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## Nueropsychological Motor Functioning in Children with Insulin-Dependent Diabetes Mellitus during Euglycemia and After a Mild Hypoglycemic Episode

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LOYOLA UNIVERSITY OF CHICAGO

NEUROPSYCHOLOGICAL MOTOR FUNCTIONING IN CHILDREN WITH  
INSULIN-DEPENDENT DIABETES MELLITUS DURING EUGLYCEMIA  
AND AFTER A MILD HYPOGLYCEMIC EPISODE

A DISSERTATION SUBMITTED TO  
THE FACULTY OF THE GRADUATE SCHOOL  
IN CANDIDACY FOR THE DEGREE OF  
DOCTOR OF PHILOSOPHY

DEPARTMENT OF CLINICAL PSYCHOLOGY

BY

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CHICAGO, ILLINOIS

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NEUROPSYCHOLOGICAL MOTOR FUNCTIONING IN CHILDREN WITH  
INSULIN-DEPENDENT DIABETES MELLITUS DURING EUGLYCEMIA  
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There have been discrepant findings among studies investigating the cognitive functioning of children with diabetes. It has been suggested that repeated incidence of hypoglycemia may produce the deficits found in this population. However little is known about whether children exhibit similar neuropsychological motor patterns after hypoglycemia and during euglycemia. This study investigated the left and right hand motor functioning of a group of right-handed school-age children during euglycemia and after recovery from a mild hypoglycemic episode. The motor performance level of this group of well-functioning diabetic children was within the average range during a period of documented euglycemia as well as after recovery from a mild hypoglycemic episode. However diabetic children performed more poorly on motor tasks than did control subjects during both test periods. Diabetic children also exhibited worse performance after a hypoglycemic episode as compared to their own performance during euglycemia. This suggests that the impact of a mild hypoglycemic episode upon cerebral functioning persists beyond the time when both the child and medical staff have determined that the child has recovered

from the episode. This impact on motor functioning appears to be limited to right hand performance and is more pronounced in children who were diagnosed with diabetes before age four. The finding of selective impact on right hand performance is consistent with patterns of impaired ratings noted for intermanual difference scores for tapping and namewriting tasks. This suggests that hypoglycemia may exert a selective impact on the left hemisphere. Duration of diabetes, type of insulin and awareness of hypoglycemia were not significantly related to motor performance. Right hand reaction time was significantly slower after recovery from a hypoglycemic episode suggesting that pure motor functioning is compromised during hypoglycemia separate from attention/concentration factors. Findings related to preferred hand motor functioning have implications for understanding previous research. Prolonged preferred hand motor functioning recovery after hypoglycemia has serious implications for the academic and social functioning of the diabetic child.

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To Bill and Elisa Maria

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## CHAPTER I

### INTRODUCTION

There have been discrepant findings among studies investigating the cognitive functioning of children with diabetes. Many studies of the intelligence of children with insulin-dependent diabetes mellitus (IDDM) have found that the level of intelligence of these children falls within the average range (Ack, Miller & Weil, 1961; Brown, 1938; Kubany, Danowski & Moses, 1956; Rovet, 1989). However, electrophysiological studies have noted abnormal patterns of electrical activity in the brains of children with IDDM (Donald, Erdahl, & Surridge, 1984; Eeg-Olofsson, 1977; Gilhaus, Daweke, Lulsdorf, Sachsse & Sachsse, 1973; Marks & Rose, 1981; Reske-Nielsen, Lundbaek & Rafaelsen, 1965; Ternand, Go & Gerich, 1982). In addition, more recent research using neuropsychological measures of cerebral functioning have found that children with diabetes perform more poorly than nondiabetic controls on tasks of memory, visual-spatial skills, motor speed, and visual motor skills (Anderson, Hagan, Barclay, Goldstein, Kandt & Bacon, 1987; Holmes & Richman, 1985; Rovet, Erlich & Hoppe, 1987; Ryan, Vega & Drash, 1985). These same studies also note an increased incidence of deficits in diabetic children who were diagnosed with the

disorder before age six as compared to those who were diagnosed with the disorder at an older age. These neuropsychological, as well as electrophysiological, studies also hypothesize that the deleterious impact of repeated hypoglycemic episodes, which are more frequent in children with early onset of diabetes, may be a mechanism underlying the deficits observed. Studies examining the intellectual, neuropsychological and neurophysiological functioning of adults with longstanding IDDM have also reported deficits in the cognitive functioning in these adults as compared to nondiabetic individuals (Holmes, Mann-Koepke, Thompson, Gyves & Weydert, 1984; Lichty & McGill, 1989; Skenazy & Bigler, 1984; Tallroth, Lindgren, Stenberg, Rosen & Agardh, 1990).

The occurrence of mild hypoglycemia (low blood sugar level) is a relatively common occurrence for the diabetic child (Cryer et al., 1989; Macdonald, 1989; Wolfsdorf, 1964). Hypoglycemia occurs when blood glucose levels drop below that necessary to meet the energy needs of the central nervous system. In the diabetic, this may occur as a result of inadequate food intake, excess insulin or increased energy expenditure (Marks & Rose, 1981). When hypoglycemia is identified by blood glucose testing or by the occurrence of symptoms such as weakness or hunger, treatment is usually focused on restoring a normal blood glucose level through the ingestion of a quickly absorbed carbohydrate such as juice or a manufactured glucose tablet.

Current treatment regimens that have as their goal the maintenance of near normal blood glucose levels have lead to an increase in the incidence of mild and severe hypoglycemia in the diabetic population (Cryer, 1988). In the absence of definitive studies documenting otherwise, it has been thought that the acute effects of hypoglycemic episodes on cerebral functioning are transient and rapidly and completely reversible after treatment by carbohydrate administration (Wolfsdorf, 1964). However, the results of studies investigating mild hypoglycemia in diabetic and nondiabetic adults and children have suggested that neuropsychological, neurophysiological and motor recovery from hypoglycemic episodes does not always accompany symptom remission or documented rises in blood glucose level (Blackman, Towle, Lewis & Spire, 1989; Heller, 1989; Herold, Polonsky, Cohen, Levy & Douglas, 1985; Macdonald, 1989; Reich, Kaspar, Puczynski, Puczynski, Cleland, Dell'Angela & Emanuele, 1990; Schroeder, Cox, Gonder-Frederick, Ling & Clarke, 1989; Tallroth et al., 1990). Impaired functioning has been noted to persist as long as 40 minutes after euglycemia has been attained in adults (Blackman et al., 1989; Heller, 1989; Herold et al., 1985; Macdonald, 1989).

These studies have utilized sensitive neuropsychological measures of functioning and investigated the impact of different levels of blood glucose on cerebral functioning. While the specific deficits that were found to result from

hypoglycemia in these studies has varied depending upon the measures used, there have been consistent findings of declines on tests with a preferred (right) hand motor functioning component during hypoglycemia (Heller, 1989; Hepburn, Patrick & Frier, 1989; Herold et al., 1985; Hinnen, Speelman, Hoffman, Conley & Knapp, 1986; Holmes, Hayford, Gonzalez & Weydert, 1983; Macdonald, 1989; Pramming, Thorsteinsson, Theilgard, Pinner & Binder, 1986). Some studies also note that functioning does not correspond to blood glucose level or symptom report (Hepburn et al., 1989; Herold et al., 1985; Pramming et al., 1986).

The above research has contributed greatly to an understanding of the acute effects of hypoglycemia on neuropsychological and motor functioning in adults with IDDM. As noted above, these studies have repeatedly shown that hypoglycemic states have a deleterious impact upon preferred hand motor functioning for as long as 40 minutes after the hypoglycemic episode has been treated. While the possibility that the effects of hypoglycemia may be selective to the left hemisphere is supported by numerous studies documenting preferred (right) hand motor deficits in adults during hypoglycemia (Heller, 1989; Herold et al., 1985; Hinnen et al., 1986; Holmes et al., 1983; Macdonald, 1989), nonpreferred (left) hand performance on these tasks has not been well documented. Thus it is not clear whether the right hand is selectively affected or both equally affected, albeit not

documented. In addition, little attempt has been made to differentiate between the attention/concentration and motor components of tasks such as reaction time, leading different researchers with the same findings of decreased preferred hand motor functioning to attribute the outcome to different mechanisms. Thus there is no consensus as to the type of or possible localization of the deficits observed in both adults and children overall and during hypoglycemia.

As both adults and children have been found to exhibit long-term neuropsychological deficits as compared to nondiabetic individuals, the assumption that repeated incidence of hypoglycemia have no immediate or long-term impact on cerebral functioning appears premature. Children are at the highest risk for hypoglycemia and this is the population for whom the immediate and long-term impact of this complication is the least well understood (Ryan, 1988). In addition, the impact of prolonged recovery or long-term deficits resulting from hypoglycemia has significant educational, psychosocial and medical ramifications for this population.

## CHAPTER II

### REVIEW OF THE RELATED LITERATURE

#### Diabetes Mellitus and Its Treatment

Diabetes mellitus comprises a heterogeneous group of disorders that have one common feature - abnormally high blood glucose levels due to either insulin deficiency or impaired effectiveness of insulin. Approximately 5.8 million people in the United States have been diagnosed by a physician as being diabetic, and an additional 4 to 5 million people are thought to have diabetes but have not yet been diagnosed (National Diabetes Data Group, 1985). There are two main types of diabetes - insulin-dependent diabetes mellitus and noninsulin-dependent diabetes mellitus. Noninsulin-dependent diabetes mellitus (NIDDM - type II) also known as "adult onset diabetes" or "maturity-onset diabetes" is predominately diagnosed in adults above age 40. It is frequently linked to obesity and its etiology is probably strongly genetic (National Diabetes Data Group, 1979). The high blood glucose levels in this type of diabetes result from any number of states that reduce the pancreas' efficiency in producing insulin and this disorder can be managed with diet modifications and injected or orally administered insulin.



Approximately 2.35% of the population of the United States has been diagnosed as having NIDDM (National Diabetes Data Group, 1985).

### Insulin-Dependent Diabetes Mellitus

Insulin-dependent diabetes mellitus (IDDM - type I) has also been called "juvenile onset diabetes", "juvenile diabetes" or "brittle diabetes" and is diagnosed primarily during childhood. Individuals with IDDM have low or absent levels of endogenous circulating insulin and are dependent on injected insulin to sustain life. Etiology is probably only partially genetic as only 35% of monozygotic twins are concordant for the disorder (Bennett, 1981; National Diabetes Data Group, 1985). In addition, the the exact mode of genetic transmission remains controversial (Spack, 1980). The annual incidence of IDDM is about 12 - 14 new cases per 100 thousand children age 16 and younger; by age 20, .3% of the population of the United States has developed this chronic disorder (Menon & Sperling, 1988). Onset may occur at any time during childhood, although clinical symptoms appear most frequently in children aged 10 through 16 years. Incidence rates are about equal for males and females but are about 1.5 times higher in Whites than in African-Americans (LaPorte & Cruickshanks, 1985).

Mortality rates of individuals with IDDM are between 5 and 20 times greater than that of a nondiabetic population

matched for age, race and gender (National Diabetes Data Group, 1985). Individuals with IDDM are at the highest risk for the both the long-term complications associated with the disorder such as retinopathy, peripheral neuropathy and cardiovascular disease and the frequent episodes of mild and severe hypoglycemia which are a common sequelae of insulin treatment (Cryer et al., 1989)

IDDM is the most common chronic endocrine disease of childhood (Gardner & Thompson, 1978; Knowles, 1971). It is a chronic metabolic disorder of energy utilization, in which the ability to convert carbohydrates into "food" that can be used to meet the body's energy needs is decreased or completely lost as a result of inadequate pancreatic function. Insulin is the substance that is produced by the pancreas that converts glucose in the blood into energy used by the body to maintain its normal functioning. The production and release of insulin is linked to the body's homeostatic needs and maintains the nondiabetic individual's blood glucose level between 100 and 160 mg/dl at most times (Rizza, 1985).

IDDM results when the insulin-producing capacity of the pancreas is markedly decreased because of the failure of the beta cells of the islets of Langerhorn where insulin is normally synthesized. The immediate effect of this compromised pancreatic functioning is increased sugar in the blood (hyperglycemia) and urine (glycosuria) combined with fatigue and extreme hunger and thirst. After a period of time,

ranging roughly from six months to two years, the capacity of the pancreas to produce insulin disappears completely. Once developed, failure of beta cells is permanent, and the individual is entirely dependent on insulin from other sources for the rest of his or her life. The nature of the process that renders the beta cells of the islets of Langerhorn ineffectual is not known. Various hypotheses have been advanced linking this process to among other things inflammation, viral effects, trauma, autoimmune disease, emotional reactions, and infections (Barglow, Berndt, Burns & Hatcher, 1986; Cahill & McDevitt, 1981). At present there are no persuasive arguments favoring a particular etiology.

### The Treatment of IDDM

#### Insulin

The isolation of insulin in 1922 revolutionized the treatment of Type I diabetes mellitus. Prior to the development of injectable insulin, individuals diagnosed as having IDDM had an extremely poor prognosis and most died within two years of diagnosis (Dorman & LaPorte, 1985). With the development of insulin, metabolic dysfunction could be attenuated and there was a significant reduction in mortality in a very short period of time. Injectable insulin that can be used by the human body has been derived from the pancreas' of pigs and cows which have circulating insulin that is the most chemically similar to that of humans. More recently

human insulin has been synthesized from bacterial sources (Martin & Quint, 1985). In this process bacteria are genetically programmed to produce the A and B chains of insulin and then these are joined chemically to manufacture human insulin. Insulin is injected into muscle tissue where it is gradually absorbed into the blood that circulates to this area.

Injected insulin functions in much the same way as does circulating insulin. To exert its effects on metabolism, it first binds to specific receptors found mainly on the surface of insulin sensitive cells. There, it activates processes which bring about changes in the permeability of the cell membrane to glucose and changes in intracellular metabolism (Marks & Rose, 1981). Without this change in permeability and metabolism, cells cannot use the circulating glucose regardless of its availability or the needs of the cell. This is why undiagnosed diabetics typically present a picture of extremely high blood glucose levels (hyperglycemia) in the presence of fatigue and other symptoms of the insufficiency of available energy for the maintenance of physiological functioning.

The nondiabetic individual secretes insulin in varying amounts during a 24 hour cycle. Blood glucose levels rise and fall, depending on diurnal body cycles, food intake and energy expenditure (Rizza, 1985). This maintenance of a small range of blood glucose levels by the secretion of insulin is

regulated by an extremely complex metabolic process. Euglycemia (normal blood sugar levels) in nondiabetic individuals is accomplished by a careful balance of insulin secretion and the secretion of a variety of counterregulatory or "anti-insulin" hormones including glucagon, epinephrine, cortisol, and growth hormone (Rizza, 1985). At present even the most complicated and attentive balance of injections of insulin, diet modification and exercise does not closely approximate this finely tuned physiological process for the diabetic. However different types of insulin have been developed that minimize the number of daily injections necessary to maintain a relatively stable level of insulin release and blood glucose level.

There are basically three types of insulin that vary in the timing of the release of insulin after the injection. **Regular** insulin is short-acting with a rapid onset and delivers an appropriate dose of insulin to counteract the rapid rise in blood glucose that occurs following a meal. **NPH** or **Lente** is an intermediate acting insulin which has its peak action 8-10 hours following administration. This insulin is used to maintain a relatively stable amount of circulating insulin in order to meet the body's energy requirement over a long period of time such as during the night. **Ultralente** is a long acting, relatively peakless insulin that provides a constant dose of insulin for between 12 and 14 hours. While ultralente provides the most stable insulin release it has the

disadvantage of the necessity of a large subcutaneous depot present at all times. In addition, given the vagaries in insulin absorption it can lead to protracted hypoglycemia in some patients and for this reason, is rarely used in children (Skyler & Reeves, 1985).

In general, the insulin dosage required to attain near-normalization of glycemia in typical IDDM patients who are within 20% of their normal body weight is .5 - 1.0 units of insulin per kilogram of body weight per day (Skyler & Reeves, 1985). During periods of illness insulin requirements may rise markedly. Dosage is also usually increased during the adolescent growth spurt. On a daily basis dose may be adjusted to compensate for increased caloric consumption or higher than normal amounts of exercise or stress. The frequent monitoring of blood glucose level is critical to the appropriate adjustment of insulin dosage in these circumstances. The use of a portable pump which delivers continuous subcutaneous insulin infusion has been heralded as a method for achieving optimal glycemic control although its use especially in children is controversial because of the increased risk of hypoglycemia (Leslie & Sperling, 1988; Rizza, 1985).

#### The measurement of blood glucose levels

A number of advances in medical technology have aided those attempting to maintain certain ranges of blood glucose in the diabetic individual. The first of these was the

development of techniques which enabled the diabetic to quickly and easily monitor blood glucose levels at home. These tools marketed under the names "Chemstrip" and "Glucoscan" measure peripheral blood glucose levels obtained from the placing of a blood sample, usually from a finger prick, onto specially treated paper strips. These strips can be read visually by comparing them to a color chart or read by a machine. This procedure allows documentation of glycemia that is attained during ordinary life and permits more careful monitoring of glycemic control. In addition, the routine use of blood glucose monitoring methods aids the development and implementation of therapeutic plans for attaining diabetic control.

Another method of assessing efficacy of diabetic control of glycemic level has been assays for glycosylated hemoglobin. The amount of glycosylation is in proportion to the ambient blood glucose concentration during the preceding several months and is a measure of the average blood glucose level for that period (National Diabetes Data Group, 1985; Skyler & Reeves, 1985). Blood samples are obtained during visits to physicians and are analyzed by laboratory procedures. Glycosylation of hemoglobin has been found to be sensitive to average blood glucose level over a four to six week period and is particularly useful in identifying a decline in level of glycemic control. It serves as an independent measure of control and according to some experts, is the best single

assessment tool currently available (Skyler & Reeves, 1985).

### Treatment regimens

The treatment of insulin-dependent diabetes mellitus is a complex process, entailing attention to insulin dosage, food intake and daily energy expenditures. Not surprisingly, there is much disagreement among physicians who treat diabetics as to the optimal balance of these components and the goals of treatment (Forbes, 1981). Traditionally, physicians have prescribed an insulin and diet regimen that was comprised of one or two injections of intermediate acting insulin per day in combination with dietary guidelines for the timing and composition of meals and snacks. The goal of this approach (termed "loose control") is the maintenance of pre-meal blood glucose levels below 200 mg/dl and the avoidance of states of hypoglycemia as well as ketonuria which is ketones in the urine as a result of insufficient insulin (Knowles, 1981). Minimal dietary restrictions and a limited number of insulin injections and blood and urine glucose measurements per day make this treatment approach flexible and relatively easily integrated into most lifestyles. Proponents of this approach offer evidence that there is no significant difference in onset or severity of complications, morbidity or metabolic control between those following this regimen and those prescribed more restrictive regimens (Knowles, 1981).

Intensive insulin therapy. In contrast, intensive



insulin therapy, also known as "strict" or "tight" control is a therapeutic strategy that has the goal of attainment of near-normal levels of glycemia. Skyler (1989) describes nine elements that are essential for a system of intensive therapy:

- (1) A multiple component insulin regimen; (2) careful balance of food intake, activity and insulin dosage; (3) Daily self-monitoring of blood glucose; (4) Patient adjustments of food and insulin dosage, and the use of insulin supplements according to a predetermined plan; (5) Defined target blood glucose levels (individualized); (6) Frequent contact between patient and [medical] staff; (7) Patient education and motivation; (8) Psychological support; (9) Assessment (glycated hemoglobin) (p. 34).

Skyler and Reeves (1985) suggest that treatment regimes should have the goal of maintaining blood glucose levels ideally in the range between 70 and 160 mg/dl using between two and four injections of a mixture of short-acting and longer acting insulin. The use of a portable pump may also be used in a regimen of intensive treatment. It has been suggested that when blood sugar levels in the diabetic individual are maintained at approximately normo-glycemic levels, the onset of the long-term complications of diabetes may be postponed or avoided (Pirart, 1978; Sherwin & Tamborlane, 1985).

Risks associated with intensive insulin therapy. In those who follow intensive regimens, unexpected stress, activity or illness, increases the individual's glucose requirements and an increased metabolism of glucose may result in hypoglycemia if compensatory changes are not made in diet

and/or insulin administration. As blood glucose levels are maintained at a lower level than in conventionally treated diabetics, any increase in glucose metabolism is more likely to result in a clinically significant drop in blood glucose level. However, this is not been seen as problematic for proponents of intensive treatment regimens as it is commonly believed that mild hypoglycemic episodes are transient phenomenon easily and completely treated with the rapid administration of a carbohydrate.

However, in order to treat a mild hypoglycemic episode it must be identified. There is evidence to suggest that intensive insulin treatment contributes to a blunted or absent hormonal response to hypoglycemia; this hormonal response is what produces the warning symptoms that diabetics use to identify hypoglycemia in time to treat it (Simonson, Tamborlane, DeFronzo & Sherwin, 1985). Thus, intensive treatment not only can increase the probability that an individual will experience mild hypoglycemia, but also decreases the diabetic individual's ability to identify these episodes in time to treat them. Untreated, mild episodes may become more severe or the individual may function for an extended period at a suboptimal glucose level.

Clearly, intensive insulin treatment is a very complex process requiring high levels of patient education, understanding, motivation and adherence as well as frequent contact between patient and physician. Opponents of this type

of approach to the management of diabetes, state that it is very rare that an individual can modify his or her lifestyle to accommodate the demands of this type of regimen (Knowles, 1981). They suggest that patients rarely if ever follow these guidelines optimally and the risks involved in an erratically followed intensive insulin program (i.e., hypoglycemia) may be far greater than the assumed benefits. Furthermore, the proposed benefit (a decrease in long-term complications) has not been unequivocally linked to good glycemic control. Many studies have found that measures of glycemic control are unrelated to the incidence of complications and that those patients purportedly following intensive treatment regimens have similar glycosylated hemoglobin values as those following more traditional treatment regimens (Daneman, Wolfson, Becker & Drash, 1981; Golden et al., 1989; Knowles, 1981).

#### Glucose Counterregulation in Diabetes

In the nondiabetic individual post-absorptive blood glucose concentration (6-14 hours after meal ingestion) is maintained between 70 and 100mg/dl by a finely tuned balance between the amount of glucose released by the liver and the amount utilized by the body. During this time, approximately 75% of the glucose released by the liver is derived from the breakdown of energy stored in the form of glycogen and 25% from the synthesis of new glucose (Rizza, 1985). The liver is exquisitely sensitive to small changes in insulin

concentration and when insulin concentrations in the blood increase as a function of the availability of an external energy supply (from a meal) glucose production is suppressed accordingly. Thus, small changes in the circulating insulin concentration may have a major effect on blood glucose levels. Other hormones such as glucagon, cortisol and catecholamine all function to increase hepatic glucose release in response to lowering of post-absorptive glucose availability. This "counterinsulin" or counterregulatory response maintains a steady level of available energy for optimal body functioning. As with glucose production, insulin and counterinsulin hormones also have opposite effects on glucose utilization. Insulin increases and counterinsulin hormones decrease glucose utilization (Cryer & Gerich, 1985; Rizza, 1985).

The large doses of exogenous insulin required to maintain functioning in the diabetic decreases the endogenous production of glucose in the manner described above. This may result in hypoglycemia if food intake is not appropriate to the amount of insulin available at a particular time. In addition, it has been noted that frequently the diabetic individual has an impaired counterregulatory system response to low blood glucose concentrations in the presence of insulin (Samols, 1986). This results in a delay in or absence of the triggering of hepatic glucose production that is needed to compensate for falling blood glucose levels. Without this switch back to endogenous glucose production blood glucose

levels continue to drop and hypoglycemia occurs.

This impairment in glucose counterregulation and impaired recovery from hypoglycemic episodes is found in a significant portion of individuals who have had diabetes for between one and five years (Bolli, Pierpaolo & Campagnucci, 1983). It does not appear to be present at diagnosis for most diabetics but is observed with greater frequency as the duration of the disease process increases (Cryer & Gerich, 1985). The defect in glucagon production and counterregulatory impairment is not reversed by improved diabetic control (Bolli, Calabrese & DeFeo, 1982) and is usually not seen in individuals with NIDDM (Rizza, 1985). Even though the risks associated with the development of hypoglycemia (increased incidence, hypoglycemia unawareness) are greater in those with counterregulatory defects, at present, there is not a reliable method for identifying individuals who have these impaired counterregulatory mechanisms (White et al., 1983).

### Complications of Diabetes

The individual diagnosed with IDDM not only must use insulin daily for the rest of his or her life but also has an extremely high probability of developing a number of inconvenient and/or life-threatening complications. Among these complications, which can appear at any time following diagnosis but occur more frequently after a long duration of the disease, the most prevalent are those associated with

changes in the eye, the cardiovascular system, the peripheral nerves or the kidney (Pirart, 1978). Clinically detectible microangiopathy involving the retina and/or the kidneys can be expected in 80-85% of patients 20-25 years after onset of diabetes (Sherwin & Tamborlane, 1985). The most common of the many potential neurological complications of the disease are hypertension, hypoglycemic coma, cerebral atherosclerosis, peripheral and autonomic neuropathy and cerebral electrolyte and neurotransmitter imbalances (Skenazy & Bigler, 1984). The occurrence of stroke in diabetics is two to six times higher than for nondiabetics (Kuller, Dorman & Wolf, 1985).

While death due to extreme metabolic decompensation has been nearly eliminated since the introduction of insulin in the 1920's, late degenerative complications continue to be a major source of morbidity and mortality for the diabetic individual. Neither the rate of appearance of complications nor the diabetic's reduced life expectancy has substantially changed in recent years (Sherwin & Tamborlane, 1985).

#### Hyperglycemia and Diabetic Complications

Neuropathy and as well as other long-term complications of diabetes are thought to result from the interaction of multiple metabolic, genetic and environmental factors (Greene & Pfeifer, 1985). A link between higher incidence of many of these often studied complications and the occurrence of prolonged or repeated states of hyperglycemia in the diabetic

patient has been suggested by numerous histopathological, epidemiological, physiological and clinical observations (Greene & Pfeifer, 1985; Pirart, 1978). Hyperglycemia is an excessively high blood glucose level - usually above 280 mg/dl. It most frequently occurs when the amount of glucose in the blood as a result of food intake is higher than the insulin available to convert this glucose into energy that the diabetic individual's body can use or store. This view, that diabetic complications are attributable to inadequate therapeutic correction of metabolic abnormality has been widely debated among health-care providers and researchers.

While this "metabolic hypothesis" is supported by many experts, others challenge this assumption pointing especially to research that suggests that some lesions antedate the onset of diabetes and thus may have a genetic rather than metabolic determinant. Pozzessere (1989) has documented reduced nervous system functioning at the onset of diabetes which progressively worsens, independent of diabetes control in adults. His findings lend support to the contention that a neuropathic (possibly genetic) process associated with diabetes produces these changes. Other criticisms of the metabolic hypothesis specifically address shortcomings in the research upon which the hypothesis is based. These include deficiencies in experimental design, inadequate methods for assessing diabetic control of blood sugar level and a reliance on inappropriate animal models to support this hypothesis

(Sherwin & Tamborlane, 1985). Furthermore, some critics cite clinical studies and specific patient examples which show no clear cut relationship between the severity of hyperglycemia and complications (Guthrie, 1981).

Many physicians who treat primarily NIDDM patients have seemingly taken a middle ground with increased attention to glycemic levels (Knowles, 1981). However the recognition of the possible relationship between high blood glucose levels and increased incidence or severity of complications, has particularly affected treatment regimes for children with IDDM. As children diagnosed with IDDM have a greater likelihood of developing complications because of the duration of illness, among other factors, intensive treatment regimes have been developed to reduce the incidence of hyperglycemia in the diabetic child with the goal of preventing or delaying the onset of these complications. However, as previously noted, there is considerable debate as to the psychosocial ramifications and physiological merits of strict attention to glycemic level (Forbes, 1981).

#### Cerebral Complications of IDDM

The vast majority of early research on the intelligence of diabetic children suggested that the performance of diabetic children on standardized tests of intelligence was within normal limits (e.g., Brown, 1938; Kubany et al., 1956). However more recent studies using sensitive measures



such as neuropsychological tests, have documented specific areas in which diabetic children perform more poorly than siblings or same-age nondiabetic peers (Eeg-Oloffson, 1977; Holmes & Richman, 1985; Franceschi et al., 1984; Haumont, Dorchy & Pelc, 1979; Ryan et al., 1985). These studies noted some lower levels of intellectual functioning in diabetic children and found that deficits were most often linked to early onset of diabetes and increased incidence of poor glycemic control including hypoglycemic coma and seizure (Ack, 1961; Ryan et al., 1985). These researchers suggest that cerebral complications of diabetes may be at least partially related to the occurrence of hypoglycemic states. A link between hypoglycemia and cerebral complications has been found in studies of adults with longstanding IDDM (Ryan, Adams & Heaton, 1990; Williams & Ryan, 1990).

Ryan et al., (1985) found that children with early onset of diabetes (before age 5) performed more poorly than both nondiabetic and later onset diabetic children on virtually all tests including intelligence, motor speed, memory and eye-hand coordination. They conclude that these deficits may be "secondary to mild brain damage that develops as a consequence of multiple episodes of serious hypoglycemia early in life" (p. 921). Ryan, Vega and Drash (1985) suggest that there may be lateralization of this damage to one hemisphere of the brain and that this lateralization may relate to the onset of diabetes and the stage of brain development at which metabolic

trauma to the central nervous system (CNS) begins to occur. Specifically, they state that longer duration of diabetes predicts deficits in left hemisphere functioning, while earlier age of onset appears to result in poorer performance on tests regarded as primarily tapping right hemisphere functioning.

Holmes and Richman (1985) found that intelligence as measured by the Wechsler Intelligence Scale for Children-Revised (WISC-R) was normally distributed in the population of children with IDDM that they studied. However they noted that children with early onset (before age 7) and long duration (over 5 years) showed a significantly poorer performance on tasks thought to tap right hemispheric functioning. They hypothesize that these performance deficits may be the result of longer latencies in cortical evoked responding and suggest that this may be related to the alternation in cortical conduction rate that has been found in the central nervous system of even newly diagnosed diabetics. Holmes and Richman (1985) also suggest that this "central diabetic neuropathy" may be related to repeated trauma to the child's developing brain caused by low glucose levels among other factors.

Rovet, Ehrlich and Hoppe (1987) compared the performance of children with early onset IDDM (before age 4) and late-onset IDDM (after age 4) to their non-diabetic siblings on tests of intellectual functioning and school achievement. In

addition they examined the relationship between gender, duration of illness, history of hypoglycemic convulsions and ketoacidosis, and diabetic control and performance of the diabetic children in their study. They found that children with early onset diabetes (EOD) scored significantly lower than other groups of diabetic children or siblings on tests of visuo-spatial ability. They also found that the incidence of hypoglycemic seizures was higher in children with EOD than in those with later onset of diabetes.

In this study, both hypoglycemic seizures and age of onset were associated with poorer performance on spatial tasks. They report that neither history of ketoacidosis or duration of illness was related to performance. Some of their results, especially those suggesting that females may be more adversely affected than males, may be confounded by the fact that children with diagnosed learning difficulties were included in the sample and were over-represented in the group of EOD females. In addition, while they frequently pointed to the deleterious effects that hypoglycemia may have on functioning, the researchers never established whether their diabetic subjects were hypoglycemic during testing. However, they conclude that children who develop diabetes before four years of age, are at greater risk for subsequent "neurocognitive impairment" especially in visuo-spatial skills. This would be consistent with Ryan et al.,'s (1985) observations that age of onset affect skills housed primarily

by the right hemisphere.

Rovet et al., (1987) further hypothesize that the visuo-spatial deficits seen in EOD children may be related to disturbances of the normal neurological development caused by diabetes related difficulties (e.g., hypoglycemia, seizures) during critical stages of brain maturation. In particular, they note that animal research suggests that diabetes may affect myelination by producing defective incorporation of acetates and glucose into nerve lipids. They point to the fact that the period between two and four years of age marks the stage of development when myelin is being formed in humans.

Rovet (1989) is presently conducting a longitudinal study of the intellectual and neuropsychological functioning of 85 newly diagnosed diabetic children. Preliminary results of her study indicate that children with IDDM do not exhibit impaired performance on standardized intellectual tests at diagnosis or at one and three years after diagnosis. However she did find that children with early onset of the disorder and more complications such as diabetic ketoacidosis have lower verbal IQ scores as compared to other diabetic children. At the three year testing, she has not observed a relationship between the occurrence of mild or severe hypoglycemia and intellectual or neuropsychological performance. However, as counterregulatory hormone response remains somewhat intact during the early years after diagnosis, it is likely that any effects of increased incidence or severity of hypoglycemia may not be

evident at this early point.

In a summary of present research on neurobehavioral complications in insulin dependent diabetes mellitus, Ryan (1988) notes that there is a well documented relationship between hypoglycemic coma and seizure and neurological and neuropsychological impairment, but that the most frequent type of hypoglycemic episodes, those which do not eventuate in neurologic crisis', are rarely studied. This is in spite of the fact that researchers have long documented that cognitive deficits are most often found in the population that has the highest incidence of mild hypoglycemia, children with early onset of the disorder (Holmes & Richman, 1985; Rovet et al., 1987). Therefore it seems possible that the deficits that have been reported in these children may not be secondary to the age of onset per se but rather the tendency of this population to experience more frequent mild and severe hypoglycemic episodes and the probable CNS damage that occurs with repeated traumas of this nature. In the absence of research that documents the immediate and long-term impact of mild hypoglycemia on the cerebral functioning of children, physicians increasingly prescribed intensive treatment regimens that increase the incidence of hypoglycemia.

#### Complications Associated With Intensive Treatment Regimens

While intensive treatment regimens are routinely prescribed for diabetic children in the hope of forestalling

the onset of complications, there are a number of characteristics of this population that render this approach to treatment more complex than in adults. School age children are more likely than adults to have highly variable levels of activity which may make difficult the prediction and adjustment of optimal food intake and insulin dosage necessary for good glycemic control. Children, especially younger children, also lack the cognitive resources to fully understand their very complex disorder and its treatment, and are not able to recognize or adequately report changes in daily activities or critical physical states that determine changes in treatment regimens (Golden, Russel, Ingersoll, Gray & Hummer, 1985; Grunt, Banion, Ling, Siegal & Frost, 1978). Therefore, hypoglycemia, both mild and severe, is the most frequent complication of diabetes for school age children. It is a more prevalent for those who follow an intensive treatment regimen as opposed to those prescribed treatment with less focus on tight control of glycemic level (Cryer, 1988; Diabetes Control and Complications Trial (DCCT) Research Group, 1987; Macdonald, 1989).

Hypoglycemia may be a particular problem for children whose counterregulatory systems no longer respond with adrenergic and cholinergic symptoms to low levels of blood glucose (White et al., 1983). Counterregulatory phenomenon produce many of the subjectively recognizable symptoms of the hypoglycemic state and therefore a child with this functioning

impaired may be unaware of the need for treatment. In these cases, a child may function for an extended period of time at potentially harmful blood glucose levels and the first indication of a problem may be when the child faints or has a seizure. There is presently no definitive test for this counterregulatory defect but it is estimated to occur in 30-50% of individuals who have had diabetes for greater than five years (Bolli et al., 1983; Cryer & Gerich, 1985; Simonson et al., 1985).

### Hypoglycemia in IDDM

Hypoglycemia is the most frequently experienced of all of the immediate and long-term complications of diabetes mellitus. Mild hypoglycemia (that which does not lead to seizure or coma) has also been considered the least problematic and most easily treated complication and is thought to have no residual effects within minutes of treatment (Wolfsdorf, 1964). With the increased prescription of intensive treatment for children, hypoglycemia has become more frequent in this population and concerns have been raised about the impact of even mild hypoglycemia on the developing brain.

### Definition of Hypoglycemia

Most body tissues have the ability to derive critical nutrients and energy from a variety of substrates. However

glucose derived from the circulation is the predominant fuel used by the CNS, supplying 90% of its energy needs (Creutzfeldt, 1975). This renders the brain particularly vulnerable to extreme fluctuations in circulating blood glucose levels and in order to preserve normal cerebral functioning, an adequate supply of glucose and oxygen is required. During hypoglycemia this supply is compromised.

In the nondiabetic child, when blood glucose falls to approximately 68mg/dl, a complex system of hormone reactions initiate a decrease in levels of circulating insulin and an increase in glucagon secretion which enables the body to transform other energy sources to glucose that the brain can use. At this time, increases in epinephrine production also limit glucose utilization. In adults this protective hormone response is not triggered until blood glucose levels drop to approximately 56 mg/dl (Jones, Boulware, Davis, Sherwin & Tamborlane, 1990). Due to this sensitive and complex system of glucose homeostasis known as the "counterregulatory response", the nondiabetic individual rarely, if ever, experiences hypoglycemia or low blood glucose levels (Marks & Rose, 1981).

However individuals with IDDM develop a selective deficiency of this homeostatic glucagon secretory response to plasma glucose decrements and blood glucose levels may drop below that necessary to meet the energy needs of the CNS (White et al., 1983). Hypoglycemia has been defined, on



statistical grounds, as a blood glucose level below 40mg/dl and this level has been found to produce electroencephalographic (EEG) changes in individuals with IDDM (Samols, 1986). However electrophysiological and neuropsychological studies of cerebral functioning during hypoglycemia have documented cerebral compromised functioning at or below a blood glucose level of 68 mg/dl ( Jones et al., 1990; Ryan, Puczynski, Atchison & Puczynski, 1989; Tallroth et al., 1990). Thus, hypoglycemia is more commonly defined in terms of the presence of symptoms and a blood sugar level below 60mg/dl and this the level at or below which physicians suggest treatment. Treatment is usually focused on restoring blood glucose level through the ingestion of a quickly absorbed carbohydrate such as juice or a manufactured glucose tablet.

#### Causes and Symptoms of Hypoglycemia

Hypoglycemic reactions in patients with IDDM result from the interplay of many factors including dose and method of insulin administration, the adequacy of counter-regulatory hormonal response, presence of insulin antibodies, and the frequency and intensity of exercise (Herold et al., 1985). Marks and Rose (1981) note that illness, drug interactions, alcohol consumption, menstruation and, most obviously, variations in carbohydrate intake may also produce hypoglycemia if insulin administration is not adjusted

appropriately. They also report that impure insulin can cause hypoglycemia in diabetic children as a result of the presence of glucagon anti-bodies.

Current trends in treatment philosophy toward maintenance of blood glucose in the normoglycemic range means that any variations in expected activity or food intake may produce hypoglycemia. Unger (1982), proposes that there is probably an underlying predilection for hypoglycemia and vulnerability to its consequences in meticulously controlled Type I diabetics. This proposition is supported by research that suggests that deficits in free fatty acid and oxidative glucose metabolism may provide some protection against hypoglycemia in poorly controlled diabetics but not in those who are well controlled (Caprio, Ameil, Tamborlane, Gelfand & Sherwin, 1990). In addition it has been found that individuals who have an earlier onset of the disorder (before age five) commonly have more difficulty controlling blood glucose levels and experience a higher frequency of hypoglycemic episodes than those with a later onset (Golden et al., 1985; Grunt et al., 1978).

Diabetic individuals may identify a hypoglycemic blood glucose level by the occurrence of one or more subjectively experienced symptoms. Hypoglycemic symptoms originate from one of two sources. The early symptoms of hypoglycemia arise from the counterregulatory cholinergic and adrenergic hormone response to declining blood glucose levels. These neurogenic

symptoms may include sweating, tremor, tachycardia, flushing and hunger. A recent study by Biggers and associates (1989) suggests that sensors in the brain rather than the periphery of the body trigger this earliest warning response in diabetic individuals. These warning symptoms allow the individual with diabetes to recognize and treat the hypoglycemia. If blood glucose levels continue to drop, symptoms such as sleepiness, psychomotor retardation, lightheadedness, confusion or visual distortions develop and these symptoms primarily reflect cerebral disruption, neuroglycopenia (Macdonald, 1989). When this occurs, the individual is often unable to initiate action to treat the hypoglycemia and requires assistance to obtain the needed ingestible glucose. If untreated, blood glucose levels continue to fall and the manifestations of severe hypoglycemia - unconsciousness, seizure or coma occur. Injectable glucagon must be administered at this time and medical attention is usually warranted.

The occurrence of and the patient's awareness of hypoglycemia varies widely among individuals (Cox, Antoun, Clarke & Gonder-Fredricks, 1990; Cox et al., 1989). Studies investigating the ability of children and adolescents to accurately identify low blood glucose levels have consistently found that these populations tend to overestimate blood glucose levels and that hypoglycemic states often go undetected even in the presence of symptoms (Freund, Bennett

Johnson, Rosenbloom, Alexander & Apperson Hansen, 1986). While diabetics may recognize a characteristic pattern of symptoms indicating low blood sugar in time to treat the episode, no symptom or symptom cluster is ubiquitous or has been found to correlate with any level of blood glucose. Marks & Rose (1981) note that the symptoms produced by hypoglycemia may be "extremely varied, non-specific, due to cerebral dysfunction [and] not invariably present when blood sugar [is] low or even extremely low" (p. 90). In addition, the occurrence of symptoms not only depends on the absolute blood glucose level but also on the rate at which the blood glucose falls (Eeg-Olofsson, 1977). Extremely rapid falls in available blood glucose may produce the previously listed symptoms even if glucose levels do not fall to below 60 mg/dl. Despite the common occurrence of hypoglycemic reactions in diabetic patients, the relationship between subjective symptoms, blood glucose level, counter-regulatory hormonal responses and cerebral functioning is yet poorly understood and hypoglycemic unawareness is considered a serious problem among those who study its impact upon cerebral functioning (Cox et al., 1990).

#### Hypoglycemia and Counterregulatory Defects

The early recognizable symptoms of hypoglycemia are linked to the body's cholinergic and adrenergic counterregulatory response to low blood sugar level. However some patients, typically those with longstanding IDDM (> 5

years), also develop a deficient epinephrine response to hypoglycemia in addition to the loss of glucagon secretory capacity (Simonson et al., 1985; White et al., 1983). This appears to be a manifestation of diabetic autonomic (adrenergic) neuropathy although clinical signs of neuropathy are not necessarily present. This counterregulatory defect is found in as many as one third of individuals with diabetes of greater than five years duration (Sherwin 1989). White et al., (1983) found an increased incidence of severe hypoglycemic episodes in patients who they deemed to have this impaired counterregulatory response to hypoglycemia.

When the diabetic individual loses these counterregulatory capacities it has two primary effects. First, the individual loses the ability to recognize falling blood glucose levels due to impairment of the hormonal changes that produce the symptoms. Secondly, loss of glucagon secretory capacity leaves the body without an important endogenous way to combat hypoglycemia by converting other body tissues into energy sources for the body and brain. Individuals with severe impairment of these systems may be unaware of moderate to severe hypoglycemia and may drift into semi-consciousness and become unable to take action to treat the hypoglycemia. Many studies have documented this lack of warning symptoms in the diabetic individual (Hoeldtke, Boden, Shuman & Owen, 1982; DeFronzo, Hendler & Christensen, 1980).

### Prevalence and Incidence of Hypoglycemia

Reports on the prevalence and incidence of mild and severe hypoglycemic episodes in individuals with diabetes vary widely. Sherwin (1989) noted that 26% of individuals experience at least one severe hypoglycemic episode during the first year after diagnosis of IDDM and 20% of these severe episodes eventuate in coma. The occurrence of severe hypoglycemia has been found to be significantly higher in those following intensive treatment regimens. Macdonald (1989) states that in a longitudinal study of 40 years duration, he and his colleagues found that intensive treatment doubled the risk of symptomatic hypoglycemia in the population they studied. The DCCT Research Group (1987) found that severe hypoglycemic episodes occur as frequently as 54 events /100 patient-year for those following an intensive treatment as opposed to 17.4 events/100 patients-year for those following conventional treatment regimens.

Bhatia and Wolfsdorf (1989) noted that 17% of the children that they studied who followed an intensive treatment regimen had a severe hypoglycemic reaction at sometime during the two year study period. They state that all subjects experienced mild hypoglycemia. Studies have also found that a higher incidence of severe hypoglycemia is linked to better glycemic control, and the higher doses of insulin that are usually associated with intensive insulin therapy (Casparie & Elving, 1985; Simonson et al., 1985).

However, using conservative criterion for severe hypoglycemia, Bergada, Suissa, Dufresne & Schiffrin, (1989) found that 7% of the children who received conventional treatment (as opposed to intensive treatment) had at least one severe hypoglycemic episode during the one year study period. They note that warning symptoms occurred in less than 28% of these episodes. This study also found that there were a significant differences in the incidence of severe hypoglycemia among groups with different durations of diabetes. Bergada and his colleagues found that while 12% of the newly diagnosed diabetics experienced a severe hypoglycemic episode during the first year after diagnosis, this rate dropped to 3% for those having diabetes for between one and five years, and climbed to 9% in children having diabetes for over five years. They attribute the high rate during the first year to inexperience in recognizing symptoms of hypoglycemia and the low rate in years two through five as due to residual glucagon secretion and residual beta cell activity that can correct for hypoglycemia. After five years, these internal protective mechanisms are generally absent resulting in an increased susceptibility to severe hypoglycemia.

The incidence of mild or asymptomatic hypoglycemic episodes has not been well documented because of methodological constraints in obtaining representative and accurate continuous assessments of blood sugar level. However,

Golden et al. (1989) found that approximately 3% of routine blood glucose monitoring revealed asymptomatic hypoglycemia in young children with diabetes who measured blood glucose between two and three times per day. Ryan et al. (1989) hypothesize that 50% of hypoglycemic episodes are not detected.

### Hypoglycemia and Type of Insulin

There has been much debate as to whether the use of human insulin increases or decreases the incidence of both mild and severe hypoglycemia. Early studies noted that individuals using human insulin reported fewer episodes of symptomatic hypoglycemia (Schluter, Petersen, Sontheimer, Enzmann & Kerp, 1982). However later studies documented that human insulin was linked to an increase in hypoglycemic **unawareness** rather than a decrease in the incidence of hypoglycemia per se (Berger & Althaus, 1987; Egger, Teuscher & Berger, 1988; Teuscher & Berger, 1987). Contrary to those early assumptions, Egger, Imhoof and Teuscher (1989) noted that an increase rather than a decrease in severe hypoglycemia was linked to the hypoglycemic unawareness produced by human insulin.

Fort, Ginsberg, Cervantes, Recker and Lifschitz (1989) warn that children using human insulin are at a greater risk for severe hypoglycemia than are children using purified beef-pork insulin. Some proponents of the use of human insulin in children have suggested that its use slows the rate of insulin



antibody production during the years after diagnosis thus preserving some endogenous insulin production capacity (Schernthaner, Borkenstein, Fink, Menzel & Schober, 1983). However recent studies have suggested that there is no difference in insulin antibody production between those receiving human or purified animal derivative insulin (Zuppinger et al., 1987).

### Effects of Hypoglycemia on Cerebral Functioning

#### Electrophysiological studies

In addition to the widely known transient symptoms associated with hypoglycemic episodes, a number of permanent sequelae of hypoglycemia have been reported. Gilhaus et al. (1973) reported a higher frequency of pathological EEG findings in diabetic children who had frequent hypoglycemic episodes than in nondiabetic controls or diabetic children with a history of few hypoglycemic episodes. They note that these EEG changes are "always the expression of a permanent cerebral change and show no tendency to improve" (p.1449). Marks and Rose (1981) describe research findings that abnormal EEGs were been found in 50% of diabetic subjects with a history of hypoglycemia while only 8% of diabetics never experiencing hypoglycemia had abnormal EEGs and that EEG abnormalities occurred more frequently among the diabetic children with the highest rates of hypoglycemic seizures and diabetic ketoacidosis.

There is a wealth of electroencephalographic studies suggesting that vital brain centers may be more sensitive to transient hypoglycemia than previously appreciated (Sherwin 1989; Tallroth et al., 1990). Sherwin (1989) states that suppression of P300 wave stimuli in the temporal lobe have been found to be sensitive to even small changes in blood glucose level. He also cited studies that documented reversible Brainstem Auditory Evoked Potential changes which occurred when blood glucose level dropped to 55mg/dl. Tallroth et al. (1990) also documented significant EEG, P300 and somatosensory evoked potential changes during mild hypoglycemia. These changes were most pronounced in anterior brain regions. Amiel et al. (1989) documented similar changes in these same brain regions using measures of EEG activity and somatosensory evoked potential in diabetic subjects.

Irreversible neurological disturbance, especially intellectual deterioration and ataxia has also been found to result from subacute or chronic hypoglycemia which may go unnoticed due to blunted sympathetic nervous system warning signals ("Hypoglycemia", 1985). Ingram, Stark and Blackburn (1967) reported a high incidence of ataxia during an 8 to 10 month follow-up of 26 children who sustained a severe hypoglycemic reaction. Further, Bigler (1984) notes that when CNS energy requirements fail, neuronal dysfunction begins to occur within seconds, and permanent structural damage may develop within minutes. It is widely accepted that even

infrequent attacks of hypoglycemia produces permanent brain damage in the neonate (Marks & Rose, 1981). Synaptic events are sensitive to even small changes in glucose concentration in the CNS and mild hypoglycemia has been found to significantly decrease acetylcholine turnover (Palmer, Werner, Hollander & Ensinnck, 1979). The effect of hypoglycemia on other neurotransmitter systems has yet to be investigated.

#### Effects of hypoglycemia on brain cell integrity

Hypoglycemic brain damage has been linked to cerebral hypoxia (insufficient oxygen) due to a lack of substrate for the intracellular energy forming process (Marks & Rose, 1981). In addition, hypoglycemia has been considered to be a form of ischemia (loss or reduction of blood flow to the brain) and the two insults have often been described as having the same neuropathology (e.g., Courville, 1957; Richardson, Chambers & Heywood, 1959; Brierly, Meldrum & Brown, 1973). More recently, research has suggested that damage occurs in hypoglycemia when an endogenous neurotoxin is produced and released by the brain into tissue and cerebrospinal fluid (Auer, 1986). This proposed neurotoxin has the characteristics of an excitotoxin and may produce neuronal necrosis through cell membrane rupture rather than simply from glucose starvation and internal catabolic death (Auer, 1986). The production of this neurotoxin has been reported to occur about the time that the EEG becomes isoelectric (flat). A

blood glucose level of less than 20 mg/dl usually gives rise to cerebral EEG isoelectricity and the resulting brain damage in the mature brain (Auer, 1986). Auer (1986) in his comprehensive review of this research on this proposed endogenous neurotoxin notes that these findings also account for the seizure phenomenon in hypoglycemia.

There has been considerable interest in whether hypoglycemia affects all parts of the brain equally or whether different parts of the brain are more sensitive to declines in glucose availability. While there is some disagreement about the exact distribution of the damage, research in animals has supported the notion that the neurons of the middle layer of the cerebral cortex (with the exception of the striate area) and hippocampus are most affected, and the basal ganglia and anterior thalamus are the next most sensitive (Agardh, Kalimo, Olsson & Siesjo, 1980). The brain stem and spinal cord neurons are the least affected according to Agardh et al., (1980). However, Auer, Wieloch, Olsson and Siesjo (1984) cite research suggesting that necrosis is seen in all neuron types in the spinal cord. In addition, electrophysiological studies of humans have suggested that anterior brain regions and temporal and parieto-occipital brain regions are particularly sensitive to hypoglycemia (Amiel et al., 1989; Sherwin, 1989; Tallroth et al., 1990).

### Behavioral correlates of hypoglycemia

While most of the research in the area of hypoglycemia has focused on what occurs at the neuronal level, some researchers have attempted to describe behavioral correlates of low blood glucose levels. These studies have with only three exceptions involved the study of adults and have varied widely in methodology, type of response studied, definition and measurement of hypoglycemia and composition of control group. Despite this variability they all have found that there are measurable behavioral and cognitive correlates of mild hypoglycemic reactions, both during and after the reaction in a majority of the individuals that were studied. Many studies have also found that cognitive and motor performance does not correspond well to subjective sense of glucose level or the presence or absence of symptoms.

Adults. Herold et al. (1985) examined the effects of insulin-induced hypoglycemia on cortical function in adult Type I diabetics and nondiabetics by measuring reaction time to a visual stimulus under varying blood glucose levels. They discovered that there is a significant amount of individual variance in cortical functioning and subjective perception of hypoglycemic states. In this study, approximately 20% of nondiabetic and 30% of the diabetic subjects exhibited no increases in reaction time even when blood glucose levels reached below 40mg/dl. Another group of subjects experienced

no subjective symptoms of hypoglycemia, yet this group displayed the most impairment in reaction time of all subjects. These investigators also observed that the mean reaction time under basal euglycemic conditions were significantly longer for diabetic subjects than for control subjects. They conclude that this may suggest the presence of a neuropathic process in the central nervous system that may result from repeated episodes of hypoglycemia in insulin-treated patients.

Another significant finding of this study was that over half of the subjects, both diabetic and control, showed a considerable delay between nadir blood glucose levels and impairment of performance even when blood glucose levels had been within normal limits for between 10 and 40 minutes. Herold and his associates note that this observation is of considerable importance for it "provide[s] objective data in support of the common clinical observation that the neurologic effects of hypoglycemia may not correlate well with simultaneous peripheral glucose level" (p. 684). This finding is consistent with those obtained by Blackman et al., (1989) who found that hypoglycemia induced cognitive dysfunction persists for approximately 45 minutes after blood glucose levels return to euglycemic levels.

Pramming et al. (1986) administered a brief battery of neuropsychological tests to 16 insulin-dependent men under four blood glucose level conditions. They found that three

quarters of the men showed impaired performance at a blood glucose level of 54mg/dl as compared to their performance under euglycemic conditions. Fifteen of the 16 men exhibited impaired performance at blood glucose levels between 27 and 37.8mg/dl. They suggest that the impairment seen was a function of the deterioration of attention, concentration and planning skills at the lower blood sugar levels. Pramming and his colleagues conclude that "possibly the frontal lobes are more sensitive to hypoglycemia than other cortical regions" (p. 650).

Pramming et al., (1986) also noted that declines in performance were frequently not accompanied by subjective awareness of the hypoglycemic state. Frier (1986), in a review of this article points out that the results of this research caution against "overscrupulous attention to glycaemic control in insulin-dependent diabetes "(p. 898). Hepburn et al., (1989) note that in the patients with hypoglycemic unawareness that they studied, severe neuroglycopenia preceded autonomic activation (which produces symptoms). They found that this autonomic activation even when present, occurred too late for perception of hypoglycemia and appropriate action.

Schroeder et al. (1989) evaluated "mental speed" and finger tapping performance in diabetic and nondiabetic adults, and contrary to most studies (i.e., Blackburn et al., 1989; Hepburn et al., 1989; Herold et al., 1985), found no motor

decrements during two hypoglycemic periods. It is of note that one "hypoglycemic" period was defined by a blood glucose level of 64mg/dl. They did, however, document a significant decrement in the ability to do a serial addition task in diabetic but not in nondiabetic subjects during times when blood glucose levels were 46mg/dl and 64mg/dl. Schroeder and his colleagues also noted that diabetic subjects exhibited significantly more errors on this task after euglycemia had been reestablished as compared to the nondiabetic group. In addition, the diabetic group did not appear to benefit from the expected practice effect while the nondiabetic group did so.

Children and adolescents. Three studies have documented the cerebral effects of mild hypoglycemia in children and adolescents, even though children with IDDM are the population at highest risk for both mild and severe hypoglycemic reactions (Flender & Lifschitz, 1976; Reich et al., 1990; Ryan et al., 1989). Ryan et al., (1989) administered tests of simple and choice reaction time, and tests of attention and cognitive speed and flexibility to six adolescents between the ages of 12 and 17. They found that at blood glucose levels between 58mg/dl and 68 mg/dl five of the six adolescents showed significant declines in performance on reaction time tasks and cognitive speed compared with euglycemic performance. Flender and Lifschitz (1976) documented decreased



"fine motor coordination" and memory in eight children, with IDDM when blood glucose levels were between 52 and 65 mg/dl. Both of these studies utilized medically induced and controlled blood glucose levels to study hypoglycemia.

Only one study, to date, has addressed the impact of mild hypoglycemia as it occurs and is experienced by the school age child. Reich et al., (1990) evaluated motor speed, concentration and memory in 24 children and adolescents at camp shortly after recovery from a mild hypoglycemic episode and at two other times. They found that even after recovery from a hypoglycemic episode, children exhibited decreased neuropsychological functioning as compared to their functioning during a euglycemic period not preceded by hypoglycemia. Results of this study suggest that the impact of hypoglycemia may last longer than assumed by the medical community and thus may have a more detrimental impact on cerebral functioning in the long term. The results of these three studies parallel those found in adult research and suggest that other findings in the adult literature may also be applicable to children and adolescents.

#### Control of blood glucose levels and cerebral functioning

Some researchers have suggested that good glycemic control lowers the glycemic threshold for neuroglycopenia in adults and children when blood glucose drops (Sherwin, 1989). However this is not borne out by the findings of a study by

widom, Topliffe and Simonson (1989). Widom and his associates investigated endocrine functioning, and visual-spatial, visual-motor and memory functioning during euglycemia and hypoglycemia in diabetic adults in good and poor control and nondiabetic subjects. In addition to their finding that glycemic control was unrelated to cerebral functioning, they found that visual-spatial and visual-motor skills deteriorate at higher glycemic level than does attention/ concentration skills. A study by Amiel et al. (1989) also corroborates these findings and the investigators note that while delayed hormone responses to and subjective awareness of hypoglycemia was delayed among those in good control, cerebral functioning was not preserved in these patients.

Macdonald (1989) has cited studies showing evidence that cognitive impairment often precedes awareness of hypoglycemia especially among diabetics in good control. A study of 10 nondiabetic and 15 diabetic individuals suggests that forced choice reaction time slows for both diabetic and nondiabetic subjects at blood glucose levels of 55mg/dl with more established slowing at 45mg/dl. Eleven of the 15 diabetics in the study reported no awareness of hypoglycemia even at 45mg/dl while 9 of 10 nondiabetic subjects reported symptoms at this blood glucose level (Heller, 1989). Consistent with these studies, Hoffman et al. (1989) found that motor skills were impaired at blood glucose levels of 50mg/dl prior to the onset of subjective symptoms of hypoglycemia.

### Evidence for cerebral adaptation to prolonged hypoglycemia

It has been documented that counterregulatory response and hypoglycemia awareness changes over the course of chronic states of low blood glucose level. Macdonald (1989) described studies that suggest that neurogenic symptoms and awareness of hypoglycemia increase steadily at prolonged blood glucose levels of 51-54 mg/dl for as long as 40 minutes. However at 60 minutes both diabetic and nondiabetic subjects reported no symptoms of hypoglycemia even though their blood sugar remained between 51 and 54mg/dl. Another finding of this study was that reaction time for these hypoglycemic subjects did not begin to slow until 15-40 minutes after the onset of the mildly hypoglycemic state.

Similar findings were described by Kerr, Macdonald and Tattersall (1989) in their study of nondiabetic individuals maintained at blood glucose levels of 54 mg/dl. They noted an absence of subjective symptoms of hypoglycemia in their subjects after 60 minutes of hypoglycemia even though levels of counterregulatory hormones remained high. Most strikingly, this decline in symptoms report corresponded to improved performance on a test of reaction time. They suggest that this provides evidence of cerebral adaption to hypoglycemia. Possible mechanisms for this adaption may be increases cerebral blood flow, increased activity of the glucose transporter or use of alternate fuels by the brain (Neil et al., 1987; McCall et al., 1986).

## Neuropsychological Assessment

The correspondence between brain states and adaptive functioning has long fascinated those in a number of disciplines including medicine, psychology and education. As techniques for brain mapping and imaging have become more sensitive and neuropsychological evaluation has become more refined, these techniques have been applied to the understanding of an increasing number of medical disorders and psychological problems. These techniques have only recently been applied to understanding the effects of chronic illnesses such as diabetes and asthma on adaptive functioning (Dunleavy & Baade, 1980; Kasenberg & Bloom, 1987).

The past three decades have been a time of rapid development in the field of neuropsychology. In combination with recent developments in neuroanatomy and neurology among other fields, it is now possible to specify with increasing reliability the relationship between events in the central nervous system and observable behavior (Rourke, Bakker, Fisk & Strang, 1983). Most of the focus in the neurosciences has been on this brain-behavior relationship in adults who exhibit deficits as a result of a cerebral accident or as part of a disease process.

The identification and localization of neuropsychological deficits in adults is usually accomplished with the use of any number of well researched techniques. In particular the

Halstead-Reitan battery (Reitan & Wolfson, 1985) and the Luria-Nebraska battery (Christenson, 1975) have been shown to have high levels of validity and reliability with adults and their use in research has provided important information about subtle aspects of brain function and structure in adults. Comprehensive neuropsychological assessment has been found to be more sensitive to brain impairment than standard intelligence tests alone or electroencephalographic or neurological examinations (Tarter, Edwards & Van Theil, 1988). Of particular interest to those investigating the relationship between medical disorders and the brain has been the localization of the most likely site of impact in order to better understand the mechanism of injury.

#### Localization in Neuropsychological Assessment

The initial basis for the use of neuropsychological testing to provide evidence of lateralization and localization of brain lesions came from repeated observations that the pattern of cognitive deficits after unilateral cerebral lesions in adults differed as a function of which hemisphere of the brain was damaged. The terms hemispheric specialization or lateralization of function refer to the organization of the human brain wherein the right and left cerebral hemispheres are specialized to process distinct types of sensory information. Functional asymmetries are based neither on a sensory modality dichotomy (e.g., auditory versus visual),

simple stimulus (e.g., verbal versus nonverbal) nor on defined activities such as reading or drawing (Witelson, 1985).

Witelson, (1985) suggests that there are two primary types of information processing that underlie cognition and that each is predominantly or solely mediated by one hemisphere. She states that in most individuals the left hemisphere is specialized for the synthesis of stimuli as "discrete, finely-tuned items within their temporal sequence and... serially organized discrete events; the right hemisphere is specialized for the synthesis of stimuli over space and time dimensions into holistic configurations" (p. 38). This conceptualization reflects the neuropsychological findings that behavior such as speech sounds discrimination, speech, syntactic comprehension and other voluntary processes are processed mainly by the left hemisphere. Conversely, right hemisphere processing is thought to govern skills such as perception of three dimensional space, face recognition and musical cords, as these skills rely on the synthesis of an array of stimuli without regard to temporal aspects. While motor skills are represented bilaterally it is hypothesized that preferred (right) hand motor performance is superior to nonpreferred (left) hand performance for serial tasks such as finger tapping because of the hemispheric specialization of the contralateral hemisphere which primarily controls the movement.

However, both of these modes are essential to the

processing of complex stimuli and thus individuals do not have a "dominant" hemisphere for cognition. Witelson (1985) notes that the frequent use of the term dominant to describe left hemispheric functioning is based on the assumption that greater skill and greater hemispheric specialization are intertwined. She suggests that this is a simplification of the understanding of the interdependence of the hemispheres for processing complex stimuli and states that most individuals have "two dominant hemispheres" (p. 39).

Using neuropsychological measures that tap specific discrete skills, a differential pattern of cognitive skills and deficits has been found to differentiate right hemisphere from left hemisphere lesions in adults with a fair degree of accuracy even in the absence of general intellectual loss. These patterns of lateralization following an injury are most pronounced shortly after the occurrence of the lesion in both children and adults. Differences in motor skills between the left and right hand have yielded particularly accurate information for the determination of lateralization of brain dysfunction (Chadwick & Rutter, 1983). The research on hemispheric differences in children is more variable and less clear cut although the general pattern has tended to be in roughly the same direction especially with older children.

#### Neuropsychological Assessment of Children

The field of child neuropsychology, while benefitting from the tremendous gains in knowledge of brain behavior

relationships that have emerged from adult neuropsychology, has distinct issues and concerns. The most obvious and perhaps most complex issue involves the relationship between development and brain structure and function. The central nervous system of the child is very different from that of the adult, both in terms of functional capacities and physiological characteristics and caution must be exercised in any generalizations made from knowledge of the mature brain. In addition, while the mature brain has been found to exhibit rather static characteristics, the developing brain is in a state of rapid change. Thus, not only must the \*neuropsychologist address the loss of functioning caused by trauma to the young nervous system but also the effect of that trauma on the further growth and development of the brain and its functions. Therefore, neuropsychological dysfunction in the child may take the form of a loss of previously attained skills and/or a failure to develop appropriate skills at a later time. Unlike acute trauma to the adult brain wherein the most severe deficits are most commonly seen immediately following the injury, significant deficits may not become obvious in the child with cerebral trauma until many years later. In addition, as with trauma to the adult brain, it has been found that the severity of functional difficulties resulting from brain trauma during childhood also varies extensively depending upon the nature of the trauma, the location of the lesion, its size, and whether it is static or



expanding (Geschwind, 1974).

### Brain injury

Rudel (1978) notes that depending on the age of the child at testing, the assessment technique used, and the location and type of damage, the child will show one of three outcomes of trauma. These may be deficits that "(a) appear early and disappear, (b) be apparent at all ages after early or late lesions, or (c) be apparent only after a delay" (p. 272). The first of these outcomes often reflects edema which is a swelling of the brain that commonly occurs as a sequelae of brain injury (including prolonged hypoglycemia) and can produce temporary deficits (Marks & Rose, 1981). In addition, recent research on the reparative functions of denervation supersensitivity, collateral sprouting and regenerative sprouting suggest that some restoration of functioning may occur through these mechanisms (Geschwind, 1974). The second way that brain trauma may affect functioning is also seen in adults and addresses the issue of loss of a previously held skill. The third outcome is vastly more common in children than in adults and specifically addresses the issue of the effect of trauma on further growth and development in the immature brain. This outcome may be seen when damaged areas are not in use at the developmental age at which the child is injured but deficits are seen when the child "grows into" the injury. This outcome may also occur when extensive damage

occurs in one cerebral hemisphere early in life which often results in the later development of all appropriate cognitive skills but at a depressed level possibly due to the structural limitations imposed by a reduction of available intact brain space (Rourke et al., 1983).

### Hemispheric lateralization and plasticity

The scientific community knows relatively little about the specific ways that particular lobes and hemispheres of the brain develop during childhood and the contributions made by environmental stimulation, endocrine function, nutrition and heredity to this development. However a predominant assumption especially among neurologists was that the developing brain is remarkably plastic and better able to compensate for a loss of functioning that results from localized lesions than is the mature brain. This was a widely held belief because it was observed that children who sustained documented brain injury at very young ages had a higher chance of a full recovery than older children or adults sustaining the same injury. Rudel (1978) notes that this conceptualization lead the eminent teacher, Margaret Kennard to counsel her students to "have our brain injuries, if we had to have them, as early as possibly could be managed" (p. 269). Empirical investigation has not provided evidence that suggests that this admonition should be followed (Rourke et al., 1983).

Indeed this relationship between age of onset of damage and recovery is now known to be much more complex than previously assumed. In particular, the role of hemispheric specialization has often been confused with the issue of plasticity in accounting for recovery of function in the immature brain. Hemispheric specialization of function is a feature of neural organization which is particularly prominent in the human brain. In the past it was believed that this specialization did not occur in children until later in development and that the plasticity of the young brain reflected a lack of hemispheric specialization (Geschwind & Galburda, 1985). However within recent years, a body of evidence has accumulated that suggests that functioning hemispheric specialization is present in infancy for at least some cognitive skills. Witelson (1985) in her extensive review and analysis of the empirical findings in the area of hemispheric specialization in children, concludes that the most parsimonious theory that could account for the bulk of the findings in this area would maintain that functional specialization of both the left and right hemispheres are present from birth and neither evolves, changes or increases over time.

Plasticity, in contrast, can be defined as a biological characteristic of all brains which allows for recovery of function under certain circumstances and is likely accompanied by neural changes. The neural changes that have been

investigated include the mechanisms of regenerative sprouting, collateral sprouting, and denervation supersensitivity which occur on the neuronal level following a lesion (Geschwind, 1974). However some theorists such as Luria (1980) postulate new organizational and behavioral strategies as the mechanism of recovery. The biological basis of these proposed organizational changes have not been determined. According to Rourke et al. (1983), neither of these theories can fully account for the process and variations in recovery that have been observed.

Rudel (1978) and others have claimed that the capacity for plasticity is greater in the immature brain. Golden (1981) notes that injuries prior to two years will result in a greater reliance on the right hemisphere for processing of language. He suggests that after age two, the results of severe injuries begin to resemble those of adults. In addition, it has been noted that injuries to the left hemisphere before age five tend to result in depressed functioning in all areas for children rather than specific language impairment (Chadwick & Rutter, 1983; Woods, 1980). This is consistent with the idea that in addition to plasticity, ongoing brain maturation may compensate for specific lesions sustained early in life but this compensation may compromise some the later development of a complex function. Thus there appears to be a critical period in which the effect of unilateral injuries are minimized, thereafter

they have more long-term effects on functioning.

Rourke et al., (1983) suggests that such plasticity is not observed when injury to the brain is diffuse or when the injuries are small. Thus paradoxically a small injury at birth may produce more deficits than a larger injury. Severe and mild hypoglycemia would fall in the category of diffuse or small injury and therefore which would likely not produce the compensatory neuronal changes that would spare functioning. Hypoglycemia or other metabolic insults may result in brain injury not because of the magnitude of the individual incident of trauma but rather through the cumulative impact of minor insults. This is consistent with the findings that previous history of minor brain injury may result in a selected vulnerability to future trauma. For the child with early onset of diabetes this would be of particular consequence as glycemic control is especially difficult in young children and the onset of hypoglycemic trauma occurs during a time of critical brain myelinization (Rovet et al., 1987). Results of numerous studies that have found an association between early onset of diabetes and an increased incidence of neuropsychological deficits, support this proposition (Holmes & Richman, 1985; Rovet et al., 1987; Ryan et al., 1985).

#### Interpretation of neuropsychological findings in children

Given developmental issues and paucity of specific information about the development of brain function, it is

obvious that the neuropsychological assessment of brain - behavior relationships in the child is an extremely complex undertaking. At the basis of this assessment is the understanding of the probability that the particular pattern of abilities and deficits exhibited by the child is due to compromised cerebral functioning as opposed to other factors. Thus it is important to rule out problems with visual and hearing acuity and motivation as well as cultural/linguistic deprivation and emotional disturbance as contributing to performance on a neuropsychological task.

Neuropsychological test interpretation takes into account: (1) whether level of performance on a task is significantly different from established normative levels for age; (2) whether the individual exhibits certain established pathnomic signs which are highly correlated to brain damage; (3) the pattern of performance with regard to specific types of skills (i.e., motor skills, memory skills, receptive language skills); and 4) whether the pattern of performance suggests marked difference in the functional integrity of the right and left hemispheres of the brain. However, Golden (1981), Reitan (1987), and Rourke et al. (1983) note that in the neuropsychological evaluation of children a pattern of performance approach offers a much more effective and accurate method of diagnosing brain injury in children. He suggests that the analysis of level of performance should be reserved for establishing the severity if a condition that is

identified by other methods. A pattern approach includes analysis of lateralization and localization of brain injury to a specific hemisphere of the brain. The guidelines used for this are similar to those used with adults.

### Statement of Problem and Hypotheses

While much has been learned from research on the cerebral effects of hypoglycemia in adults, this information does not shed light on whether the neuropsychological deficits documented in children with diabetes arise from repeated incidence of hypoglycemia common to young diabetics. Even less is known about the possible effects of hypoglycemia on the specific hemispheres of the brain. Information about the motor functioning of diabetic children during documented normal blood sugar levels (euglycemia) and after treatment for a documented hypoglycemic episode would provide information that could integrate and explain the findings that suggest that repeated incidence of hypoglycemia may underlie the deficits observed during general intellectual and neuropsychological testing. Comparison of preferred and nonpreferred hand performance using established neuropsychological guidelines would permit more accurate information to be obtained about possible selective impact upon one cerebral hemisphere (Reitan & Herring, 1986).

The present study seeks to evaluate motor functioning both during times of documented euglycemia and after standard

treatment for mild hypoglycemia to investigate whether there are similar patterns of motor performance in diabetic children under both conditions. This information will be collected as mild hypoglycemia develops and is experienced by children during the course of activities as opposed to during invasive medical procedures in a hospital setting. This also serves the function of investigating whether children show the same lag in recovery time that has been observed in adults and provides more externally valid results without compromising the health and well-being of the subjects.

Neuropsychological tests have been found to be more sensitive to brain impairment than standardized intelligence tests alone or electroencephalographic or neurological examinations (Tarter et al., 1988). The use of a battery of neuropsychological measures of motor functioning that document both left and right hand functioning permits analysis of whether hypoglycemia or diabetes has a selective impact on the left or right hemisphere of the brain. A battery of tests focusing on motor functioning of both preferred and nonpreferred hands has many advantages including documented stability over time, minimal if any practice effects that may confound interpretation of repeat testing and sensitivity to lateralization of brain dysfunction in children (Bornstein, Baker & Douglass, 1987; Golden, 1981; Matarazzo, Weins, Matarazzo & Goldstein, 1974; Morrison, Gregory & Paul, 1979; Rourke et al., 1983).



Extensive normative data from both normal and brain injured children are available for these measures and studies have documented that subjects without brain impairment very rarely receive rating scores that fall within the impaired range even with multiple testings (Bornstein, et al., 1987). Examination of possible lateralization of the effect of hypoglycemia is also possible by calculating intermanual differences in performance. The established expected criterion of 10% difference between preferred and nonpreferred hand motor performance with better performance with the preferred hand in those without brain impairment has been well documented in both adults and children (Bornstein, 1986; O'Donnell, 1983; Thompson, Heaton, Matthews & Grant, 1987; Todor, Kypric & Price, 1982). The analysis of intermanual differences on motor tasks has been found to reliably distinguish between brain lesions of the right and left hemisphere (Bornstein, 1986; O'Donnell, 1983, Reitan, 1987). Reitan (1987) has developed cutoff scores for intermanual differences on tapping and namewriting tasks that categorize this difference as reflecting the range of performance from "perfectly normal" to "impaired".

Variables such as type of insulin used, the child's awareness of hypoglycemia and onset and duration of diabetes have been identified as important variables that may relate to the performance of diabetic children and may shed light on the etiology of any observed deficits (Hepburn et al., 1989;

Holmes & Richman, 1985; Macdonald, 1989; Ryan, 1988). As endocrine functioning cannot be assessed in this naturalistic setting, duration of diabetes and awareness of hypoglycemia may also offer an indirect measure of whether the counterregulatory response is intact in individual children and how this is related to performance.

#### Hypothesis 1

Some researchers have documented intellectual and neuropsychological deficits in diabetic children as compared to nondiabetic control groups, siblings and normative data (Anderson et al., 1987; Holmes & Richman, 1985; Rovet et al., 1987; Ryan et al., 1985). These deficits are most often seen on tasks that have a preferred(right) hand motor performance component. Therefore it is hypothesized that during euglycemia, children with diabetes will exhibit impaired motor speed using their preferred hand as compared to normative data and nondiabetic controls.

#### Hypothesis 2

Discrepant findings have been reported as to the hemisphere of the brain that is more affected by diabetes although deficits are most often seen on tasks that require preferred hand motor functioning (Rovet et al., 1987; Ryan et al., 1985; Schroeder et al., 1989). However no study has used a battery of motor measures, which are relatively sensitive indicators of lateralization of impairment in children, to

assess both preferred and nonpreferred hand functioning. Thus it is hypothesized that a comparison of preferred versus nonpreferred hand motor performance during euglycemia in children with IDDM will reveal a relative deficit in preferred hand functioning as compared to nonpreferred hand performance.

### Hypothesis 3

Researchers note that the incidence of neuropsychological and intellectual impairment found in children with diabetes is higher in those who had early onset of the disorder or longer duration of the disorder (Anderson et al., 1988; Holmes & Richman, 1985; Rovet, 1989; Rovet et al., 1987; Ryan et al., 1985). These findings have been attributed to: (1) the increased incidence of hypoglycemia in diabetics under age five (Golden et al., 1985; Grunt et al., 1978); and (2) counterregulatory hormone response deficits to hypoglycemia and the resulting lack of cerebral protection that occurs in 22-50% of diabetics who have had the disorder longer than 5 years (Sherwin & Tamborlane, 1987). In addition it is thought that hypoglycemia may have a more deleterious impact on the developing brain than upon the mature brain (Ryan, 1988). It is therefore hypothesized that children who were diagnosed with diabetes at age four or earlier and/or children who have had diabetes for longer than five years will show more impairment in motor functioning than children who have had the disorder a shorter period of time or had it diagnosed at an older age.

#### Hypothesis 4

Decreased reaction time performance has been noted during medically induced and controlled hypoglycemia in adults (Heller, 1989; Herold et al., 1985; Hinnen et al., 1986; Holmes et al., 1983; Macdonald, 1989). These decrements have been noted to persist in some subjects for as long as 40 minutes after euglycemia has been attained (Hepburn et al., 1989; Herold et al., 1985; Pramming et al., 1986). Parents of diabetic children have noted that their children are often more "clumsy" or "uncoordinated" after recovery from a hypoglycemic episode. Therefore it is hypothesized that after treatment and recovery from a hypoglycemic episode, diabetic children will exhibit decreased motor performance as compared to their own performance during a euglycemic period.

#### Hypothesis 5

While decreased reaction time and motor performance has been consistently observed in studies of hypoglycemia in adults (Heller, 1989; Herold et al., 1985; Hinnen et al., 1986; Holmes et al., 1983; Macdonald, 1989), no research to date has explored whether these effects of hypoglycemia have a selective impact on the motor performance of one hand or affect both in the same manner. Examination of intermanual difference patterns on tapping and namewriting tasks have proven valuable in detecting differences between the functioning of the right and left cerebral hemispheres (Reitan

& Herring, 1985). Information about whether hypoglycemia exerts a selective impact on one hand will offer information about the hemisphere of the brain that is most affected by hypoglycemia and may offer clues as to what other skills may also be compromised. It is therefore hypothesized that a comparison of the motor performance of both the left and the right hand of diabetic children after recovery from a hypoglycemic episode, using Reitan's (1987) norms for expected difference, will reveal that hypoglycemia has a selective impact of one hand, or hemisphere of the brain.

#### Hypothesis 6

Researchers have found significant variability in whether subjects exhibit motor deficits during or after medically induced and controlled hypoglycemia (Ryan et al., 1989; Schroeder et al., 1989; White et al., 1983). This variability may be due to the individual's endocrine response to hypoglycemia and the concomitant increase in the frequency of these episodes. Within two years after onset of diabetes residual beta cell activity ceases and by five years duration defective counterregulatory response has developed in a significant number of diabetics (Sherwin & Tamborlane, 1987).

These changes represent a significant loss of protective endocrine responses to hypoglycemia. It has been suggested that individuals with inadequate counterregulatory response have an increased incidence of mild and severe hypoglycemia

(Bergada et al., 1989; Herold et al., 1985) although these episodes may sometimes go undetected (White et al., 1983). The cumulative effects of multiple incidence of hypoglycemia on brain functioning may render the brain of the child with these counterregulatory defects more sensitive to changes in blood glucose level. Therefore it is hypothesized that diabetic children who have had diabetes for more than five years will have a higher incidence of motor impairment after hypoglycemia than children who have had diabetes for less than two years.

#### Hypothesis 7

Recent studies have documented cerebral adaptation to hypoglycemia when it is sustained for longer than 40 minutes. (Kerr et al., 1989; Macdonald, 1989) In addition, it has been found that the identification of hypoglycemia and response to symptoms is a complex process in children, mediated by both situational and endocrine variables (Cox et al., 1989). The child who is not responsive to or has an impaired endocrine response to low blood glucose levels may remain hypoglycemic for a period of time before it is identified and thus relatively unimpaired performance after prolonged hypoglycemia may reflect cerebral adaption rather than the absence of a cerebral response to hypoglycemia. Therefore it is hypothesized that children who have hypoglycemia identified during routine blood glucose monitoring periods will exhibit a lower frequency of impaired motor functioning after recovery

than children who identify hypoglycemia by the occurrence of symptoms.

#### Hypothesis 8

Studies have suggested that individuals using human insulin as opposed to pork, beef or beef-pork insulin have a greater incidence of hypoglycemic unawareness (Berger et al., 1987; Egger et al., 1989; Egger et al., 1988; Teuscher & Berger, 1987). It is therefore hypothesized that a greater percentage of children who use human insulin will be identified as hypoglycemic during routine blood glucose monitoring as opposed to identifying hypoglycemia by symptom recognition.

## CHAPTER III

### METHOD

#### Subjects

##### Diabetic Group

Twenty-nine children diagnosed with Insulin-Dependent Diabetes Mellitus were recruited from 56 children ages 6 to 14 attending a two week residential camp sponsored by the American Diabetes Association. Eighty-four percent of the children attending this camp had parental consent to participate in this study which was part of a larger study investigating the temporal course of neuropsychological functioning after a hypoglycemic episode. Of these 47 children, three were excluded from the study sample because school histories indicated learning problems. One child was excluded because of a medical history of neurological problems. The total possible study sample was comprised of 44 well-functioning children with IDDM without known additional medical or educational problems.

All children in the final sample were right-handed and had been diagnosed as having had insulin dependent diabetes mellitus for between 7 months and 13 years. Age at diagnosis ranged from 11 months to 13 years with 15 subjects having been



diagnosed with diabetes at or before age 5. While on a variety of insulin regimens the vast majority were maintained on two to four split and mixed doses of insulin each day and followed an American Diabetes Association(ADA) diet or modified ADA diet. Approximately half of the children received human insulin and the other half were maintained on a variety of insulins derived from animals (7% beef, 14% pork and 31% beef-pork). No child used a subcutaneous insulin pump or extra lente insulin.

Children were screened for blood glucose level during camp registration. Those children with euglycemic blood level who reported no hypoglycemia within the past 24 hours were administered the battery of neuropsychological tests ( $n=10$  ). As all children meeting the criterion could not be tested at this time five campers completed the battery during a euglycemic period the following day (total  $n=15$ ). Twelve of these 15 children experienced a hypoglycemic episode during camp and received an additional testing immediately after recovery from this hypoglycemic episode.

Another group of 14 children received their euglycemic testing during camp at least 24 hours after a documented hypoglycemic episode. These children were tested an additional time between the hypoglycemic testing and the euglycemic testing as part of a related study.

### Nondiabetic Group

A control group of 14 right-handed children with no diagnosed chronic illnesses, neurological impairment or educational difficulties were also tested. Younger children were recruited from an inner city parochial school and older children were recruited from a suburban public high school. All children had economic backgrounds similar to the camp population.

Statistical analysis revealed no significant differences between control subjects and diabetic subjects for gender or age (see Table 1). In addition there were no significant differences between diabetics initially tested prior to and those tested after hypoglycemic episodes for age, gender, age at onset of diabetes, duration of illness, time between hypoglycemic episode recognition and testing, number of symptoms reported at time of hypoglycemic episode or blood glucose level during the hypoglycemic episode (see Reich et al., 1990).

### Materials

#### Blood Glucose Level Measure

Peripheral blood glucose levels were assessed using Chemstrip bG chemical reagent strips (Boehringer Mannheim Diagnostics) according to manufacturers' instructions. Blood was obtained from a sterile finger puncture; results were visually compared to color coded charts. Blood glucose levels

TABLE 1  
SUBJECT CHARACTERISTICS

Characteristics	Group	
	Diabetic	Control
#Sample:	29	14
Female	17	8
Male	12	6
Age (months)	<u>M</u> 141.8 <u>SD</u> (32.4)	133.7 (39.4)
Age onset IDDM (months)	<u>M</u> 76.2 <u>SD</u> (35.9)	...
Duration IDDM (months)	<u>M</u> 67.6 <u>SD</u> (45.2)	...
Blood glucose level (mg/dl)		
Hypoglycemia	<u>M</u> 43.4 <u>SD</u> (11.0)	...
Euglycemia	<u>M</u> 150.0 <u>SD</u> (52.6)	...
Time MHE* to post-MHE testing	<u>M</u> 20.4 <u>SD</u> (11.4)	...
Insulin type		...
#Human	14	
#Beef/Pork	15	

\* mild hypoglycemic episode

were first read by the child, confirmed by a nurse or physician and recorded in the child's camp medical record.

### Neuropsychological Measures

Measures were selected to meet four criterion: (1) sensitivity to impairment of fine motor functioning; (2) quickness and ease of administration; (3) availability of established normative data; and (4) minimal practice effects over repeated testing. Specific tests meeting these four criterion were taken from the Halstead-Reitan Neuropsychological Test Battery for Children (Reitan, 1987) and the Klove-Matthews Motor Steadiness Battery (Klove, 1963). These tests were administered according to standard instructions in random order by two graduate students in child-clinical psychology who were trained in the neuropsychological assessment of children. Tests used from the Halstead-Reitan Battery (Reitan, 1987) were:

1. Lateral dominance exam. This test which provides information about preferred handedness and lateral dominance and requires the subject to pantomime actions such as throwing a ball and opening a door.

2. Name writing task (a subtest of the lateral dominance exam). Children were asked to write their full name on a blank sheet of paper, first with the preferred hand and then with the nonpreferred hand. The score represents the number of seconds to complete each task.

3. Finger oscillation test/finger tapping test (Reitan Neuropsychological Laboratory). This test which measures motor speed, was administered for both the preferred and nonpreferred hands using the age appropriate electronic tapper (ages 7-9) or the manual tapper (ages 10 and older) The score represents the average number of taps in a 10 second period for five trials within five taps of each other. A total of seven trial were permitted and if five trials within five taps of each other were not obtained, the five scores closest in number were averaged to obtain the mean tapping score. Children were permitted to familiarize themselves with the task prior to trials in order to obtain optimal performance.

4. Klove-Matthews Motor Steadiness Battery: Maze test (Klove, 1963). In this test the child is instructed to run a metal stylus through a maze with its blind alleys blocked without touching the stylus to the sides of the maze. The maze rests upright at a 70 degree angle and the child is not permitted to stabilize his/her arm or hand against the maze or the table upon which it rests. Immediate feedback for errors is provided by an audible bell when the stylus comes in contact with the side of the maze path. Children were permitted to manipulate the stylus and experience the warning bell prior to beginning of the test in order to obtain optimal performance. Scores obtained include the number of times the stylus touches the side and the amount to time in seconds that the stylus rested against the edge of the maze. This task is

primarily a measure of motor steadiness and reaction time.

## Procedure

### Diabetic Children

All medical and educational information was obtained from a form completed by the camper's primary physician prior to camp and a brief interview with parents during camp registration. Children were screened for blood glucose level and informed consent to participate in the study was obtained from both the parent and child during the registration period. Those children with euglycemic blood glucose levels (80-240mg/dl) who reported no hypoglycemic blood glucose levels or symptoms during the previous 24 hours were administered the battery of neuropsychological tests in random order at that time. Children who met these criterion but could not be tested during registration were tested at a euglycemic period the following day provided they had not experienced a hypoglycemic episode in the intervening period.

According to camp policy, blood glucose level (BGL) was routinely assessed in all campers at 7:30 a.m., 12 noon, 5:00 p.m. and 9:00 p.m. each day as well as each time a camper presented with symptoms of hypoglycemia. All campers with a blood glucose level of 60mg/dl or less were deemed hypoglycemic and assessed and treated in the centrally located camp infirmary by either a pediatrician, an endocrinologist or a pediatric nurse.

Campers experiencing a hypoglycemic episode were identified either through blood glucose level assessment upon presenting at the infirmary with symptoms of hypoglycemia ( $n=13$ ) or during one of the four daily blood glucose level assessment times ( $n=13$ ). When a camper had a documented blood glucose level of 60mg/dl or less he or she was administered a standard quantity of glucotabs or orange juice needed to restore BGL to euglycemic levels. After treatment, the camper was monitored by medical personnel and released to return to activities when symptoms had subsided. At this time those campers with parental and child consent were asked to participate in the testing procedure. The time from the documentation of the hypoglycemic state to the beginning of testing ranged from 10 to 40 minutes with a mean and mode of 20 minutes. In order to control for the possible effects of multiple hypoglycemic episodes upon functioning, no child was tested if she or he had experienced a hypoglycemic episode in the 24 hours preceding this testing.

Children who had not received a baseline euglycemic testing prior to this testing were tested during a documented euglycemic period approximately 24 hours after the post-hypoglycemic testing. Children experiencing an additional hypoglycemic episode within this 24 hour period were excluded from the study to control for the impact of multiple episodes on functioning.

### Nondiabetic Children

Parental and child consent for participation of the 14 control group children was obtained from a written consent form sent home to a group of parents of children whom the school principal reported to be free of chronic medical conditions, physical handicaps, neurological disorders or learning problems. The control group children were tested using the same battery of neuropsychological tasks administered in random order once early in the day and once approximately six hours later. All control children reported feeling well and as having eaten a normal meal prior to testing.



## CHAPTER IV

### RESULTS

#### Score Transformations

Prior to analysis, raw scores for tapping and name-writing tasks were transformed to age-standard scores to eliminate age differences as a confound. Each assessment was transformed to an age-standard T-score by  $(X - \underline{M} / \underline{SD}) \times 10 + 50$ , where X equals the raw score. Higher scores represent better performance and for a given subject in a given group,  $\underline{M} = 50.0$ ,  $\underline{SD} = 10.0$ . Age appropriate means and standard deviations for the transformations of these scores were taken from the Revised Smoothed Normative Data on the Neuropsychological Test Battery for Children (Knights & Norwood, 1980) and norms reported by Klonoff and Low (1974). During transformation of scores it was discovered that the administration of the maze test for this study was different from that used in the development of the norms and no norms were available to transform maze error and maze time scores to age standard scores. Therefore raw scores were used to calculate a maze reaction time score equal to maze contact time/maze errors.

For each test (tapping preferred, tapping nonpreferred,

namewriting preferred, namewriting nonpreferred) standard scores obtained from both testings of diabetic and control subjects were rank ordered with the best score receiving a ranking of one. Rankings were calculated in the same manner for raw scores for reaction time preferred hand and reaction time nonpreferred hand. A total mean performance score for each individual was obtained for each testing (baseline and post hypoglycemia) equal to the sum of the rankings for all tasks for this testing divided by the number of tests. Preferred and nonpreferred motor performance rankings for each individual for each testing was calculated in the same manner.

This ranking reflects a pattern of motor performance for a given testing. It was expected that if there was no impact of either hypoglycemia or variables related to diabetes on motor performance that an individual's relative ranking for each test (and thus for a grouping of tests) would remain approximately the same across testings. Furthermore various groupings of subjects based on diabetes related variables would not be expected to differ significantly in the rankings of their members if the variable did not have a differential impact upon motor performance.

In order to further assess possible left-right hemisphere differences in performance, intermanual differences were calculated for tapping and namewriting raw scores as  $1 - (\text{preferred} / \text{nonpreferred})$ . This score was compared to Reitan (1987) tables for normative performance and ratings of between

zero and three were assigned with the lower score representing better performance. Scores of zero and one were considered within the normal range while scores of two or three were considered to reflect impairment (Reitan, 1987).

Motor tasks have been generally found to show minimal practice effects over repeat testings (Bornstein et al., 1987). Analysis of first and second testings for the control group confirmed that neither standard scores, rankings or reaction time scores were significantly different between testings for this group (see Reich et al., 1990). Thus scores for diabetic subjects receiving their baseline testing before their post-hypoglycemic testing and those receiving it 24 hours after the post-hypoglycemic testing were combined.

### Results of Statistical Analyses

Analyses of variance revealed no significant main effects of duration of IDDM, blood glucose level, or time from identification of hypoglycemic episode to testing, on  $T$ -scores for individual tests, motor performance rankings or reaction time scores for diabetic subjects in this study (see Reich et al., 1990).

#### Hypothesis 1

The performance level of children with diabetes during baseline testing was well within the average range as compared to normative data. Diabetic children as a group received mean

right hand  $T$ -scores of 56.1 ( $SD=7.68$ ) during baseline testing. However one-tailed  $t$ -tests revealed that diabetic children had significantly lower rankings on right hand motor performance during baseline as compared to nondiabetic controls,  $t(41)=2.99$ ,  $p < .01$ . Rankings for left hand motor performance were not significantly different between these groups,  $t(41)=1.58$ ,  $p=.122$ .

### Hypothesis 2

Paired  $t$ -test revealed no significant difference,  $t(28)=.18$ ,  $p=.857$ , between the motor performance rankings for right hand and those for the left hand during baseline testing for diabetic children.

### Hypothesis 3

Oneway analyses of variance revealed no main effects for duration or onset of diabetes on motor performance ranking during baseline or post hypoglycemic testings. One-tailed  $t$ -tests revealed no significant differences between diabetics with duration of diabetes longer than or less than five years for left,  $t(24)=1.25$ ,  $p=.225$ , or right,  $t(24)=.18$ ,  $p=.858$ , hand rankings during post-hypoglycemic testing. However, children with early onset of diabetes (before age 4) displayed significantly worse motor performance rankings with the right hand as compared to children with later onset of the disorder,  $t(24)= 2.15$ ,  $p < .03$ . Left hand motor performance rankings were not significantly different between onset groupings although

the trend was in the same direction (see Table 2).

#### Hypothesis 4

One-tailed paired  $t$ -tests on post-hypoglycemic and baseline rankings for right hand performance revealed significantly poorer performance after recovery from mild hypoglycemia,  $t(25)=-1.88$ ,  $p < .05$ . Rankings for left hand performance during baseline were not significantly different from those obtained during post-hypoglycemia testing,  $t(25)=.85$ ,  $p=.402$ .

In addition, one-tailed paired  $t$ -tests revealed that right hand reaction time during the post-hypoglycemic testing was significantly slower than during baseline testing,  $t(28)=-1.69$ ,  $p=.05$ . Left hand reaction time remained consistent across testings for diabetic subjects,  $t(28)=.75$ ,  $p=.46$ , as did reaction time for control subjects for both right,  $t(13)=.119$ ,  $p=.822$ , and left,  $t(13)=.17$ ,  $p=.868$ , hands.

#### Hypothesis 5

To determine whether diabetic subjects had a higher frequency of impairment ratings in the impaired range after recovery from a hypoglycemic episode, chi-square analyses using expected frequencies obtained during baseline testing were calculated for namewriting and tapping tasks. Namewriting, chi-square(1)=.408,  $p=.523$  and tapping, chi-square(1)=.708,  $p=.400$ , intermanual difference impairment ratings did not differ significantly between baseline and

TABLE 2

MEAN RANKINGS FOR DIABETIC SUBJECTS BY AGE AT ONSET OF  
DIABETES DURING BASELINE AND POST-MHE<sup>a</sup>

Mean Rankings <u>M</u> ( <u>SD</u> )	Onset of Diabetes	
	Early Onset <sup>b</sup> ( <u>n</u> =8)	Later Onset <sup>c</sup> ( <u>n</u> =21)
Right hand Baseline	46.0 (13.1)	42.3 (11.1)
Left hand Baseline	43.2 (12.2)	42.9 (16.3)
Total (left+right) Baseline	44.6 (11.6)	42.6 (12.5)
Right hand Post-MHE <sup>d</sup>	50.8 (12.5)	42.0 (14.9)
Left hand Post-MHE	56.0 (12.2)	44.4 (12.9)
Total (left+right) Post-MHE <sup>d</sup>	53.4 (10.3)	43.2 (12.3)

Note: Larger values indicate worse scores

<sup>a</sup> mild hypoglycemic episode

<sup>b</sup> onset before 48 months of age

<sup>c</sup> onset after 48 months of age

<sup>d</sup> One-tailed t-test  $p < .03$

post-hypoglycemia test periods.

However, a large proportion of diabetic subjects obtained impairment rating scores that fell in the impaired range for tapping and namewriting intermanual difference scores during both baseline and post-hypoglycemic testings (see Table 3). The percentage of diabetic subjects receiving impaired ratings within each onset and duration subgroup varied considerably. Differences between these groups in impairment ratings for baseline and post-hypoglycemic testings could not be calculated due to the fact that, in this sample, onset was very highly correlated with duration,  $r(29) = -.68$ ,  $p < .001$ . Percentages differed between onset groups as to whether the impairment score reflected possible right hemisphere or left hemisphere involvement (see Table 4).

#### Hypothesis 6

Analysis of motor performance rankings post-hypoglycemia between those diabetics who had a duration of diabetes greater than five years and those with a duration of less than two years revealed no significant differences for right hand,  $t(18) = .57$ ,  $p = .578$ , or left hand,  $t(18) = .09$ ,  $p = .929$ , motor functioning.

#### Hypothesis 7

Motor performance rankings between those subjects who identified the hypoglycemic episode by symptom and those who identified it during a routine testing time revealed no

TABLE 3

PERCENTAGE OF SAMPLE IN EACH CATAGORY OF IMPAIRMENT RATING<sup>a</sup>  
FOR INTERMANUAL DIFFERENCE (IMD) BY DURATION<sup>b</sup> AND ONSET<sup>c</sup> OF  
IDDM

Test	Duration/Onset	Impairment Rating	
		Normal <sup>d</sup>	Impaired <sup>e</sup>
Tapping Baseline			
	short duration ( <u>n</u> =12)	58.2	41.8
	long duration ( <u>n</u> =16)	75.0	25.0
	early onset ( <u>n</u> =7)	71.4	28.6
	late onset ( <u>n</u> =21)	66.6	33.3
Tapping Post-hypoglycemia			
	short duration ( <u>n</u> =11)	45.0	55.0
	long duration ( <u>n</u> =14)	71.6	28.4
	early onset ( <u>n</u> =7)	57.1	42.9
	late onset ( <u>n</u> =18)	61.1	38.9
Namewriting Baseline			
	short duration ( <u>n</u> =12)	25.0	75.0
	long duration ( <u>n</u> =14)	85.6	14.4
	early onset ( <u>n</u> =7)	71.4	28.6
	late onset ( <u>n</u> =19)	52.6	47.4
Namewriting Post-hypoglycemia			
	short duration ( <u>n</u> =12)	50.0	50.0
	long duration ( <u>n</u> =13)	77.0	23.0
	early onset ( <u>n</u> =7)	42.9	57.1
	late onset ( <u>n</u> =11)	72.2	27.8

<sup>a</sup> Reitan (1987)

<sup>b</sup> short duration = IDDM < 60 months  
long duration = IDDM > 60 months

<sup>c</sup> early onset = diagnosis of IDDM < 48 months of age  
late onset = diagnosis of IDDM > 48 months of age

<sup>d</sup> perfectly normal or normal

<sup>e</sup> mildly impaired or impaired



TABLE 4

PERCENTAGE OF DIABETIC CHILDREN RECEIVING IMPAIRMENT RATINGS<sup>a</sup>  
ON INTERMANUAL DIFFERENCE SCORES (IMD) REFLECTING LEFT OR  
RIGHT HAND INVOLVEMENT

		Left Hand <sup>b</sup>	Right Hand <sup>c</sup>	Total
Tapping				
baseline	( <u>n</u> =7)	17.2%	24.1%	41.3%
post- MHE <sup>d</sup>	( <u>n</u> =8)	10.3%	17.2%	27.5%
Namewriting				
baseline	( <u>n</u> =12)	10.3%	13.8%	24.1%
post-MHE	( <u>n</u> =8)	10.3%	17.2%	27.5%

<sup>a</sup> Reitan (1987)

<sup>b</sup> IMD Tapping < .02 (ages 6-8)  
< .03 (age 9 and older)

IMD Namewriting > 23 secs (ages 6-8)  
> 21 secs (age 9 and older)

<sup>c</sup> IMD Tapping > .19  
IMD Namewriting < 0 secs (ages 6-8)  
< 7 secs (age 9 and older)

<sup>d</sup> Mild Hypoglycemic Episode

significant differences in rankings between these groups for right hand,  $t(24)=.76$ ,  $p=.455$  or left hand,  $t(24)=1.07$ ,  $p=.276$ , during post hypoglycemic testing.

#### Hypothesis 8

Chi-square analyses revealed diabetics who identified hypoglycemia by symptoms were no less likely to be using human insulin than those diabetics identifying hypoglycemia during routine testing periods, chi-square(1) < .619,  $p>.431$ .

## CHAPTER V

### DISCUSSION

#### Summary of Results

The results of this study document that the motor performance level of a group of well-functioning diabetic children is within the average range during a period of documented euglycemia as well as after recovery from a mild hypoglycemic episode. However diabetic children performed more poorly on motor tasks than did control subject both during baseline testing and after a hypoglycemic episode. The results also provide evidence that the impact of a mild hypoglycemic episode upon cerebral functioning persists beyond the time when both the child and medical staff have determined that the child has recovered from the episode. This impact on motor functioning appears to be limited to right hand performance and is more pronounced in children who were diagnosed with diabetes before age four as compared to those diagnosed at an older age. The finding of selective impact on right hand performance is consistent with patterns noted for intermanual difference scores for tapping and namewriting tasks. Diabetic subjects received impairment ratings for these intermanual difference scores which are consistent with left hemisphere

difficulties both during hypoglycemia and during baseline testing. Examination of these effects in light of diabetes related variables revealed that duration of diabetes, type of insulin and the manner in which hypoglycemia was identified were not significantly related to overall motor performance or to impairment ratings. The finding that right hand reaction time was significantly slower after recovery from a hypoglycemic episode suggests that pure motor functioning is compromised during hypoglycemia separate from the impact of difficulties related to attention/concentration.

#### Performance Level of Diabetic Children as Compared to Controls and Normative Data

The hypothesis that children with IDDM exhibit slower motor performance as compared to normative data was not supported by the results of this study. This consistently average performance of diabetic subjects may be attributable, at least in part, to the selectivity of the inclusion criterion for the study. The exclusion of children with reported or observed learning or emotional difficulties, while permitting more accurate analysis of the impact of hypoglycemia on performance, may have masked any significant differences in the performance of these children as compared to a normative sample. Of particular interest is that despite this selective sampling and overall average level of performance, diabetic subjects performed more poorly with

their right hand on motor tasks than did control subjects. As expected, this is a replication of the same vexing finding noted in other studies examining the cognitive functioning of children with diabetes. Earlier studies found that diabetic subjects performed well within the average range for age on all individual tasks but their level of performance is consistently poorer than control groups with varying characteristics, siblings, medical patients, etc. (Holmes & Richman, 1985; Rovet et al., 1987; Ryan et al., 1985).

This finding of relatively slower right hand motor performance as compared to nondiabetic controls is also consistent with the results of studies that have documented slower motor speed in both adults and children with diabetes as compared to controls (Heller, 1989; Hepburn et al., 1989; Hinnen et al., 1986; Holmes et al., 1983). However results of the present study further define the effect as limited to the right hand. These results raise questions as to whether studies which have found relative deficits in visual-motor and visual-spatial skills in diabetic children were in actuality documenting a motor slowing with the preferred hand rather than compromised higher cognitive skills. While slower right hand motor performance as compared to controls is an alternate explanation of the findings of these studies, the slower right hand performance found in the present study would be inconsistent with their assertion that diabetes has a selective impact on right hemispheric functioning (Rovet et

al., 1987; Ryan et al., 1985).

Even though these results are consistent with the findings of other studies as well as further defining the possible impact of diabetes on cerebral functioning, these results do not lend any clarity to the question of whether relative deficits noted represent a "diabetic neuropathy", slowed conduction rate or some other unknown factor. Examination of the results related to recovery from hypoglycemia and intermanual difference impairment ratings offers some additional insight into the possible origins of these findings.

### Hypoglycemia in the Diabetic Child

#### The Impact of Hypoglycemia on Motor Functioning

As expected, diabetic subjects exhibited poorer motor performance after recovery from a mild hypoglycemic episode as compared to their own performance during baseline testing. This is consistent with findings of poorer motor performance in adults and children during and after recovery from a medically induced hypoglycemic episode (Blackman et al., 1989; Heller et al., 1989; Herold et al., 1985; Macdonald, 1989; Schroeder et al., 1989). This is also consistent with Reich et al.'s (1990) findings that the impact of a hypoglycemic reaction on neuropsychological functioning persists beyond the point in time when both the child and medical profession have deemed the child "recovered". However the present study adds

two important dimensions to this finding.

The first of these is that the impact of hypoglycemia on motor skills appears to be focused on right hand motor functioning. Previous research has made no attempt to separate left from right hand functioning and postulated that decrements were a function of depressed motor functioning overall (Heller, 1989; Herold et al., 1985; Hinnen et al., 1986; Holmes et al., 1983; Macdonald, 1989; Ryan et al., 1989). The second of these is that this impact of hypoglycemia on right handed motor functioning appears to have a relatively pure motor component in addition to any difficulties mediated by attentional variables.

The fact that reaction time on a task requiring sustained attention to complete was significantly slower after recovery from a hypoglycemic episodes suggests that motor performance in and of itself may be affected by hypoglycemia. This raises questions as to whether other studies which interpreted declines in reaction time on vigilance tasks as reflecting problems with attention/concentration, were also documenting difficulties in motor performance. (Heller, 1989; Herold et al., 1985; Hinnen et al., 1986; Holmes et al., 1983; Macdonald, 1989; Ryan et al., 1989).

This is not to say that attention/concentration factors are not a significant component of the deficits seen during and after a mild hypoglycemic episode. The study by Reich et al. (1990) documented attentional deficits after recovery from

mild hypoglycemia using a test with no motor component. In addition, numerous electroencephalographic and neurophysiological studies have documented changes in activity in anterior portions of the brain during and after hypoglycemia, consistent with the attentional hypothesis (Ameil et al., 1990; Blackman et al., 1989; Sherwin et al., 1989; Tallroth et al., 1990). In fact, the possibility that both motor and attentional factors contribute to poor performance on neuropsychological tasks during and after a hypoglycemic episode may be at least partially explained by the results of endocrine studies. These studies have found that neurogenic (motor) symptoms occur first during hypoglycemia in response to the release of epinephrine among other hormones. As blood glucose levels continue to drop neuroglycopenic (attentional) symptoms develop in response to hypoglycemia (Amiel et al., 1989; Macdonald, 1989; Widom et al., 1989). It appears possible, perhaps even likely, that recovery from hypoglycemia may proceed in reverse with neuroglycopenic symptoms resolving first and motor performance lagging behind as blood glucose levels rise. This would also explain why the resolution of grossly apparent symptoms of neuroglycopenia (attention/concentration) may be interpreted as resolution of the hypoglycemic episode while the resolution of the earliest and more subtle signs of impairment, motor difficulties, lag behind and are rarely detected.



Incidence and Detection of Mild Hypoglycemia  
in Children with IDDM

Another striking and somewhat unexpected finding of this study was the frequency of the occurrence of mild hypoglycemia in this sample of diabetic children. It was clear that mild hypoglycemia is indeed a frequent occurrence for the diabetic child and that these episodes often go undetected. Only three of the 15 children who received baseline testing shortly after arriving at camp did not experience a hypoglycemic episode within the following four days. In addition, five subjects who received their first testing following a hypoglycemic episode had to be excluded from the study because they experienced additional hypoglycemic episodes before they could receive a baseline testing 24 hours later. This may be related to the fact that the vast majority of campers followed intensive insulin regimens and may have been more physically active than usual.

In addition, fully 50 percent of the children included in our final sample were not aware of symptoms or chose not to seek medical attention for symptoms of hypoglycemia before it was documented during routine testing times. It is unlikely that hypoglycemia arose suddenly during routine testing for all of these children and suggests that a high percentage of the campers routinely functioned at suboptimal glyceic levels. It is of note that all but one of the subjects identifying mild hypoglycemia during these routine testings

retrospectively reported symptoms. However, these symptoms obviously were not attended to or noticed during the course of the activities prior to blood glucose monitoring. It is unclear whether this behavioral manifestation of hypoglycemia unawareness was related to counterregulatory variables or that children simply did not attend to symptoms when engaged in enjoyable camp activities. Regardless, these findings underscore the difficulties inherent in establishing the frequency and the impact of mild hypoglycemia on the functioning of this population.

#### Lateralization of the Impact of Diabetes

As all subjects were right handed, the results of this study may be interpreted as supporting the hypothesis that diabetes and/or hypoglycemia has a selective impact on motor functioning monitored by the left cerebral hemisphere. This interpretation is based on the consistency of the findings of both the analyses of impairment ratings for intermanual difference scores and that it was only right hand functioning that was significantly different in comparisons between various groupings of diabetics and to nondiabetic children. However, as scores were well within the average range it is clear that whatever impact diabetes/hypoglycemia has had upon the left hemisphere, it has not compromised the motor performance of these subjects in a way that has made them unable to perform at the average levels of their peers.

The interpretation of these seemingly contradictory findings point to issues that frequently arise in the interpretation of neuropsychological testing findings of children, both individually and as a group. That is the differences between the statistical significance, theoretical significance and the diagnostic significance of a particular score or pattern of scores.

Due to small sample size and correlations between onset and duration groupings, differences in impairments ratings for these groups could not be established statistically. In addition, while theoretically one would not expect to find any ratings of "impaired" on intermanual difference scores for either testing in this well functioning sample, no norms exist that would allow statistical analyses of the unexpectedly high incidence of intermanual difference impairment scores for both testings.

Theoretically the presence of such a large number of ratings of "impaired" in this purportedly well-functioning sample is highly significant. Rourke and his colleagues (1983) note that these comparisons between performance on two sides of the body "...can yield very valuable information with respect to the relative intactness of the two cerebral hemispheres" (p. 142). They further note that these differences are particularly significant when found in cases of mild impairment.

According to Rourke et al., (1983) it is thus

theoretically highly unlikely that these scores would have been obtained if the left hemisphere was not significantly compromised as compared to the right hemisphere. In addition, the finding of a left hemisphere motor performance decrement among those with early onset of the disorder as compared with those with later onset is consistent with the hypotheses of Rovet et al. (1987) and Ryan et al. (1985) that early brain trauma related to hypoglycemia may have affected myelination of the brain during a time of critical language (left hemisphere) development.

Diagnostically, these results are at best interesting. In the absence of documented performance problems, and seen in isolation these intermanual difference discrepancies during baseline testing can not be interpreted as reflecting a significant problem for the child. The presence of a high incidence of ratings of "impaired" on intermanual difference scores cannot be said to constitute "proof" of diabetes related brain damage to either hemisphere.

## Diabetes Related Variables and Motor Performance

### Age at Onset and Duration of Diabetes

Previous studies have documented that children with early onset and/or long duration of diabetes are at higher risk for neuropsychological impairment than are those with later onset or shorter duration of the disorder (Holmes & Richman, 1985; Rovet et al., 1987; Ryan et al., 1985). While this study did

not note any differences between these groups during baseline testing, children with earlier onset of diabetes (before age 4) performed significantly more poorly than those with later onset of the disorder after recovery from a mild hypoglycemic episode. While duration per se was not linked to poorer performance after hypoglycemia, three quarters of the children with early onset of diabetes also had a duration of the disorder of longer than five years. Therefore it was not possible to determine whether this prolonged recovery time after hypoglycemia was related to age of onset or the additive effects of early onset and long duration.

The absence of significant differences between these groups during baseline testing likely reflects the fact that the subjects in this study were selected because they were functioning well academically. However the fact that there were differences in performance between onset groups is nevertheless consistent with the hypothesis that repeated incidence of hypoglycemia common to those with early onset of the disorder may underlie the deficits documented in other studies (Holmes & Richman, 1985; Rovet et al., 1987; Ryan et al., 1985). In addition, this slower recovery time from hypoglycemia also may be a first indication that these children are at risk for subsequent difficulties. In light of overall average performance this finding is consistent with suggestions that hypoglycemia may exert its impact cumulatively and or that these children may be "growing into"

their deficit as they get older (Ryan et al., 1985; Rudel, 1978).

### Counterregulatory Response

The hypothesis that duration of diabetes (less than two years or more than five years) would be an adequate measure of whether counterregulatory hormonal response was intact and that this would be reflected in differences in performance level for these groups was not supported by the results of this study. The relationship between counterregulatory hormonal response and awareness of and recovery from hypoglycemia is a complex one. Thus this finding as well as lack of significant findings of cerebral adaption to hypoglycemia likely reflect the insensitivity of the measures employed rather than providing proof that these mechanisms are not operative for this population.

### Insulin Type

In this sample, the use of human insulin was not associated with a behavioral rating of decreased awareness of hypoglycemia (identification of hypoglycemia only during routine testing times). The type of insulin used by the children was also not related to motor performance level or the incidence of intermanual difference impairment ratings during post-hypoglycemic or baseline testings.

## Implications of These Findings

### Neuropsychological Implications

The finding that diabetes and/or hypoglycemia exerts a selective impact upon motor functioning monitored by the left hemisphere raises questions as to what other skills housed primarily in the left hemisphere may be compromised by diabetes related variables. Previous research has generally not documented significant language related problems in this population which would be consistent with left hemisphere involvement. It may be that motor functioning is most sensitive to diabetes related factors.

However, these findings do have implications for the interpretation of previous and future research on the cognitive functioning of diabetic children. The finding of a consistent right hand motor effect underscores the importance of following the established neuropsychological practice of ruling out basic sensory and motor deficits before postulating difficulties in higher level cognitive skills. This practice has been largely ignored in other studies employing neuropsychological measures and has likely contributed to what appeared to be wide discrepancies in their findings. In actuality, all of these findings can be explained at least in part by the presence of a preferred hand motor deficit.

### Implications for the Use of Intensive Treatment Regimens

In addition to providing evidence for delayed motor

recovery after mild hypoglycemia, the present study also documented the high incidence of mild hypoglycemia in a group of diabetic children who follow intensive treatment regimens. The present study also provided additional support for the notion that children are not adept at subjectively monitoring their own glycemic levels. Of particular concern is that children appear to either not become aware of or ignore symptoms of hypoglycemia and do not seek treatment when engaged in camp activities. In the absence of definitive proof that hyperglycemia produces a higher incidence of diabetic complications, these findings in and of themselves would seem to contraindicate attempts to maintain relatively normoglycemic blood glucose levels in active children because these levels can lead to an increase in hypoglycemic episodes. However in light of what appears to be evidence consistent with the hypothesis that repeated incidence of hypoglycemia may underlie deficits documented in other studies, the reexamination of the practice of routinely prescribing intensive treatment regimens for children with IDDM appears warranted.

#### Implications for the Social/Emotional Functioning of Children with IDDM

The finding of this study, that right hand motor slowing persists beyond the point when a child had been deemed recovered from a mild hypoglycemic episode has considerable implications for the social and emotional well-being of the



child with diabetes. It has been documented that children with chronic illnesses, including diabetes, have a higher incidence of emotional and behavioral problems as well as lower self-esteem than the normal population (Hamp, 1984; Gardner & Thompson, 1978). The stresses associated with the treatment and complications of diabetes are also very high for both the child and those who care for the child with IDDM.

The school age child whose motor functioning remains impaired after apparent recovery from a mild hypoglycemic episode may be more accident-prone or have difficulty completing school tasks that have a preferred hand motor component. This may produce feelings of inadequacy in the child if authority figures insist that these problems cannot be related to the hypoglycemic episode as the child's blood glucose level is within normal ranges. Alternately, the child may be labeled as lazy, clumsy or as "faking" diabetes related symptoms in order to gain the attention or sympathy from those around him or her.

#### Methodological Issues in This Study

Many of the methodological short-comings of this study were related to the limitations inherent in collecting data in a naturalistic setting. While this approach is also a strength of the study, providing more externally valid and generalizable results, it limited the amount of medical information that could be gathered. This additional

information might have permitted a more complete interpretation of the results.

Access to an accurate history of severe hypoglycemic reactions, seizures, episodes of diabetic ketoacidosis and other diabetes complications for each subject might have provided information as to whether these factors individually or in combination may have predicted overall performance or performance after recovery from hypoglycemia. The present study was also not able to document level of diabetes "control" of the subjects to determine whether diabetics in poorer control exhibit a different pattern of performance, recovery or pattern of symptom report after hypoglycemia as has been seen in some medical studies (Caprio, et al., 1990; Jones et al., 1990). Glycosylated hemoglobin values which are the best single measure of control, were not available as part of camp medical records. Self-report would not have been a valid indicator as no difference in these values have been found to exist between those who report that they follow an intensive insulin regimen and those who report following a less intensive regimen (Daneman et al., 1981; Golden et al., 1985; Knowles, 1981).

Another problem in relating medical and demographic information to the findings exists because of the small sample size. For example, as each of the individual categories of onset and duration were highly correlated with each other it was impossible to differentiate between the impact of onset

and duration. The availability of only a small sample of children also did not permit the use of more powerful statistical approaches to the analysis of the data or a more complex design of the study. A more inclusive as well as larger sample would also likely show more variation in level of performance and permit analysis of whether diabetes related variables were related to performance patterns during euglycemia.

The use of a ranking to determine whether there were differences between groups is a somewhat unorthodox, although not statistically biasing, approach but was necessitated by the absence of normative data for the maze test that would allow a mean motor standard score to be calculated. However the fact that the control group received rankings for each individual test, for each testing and as a group that were consistent across these parameters as well as consistently better than diabetic subjects performance suggests that these rankings were sensitive to the impact of diabetes and/or hypoglycemia in this sample. In addition, this approach is consistent with pattern of performance analysis which has been found to be of particular value in the neuropsychological assessment of children (Rourke et al., 1983).

#### Directions for Future Research

As with most research on complex phenomenon only a multi-disciplinary, longitudinal approach to the study of these

issues could even begin to provide a definitive answer to the question of whether diabetes, its treatment and/or complications compromise the cerebral functioning of children with the disorder. A study of this nature would entail following children from diagnosis through adulthood with repeated cognitive evaluations. Neurological and psychological variables as well as endocrine activity changes would need to be monitored frequently. In addition, accurate records of diabetic control, incidence of complications and - as much as possible- incidence of mild hypoglycemia would need to be kept in order determine the relationship between these variables and cognitive functioning.

Other research questions that are provoked by the results of this study include whether the child's experience of symptoms of hypoglycemia, even in the absence of documented low blood glucose levels, correspond to a change in cognitive functioning. This would be particularly interesting in light of the fact that children vary as to the level of blood glucose that triggers the endocrine response to hypoglycemia. Related to this question would be whether there are differences in cognitive functioning or recovery from hypoglycemia between children whose counterregulatory hormone response to hypoglycemia is intact and those who have developed defects in this protective endocrine response system. Proponents of the metabolic hypothesis of diabetic complications suggest that it is hyperglycemia, not

hypoglycemia that is responsible for long-term cerebral complications. Although this has not been borne out by some limited research in the area no one has studied the impact of transient hyperglycemia on functioning.

As previously mentioned, the finding of a preferred hand motor effect underscores the need to evaluate basic sensory and motor functioning before a deficit is attributed to a complex cognitive function. The use of tests of sensori-motor integrity in future research would be important in ruling out basic sensory deficits as producing even these motor findings.

#### Summary

It may be tentatively proposed that the cognitive deficits that have been found in the research on diabetic children may be in part due to the impact of hypoglycemia. Supporting this proposition are the findings of this study which document that the pattern of results found and hemisphere of the brain apparently affected by hypoglycemia is consistent with the deficit patterns reported in other studies (Haumont et al., 1979; Holmes & Richman, 1985; Rovet et al., 1987; Ryan et al., 1985). However, as glycemic levels of the subjects were rarely documented in these studies, it is certainly possible that the results of these previous studies are consistent with those found in this study after recovery from hypoglycemia because both findings are attributable to the impact of hypoglycemia.

The possibility that neither examiner nor child might be aware of a hypoglycemic state was clearly demonstrated during a pilot study related to this current research. At that time a diabetic child received a baseline testing that was not immediately preceded by a blood glucose level screening. The child appeared normal in all respects, denied symptoms of hypoglycemia but performed very poorly on neuropsychological tests. A blood glucose screening immediately after testing revealed that he had indeed been hypoglycemic during testing although he appeared normal to the examiner and he was unaware of his glyceic state. This case also demonstrated the sensitivity of neuropsychological testing to changes in glyceic level even in the absence of symptoms.

The results of this study are also consistent with the findings of previous studies that diabetic children fall within the average range of intellectual functioning. The prevalence of intermanual difference ratings in the impaired range is also consistent with studies that have found abnormal patterns of brain activity in diabetics. This is also consistent with studies that have documented patterns of poorer performance on neuropsychological tests in the presence of generally average performance overall.

The implications of these results for further research, the medical management of the child with IDDM and the social/emotional well-being of the diabetic child are clear. Additional research combining the expertise and unique

perspectives of professionals in different disciplines will be necessary to unravel the complex relationship between this disorder and the cognitive functioning of the diabetic child.

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## VITA

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