutes and then increased 1 minute each session to a maximum of 40 to 45 minutes sessions.

Participants were at the maximum level for approximately the last half of the intervention. Anaerobic sessions followed the same schedule as aerobic sessions and also increased in level of difficulty. Pretests and post-tests were administered before and after the interventions. Fabre et al. (2002) undertook a randomized trial of 32 adults, age 60 to 76 years, for which subjects were randomly assigned to one of four groups, resulting in eight study subjects per group. The four groups were individualized aerobic training intervention, cognitive training intervention, a combined cognitive and individualized aerobic training intervention, and a control group. Aerobic training (for both the aerobic training and combined aerobic and cognitive training groups) consisted of two sessions each week for a period of 2 months. Each session was an hour long, including a 5-minute warm-up and a 10-minute cool down, and was individually tailored, and gradually increasing in intensity.Subjects were given a pretest and then participated in
the various interventions for 2 months. Those in the control group also met during the 2-month period after the pretest.

At the end of the 2-month period, all study subjects were given a post-test. Results from the Wechsler memory scale indicated that subjects in the three intervention groups all improved between the pretests and post-tests (P < .01), whereas the control group showed no statistically significant improvement. In addition, participants in the combined cognitive and aerobic intervention group showed greater improvement than all of the other groups (P < .001), intervention and control. The cognitive training intervention group improved scores by 7.4%, the aerobic group by 8.5% and the combined aerobic and cognitive training group by 9.2%.

2.19 MINI-MENTAL STATE EXAM (MMSE)

- Goals

The Mini-Mental State Exam (MMSE) (Folstein et al. 1975) was originally designed to provide a brief, standardized assessment of mental status that would serve to differentiate between organic and functional disorders in psychiatric patients. As experience with the test has increased over the years, its major function has now become to detect and track the progression of cognitive impairment associated with neurodegenerative disorders such as Alzheimer’s disease.

- Description

The MMSE is a fully structured scale that consists of 30 points grouped into seven categories: orientation to place (state, county, town, hospital and floor), orientation to time (year, season, month, day and date), registration (immediately repeating three words), attention and concentration
(serially subtracting 7, beginning with 100 or alternatively, spelling the word world backward), recall (recalling the previously repeated three words), language (naming two items, repeating a phrase, reading aloud and understanding a sentence, writing a sentence, and following a three-step command), and visual construction (copying a design). Several shortened forms of the MMSE have been developed on the basis of linear regression analyses that used the individual test items to predict the total score. Although these versions vary somewhat, they are generally limited to the orientation, attention and concentration, and recall items. There are also at least two telephone versions: the Telephone-Assessed Mental State (TAMS) (Lanska et al. 1993) and the Telephone Interview for Cognitive Status (TICS) (Brandt et al. 1988).

Several expanded versions of the MMSE have been developed to assess a greater range and depth of cognitive functioning or to increase the test’s sensitivity to subtle cognitive deficits that may occur in specific neurological diseases such as multiple sclerosis (e.g., the Cognitive Abilities Screening Instrument (CASl) (Teng et al. 1994), the Modified Mini-Mental State (3MS) Examination (Teng and Chui 1987), and the expanded MMSE).

The MMSE is scored in terms of the number of correctly completed items; lower scores indicate poorer performance and greater cognitive impairment. The total score ranges from 0 to 30 (perfect performance). Although scoring for most MMSE items is simple and straightforward, several different scoring methods have been used for the attention and concentration item. The most commonly used procedure is to present both the serial subtraction and backward spelling items and use the higher of the two scores in calculating the MMSE total score. Comprehensive normative data (N = 18,056) on the MMSE (Crum et al. 1993) collected through the Epidemiologic Catchment Area (ECA) study
provide age- and education-related median, upper quartile, and lower quartile scores that can be used to identify abnormal performance. An initially recommended MMSE cut off score of 23 or 24 provides good sensitivity and specificity for the detection of dementia; however, several recent studies suggested that this cut off score may be too low, particularly with highly educated individuals. These studies showed that dementia can be clinically diagnosed with good accuracy in many individuals who score between 24 and 27 on the MMSE. However, these figures are focused on accuracy in community populations. For clinical purposes, even a score of 27 may be insufficiently sensitive to detect dementia in individuals with extensive education, whereas a cut off score of 24 may be insufficiently specific in individuals with little education.

- **Practical Issues**

  It takes approximately 5-10 minutes to administer the MMSE. The test is designed to be easily administered by any healthcare professional or trained technician who has received minimal instruction in its use. The MMSE is not commercially available, but the test items, instructions for administering, and extensive normative data have been published (Crum et al. 1993; Folstein et al. 1975).

- **Clinical Utility**

  The MMSE is a very brief, easily administered mental status examination that has proved to be a highly reliable and valid instrument for detecting and tracking the progression of the cognitive impairment associated with neurodegenerative diseases. Consequently, the MMSE is the most widely used mental status examination in the world. The test has been translated into many languages and has been used as the primary cognitive
screening instrument in several large-scale epidemiological studies of dementia. The test is also used widely in clinical practice and is often reported in research studies as a benchmark of the severity of dementia that can be used to compare patient cohorts across studies. This prominence of the MMSE as a cognitive screening instrument is attested to by its inclusion along with the Diagnostic Interview Schedule (DIS), in the National Institute of Mental Health ECA study and by its listing as a recommended measure of cognitive functioning in the diagnostic criteria for Alzheimer’s disease developed by the consortium of the National Institute of Neurological and Communication Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (Mc Khann et al. 1984).

Extensive psychometric data on the MMSE confirm that the test has very good test-retest and joint reliability and excellent validity as measured against independent clinical diagnosis of dementia and Alzheimer’s disease, measures of functional impairment, or performance on other (often more rigorous) neuropsychological tests and against neuropathological features of Alzheimer’s disease. Because performance on the MMSE can be adversely affected by low education in psychiatratically healthy elderly individuals, some investigators recommend the use of age- and education-adjusted cut off scores for the detection of dementia. The MMSE has been shown to be sensitive to cognitive decline in patients with Alzheimer’s disease; scores decline an average of 1.8-3.2 points per year. This feature of the scale has led to its use as a primary or secondary outcome measure in some studies that have examined the efficacy of pharmacological agents that might slow the progression of cognitive deterioration in patients with Alzheimer’s disease. The MMSE is also somewhat effective in differentiating between dementing disorders that differ in their etiology and sites of predominant neuropathology.
For example, in one study, it was reported that Alzheimer’s disease and Huntington’s disease patients differed in the profile of deficits they produced on the individual MMSE items.

The most commonly cited limitations of the MMSE are its marginal or absent assessment of some cognitive abilities that are affected early in the course of Alzheimer’s disease or other dementing disorders (e.g., limited memory and verbal fluency items and no problem solving or judgment items), its relative insensitivity to very mild cognitive decline (particularly in highly educated individuals), and its susceptibility to floor effects in tracking the progression of dementia in patients with moderate to severe cognitive impairment. Although these limitations diminish the usefulness of the MMSE to some degree, the test remains a very valuable instrument for the assessment of cognitive decline.

2.20 DIETARY AND LIFE STYLE ASPECTS OF COGNITIVE IMPAIRMENT

In a study of the association of rates of cognitive change and dietary consumption of fruits and vegetables, 3718 older (average age 74 years) subjects completed a food frequency questionnaire and cognitive assessments were made at baseline, 3 and 6 years (Reaven et al. 1990). Individuals in the lowest quintile of vegetable intake (less than one serving daily) had a 40% (P = 0.02) decrease in the cognitive score compared with those in the fifth (highest) quintile, averaging four servings daily. In the Rotterdam study, a population based, prospective cohort trial was reported by Munshi et al. (2000).

A total of 5395 participants aged at least 55 years, who were free of dementia, and who had a reliable dietary assessment, were followed for a
mean of 6 years. A total of 197 developed dementia of which 146 were
diagnosed with Alzheimer’s disease. After adjustments were made for age,
gender, Mini Mental State examination (MMSE) score, alcohol intake,
education, smoking habits, BMI, total energy intake, and use of anti oxidant
supplements, high intake of vitamin C and E was associated with lower risk
of Alzheimer’s Disease, Rate ratio per I standard deviation increase in intake
were 0.82 (95% CI, 0.68-0.99) and 0.82 (95 % CI, 0.66-1.00), respectively.
Association did not vary by education ApoE genotype.

But weight is almost always an accompaniment of disproportion
of dietary intake and energy consumption, so the presence of obesity must
be considered as a potential correlate to impact of diet on specific disease
problems. The relationship between BMI and dementia risk was examined in
a representative co hart of 392 non demented Swedish adults who were
followed from age 70-85 years, with neuropsychiatric and other
measurements (Messier 2005).

The effect of exercise on cognition were recognized, if not
quantified many years (2000+) ago when Cicero wrote that “It is exercise
above that supports the spirirts,and keeps the mind in vigor” (Gallo 1995,
Backman and MacDonald 2006). A study of osteoporotic fracture provided
an opportunity for a perspective study of physical activity and cognitive
decline (Ramachandran and Snehalatha 2001). Adults who engage in regular
physical activity also have inflammatory markers (Chitra et al 2010).
Because obesity control in volume both exercise the relationship between
cognitive function and the features of metabolic syndrome, a clustering of
cardiovascular disease risk factors that includes abdominal obesity, high
triglycerides, low high density lipoproteins, hypertension and
hypoglycaemia.
2.21 DIABETES MELLITUS EDUCATION, SELF-CARE AND METABOLIC CONTROL

A number of workers concerned with diabetic education have developed questionnaires to measure knowledge about diabetes, and have generally found patients to be disturbingly ignorant about the condition. Beaser (1956) was apparently the first to use a multiple-choice questionnaire and found the patients he studied were “all distinctly deficient in knowledge of the disease”. Etzwiler (1962) used a similar method to study 74 diabetic children who were ignorant of basic facts relevant to the control of diabetes. In children under the age of 12 this lack of knowledge was so gross that Etzwiler suggested that such children should not normally be entrusted with the control of their own condition. Further studies of the diabetic children’s parents and of nurses, dietitians and physicians (Etzwiler 1967) also revealed disturbing areas of ignorance about the management of diabetes.

Finally, Etzwiler (1967) undertook a survey of knowledge about the control of diabetes among diabetic school-children and their parents. This study differed from the previous ones in that an attempt was made to contact the whole population of diabetic children in the Minneapolis area through the school authorities. It was therefore a broader and more representative sample than had been used in previous work. Again disturbing areas of ignorance were uncovered. An important distinction needs to be made between how much patients know about diabetes in general, and whether or not they know how they should manage their condition in practice.

Hulka et al. (1975) carried out a careful survey of the communication of information about the management of their diabetic condition to 242 patients. A third of the information the physician had tried
to communicate could not be recalled at an interview carried out at the patients’ homes 2 weeks later. Most patients had remembered at least 40%, of the information, but beyond this point recall deteriorated sharply. Unfortunately this study had no independent check on what information was communicated and relied on physicians’ reports. No correlation was found between the volume of information presented to the patient and the proportion correctly remembered. It is noteworthy that patients who had had diabetes for longer and were being treated by insulin were more likely to remember the information communicated to them. However, there was no correlation between memory for information transmitted and either compliance in taking the prescribed medication or metabolic control. This may be partly explained by the fact that not all the information communicated was critical for compliance. For example, 39% of patients on oral medication could not say what medication they had been prescribed, though half of these patients were taking the correct medication. Thus knowledge of the medication contributed to, but was not essential to, actually taking what had been prescribed. The problem of patients not remembering what their doctors tell them is a very common one (Ley and Spelman 1967). It is especially disturbing that doctors’ advice about the treatment of a medical problem is recalled much less well than diagnostic information.

2.22 EDUCATION PROGRAMMES

A variety of education programmes have been developed to improve diabetic patient’s knowledge of their condition, and their effects evaluated. A distinction needs to be made between direct effects on knowledge about diabetes and their indirect effects on patients’ metabolic control. (Graber et al. 1977) have reviewed the effects of a number of diabetic education programmes, and reached the conclusion that they
significantly improve knowledge about diabetes but fail to affect metabolic control. This is true for example of the education programme developed by (Etzwiler and Robb 1972). An important, recent study was carried out by (Sulway 1977). The education was designed to be spread over a 6 month period, which allowed time for the groups of patients going through the programme to get to know each other and to put into practice what they were being taught. The patients were expected to bring a relative with them. As well as increasing diabetic knowledge, the programme seemed to have a valuable supportive function. Many of the patients involved valued the programme and wished it to continue. However, again no clear advantages in the patients’ metabolic control could be demonstrated.

Various other education methods have been tried including automated teaching programmes (e.g. McDonald and Kaufman 1963; Spiegel 1967; Tani and Hankin 1971). It has been shown that this can be an effective, way of providing information about diabetes, and may have a useful place in the routine instruction of new diabetic patients. However, there is no reason to think that it will be more successful in improving metabolic control than other educational methods. Clearly the value of diabetic education programmes is limited if they simply provide information, and have no other clinical value. It might be more useful to concentrate on ensuring that patients remember exactly what treatment has been prescribed for them by their doctors. This is clearly important if they are to comply with the prescribed treatment.

A variety of steps can be taken to improve recall of doctor’s instructions. If the most important information is placed first, it is more likely to be recalled. Perhaps more important is to structure the material carefully. The doctor following this method mentions the various categories of information he is going to give, under numbered headings, and in a
logical order, before giving the information. This considerably improves recall (Ley et al. 1973). Perhaps it should also be routine practice for a doctor to check at the end of a consultation whether the information has been recalled, and where necessary take the precaution of writing it down.

2.23 SELF CARE

One of the most important findings to emerge from general research on treatment compliance (Haynes and Sackett 1976) is that complicated regimens, persisting over a long period of time and requiring substantial degrees of behavioural change are associated with particularly poor treatment compliance. Hardly a surprising finding, but it is worth noting that from this point of view diabetes is likely to raise particular compliance problems. Once a patient becomes diabetic he remains diabetic for life. He needs to follow a strict diet, both as far as what he eats and when he eats it are concerned. Unless he is a relatively mild diabetic he will need to give himself insulin injections once or possibly twice a day. He will need to use the correct insulin, measure the correct dosage at the correct time. He will also be asked to test his urine daily, interpret the tests correctly and take appropriate action if the results are not within the acceptable range. Not surprisingly there have been repeated reports (Tunbridge 1953; Stone 1961), that diabetic patients’ level of self care leaves a great deal to be desired. The collection of accurate data about compliance obviously presents a considerable problem.

However, the most thorough of the available surveys of diabetic self-care (Williams et al. 1967 and Watkins et al. 1967a) did most of what could reasonably be done to obtain accurate information. Structured interviews were conducted at the patients’ homes by public health nurses. During the interview the patients were asked to demonstrate their daily
routines of insulin and urine testing. Dietary information was based on (a) a food frequency intake for one week, (b) a 24-hr food recall and (c) a daily record of food intake for a week. Obtaining accurate information about diet is very difficult, but short of weighing the food patients eat, a food record is probably the most satisfactory (Young and Trulson 1960).

Fifty eight percent of the patients with Diabetes Mellitus administered the wrong dosage. Seventy-seven per cent either tested their urine incorrectly or interpreted the results “in a manner likely to be detrimental to their treatment”. Seventy-five per cent were not eating the prescribed foods and 75% were not eating with satisfactory regularity.

The patients for these studies came from various sources: university clinics in North Carolina, a North Caroline private practice and New York diabetics with a health insurance plan for their families. There is no reason to think that patients from these sources would show unusually poor self-care.

There is also a minority of patients who seem to deliberately interfere with the proper management of their condition. Perhaps the most influential report of this phenomenon has been the (Rosen and Lidz 1949) study of 12 patients who went into repeated insulin comas. Similar reports (Peck and Peck 1956 and Stearns 1959) have appeared subsequently. The use of overdoses of insulin in suicide attempts have also been reported (Blotner 1954). Not a great deal is known about the characteristics of patients who deliberately disturb the management of their condition, though most of such patients reported in the literature seem to be under 25, to be regarded as immature and to have failed to make a satisfactory, independent social adjustment.
2.23.1 Improving Self-care

It seems beyond serious dispute that treatment compliance in diabetics is very poor. What then can be done about it? It has presumably been one of the aims of education programmes to improve the quality of patients’ self-care. Unfortunately this has seldom been assessed. Indeed, the majority of studies that have examined the correlation between knowledge and compliance in medicine have not found the two significantly correlated (Haynes and Sackett 1976). This makes it unlikely that education programmes are an efficient way of improving self-care. It must, however, be admitted that the only study to have examined the correlation between knowledge and compliance in diabetic subjects found it to be significantly positive (Watkins et al. 1967b).

It is relevant to consider which factors have regularly been shown to be associated with good compliance in the general research literature on this subject (Haynes and Sackett 1976). Health beliefs are clearly one important factor. Compliance is better when the patient regards the disease as serious and considers himself personally at risk (Becker 1976). It is also helpful if he believes that the treatment is effective, though the evidence for this component in the health belief model is less strong.

Currently, very little is known about the health beliefs of diabetics and their association with the level of self-care. There is some relevant data in a study reported by (Sanders et al. 1975) but unfortunately there is very little information about the details of the assessment procedure, the reliability of the way patients were categorised, etc. However, it is noteworthy that the 23 of patients who were aware of possible problems arising from the disease in the future, but who thought that they would personally escape them seemed to be very well motivated to manage their
condition carefully. The remainder of the patients were about equally divided between those who were aware of no possible problems, and those who were both aware of possible problems and worried about them. If replicated, such results have important implications for the kind of attitudes to diabetes that should be inculcated. There would be a place here for some of the standard attitude change procedures such as requiring patients to play the part of someone advocating a particular view (Janis and King 1954) in this case the importance of good self-care. Such attitude-change procedures have been successfully applied to other health problems (Janis 1968; Broadhurst 1976).

Another relevant set of findings in the general literature on compliance are the effects of closer monitoring and supervision of self-care. In general closer supervision has been found to be associated with better compliance (Haynes and Sackett 1976). It might well be valuable to link this with a programme requiring the patient to monitor his level of self-care. There have been many demonstrations that self-monitoring is a ‘reactive’ procedure, with useful self-regulatory functions (Thoresen and Mahoney 1974). Patients could be given a form on which to check off each day the tasks they needed to perform in managing their diabetes, and perhaps to give themselves an overall rating for each day’s performance. Their check lists would then be shown regularly to a member of the clinic staff. The effects of self-monitoring on compliance deserve more attention than they have so far received.

A substantial part of the compliance problem in diabetics relates to dieting. Many diabetics are obese. Incidentally, these obese diabetics seem to be a genetically distinct group, predominantly female, and with an age of onset over 40 (Murray and Wang 1956). It is likely that obese diabetics show the same kind of eating behaviour as other obese people
(Leon and Roth 1977) and would respond to the same modification methods of which those that concentrate on the self-regulation of patterns of eating seem to be the most successful in reducing obesity (Leon 1976; Green 1978) has reported the successful modification of a psychiatric patient with diabetes using operant methods. The content of the diet is important, as well as the problem of eating behaviour. Though traditionally emphasis has been placed on carbohydrate portions, there is evidence (West 1973) that a liberal carbohydrate diet can be tolerated provided the total calorie content is effectively limited. There is some doubt about how necessary it is for patients to adhere to a very strict diet. (Knowles 1965) published an influential study, examining the effects of allowing juvenile diabetics a free diet, and found that they fared no worse than those on a regulated diet in terms of metabolic control.

Though there have been other studies, many of them referred to by Knowles et al. (1965) the thoroughness and the prospective design of this study gave it particular weight. Clearly there is no virtue in taking measures to improve compliance with a strict diet unless metabolic control will be improved as a result. As far as patients who appear to deliberately interfere with their treatment are concerned, it would be helpful to investigate whether they show any differences from other patients in the perceived unpleasantness of a diabetic coma, or in the perceived likelihood of a coma occurring as a consequence of the abandonment of insulin treatment. This could best be carried out in the framework of an analysis of the ‘subjective expected utility’ of this course of action (Broadhurst 1976). For example, there may be consequences of being hospitalised in a comatose state that provide an incentive for the abandonment of the insulin treatment.

The comments made by (Rosen and Lidz 1949) about the ‘dependent’ personalities of these patients makes this hypothesis quite
likely. The better understanding of such factors should have implications for the improved management of these patients. One of the most important points to be made about poor self-care in diabetes is the variety of causes that it may be due to. No single kind of intervention is likely to improve self-care in all patients who present problems in this area. It is therefore essential that the reasons for a particular patient’s poor self-care should be investigated before any intervention is made. Factors such as the following need to be checked (a) whether the patient knows how to manage the diabetes, (b) whether the patient regards the diabetes as worth controlling, (c) whether he has an accurate impression of how well he is carrying out the treatment programme (many patients seem to believe their self-care is better than it is), (d) whether the patient feels adequately supervised in his self-care etc. Only when the reason for poor self-care in a particular patient has been identified can an appropriate intervention be made.

2.24 METABOLIC CONTROL

The measure of metabolic control that is most widely used by patients in day to day monitoring of their condition is the urine sugar level. Unfortunately, it is affected by too many irrelevant factors (the concentration of the urine, the patients’ renal threshold, his recent intake of sodium chloride) to be a satisfactory measure. In addition it does not provide a fully up-to-date index of the patient’s metabolic state. Further, the empirical correlation between urine and blood sugar levels is known to be low (Bowen et al. 1997). Blood sugar levels are a more direct and therefore satisfactory measure. However, like urine sugars, they show considerable instability. Poorly controlled diabetics show not only higher average blood sugar levels but also much greater variance. To assess this, an adequate sampling of blood sugar levels is needed. Alternatively a combination of blood and urine sugars may be helpful. There has also been growing interest
in the use of serum (lipid) measures in research on diabetes. Serum cholesterol levels are markedly elevated in poorly controlled diabetics (Knowles et al. 1965). Free fatty acids have also attracted attention (Baker and Barcai 1970). Among other measures fluctuations in weight are of some value, as are freedom from insulin reactions and acidosis, though neither of the latter can be regarded as very sensitive measures of control.

2.25 EMOTIONAL STRESS AND CONTROL

Emotional factors have an important role in the control of diabetes. The relevant evidence is of two kinds. The first is to do with the effects of emotional stress on metabolic states; the second is to do with general differences in emotional adjustment between well controlled and poorly controlled diabetics. Of the early studies (Treuting 1962) on the metabolic effects of stress, those of (Hinkle and Wolf 1952) have become classics. A series of 64 diabetic patients were seen for regular interviews over a period of 3 year to examine the relationship between life events and fluctuations in diabetic control.

When a hypothesis was formed about the relationship of a particular life stress to fluctuations in the control of a particular patient, it was tested in a single case experiment. After a base-line period, the topic of life stress was brought up abruptly and vigorously in an interview. Later on in the interview a reassuring and supportive style was reintroduced, this experimentally induced stress produced an increase in the excretion of ketones in the urine and in the volume of urine together with fluctuations in blood and urine glucose levels. These changes were elicited and reversed within a single hour of experimental observation. As a further control measures were taken during a comparable period in which a more neutral topic was raised in interview, but the metabolic changes were not observed.
The reactions of non-diabetic and diabetic patients to this kind of experimentally induced stress were found to be essentially similar, though more extreme in the diabetics. The more severe diabetics tended to show the most marked metabolic reactions.

Subsequent reports from other workers have generally supported the destabilising effects of emotional stress. A puzzling feature of the work, however, is that blood sugar levels can be either increased or decreased by stress. The direction of change in blood sugar levels no doubt depends on a variety of factors, but the amount of insulin the subject has available and the kind of stress he is subjected to are no doubt critical. (Vandenbergh 1966) found that hypnotically induced emotion reliably led to decreases in blood sugar levels, though (Kline and Zinder 1969) have speculated that this is a characteristic of this particular form of stress. (Bradley 1978) demonstrated effects of performance under noise stress on sugar levels, and found decreases in low blood sugar diabetics but increases in those with high sugar levels. Baker and Barcai (1970) carried out stress interviews similar to those of Hinkle and Wolf on two unstable diabetics, but monitoring free fatty acid levels. They demonstrated 100’ rises in interviews that raised conflicts of particular importance to the patient. Such changes were not seen with other ‘non-specific’ stresses. Recent developments in the measurement of life events have permitted a test of the hypothesis that this form of stress affects metabolic control. Such a relationship was indicated by (Grant et al. 1974) and confirmed in a more satisfactory study by (Bradley 1979).

There has been some speculation that there is a characteristic personality and family profile in unstable diabetics and (Simonds 1977) has shown that poorly controlled diabetic children have significantly more interpersonal conflicts than well controlled diabetics. However the nature of the emotional conflicts is probably varied. (Crowell 1953) and (Koch and
Molnar 1974) did not find any particular type of personality pattern in poorly controlled diabetics. It is clear that emotional stress is one factor that can affect metabolic control. There is also a suggestion that it may be a particularly important factor in generally unstable diabetics, though this has not been properly tested. It would be necessary to show that stress has relatively larger effects on control in unstable diabetics compared to other factors such as exercise or infection. Unstable diabetics may simply be relatively sensitive to all factors affecting control. However, it is clear that if good control is to be achieved, it will often be necessary to take steps to reduce the destabilising effects of stress.

2.26 IMPROVING CONTROL

Before discussing methods of improving control it is necessary to consider what degree of control patients need to achieve to gain whatever advantages there may be in good control. It is obviously important to avoid both acidosis and insulin reactions, but the level of control needed for this is not very tight. Beyond this, the main pragmatic question is how far good control can prevent the degenerative complications (peripheral neuropathy, impairment of eyesight, etc.) that are quite common in diabetes.

The relationship between control and degenerative changes has been a controversial subject for many years in diabetic circles. It seems clear (Bloom et al. 1967) that there is a correlation between the two, and poor control is one factor contributing to degenerative changes. However, it also seems certain that poor control is not the only cause of degenerative changes, degenerative complications, apparently specific to diabetes have been reported as developing before abnormal glucose levels (Ellenberg et al. 1962). This alone would seem sufficient to indicate that other aetiological factors besides abnormal sugar levels need to be considered. Among the
multiple predictors of diabetic complications that will no doubt emerge, there will be some that are amenable to behavioural management. It is worth noting that hypertension is a significant predictor of diabetic mortality (Martin and Warne 1975).

As far as blood sugar levels are concerned, there is a growing feeling that these need to be kept very close to normal indeed if degenerative changes are to be avoided. This is very difficult to achieve as control is affected by a great many other factors apart from the treatment programme. Sugar levels are increased by colds, infections, vomiting, diarrhoea, pregnancy and many other factors.

Fluctuations in amount of exercise also affect the need for food and insulin. This all means that if the patient is to maintain himself in good control, it may not be sufficient for him to simply keep to the prescribed diet and insulin. To this end it is common for patients to be asked to test their urine, but it has already been pointed out that very few can both do this correctly and make appropriate use of the information.

Peterson et al. (1978) have carried out an intensive training programme on a sample of 10 diabetics to explore the feasibility of achieving really tight control. Patients were on 2 or 3 insulin injections a day, using both short and long acting insulin. Besides being trained to monitor their own blood sugar levels (a more satisfactory measure than the urine sugar which patients normally monitor) and adjust food and insulin appropriately, they were also trained to monitor the effects of exercise. Preliminary observations suggest that this programme was successful in improving metabolic control, and was acceptable to the patients using it clearly, not all patients are going to have the necessary intelligence and co-operation for such a programme, but its value for those who could make
use of it deserves further study. If this is what is necessary to achieve good control of diabetes, then those concerned with treatment compliance will have to pitch their sights much higher than simply getting patients to stick to their prescribed diet and insulin injections. Incidentally if patients are able to see the beneficial effects of such a thorough programme on their level of control, it may provide them with the necessary reinforcement to undertake it. The point has already been made that an important reason for poor compliance is that patients do not see the value of the treatment.

In addition, measures will need to be taken in some patients to reduce the destabilising effects of emotional stress. (Hinkle and Wolf 1952) claimed encouraging results from supportive counselling of poorly controlled diabetics. (Baker and Barcai 1970) are doubtful about the usefulness of supportive work and preferred crisis-intervention family work. From a behavioural point of view it would be valuable to explore the value of a self regulation approach. This would involve, firstly, an intensive training period with frequent monitoring of blood sugar levels through which patients would learn to predict the metabolic effects of particular stressful events. They would also need to learn methods, perhaps similar to existing methods of anxiety management, of counteracting the effects of stress. The preliminary work of Fowler et al. (1976) suggests that relaxation has a useful place here. None of this has been subjected to a controlled evaluation, so the value of these methods in promoting good control remains a matter of speculation.

2.27 EDUCATION AND COGNITIVE DECLINE

Education is useful as a measure of a population’s socioeconomic status and may reflect nutritional status, health behaviors, or access to health care, factors that may have biological consequences in later life (Hall and
Gao et al. 2000). Individuals with lower educational attainment have increased risk of cognitive decline. Educational attainment may potentially influence genetic effects on cognitive aging and future neurodegenerative disease (Coffey et al. 1999, Katzman et al. 1993 and Schuit et al. 2001).